Cover Page – Statistical Analysis Plan

STATISTICAL ANALYSIS PLAN	
Clinical Investigation Plan Title	Pipeline Flex with SHield Technology Embolization - An International MulticEnter ObservationaL Post Market StuDy of treated Intra Cranial Aneurysms (SHIELD)
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Medtronic **Statistical Analysis Plan**	
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Table of Contents

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Initial Release	[redacted] Principal Biostatistician
2.0	• Revision to update statistical analysis approach, defining of endpoints and other analysis, and provide guidance on methodology of data utilization.	[redacted] Biostatistician [redacted] Biostatistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Abbreviated Term	Definition
AE	Adverse Event	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.
CEC	Clinical Events Committee	Independent committee responsible for the review and adjudication of events that are identified to be adjudicated that occur over the course of the Study.
CSR	Clinical Study Report	Clinical Study Report
DAPT	dual antiplatelet therapy	dual antiplatelet therapy
DRF	Data Release Form	Data Release Form
eCRF	Electronic Case Report Form	An electronic document designed to record all of the protocol requested information to be reported to the sponsor on each study patient. eCRFs are "living documents" in the respect that new information on the patient is continually gathered throughout the study.

Abbreviation	Abbreviated Term	Definition
FAS	Full Analysis Set	The Full Analysis Set (FAS) population is a subset of ITT including only those subjects in whom the Pipeline™ device was implanted.
FDA	Food and Drug Administration	Food and Drug Administration
IA	Intracranial aneurysm	Intracranial aneurysm
ICF	Informed Consent Form	The written, signed and dated document that provides objective evidence of the process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate (21 CFR 50).
ICH	International Conference for Harmonization	An Organization whose main purpose is to achieve greater harmonization to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner.
IDE	Investigational Device Exemption	An approved IDE permits a device that would otherwise be required to comply with a performance standard or would require a premarket approval to be shipped lawfully for the purpose of conducting investigations of that device (21 CFR 812).
I/E	Inclusion/Exclusion Criteria	A list of conditions that would include or exclude a patient from enrolling/participating in a clinical study as outlined in the study protocol.
Implant Failure	Implant Failure	Enrolled subjects who underwent the study procedure and in whom an attempt to implant the device was made but was unsuccessful

Abbreviation	Abbreviated Term	Definition
IRB	Institutional Review Board	Any board, committee, or other group formally designated by an institution to review biomedical research involving subjects and established, operated and functioning in conformance with 21 CFR 56.
ITT	Intent-to-Treat	The Intention to Treat (ITT) population includes all enrolled subjects in whom deployment of the Pipeline™ device with Shield Technology™ was attempted. It is possible that the Pipeline™ device with Shield Technology™ may not reach the target site and the operator would not attempt to deploy it, in the rare event that happens, that patient will not be considered part of the ITT population.
MedDRA	Medical Dictionary for Regulatory Activities	Standardized medical terminology developed by ICH to facilitate sharing of regulatory information internationally for medical products used by humans. It is used for registration, documentation and safety monitoring of medical products both before and after a product has been authorized for sale. Products covered by the scope of MedDRA include pharmaceuticals, vaccines and drug-device combination products.

Abbreviation	Abbreviated Term	Definition
mRS	Modified Rankin Score	Scale for measuring general neurological function. 0 No symptoms at all 1 No significant disability despite symptoms; able to carry out all usual duties and activities 2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance 3 Moderate disability; requiring some help, but able to walk without assistance 4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance 5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention 6 Dead
NIHSS	National Institute of Health Stroke Scale	Method for quantifying neurologic deficits developed by the National Institutes of Health. It is used to assess the severity of a stroke.
PED	Pipeline Endovascular Device	Pipeline Endovascular Device

Abbreviation	Abbreviated Term	Definition
Primary Efficacy Endpoint	Complete aneurysm occlusion (defined as Raymond-Roy grade 1[55]) without significant parent artery stenosis (≤ 50%) or retreatment of the target aneurysm 1-year post-procedure	The primary effectiveness endpoint assessed by: • Occlusion status: by a 3-member adjudicated read by the imaging Core Laboratory according to the Scale of Roy • Parent Artery stenosis: by the 3-member adjudicated read by the imaging Core Laboratory. • Retreatment: by the investigator reported events of retreatment.

Abbreviation	Abbreviated Term	Definition
Primary Safety Endpoint	Major Stroke or Neurological Death at 1 year	Stroke Definition: A focal neurological deficit of presumed vascular origin persisting more than 24 hours from symptom onset and a neuro-imaging study or other quantitative study that does not indicate a different etiology. The definition includes subjects presenting with clinical signs and symptoms suggestive of subarachnoid hemorrhage, intracerebral hemorrhage, or cerebral ischemia. The definition also includes sudden loss or worsening of vision due to retinal artery occlusion or retinal emboli. The definition excludes slowly progressive cranial nerve palsies or progressive visual field deficits due to continued aneurysm growth. The definition also excludes external events such as trauma and also excludes transient ischemic attacks in which the symptoms resolve on their own within 24 hours. Stroke will be classified by the Clinical Events Committee as major or minor: • Major Stroke: A stroke, in which the NIHSS of the subject increases by ≥ 4 and persists for 7 days and more. Minor Stroke: A stroke, which resolves completely within seven days OR increases the NIHSS of the subject by ≤ 3.

Abbreviation	Abbreviated Term	Definition
SAE	Serious Adverse Event	Adverse event that a) led to death, b) led to serious deterioration in the health of the patient, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) 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. 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.
SADE	Serious Adverse Device Effect	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
SAP	Statistical Analysis Plan	Statistical Analysis Plan
SD	Standard Deviation	Standard Deviation
UADE	Unanticipated Adverse Device Effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the Investigational Plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
ULN	Upper Limit of Normal	Upper limit within a particular range.
USADE	Unanticipated Serious Adverse Device Effect	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

3. Introduction

This document provides a detailed description of the statistical methods and procedures to be implemented during the analysis of the SHIELD study. The methods and procedures described in this document are intended to support the generation of a Clinical Study Report (CSR) for Clinical Protocol NV-PED-10, including detailed descriptions of the populations, methodologies, post-text tables, analysis summary tables, patient data listings, and descriptive graphics. The information collected during this clinical investigation will be used to assess specific parameters and contrast these results with other Pipeline studies where the Pipeline device did not have the Shield Technology™. Likewise, the information analyzed herein will help us to assess safety and efficacy of the device for, but not limited to, a US indication evaluation.

This study is a multi-country, prospective, single-arm, multi-center clinical investigation evaluating outcomes in subjects with intracranial aneurysms who are treated with the Pipeline™ Flex Embolization Device with Shield Technology™. Within this current study, the safety and effectiveness of the Pipeline™ Flex Embolization Device with Shield Technology™ device in subjects undergoing treatment for intracranial aneurysms will be analyzed.

Subjects will be considered enrolled in the study once the patient has signed and dated the Informed Consent or DRF and the Pipeline™ Flex Embolization Device with Shield Technology™ is advanced into the micro catheter inside the patient.

