Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	The Degen study: Post-market clinical follow-up on the PASS LP, PASS DEGEN and PASS Tulip systems
Clinical Investigation Plan Identifier	# 0313
Clinical Investigation Plan Version	V9.0
Statistical Analysis Plan Version Date	06 NOV 2024
Sponsor/Local Sponsor	Sponsor: Medtronic PLC Cranial and Spinal Technologies 1800 Pyramid Place Memphis, Tennessee 38132 USA Local Sponsor: MEDICREA® International 5389 Route de Strasbourg 69140 Rillieux la pape France

Confidentiality Statement

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	[redacted], Principal Statistician
2.0	• In 7.2, "if applicable" for analyzing number of events, and number of patients at each visit period is deleted. • In 7.3, "different investigational sites" is changed to "4 participating investigational sites". • In 7.7, more detailed information about duration of intervention, instrumented vertebra, and device is added. • In 7.9.1, a language "if present" for off-label subjects is added. • In 7.9.2.2, a statement for inclusion of a footnote for ODI summary table for non-validated ODI if confirmed is added. • In 7.9.2.5, the descriptions on how non-validated SF-12 is summarized are modified. • In 7.9.2.7, "Surgeon's Satisfaction" is changed to "Surgeon's Opinion. • In 7.9.3, the combined PASS LP/PASS DEGEN is added for the subgroup analysis.	[redacted], Principal Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
Al	Aluminum
CE	Conformite Europeenne (French)
CE Mark	Product has been verified and meets EU safety, health and environmental requirements
CIP	Clinical Investigation Plan
CT	Computerized Tomography
CTA	Clinical Trial Agreement
ELI	Extra Low Interstitial
EU MDR	European Medical Device Regulation
MRI	Magnetic Resonance Imaging
ODI	Oswestry Disability Index
PSI	Patient Satisfaction Index
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SF-12	Short Form Health Survey 12
Ti	Titanium
V	Vanadium
VAS	Visual Analog Scale

3. Introduction

The patients with degenerative disease may suffer back pain, leg pain, neurological symptoms, and/or functional disabilities. When the symptoms can't be improved from conservative cares or the disability suffered from the disease is too severe, surgery may be performed with implants (rods, screws, plates, connectors, etc.) to stabilize the instrumented spinal segments and promote osteosynthesis. The patients with degenerative disease in the thoracic, lumbar, and sacral spine regions treated with the PASS LP®/PASS DEGEN/PASS Tulip system manufactured by MEDICREA® International are included in this study. The products used in this study are all CE-marked. The PASS LP® system is composed of pedicle screws, sacral plates with sacral screws, rod-plates, crosslinks, connectors, breakaway nut, and rods made of Titanium Alloy (Ti-6Al-4V ELI). The PASS DEGEN system derived from PASS LP® system and with shorter screws extensions is comprised of ring rods, breakaway nut, short angulated connector, short initial connector, short post screw, crosslinks, and revision post made of Titanium alloy (TiAl6V4 ELI). The PASS TULIP™ system consists of two sub-systems, the sub-system considered in this study is PASS TULIP™ PRIME which features the screws with top loading of the rod. These systems provide stabilization of spine while the fusion of the instrumented segments occurs after surgery.

This is a retrospective-prospective, multicenter, non-comparative, observational, and post-market clinical follow-up study. The purpose of this study is to evaluate the safety and effectiveness of the PASS LP®/PASS DEGEN/PASS Tulip systems for the clinical evaluation report as mandated by the EU regulatory authority.

4. Study Objectives

This post-market clinical follow-up study aims to collect and evaluate the data about the performance and safety of MEDICREA's products, PASS LP®/PASS DEGEN/PASS Tulip systems, for the treatment of thoraco-lumbar degenerative diseases. It will be used to generate the clinical evaluation report and support the EU MDR submission.

4.1 Primary Objective

The primary objective of the study is to assess the fusion rate at the 24-month visit postoperatively.

4.2 Secondary Objectives

The secondary objectives include:

- To assess fusion rate at the 1/6-month and 12-month visit.
- To describe the evolution of the patients' quality of life before and at each follow-up after the surgery (change of ODI score, change of back pain score, change of leg pain score, change of non-validated SF-12 score, patient satisfaction).
- To collect data about the surgeons' satisfaction, with these implants and instruments during the surgery, and regarding the patients' evolution.
- To collect data about the safety of the implants (device- or procedure-related adverse events and all SAEs up to 24 months).

