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APPROVALS

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Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	A Prospective, Multicenter Evaluation of the CD HORIZON® Fenestrated Screw Spinal System with Fenestrated Screw Cement When Used in the Treatment of Spinal Conditions in subjects with Compromised Bone Quality (FNS Study)
Clinical Investigation Plan Identifier	MDT17040SD1703
Clinical Investigation Plan Version	2.0
Sponsor/Local Sponsor	Medtronic Bakken Research Center BV Endepolsdomein 5 6229 GW Maastricht The Netherlands

Table of Contents

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Jay Dong, Principal Statistician
2.0	• Introduction: Added a statement regarding the change of the study objective and reasons behind the change. • Study Objectives: Objectives were not divided into Primary and Secondary Objectives. The following objectives, including neurological success, radiographic assessment of stabilization of the pedicle screw instrumentation, radiographic fusion status, and changes in coronal and sagittal spinopelvic parameters, were removed. The endpoint analyses at 24-month visit were removed. • Investigational Plan: Removed the language regarding 100 subjects with two indication groups (50 each) to be enrolled in 10 investigational sites. Removed the requirement for data collection at 12- and 24-month visits. Limited the scope of the data collection to VAS back and leg pain, ODI, EQ-5D 5L, and adverse events and/or device deficiencies. • Determination of Sample Size: Removed the descriptions about how the sample size was calculated. Added a language stating that the number of the anticipated available subjects will be around 20. • Analysis Datasets: Datasets were not separated into Primary Analysis Dataset and Per-Protocol Analysis Dataset. Added the language stating that for subjects who already had a data collection beyond 3 months at time of the premature termination announcement, the data beyond 3 months will be summarized, and for the subjects who enrolled and underwent surgery but will not be able to complete 3-month follow-up visit by the scheduled study closure, they will be included in the analysis. • Definition of Time Periods: Removed 24 months from the definition and the language about the life table method of the time-to-event analysis. • Clinical Data and analysis: Removed the requirement of analysis for spinopelvic parameters, neurological status, and medication use. Removed the time-to-event analysis method. • Center Pooling: Changed 10 study sites to 6 study sites.	Jay Dong, Principal Statistician

Version	Summary of Changes	Author(s)/Title
	• Interim Analysis: Deleted the requirement for an interim analysis. • Evaluation of Objectives: 1. Deleted the subtitles "Primary Objective and Analysis" and "Secondary Objectives and Analyses". 2. Removed Analyses for ODI improvement, VAS back and leg pain improvement, and EQ-5D 5L improvement at 24 months. Defined "Improved" and "Not Improved" in each clinical measure. Added the language for summary of "Improved" and "Not Improved" subjects. 3. Deleted requirements of analyses for neurological success, stabilization of pedicle screw instrumentation, radiographic fusion status, and changes of coronal and sagittal spinopelvic parameters. 4. Added the Section 7.9.8 of Data Listing for neurological status, stabilization of pedicle screw instrumentation, fusion status, and spinopelvic parameters. • Changes to Planned Analysis: Modified the statement "No changes have been made to the original planned analyses…" to "Changes have been made to the original planned analyses…".	

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
CIP	Clinical Investigation Plan
DD	Device Deficiency
EC	Ethics Committee
EQ-5D 5L	European Quality of Life – 5 Dimension, 5 Levels
FDA	U. S. Food and Drug Administration
FNS	Fenestrated Screws
PIC	Patient Informed Consent
IFU	Instructions for Use
ODI	Oswestry Disability Index
PMMA	Polymethylmethacrylate
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analog Scale

3. Introduction

CD HORIZON® Fenestrated Screws (FNS) Spinal System with Fenestrated Screw Cement is a thoracolumbar surgical device for the treatment of degenerative disc disease, ankylosing spondylitis, spondylolisthesis, trauma, spinal stenosis, curvatures (scoliosis, kyphosis or lordosis), tumor, and failed previous fusion (pseudoarthrosis) in Europe. In US, it has been approved for the treatment of the patients with advanced stage tumors only. The surgery utilizes pedicle screws and rod systems for posterior stabilization and immobilization of the thoracolumbar spine. Compromised bone is prone to poor screw anchorage resulting in screw loosing, screw pullout, screw toggle, and/or complete hardware failure. Therefore, the success of the surgery depends on how strong the fixation of pedicle screws within the vertebrae of a spinal segment is.

