Medtronic ELEVATE Study - MDT19025TRACER
EvaLuate EndoVascular Treatment of Acutely Ruptured Shallow Intradural Aneurysms With the Pipeline™ Flex Embolization Device With Shield TEchnology™ (ELEVATE)
Statistical Analysis Plan Version A
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Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	**E**va**L**uate **E**ndo**V**ascular treatment of **A**cutely ruptured wide-neck intradural aneurysms with the Pipeline™ Flex Embolization Device with Shield **TE**chnology™ (**ELEVATE**)
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1. Version History

Version	Summary of Changes	Author(s)/Title
A	• Not Applicable, New Document	Jing Lu, Prin. Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
CIP	Clinical Investigation Plan
CP	Conditional Power
DMC	Data Monitoring Committee
DSA	Digital Subtraction Angiography
eCRF	Electronic Case Report Forms
ICH	International Conference Harmonization
IDE	Investigational Device Exemption
IQR	Interquartile Range
ITT	Intention to Treat
LAR	Legally Authorized Representative
mITT	Modified Intention to Treat
mRS	Modified Rankin Scale
OUS	Outside United States
PP	Per Protocol
RIA	Ruptured Intracranial Aneurysm
SAE	Serious Adverse Event
SAH	Subarachnoid Hemorrhage
SSR	Sample Size Re-estimation

3. Introduction

Ruptured intracranial aneurysms (RIAs) are amongst the most dangerous cerebrovascular lesions, characterized by acute presentation and dismal natural history if not correctly diagnosed and treated promptly. Aneurysmal subarachnoid hemorrhage (aSAH) is associated with a high case fatality rate, occurs at a relatively young age compared with other types of stroke, and many survivors are left in a functionally dependent state. Two most common causes of death among patients with RIAs are rebleeding or neurological deterioration due to the initial rupture.

For the treatment of RIAs, deconstructive treatment such as endovascular trapping or parent artery occlusion is often an unacceptable or suboptimal strategy, particularly in the setting of SAH. Additionally, not all RIAs are amenable to either surgical clipping or coil embolization. Reconstructive surgical treatment in ruptured aneurysms could be hazardous, as the vessel often lacks the structural

integrity to hold aneurysm clips, leading to very high rates of intra-operative rupture and a high risk of parent vessel stenosis or occlusion.

Reconstructive endovascular treatment using a traditional strategy of coil embolization may not be optimal for all cases if a well-defined saccular component of the aneurysm either does not exist or is too small to safely accommodate the introduction of coils, or if the parent vessel is friable with circumferential involvement of the wall over a relatively long segment of the vessel. For these reasons, endovascular reconstruction of the diseased segment with stents has gained increasing acceptance due to lower rate of recurrence and procedure-related mortality.

The Pipeline™ Flex embolization Device with Shield Technology™, the Pipeline™ Shield Device, is a flow diverter that represents a promising treatment option for the treatment of RIAs. The low porosity and high mesh density of flow diverters facilitate aneurysmal occlusion by reducing the blood flow into the aneurysms and by serving as a scaffold for endothelialization across the aneurysm neck leading to progressive occlusion and reduced rates of recanalization of the treated aneurysm due to progressive thrombosis and shrinkage of the lesion. Shield Technology™ reduces the material thrombogenicity of the braid surface compared to the bare metal Pipeline™ Flex Device implant based on bench data with human platelets and plasma. The SHIELD OUS and PFLEX prospective, multi-center, post-market studies have demonstrated that the Pipeline™ Shield Device is effective and safe for the endovascular treatment of intracranial aneurysms. These studies are described in more detail in the ELEVATE Clinical Investigation Plan (CIP).

The ELEVATE study is a prospective, multi-center, single-arm adaptive IDE study of the Pipeline™ Shield Device for the treatment of adults (≥ 22 and ≤ 80 years of age) with acutely ruptured wide-neck (neck ≥4mm or dome to neck ratio ≤1.5) intradural aneurysms not amenable to surgical clipping or coiling alone. The primary purpose of the ELEVATE study is to assess the safety and effectiveness of constructive treatment with the Pipeline™ Shield Device in adults with acutely ruptured wide-neck aneurysms not amenable to surgical clipping or coiling alone. The primary safety and effectiveness of the Pipeline™ Shield Device will be assessed through incidence of major stroke in the territory supplied by the treated artery or neurological death through 365-day follow-up, and complete angiographic occlusion without significant stenosis (≤ 50%), and no rebleeding or retreatment of the target aneurysm through 365-day follow-up post-procedure, respectively.

This Statistical Analysis Plan (SAP) for the ELEVATE CIP will describe and document the planned interim assessment and final analyses of the study that will be included in study reports. The SAP has been prepared in agreement with Medtronic internal procedures and using the International Conference Harmonization (ICH) guidelines E3, E6 and E9.[1,2,3]

4. Study Objectives

The objective of the study is to assess the safety and effectiveness of constructive treatment with the Pipeline™ Shield Device in adults with acutely ruptured wide-neck (neck ≥4mm or dome to neck ratio ≤1.5) intradural aneurysms not amenable to surgical clipping or coiling alone.