The study population will consist of patients who have an intracranial aneurysm and qualify for enrollment into the study. The treated aneurysm may be ruptured (with a Hunt and Hess grade of ≤3); under these clinical conditions, Pipeline™ Flex Embolization Device with Shield Technology™ may be used according to the Instructions for Use and the intended use statement during the treatment regimen. The term Primary Study Procedure refers to the initial study procedure and is used consistently to discriminate between the primary study procedure and re-treatment of the target aneurysm. If more than one aneurysm can be covered by a single Pipeline device or two overlapped devices, the multiple aneurysms treated by that device(s) may all be included in the study. If the patient has more than one aneurysm and all aneurysms requiring treatment cannot be covered by a single Pipeline device or two overlapped devices, the non-target aneurysms should be treated first. After waiting at least 30 days, the patient may return for treatment of the target aneurysm with the Pipeline™ Flex Embolization Device with Shield Technology™.

The maximum number of subjects to be enrolled in this clinical investigation is 200. The maximum number of sites permitted to participate in this clinical investigation is 25 with no more than 30 subjects enrolled per site.

All images taken of the aneurysm (e.g., angiograms, CT, MR, rotational angiography with 3D reconstruction, cone beam CT, etc.) will be sent to the Independent Core Lab designated for this clinical investigation for adjudication.

The planned analyses identified in this statistical analysis plan (SAP) may be included in regulatory submissions and/or future manuscripts. Exploratory analyses, not identified in this SAP, may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses that are performed but not identified in this SAP will be clearly identified in the CSR. The structure and content

of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials.

This statistical analysis plan (SAP) is based on revision B of the protocol dated 24-Jun-2016.

4. Study Objectives

The primary objective of this study is to assess the *outcomes* of the Pipeline™ Flex Embolization Device with Shield Technology™ in patients undergoing treatment for intracranial aneurysms in a large real-world, post-market setting. *Outcomes* will be assessed based on a series of standardized measurements recorded during the procedure and during the post-procedure follow-up period.

Attributes and parameters to characterize the outcomes of the Pipeline™ Flex Embolization Device with Shield Technology™ during the procedure will be addressed based on the following assessments (as observed):

- Successful deployment of the study device to the target site
- Implantation of the study device
- Entire IA neck covered by the study device
- Device malfunction during the delivery system preparation
- Adverse Events: By seriousness (Serious or Non-Serious) peri-procedural (Day 0), by relatedness (Procedure, Device and Anti-platelet therapy)

Attributes to characterize the outcomes of the study device post-procedure will addressed based on the following assessments:

- Aneurysm occlusion (Class 1: Complete obliteration, Class 2: Residual neck, or Class 3: Residual Aneurysm)
- Adverse events: By Seriousness (serious and non-serious) ; per relatedness (procedure, device or antiplatelet therapy) and time of event (Acute 1-30 days, and Delayed 31-Study exit)
- Modified Rankin Scale (mRS)
- NIH Stroke Scale (NIHSS)
- Retreatment
- Major stroke in the territory supplied by the treated artery or neurological death
- Delayed Intracerebral hemorrhage (ICH) > 30 days post-procedure
- Parent artery stenosis (per Core Lab)
- Device migration (per Core Lab)

5. Investigation Plan

A prospective, single-arm, multi-center post-market observational study.

Up to 200 subjects who meet the Inclusion/Exclusion Criteria may be enrolled over a period of approximately 2 years to reach a target number of subjects. Study participation includes initial screening

and baseline evaluation, treatment using the Pipeline™ Flex Embolization Device with Shield Technology™, and follow-up visits at the discretion of the treating physician for 1 year beyond the index procedure. The total study duration is expected to be approximately 3 years.

Study Design:

Subjects will be considered enrolled in the study once the patient has signed and dated the Informed Consent or DRF and the Pipeline™ Flex Embolization Device with Shield Technology™ is advanced into the micro catheter inside the patient. All enrolled subjects who underwent the study procedure and in whom an attempt to implant the device was made will be included in the analysis population.

A CEC will be in place for the study using a minimum of three physicians knowledgeable in the appropriate disciplines and medical specialties pertinent to the disease state being evaluated in this clinical study. This committee will be responsible for the review and adjudication to the study variables of all events identified in the CEC Charter/Manual of Operations.

The CEC will independently adjudicate to specified endpoint event definitions, event relatedness, event severity, and event outcomes.

The imaging core laboratory will be responsible for the qualitative image analysis to determine aneurysm occlusion, parent artery stenosis, and device migration. An imaging protocol will be provided to the site.

Pre-Specified Study Endpoints:

The pre-specified study endpoints and analysis listed here are the primary body of data that will be collected, analyzed, and summarized in a series of tables, lists, and graphs as part of the final report for this study. Other analysis will be conducted as part of the final report but these are the core set of analyses that will constitute the foundation of the clinical study report.

Primary endpoints:

Safety:

- Occurrence of major stroke in the territory supplied by the treated artery or neurological death post-procedure (1-year)

Effectiveness:

- Complete aneurysm occlusion (defined as Raymond-Roy grade 1) without significant parent artery stenosis (≤ 50%) or retreatment of the target aneurysm post-procedure (1-year)

Secondary endpoints:

Safety:

- Occurrence of major stroke in the territory supplied by the treated artery or neurological death at 30 days post-procedure due to procedural complications
- Delayed intracerebral hemorrhage > 30 days post-procedure

Effectiveness:

- Device deployment success rate at the target site

Additional Safety Analyses:

- [redacted]
- [redacted]

- [redacted]
  - [redacted]
  - [redacted]

Additional Effectiveness Analyses:

- [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Study Procedure:

Subjects will be considered enrolled in the study once the patient has signed and dated the Informed Consent or DRF and the Pipeline™ Flex Embolization Device with Shield Technology™ is advanced into the micro catheter inside the patient. Per each site's standard of care procedure, at screening, each patient can undergo a neurologic examination and assessment using the mRS and NIHSS, blood draw for hematocrit, platelet count, platelet function testing, serum creatinine, and a pregnancy test (if applicable). Pertinent medications taken by the study participant starting on the day of study procedure were collected while for platelet reactivity start date can also be > 30 days before procedure (in case patient was already under antiplatelet, including anticoagulants and antiplatelet therapy). Subjects will be assessed and documented at baseline. Patient eligibility assessment is to be performed based on data available to the investigator at the time of screening. Patient will be considered a screen failure if:

- The patient signs the informed consent or DRF but fails to meet study inclusion/exclusion criteria during the screening and baseline phase.
- The patient signs the informed consent or DRF, meets the study inclusion/exclusion criteria but an attempt to implant the Pipeline™ Flex Embolization Device with Shield Technology™ is not performed.

The investigator will assess device occlusion, device placement and overall status of the aneurysm. At the investigator's discretion, the target IA may be retreated at any time during the study. In such situations, the date of the initial procedure (and not the date of the retreatment) will be considered Day 0.

If the target IA undergoes an attempted deployment with the Pipeline™ device with Shield Technology™ but is not implanted or receives an alternate treatment (e.g., coils), the patient is considered an implant failure and will be followed up until hospital discharge. However, if the target IA does not undergo an attempted deployment with the Pipeline™ device with Shield Technology™ and is not treated or receives an alternate treatment (e.g., coils) during the initial procedure, the patient is considered a screen failure and no further follow up is required.

The patient will be tested at the discretion of the site per standard of care procedures for antiplatelet response and the appropriate dose of antiplatelet agents will be given after the Pipeline™ device with Shield Technology™ placement procedure. Medications could be continued as medically indicated.

