Medtronic

Statistical Analysis Plan	
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	New document	[redacted]
2.0	Update SAP according to the CIP amendment - increasing subject follow-up requirements through period to 60 months (5 years). The analyses of corresponding outcomes are all extended to 5 years.	[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
CEC	Clinical Event Committee
CIP	Clinical Investigation Plan
CRF	Case Report Form
DMC	Data Monitoring Committee
DTAA	Descending Thoracic Aortic Aneurysm
DMC	Data Monitoring Committee
IDE	Investigational Device Exemption
IPR	Independent Physician Reviewer
FDA	The US Food and Drug Administration
MAE	Major Adverse Event

MDE	Major Device Effect
MedDRA	Medical Dictionary for Regulatory Activities
OUS	Outside the United States
PG	Performance Goal
PMA	Premarket Approval
PMA-s	Premarket Approval - Supplement
PT	Preferred Term
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SOC	System Organ Class
US	The United States

3. Introduction

This document outlines the detailed statistical methods to be implemented for the data collected within the scope of Valiant Evo US Clinical Trial and in conjunction with data collected during the concurrently enrolling Valiant Evo International Clinical Trial. This document is designed for internal use as a guideline for study Biostatistician and Statistical Programmer(s). Study protocol of the Valiant Evo US Clinical Trial is the primary resource if clarification is needed for the contents of this document. Analysis results obtained from the analyses outlined in this document will be the basis of the Clinical Study Report for this study.

As with any statistical analysis plan, the proposed methods and approaches to the data analysis should be viewed as flexible. Changes to the plan may arise if the emerging picture suggests that deviations from the original plan would provide a more reliable and valid analysis of the data. The purpose of this plan is to provide general, and in some instances, specific guidelines from which the analysis will proceed. Nonetheless, sound statistical reasoning must substantiate deviations from these guidelines.

4. Study Objectives

The purpose of the Valiant Evo US Clinical Trial is to demonstrate the safety and effectiveness of the Valiant

Evo Thoracic Stent Graft System in subjects with a descending thoracic aortic aneurysm (DTAA) who are candidates for endovascular repair.

The clinical evidence collected as part of this trial will be used in conjunction with data collected during the concurrently enrolling Valiant Evo International Clinical Trial to support PMA Approval of the Valiant Evo Thoracic Stent Graft System.

5. Investigation Plan

The Valiant Evo US Clinical Trial is a prospective, multi-center, pre-market, non-randomized, single-arm trial.

Subject population will include subjects diagnosed with DTAA who are considered candidates for endovascular repair, and who meet the Inclusion/Exclusion Criteria for the Valiant Evo US Clinical Trial. Inclusion and exclusion criteria are defined in the Clinical Investigation Plan Section D.

At enrollment, those subjects who sign and date the informed consent document, meet all of the study eligibility criteria, and are approved by the IPR will be eligible for inclusion into the Valiant Evo US Clinical Trial. The subject will only be considered enrolled when arterial access is established and an attempt to introduce the Valiant Evo Thoracic Stent Graft is made. A single, primary stent graft may be used by itself if its size is sufficient to provide the desired coverage. Alternatively, it may be used in combination with additional stent graft sections that increases the graft length distally or proximally to the primary section.

The Valiant Evo Global Clinical program will be conducted under both the Valiant Evo US Clinical Trial protocol and Valiant Evo International Clinical Trial protocol, and will enroll up to 37 sites worldwide. Inclusion will be halted at sites that reach the 20% inclusion cap. There will be no minimum number of subjects for a single investigational site. Globally, a total of 100 subjects will be concurrently enrolled in the United States and outside the United States to support the primary endpoints. Up to 50% of subject data used to support PMA approval may come from subjects enrolled at sites outside of the US under the Valiant Evo International Clinical Trial protocol.

The primary endpoint analysis will be completed upon 87 evaluable subjects reaching the 30 day endpoint. The data obtained from these 87 evaluable subjects will be used to support PMA-s Approval of the Valiant Evo Thoracic Stent Graft System and to support any other future Medtronic submissions to regulatory bodies.

Subjects enrolled under the Valiant Evo US Clinical Trial require follow-up evaluations at the following time points:

- 1 month following the index procedure (30 ± 15 days)
- 6 months following the index procedure (183 ± 30 days)
- 12 months following the index procedure (365 ±60 days)
- 24 months following the index procedure (730 ±60 days)
- 36 months following the index procedure (1095 ±60 days)

- 48 months following the index procedure (1460 ±60 days)
- 60 months following the index procedure (1825 ±60 days)

Note that the 6-month follow up is not mandatory for subjects enrolled under the Valiant Evo International Clinical Trial protocol. Available 6-month follow-up data from the international trial will be used for analysis.

