# Statistical Analysis Plan

## A PROSPECTIVE, MULTICENTER, RANDOMIZED CONTROLLED STUDY TO EVALUATE THE WOUND CLOSURE EFFICIENCY OF [redacted] KNOTLESS TISSUE CONTROL DEVICE [redacted] COMPARED TO CONVENTIONAL SUTURES IN TOTAL KNEE ARTHOPLASTY (TKA)

| | |
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# TABLE OF CONTENTS

# ABBREVIATIONS

| Abbreviation | Term |
|---|---|
| ADE | Adverse Device Effect |
| AE | Adverse Event |
| AIRE | Acute Inflammatory Response Evaluation |
| ASADE | Anticipated Serious Adverse Device Effect |
| BMI | Body Mass Index |
| CDC | Centers for Disease Control |
| CFDA | China Food and Drug Administration |
| CFR | Code of Federal Regulations |
| CHU | Complaint Handling Unit |
| EC | Ethics Committee |
| eCRF | Electronic Case Report Form |
| ESC | [redacted]Surgical Care |
| EDC | Electronic Data Capture |
| FPG | Fasting Plasma Glucose |
| GCP | Good Clinical Practice |
| ICD | Informed Consent Document |
| mITT | Modified Intent-to-Treat |
| IVRS | Interactive Voice Response System |
| IWRS | Interactive Web Response System |
| MedDRA | Medical Dictionary for Regulatory Activities |
| OR | Operating Room |
| PI | Principal Investigator |
| PT | Preferred Term |
| PP | Per-Protocol |
| QoL | Quality of Life |
| ROM | Range of Motion |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SOC | System Organ Class |
| SSI | Surgical Site Infection |
| TKA | Total Knee Arthoplasty |

| Abbreviation | Term |
|---|---|
| TSA | Topical Skin Adhesive |
| USP | United States Pharmacopeia |
| VAS | Visual Analogue Scale |

# 1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Protocol <ESC-16-001> Administrative Change 1 ( 27 May 2017).

## 1.1 STUDY OBJECTIVES

### 1.1.1 Primary Objective(s)

The primary objective of this prospective, randomized controlled study is to evaluate the wound closure efficiency of [redacted] compared to conventional sutures in patients undergoing Total Knee Arthoplasty (TKA). For the purpose of this study, wound closure efficiency is defined as the total time required to close the surgical incisions in patients undergoing TKA procedures using [redacted] compared to those using traditional sutures.

### 1.1.2 Secondary Objective(s)

Secondary objectives will include the evaluation of differences in overall surgical procedure time, operation room (OR) time, length of stay, procedure costs, quality of life measures including pain, and range of motion (ROM).

### 1.1.3 Other Objective(s)

The difference in the safety profiles for both wound closure procedures will be evaluated through the analysis of the incidence of wound complications including dehiscence, wound infections, and other adverse events.

## 1.2 STUDY ENDPOINTS

### 1.2.1 Primary Efficacy Endpoint(s)

The primary endpoint will be the total time required to close the surgical incisions between treatment groups. The time to close each surgical incision is defined as the time in minutes between placements of the first suture throws in the deep tissue to the completion of Intradermal layer closure (capturing the suturing time only).

### 1.2.2 Secondary Efficacy Endpoint(s)

Secondary efficacy endpoints include:

1. Duration of procedure (Total Operation Time): defined as the time in minutes elapsed from first incision to the skin closure;

2. Overall operating room (OR) time: defined as the time in minutes from the patient entering to exiting the OR;

3. Length of stay between surgery and discharge;

4. TKA related Quality of Life (QoL) assessments:

   a. Knee Pain: pain at rest and pain during mobilization is measured using a 10 centimeter Visual Analogue Scale (VAS) in which patient is asked to describe degree of pain with 0 being no pain and 10 being the worst pain;

   b. Health-related Quality of Life (EQ-5D-3L): patient is asked to confirm his/her health state by selecting the most appropriate level for each of the following 5 dimensions. Refer to Table 1.

