Pivotal Study of the MicroVention, Inc. Flow Re-Direction Endoluminal Device (FRED) Stent System in the Treatment of Intracranial Aneurysms

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STATISTICAL ANALYSIS PLAN

Protocol Title (Number):

Pivotal Study of the MicroVention, Inc. Flow Re-Direction Endoluminal Device Stent System in the Treatment of Intracranial Aneurysms

Study Number: CL12001
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Version 2

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CONFIDENTIAL

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Abbreviations

Table of Abbreviations

Abbreviation	Definition
AE	Adverse Event
CEC	Clinical Events Committee
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computerized Tomography
DSMB	Data Safety & Monitoring Board
FDA	United States Food and Drug Administration
ITT	Intent-To-Treat Population
IA	Intracranial Aneurysm
FRED	Trial Name from protocol
mRS	Modified Rankin Scale
NIHSS	NIH Stroke Scale
OPC	Objective Performance Criterion
OUS	Outside of United States
PP	Per-Protocol Population
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
US	United States

1 SUMMARY

Title	Pivotal Study of the MicroVention, Inc. Flow Re-Direction Endoluminal Device Stent System in the Treatment of Intracranial Aneurysms
Preface	This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for protocol CL12001 (Pivotal Study of the MicroVention, Inc. Flow Re-Direction Endoluminal Device Stent System in the Treatment of Intracranial Aneurysms.). This study is being completed to assess the safety and effectiveness of the FRED for the treatment of intracranial aneurysms. The following documents were reviewed in preparation of this SAP: • Clinical Research Protocol CL12001 rev 4, issued September 27, 2016

	• Annotated eCRF Live v1.0 dated 19Apr2016 • FDA Presubmission Q140977
Purpose	The purpose of this SAP is to prospectively outline the planned analyses to be completed to support the completion of the Clinical Study Report (CSR) for protocol CL12001. The planned analyses identified in this SAP will be included in regulatory submissions and future manuscripts. Any post-hoc, exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported in appendices to the CSR.
Device Name And Intended Use	The device is called FRED (Flow Re-Direction Endoluminal Device) is indicated for the endovascular treatment of adults harboring intracranial aneurysms with a high likelihood for failure or recurrence with conventional techniques including wide-necked or geometrically complex intracranial aneurysms (including fusiform aneurysms) in the anterior and posterior cerebral circulation.
Primary Endpoints	The primary effectiveness endpoint is successful aneurysm treatment with the FRED Device as defined by complete occlusion utilizing the Raymond scale of the target aneurysm and ≤50% stenosis of the parent artery at the target IA at 12 months as assessed by angiography and in whom an alternate treatment of the target IA has not been performed within 12 months post-FRED Device placement. The primary safety endpoint is death or major stroke within 30 days post procedure, or neurological death or major ipsilateral stroke within 12 months post-procedure.
Secondary Endpoints	Secondary endpoints described in the protocol are listed below: 1) Proportion of subjects with clinically acceptable (90-100%) occlusion of the target aneurysm, ≤ 50% stenosis of the parent artery at the target IA at 12 months (+ 60 days, -30 days). as assessed by angiography, and in whom an unplanned alternative treatment of the target IA had not been performed within 12 months 2) Proportion of subjects in whom an unplanned alternative treatment of the target IA had not been performed within 12 months 3) Proportions of subjects with clinically acceptable aneurysm occlusion (90 %-100 %) of the target aneurysm at 12 months (+ 60 days, -30 days). 4) Incidence of ≥ 50% In-Stent Stenosis (ISS) at the target IA at 12 months as assessed by angiography at an independent corelab 5) Proportion of subjects with complete occlusion of the target aneurysm on 12-month angiography (+ 60 days, -30 days). 6) Incidence of FRED System procedure related Serious Adverse Events 7) Incidence of FRED System device-related Serious Adverse Events; 8) Incidence of unsuccessful delivery of the FRED system implant; 9) Incidence of unsuccessful deployment of the FRED flow-diverter intra-cranial stent 10) Incidence of migration of the FRED system implant at 12 months; 11) Unplanned alternative treatment on the target IA within 12 months, defined as re-treatment of the target aneurysm with an alternative treatment modality including open repair, endovascular placement of an additional stent or treatment of In-stent Stenosis observed at the 180 day or 12 month follow-up time-points or at an unscheduled study follow up visit. 12) Change in clinical and functional outcomes at 180 days and 1 year follow up, as measured by an increase in the modified Rankin Scale compared to baseline; 13) Incidence of major stroke, as measured by NIHSS at 12 months (and ophthalmic examination related to the target aneurysm if determined appropriate.