Subjects will be followed until the last subject enrolled has completed the 1 year follow-up visit or until PMA approval is obtained in the US (whatever is later), however, Medtronic will work with FDA to determine if longer term follow after PMA approval is required. A post-approval analysis of 1-year Major Device Event (MDE) rate is planned.

6. Determination of Sample Size

One hundred (100) enrolled subjects will ensure 87 evaluable subjects at 30 days. The primary endpoint analysis will be completed upon 87 evaluable subjects reaching the 30 day endpoint. Based on Valor II study results, Valiant Evo is expected to perform similarly and have 6% of MDE combined with access and/or deployment failures at 30 days. The sample size of 87 evaluable subjects will provide 85% statistical power for the study hypothesis. The type I error is controlled at the one-sided 0.025 level.

Table 1: Power Analysis

True rate of MDEs combined with access and/or deployment failures at 30 day with Valiant Evo	6%
Performance Goal	16%
Significance level	0.025
Statistical test	One-sided binomial test
Evaluable sample size	n=87
Enrollment	Minimum of 100 subjects enrolled to ensure 87 evaluable subjects
Statistical power from the 87 evaluable subjects	85%

One hundred (100) enrolled subjects will also ensure 63 evaluable subjects at 1-year on MDE rate for the post-approval analysis. The VALOR II study with the Valiant stent graft system enrolled 160 patients with DTAA and was assessed through 12 months for purposes of PMA (P100040) approval. Through 1-year post-

treatment, the rate of MDEs combined with access and/or deployment failures was 7.1% (11/153) (Medtronic internal data using the Valiant Evo proposed definition). Therefore, for the purpose of post approval analysis, the rate of MDEs combined with access and deployment failures at 1-year with Valiant Evo is estimated to be 7.1% (refer to Table 22 below for power analysis assumptions).

Table 2: Power Analysis for Post-approval Analysis of 1-year Endpoint

Estimated rate of MDEs combined with access and/or deployment failures at 1 year with Valiant Evo	7.1%
Performance Goal (PG) at 1-year	20%
Significance level	0.05
Statistical test	One-sided binomial test
Evaluable sample size	N = 63 at 1 year
Enrollment	IDE cohort will enroll a minimum of 100 subjects and is expected to have a minimum of 63 evaluable subjects at 1-year follow up.
Statistical power from 63 or more evaluable subjects	92% (overall study power for passing both hypotheses is 81%)

7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

Summaries of subject accountability will be created for subjects enrolled in the US Clinical Trial and the International Clinical Trial as well as two cohorts combined. Subjects discontinued or dropped off from the study will be listed by last day in study and reason for discontinuation.

7.1.2. Clinical Investigation Plan (CIP) Deviations

Clinical Investigation Plan (CIP) deviations will be reported and summarized. Major deviations will include violation of informed consent and/or inclusion/exclusion criteria.

7.1.3. Analysis Sets

Analysis set to be used for each endpoint analysis will consist of all subjects who were enrolled. The subject will only be considered enrolled when arterial access is established and an attempt to introduce the Valiant Evo Thoracic Stent Graft is made.

7.2. General Methodology

In general, qualitative parameters will be described by their distribution frequencies; quantitative parameters will be described by their mean, standard deviation, minimum, maximum, median, and number of subjects with assessable data.

For events such as adverse events (AE), deaths and secondary procedures, that can occur or are observed at any time during the study, no time window will be applied. For such events, an event that occurs "within 1 month or 30 days" is an event that takes place between Days 0 to 30, inclusive. Similarly, an event that occurs "within 12 months or 365 days" is an event occurring between Day 0 to Day 365, inclusive. Date of event onset will be used to determine when the event occurred. Day 0 is referring to the day of index procedure.

For image-based assessments, such as stent-graft endoleak, patency, and other observations, the following time windows will be applied for by-visit data summaries:

Table 3: Time Windows for Statistical Analyses

Study Visit	Target Day	Time Window
Implant	Day 0	Day 0
1 Month	Day 30	1 – 90 days
6 Months	Day 183	91 – 304 days
12 Months	Day 365	305 – 548 days
24 Months	Day 730	549 – 913 days
36 Months	Day 1095	914 – 1278 days
48 Months	Day 1460	1279 – 1643 Days
60 Months	Day 1825	1644 – 2009 days

Unless otherwise specified, if different type of images are used and have different finding in the same time window, the imaging technique and sensitivity matrix (CIP Appendix L.3, also see Table 4 below) will be applied. Finding from higher visibility image will be used for analysis. If there are two or more assessments in the same time window, then the assessment closest to the target day will be used in the analysis of event rate at a given time point.