   - Mobility
   - Self-care
   - Usual activities
   - Pain/discomfort
   - Anxiety/depression

**Table 1: EQ-5D-3L**

**By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.**

**Mobility**

I have no problems in walking about □

I have moderate problems in wlaking about □

I am unable to walk about

**Self-care**

I have no problems washing or dressing myself □

I have moderate problems washing or dressing myself □

I am unable to wash or dress myself □

**Usual Acitivities (i.e work, study, housework, family or leisure activities)**

I have no problems doing my usual activities □

I have moderate problems doing my usual activities □

I am unable to do my usual activities □

**Pain/Discomfort:**

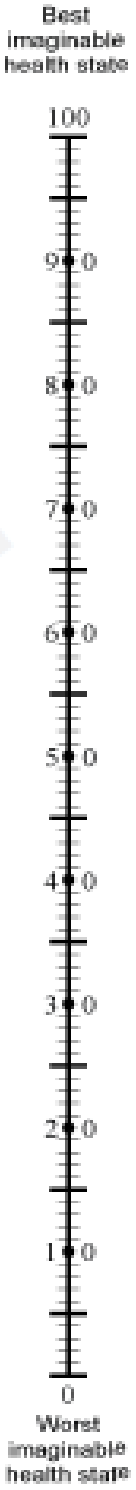
I have no pain or discomfort □

| | |
|---|---|
| I have moderate pain or discomfort | □ |
| I have extreme pain or discomfort | □ |
| **Anxiety/Depression** | |
| I am not anxious or depressed | □ |
| I am moderate anxious or depressed | □ |
| I am extremely anxious or depressed | □ |

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked **100** and the worst state you can imagine is marked **0**.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



### 1.2.3 Safety Endpoints

Safety endpoints include:

1. The incidence of SSI following surgery as defined by:

   a. CDC criteria[1]:

      1) Superficial incisional SSI:

         Infection occurs within 30 days after the operation and infection involves only skin or subcutaneous tissue of the incision and at least one of the following:

         - Purulent drainage, with or without laboratory confirmation, from the superficial incision;
         - Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision;
         - At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and superficial incision, is deliberately opened by surgeon, unless incision is culture-negative;
         - Diagnosis of superficial incisional SSI by the surgeon or attending physician.

         Do not report the following conditions as SSI:

         - Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration);
         - Infection of an episiotomy or new born circumcision site;
         - Infected burn wound;
         - Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI).

         Note: Specific criteria are used for identifying infected episiotomy and circumcision sites and burn wounds.

      2) Deep incisional SSI:

         Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to, be related to the operation and infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision and at least one of the following:

- Purulent drainage from the deep incision but not from the organ/space component of the surgical site;
- A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38ºC), localized pain, or tenderness, unless site is culture-negative;
- An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination;
- Diagnosis of a deep incisional SSI by a surgeon or attending physician. Notes:
- Report infection that involves both superficial and deep incision sites as deep incisional SSI;
- Report an organ/space SSI that drains through the incision as a deep incisional SSI.

3) Organ/Space SSI:

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to, be related to the operation and infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation and at least one of the following:

- Purulent drainage from a drain that is placed through a stab wound into the organ/space;
- Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space;
- An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination;
- Diagnosis of an organ/space SSI by a surgeon or attending physician.

No confirmatory culture will be required unless deemed by the physician per local standard of care to provide appropriate treatment to subject.

b. ASEPSIS Score (only for patients with confirmed SSI): assesses severity of wound infection using numerical scoring (as opposed to the CDC's absence or

presence of SSI and type). The ASEPSIS Wound Score evaluates would characteristics and additional treatments as predictors of infection that may develop once the subject leaves the hospital. These include the presence of serous exudates, erythema, purulent exudates, separation of deep tissues, antibiotics, drainage of pus, wound debridement, isolation of bacteria, and requirement for inpatient stay. Surgeons assess each parameter and provide a numerical score based upon objective criteria of wound appearance and clinical consequences of the infection. Extra points were added for antibiotic treatment of SSI (10 points), drainage of pus under local anesthesia (5 points), debridement of the wound under general anesthesia (10 points), isolation of bacteria from the wound (10 points), and an inpatient stay of more than 14 days (5 points). An overall score, ranging from 0 to 100, is then calculated to define wound severity according to the proportion of the wound affected by each of these characteristics [2, 3]. Refer to Table 2;

2. Use Acute Inflammatory Response Evaluation (AIRE) score measuring inflammatory tissue reaction. Of note, an AE will be reported when the score is >1. Refer to Table 3;