5. Investigation Plan

There are 3 arms of patients for this retrospective-prospective and observational study: PASS LP, PASS DEGEN, and PASS TULIP Prime. No control group is implemented for this study. For the patients whose data are retrospectively collected, an inform note with certificate of information and consent is signed by them. For the patients who involve in prospective study, a consent form for agreement to collecting their data is signed at the time of their enrollment.

The patients met the following criteria are eligible for the enrollment of this study (**Inclusion Criteria**):

- Patients at least 18 years old
- Patients suffering from a spinal degenerative disease
- Patients requiring spinal surgery for less than 4 levels of a spinal degenerative disease
- Patients implanted with MEDICREA's products or patients who are candidates to receive MEDICREA's products, including at least PASS LP and/or PASS DEGEN and/or PASS TULIP Prime implants
- Patients affiliated with a national insurance system

The patients with the following conditions are not eligible for the enrollment of this study (**Exclusion Criteria**):

- Patients unable or unwilling to sign and understand an information note with proof of patient consent

- Patients unable to complete a self-administered questionnaire
- Patients presenting contra-indications to an Xray follow-up
- Patients of more than 18 years old under a protection procedure
- Patients judged as non-compliant by the investigator or not able to come back for follow-up visits for up to 2 years

Patients will be followed up between 1 and 6 months, 12 months, and 24 months. The data will be collected at preoperative, surgery, immediate postoperative (if available), 1-6 months, 12 months, and 24 months.

At preoperative visit, patients' demographics, etiology, history of spinal surgery, medical history, comorbidity, professional and physical activity, spinal symptoms (sensory deficits, motor deficits, sciatica and cruralgia), VAS back pain, VAS leg pain, ODI, and non-validated SF-12 are collected.

At surgery, duration of intervention, blood loss, implant types, materials and levels, surgeon's satisfaction on the implants, adverse events, and device deficiency (if available) are recorded.

During postoperative visits, fusion and implant status based on radiographic assessment, analgesic use, professional and physical activity, spinal symptoms (sensory deficits, motor deficits, sciatica and cruralgia), VAS back pain, VAS leg pain, ODI, non-validated SF-12, surgeon's opinion, patient's satisfaction, adverse events, and device deficiency (if available) are collected.

Radiographic assessment based on X-ray and/or CT-scan/MRI is performed by the site surgeon. In case multiple imaging has been performed for fusion assessment, a CT scan is considered as the preferred imaging, followed by X-ray and then MRI. Implant status such as broken, dislocated, loosened, and misplaced is determined by the site surgeon.

6. Determination of Sample Size

The sample size is not determined but rather is determined by the sponsor to enroll 25 subjects in each device group (PASS DEGEN, PASS LP & PASS Tulip). to support EU MDR requirement.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

The approval of Ethics Committee (EC) for each site must be obtained before patient enrollment. Patients who meet the inclusion and exclusion criteria are enrolled, and will be followed up to 24 months after surgery and exit the study (completed). However, patients may exit the study at any time in the following situations:

- Adverse event
- Death
- Lost to follow-up
- Physician decision
- Protocol deviation

- Screen failure
- Sponsor request
- Technical problems
- Unsuccessful procedure
- Withdrawal by subject
- Other

7.1.2 Clinical Investigation Plan (CIP) Deviations

A study deviation is defined as an event within a study that did not occur according to the CIP or the CTA. The study deviations will be classified into minor and major deviations. The patients whose inform consent has not been obtained during the study process will not be included in analysis. The major protocol deviation may arise from the following situations (per CRF):

- Eligibility criteria not met
- Enrolled subject did not meet enrollment criteria
- Information note with proof of patient consent not done
- Study treatment deviation

7.1.3 Analysis Sets

7.1.3.1 Primary Analysis Set

Primary analysis will be conducted for the patients who are enrolled and implanted with the treatment of PASS LP®/PASS DEGEN/PASS Tulip systems. The missing data will not be imputed, and the analysis will be based on the observed data.

7.1.3.2 Per-Protocol Analysis Set

The per-protocol dataset is a subset of patients who are included in the primary dataset. The patients who have major protocol deviations, if available, will be excluded from the per-protocol analysis. Major protocol deviations include eligibility criteria not met, enrollment criteria not met, and study treatment deviation. The per-protocol analysis will only be carried out for the primary endpoint.

