PAREXEL International

Smith + Nephew Pty Ltd

MINI.PMCF.2018.11

Safety and Performance of MINITAC◊ Ti 2.0 Suture Anchor in Extremities

Statistical Analysis Plan

Version: 1.0

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Approved by: M. Foster 30 Jan 2020

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Signatures below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
0.5	28 01 20	Final Draft

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
aCRF	Annotated Case Report Form
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
BSI	British Standards Institute
CIP	Clinical Investigational Plan
DD	Device Deficiency
EC	Ethics Committee
EU	European Union
HREC	Human Research Ethics Committee
IP	Investigational Product
PI	Principal Investigator
PP	Per-Protocol Population
ROM	Range of Motion
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analogue Scale

1 INTRODUCTION

This retrospective, non-interventional cohort study is designed to evaluate intra-operative, 6 months and 12 months safety and performance of the MINITAC◊ Ti 2.0 Suture Anchors for extremities repair to meet post-market clinical follow-up requirements for extremities repair indications as outlined by the Notified Body (British Standards Institute (BSI)).

The purpose of the statistical analysis plan (SAP) is to lay out key elements including definitions and statistical methods for the planned analyses. As this is a descriptive study, all analyses will be of a descriptive nature, unless otherwise specified (i.e., no a priori statistical hypotheses will be tested). The final study report will detail all analyses, including minor modifications and any deviations from the planned analyses, and may describe analyses included in future abstracts and manuscripts. A regulatory submission is not planned.

The data source of the study is the medical charts of each participating subject to the extent that data are available. These will then serve as the input for the electronic Case Report Form (eCRF).

This SAP is based upon the following study documents:

- Study Protocol MINI.PMCF.2018.11, Version 3.0 (Aug. 20, 2019)
- eCRF, Version 3.0 (Jun. 21, 2019)

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objective of this study is to assess safety and performance of the MINITAC◊ Ti 2.0 Suture Anchor in extremities over a time period of 6 months after intervention.

2.2 Secondary Objective(s)

The secondary objective of this study is to assess safety and performance of the MINITAC◊ Ti 2.0 Suture Anchor in extremities over a time period of 12 months after intervention.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

This is a retrospective, multi-center, non-interventional cohort study to collect clinical data that will permit the evaluation of the safety and performance of the MINITAC◊ Ti 2.0 Suture Anchor for indications in extremities. Up to 3 sites in Australia and the EU (European Union) will participate in the study enrolling a minimum of 30 subjects up to a maximum of 50 subjects into the study. Each enrolling site will enroll a minimum of 10 subjects.

Data from enrolled subjects will be recorded from the subject medical file on designated CRFs. Data will be collected retrospectively for different time points including preoperative, operative, 6 months postoperative and 12 months post-operative.

3.2 Identification of Analysis Populations

3.2.1 Full Analysis Set

The Full Analysis Set (FAS) includes all subjects enrolled in the study who had previously undergone arthroscopic repair using the MINITAC$^{\Diamond}$ Ti 2.0 Suture Anchor. The FAS will be used for the analysis of all measures and endpoints.

3.3 Subgroup Analysis

Subgroup analyses will be performed to assess the consistency and robustness of the study product's performance mainly for the clinical success rate (%) of the MINITAC$^{\Diamond}$ Ti 2.0 Suture Anchor in extremities at 6 months and 12 months postoperative with clinical success.

The following subgroups will be explored:

- Sex (male vs female)
- Age ($\leq$ 40, >40 to $\leq$ 60 vs > 60 years old)
- Race (white vs others)
- Ethnicity (Hispanic or Latino, Non-Hispanic or Latino)

- Primary diagnosis body system (foot, ankle, elbow, wrist vs hand)
- Body Mass Index (<25, $\geq$ 25 to < 35 vs $\geq$ 35 kg/m^2)

3.4 Interim Analysis

There is no interim analysis for this non-interventional study.

3.5 Study Endpoints

3.5.1 Primary Endpoint

The primary endpoint is the clinical success rate (%) of the MINITAC$^{\Diamond}$ Ti 2.0 Suture Anchor in extremities at 6 months postoperative with clinical success defined as extremity repairs without signs of device failure and/or re-intervention as assessed by the surgeon. Device failure is also referred to as device malfunction which is failure to perform in accordance with the device's intended purpose when used in accordance with the instruction for use or the protocol.