	14) Incidence of minor stroke, as measured by NIHSS at 12 months (and ophthalmic examination related to the target aneurysm if determined appropriate..
Study Design	A multi-center, prospective, single-arm study with follow-up at discharge, 30 days (± 7 days), 180 days (± 30 days) and 12 months (+ 60 days, -30 days). Data will be analyzed according to nominal visit, e.g. 30 days, 180 days, 12 months as opposed to actual date. The intent-to-treat (ITT) population as defined below will be the primary population for all efficacy analyses and the safety population for all safety analyses. One hundred forty-five (145) subjects will constitute the ITT cohort, which is identical to the Safety cohort. These subjects were enrolled and treated at 23 sites located in United States and Japan. Subjects are included in study analyses consistent with the prospective literature control, with efficacy and safety objective performance criteria (OPCs) used to determine sample size. Two OPC sets will be considered in support of efficacy and safety as per the original protocol (primary) as well as more strict (supportive) OPCs as follows: • Primary: Original PG specified in the protocol (45% for efficacy and 25% for safety) • Supportive: Updated PG presented to FDA at the Feb 2017 meeting (46% for efficacy and 15% for Safety). Study success is defined as achieving statistical significance for the primary OPCs. Primary Analyses: The powers will be 80% to rule out a 45% OPC (efficacy) margin (lower bound) and 80% to rule out a 25% OPC (safety) margin (upper bound) using one-sided tests. The trial will be considered successful if the one-sided 95% credible lower bound of the efficacy rate exceeds the 45% OPC and the one-sided 95% credible upper bound of the safety rate is below the 25% OPC. The use of one-sided testing is consistent with the protocol. Supportive Analyses: The powers will be 90% to rule out a 46% OPC (efficacy) margin (lower bound) and 90% to rule out a 15% OPC (safety) margin (upper bound) using two-sided tests. The trial will be considered successful if the two-sided 95% credible lower bound of the efficacy rate exceeds the 46% OPC and the two-sided 95% credible upper bound of the safety rate is below the 15% OPC. The use of two-sided testing is consistent with the PIPELINE PMA and FDA guidance.
Follow-Up Schedule	All enrolled and treated subjects had follow up scheduled at 30 day (± 7 days), 180 days (± 30 days), and 12 months (+ 60 days, -30 days).
Interim Analyses	No interim analysis are planned.
Final Analyses	This SAP covers analyses planned for the FRED trial, designed to investigate the safety and efficacy of the FRED during the course of treatment and through 12 months following treatment. All analyses identified in this SAP relate to subject data up to and including the 12-month follow-up visit. Any post-hoc, or unplanned, analyses not identified in this SAP will be clearly identified in the CSR.

2 PROSPECTIVE STUDY OVERVIEW

FRED is a single-arm pivotal study in the treatment of intracranial aneurysms in which subjects will be implanted with FRED. Current common therapies, such as surgical or endovascular approaches, are not able to treat intracranial aneurysms with wide necks effectively. Currently in the US, there is one flow diverter, the Pipeline Embolization Device (PED), approved by FDA and there are currently three CE Mark approvals for Pipeline, SILK and the NeuroEndoGraft.

Subjects enrolled into the study and treated with FRED shall be followed at discharge and 30 days, 180 days and 12 months. A subject considered enrolled but not treated because of a failed FRED deployment because of issues related to the procedure shall be closely monitored for one (1) week. If the device entered the blood stream and the subject has an Adverse Event, that subject will have the 30-day, 180 days and 12-month clinical follow-ups. If the FRED Device enters the blood stream and cannot be deployed secondary to technical issues with the device itself (e.g., FRED Device malfunction or failure to access the target site due to the FRED Device), the Subject will be counted as enrolled with intent-to-treat. This will be considered as a secondary endpoint failure. The Subject will be maintained within the study and will not be replaced by another Subject. If the FRED device never entered the subject's bloodstream that subject will be excluded from all the analysis populations. No additional analysis is planned for data collected beyond 12 months study follow up period.