7.2 General Methodology

For continuous variables including demographics, treatment characteristics or clinical outcome scores such as age, BMI, blood loss, ODI, back pain, leg pain, and non-validated SF-12 (if available), the summary statistics (n, mean, median, standard deviation, minimum and maximum) will be presented. The changes from preoperative for clinical outcome scores 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 variables, frequency and percentage of each category will be summarized. The two-sided 95% exact binomial confidence interval for the endpoints related to the primary endpoint (fusion rate) will be calculated.

A time-to-event analysis for fusion will be performed, if applicable, and the median time to fusion will be presented.

For adverse events including serious ones, they will be summarized with number of events, and number of patients at each visit period as well as number of events and percentage of patients for a cumulative period of visits. Since AEs may occur at any time during the course of this study, a series of analysis time windows are defined in accordance with the corresponding study visit windows as follows for the purpose of data analysis:

Study Visit	**Analysis Time Window**
Surgery	Day 0
1-6 Months	Day 1 to 213
12 Months	Day 214 to 547
24 months	Day 548 to 914
After 24 months (if available)	> Day 914

The determination of an analysis time window depends on the availability of AE or SAE onset date and surgery date. If either of the AE or SAE onset date and surgery date is not present in the data, the analysis time window can't be determined.

7.3 Center Pooling

Data collected from the 4 participating investigational sites will be pooled for analysis.

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

Missing data due to missed follow-ups, lost to follow-ups, withdrawals, or failure to answer CRF questions during office visits will not be imputed for analyses. The analyses will be based on observed data including those collected before missed follow-ups, lost to follow-ups or withdrawals.

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 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 gender, etiology, history of spinal surgery and patient history, comorbidities, spinal symptoms, frequency and percentage in each category will be summarized. For ordinal variables, median and minimum and maximum will be presented if needed.

7.7 Treatment Characteristics

Information related to surgery such as duration of intervention (from incision to closure, blood loss, instrumented vertebra (proximal and distal and level number) and device materials (rods, screws, bands and hooks) linked to levels of implantation/region(s) if available, will be summarized.

7.8 Interim Analyses

No interim analysis will be carried out for this study.

7.9 Evaluation of Objectives

7.9.1 Primary Objective and Endpoint Analysis

The primary objective of this study is to assess the fusion status at the 24-month visit postoperatively.

When fusion is assessed through CT scan, the criterion for fusion is bonny bridging: both extragraft bone bridging and intragraft bone bridging need to be achieved for a treated level to be considered as fused. When fusion is assessed using X-ray, the criteria include bonny bridging, motion on flexion/extension < 4˚, and integrity of instrumentation (implanted devices). A patient is considered to be fused if all the instrumented segments are fused. The fusion status is presented per patient.

Two methods are proposed to analyze fusion. The first method is to analyze the observed data, and no imputation for fusion status is involved. In this method, the fusion status will be summarized based on the data present in the database. In addition, the last fusion status will also be summarized. For example, the fusion status (fused / not fused) at 1-6-month visit will serve as the last fusion status if the fusion status at 12-month and 24-month visits is missing. Similarly, the fusion status (fused / not fused) at 12-month visit will serve as the last fusion status if the fusion status at 24-month visit is missing.

The second method is based on the imputation from prior fusion status. If the fusion status at 12-month and 24-month visits is missing but it is fused at 1-6-month visit, then the status at 12-month or 24-month visit will be considered as fused. If the fusion status 24-month visit is missing but it is fused at 12-month visit, then the status at 24-month visit will be considered as fused. If the fusion status prior to 24-month visit is missing, then the status at 24-month visit will be used.

The primary endpoint is to assess the fusion rate at 24-month visit with two-sided 95% exact binomial confidence interval. A time-to-event analysis for fusion will be carried out, if applicable, and the median time to fusion will be present.

Separate analyses on the fusion rates at 24 months for the patients implanted with PASS LP, PASS DEGEN, and PASS Tulip system as well as a combined analysis for the patients implanted with PASS LP and PASS DEGEN will be performed. For the combined PASS LP and PASS DEGEN, the off-label subjects (i.e., not degenerative indication), if present, will be separated out for summary.