4.1 Primary Endpoints

Primary Safety Endpoint: Incidence of major stroke in the territory supplied by the treated artery or neurological death through 365-day follow-up.

- Major stroke is defined as a stroke which is present for ≥ 24 hours and increases the NIHSS of the subject by ≥ 4.

Primary Effectiveness Endpoint: Complete angiographic occlusion without significant stenosis (≤ 50%), and no rebleeding or retreatment of the target aneurysm through 365-day follow-up post-procedure.

- Living subjects who do not present for 365-day follow up angiography will be treated as missing at follow-up and imputed using a multiple imputation procedure.
- Aneurysm occlusion according to the Raymond Roy Scale and parent artery stenosis will be assessed by the imaging Core Lab. Rebleeding and retreatment will be assessed by the Investigator.

4.2 Secondary Endpoints

1. Incidence of Pipeline™ Shield Device deployment success*
2. Incidence of target aneurysm rebleed through 180-day and 365-day follow-up post-procedure
3. Incidence of neurological hemorrhagic serious adverse events post-procedure through 180-day and through 365-day follow-up
4. Incidence of ipsilateral major stroke**# or neurological death post-procedure after 30 days through 180-day and through 365-day follow-up
5. Incidence of any ipsilateral stroke post-procedure after 30 days through 180-day and through 365-day follow-up
6. Incidence of good clinical outcome (mRS 0-2) at 30-day, 180-day, and 365-day follow-up
7. Incidence of parent artery thrombosis through 365-day follow-up
8. Incidence of in-construct stenosis > 50% through 365-day follow-up
9. Incidence of target aneurysm retreatment through 180-day and through 365-day follow-up
10. Incidence of peri-/post-procedural serious adverse events related to the device, procedure or antiplatelet therapy through 180-day and through 365-day follow-up
11. Incidence of neurological death or major stroke** post-procedure through 180-day follow-up
12. Incidence of complete angiographic occlusion without significant stenosis (≤ 50%), and no rebleeding or retreatment of the target aneurysm through 180-day follow-up post-procedure

*Device deployment success is the successful implantation of the device at the target location.

**#Major stroke: A stroke, which is present for ≥ 24 hours and increases the NIHSS of the subject by ≥ 4.

5. Investigation Plan

This is a prospective, single-arm, multi-center, adaptive IDE study to assess the safety and effectiveness of constructive treatment with the Pipeline™ Shield Device in adults with acutely ruptured wide-neck intradural aneurysms not amenable to surgical clipping or coiling alone.

Up to 200 subjects may be enrolled (consented) to attain a target sample size of 100 evaluable subjects who will undergo treatment with available data up to 365 days. Up to 45 investigational sites may participate; inclusive of up to 40 investigational sites in the U.S. and up to 5 investigational sites outside U.S. (OUS). To avoid site-specific bias, the attempted procedure will be allowed for a maximum of 20% of the total number of evaluable subjects at each participating investigational site.

Subject data will be collected at the time of enrollment (consent) through subsequent follow-up visits until conclusion of subject's study participation (e.g. completion of 365-day visit, subject/physician withdrawal, etc.). Subjects with an attempted procedure to deploy Pipeline™ Shield Device are required to participate in the study for 365 days and are expected to complete follow-up visits at 30-day, 90-day, 180-day and 365-day.

The proposed study design is a single-arm study. A randomized controlled study is not feasible for the evaluation of the Pipeline™ Shield Device due to the lack of an appropriate control or specific device with regulatory clearance to treat acutely ruptured wide-neck intradural aneurysms not amenable to surgical clipping or coiling alone. Subjects and clinical site personnel are not blinded to treatment based on the design of this study.

An adaptive sample size re-estimation (SSR) approach will be used in this study. This adaptive design will only allow for an increase in the sample size if the results are promising at the interim assessment; early stopping for effectiveness is not an option with this study design. The interim assessment for evaluation of the sample size will be predicated on the primary effectiveness and primary safety endpoints and conducted using a Conditional Power (CP) approach as described by Mehta and Pocock (2011).[10]

5.1 Selection of Subjects

The study population will consist of adults (≥ 22 and ≤ 80 years of age) with acutely ruptured wide-neck (neck ≥4 mm or dome to neck ratio ≤ 1.5) intradural aneurysms not amenable to surgical clipping or coiling alone. A subject is considered enrolled when the informed consent has been signed by the subject (or subject's legally authorized representative (LAR)).

Subjects for this study must meet all of the inclusion criteria and shall be excluded from the study if any of the exclusion criteria are met. Full details of inclusion and exclusion criteria are in the ELEVATE CIP.