Table 4: Imaging Matrix

Anatomy/Stent Graft Issue Detected	CT with contrast	CT without contrast	MRI with contrast	MRI without contrast	Angiogram/, Aortogram, and Arteriogram
Diameter and Length	1	2	1	2	3
Stent graft migration	1	2	1	2	2-3
Stent graft fracture	2	3	2	3	2-3
Stent graft kinking	2	3	2	3	2-3
Collapse of stent graft	2	3	2	3	2-3
Stent graft twisting	2	3	2	3	2-3
Stent graft patency	1	4	1	4	2-3
Endoleaks	1	4	1	4	2-3
False lumen perfusion	1	4	1	4	2-3
Occlusion	1	4	1	4	2-3
Stenosis	1	4	1	4	2-3
Stent Graft Fabric Defect	1	4	1	4	2-3
1= Highly visible	2 = visible	3 = Not very visible (potential artifacts)		4 = Invisible	

Statistical analyses for this study will be performed using the Statistical Analysis System (SAS) for Windows (Version 9.1 or higher) or other widely-accepted statistical or graphical software.

7.3. Data Pooling

The data poolability of subjects enrolled in the Valiant Evo US Clinical Trial and subjects enrolled in the Valiant Evo International Clinical Trial is assumed given that both study protocols will be similar with respect to, inclusion/exclusion criteria, clinical treatment, definitions of clinical events, one data monitoring plan, Data

Monitoring Committee (DMC), Clinical Event Committee (CEC), Independent Physician Reviewer (IPR) and core imaging laboratory.

At the data analysis stage, the data poolability will be reviewed for the primary endpoint. Results from Valiant Evo US Clinical Trial and Valiant Evo International Clinical Trial subjects will be presented separately for clinical review as well as tested using a Chi-square test.

A poolability analysis among geographies/investigational sites will be assessed descriptively for the primary endpoints by geographic regions. Small investigational sites (less than 5 subjects) will be grouped with other nearby sites for the by-region analysis.

7.4. Handling of Missing Data and Dropouts

During statistical analysis, imputation of missing data will not be performed except for data related to the onset date of an adverse event or a death. In cases where the onset date of an event or a death is incomplete and unresolvable via data query, the 15th day of the known month or July 1st of the known year will be used.

Sensitivity analysis using tipping point method may be performed, as needed, to assess the impact of missing data for the primary endpoint.

7.5. Adjustments for Multiple Comparisons

One hypothesis test on the primary study endpoint will be performed at the time of PMA submission. Therefore, there is no multiple comparisons/multiplicity issue.

When the post-approval analysis is carried out, no multiplicity adjustment is needed due to the fact that the post-approval analysis is conditioning on the PMA approval.

7.6. Demographic and Other Baseline Characteristics

Descriptive statistics will be provided for demographic (age, gender, and race) and other baseline characteristic variables such as medical history and baseline thoracic aorta measurements. Note that race will be summarized for subjects enrolled in the US only, since collection of race and ethnicity data may not be allowed outside the US as per local law and regulation.

7.7. Treatment Characteristics

The following acute procedural observations and clinical utility measures will be analyzed using descriptive statistics:

- Mean duration (min) of procedure
- Proportion of subjects who underwent general anesthesia
- Proportion of subjects who underwent percutaneous access
- Proportion of subjects requiring blood transfusions

- Mean number of units of blood transfused, if required
- Mean volume (cc) of estimated blood loss
- Mean length of time (hours) in intensive care unit
- Mean length of time (days) of hospital stay (from the index procedure to hospital discharge)

Study device disposition will be summarized by type and size. Number of study devices used on each subject will be analyzed descriptively.

7.8. Interim Analyses

No interim analysis intended for sample size recalculation is planned prior to the PMA submission.

Data reports will be generated for Data Monitoring Committee (DMC) review during the trial. A design dossier including clinical evaluation of the Valiant Evo Stent Graft System will be created for the CE mark submission. However, there is no plan to modify the Valiant Evo US Clinical Trial based on these reports.

7.9. Evaluation of Objectives

Primary Endpoint

The primary objective will be assessed by the composite safety and effectiveness endpoint that is based on the proportion of subjects who experienced:

(a) Access and/or deployment failures; and/or

(b) Major device effects (MDE) within 30 days post index procedure

MDEs include the occurrence of any of the following:

- Device-related secondary procedures
- Device-related mortality
- Conversion to open surgery
- Thoracic aortic aneurysm rupture

Detailed definitions of MDEs are defined in Clinical Investigational Plan Appendix L.5.