3.5.2 Secondary Endpoints

The secondary endpoint is the clinical success rate (%) of the MINITAC◊ Ti 2.0 Suture Anchor in extremities at 12 months postoperative with clinical success defined as extremity repairs without signs of device failure and/or re-intervention as assessed by the surgeon. Again, device failure is also referred to as device malfunction which is failure to perform in accordance with the device's intended purpose when used in accordance with the instruction for use or the protocol.

3.5.3 Other Endpoints

Additional endpoints include surgeon reported outcomes as well as safety endpoints. There is expected to be a large volume of missing data associated with the surgeon reported outcomes.

3.5.3.1 Surgeon Reported Outcomes

Surgeon reported outcomes include specific data collected as standard of care and documented in the medical records. This will include:

- Range of Motion (ROM)
- Pain assessed by Visual Analogue Scale (VAS)
- Device Failure Criteria

A listing of device failure criteria will be collected for subjects that were assessed by the surgeon to have signs of device failure and/or re-intervention and therefore not meeting the definition of clinical success.

3.5.3.2 Safety Endpoints

Safety endpoints include the collection of the following events from the subjects' medical record:

- All adverse events (AEs) and complications occurring from the time of subject enrollment until study termination or study completion including intra-operative adverse events and complications
- Device related re-intervention
- Device deficiencies (DDs)

4 DATA SOURCE

The data source of the study is the medical charts of each participating subject to the extent it is available, which will serve as the input for the eCRF.

5 STATISTICAL METHODS

5.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Parexel procedures for analysis and reporting.

5.2 General Presentation Considerations

As this study is of a descriptive nature, the analysis results will be reported using descriptive statistics.

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated. Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator.

Given the small, convenience study sample, as well as the absence of *a priori* statistical hypotheses, no formal tests of statistical significance are planned, and as such, no p-values or statistical intervals will be calculated.

All report outputs will be produced using SAS® version 9.3 or a later version in a secure and validated environment. All report outputs will be provided to the Sponsor as individual .rtf files and as a consolidated .pdf document.

5.3 Statistical methods

5.3.1 General Analysis Definitions

Screening / Enrollment: For screening, only information available in the medical records will be reviewed. When all inclusion criteria and none of the exclusion criteria have been met for a subject and the informed consent process has been completed or a waiver of consent has been granted by the HREC/EC, the subject will be considered enrolled.

Baseline: Unless specified otherwise, the last non-missing value before study product installation/operation collected at the screening visit is considered as the baseline value.

Study Day:
Study Day = assessment date – study product installation/operation date + 1 for assessments post operation;
Study Day = assessment date – study product installation/operation date for assessments prior to operation;

All durations are calculated as the stop date minus the start date +1 unless otherwise specified.

End of Study: Due to the retrospective design of the study, end of the study is defined as the date when the last subject is documented on CRFs.

5.3.2 Analysis of the Primary Endpoint

The proportion of subjects with clinical success at 6 months post operation (182 days + 30 / -150 days) will be summarized with a frequency and percentage. Clinical success is achieved only if all of the following are true for a patient (as indicated by the items in the impact status form in the study case report form):

- Did not experience any inflammation;
- Did not have any device related AEs;
- Did not have any device deficiencies;
- Did not experience any device failure (malfunction);
- Did not have any signs of repair failure, and;
- Did not undergo any re-intervention.

Subgroup (defined in section 3.3) corresponding proportions will be presented in tabular form. All analyses will be carried out using the FAS.

In addition, the primary endpoint will also be estimated for +/- 3 months (3-9 month window) as per standard of care.

Incidence rates of the post-operative device failure and/or device related re-intervention at 6 months will be estimated. Specifically, the following will be summarized and estimated:

- The number of patients at risk of an event;
- The number of patients with events;
- The number of events;
- Total person-months;
- Crude rate/person-months;
- Estimated rate.

Person-months are months for each patient between baseline and 6 months included in the FAS. The estimated rate will be derived using Poisson regression with an offset as (the log of) the duration at risk for each patient.

5.3.3 Analysis of the Secondary Endpoint

The proportion of subjects with clinical success at 12 months post operation (365 days + 30 / - 150 days) will be summarized with a frequency and percentage. . As with the primary endpoint, subgroup (defined in section 3.3) corresponding proportions will be presented in tabular form. .

Incidence rates of the post-operative device failure and/or device related re-intervention at 12 months will be estimated as described above for the analysis of the primary endpoint.