Subjects who sign the informed consent but is determined as ineligible prior to the index procedure and device implant will be considered a screen failure. A screen failure subject can be classified as:

- Pre-screen Failure: A subject who did not meet eligibility and consent was not signed.
- Screen Failure: An enrolled subject who was determined to be ineligible for the study prior to the arterial puncture on the day of the index procedure.
- Procedural Screen Failure: An enrolled subject who was determined to be ineligible after arterial puncture per the pre-procedural digital subtraction angiography (DSA) imaging on the day of the index procedure prior to device implant.

Screen failure subjects should be exited from the study and require no further follow-up.

5.2 Schedule of Events

An overview of the assessments to be performed at each follow-up interval, along with the required window, and a flow diagram of the overall study is provided in the Study Procedures section of the ELEVATE CIP.

6. Determination of Sample Size

6.1 Determination of Target Sample Size

A total of up to 200 subjects may be enrolled (consented) to attain a target sample size of 100 evaluable subjects who will undergo treatment with available data up to 365 days. The minimum target sample size for this clinical investigation is 100 subjects (Intention to Treat (ITT) population). The upper limit of up to 200 subjects to be enrolled accounts for a potential increase in the target number of evaluable subjects post-interim analysis and for a higher number of screen failures due to the emergent nature of this study in which subjects cannot be screened based on inclusion and exclusion criteria prior to arterial puncture and cannot be assessed by a Physician Screening Committee until after consent.

The sample size for this clinical investigation was based on the primary effectiveness and primary safety endpoints.

- Primary Effectiveness Endpoint: Complete angiographic occlusion without significant stenosis (≤ 50%), and no rebleeding or retreatment of the target aneurysm through 365-day follow-up post-procedure.

The test statistic for the hypothesis testing will be derived from a 1-tailed exact binomial test with a type 1 error rate of 2.5%. The expectation with the Pipeline™ Shield Device is that the incidence for the primary effectiveness endpoint will be significantly greater than 41%.

For effectiveness, testing against an a priori threshold of 41% with a power of 90% and a target type 1 error rate of 2.5% with the expectation of 58% of the subjects experiencing the primary effectiveness endpoint requires a sample size of 100 subjects. Based on the sample size estimation, the null hypothesis would be rejected if ≥52 (upper critical value) subjects met the endpoint. The exact test was specified to derive the power using SAS software. The actual type 1 error rate derived in the simulation was 1.70%. The calculated power was 90.6%.

- Primary Safety Endpoint: Incidence of major stroke in the territory supplied by the treated artery or neurological death through 365-day follow-up.

The test statistic for the hypothesis testing will be derived from a 1-tailed exact binomial test with a type 1 error rate of 2.5%. The expectation with the Pipeline™ Shield Device is that the incidence for the primary safety endpoint will be significantly less than 35%.

For safety, testing against an a priori threshold of 35% with a power of 90% and a target type 1 error rate of 2.5% with the expectation of ≤20% of the subjects experiencing the primary safety endpoint requires a sample size of 100 subjects. The exact test was specified to derive the power using SAS software. The actual type 1 error rate derived in the simulation was 2.11%. The calculated power was 91.3%. The minimum target sample size for this clinical investigation is 100 subjects.

The target sample size for both the composite effectiveness endpoint and the safety endpoint is 100 patients. Based on the results of the interim assessment, the sample size could be increased if the results are promising based on the calculation of CP.

The expectation with the Pipeline™ Shield Device is to achieve primary effectiveness endpoint success (occlusion, stenosis, rebleeding and re-treatment) in >50% of the patients. Establishing an a priori threshold of 41% is an aggressive expectation where the observed incidence of success for the primary effectiveness endpoint would need to exceed the incidence from the peer-reviewed literature for clipping and coiling. For the primary effectiveness endpoint, a threshold of 41% in this patient population is defensible and not conservative from the peer-reviewed literature and the direction provided by the Steering Committee. This estimate is predicated on the assumption that the inability to coil or clip does not translate into a dampened expectation with the Pipeline™ Shield Device.

Additionally, the effect of the Pipeline™ Shield Device on mortality would need to be pronounced in order to have an incidence of composite endpoint success statistically greater than 41%. In order to have a reasonable chance of achieving the composite effectiveness endpoint, at least 50% of the patients must survive for 365 days. A sample size of 100 patients will yield a significant result for the primary safety endpoint if the mortality and incidence of major stroke is not greater than 24%.