3.Incidence of would separation or dehiscence requiring intervention;

4.Incidence of delayed wound healing events;

5.Incidence of wound closure related adverse events and serious adverse events;

**Table 2: ASEPSIS Score**

| **Wound Characteristic** | **Proportion of Wound Affected** | | | | | |
|---|---|---|---|---|---|---|
| | 0 | <20 | 20-39 | 40-59 | 60-79 | >80 |
| Serous Exudate | 0 | 1 | 2 | 3 | 4 | 5 |
| Erythema | 0 | 1 | 2 | 3 | 4 | 5 |
| Purulent Exudate | 0 | 2 | 4 | 6 | 8 | 10 |
| Separation of Deep Issue | 0 | 2 | 4 | 6 | 8 | 10 |
| Points are scored for daily wound inspection. | | | | | | |
| | | | | | | |
| **Additional Treatment** | **Points** | | | | | |
| Antibiotics | 10 | | | | | |
| Drainage of Pus under local anesthesia | 5 | | | | | |
| Debridement of Wound (General Anesthesia) | 10 | | | | | |
| Serous Discharge* | Daily 0-5 | | | | | |
| Erythema* | Daily 0-5 | | | | | |
| Purulent Exudate* | Daily 0-10 | | | | | |
| Separation of Deep Tissues* | Daily 0-10 | | | | | |

| | |
|---|---|
| Isolation of Bacteria | 10 |
| Stay as In-patient Prolonged Over 14 Days | 5 |
| *Given scores on 5 of 7 days and the highest weekly score used. | |
| | |
| **Category of Infection** | |
| **Total Score**** | **Definition** |
| 0-10 | Satisfactory Healing |
| 11-20 | Disturbance of Healing |
| 20-30 | Minor Wound Infection |
| 31-40 | Moderate Wound Infection |
| >40 | Severe Wound Infection |
| **Total Score calculated adding scores for individual wound characteristics and additional treatment. | |

**Table 3: Acute Inflammatory Response Evaluation (AIRE) Score**

| Score | Erythema | Oedema | Pain | Temperature |
|---|---|---|---|---|
| 0 | None observed | None observed | None | None |
| 1 | Slight blanching redness along incision closure line | Slight increase in tissue firmness (turgor) | Pain at site with pressure | Slightly warmer compared to adjacent skin |
| 2 | Moderate redness extending < 2 mm | Pitting of skin around incision with mild pressure | Pain at site with touch | Definitely warmer compared to adjacent skin |
| 3 | Intense redness extending > 2 mm | Tense firmness of skin around incision | Continuous pain | Radiating heat at incision site |

## 1.3 SUMMARY OF THE STUDY DESIGN

### 1.3.1 General Study Design and Plan

This is a multicenter, single blind, prospective, randomized controlled study in patients undergoing elective TKA and meeting the study's eligibility criteria. Eligible patients will be randomized on 1:1 basis to have the surgical incision closed with either [redacted] or conventional sutures. Wound closure and surgical procedure times will be determined perioperatively. Patients will remain blinded to the type of sutures utilized for closure of the incision.

The schedule of events is depicted in Table 4 below.

**Table 4: Schedule of Events**

| Event | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 |
|---|---|---|---|---|---|
| | Baseline/ Screening[a] | Randomization | Procedure | Post-Op through Discharge[b] | 30-42 days[c] (post procedure) |
| Informed consent | X | | | | |
| IWRS/IVRS[d] | | X | | | |
| Inclusion/Exclusion | X | X | | | |
| Urine/blood pregnancy test | X | | | | |
| Demographics | X | | | | |
| Medical/Surgical history | X | | X | | |
| Physical examination[e] | X | | | X | X |

| Event | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 |
|---|---|---|---|---|---|
| | Baseline/ Screening[a] | Randomization | Procedure | Post-Op through Discharge[b] | 30-42 days[c] (post procedure) |
| Knee pain VAS | X | | | X | X |
| EQ-5D-3L | X | | | X | X |
| Concomitant medications[f] | X | X | X | X | X |
| Length of stay[g] | | | | X | |
| Health Economic | | | | X | |
| Procedural data[h] | | | X | | |
| Adverse events | | | X | X | X |
| Wound | | | X | X | X |
| SSI/ASEPSIS score[i] | | | | X | X |
| AIRE score | | | | X | X |
| Study completion | | | | | X |

a. To be performed within 30 days of surgery.