Time to the first case of postoperative device failure and/or device-related re-intervention from operation date will be analyzed using the Kaplan-Meier method to estimate median time and related 25th and 75th percentiles. Patients without postoperative device failure or device related re-intervention will be censored at the latest date of assessment based on CRF data or date of death, whichever is earlier.

A by-subject listing of clinical success status will be provided for all subjects in the safety population. The listing will include subject identifier, date of 6-month visit, date of 12-months visit, clinical success status at 6-month visit or 12-month visit, date of device failure, description of failure, date of re-intervention, reason of re-intervention, and other information.

5.3.4 Sensitivity Analyses

No sensitivity analyses are planned.

5.3.5 Analysis of the Other Endpoints

5.3.5.1 ROM

The number and proportion of patients with full functional arc will be presented. In addition, summary statistics (N, mean, SD, median, and range) will be calculated at 6 months and 12 months within side, body location and motion direction (i.e., internal, external).

5.3.5.2 VAS

Summary statistics (N, mean, SD, median, and range) will be calculated for the raw data and for their absolute and percent change from baseline by scheduled visits.

5.3.5.3 Device Failure Criteria

The device failure criteria provided by the surgeon will be summarized as frequency (N) and percentage (%) by scheduled visit.

Other surgeon reported outcomes may be input to the database. These possible outcomes will be summarized as appropriate using descriptive summary characteristics for continuous or categorical endpoints. Differences from screening/baseline to 6 months and 12 months will be similarly summarized.

5.3.6 Safety Analysis

All safety endpoints will be summarized using the FAS. The adverse events (AEs) will be coded using the internal Smith + Nephew coding dictionary.

5.3.6.1 Definition of AE Categories

The definitions for each of the AE categories are based on ISO 14155:2011 [2].

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical sign (including abnormal laboratory findings) in subjects, users or other persons, whether or not it is related to the investigational product (IP) or the procedure.

An Adverse Device Effect (ADE) is an AE that is possibly, probably or definitely related to the use of the investigational product (IP) or the procedure.

An AE or ADE is considered a Serious Adverse Event (SAE) or Serious Adverse Device Effect (SADE) if, in the view of either the Investigator or the Sponsor, the event:

a) led to death,
b) led to serious deterioration in the health of the subject, that either resulted in
- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- in-patient or prolonged hospitalization, or
- medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

Planned hospitalization for a pre-existing condition, or a procedure required by the study protocol, without serious deterioration in health, is not considered a serious adverse event.

An Unanticipated Serious Adverse Device Effect (USADE) is a serious ADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. On the other hand, anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

The severity of every AE will be assessed by the Principal Investigator (PI) or medically qualified site staff to whom the responsibility has been delegated and documented on the delegation of authority log. AE should be classified as mild, moderate, or severe, regardless of whether or not the AE are considered to be serious or non-serious.

5.3.6.2 AE Analysis

All AEs and complications occurring from the time of subject enrollment until study termination or study completion including intra-operative AEs and complications, will be summarized by coded term, and by action taken.

An overall summary table of AEs, ADEs, SAEs, SADEs, USADEs, ASADEs, AEs leading to death, AEs leading to permanent impairment, removal/revision, DD, device failure and participation discontinuation will be presented. For each AE, the percentage of subjects who experience ≥ 1 occurrence of the given event will be summarized. The same summary will be provided for SAEs, SADEs, USADEs, ASADEs, as well as AEs leading to death, a permanent impairment of a body structure or body function, removal/revision, DD, device failure or study participation discontinuation.

AE summaries will be ordered in terms of decreasing frequency, and then alphabetically for the coded terms by Nonoperative Site Systemic Codes, or Operative Site Codes and associated sub-categories (if provided).

For each subject and each AE, the worst severity recorded will be attributed and used in the by-severity summaries. Similarly, the worst causality (most related to IP or the procedure) will be attributed and used in the by-causality summaries. As an exception, AEs that have missing causality (after data querying) will be assumed to be related to study drug.

By-subject listing of all AEs will be provided. The listings will include: subject identifier, adverse event (coded term), Nonoperative or Operative Site Codes and associated sub-categories (if provided), start/end dates and corresponding study day, relatedness to IP or procedure, seriousness, anticipated or not, leading to death, removal/revision or DD, leading to study participation discontinuation and other information. Additional summaries or listings may be provided, as appropriate.

Implant status collected will also be summarized by scheduled visit.