6.1.1 Justification for Safety Endpoint Threshold

The primary safety endpoint for this clinical investigation is incidence of major stroke in the territory supplied by the treated artery or neurological death through 365-day follow-up. Systematic literature search was undertaken to evaluate all published literature on the treatment of unclippable **and** uncoilable ruptured intracranial aneurysms. However, out of 33 publications that were screened, either no relevant publications (publications assessing treatment of unclippable **and** uncoilable ruptured

aneurysms) were found or the sample sizes in the publications were inadequate for statistical evaluation. Ruptured aneurysms that are unclippable and uncoilable have limited treatment options or no treatment options at all. Hence, a literature search on the natural history of untreated aneurysms was initiated using key words “ruptured”, “aneurysm”, “natural history” and “intracranial” which resulted in 213 articles in the search output. After screening the articles in the search output, nine relevant publications were found describing the natural history of ruptured intracranial aneurysms that were either untreated or conservatively managed. Out of these nine publications, three publications with a minimum of 100 patients with ruptured aneurysms that were either untreated or conservatively managed were obtained for further evaluation, Korja et al, 2017[5] (510 patients), Nishioka et al, 1984[6] (568 patients) and Sodhi et al, 2014[4] (152 patients). Together, these three publications reported data on 1,230 patients with ruptured intracranial aneurysms that were untreated. Note that the population included in these three natural history publications is similar to the population to be enrolled in the ELEVATE study as they have minimal or no other treatment options.

Additionally, data from three meta-analysis (that were included for primary effectiveness endpoint threshold determination - Zhang et al, 2019[9], Zhang et al[8] and Li et al[7]) on patients with ruptured aneurysms treated with clipping or coiling were also considered for safety threshold determination. Zhang et al, 2019[9], Zhang et al[8] and Li et al[7] reported data on 1004, 1408, and 11568, respectively; together, these three publications reported data on 13,980 patients with ruptured aneurysms treated with either clipping or coiling. Note that patients from the three meta-analyses includes those that can be treated with coiling or clipping and are not similar to the population to be studied in the ELEVATE study which includes subjects that are unfavorable for both, clipping and coiling. However, in the absence of relevant published clinical data, these 3 studies[7,8,9] were included as these are large meta-analysis (with > 13,000 patients) that provides general mortality rates for ruptured aneurysms.

A summary of the mortality results by reference is broken down by (a) treated ruptured aneurysms and (b) untreated ruptured aneurysms. Note: One of 3 articles on natural history (Sodhi et al, 2014[4]) also reported on 330 patients who did undergo treatment; this information has been added to the discussion on treated ruptured aneurysms.

a) Treated Ruptured Aneurysms:

Data from four publications, Zhang et al, 2019[9] (1004 patients), Zhang et al[8] (1408 patients), Li et al[7] (11,568 patients) and Sodhi et al, 2014[4] (330 patients), were evaluated. The four publications reported mortality rates of 1.8% - 17.4%[4,7,8,9] for endovascular coiling and 10.4% - 25.76%[4,7] for clipping.

In summary, mortality rates ranged between 1.8% to 25.76% for ruptured intracranial aneurysms treated with clipping or coiling. The most relevant statistic comes from the 330 treated patients in Sodhi et al (2014)[4]. The upper bound of the 2-sided 95% binomial confidence interval for 89/330 patients who died within 3 months of treatment is 30.83%.

b) Untreated Ruptured Aneurysms:

Data from three publications, Korja (2017)[5], Nishioka (1984)[6] and Sodhi et al (2014)[4] were evaluated. The three publications reported mortality rates of 76.97%[4] at the end of hospital stay, and 65%[5] and 40.49%[6] at 6 months in 152, 510 and 568 patients with untreated or conservatively managed ruptured intracranial aneurysms, respectively. While Nishioka et al,[6] may be considered a dated reference, there is no evidence to suggest that the reported population of patients with an untreated ruptured intra-cranial aneurysm would have a significantly different rate of survival today compared to 30 years ago.

The survival element of the primary safety endpoint is only a portion of the definition. Major stroke is the second element of the definition and has not factored into the calculations.

In summary, there is a wide divergence among the reported results with mortality rates ranging from 40% to 77%[4,5,6] across the three articles on untreated or conservatively managed ruptured intracranial aneurysms. Based on these mortality estimates for patients who did not undergo treatment, 40% mortality at 6-months post-rupture would not be unexpected and is an extremely conservative estimate.

Conclusion

A review of the published landscape based on the published literature resulted in a reasonable heuristic for consideration:

- For treated aneurysms that have ruptured, the peer-reviewed evidence suggests that mortality at 3 months with endovascular treatment will be as high as 31% with 95% confidence.
- Left untreated, the peer-reviewed evidence suggests that mortality may be as high as 77% and as low as 40% 6-months post rupture.

However, patients who present with a ruptured aneurysm and are able to undergo clipping or coiling is not the population to be enrolled in the ELEVATE study. The expectation with the ELEVATE study device is to achieve > 65% survival 180 days from the date of the intra-cranial rupture. The a priori threshold for statistical evaluation will be set at 35%.

It is also important to acknowledge that the incidence of major stroke has not been factored into the derivation of the a priori threshold, thereby making the 35% declaration a conservative estimate for testing.