Bone cement consisting of polymethacrylate (PMMA) has been widely used for implant fixation in various surgeries. In CD HORIZON® FNS Spinal System, an FNS screw is cannulated at center and contains six fenestrations (openings) at the distal end of the screw. The bone cement is injected through a continuous tract in the adapter and into the screw cannula. The cement is extruded through those fenestrations into the targeted vertebral body in a controlled manner. The self-curing PMMA cement serves as the screw interface and provides holding power of the screws. It has been shown to significantly increase the screw pull-out strength. As a result of the cement-augmented pedicle screw fixation, the procedure improves clinical outcomes resulted from spinal diseases such as spinal stenosis. One of the side effects associated with the application of bone cement is potential cement extravasation which could lead to clinical complications. The risk, however, can be reduced through various measures such as improved accuracy of the cement delivery.

CD HORIZON® Fenestrated Screws (FNS) Spinal System has been CE-marked since 2011 for the treatment of a wide range of spinal diseases including degenerative disc disease, spondylolisthesis, etc., and received 510(k) clearance from FDA since 2016 for the treatment of the patients diagnosed with advanced stage cancers involving the thoracolumbar spine. The initial objective of this proposed study was to evaluate the safety and effectiveness of CD HORIZON® Fenestrated Screws (FNS) Spinal System with Fenestrated Screw Cement for stabilization and immobilization of spinal segments in subjects with compromised bone quality, and to support FDA 510(k) application for expanded indications in US. However, the objective has been changed and the study will be prematurely terminated one year after the study was initiated due to the following reasons: A. Expanding the indications in the US for Fenestrated Screws with Fenestrated Screw Cement is no longer a business priority; B. Alternative data sources to support the products and regulatory submission are available; C. Current slow enrollment significantly protracts the timeline for study completion, which will result in significant increase in the study budget. The initial proposed study was a prospective, multicenter, and post-market clinical trial for 100 subjects with degenerative spinal disease or deformity to be treated at one to multiple thoracolumbar levels located from T1 to S2. The premature termination of the study will stop further enrollment of patients, but the study will continue to follow-up the already enrolled patients until the 3-month follow-up visit with a visit cut-off of 15 July 2020. This new version of SAP is intended to make adjustment for the objectives and endpoints defined in the initial SAP as a result of the premature termination of the study.

4. Study Objectives

The objective is to assess the following endpoints for subjects with compromised bone quality, who will receive a surgical procedure requiring posterior stabilization and/or immobilization of one or more spinal segments using CD HORIZON® Fenestrated Screw Spinal System with Fenestrated Screw Cement:

- Improvement of ODI at 3- and 12-month visits from baseline;
- Improvement of VAS back and leg pain score at 3- and 12-month visits from baseline;
- Improvement of EQ-5D 5L at 3- and 12-month visits from baseline;
- Intraoperative cement extravasation/leakage;
- Device and/or procedure related adverse events up to 3- and 12-month visits;
- Secondary spinal surgeries at index and/or adjacent level(s) up to 3- and 12-month visits.

5. Investigation Plan

This is a prospective, single-arm, multicenter study involved in the treatment of subjects with compromised bone quality using CD HORIZON® Fenestrated Screw Spinal System with Fenestrated Screw Cement in Europe. All subjects participating in this study will be required to sign a Patient Informed Consent (PIC) form which must be approved by the Ethics Committee (EC) before enrollment.

The enrollment will be cut off when the anticipated decision of the premature termination is announced to the investigators. The data of the available enrolled and treated subjects across current 6 investigational sites in Europe will be collected from baseline to 3-month (and 12-month if available) postoperative follow-up visit(s). There may be more than one pre-planned surgery for the treatment procedure. The pre-planned secondary surgery should be conducted within 3 months following the initial surgery. There should be at least 1 month in between the pre-planned secondary surgery and 3-month follow-up visit to reduce any bias on the patient reported outcomes. The pre-planned secondary surgery should not be reported as an adverse event. The initial surgery date will be used to determine the time period for an adverse event as described in the section 7.2.1.