b. Data will be collect on 3-5 days after surgery (expect for the length of stay and health economic data).

c. Unless withdrawn from the study, subject's status will be confirmed at the time of in-person visit at 30-42 days following surgery. If possible, an in-person visit will be scheduled to confirm status for patients withdrawn prematurely from the study for any reason.

d. Interactive web response system/ Interactive voice response system.

e. The physical examination at baseline/screening visit includes height, weight and ROM of knee, and the post-procedure physical examination only includes ROM of knee.

f. Including pain medications and antibiotics (except for anesthesia medications).

g. Defined as time between procedure and discharge.

h. Procedure time, overall OR time, intra-operative device failure rates, operating room resource utilization (if applicable), and anesthesia method (e.g., general or lumbar anesthesia).

i. ASEPSIS score will be applied only after SSI confirmed.

### 1.3.2 Randomization and Blinding

Randomization will occur if the patient meets all inclusion criteria and does not meet any exclusion criteria. Each case will be randomized to one of two groups (STRATAFIX or conventional sutures) in a 1:1 ratio. The only difference between the groups will be the suturing material and technique.

Blinding practices for this study will include the following:

Patients: Patients will be informed of the 1:1 randomization between the different suturing material and technique, but will remain blinded as to which implant they actually received until after they have completed all study follow-up.

Implanting surgeon: It is not possible to blind the implanting physician due to the different suturing technique and products.

Medical Records: All medical records (source documents) documenting the implant procedure through hospital discharge and all follow-ups will not be blinded because the devices used will be descript in the operation record.

Monitors: Monitors will not be blinded because the detachable labels provided with the product identify the product and may be used in the study device accountability records and patient research file for the purpose of device accountability and source document validation.

### 1.3.3 Sample Size and Statistical Power Considerations

The proposed sample size of 92 patients per arm (184 total) is considered adequate to test the hypothesis that [redacted] can reduce the time for incision closure compared to conventional sutures. Based upon a review of the literature, the mean incision closure time was assumed to be 16.89 minutes for conventional sutures, being calculated as a weighted (based on number of subjects) mean of the means observed in the studies reviewed. The studies reported incision closure times ranging between 14.4 to 26.5 minutes [4-8]. It is expected that the [redacted] can reduce the incision closure time by [redacted] compared to conventional sutures; therefore, the assumed mean closure time for [redacted] is [redacted] minutes. The standard deviations observed in the reviewed literature range from [redacted] to [redacted] minutes for the conventional sutures; the standard deviation for this study was conservatively assumed to be [redacted] minutes in both groups for several reasons, such as the lack of data for [redacted] and that this patient sample may be older and with larger Body Mass Index (BMI). The distribution of incision closure time is assumed to be normal.

The statistical hypotheses for the primary endpoint are as follows:

- $H_0$: Mean Barbed ≥ Mean conventional suture tested against the alternative hypothesis
- $H_a$: Mean Barbed < Mean conventional suture;

Where:

- The assumed mean time to incision closure in conventional group is [redacted] minutes;
- The mean time to closure in [redacted] is [redacted] minutes;

- The assumed standard deviations in the two groups are both

Based upon these assumptions, a total seventy-seven (77) evaluable subjects per arm will achieve 90% power to detect a difference of minutes (expected mean for of minutes and the conventional group of minutes) with estimated group standard deviations of using a one-sided two-sample t-test. The assumed one-sided significance level is

If the higher limit of the one-sided 97.5% confidence interval for the difference in the Mean time minus the Mean closure time for conventional suture is smaller than 0, then it will be concluded that is considered to be superior to conventional suture. The sample size is adjusted to 92 per arm to account for a 16% withdraw rate [9-12].

# 2 STATISTICAL CONSIDERATIONS

## 2.1 GENERAL CONSIDERATIONS

All descriptive statistics for continuous variables will be reported using number of subjects (missing), mean, standard deviation (SD), median, quartile (Q1, Q3), minimum and maximum. Categorical variables will be summarized as number of subjects (missing), and frequencies along with the associated percentages.