Note that the primary effectiveness threshold of 41% and the primary safety threshold of 35% are substantially different from other trials on the Pipeline™ family of devices. This difference is based on the specific sub-set of subjects to be enrolled in the ELEVATE study *i.e.,* subjects with acutely ruptured wide-neck aneurysms that are not amenable to surgical clipping or coiling alone and thus have minimal or no treatment options. Note that several large studies have reported high mortality rates ranging from 65%-90% when patients with ruptured aneurysms are untreated.[4,5,6]

6.1.2 Justification for Effectiveness Endpoint Threshold

The primary purpose of the ELEVATE study is to assess the safety and effectiveness of constructive treatment with the Pipeline™ Shield Device in adults with acutely ruptured wide-neck intradural aneurysms that are not amenable to surgical clipping or coiling alone. The primary effectiveness endpoint for this clinical investigation is complete angiographic occlusion without significant stenosis (≤ 50%), and no rebleeding or retreatment of the target aneurysm through 365-day follow-up post-procedure. Systematic search was undertaken to evaluate all published literature on the treatment of unclippable **and** uncoilable ruptured intracranial aneurysms. However, out of 33 publications that were screened, either no relevant publications (publications assessing treatment of unclippable **and** uncoilable ruptured aneurysms) were found or the sample sizes in the publications were inadequate for statistical evaluation. Hence a literature search on treatment of all ruptured aneurysms between 2015 and 2019 was initiated using key words "ruptured", "aneurysm" and "intracranial" which resulted in 2050 articles in the search output. Due to this high volume of publications, the literature search was filtered for meta-analyses with a minimum of 1000 patients and with treatments other than flow diverters. Based on these criteria, three relevant publications were obtained for further evaluation, Zhang et al, 2019 (1004 patients), Zhang et al (1303 patients), and Li et al (11,568 patients). Together, these three publications reported data on 13,875 patients with ruptured aneurysms.

The primary effectiveness endpoint threshold for the ELEVATE study was derived based on reported rates of complete aneurysmal occlusion, stenosis, rebleeding and retreatment in patients with ruptured intracranial aneurysms as noted in **Table 6-1**.

Table 6-1. Data Analysis for Effectiveness Endpoint Derivation

ARTICLE	N	WEIGHTING FACTOR	OCCLUSION	OCC. WEIGHTED	STENOSIS	STENOSIS WEIGHTED	REBLEEDING	REBLEED WEIGHTED	RE-TREATMENT
Zhang 2019 Endovascular Treatment of Ruptured	1004	0.07236036	63.3	4.5804	15.4	1.1143	5	0.3618	Not Reported
Zhang 2019 Stent assisted coiling	1303	0.09390991	61	5.7285	8.4	0.7888	4.6	0.4320	16.6
Li 2012 Clipping	7230	0.521081081	84	43.7708	16.1	8.3894	1.1	0.5732	Not Reported
Li 2012 Coiling	4338	0.312648649	66.5	20.7911	20.9	6.5344	3	0.9379	Not Reported
	Sum: 13875	Sum: 1	Ave: 68.7%	Ave: 74.8709%	Ave: 15.2%	Ave: 16.8270%	Ave: 3.425%	Ave: 2.3049%	14.6%*
*The value 14.6% is the lower bound of the 2-sided 95% exact binomial confidence interval for retreatment obtained from Zhang et al, Journal of neurointerventional surgery. 2019;11(5):489-496									

Weighted stenosis percentage (16.8270%), weighted rebleeding percentage (2.3049%) and the lower bound of the 2-sided 95% exact binomial confidence interval for retreatment (14.6%), were all

subtracted from weighted occlusion percentage (74.8709%) to arrive at 41.14% as the threshold for primary composite effectiveness endpoint for the ELEVATE study. It is understood that the four events, complete aneurysmal occlusion, stenosis, rebleeding and re-treatment, may not be mutually exclusive; however, the data reported in the three publications regarding the four events are not separable and therefore treated as mutually exclusive for the purposes of this analysis. Please note that the outcomes reported in the above-mentioned publications are for all ruptured aneurysms, which include those that can be treated with clipping and coiling with traditionally established techniques. However, the patient population of the ELEVATE study is more challenging to treat since these patients have unclippable **and** uncoilable ruptured intradural aneurysms and typically have minimal or no treatment options. Hence the objective performance criterion of 41% for the effectiveness threshold is justified.

Additionally, clinical experience regarding the treatment of unclippable **and** uncoilable ruptured intradural aneurysms was sought from the Steering Committee. Based on the outcomes for these specific sub-set of aneurysms they see in their clinical practice, the Steering Committee agrees with the 41% threshold for the primary composite effectiveness endpoint.

6.2 Interim Assessment for Sample Size Re-Estimation

An adaptive sample size re-estimation approach will be used in this study. The interim assessment for evaluation of the sample size will be predicated on the primary effectiveness and primary safety endpoints and conducted using a CP approach as described by Mehta and Pocock (2011).[10]

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Disposition of subjects will be reported. The number of individuals at each stage of study will be reported, including the following.

- Number enrolled
- Number of procedural screen failures
- Number of eligible subjects (per all eligibility criteria and physician screening committee approval)
- Number analyzed for each analysis set
- Number with follow-up (24-hour, 30-day, 90-day, 180-day, 365-day)

Reason for non-participation at each stage will be reported where known.