Data will be collected at baseline, surgery, postoperative period prior to hospital discharge, and postoperative visits at 3 months and 12 months (if available). At baseline, data collected for analysis include medical and surgical history, conservative care types, indications to be treated, demographics, VAS back and leg pain, ODI, and EQ-5D 5L. During surgery, the following data are collected for analysis: surgery time, blood loss, number of levels treated, procedure types, devices and their components (such as screws and cement), intraoperative cement extravasation/leakage, and adverse events and/or device deficiencies. At postoperative assessment prior to hospital discharge, the data collected for analysis include adverse events and/or device deficiencies. During postoperative visits at 3 months and 12 months (if available), the following data will be collected for analysis: VAS back and leg pain, ODI, EQ-5D 5L, secondary spinal surgeries, and adverse events and/or device deficiencies.

6. Determination of Sample Size

The initial sample size with 100 subjects was calculated based on the defined primary endpoint (i.e. improvement of ODI at 12 months from baseline). Due to the premature termination of the study, the number of available subjects is anticipated to be around 20. These are the ones already enrolled at time of announcement of the study termination and continued to be followed up until the visit cut-off of 15 July 2020.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

The study subjects will include those who have signed the Informed Consent and underwent surgery. Subjects are scheduled to be followed up to the visit cut-off date (15 July 2020) after index surgery. During the follow-up period, a subject can voluntarily withdraw from the study at any time and for any

reason. The site investigator can only withdraw a subject from the study with a valid reason. The following may be some of the reasons for withdrawal or exit of a subject: PIC procedure not followed, eligibility criteria not met, death, subject voluntary withdrawal from the study, and the fenestrated screw procedure defined in CIP not followed. For the lost to follow-up subjects, the site investigator should make every effort to contact the subject. At least three contact attempts should be made via phone calls, text messages and/or emails.

With the visit cut-off date of 15 July 2020, it is expected that the majority of the subjects who enrolled and treated, if not all, would be followed up through 3 months after surgery. It is also expected that two subjects will complete the 12-month follow-up visit.

7.1.2 Protocol Deviations

A study protocol deviation exists if any one or more following conditions are met:

- PIC procedure not followed;
- Inclusion/Exclusion criteria not met;
- Visit not done;
- Required assessment(s) at the visit not performed;
- Visit fallen outside the CIP defined visit window;
- The fenestrated screw procedure not followed as defined in this protocol;
- Improper AE / SAE / ADE / SADE / DD reporting;
- EC approval not obtained, if required.

7.1.3 Analysis Datasets

Analysis will be conducted for the subjects who are enrolled in the trial, undergo the designated surgical procedure, and receive the treatment of the CD HORIZON® Fenestrated Screw Spinal System with Fenestrated Screw Cement. The subjects who are enrolled but do not receive intended medical devices (such as competitor's screws and/or cement) will not be included in analysis. The missing data will not be imputed, and all analyses will be based on the observed data. For the subjects who already had a data collection beyond 3 months at time of the premature termination announcement, the data from beyond 3 months will be summarized. For those who enrolled and underwent surgery but will not be able to complete 3-month follow-up visit by the scheduled study closure, the data, if available, will be included in the analysis.

7.2 General Methodology

7.2.1 Definition of Time Periods

For analysis on adverse events and secondary spinal surgeries, time periods used in this study are defined in Table 1.

Table 1: Time Periods Used for Summaries of AEs and Secondary Spinal Surgeries

Time Period	Duration (Days*)
Operative	0 day
1 Day to 4 Weeks	≥1 Day and <28 days
6 Weeks (≥ 4 weeks and < 2 months)	≥28 days and <(2x30.4-1) days
3 Months (≥ 2 months and < 5 months)	≥(2x30.4-1) days and < (5x30.4-1) days
6 Months (≥ 5 months and < 9 months)	≥(5x30.4-1) days and < (9x30.4-1) days
12 Months (≥ 9 months and < 19 months)	≥(9x30.4-1) days and < (19x30.4-1) days

* Days = Event Onset Date – Index Surgery Date. For subjects with a pre-planned second surgery, the initial surgery date is used as the index surgery date.