## 2.2 DEFINITIONS OF ANALYSIS SETS

There will be three analysis sets defined:

- Modified Intent-to-treat set (mITT set) consists of all randomized subjects who had the surgical incisions closed using the randomized suture
- Evaluable [or Per-Protocol (PP)] set consists of all mITT subjects who have no major protocol violations.
- Safety set consists of all subjects who receive surgery.

Major protocol deviations are deviations that have an impact on the primary endpoint, or that have an impact on the randomization assignment. These will be determined prior to database lock.

## 2.3 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

### 2.3.1 Baseline Definition

Baseline: The baseline value is defined as the most recent value reported just prior to Procedure. Visit 1 (Baseline/Screening) occurs prior to the study procedure (performed within 30 days of surgery), and the evaluation performed at this Visit will be considered the “baseline” evaluation for analysis.

### 2.3.2 Study Day

Study Day will be calculated from the reference start date and will be used to show the day of assessment or start/stop day of events.

Reference start date (Day 0) is defined as the day of randomization.

Event Day = (date of event – reference start date).

### 2.3.3 Follow-Up Time

The follow-up duration for a subject is the time from randomization to the last non-missing visit post-baseline.

### 2.3.4 Analysis Visit Windows

No analysis window period will be used. Endpoint data will be collected at visit 3 (Surgical Procedure), visit 4 (Post-Op through Discharge), and visit 5 (30-42 Days Post Procedure).

### 2.3.5 Missing Data Handling Rules

All summaries of efficacy endpoints will be performed only on subjects who are randomized, and only observed data will be summarized. There will be no imputation for missing data or imputation of data for early terminated subjects.

## 2.4 MULTIPLE COMPARISONS/MULTIPLICITY

All secondary endpoints and/or any further sensitivity or exploratory analyses for the primary and secondary endpoints will serve as supportive evidence only and therefore no adjustment for multiple comparisons will be performed.

## 2.5 POOLING OF CENTERS

No adjustment for this multicenter study will be performed.

# 3 STATISTICAL ANALYSES

## 3.1 SUBJECT INFORMATION

3.1.1 Disposition of Subjects

The number of subjects screened and the frequencies (percentages) of subjects who failed screening and the reasons for screen failure will be summarized, based on data reported on the Visit1 - Baseline/Screening CRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each treatment group and overall.

Completion of Study Treatment: The frequencies (percentages) of randomized and treated subjects who completed study treatment and who terminated early from study will be

summarized according to the reason for subject's early termination, based on data reported on both the Visit 2- Randomization CRF and End of Study CRF.

### 3.1.2 Protocol Deviations

A deviation (any activity conducted outside the parameters established by the study protocol) can be identified from a number of sources. Potential sources include, but are not limited to: a member of the Investigator's staff, a Sponsor representative during monitoring visits, or a member of the data management or statistical groups when entering or analyzing data. Regardless of the source, it is crucial to document the deviation. The Principal Investigator (PI) will report protocol deviations to the IRB as required by the IRB procedures.

Major protocol deviations are deviations that have an impact on the primary endpoint, or that have an impact on the randomization assignment.

The protocol deviations will be identified prior to database lock .

The frequencies (percentages) of subjects in the mITT Population will be presented by treatment group according to deviation type, and a listing of all collected protocol deviations cases will be presented in an appendix listing.

### 3.1.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics for all enrolled subjects, as well as for the mITT subjects, will be summarized for each treatment group and overall, using descriptive statistics. Continuous demographic and baseline characteristics including age at time of informed consent, height, weight, BMI, and ROM of Knee will be summarized descriptively by number of subjects (missing), mean, standard deviation, median, quartile (Q1, Q3), minimum, and maximum; categorical variables including gender, race, ethnicity, education, occupation categories, urine/blood pregnancy test results, knee pain, Health-Related Quality of Life (EQ-5D-3L) will be summarized descriptively by frequencies along with the associated percentages.

### 3.1.4 Medical History

The Medical/Surgical History will be coded by Medical Dictionary for Regulatory Activities (MedDRA 20.0 or higher Version) or higher version. The frequencies (percentages) of subjects reporting a medical/surgical history, as recorded on the CRF, will be summarized for all enrolled subjects, as well as for the mITT set, for each treatment group and overall. A subject data listing of medical and surgical history will be provided.

### 3.1.5 Concomitant Medication and Non-drug Treatment

All terms for Concomitant medications recorded on the CRF will be coded using the World Health Organization (WHO) Drug Dictionary (JUN 1st 2017).