7.1.2 Clinical Investigation Plan (CIP) Deviations

All deviations will be collected in the electronic Case Report Forms (eCRF), with the type of the deviation and the reason for the deviation. All deviations will be reported in Tables and Listings.

7.1.3 Analysis Sets

The results of this study will be presented using 2 populations defined as analysis sets.

The Intention to Treat (ITT) analysis set includes all subjects who were consented and in whom deployment of the Pipeline™ Shield Device was attempted (i.e., puncture at the arterial access site), independent of the procedure being completed successfully. The ITT analysis set will be used to evaluate all safety and effectiveness endpoints.

The Per-Protocol (PP) analysis set will include all subjects that do not have an eligibility violation, are successfully implanted with Pipeline™ Shield Device, and receive the pre-specified regimen of post-procedural anti-platelet medications. This population will be used for secondary sensitivity analyses of the primary and secondary outcomes.

7.2 General Methodology

Summary tables will summarize data for all subjects in aggregate. Descriptive statistics will be used to summarize demographic and baseline characteristic variables for the ITT and PP analysis sets. Continuous data will be summarized using standard descriptive statistics including the mean, standard deviation, median and interquartile range (IQR), minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages for categorical variables. For events that can occur more than once in a single subject, such as adverse events, the percentage will be based on subjects experiencing the event; both subject and event counts will be reported.

For the evaluation of binary outcomes assessed relative to an *a priori* defined threshold, a 1-tailed exact binomial test will be used. Incidence rates for binary outcomes, including the primary objective, will be expressed with the corresponding 95% exact confidence intervals.

All statistical analyses will be performed using Statistical Analysis System (SAS) (version 9.4 or higher, SAS Institute Inc. Cary, NC).

7.3 Center Pooling

Heterogeneity across study sites will be assessed for the primary effectiveness endpoint using logistic regression with Firth's bias-reducing penalized likelihood. The dependent variable will be the binary response, and study site will be included as a fixed effect. A type I error threshold of 0.10 will be used to identify whether variability in the outcome is explained by differences in study sites. The center pooling test will be performed after combining all low-enrolling sites together into one group according to the geographical region, as defined by the Census Bureau (West, Midwest, Northeast, South). A low-enrolling site is defined as any site that enrolls 5 or fewer subjects.

If site is a statistically significant factor, further site-specific tests will be used to identify sites whose response rates differ substantively from other sites. Sensitivity analyses excluding these sites will be performed for the primary effectiveness endpoint. If the results of sensitivity analyses are consistent with the primary analysis, outcomes will be reported with all sites pooled. The pooling of US and OUS sites will also be assessed using this approach.

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

Every effort will be made to keep missing data, particularly the 365-day outcomes, to a minimum. Despite the investigational sites' best efforts, some missing data may be inevitable mainly due to lost-to-follow-up (LTFU). All data collected up to the time the subject discontinues participation in the study will remain in the study database and will be used for analysis.

The number and proportion of subjects eligible for, and compliant with, each follow-up examination will be presented. Subjects who withdraw from the study will be tabulated with reasons for withdrawal. Since the 365-day effectiveness endpoint is based upon conventional angiographic follow-up, the primary endpoint will be reported for all subjects who undergo the examination; all other ITT subjects without imaging will be treated as missing. This same approach will be used for the primary safety endpoint: the disposition of subjects who do not present for 365-day follow up and/or for whom no evidence is available regarding a major stroke in the territory supplied by the treated artery or neurological death will be treated as missing.

Multiple imputation will be employed via SAS PROC MI to impute missing data for subjects who fail to attend the 180-day evaluation visit. This procedure will provide an assessment of all subjects in the ITT population. The multiple imputation model will incorporate available baseline data to minimize predictive variability.

7.5 Adjustments for Multiple Comparisons

No multiplicity adjustments for multiple comparisons will be applied in the analysis of this study.

7.6 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be reported for the ITT analysis set. Continuous data will be summarized using standard descriptive statistics including the mean, standard deviation, median and IQR, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages for categorical variables.

7.7 Treatment Characteristics

Surgical procedure characteristics and concomitant therapies and medications will be reported for the ITT and PP analysis sets. Continuous data will be summarized using standard descriptive statistics

including the mean, standard deviation, median and IQR, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages for categorical variables.

7.8 Interim Analyses

An adaptive sample size re-estimation approach will be used in this study. This adaptive design will only allow for an increase in the sample size if the results are promising at the interim assessment, early stopping for effectiveness is not an option with this study design. The interim assessment for evaluation of the sample size will be predicated on the primary effectiveness and primary safety endpoints and conducted using a CP approach as described by Mehta and Pocock (2011)[10].