Estimated Duration of Patient Participation

Up to 200 subjects will be enrolled over a period of approximately 24 months. The study is intended to have 200 subjects undergo attempted deployment of the Pipeline™ device with Shield Technology™. Each study patient will be followed for 1 year after the primary study procedure. Study participation includes consent, initial screening and baseline, treatment using the Pipeline™ device with Shield Technology™, discharge exam and follow-up visits at approximately 30, 90, 180 days, and 1 year. The total study duration is expected to be approximately 3 years.

Schedule of Assessments

	Baseline	**Procedure**	**Discharge**	**1 Month**	**3 Months**	**6 Months**	**1 Year**	**Unscheduled**
Schedule		Day 0		±14 days	±30 days	±6 weeks	±8 weeks	
Eligibility	X							
Demographics	X							
Aneurysm Symptoms	X	O	O	O	O	O	O	OR
Medical History		X						
Study Procedure		X						
Procedure Imaging		XR						
Ancillary Devices		X						
Study Device		XR						
Discharge			X					
Follow Up				X	X	X	X	XR
Follow-Up Imaging				OR	OR	OR	OR	OR
NIHSS	O	X		O	O	O	O	OR
mRS	O	X		O	O	O	O	OR
Exit			X					

Retreatment Study Procedure				OR	OR	OR	OR	OR
Labs	OR	OR	O	O	O	O	O	OR
Device Specific Event		OR	OR	OR	OR	OR	OR	OR
Adverse Event Assessment		OR	OR	OR	OR	OR	OR	OR

Key: Required= X Optional=O Repeatable=R

ANALYSIS POPULATIONS

The following populations will be considered for the analysis of data for this study:

Intent to Treat (ITT)

The Intention to Treat (ITT) population includes all consented subjects in whom deployment of the Pipeline™ device with Shield Technology™ was attempted.

Full Analysis Set (FAS)

The Full Analysis Set (FAS) population is a subset of the ITT population including only those subjects in whom the Pipeline™ device with Shield Technology™ was implanted.

Internal Carotid Artery (ICA) Population

The Intra-Cranial Artery Population (ICA) is a subset of the ITT population including only those subjects in whom the Pipeline™ device with Shield Technology™ was implanted in the ICA (segments C2-C7).

Non-ICA Population

The non-ICA is a subset of the ITT population including only those subjects in whom the Pipeline™ device with Shield Technology™ was implanted in the arterial vessels other than those specified in the ICA population.

6. Determination of Sample Size

No formal estimates were prepared for examining the individual variables. However, the incidence of certain events will be examined relative to the thresholds used in research treating a similar population. Device outcomes variables recorded on a dichotomous scale will be summarized using a 2-sided 95% Clopper-Pearson exact binomial confidence interval. The upper and lower bounds of the confidence interval will be examined relative to results in the peer-reviewed literature and studies using the

Pipeline device without the Shield Technology™. Specifically, the incidence at 1 year post-procedure of a major stroke in the territory supplied by the treated artery or neurological death will be examined relative to an a priori threshold of 15%. The incidence at 1 year post-procedure of aneurysm occlusion without significant parent artery stenosis will be examined relative to an a priori threshold of 50%.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subject disposition (e.g., number completing the study, number lost-to-follow-up) will be summarized with frequency tables.

7.1.2 Clinical Investigation Plan (CIP) Deviations

CIP deviation is defined as an event where the Investigator or study personnel did not conduct the study according to the CIP. Deviations shall be reported regardless of whether medically justifiable or taken to protect the subject in an emergency.

7.1.3 Analysis Sets

The following population will be considered the primary population, but not limited to, in the analysis of data for this study: Intent to Treat Population.

The Intent to Treat (ITT) population includes all subjects who have signed and dated the patient informed consent (ICF) or Data Release Form (DRF) and in whom deployment of the Pipeline™ Flex Embolization Device with Shield Technology™ was attempted.

7.2 General Methodology

All statistical analyses will be performed using Statistical Analysis System (SAS) for Windows (version 9.2 or higher, SAS Institute Inc. Cary, NC) or other widely accepted statistical or graphical software. In general, data for all study Subjects combined will be presented. Individual data will be presented in subject listings.

Descriptive statistics will be used to present the data and to summarize the results. Discrete variables will be presented using frequency distributions and cross tabulations. Continuous variables will be summarized by presenting the number of observations (N), mean, standard deviation, median, minimum, and maximum values.

For Adverse Event reporting, which includes primary and secondary variables, the primary analysis will be based on Subject counts (e.g., the number and percentage of Subjects with event among the total number of Subjects). The data will be presented in the format of p% (x/N) [e], with p and x being the percentage and number of Subjects with events, respectively, N being the sample size of the analysis population, and e being the total number of events occurred in the x Subjects.

For device-related outcomes (e.g., device deployment success rate), the unit of analysis will be the device.

For occlusion outcomes, the unit of analysis will be the aneurysm.

7.2.1 Analysis Conventions

Specific algorithms are discussed for imputing missing or partially missing dates, if deemed appropriate, under specific data topics. Imputed or derived data will be flagged in the individual patient data listings. Imputed data will not be incorporated into any raw or primary datasets. These data are retained in derived (or analysis) datasets.

The term *Primary Study Procedure* refers to the initial study procedure, *Re-treatment Procedure* refers to the treatment performed after the *Primary Study Procedure*.

Total duration on study will be calculated as the difference between the date of procedure (Day 0) and the last on-study observation. All calculations defining the duration on study will be performed relative to the date of procedure and follow the algorithm DURATION = [STUDY COMPLETION OR WITHDRAW DATE – PROCEDURE DATE].

Post-procedure angiograms will be reviewed to assess aneurysm occlusion according to the scale of Roy:

- Complete = Complete occlusion, no flow of contrast seen in the aneurysm sac
- Residual Neck = Partial occlusion, some flow or eddying flow in the aneurysm sac
- Residual Aneurysm = Incomplete occlusion, apparent flow in the aneurysm sac

Procedure time will be calculated based on the following sentinel events. Start Time: Time of skin incision. End Time: skin closure

Major Stroke: A stroke, in which the NIHSS of the subject increases by ≥ 4 and persists for 7 days and more.

Minor Stroke: A stroke, which resolves completely within seven days OR increases the NIHSS of the subject by ≤ 3.

Neurological Death is any patient death due to neurological reasons.

7.2.2 General Conventions for Summarization

Summary statistics will consist of the number and percentage of responses or counts at each level for categorical variables (e.g. gender). For continuous variables, the sample size (n), mean, median, standard deviation (SD), minimum, and maximum values will be presented.

All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.

The number and percentage of responses will be presented in the form XX (XX.X%).

- All summary tables will include the analysis population sample size (i.e., number of subjects).
- Relative Study Day 0 is defined as the day the patient underwent the study procedure. All study days are determined relative to the day the patient underwent the study procedure.
- Baseline values will be defined as those values recorded immediately prior to the study procedure.
- Change from baseline for differences will be calculated as follows:

  Change = Post-baseline value - baseline value

- Missing data may have an impact upon the interpretation of the trial data. The primary presentation of the overall primary endpoint results will be based on the observed data with multiple imputation for missing data using SAS PROC MI. A methodology is also defined in this section for addressing missing dates.
- Date variables will be formatted as DDMMMYYYY for presentation; SAS Date9. format.