The Non-drug Treatment will be coded by Medical Dictionary for Regulatory Activities (MedDRA 20.0 or higher Version) or higher version.

The frequencies (percentages) of subjects who took concomitant medications or non-drug treatment will be summarized for all enrolled subjects, as well as for the mITT set by treatment group and overall.

#### 3.1.6 **Treatment Compliance**

Descriptive summary statistics will be provided for compliance for each treatment group and all patients in the mITT set. The frequencies and percentage of patients participating in visit 3 through visit 5 will be provided.

## 3.2 EFFICACY ANALYSES

### 3.2.1 Primary Efficacy Analysis

#### 3.2.1.1 Primary Analysis

The primary efficacy endpoint will be analyzed using the mITT and Per-Protocol analysis sets. The mITT analysis will be considered primary analysis.

For the primary efficacy endpoint, a one-sided 97.5% confidence interval for the difference in treatment group means (Mean [redacted] closure time minus the Mean closure time for conventional suture) will be constructed using the t-distribution. If the higher limit of the confidence interval is smaller than 0, then it will be concluded that [redacted] is considered to be superior to conventional suture.

The primary efficacy endpoint will be summarized by treatment group, reporting number of subjects (missing), mean, standard deviation, median, quartile, minimum and maximum.

### 3.2.2 Secondary Efficacy Analyses

All secondary efficacy endpoints will be analyzed using the mITT analysis set.

All secondary efficacy endpoints (see section 1.2.2) will be summarized descriptively by treatment group. The continuous variables will be summarized descriptively using number of subjects (missing), mean, standard deviation, median, quartile, minimum and maximum. Categorical data will be summarized descriptively by frequencies along with the associated percentages. No inferential statistics will be generated for the secondary efficacy endpoints.

## 3.3 SAFETY ANALYSIS

Safety variables include the incidence of SSI, ASEPSIS score (only for subjects with confirmed SSI), AIRE score, incidence of wound separation or dehiscence requiring intervention, incidence of delayed wound healing events, incidence of AEs and SAEs associated with wound closure.

All safety endpoints (see section 1.2.3) will be summarized descriptively by treatment group for the Safety analysis set using available data. There will be no missing data imputation for the safety analysis. The continuous variables including ASEPSIS total score (ranging from 0 to 100), and AIRE total score (ranging from 0 to 12) calculated as the sum

of individual scores for Erythema, Oedema, Pain and Temperature, will be summarized descriptively by number of subjects, mean, standard deviation, minimum, and maximum. Categorical data including the incidence of SSI, incidence of wound separation or dehiscence requiring intervention, incidence of delayed wound healing events, incidence of AEs and SAEs associated with wound closure will be summarized descriptively by frequencies along with the associated percentages. No inferential statistics will be generated for the safety endpoints.

### 3.3.1 Extent of Exposure

The descriptive statistics will be provided for subject follow-up time.

Follow-up time in days will be derived from the following formula:

Follow-up Time (days) = (date of last visit) – (date of randomization) + 1;

### 3.3.2 Adverse Events

An AE is defined as any untoward medical occurrence, regardless of its relationship to the study device (study suture) or the study procedure (TKA), which includes any new, undesirable medical experience or worsening of a pre-existing condition, which occurs at any point from the surgery to Final Visit.

The adverse event verbatim descriptions (investigator terms from the CRF) will be classified into medical terminology using MedDRA 20.0 or higher Version. Adverse events will be coded to primary System Organ Class (SOC) and PT using MedDRA (Version 20.0 or higher). All AEs will be summarized by treatment group. The incidence of AEs will be reported as the frequencies (percentages) of subjects with AEs within SOC and PT. Subjects will be counted only once within a SOC and PT, even if the subject experienced more than one TEAE within a specific SOC and PT. The frequencies (percentages) of subjects with AEs will also be summarized by maximum severity (mild, moderate, or severe), relationship to the study device and outcome.

All AEs will be presented in subject data listings.

#### 3.3.2.1 Deaths, Serious and Other Significant Adverse Events

The frequencies (percentages) of subjects with AEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided.

The frequencies (percentages) of subjects with serious adverse events (SAEs) will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided.

### 3.3.3 Clinical Laboratory Parameters

Clinical Laboratory Parameters will include pregnancy test which is collected at screening/baseline visit. A subject data listing of pregnancy test result will be provided.