At the interim assessment, the CP for both the primary endpoints will be assessed when at least 50 subjects complete the 365-day evaluation or withdraw/die prior to the 365-day evaluation. If the CP for at least one of the primary endpoints is too low, the sample size will not be increased. If the CP falls in a range defined promising ($30\% \leq CP < 80\%$), then the sample size will be increased up to a pre-determined upper limit in order to increase the CP up to the 80% level. If an increase in the sample size is required for at least one of the two primary endpoints, and the re-estimation is within the defined sample size limits pre-specified by the CIP, the Data Monitoring Committee (DMC) will communicate the revised target sample size to the trial sponsor. Enrollment will continue towards the new target sample size, and the analyses performed by the DMC will not be released to the trial sponsor.

The DMC will make one of following recommendations to the sponsor according to the interim results:

- Favorable: the interim results are sufficiently favorable that the trial continues to the original sample size without the need to increase the trial size
- Promising: the interim result is not disappointing, but it is not good enough. In this case the sample size is increased without exceeding pre-defined maximum sample size
- Unfavorable: the interim result is disappointing, and it is not worth increasing the sample size to retrieve conditional power. If unfavorable, there will not be a sample size recalculation and study will continue as planned.

7.9 Evaluation of Objectives

Detailed information about each objective is included together with calculations and derivations of outcome parameters, analysis methods, and datasets analyzed.

7.9.1 Primary Objectives

7.9.1.1 Statistical Evaluation of Primary Effectiveness and Primary Safety Endpoints

Primary Effectiveness Endpoint:

Complete angiographic occlusion without significant stenosis (≤ 50%), and no rebleeding or retreatment of the target aneurysm through 365-day follow-up post-procedure

H_o: Percentage of primary effectiveness endpoint through 365-days ≤ 41.0%

H_a: Percentage of primary effectiveness endpoint through 365-days > 41.0%

Success of the primary effectiveness endpoint will be evaluated using a 1-tailed exact binomial test with a type 1 error rate of 2.5% based on ITT population. Subjects who were consented, confirmed eligible per the PSC criteria, and in whom the implant procedure was attempted but not successful (i.e. successful introduction of the Pipeline™ Shield Device into the microcatheter, but access to the aneurysm was not achieved or the Pipeline™ Shield Device was not deployed) will be counted as not having the event of interest.

Primary Safety Endpoint:

Neurological death or major stroke post-procedure through 365-day follow-up

H_o: Incidence of neurological death or major stroke through 365-days ≥ 35.0%

H_a: Incidence of neurological death or major stroke through 365-days < 35.0%

Success of the primary safety endpoint will be evaluated using a 1-tailed exact binomial test with a type 1 error rate of 2.5% based on ITT population.

The analyses of primary endpoints will be based on the observed data with multiple imputation for missing endpoint data. To claim study success, both primary safety and effectiveness endpoints should be met.

7.9.1.2 Subgroup Analyses

Subgroup analyses will be performed based on aneurysm location and size. Additional subgroup analyses will be performed based on intracranial aneurysm morphology (e.g. fusiform, saccular) to evaluate the probability of occurrence of ischemic events in each subgroup following aspirin or antiplatelet agent discontinuation. Note that these subgroup analyses are not independently powered and they are for exploratory purpose only.

7.9.2 Secondary Objectives

Secondary analyses will be conducted with the understanding that the results are for greater clarity ascribed to the procedure and the device and are not powered to detect a specific magnitude of difference. There are 12 secondary endpoints; each endpoint will be identified as either a technical endpoint or a clinical endpoint.

7.9.2.1 Technical Outcomes

Incidence of Pipeline™ Shield Device deployment success

This technical outcome will be analyzed using the ITT population. Subjects without device deployment success will be counted as not having the event of interest. Results for this binary outcome will be summarized using counts, percentages, and 95% exact binomial confidence intervals.

[#]Device deployment success is the successful implantation of the device at the target location.

7.9.2.2 Clinical Outcomes

Incidence of target aneurysm rebleed through 180-day and 365-day follow-up post-procedure

This clinical outcome will be analyzed using the ITT population. Subjects without evidence of a rebleed will be counted as not having the event of interest. Results for this binary outcome will be summarized using counts, percentages, and 95% exact binomial confidence intervals.

Incidence of neurological hemorrhagic serious adverse events post-procedure through 180-day and through 365-day follow-up

This clinical outcome will be analyzed using the ITT population. Subjects without this SAE will be counted as not having the event of interest. Results for this binary outcome will be summarized using counts, percentages, and 95% exact binomial confidence intervals.

Incidence of ipsilateral major stroke or neurological death post-procedure after 30 days through 180-day and through 365-day follow-up

This clinical outcome will be analyzed using the ITT population. Major stroke is defined as a stroke which is present for ≥ 24 hours and increases the NIHSS of the subject by ≥ 4. Subjects without evidence of this event will be counted as not having the event of interest. Results for this binary outcome will be summarized using counts, percentages, and 95% exact binomial confidence intervals.

Incidence of any ipsilateral stroke post-procedure after 30 days through 180-day and through 365-day follow-up

This clinical outcome will be analyzed using the ITT population. Subjects without evidence of this event will be counted as not having the event of interest. Results for this binary outcome will be summarized using counts, percentages, and 95% exact binomial confidence intervals.