The primary study endpoint will be tested against a performance goal of 16% at 30 days:

H_0: $p \geq 16\%$ vs. H_a: $p < 16\%$,

where p denotes the true event rate of primary study endpoint in the target population. If the null hypothesis

(H_0) is rejected at the one-sided 0.025 statistical significance level, it is considered that the performance goal for the primary endpoint has been reached.

The analysis set of all enrolled subjects will be used for the analysis. The primary study endpoint is a dichotomous study outcome; hence, an exact method based on the binomial distribution will be used for the hypothesis testing.

Primary Endpoint Calculation:

A subject will be a failure on the primary endpoint if the subject either failed on access/deployment or had an MDE within 30 days. A subject will be a success on the primary endpoint if the subject is confirmed for access and deployment success as well as free from MDE. The failure rate of the primary endpoint is the percent of failures in all the evaluable subjects for the endpoint, i.e., in total number of failures and successes. Note that a subject who had an MDE within 30 days is one of the subjects in m as defined below. A subject who is free from MDE is one of the subjects in k as defined below.

MDE Rate Calculation:

All MDEs will be adjudicated by the Clinical Event Committee (CEC) per study protocol. MDE rate will be calculated as follows (Table 5):

Table 5: MDE Rate Calculation:

MDE rate = m/(m + k)	Within 30 Days	Within 183 Days	Within 365 Days
m = No. of Subjects Who Had MDE(s)	No. of subjects who had at least one MDE with onset day from Day 0 to Day 30, inclusive.	No. of subjects who had at least one MDE with onset day from Day 0 to Day 183, inclusive.	No. of subjects who had at least one MDE with onset day from Day 0 to Day 365, inclusive.
k = No. of Subjects Who Had No MDE	No. of subjects who have been in study for at least 1 day and without an MDE.	No. of subjects who have been in study for at least 91 days and without an MDE.	No. of subjects who have been in study for at least 305 days and without an MDE.

If a subject is early terminated from the study, the last day that the subject has been seen will be the duration in study, which can be the day of last follow-up, last imaging taken, an AE reported, or withdrawal from the study. If a subject is still in the study, the duration in study will be the time from index procedure to the cut off day that the database is locked or data snapshot is taken.

Subgroup analyses by-sex, by-race (based on subjects enrolled in the US only, since collection of race and ethnicity data may not be allowed outside the US as per local law and regulation), FreeFlo versus Closed Web configuration as proximal component, percutaneous access versus non-percutaneous, and by-region/study site will be performed on the primary study endpoint using descriptive statistics and reviewed for

clinical significant difference.

Secondary Endpoints

30-day Secondary Endpoint

The following secondary endpoints will be evaluated within 30 days post treatment:

- Peri-operative mortality
- All adverse events (AE) within 30 days including:
    - Major Adverse Event(s) (MAE)
    - Serious Adverse Event(s) (SAE)
- Secondary procedures
- Loss of stent graft patency at 30 day visit based on imaging findings
- Endoleaks at 30 day visit based on imaging findings

Detailed definitions of MAEs are defined in the Clinical Investigational Plan Appendix L.2.2. MAEs will be identified using codes in the Medical Dictionary for Regulatory Activities (MedDRA) provided by the Medtronic Clinical Safety group.

6-month Secondary Endpoints:

The following secondary endpoints will be evaluated:

- All-cause mortality within 183 days
- Aneurysm-Related Mortality within 183 days
- MDEs within 183 days
- All AEs within 183 days including:
    - MAEs
    - SAEs
- Secondary procedures within 183 days
- Loss of stent graft patency within 6 months based on imaging findings
- Endoleaks at 6 months based on imaging findings

- Stent graft migration at 6 months as compared to 1-month imaging
- Aneurysm expansion > 5mm at 6 months based on imaging findings relative to the 1-month visit

12-month Secondary Endpoints

The following secondary endpoints will be evaluated:

- All-cause mortality within 365 days
- Aneurysm-Related Mortality within 365 days
- MDEs within 365 days
- All AEs within 365 days including:
    - MAEs
    - SAEs
- Secondary procedures within 365 days
- Loss of stent graft patency within 12 months based on imaging findings
- Endoleaks at 12 months based on imaging findings
- Stent graft migration at 12 months as compared to 1-month imaging
- Aneurysm expansion > 5mm at 12 months based on imaging findings relative to the 1-month visit

Secondary endpoints are to be assessed beyond 12 months. The following secondary endpoints are to be evaluated at 24, 36, 48, and 60 months:

- All-cause mortality
- Aneurysm-Related Mortality
- MDEs
- All AEs and SAEs
- Secondary procedures
- Loss of stent graft patency based on site reported imaging findings
- Endoleaks based on site reported imaging findings

- Stent graft migration as compared to 1-month imaging
- Aneurysm expansion > 5mm based on site reported imaging findings relative to the 1-month visit

Health-related quality of life outcomes are to be assessed at all scheduled follow-up visits using the EQ-5D questionnaire.