7.2.2 Clinical Data and Analyses

For continuous clinical outcome scores such as ODI score, VAS back and leg pain score and EQ-5D 5L, the summary statistics (n, mean, median, standard deviation, minimum and maximum) at the postoperative time point will be presented. The changes at postoperative visit(s) from preoperative will be analyzed using paired t-test for normally distributed data or Wilcoxon signed-rank test for not normally distributed data where the test is appropriate.

For categorical clinical outcomes such as the sex of subjects, frequency and percentage of subjects will be summarized at postoperative time point(s).

For AEs and secondary surgeries, the number of events and subjects at each time period as well as the rate up to 3 months and 12 months will be summarized.

The summary results of the two indication subgroups (degenerative disc disease and deformity) will be presented where appropriate.

7.3 Center Pooling

The Data collected across study sites will be pooled for analysis.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

All available data for the subjects who are enrolled, received the intended treatments will be included in the data listings and tabulations. Missing data due to incomplete medical records or lost to follow-up 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 carried out.

7.6 Demographic and Other Baseline Characteristics

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

7.7 Treatment Characteristics

Data related to surgical procedures, surgery time, blood loss and transfusion, intraoperative cement extravasation / leakage, device models and adverse events/device deficiencies during surgery will be summarized.

7.8 Interim Analyses

No interim analysis will be carried out.

7.9 Evaluation of Objectives

7.9.1 Improvement of ODI from Baseline

The analysis for improvement of ODI at 3 and 12 months from preoperative will be performed. The summary statistic, n, mean, median, standard deviation, maximum and minimum, will be summarized. The improvement of ODI score (μ_{ODI}) of each subject is indicated by baseline score – postoperative score. If $\mu_{ODI} > 0$, then ODI is considered to be improved. Otherwise, ODI is not improved. The frequency and percentage of the "improved" and "not improved" subjects will be summarized. The null hypothesis H_0 and the alternative hypothesis H_a are as follows:

H_0: $\mu_{ODI} \leq 0$

H_a: $\mu_{ODI} > 0$

The null hypothesis will be rejected if one-sided p-value is less than 0.05 (level of alpha), and the alternative hypothesis will be accepted, indicating that the improvement of ODI score from baseline is significantly greater than zero.

If the data is normal, the paired t-test for the changed score from baseline will be applied in the analysis. The assumption of normality will be assessed by using the Shapiro-Wilks test. If the assumption of normality is not met, analysis will be performed using the non-parametric method, Wilcoxon signed-rank test.

7.9.2 Improvement of VAS Back and Leg Pain Score from Baseline

The improvement of VAS back and leg pain score (μ_{VAS}) of each subject is indicated by baseline score – postoperative score. If $\mu_{VAS} > 0$, then VAS back or leg pain is said to be improved. Otherwise, VAS back or leg pain is not improved. VAS back and leg pain scores at preoperative, 3 months and 12 months as well as the changes at 3 months and 12 months from baseline will be summarized. The summary statistic, n, mean, median, standard deviation, maximum and minimum, will be produced. The frequency and percentage of the "improved" and "not improved" subjects will be summarized. The null hypothesis H_0 and the alternative hypothesis Hα are as follows:

H_0: $\mu_{VAS} \leq 0$

Hα: $\mu_{VAS} > 0$

The null hypothesis will be rejected if one-sided p-value is less than 0.05, and the alternative hypothesis will be accepted, indicating that the improvement of VAS back and leg pain score from baseline at a specific follow-up visit is significantly greater than zero. The paired t-test for the changed score from baseline will be performed if the distribution of the data is normal, and the Wilcoxon signed-rank test will be carried out if the distribution of the data is not normal.

