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Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	An Investigation of The Metal Concentration In Patients Implanted With The PRESTIGE LP™ Cervical Disc At Two Contiguous Levels In The Cervical Spine
Clinical Investigation Plan Identifier	MDT16060SD1701
Clinical Investigation Plan Version	6.0
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Table of Contents

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Not Applicable, New Document	[redacted]
2.0	• Update address of Sponsor/Local Sponsor on the cover page. • Update Section 5 to remove 3 months, 6 months and 24 months for the serum sample collection schedule and to remove 24 months for other data collection schedule. • In Section 7.1.3, add some languages for more clear definition of Primary Analysis Dataset and Per-Protocol Analysis Dataset. • In Section 7.8.1, remove 3 months, 6 months and 24 months for the serum data collection. • In Section 7.8.2.8, add data summary requirement for Serious Adverse Device Effect (SADE) if available. • In Section 7.8.3, add data summary requirement for Doctor's Perception of Results.	[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
CIP	Clinical Investigational Plan
CRF	Case Report Form
FDA	U. S. Food and Drug Administration
NDI	Neck Disability Index
PCS	Physical Component Summary
SADE	Serious Adverse Device Effect
SF-36	Medical Outcome Study 36-Item Short Form Health Survey

3. Introduction

The PRESTIGE LP™ Cervical Disc is a two-piece articulating device that is inserted into the intervertebral disc space as a single unit at a single or two contiguous cervical levels using an anterior approach. The device is manufactured from a titanium ceramic composite (titanium alloy (Ti-6Al-4V) with 10% Titanium

Carbide) and consists of two low-profile metal plates that interface through a ball and trough mechanism, permitting segmental spinal motion. The superior component of the implant contains the ball portion of the mechanism, and the inferior component contains the trough portion. These two features engage to create an interface designed to allow for motion after implantation. Each component is affixed to the adjacent vertebral body by two rail geometries incorporating anti-migration teeth, which are press fit into two pre-drilled holes in the vertebral bone. The portion of the flat surface between the rails and contacting the vertebral endplate contains commercially pure titanium (CP Ti) plasma thermal sprayed coating designed to permit bony on-growth for additional device incorporation. The remaining portion of the flat surface is titanium ceramic roughened to enhance fixation.

The device is indicated in skeletally mature patients with radiculopathy or myelopathy or both caused by degenerate disc disease from C3-C7. FDA approved PRESTIGE LP™ Supplement P090029/S003 indicating to use at two contiguous levels and to add a 5mm device height for use at either one or two contiguous cervical levels on July 7, 2016. As a condition of approval, the FDA requested the sponsor to investigate the metal concentrations in patients implanted with the PRESTIGE LP™ Cervical Disc at two contiguous levels in the cervical spine in a post approval study.

4. Study Objectives

4.1 Primary Objective

The primary objective of this clinical study is to assess the metal concentrations in the blood serum of patients implanted with the PRESTIGE LP™ Cervical Disc at two contiguous cervical levels for the presence of metal concentrations. The metal to be assessed will include:

- Titanium (Ti)
- Vanadium (V)
- Aluminum (Al)

4.2 Secondary Objectives

Secondary objectives of this study are:

- To evaluate overall success rate.
- To assess the postoperative Neck Disability Index (NDI) score improvement from preoperative;
- To evaluate postoperative Neurological Status change from preoperative.
- To assess the safety of the PRESTIGE LP™ Cervical Disc as reported through AEs and secondary surgeries.
- To assess the postoperative Neck and Arm Pain score change from preoperative.
- To assess the postoperative SF-36 PCS score change from preoperative.

5. Investigation Plan

This will be a prospective study in which up to five investigational sites in the U. S. will be participated. There will be no control group involved. All subjects participated in this study will be required to sign off the informed consent and to meet all of the inclusion and exclusion criteria.

Serum samples will be collected at preoperative, 6 weeks, and 12 months after surgery. Titanium and vanadium concentrations in serum will be analyzed by the Trace Metal Analysis Laboratory (TMAL), Department of Orthopedic Surgery at Rush University Medical Center, following a serum testing protocol developed by the lab. Aluminum in serum will be determined by the Metals Laboratory of Mayo Medical Laboratories Rochester MN.

Demographics and medical and surgical history of the subjects will be collected at preoperative. NDI, neurological, neck and arm pain, pain medication use, and SF-36 PCS Health Survey will be evaluated at preoperative, 6 weeks, 3 months, 6 months, and 12 months after index surgery.

6. Determination of Sample Size

Thirty subjects enrolled at up to five sites will receive the treatments at two contiguous levels using PRESTIGE LP™ investigational devices. This is a single arm study to meet the FDA conditional approval requirements.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

The disposition of subjects including those enrolled, died, withdrawn, and evaluated will be summarized in an accountability table at all follow-up periods.

7.1.2 Protocol Deviations

A study protocol deviation is an instance when the Investigator or site personnel did not conduct the study according to the protocol, clinical investigational plan (CIP), or Investigator agreement. A protocol deviation is classified as a minor or major deviation according to the type of deviations.