Data from this study, when applicable will be presented in a listing format. All listings will be sorted by patient number and date, as applicable.

7.3 Center Pooling

This is a multi-center clinical study, with standardization of subject enrollment, data entry and Adverse Event reporting. All investigational sites will follow the requirements of a common protocol, data collection procedures and forms. To present the data from this clinical study in a summary form, a comparison of the following variables will be completed to assess the appropriateness of pooling data from across all sites:

- Baseline demographics such as age, and gender

The distributions of the above variables across the sites will be tabulated. To detect site differences, the Kruskal-Wallis test will be used for continuous variables and the Chi-Square test or the Fisher's exact test will be used for categorical variables, depending on variable distribution.

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

Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measure.

Subjects with missing data that cannot be resolved prior to database lock may not be included in the tabulation and excluded from the summary statistics if deemed necessary; a listing will be compiled identifying the subjects. The number and percentage of subjects with each characteristic will be presented. The tabulation of subjects across the different characteristics and conditions is independent; multiple subjects can have multiple conditions. Results will be presented based on the number of respondents in each category using counts and percentages.

When calculating rates of Adverse Events, missing and partial dates will be handled as follows. If the entire Adverse Event start date is missing, then the procedure date will be used for the start date. If the month and the day of the month are missing but the year is available, and the year is the same as the year of the procedure then the procedure date will be used for the start date. If the year is greater than the year of the procedure, then January 1st will be used for the month and day of the start date. If the day is missing, but the month and year are available, then the 1st will be used as the day of the start date unless the imputed date would before the procedure in which case the procedure date will be used for the start date of the Adverse Event.

For baseline categorical variables, "unknown" responses will be counted as not having the characteristic and will be included in the denominator. Missing values will not be counted in rate denominators.

Handling of Missing Start-dates for Interventions

Rules for imputing a full date for interventions with incomplete or missing start-dates are addressed below. In the unusual case that the month portion of an intervention start-date is missing but the day portion is not missing, the day portion of the intervention will be assumed to be missing. Likewise, in the case where the year portion of an intervention start-date is missing but the month and/or day portion is not missing, the month and/or day portion of the intervention start-date will be assumed to be missing. All missing portion(s) of the intervention starting dates will be handled using the same rules:

- In the event that the day portion (and only the day portion) of the intervention start-date is missing:
    - If the intervention started in the same month and year as the study procedure, the intervention start-date will be assumed to be the date of the study procedure (i.e., Study Day 0);
    - Otherwise, the intervention start-date will be assumed to be the 15th day of the given month and year, e.g., XX–DEC-2015 ▪ 15-DEC-2015 where XX represents an unknown value.
- In the event that the day and month portion (and only the day and month portion) of the intervention start-date are missing:
    - If the intervention started in the same year as the study procedure, the intervention start-date will be assumed the date of the study procedure (i.e., Study Day 0);
    - Otherwise, the intervention start-date will be treated as June 15th of the given year, e.g., XX-XXX-2015 ▪ 15-JUN-2015.
- In the event that the day, month, and year portion of the intervention start-date are missing, the start-date of the intervention will be assumed to be the date of the study procedure (i.e., Study Day 0).

Note: With the exception of following special cases, this conservative scheme ensures that an intervention with a partially or completely missing start-date will be treated as post-procedural.

Special Cases on Missing Intervention Start-dates

- Using the above rules for the handling of missing intervention start-dates, if the assumed intervention start-date:
    - is later than the reported intervention stop-date, the assumed intervention start-date will be reset and assumed to be the intervention stop-date.
- If, based on the above rules, it cannot be determined whether the intervention was taken prior to the study procedure, it will be assumed to be post-procedural.

Investigation of the Effect of Investigational Sites

As an exploratory analysis, the results by site will be examined: Small sites (i.e., sites that have less than 4 subjects) will be identified and the following method will be used for combining the data. Data from all small sites (<4 subjects) will be combined to form a single site in order to obviate non-estimable situations in the evaluation of site and site interaction effects. Once combined, the pooled site will remain as such for all analyses for which a site effect is determined. If the pooled smaller sites represent a single site that has more than twice as many subjects as the largest single site, however less than 3

times as many subjects, the small sites will be ranked by size and divided into 2 pooled assignments using an alternating sequence (ABABAB). If the pooled smaller sites represent a site that has more than three times as many subjects as the largest single site, however less than 4 times as many subjects, the small sites will be ranked by size and divided into 3 pooled assignments using an alternating sequence (ABCABCABC).

Imputation of Outcome Data

Missing data for subjects who fail to complete study follow-up without any evidence of a major stroke in the territory supplied by the treated artery or neurological death will be imputed in the analysis of primary safety using the multiple imputation procedure from SAS (Proc MI). Subjects who withdraw from the study prior to completion and have experienced a major stroke in the territory supplied by the treated artery or neurological death at any time will be counted as having experienced the event of interest. A separate tabulation will be provided based on the observed data: subjects who withdraw from the study prior to completion without any evidence of a major stroke in the territory supplied by the treated artery or neurological death will be counted as not having experienced the event of interest.

For effectiveness, since follow-up imaging of the target aneurysm was not required at each study visit but was instead performed according to standard of care, the primary endpoint will be assessed using a selection rule, according to the following preferences:

- Imaging from day 141 (the opening of the 6-month follow-up window) onward is eligible to be included; imaging earlier than day 141 is disregarded for this analysis but imaging after the end of the 1 year window is still eligible.
- We will use the last adjudicated image at any time starting from day 141, UNLESS
- - o The last image is a CTA and there is a DSA within 90 days prior to the CTA, in which case the DSA will be used, OR
  - o The last image is an MRA and there is a DSA or CTA within 90 days prior to the MRA, in which case the DSA or CTA will be used. For this sub-rule we will prefer DSA over CTA if both exist.

The rules above define the available data for the purpose of endpoint calculations and effectiveness tables and listings. For subjects with no qualifying imaging per the above preference rules, multiple imputation will be employed to handle missing data for primary effectiveness.

In all cases, primary effectiveness will be defined according to the angiographic core laboratory's adjudication of images received.

Patient Accounting and study disposition

A complete accounting of patient participation in the study by analysis population will be presented in Table 14.1.1a entitled *Patient Accounting*. The purpose of this table is to provide an accounting of subjects from their entrance into the study through the final visit and to account for the evaluations of subjects in the analyses of efficacy and safety, including reasons for early study termination. The table will display the number of subjects that were consented and the number and percentage of subjects from the ITT, FAS, ICA, and non-ICA populations that:

- Underwent the study procedure (n/%)
- Evaluated at the 30-day follow-up visit (n/%)
- Evaluated at the 90-day follow-up visit (n/%)

- Evaluated at the 180-day follow-up visit (n/%)
- Evaluated at the 1-year follow-up visit (n/%)

The final study disposition of all subjects participating in the study by analysis population will be presented in Table form entitled *Patient Final Study Disposition*. A table entitled *Patient Accounting by Investigational Site* will follow a similar format and method of tabulation; however, this table will be presented by investigation site. A table entitled *Reasons for Screen/Implant Failures* will contain a tabulation of the number of subjects classified as screen/implant failures by individual reason.