#### 3.3.4 Physical Examination

##### 3.3.4.1 Physical Examinations

Physical examination results are collected at visit 1 – screening/baseline visit, visit 4 – post-op through discharge and visit 5 – 30-42 days post procedure. The physical examination at baseline/screening visit includes height, weight and ROM of knee, and the post-procedure physical examination includes ROM of knee.

Physical examination results at each visit will be summarized by treatment group using number of subjects (missing), mean, standard deviation, median, quartile, minimum and maximum.

#### 3.3.5 Other Safety Analyses

No other safety analyses are planned for this study.

### 3.4 OTHER EXPLORATORY ANALYSIS

Not applicable.

## 4 INTERIM ANALYSIS AND DATA MONITORING COMMITTEE (DMC)

### 4.1 INTERIM ANALYSIS

No interim analyses are planned for this study.

### 4.2 DATA MONITORING COMMITTEE

No data monitoring committee is planned for this study.

## 5 SUMMARY OF MAJOR CHANGES IN THE PLANNED ANALYSES

No changes occurred.

## 6 REFERENCES

1. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Committee. American Journal of Infection Control 1999: 27: 97-132. http://www.cdc.gov/hicpac/pdf/guidelines/SSI_1999.pdf

2. Wilson AP, Treasure T, Sturridge MF, Gruneberg RN. A scoring method (ASEPSIS) for postoperative wound infections for use in clinical trials of antibiotic prophylaxis. Lancet 1986: I: 311-313.http://dx.doi.org/10.1016/S0140-6736(86)90838-X

3. Wilson AP, Weavill C, Burridge J, Kelsey MC. The use of the wound scoring method 'ASEPSIS' in postoperative wound surveillance. Journal of Hospital Infection 1990: I6: 297-309. PMID: 1980502

4. Gililland JM, Anderson LA, Barney JK, Ross HL, Pelt C.E, Peters Cl. Barbed Versus Standard Sutures for Closure in Total Knee Arthroplasty: A Multicenter Prospective Randomized Trial The Journal of Arthroplasty 29 Suppl. 2 (2014) 135–138.http://dx.doi.org/10.1016/j.arth.2014.01.041

5. Borzio RW, Piveci R, Kapadian BH, Jauregui JJ. Maheshwari AV. Barbed sutures in total hip and knee arthroplasty: what is the evidence? A meta-analysis. International Orthopaedics (SICOT) (2016) 40:225–231.doi 10.1007/s00264-015-3049-3

6. Ting NT, Moric MM, Della Valle CJ, Levine BR. Use of Knotless Suture for Closure of Total Hip and Knee Arthroplasties A Prospective, Randomized Clinical Trial. J or Arthoplasty. 2012; 27(10):1783-88. http://dx.doi.org/10.1016/j.arth.2012.05.022

7. Smith EL. DiSegna ST, Shukla PY, Matzkin EG.Barbed Versus Traditional Sutures: Closure Time, Cost, and Wound Related Outcome in Total Joint Arthroplasty. The Journal of Arthroplasty. 2014; 29: 283–287.doi: 10.1016/j.arth.2013.05.031

8. Gililland JM, Anderson LA, Sun G, Ericksoo JA, Peters CL. Perioperative Closure-related Complication Rates and Cost Analysis of Barbed Suture for Closure in TKA. Clin Orthop Relat Res. 2012; 470:125–129. doi 10.1007/s11999-011-2104-7.

9. Julious, S. A. 2010. Sample Sizes for Clinical Trials. Chapman & Hall/CRC. Boca Raton, FL.

10. Chow, S.-C., Shao, J., and Wang, H. 2008. Sample Size Calculations in Clinical Research (Second Edition). Chapman & Hall/CRC. Boca Raton, FL.

11. Machin, D., Campbell, M., Fayers, P., and Pinol, A. 1997. Sample Size Tables for Clinical Studies, 2nd Edition. Blackwell Science. Malden, MA.

12. Zar, Jerrold H. 1984. Biostatistical Analysis (Second Edition). Prentice-Hall. Englewood Cliffs, New Jersey.

# 7 ATTACHMENT

The table/listing/figure (TLF) shells will be presented as an attachment in a separate document outside of the SAP.