5.3.6.3 Device Related Re-intervention

Device related re-intervention will be summarized by scheduled visits for re-intervention reasons, related to AE, time to re-intervention from operation, failed anchors, whether or not the component well fixed was in place, the component damage, the component removed or revised, and component description. A listing of device-related re-intervention will be provided.

5.3.6.4 Device Deficiencies (DDs)

DDs will be summarized by scheduled visits for deficiency category, related to AE, investigational product reference number, timing of deficiency, time to deficiency from operation if post operation, and if product returned to sponsor. A listing of DDs will be provided.

5.3.6.5 Concomitant Medication/Therapy

Medications/therapies will be classified as Concomitant if used in the period from operation date to the 12-month visit. Concomitant medications until end of study will be summarized by generic name and indication. A by-subject listing of concomitant medications will be provided.

5.4 Study Subjects

5.4.1 Disposition of Subjects

Disposition information will be tabulated and summarized with descriptive statistics. This summary includes, but, is not limited to: total enrolled, total completed 6-month visit, total completed 12-month visit, total completed or terminated early in the study and reasons for discontinuation. End of study status will be listed.

5.4.2 Protocol Deviations

Major protocol deviations are defined as those deviations from the protocol that are likely to have an impact on subject's right, safety, well-being, and/or the validity of data for analysis. Major protocol deviations and any action to be taken regarding the exclusion of subjects or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification.

Subjects with major protocol deviations will be listed. Protocol deviations will be based on clinical review mainly of the following categories: (1) Entered but did not satisfy eligibility criteria; (2) other.

A summary of the number and percentage of enrolled subjects with a major protocol deviation by category of deviation will be provided.

5.5 Demographic and Other Baseline Characteristics

Demographics and baseline characteristic data will be summarized for the safety population. Demographics data such as age (year), sex, ethnicity, race, weight (kg), height (cm) and BMI (kg/m^2) will be summarized as reported in the eCRF. In addition, the following derived characteristics will also be summarized as categorical data:

- Age (≤ 40, > 40 to ≤ 60, > 60 years old)
- Body Mass Index (< 25, ≥ 25 to < 35, ≥ 35 kg/m^2)

Medical history will be summarized for the medical history term. The primary diagnosis will be tabulated for body system, site and previous surgery. Operative data will be summarized for type of surgery, location and side, surgical technique, general anesthetic, local regional anesthetic, blood loss, tourniquet use, intervention, and time from surgery to enrolment. Discharge data will also be tabulated for ambulatory support use on discharge, primary ambulatory support and places the subject was discharged to.

5.6 Handling of Missing and Uninterpretable Data

Missing data will not be imputed, and the data will be analyzed as they were entered in the study database.

5.7 Determination of Sample Size

This study is precision-based, as a result, the sample size is not based on statistical power calculations. It is reasonable to assume a success rate of 95% for the MINITAC◊ Ti 2.0 Suture Anchor in this study. With a further assumption of a ±10% precision in order to obtain a 95% CI of 85% to 100%, enrolling 30 subjects into the study will provide 55.4% probability. Across all investigational sites therefore, a minimum of 30 subjects (minimum of 10 subjects per site) up to a maximum of 50 subjects overall (98.8% probability) across all sites will be enrolled into this study.

5.8 Changes in the Conduct of the Planned Analysis

The following are changes from the protocol in the conduct of the planned analyses:

- In the protocol section 10.1, it is mentioned that generally all significance tests will be two-sided, performed at the 5% significance level, and resulting p-values will be quoted. However, for this study, given the small convenience study sample, the nature of non-intervention, as well as the absence of a priori statistical hypotheses, no formal hypothesis tests of statistical significance are planned, and as such, no p-values will be calculated. Relatedly, since statistical intervals are based on the same statistical assumptions as p values, no 95% confidence intervals will be estimated;
- The study will not employ separate safety and per protocol analysis sets. Instead, only one analysis set, the FAS as defined above, will be employed for all analyses;
- Kaplan-Meier estimation will not be used to estimate the event rate of postoperative device failure and/or device-related re-intervention at both 6 and 12-months. Instead incidence rates crude and model estimated incidence rates will be calculated;
- An analysis of the primary endpoint is included here +/- 3 months (3-9 month window) as per standard of care.

6 REFERENCES

[1] Clinical investigation of medical devices for human subjects - Good clinical practice (ISO 14155:2011), (2011).

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