7.9.3 Improvement of EQ-5D 5L from Baseline

The improvement of EQ-5D 5L score (μ_{EQ5D5L}) of each subject is indicated by postoperative score - baseline score. If $\mu_{EQ5D5L} > 0$, then EQ-5D 5L is considered to be improved. Otherwise, EQ-5D 5L is not improved. EQ-5D 5L scores at preoperative, 3 months and 12 months as well as the changes at 3 months and 12 months from baseline will be summarized. The summary statistic, n, mean, median, standard deviation, maximum and minimum, will be generated. The frequency and percentage of the "improved" and "not improved" subjects will be summarized. The null hypothesis H_0 and the alternative hypothesis Hα are as follows:

H_0: $\mu_{EQ5D5L} \leq 0$

Hα: $\mu_{EQ5D5L} > 0$

The null hypothesis will be rejected if one-sided p-value is less than 0.05 (level of alpha), and the alternative hypothesis will be accepted, indicating that the improvement of EQ-5D 5L score from baseline at a specific follow-up visit is significantly greater than zero. If the data is normal, the paired t-test for the changed score from baseline will be performed in the analysis. If data is not normally distributed, the Wilcoxon signed-rank test will be carried out.

7.9.4 Intraoperative Cement Extravasation/Leakage

Cement extravasation/leakage status is recorded during surgery. The status includes no leakage, leakage with clinical symptom, and leakage with no clinical symptom. Frequency of the leakage status will be summarized.

7.9.5 Device and/or Procedure Related Adverse Events

Adverse events (AEs) will be independently assessed by the site investigators and the sponsor, Medtronic, plc. If an adverse event is determined to be related to any of the following device components, then the event is said to be device related:

- Access system
- Cage/Interbody
- Anterior plate
- Bone grafts and substitutes
- Rod system
- Fenestrated screws
- Fenestrated screw cement
- Other components of the Fixation (Stabilization) System

The causality of AEs is classified into the following categories:

- Not related
- Unlikely
- Possible
- Probable
- Causal relationship

For a conservative consideration, an adverse event with a possible, probable or causal relationship is considered as device and/or procedure related. AEs at individual time intervals as well as cumulative up to 3 months and 12 months will be summarized.

7.9.6 Secondary Spinal Surgeries

Secondary spinal surgical procedures resulted from AE(s) can be classified into four categories: revision, removal, reoperation, and other. Secondary spinal surgeries at index and/or adjacent levels at individual time intervals as well as cumulative up to 3 months (and 12 months if available) will be summarized. Although the use of external bone growth stimulators (BGS) is not considered as a secondary spinal surgical procedure, it will be recorded in the database and summarized.

7.9.7 Other Analyses

Medtronic and the site investigator will independently classify each adverse event according to ISO 14155:2011. Serious adverse event is defined according to ISO 14155:2011 3.37 and is an adverse event that met any of the following conditions:

- Led to death,
- 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 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,
- Led to foetal distress, foetal death or a congenital abnormality or birth defect.

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

SAEs and device related SAEs at individual time intervals as well as cumulative up to 3 months (and 12 months if available) will be summarized.

7.9.8 Neurological Status, Stabilization of Pedicle Screw Instrumentation, Fusion Status and Spinopelvic Parameters

For the endpoints including neurological status, stabilization of pedicle screw instrumentation, fusion status for the subjects where fusion is intended, and radiographic assessment of spinopelvic parameters, the data summaries and/or analyses will not be performed due to only two subjects who will complete 12-month follow-up visit by the study cut-off date of 15 July 2020. Instead, the data listings will be provided.

7.10 Safety Evaluation

Device deficiency, Unanticipated Serious Adverse Device Effects (USADEs) and Unanticipated Adverse Device Effects (UADEs), if available, will be summarized. Information about how adverse events and serious adverse events, device and/or procedure related adverse events are analyzed can be found in the sections 7.9.5 and 7.9.7.

7.11 Health Outcomes Analyses

The analyses for the various clinical measurements as well as safety outcomes related to the Evaluation of Objectives are detailed in the sections 7.9. If necessary, any other available health outcomes such as medication usages will be analyzed.

7.12 Changes to Planned Analysis

This Statistical Analysis Plan was completed according to the relevant information presented in the CIP v2.0. The changes have been made to the original planned analyses proposed in the CIP due to the premature termination of the study with the reasons detailed in the section 3. Any change(s) from the SAP will be reported in the final study report along with the justification for the change(s).

8. Validation Requirements

The validation of data summary and analysis will be conducted at level I per the Global Work Instruction 056-WI181, Statistical Programming Code Quality Control and Validation. The outputs generated by two independent statisticians/statistical programmers will be compared and any discrepancy of the results will be resolved before being incorporated into the final report.