Stent graft migration will be determined by the core lab or site imaging case report from (CRF). Core lab assessment and site reported result will be analyzed separately. Aneurysm expansion will be calculated. When 1-month image is not available, the latest image taken prior to 1-month will be used for calculation.

Descriptive statistical analyses will be performed on secondary endpoints. No inferential statistical analysis is planned for secondary endpoints.

Non-image endoints event rates such as mortality, secondary procedures, MAEs, SAEs, conversion to open surgery, and thoracic aortic aneurysm ruptures through 1 year will be calculated in the same way as the MDE rate, specified in Table 5. The event rates beyond 1 year through 5 years will be analyzed using Kaplan Meier method.

Imaging based Event Rate Calculation:

Unless otherwise specified, imaging assessment will be performed by site as well as the core lab. Assessments from the core lab will be the primary result for the PMA and PMA-s submissions and analyzed separately from those by site. Imaging based event rate will be calculated using statistical analysis windows as follows (Table 6):

Table 6: Imaging based Event Rate Calculation:

Event rate = m/n	At 1 Month	At 6 Months	At 12 Months
m = No. of Subjects Who Had Event(s)	No. of subjects who had an event with scan day within the 1-month window.	No. of subjects who had an event with scan day within the 6-month window.	No. of subjects who had an event with scan day within the 12-month window.
n = No. of Subjects Who Had Readable Images	No. of subjects who had a readable image within the 1-month window.	No. of subjects who had a readable image within the 6-month window.	No. of subjects who had a readable image within the 12-month window.
Event rate = m/n	Through1 Month	Through 6 Months	Through 12 Months
m = No. of Subjects Who Had Event(s)	No. of subjects who had an event with scan day within the 1-month window.	No. of subjects who had an event with scan day within 1- or 6-month windows.	No. of subjects who had an event with scan day within 1-, 6- or 12-month windows.
n = No. of Subjects Who Had Readable Images	No. of subjects who had a readable image within the 1-month window.	No. of subjects who had an event (counted in m) or had a readable image within the 6-month window.	No. of subjects who had an event (counted in m) or had a readable image within the 12-month window.

The imaging based event rates by visit at 24, 36, 48 and 60 months will be calculated in a similar way as above; i.e., m = number of subjects who had an event with scan day within the statistical analysis window of the specific time point; n = number of subjects who had a readable image within the 12-month window.

The cumulative event rate through 24, 36, 48 and 60 months will be estimated using survival analysis. Kaplan-Meier estimates, along with its standard error using the Greenwood method, will be reported for non-image based events. The image-based events are interval censored data and the interval censored survival analysis method will be used to calculate the event rates.

When reporting the site reported endoleaks, both site imaging findings and the events treated during secondary procedures will be accounted for in the analysis.

7.10. Safety Evaluation

All adverse events (AE) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and categorized by System Organ Class (SOC) and Preferred Term (PT) for summary. Device-related AEs, procedure-related AEs, and serious AEs will be tabulated separately and by time period. The denominator in event rate calculation will be based on the number subjects available at the beginning of each time period. The relationship to device and procedure as well as seriousness will be based on site-reported data from the AE case report form (CRF).

The survival from all-cause mortality and aneurysm-related mortality over one year time or longer will be described by the Kaplan-Meier survival curve and the associated Kaplan-Meier estimate will be calculated along with its standard error using the Greenwood method.

7.11. Health Outcomes Analyses

Health-related quality of life outcomes will be assessed at all scheduled follow-up visits using the EQ-5D questionnaire. For each dimension of EQ-5D score, a frequency table will be presented. For visual analogue scale score, EQ-5D Index and change from baseline in EQ-5D Index, number of subjects with known value, mean, standard deviation, median, minimum and maximum will be reported. The scoring algorithm by Shaw JW *et al* (2004*)* will be used to compute the US preference-weighted index score.

8. Validation Requirements

Level I validation is required for each computer programmed table and listing used in the PMA and PMA-s submissions.

9. References

Shaw JW, Johnson JA, Coons SJ (2004). U.S. Valuation of the EQ-5D Health States: Development and Testing of the D1 Valuation Model. Medical Care. Submitted 2004.