For the combined PASS LP and PASS DEGEN, an analysis for the fusion rates at 24 months will be carried out by the degenerative indication (degenerative disc disease, degenerative spondylolisthesis, degenerative stenosis, and herniated disc) and deformity indication (deformity), if applicable.

7.9.2 Secondary Endpoints and Analyses

7.9.2.1 Fusion Status at 1-6-Month and 12-Month Visits

Frequency count and percentage of fusion at 1-6 months and 12 months will be calculated and presented. The handling method for missing fusion status is the same as that stated in the section 7.9.1.

7.9.2.2 ODI

ODI score at each visit and its change from preoperative at each postoperative visit will be summarized with the descriptive statistics, n, mean, median, standard deviation, minimum and maximum. The paired t-test for normally distributed ODI score or Wilcoxon signed-rank test for not normally distributed ODI score will be carried out for the change from preop.

In addition, percentage change at each postop visit from preop will be summarized: Percent change = 100x(postop score – preop score) / preop score (%).

Note that ODI is characterized as “non-validated ODI” in the CIP v9.0. If confirmed, a footnote to indicate non-validated ODI in ODI summary table will be included.

7.9.2.3 VAS Back Pain

VAS back pain score at each visit and its change from preoperative at each postoperative visit will be summarized with the descriptive statistics, n, mean, median, standard deviation, minimum and maximum. The paired t-test for normally distributed back pain score or Wilcoxon signed-rank test for not normally distributed back pain score will be carried out for the change from preop.

In addition, percentage change at each postop visit from preop will be summarized: Percent change = 100x(postop score – preop score) / preop score (%).

7.9.2.4 VAS Leg Pain

VAS leg pain score at each visit and its change from preoperative at each postoperative visit will be summarized with the descriptive statistics, n, mean, median, standard deviation, minimum and maximum. The paired t-test for normally distributed leg pain score or Wilcoxon signed-rank test for not normally distributed leg pain score will be carried out for the change from preop.

In addition, percentage change at each postop visit from preop will be summarized: Percent change = 100x(postop score – preop score) / preop score (%).

7.9.2.5 Non-Validated SF-12

The categories of each non-validated SF-12 questionnaire will be summarized with frequency count and percentage. Non-validated SF-12 PCS and MCS scores for each subject are set to be generated using the PRO CoRE software license purchased from QualityMedtric. If it works as expected, further data summary and statistical analysis will be conducted similarly to the other continuous variables as mentioned above.

7.9.2.6 Patient Satisfaction Index (PSI)

Patient satisfaction questionnaire is filled out by patients at postoperative visits as follows:

- Surgery met my expectations
- I did not improve as much as I had hoped but I would undergo the same operation for the same results

- Surgery helped but I would not undergo the same operation for the same outcome
- I am the same or worse as compared to before the surgery

PSI at each postoperative visit will be summarized with the descriptive statistics, frequency count and percentage. If necessary, PSI can be coded and treated as an ordinal variable and summarized with the statistics including median, minimum and maximum.

7.9.2.7 Surgeon's Opinion

The following surgeon's opinion will be collected after surgery:

- Entirely satisfactory: the expected outcomes were achieved with the surgery
- Satisfactory: the patient's condition improved, but not as much as we had hoped
- Partly satisfactory: the outcomes were not what we had expected or the patient's condition did not change
- Not satisfactory: the patient's condition worsened

Surgeon's satisfaction on surgical results at each postoperative visit will be summarized with the descriptive statistics, frequency count and percentage.

7.9.3 Subgroup Analysis

The subgroup analyses will be carried out by age (>median age and <=median age), BMI (>median BMI and <=median BMI), sex (female/male), and the presence of a herniated disc (Yes/No), if applicable, for the primary endpoint for PASS LP, PASS DEGEN, and PASS Tulip system as well as the combined PASS LP/PASS DEGEN subjects. Due to the data privacy protection regulations, data summary and analysis for a subgroup containing less than two subjects will not be carried out.

7.10 Safety Evaluation

All adverse events, study procedure related adverse events, study device related adverse events, instruments related adverse events, and serious adverse events will be collected and analyzed. The number of events and patients in each visit period (if applicable) as well as percentage of the patients with the events up to 12 months and 24 months postoperatively will be summarized.

In addition, device deficiency and serious adverse device effect (SADE) will be summarized, if applicable.

8. Validation Requirements

The validation of data summary and analysis will be conducted 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.