A table entitled *Summary of Protocol Deviations* will contain a tabulation of the number and percentage of subjects from the ITT population with a deviation by deviation code. Multiple deviations per patient within the same category will only be counted once.

A listing entitled *Patient Disposition* supports various tables. This listing will be sorted by patient number. A listing entitled *Inclusion Criteria* displays the data from the Inclusion Criteria case report form. The data will be displayed for each patient and for each inclusion criterion. The listing will be sorted by patient number. A listing entitled *Exclusion Criteria* displays the data from the Exclusion Criteria case report form. The data will be displayed for each patient and for each exclusion criterion. The listing will be sorted by patient number. A listing entitled *Protocol Deviations* will list all protocol deviations for each patient. The listing will be sorted by patient number. The deviation code and description, visit and action, will also be included in the listing.

From the CRF, the following information will be presented in the listing:

- *What was the protocol deviation start date*
- *What was the associated visit*
- *What was the protocol deviation description*
- *What was the protocol deviation*
- *What was the reason for the protocol deviation*
- *Action taken? (Y/N)*
- *If action taken, please describe*

7.5 Adjustments for Multiple Comparisons

No adjustments will be made.

7.6 Demographic and Other Baseline Characteristics

Patient demographics, medical history, aneurism symptoms, and baseline neurological status will be summarized using descriptive statistics for continuous variables (mean, standard deviation, number of observations, minimum and maximum) and frequency tables for discrete variables.

Baseline Demographic and Risk Factors

Data will be summarized and reported in a table entitled Summary of Patient Demographics (ITT population); A similar table will be restricted to the ICA population. This table summarizes the patient population with respect to age at entry into the study, gender and risk factors. Age will be reported in years. Age will be summarized using descriptive statistics: n, arithmetic mean, standard deviation, median, and range (i.e., minimum and maximum values). Age will also be presented in mutually-

exclusive categories: ≥18 to ≤60 and >60 years of age. Subjects with missing data that cannot be resolved prior to database lock will not be included in the tabulation and excluded from the summary statistics; all demographic data will be presented in a listing. Gender and individual risk factors will be summarized using counts and percentages. In addition to the reported values, unknown or unreported values will also be reported.

The supportive data for the demographics table will be presented in a listing entitled Patient Demographics. This listing will be sorted by patient number.

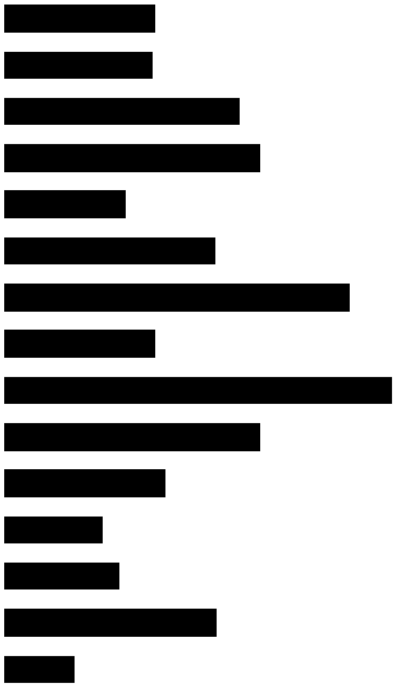
From the CRF (site reported data), the following information will be tabulated for the tables (present yes or no) and presented in the listing:

[redacted]

Aneurysm Symptoms and Characteristics

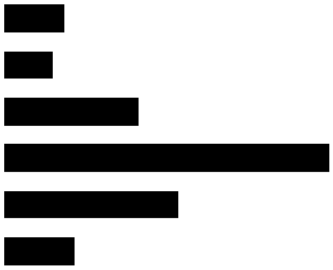
Site reported data will be summarized and reported in a table entitled Summary of Target Aneurysm Characteristics (ITT population); a similar table will be restricted to the ICA population. Results will be based on the following solicited symptoms.

[redacted]



Results will be summarized by type using counts and percentages.

The type of imaging modality will be summarized using counts and percentages.



If there are multiple types of imaging used for a patient, the image with the highest quality and used in the independent core lab read will be reported.

The type of aneurysm will be summarized using counts and percentages (per Core Lab).

Determining the side and location of the Internal Carotid Artery, Vertebral Artery, Anterior Cerebral Artery, and Middle Cerebral Artery will be summarized using counts and percentages (per Core Lab). Precise parent artery location will be summarized using counts and percentages (per Core Lab). Continuous variable measurements for Aneurysm maximal diameter (mm), Aneurysm dome (mm), Aneurysm neck length (mm), Dome/neck ratio, Parent artery diameter distal to the target aneurysm (mm) and Parent artery diameter proximal to target aneurysm (mm) will be summarized using

descriptive statistics (sample size, mean, median, standard deviation, minimum and maximum values) (per Site Reported data). From the following elements are recorded (per Core Lab):

The incidence of previously ruptured aneurysms will be summarized using counts and percentages. Summary statistics will be presented on the timing of the rupture relative to the study procedure. The percentage of thrombosis will be summarized using descriptive statistics.

Aneurysm partially thrombosed prior to PFED treatment?

From the Core laboratory, the following segments will be reported:

- [redacted]
  - [redacted]
  - [redacted]
- [redacted]

Determination if the target IA partially thrombosed will be summarized using counts and percentages. The number of small (<7mm), medium (7-12mm), large (13-24mm), and giant (≥25mm) target IAs will be presented using counts and percentages.

Treatment for previous ruptured aneurysms will be summarized based on the following clinical options; other will be presented in the listings.

Was target aneurysm previously treated? *No* *Yes*

Check all previous treatments for target aneurysm:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

A table entitled *Summary of All Aneurysm Characteristics* (ITT population) will summarize all aneurysms using the target and non-target aneurysms as the sampling unit; a similar table will be restricted to the ICA population. The column heading will reflect the number of aneurysms and will serve as the denominator for all ratio variables. The supportive data for Tables 14.1.3 and 14.1.3.1 will be presented in Listing 16.4.2 entitled Aneurysm Characteristics. This listing will be sorted by patient number.

Medical History

For this clinical investigation, only those pre-existing conditions that are currently on-going on the date of the study procedure were recorded. Data will be summarized and reported in a table entitled Summary of Medical History (ITT population) per SOC and MeDRA coding conventions; a similar table will be restricted to the ICA population.

Neurological Assessments at Baseline

Subjects may undergo (as indicated by site per standard of care) a neurologic examination and assessment using the mRS and NIHSS at baseline and also prior to the procedure. Data will be summarized and reported in a table entitled Summary of Neurological Assessments at Baseline (ITT population); a similar table will be restricted to the ICA population. The summary will include the baseline results for the mRS (Baseline) and NIHSS (recorded pre-procedure). The mRS, results will be presented using counts and percentages for each mRS score. For the NIHSS, results will be summarized using descriptive statistics as observed.

A NIHSS table will be presented in a listing format entitled NIH Stroke Scale (NIHSS) Scores will contain the baseline pre-procedure and post-procedure scores by patient, as well as the date and time the score was recorded. This listing will be sorted by patient number. As the screening/baseline assessments may be performed prior to the procedure at Day 0 some subjects will have only a single value for NIHSS. In this case the screening/baseline value will be left blank in the listing. A listing entitled Modified Rankin Scale (mRS) Scores will contain the pre-procedure and post-procedure scores by patient and date the score was recorded. This listing will be sorted by patient number.