Incidence of good clinical outcome (mRS 0-2) at 30-day, 180-day, and 365-day follow-up

This clinical outcome will be analyzed using the ITT population. Subjects without an mRS at this time point will be treated as missing; the results for these subjects will be imputed using multiple imputation. Results for this multinomial outcome will be summarized using categorization (0-2) and the median score. The percentage of subjects with an mRS of 0-2 will be summarized using counts, percentages, and 95% exact binomial confidence intervals.

Incidence of parent artery thrombosis through 365-day follow-up

This clinical outcome will be analyzed using the ITT population. Subjects without evidence of this event will be counted as not having the event of interest. Results for this binary outcome will be summarized using counts, percentages, and 95% exact binomial confidence intervals.

Incidence of in-construct stenosis > 50% through 365-day follow-up

This clinical outcome will be analyzed using the ITT population. Subjects without an image at this time point will be treated as missing; the results for these subjects will be imputed using multiple imputation. Results for this binary outcome will be summarized using counts, percentages, and 95% exact binomial confidence intervals.

Incidence of target aneurysm retreatment through 180-day and through 365-day follow-up

This clinical outcome will be analyzed using the ITT population. Subjects without evidence of this event will be counted as not having the event of interest. Results for this binary outcome will be summarized using counts, percentages, and 95% exact binomial confidence intervals.

Incidence of peri-/post-procedural serious adverse events related to the device, procedure or antiplatelet therapy through 180-day and through 365-day follow-up

This clinical outcome will be analyzed using the ITT population. Subjects without evidence of this event will be counted as not having the event of interest. Results for this binary outcome will be summarized using counts, percentages, and 95% exact binomial confidence intervals.

Incidence of neurological death or major stroke post-procedure through 180-day follow-up

This clinical outcome will be analyzed using the ITT population. Subjects without evidence of this event will be counted as not having the event of interest. Results for this binary outcome will be summarized using counts, percentages, and 95% exact binomial confidence intervals.

Incidence of complete angiographic occlusion without significant stenosis (≤ 50%), and no rebleeding or retreatment of the target aneurysm through 180-day follow-up post-procedure.

This clinical outcome will be analyzed using the ITT population. Subjects without evidence of this event will be counted as not having the event of interest. Results for this binary outcome will be summarized using counts, percentages, and 95% exact binomial confidence intervals.

7.10 Safety Evaluation

All adverse events (AEs) will be collected and evaluated from the time of arterial puncture through study exit. All AEs will be reported with Tables and supporting data Listings.

7.11 Changes to Planned Analysis

Any deviation from this Statistical Analysis Plan will be described and justified in the final clinical study report, as appropriate.

8. Validation Requirements

The primary analysis outcomes will be validated by independent programming, and primary and secondary analysis results will also be validated by the study biostatistician.

9. References

1. International Conference on Harmonisation, E3 Structure and Content of Clinical Study Reports (https://database.ich.org/sites/default/files/E3_Guideline.pdf).
2. International Conference on Harmonisation, E6 Good Clinical Practice (https://database.ich.org/sites/default/files/E6_Guideline.pdf).
3. International Conference on Harmonisation, E9 Statistical Principles for Clinical Trials (https://database.ich.org/sites/default/files/E9_Guideline.pdf).
4. Sodhi HB, Savardekar AR, Mohindra S, Chhabra R, Gupta V, Gupta SK. The clinical profile, management, and overall outcome of aneurysmal subarachnoid hemorrhage at the neurosurgical unit of a tertiary care center in India. *J Neurosci Rural Pract.* 2014;5(2):118-126.
5. Korja M, Kivisaari R, Rezai Jahromi B, Lehto H. Natural history of ruptured but untreated intracranial aneurysms. *Stroke; a journal of cerebral circulation.* 2017;48(4):1081-1084.
6. Nishioka H, Torner JC, Graf CJ, Kassell NF, Sahs AL, Goettler LC. Cooperative study of intracranial aneurysms and subarachnoid hemorrhage: a long-term prognostic study: II. Ruptured intracranial aneurysms managed conservatively. *Archives of neurology.* 1984;41(11):1142-1146.

7. Li H, Pan R, Wang H, et al. Clipping versus coiling for ruptured intracranial aneurysms: a systematic review and meta-analysis. *Stroke; a journal of cerebral circulation.* 2013;44(1):29-37.
8. Zhang X, Zuo Q, Tang H, et al. Stent assisted coiling versus non-stent assisted coiling for the management of ruptured intracranial aneurysms: a meta-analysis and systematic review. *Journal of neurointerventional surgery.* 2019;11(5):489-496.
9. Zhang X, Zhou Y, Duan G, et al. Endovascular treatment of ruptured middle cerebral artery aneurysms: a single armed meta-analysis and systematic review. *World neurosurgery.* 2019.
10. Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. *Statistics in medicine.* 2011;30(28):3267-3284.