This study incorporates the use of an independent blinded Clinical Events Committee (CEC) which reviewed and adjudicated all the primary and secondary safety outcome measures of the study, as well as all the adverse events and technical events reported in the study. In addition, independent blinded Data Safety and Monitoring Board which provided study safety and efficacy oversight reviewed all the site-reported and CEC adjudicated clinical data of the FRED study, and an independent angiographic core laboratory determined aneurysm occlusion and the degree of device stenosis reported by the investigational sites.

2.1 STUDY ASSESSMENTS

All subjects enrolled into the study and treated with the FRED shall be followed as stated in the study protocol, at discharge and 30 days (± 7 days), 180 days (± 30 days), and 12 months (+60 days, -30 days):

1. Discharge interval shall include a clinical and neurological evaluation
2. 30-day follow-up shall include a clinical and neurological evaluation
3. 6-month follow-up shall include a clinical, neurological and angiographic evaluation
4. 12-month follow-up shall include a clinical, neurological and angiographic evaluation

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 STUDY OBJECTIVE

The objective of this study is to evaluate the safety and effectiveness of the MicroVention FRED System when used in the treatment of wide-necked intracranial aneurysms.

3.2 PRIMARY ENDPOINTS

Primary Safety Endpoint:
The primary safety endpoint is the proportion of subjects who experience one or more of the following:

a. death or major stroke within 30 days post procedure
b. neurological death or major ipsilateral stroke within 12 months post procedure

- *A major stroke is defined as a new neurological event that persists for > 24 hours and results in a ≥ 4-point increase in the NIHSS score compared to baseline or compared to any subsequent lower score.*
- *A major ipsilateral stroke is defined as that occurring within the vascular distribution of the stented artery*
- *Neurologic death is defined as a death which has been adjudicated by the independent clinical events committee to have directly resulted from a neurologic cause*

Primary Effectiveness Endpoint:
Proportion of subjects with complete occlusion of the target aneurysm utilizing the Raymond Scale and ≤ 50% stenosis of the parent artery at the target IA at 12 months as assessed by angiography and in whom an alternative treatment of the target IA had not been performed within 12 months post-FRED placement; where an alternative treatment is defined as re-treatment of the target aneurysm with an alternative treatment modality including open repair, endovascular placement of an additional stent or treatment of In-stent Stenosis observed at the 180 day or 12 month follow-up time-points or at an unscheduled study follow up visit.

3.3 STUDY SUCCESS

Study success is defined as establishing the one-sided 95% credible bounds (primary) for both the safety and efficacy endpoints according to the respective OPCs.

3.4 SECONDARY ENDPOINTS

Secondary endpoints described in the protocol are listed below:

1. Proportion of subjects with clinically acceptable (90-100%) occlusion of the target aneurysm, ≤ 50% stenosis of the parent artery at the target IA at 12 months (+ 60 days, -30 days). as assessed by angiography, and in whom an unplanned alternative treatment of the target IA had not been performed within 12 months

2. Proportion of subjects in whom an unplanned alternative treatment of the target IA had not been performed within 12 months
3. Proportions of subjects with clinically acceptable aneurysm occlusion (90 %-100 %) of the target aneurysm at 12 months (+ 60 days, -30 days).
4. Incidence of ≥ 50% In-Stent Stenosis (ISS) at the target IA at 12 months as assessed by angiography at an independent corelab
5. Proportion of subjects with complete occlusion of the target aneurysm on 12-month angiography (+ 60 days, -30 days).
6. Incidence of FRED System procedure related Serious Adverse Events
7. Incidence of FRED System device-related Serious Adverse Events;
8. Incidence of unsuccessful delivery of the FRED system implant;
9. Incidence of unsuccessful deployment of the FRED flow-diverter intra-cranial stent
10. Incidence of migration of the FRED system implant at 12 months;
11. Unplanned alternative treatment on the target IA within 12 months, defined as re-treatment of the target aneurysm with an alternative treatment modality including open repair, endovascular placement of an additional stent or treatment of In-stent Stenosis observed at the 180 day or 12 month follow-up time-points or at an unscheduled study follow up visit.
12. Change in clinical and functional outcomes at 180 days and 1 year follow up, as measured by an increase in the modified Rankin Scale compared to baseline;
13. Incidence of major stroke, as measured by NIHSS at 12 months (and ophthalmic examination related to the target aneurysm if determined appropriate.
14. Incidence of minor stroke, as measured by NIHSS at 12 months (and ophthalmic examination related to the target aneurysm if determined appropriate.