Platelet Reactivity Test Results

Data will be summarized and reported in a table entitled Summary of the Platelet Reactivity Test Results Recorded at Baseline (ITT population); a similar table will be restricted to the ICA population. The last results prior to the procedure will be reported for each patient. The platelet test results will be summarized using descriptive statistics: n, arithmetic mean, standard deviation, median, range (i.e., minimum and maximum values). Subjects with missing data that cannot be resolved prior to database lock will not be included in the tabulation and excluded from the summary statistics; all data will be presented in a listing. A summary of the platelet reactivity data recorded after the procedure will be presented in a table entitled Summary of Post-Procedure Platelet Reactivity Test Data; a similar table will be restricted to the ICA population. The supportive data for Table platelet reactivity will be presented in a listing format entitled Platelet Reactivity Test Results. This listing will be sorted by patient number. The individual elements to be presented from the CRF are presented below.

[redacted]

[redacted]

7.7 Treatment Characteristics

Procedure characteristics, study device usage and procedure imaging information will be summarized using descriptive statistics for continuous variables (mean, median, standard deviation, number of observations, minimum and maximum) and frequency tables for discrete variables.

Pipeline™ device STUDY PROCEDURE with Shield Technology™ and Efficacy

This section will discuss the tabulation and analysis of the study procedure, type and size of the Pipeline™ device with Shield Technology™ and follow-up. Detailed descriptions of the statistical procedures that will be used to analyze the study variables will be described below.

In the design of the outcome data from this registry, a collective approach has been used to compile the results within an overall summary table. Given there is clinical interest to examine multiple variables for the various populations, this approach has been adopted. Separate subset tables may be extracted for discussion for the overall summary table.

Study Procedural Characteristics

The summarization of the procedural data for the ITT population will be presented in a table entitled Summary of the Primary Study Procedure Characteristics; a similar table will be restricted to the ICA population. The term Primary Study Procedure refers to the initial procedure, given the patient may require re-treatment.

Time of skin incision to time of first Pipeline™ device with Shield Technology™ introduction will be calculated and presented in minutes. The time of first Pipeline™ device with Shield Technology™ introduction to last Pipeline™ device with Shield Technology™ delivery system removal will be calculated and presented in minutes. Time of skin incision to time of skin closure will be calculated and presented in minutes. Cumulative flouro time will be summarized for the ITT population in minutes. The time interval data described above will be summarized using descriptive statistics: n, arithmetic mean, standard deviation, median, range (i.e., minimum and maximum values). Subjects with missing data that cannot be resolved prior to database lock will not be included in the tabulation and excluded from the summary statistics; all data will be presented in a listing.

The information collected and to be summarized and reported in the listings is presented below:

[redacted]

[redacted]

Pipeline™ Device with Shield Technology™ Deployment

A summary of the use of the Pipeline™ devices for the ITT population will be presented in a table entitled *Summary of Pipeline™ Device Deployment;* a similar table will be restricted to the ICA population. The number of Pipeline™ devices used and the reasons for multiple device use for the primary study procedure will be presented. The count and percentage for the following categories applicable to the SHIELD device will be summarized:

[redacted]

Side branches covered by PFED?

- [redacted]

The following analyses will be based on data from the independent core lab unless otherwise indicated. The count and percentage of each of the following summarized parameters will be provided.

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

The supportive data will be presented in a listing entitled *Pipeline™ Device with Shield Technology™ Deployment – Primary Study Procedure* and a listing entitled *Pipeline™ device with Shield Technology™ Deployment – Complete Re-Treatment Information*. A listing of the subjects and the Pipeline™ device with Shield Technology™ identification number will be presented in a listing entitled *Pipeline™ device with Shield Technology™ Accountability.* All three listings will be sorted by patient number. The information collected and to be summarized and reported in the listings for re-treatment is presented below:

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

Ancillary Device Devices Used During the Procedure

A summary of ancillary devices used for the ITT population will be presented in a table entitled *Summary of Ancillary Devices;* a similar table will be restricted to the ICA population. Results will be presented using counts and percentages based on the list of devices presented below. The information collected and to be summarized and reported in the listings is presented below:

[redacted]

- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
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- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

The supportive data for ancillary devices table will be presented in a listing entitled *Ancillary Devices*. This listing will be sorted by patient number. The list of study devices will be presented in a listing entitled *Pipeline™ device with Shield Technology™ Accountability*.

Overall Summary of Device and Peri-Procedure Variables

The overall summary of the results (site reported when Core Lab adjudicated data not available) from the study procedure will be summarized in a table entitled *Overall Summary of the Device and Peri-Procedure Variables;* a similar table will be restricted to the ICA population. Within this table, 9 separate parameters will be summarized:

- Successful deployment of the study device to the target site. Successful deployment has a binary outcome and comes directly from the clinical case report form.
- Implantation of the study device. The determination of implantation has a binary outcome and comes directly from the clinical case report form.
- Number of times re-sheathing was attempted. The count (0, 1, 2, or >2) comes directly from the clinical case report form.
- Entire IA neck covered by the study device. Complete neck coverage has a binary outcome and comes directly from the core lab
- Side branches covered by the study device. Complete side branch coverage has a binary outcome and comes directly from the core lab
- Post-deployment stasis (complete, significant, or no disruption of inflow jet); evaluated as 1 of 3 possible states, comes directly from the core lab
- Target aneurysm partially thrombosed; a binary endpoint that comes directly from the core lab
- Percentage of target aneurysm thrombosis; a continuous endpoint that comes directly from the core lab
- Achievement of wall apposition; a binary endpoint that comes directly from the core lab.

The duration of the procedure (min) will also be summarized and presented using descriptive statistics.

The supportive data for these series of tables will be presented in a listing entitled *Device and Peri-Procedure Analyses*. This listing will be sorted by patient number.

Overall Summary of the Post-Procedure Variables Recorded Over Time

The post-procedure analyses will be summarized for the following 5 time points: Post-Procedure Discharge, 1 Month Post-Procedure, 3 Months Post-Procedure, 6 Months Post-Procedure, and 1 Year Post-Procedure. The following 10 separate parameters will be summarized:

- Aneurysm occlusion (Class 1: Complete obliteration, Class 2: Residual neck, or Class 3: Residual Aneurysm), derived from the post-procedure imaging adjudicated by core lab.
- Modified Rankin Scale (mRS). The mRS score at 1 year will be dichotomized (>2 vs. ≤2) and summarized using counts, percentages, and 2-sided 95% exact binomial confidence intervals.
- NIH Stroke Scale (NIHSS)
- Platelet reactivity testing
- Change in antiplatelet therapy because of the platelet reactivity testing
- Retreatment of the target aneurysm
- Major stroke in the territory supplied by the treated artery or neurological death at 30 days post-procedure due to procedural complications
- Intracerebral hemorrhage (ICH) > 30 days post-procedure (Delayed ICH)
- Parent artery stenosis (per Core Lab)
- Device migration (per Core Lab)

The incidence of complete aneurysm occlusion without significant parent artery stenosis (≤50%) at 1 year post-procedure and without re-treatment of the target aneurysm (Primary Efficacy Endpoint) will be based on the Scale of Roy. Results will be based on the ITT population and will include the target aneurysm for each patient. The target aneurysm is defined as the largest aneurysm treated in the study procedure as identified by the core laboratory.