7.1.3 Analysis Datasets

7.1.3.1 Primary Analysis Dataset

Primary Analysis will be conducted for the subjects who received the treatment of the PRESTIGE LP™ investigational devices at two contiguous levels. The subjects who enrolled but did not receive any

treatments or who enrolled and received the investigational treatment but exited the study following the surgery with no postoperative follow-up will not be included in this primary analysis. The missing data will not be imputed, and the analysis will be based on the observed data. However, the data prior to the secondary failure will be carried forward to the latest visit for those who had a secondary surgery failure.

7.1.3.2 Per-Protocol Analysis Dataset

Per-protocol analysis dataset is the subset of the primary analysis dataset. Per-protocol analysis will be performed for the subjects who received the treatment of the PRESTIGE LP™ investigational devices at two contiguous levels but had no major protocol deviations, such as violation of inclusion and exclusion criteria or receiving different treatments other than intended treatment. Per-protocol analysis will only be carried out for overall success status.

7.2 General Methodology

7.2.1 Laboratory Data and Analysis

Data of the metal concentrations in serum generated by the labs will be documented and provided to Medtronic, and the summary statistics (n, mean, median, standard deviation, minimum and maximum) at each time point will be presented. The changes in metal concentrations from preoperative at each post-operative visit will be analyzed using paired t-test for normally distributed data or Wilcoxon signed rank test for not normally distributed data. Further analysis on simple correlation of the metal concentration with continuous clinical outcome scores (NDI, neck pain, arm pain, and SF-36 PCS) and subgroup analysis on the metal concentrations by binary outcomes (neurological success, NDI success and overall success) will be carried out.

7.2.2 Clinical Data and Analysis

For continuous clinical outcome scores such as NDI, neck pain, arm pain, SF-36 PCS, and surgery data, the summary statistics (n, mean, median, standard deviation, minimum and maximum) at each time point will be presented. The changes from preoperative at each postoperative visit will be analyzed using paired t-test for normally distributed data or Wilcoxon signed-rank test for not normally distributed data.

For categorical clinical outcomes such as overall success, neurological status, NDI success, and pain medication use, frequency and percentage of subjects will be summarized at each time point.

For secondary surgery and adverse events, the rates will be summarized using the life-table method of time-to-event analysis. The Kaplan-Meier analysis will be applied to return-to-work summary.

7.3 Center Pooling

Data collected from different investigational sites will be pooled.

7.4 Handling of Missing Data and Dropouts

Missing data due to missed follow-ups, lost to follow-ups (dropouts), or failure to answer CRF questions during office visits will not be imputed for analyses. Therefore, only observed data are analyzed.

7.5 Adjustments for Multiple Comparisons

No adjustments for multiple comparisons will be made.

7.6 Demographic and Other Baseline Characteristics

Demographic and other baseline variables will be summarized with descriptive statistics. For continuous variables such as age, height and weight, the summary statistics including n, mean, standard deviation, median, and minimum and maximum, will be presented. For categorical variables such as race and gender, frequency and percentage of the subjects in each category, will be summarized.

7.7 Interim Analyses

No interim analysis will be conducted for this study.

7.8 Evaluation of Objectives

7.8.1 Primary Objective and Primary Measurement Analyses

The primary objective of this study is to assess the concentrations of Titanium (Ti), Vanadium (V), and Aluminum (Al) in the blood serum of patients implanted with the PRESTIGE LP™ Cervical Disc at two contiguous cervical levels. The primary measurement analyses associated with the primary objective include:

- The metal concentrations of Titanium (Ti), Vanadium (V), and Aluminum (Al) at preoperative, 6 weeks, and 12 months after index surgery. The summary statistics including n, mean, median, standard deviation, minimum and maximum will be summarized.
- The summary statistics for the changes in the metal concentrations from preoperative will be presented, and the two-sided paired t-test for normally distributed data or Wilcoxon signed-rank test for not normally distributed data will be performed.
- The summary for titanium concentrations from this study will be presented side by side with the one from the Prestige LP™ one-level metal study.
- Pearson correlation analysis will be carried out between the metal concentrations and continuous clinical outcome variables including NDI, arm pain, neck pain, and SF-36 PCS scores at postoperative time points.
- Subgroup analysis of the metal concentrations by binary outcomes including overall success, NDI success and neurological success will be carried out. No statistical inference will be made.

7.8.2 Secondary Objectives and Secondary Measurement Analyses

The secondary objectives of this study are to evaluate overall success, NDI score and success, neurological success, neck pain score and success, arm pain score and success, SF-36 PCS scores and success, secondary surgery, and adverse events.

7.8.2.1 Overall Success

Overall success is claimed when the following four conditions are met:

- Postoperative NDI score improvement of at least 15 points from preoperative;
- Maintenance or improvement in neurological status;
- No serious, implant or implant/surgical procedure associated adverse event; and
- No secondary surgical procedure classified as “failure”.

Frequency and percentage of overall success at postoperative time points will be summarized, and no statistical conclusion will be drawn.