Results based on the ITT population will be presented in a table entitled *Overall Summary of the Post-Procedure Variables by Time*. The table will contain the point estimate and the confidence limit based on the exact Clopper-Pearson method. The supportive data for this table will be presented in a listing entitled *Post-Procedure Variables*. This listing will be sorted by patient number. Results based on the ICA population will be presented in a similar table and results based on the FAS population will be presented in a similar table.

Concomitant Medications

Concomitant medications refer to all medications taken from Day 0 thru study exit. *Antiplatelet medications were collected per their actual start date even if these were started prior to the study treatment (Day 0). Prior medications* refer to all medications that were started and stopped prior to the first treatment with the Pipeline™ device with Shield Technology™ and will not be reported as concomitant.

The count and percent of subjects on anti-platelet medications will be summarized for 7 days pre-procedure, as well as for post procedure (were available) and presented in tables entitled *Summary of Dual Antiplatelet Therapy (DAPT)*. A summary of the concomitant medications will be presented in a table entitled *Summary of Concomitant Medications*, containing a clear declaration regarding the start date of the medication relative to the study procedure. The concomitant medications taken by the ITT population will be displayed in a listing entitled *Concomitant Medications*.

7.8 Interim Analyses

None

7.9 Evaluation of Objectives

As previously described, the primary objective of this study is to assess the *outcomes* of the Pipeline™ Flex Embolization Device with Shield Technology™ in patients undergoing treatment for intracranial aneurysms in a large real-world, post-market setting. *Outcomes* will be assessed based on a series of standardized measurements recorded during the procedure and during the post-procedure follow-up period.

The Intent to Treat (ITT) will be considered the primary population, but not limited to, in the analysis of data for this study. When analyzing an outcome within a population, missing data will be reflected as the function of the denominator reported (xx.x% n/N) while the population number will remain constant. [i.e. ITT n=200 outcome Y (50%, 98/196)]

The pre-specified study endpoints and analysis listed here are the primary body of data that will be collected, analyzed, and summarized in a series of tables, lists, and graphs as part of the final report for this study. Other analysis will be conducted as part of the final report but these are the core set of analyses that will constitute the foundation of the clinical study report.

Primary endpoints:

Safety:

- Occurrence of major stroke in the territory supplied by the treated artery or neurological death post-procedure (1-year)

Effectiveness:

- Complete aneurysm occlusion (defined as Raymond-Roy grade 1) without significant parent artery stenosis (≤ 50%) or retreatment of the target aneurysm post-procedure (1-year)

Secondary endpoints:

Safety:

- Occurrence of major stroke in the territory supplied by the treated artery or neurological death at 30 days post-procedure due to procedural complications
- Delayed intracerebral hemorrhage > 30 days post-procedure

Effectiveness:

- Device deployment success rate at the target site

Analysis for primary effectiveness endpoint interaction of site homogeneity and poolability testing will be conducted and reported.

Analysis of primary effectiveness endpoint by:

- Missing Data by Worst Case Scenario
- Aneurysm Location (with observed data)
- Aneurysm Location by Artery Segments (ITT population with observed data)
- By age (ITT and FAS population with observed data)

Analysis for primary effectiveness endpoint tipping point for incidence of complete target aneurysm occlusion at 1 year post procedure (ITT population)

CEC event of interest through 1 year will be reported for:

- GUSTO Bleeding
- Procedural:
  - Access Site Complications
  - Procedural Systemic Complications
  - Vasospasms
- Neurological Events:
  - Focal Neurological Deficit
  - Cerebral Infraction
  - Transient Ischemic Attack (TIA)
  - Intracranial Hemorrhage (ICH)
  - Stroke
  - Death

7.10 Safety Evaluation

All summaries of Adverse Events will be primarily reported, but not limited to, for the ITT population.

The Clinical Events Committee (CEC) will be responsible for the review and adjudication of all adverse events per the definitions established in the CEC Charter/Manual of Operations.

Site Reported and CEC adjudicated events shall be summarized in incidence and frequency tables coded by System Organ Class (SOC) and MeDRA preferred term (PT).

A table reporting CEC adjudication disposition will be presented (Site Reported, CEC adjudicated).

CEC adjudicated Adverse Events will be mapped to preferred terms and body systems using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The number and percentage of subjects experiencing Adverse Events will be summarized by system organ class and preferred term for all Adverse Events.

CEC adjudicated Adverse Events will be presented by system organ class and preferred term.

Summaries of CEC adjudicated AEs by the maximal severity (Mild, Moderate and Severe), relatedness (e.g., to the study device, procedure, anti-platelet therapy.), seriousness (serious, non-serious) and timing (Peri-procedural- Day 0, Acute- day 1-30 and Delayed, Day 31-Study Exit) shall be presented.

Causality Assessment (Relatedness)

CEC adjudicated relationship of each adverse event will be presented as follows:

- Device: Medical device: (Medical device investigated in the Investigation)
- Procedure: The medical -surgical procedure on day 0
- Anti-platelet therapy: Related to the anti-platelet agent therapy, that is required per standard of care for treatment.

Missing and Partial Adverse Event Dates

The recorded dates for adverse events are important for an accurate tabulation of both events and patients, and required for the following:

1. Defining the start of the event
2. Designation of unique adverse event occurrences recorded intra-patient.

Completely missing or partially missing adverse event dates will be imputed as follows:

- If the adverse event start date is completely missing the adverse event will be counted to the date of the study procedure.
- If the adverse event start date is partially missing and the partial date is not sufficient to determine if the event occurred after the start of the study procedure, then the adverse event will be counted with a start date of the procedure date.

Summaries of Adverse Events

All summaries of adverse events will be reported for the ITT and ICA population and based on counted adverse events.

Site Reported events shall be summarized. Adverse events will be mapped to preferred terms (PT) and system organ class (SOC)using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

The number and percentage of patients experiencing adverse events will be summarized by system organ class (SOC), MeDRA preferred term and

In addition to a similar table, CEC adjudicated data will additionally be presented by:

Relatedness: Summaries AE relatedness (e.g., to the Pipeline™ device with Shield Technology™, procedure, and anti-platelet therapy.) by SOC and MeDRA.

Seriousness: Serious and non-serious adverse events will be presented by SOC and MeDRA PT.

Severity: With respect to maximal severity, will be presented by SOC and MeDRA PT

Timing: With respect to timing, will be presented by Peri-Procedural (Day 0), Acute (Day 1-30) and Delayed (Day 31-study exit) per SOC and MeDRA PT

The number and percentage of patients experiencing 1 or more adverse events will be presented counts of events and percentages.

A table entitled *Summary of CEC Adjudicated Adverse Events by System Organ Class and Preferred Term by Site* contains the primary presentation of the adverse event data by site. This table is prepared without defining the causality or relationship to the study procedure or device. Patients will be counted only once at the system organ class level and will be counted once for each applicable preferred term; multiple occurrences of the same preferred term for a patient will only be counted once, in addition the event counts will be provided for completeness of data. The number and percentage of patients experiencing each event by system organ class and preferred term will be displayed. System organ classes, and preferred terms within a system organ class will be displayed alphabetically. The overall adverse event rates will be summarized using counts and percentages. This table will be repeated for the site-reported adverse events; results will be summarized and presented in a table entitled *Summary of Site Reported Adverse Events by System Organ Class and Preferred Term by Site.*

A table entitled *Summary of CEC Adjudicated Adverse Events by Preferred Term Leading to Study Discontinuation* provides the presentation of adverse events leading to study discontinuation. This table

will have the same structure as that of the previously described table however, only those adverse events that led to study discontinuation will be displayed. The number and percentage of patients experiencing each system organ class and preferred term will be displayed.

A listing entitled *Adverse Events (Site Reported)* provides supportive data and is sorted by patient and relative day of the study procedure.

A listing entitled *Adverse Events (CEC Adjudicated)* provides supportive data and is sorted by patient and relative day of the study procedure.

A patient profile shall be generated for each individual patient detailing all adverse events mapped to their adjudicability status and CEC adjudicated disposition. The heading for each profile will contain the patient identifier; the collective set of all profiles will be titled *Profile of Adverse Events by Patient.* A listing presenting this information will be included in a listing entitled Adverse Event Mapping. A summary table presenting the number of site reported events deemed adjudicable and their adjudication disposition will be presented in A table entitled *Summary of Site Reported Adverse Events and Adjudication Status*.

7.11 Health Outcomes Analyses

This section is not applicable to this study.

7.12 Changes to Planned Analysis

Planned analyses will be performed as indicated and per CIP. Other analyses can be conducted addition to the prespecified analyses as to further elucidate findings that may be useful to the Sponsor or the medical community.

7.13 Analyses in addition to the CIP (to include but not limited to:)

7.13.1 Additional Analyses

Within the study protocol there was no declaration regarding the ranking of the analyses. Additionally, there was no formal statistical testing strategy or formal estimate regarding the sample size and statistical power for this clinical investigation. For presentation of the results, the analyses will be categorized into 2 major categories: ***Device and Peri-Procedure Analyses*** and ***Post-Procedure Analyses***.

7.13.2 Device and Peri-Procedure Analyses

The **Device and Peri-Procedure** analyses to be summarized will address device deployment. Within this analysis, there are 9 separate variables:

- Successful deployment of the study device to the target site. Successful deployment has a binary outcome and comes directly from the clinical case report form.
- Implantation of the study device. The determination of implantation has a binary outcome and comes directly from the clinical case report form.
- Number of times re-sheathing was performed. The count (0, 1, 2, or >2) comes directly from the clinical case report form.
- Entire IA neck covered by the study device. Complete neck coverage has a binary outcome and comes directly from the core lab.

- Achievement of wall apposition; a binary endpoint that comes directly from the core lab
- Device deficiency/ malfunctions; a binary endpoint and comes directly from the clinical case report form.
- Procedure time, a continuous variable and comes directly from the clinical case report form
- Cumulative Fluoroscopy time, a continuous variable and comes directly from the clinical case report form
- Serious Adverse Events during the procedure (Day 0)

7.13.3 Post-Procedure Analyses

The first series of **Post-Procedure** analyses to be summarized will address the outcomes after the procedure. Within this series, there are 9 separate parameters:

- Aneurysm occlusion (Class 1: Complete obliteration, Class 2: Residual neck, or Class 3: Residual Aneurysm), derived from the post-procedure imaging adjudicated by Core Lab.
- Modified Rankin Scale (mRS); a multinomial endpoint that comes directly from the site reported case report form for evaluating the intra-patient over time and the change from baseline. The mRS will be scored for each patient by an evaluator at the clinical site. The mRS is a well-accepted and defined scoring system for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke using a multinomial ordinal scale:
    - 0 No symptoms at all
    - 1 No significant disability despite symptoms; able to carry out all usual duties and activities
    - 2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance

  The mRS score at 1 year will be dichotomized (>2 vs. ≤2) and summarized using counts, percentages, and 2-sided 95% exact binomial confidence intervals.
- NIH Stroke Scale (NIHSS); a continuous endpoint that comes directly from the site reported clinical case report form for evaluating the intra-patient over time and the change from baseline. The NIHSS is a 15-item neurologic examination stroke scale used to evaluate the effect of acute cerebral infarction on the levels of consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss.
- Platelet reactivity testing, based on the VerifyNow, VASP, MEA, TEG, LTA testing reported as a percentage. A continuous endpoint that comes directly from the site reported clinical case report form.
- Change in antiplatelet therapy because of the platelet reactivity testing; a binary variable and comes directly from the site reported clinical case report form.
- Retreatment of the target aneurysm; a binary variable adjudicated by the imaging core laboratory. The recurrence of the aneurysm will be summarized using the percentage of subjects that experience aneurysm recurrence. Aneurysm recurrence is defined as an aneurysm that achieves complete occlusion at 6 months post-procedure, and then is no

longer completely occluded, based on Core Lab, (i.e., residual neck or residual aneurysm is found by Core Lab) at 12 months post-procedure. This endpoint will only be defined in those subjects with both 6- and 12-month imaging adjudicated. The percentage of subjects that undergo retreatment of the target aneurysm after the initial PED treatment will also be presented. Major stroke in the territory supplied by the treated artery or neurological death at 30 days post-procedure due to procedural complications; the event and event-relatedness will be adjudicated by the CEC. The 1-year event rate will also be tabulated and reported. A binary variable, and the event will be adjudicated by the CEC.

- Intracerebral hemorrhage (ICH) > 30 days post-procedure; the event will be adjudicated by the CEC. The 1-year event rate will also be tabulated and reported. A binary variable, and the event will be adjudicated by the CEC.
- Parent artery stenosis; continuous variable from the post-procedure imaging adjudicated by Core Lab, dichotomized into >50% and ≤50% stenosis. Additionally, stenosis will be presented by quartile.
- Device migration; a categorical variable from the post-procedure imaging adjudicated by Core Lab.

The second series of **Post-Procedure** variables to be summarized will address the safety and efficacy profile over the course of the entire clinical investigation.

- The device-related neurologic adverse event rate at 1 year post-procedure will be presented with the relationship between the device and the neurologic adverse events adjudicated by the independent CEC. Disabling stroke or neurological death at 1 year (as observed)
- Ischemic and Hemorrhagic Cerebrovascular Events (as adjudicated by CEC) : includes incidence of Stroke (Major or Minor, Ipsilateral or Contralateral), Cerebral Infarction (Symptomatic or Asymptomatic), Intracranial Hemorrhage, Transient Ischemic Attack, and Target Aneurysm Rupture
- Aneurysm recurrence
- Device Related Serious Adverse Events
- Procedure related Serious Adverse Events

8. Validation Requirements

Output will be validated by level I or II validation.

Level I: The peer reviewer independently programs output and then compares the output with that generated by the original Statistical Programmer.

Level II: The peer reviewer reviews the code; where appropriate, performs manual calculations or simple programming checks to verify the output.

9. References

1. SAS Institute Inc., SAS▪ Version 9.4 software, Cary, NC.

2. Roy, D., Milot, G. & Raymond, J. Endovascular treatment of unruptured aneurysms. Stroke 32, 1998-2004 (2001).