7.8.2.2 NDI Score and Success

The summary statistics including n, mean, median, standard deviation, minimum and maximum for NDI score and change from preoperative will be summarized. The paired t-test for normally distributed NDI score or Wilcoxon signed-rank test for not normally distributed NDI score will be carried out to test whether the change from preoperative is significant.

NDI success is defined as follows:

Preoperative score – Postoperative score ≥ 15.

The frequency and percentage of NDI success status will be summarized, and no statistical inference will be made.

7.8.2.3 Neck Pain

Neck pain is composed of pain intensity and duration, and its score is the sum of the numerical ratings of both. The summary statistics including n, mean, median, standard deviation, minimum and maximum for neck pain score at all visits and change at postoperative visits from preoperative will be summarized. The paired t-test for normally distributed pain score or Wilcoxon signed-rank test for not normally distributed pain score will be performed to test whether the change from preoperative is significant.

Neck pain success is defined as follows:

Preoperative score – Postoperative score > 0.

The frequency and percentage of neck pain success status will be summarized, and no statistical inference will be made.

7.8.2.4 Arm Pain

Arm pain consists of pain intensity and duration, and its score is derived by adding the numerical ratings of both. The summary statistics including n, mean, median, standard deviation, minimum and maximum for arm pain score at all visits and change at postoperative visits from preoperative will be summarized. The paired t-test for normally distributed pain score or Wilcoxon signed-rank test for not normally distributed pain score will be performed to test whether the change from preoperative is significant.

Arm pain success is defined as follows:

Preoperative score – Postoperative score > 0.

The frequency and percentage of arm pain success status will be summarized, and no statistical inference will be made.

7.8.2.5 SF-36 PCS

The component of SF-36, PCS, is derived from the self-evaluated questionnaires based on the algorithm formulated by the Medical Outcomes Trust, the developer of the SF-36 survey form. The summary statistics including n, mean, median, standard deviation, minimum and maximum for PCS score at all visits and change at postoperative visits from preoperative will be summarized. The paired t-test for normally distributed PCS score or Wilcoxon signed-rank test for not normally distributed PCS score will be performed to test whether the change from preoperative is significant.

PCS success is defined as follows:

Postoperative score - Preoperative score ≥ 0.

The frequency and percentage of PCS success status will be summarized, and no statistical inference will be made.

7.8.2.6 Neurological Success

Success of each element is defined as maintenance or improvement from preoperative. Failure of each element is defined as deterioration from preoperative. Success of each neurological component (Motor function, Sensory function, or Reflexes) is defined as success of all elements, and failure of each component is defined as failure of at least one element. Success of overall neurological status is defined as success of all three components, and failure as failure of at least one component. Frequency and

percentage of each component as well as overall neurological success status will be summarized, and no statistical comparisons will be carried out.

7.8.2.7 Secondary Surgical Interventions

A time-to-event analysis (life-table method) will be carried out to summarize the secondary surgeries including revision, removal, supplemental fixation, reoperation, and other categories.

7.8.2.8 Adverse Events

Causality of AEs is categorized as implant associated, surgical procedure associated, implant/surgical procedure associated, undetermined, or not related. AE severity is characterized into four categories: mild (Grade 1), moderate (Grade 2), severe (Grade 3), and life-threatening (Grade 4). For a conservative consideration, implant or implant/surgical procedure associated AEs are considered to be implant associated. Analysis using life-table method will be carried out for all adverse events, implant or implant/surgical procedure associated AEs, Grade 3 or Grade 4 AEs, and Grade 3 or Grade 4 AEs that are implant or implant/surgical procedure associated. In addition, serious adverse device effect (SADE) will be summarized if available.

7.8.3 Other Measurement Analyses

7.8.3.1 Work Status

Work status is classified as currently working and not working. Frequency and percentage of subjects at each time point will be summarized, and no statistical inference will be made.

7.8.3.2 Pain Medication Use

Pain medications are categorized as Non-Narcotic Medications, Weak Narcotic Medications, Strong Narcotic Medications, and Muscle Relaxant Medications. There are five values listed for frequency of usage in each category of the medication use. Frequency and percentage of subjects in each value listed for frequency of usage of the medication use will be summarized, and no statistical inference will be made.

7.8.3.3 Surgery Data

Estimated blood loss, length of surgery, and length of hospital stay (calculated from date of surgery until date of discharge) will be summarized, and the summary statics including n, mean, median, standard deviation, minimum and maximum will be presented.

7.8.3.4 Return to Work

Return to work based on the first date on which a subject returned to his/her job duty after surgery will be analyzed using Kaplan-Meier method. The median return to work time (in days) will be calculated.

7.8.3.5 Doctor's Perception of Results

Doctor's Perception of Results, Excellent, Good, Fair or Poor, will be summarized with frequency and percentage of each category of perceptions.

8. Validation Requirements

The validation of data summary and analysis will be conduct at the level I. The outputs generated by two independent statisticians will be compared and any discrepancy of the results will be resolved before being incorporated into the final report.