4 PLANNED ANALYSES

4.1 ANALYSES AND REPORTING

Study analyses for primary efficacy and safety endpoints will be conducted using Bayesian methods, consistent with other medical device submissions to CDRH to allow the computation of credible limits for assessment of the statistical hypotheses. This decision was made in advance of any data assessments for either efficacy or safety. Other outcomes, including secondary endpoints for which formal hypothesis testing is not prespecified, will be presented descriptively with Bayesian credible intervals to correspond to the primary or supportive analyses.

All analyses identified in this SAP relate to primary, secondary, and exploratory endpoints focused at time points, 30 days, 180 days, and up to and including 12 months. Key statistics and study results will be made available to the Project Team following database lock and prior to completion of the final CSR. Any post-hoc, exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported in

appendices to the CSR. Any results from these unplanned analyses will also be clearly identified as post hoc in the text of the CSR.

Safety data will be reviewed and adjudication of all adverse events reported in the study will be performed by an independent blinded Clinical Events Committee (CEC); the CEC will also review all protocol deviations. Safety will be based on the CEC findings. In addition, a Data Safety and Monitoring Board (DSMB) will review all site-reported and CEC-adjudicated clinical data. These safety reviews will be conducted only for the benefit of members of the DSMB in accordance with the DSMB charter. Because these interim safety reviews will not include inference procedures (confidence intervals or hypothesis tests), and because these safety analyses reviews will not be shared outside the DSMB, no alpha spending adjustments are required for the final analyses.

4.2 INTERIM ANALYSES

No interim analyses are planned.

4.3 FINAL ANALYSES

Final statistical analyses will be performed as detailed below.

Two OPC sets will be considered in support of efficacy and safety as per the original protocol as well as more restrictive OPCs as follows:

- Primary: Original PG specified in the protocol (45% for efficacy and 25% for safety)
- Supportive: Updated PG presented to FDA at the Feb 2017 meeting (46% for efficacy and 15% for Safety).

Primary Analyses: The powers will be 80% to rule out a 45% OPC (efficacy) margin (lower bound) and 80% to rule out a 25% OPC (safety) margin (upper bound) using one-sided tests. The trial will be considered successful if the one-sided 95% credible lower bound of the efficacy rate exceeds the 45% OPC and the one-sided 95% credible upper bound of the safety rate is below the 25% OPC. The use of one-sided testing is consistent with the original protocol.

Supportive Analyses: The powers will be 90% to rule out a 46% OPC (efficacy) margin (lower bound) and 90% to rule out a 15% OPC (safety) margin (upper bound) using two-sided tests. The trial will be considered successful if the two-sided 95% credible lower bound of the efficacy rate exceeds the 46% OPC and the two-sided 95% credible upper bound of the safety rate is below the 15% OPC. The use of two-sided testing is consistent with the PIPELINE PMA and FDA guidance.

Study success is defined as achieving statistical significance for the primary OPCs.

Thus, both one-sided and two-sided credible intervals will be computed for the primary (one-sided) and supportive (two-sided) analyses. However, since the success standards are higher for both safety and efficacy for the supportive analyses than for the primary analyses, credible interval claims in support of labeling will be sought based on the more restrictive supportive analyses which are nested within the alternative hypotheses.

5 ANALYSIS POPULATIONS

The statistical analysis will use three populations:

1) The Intent to Treat (ITT) population will consist of all enrolled subjects who had an introduction of the FRED Implant System into the bloodstream. The ITT population will be used for all effectiveness analyses to test the efficacy hypothesis for both OPC sets.

2) The Safety Population will consist of all subjects in whom the investigational device was implanted as well as deaths due to technical failures during the index procedure. The Safety Population will be used to test the safety hypothesis for both OPC sets.

3) The Per Protocol Population will consist of all subjects in the ITT Population for whom there were no major protocol deviations. All protocol deviations will be assessed by the Clinical Events Committee.

The primary and secondary effectiveness endpoints will also be evaluated for the Per Protocol Population.

6 GENERAL CONSIDERATIONS

6.1 BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to or on the study start date/time.

6.2 CRITERIA FOR SUCCESS FOR PRIMARY ENDPOINT ANALYSES

Primary efficacy and safety will be assessed by employing a Bayesian approach. Bayesian statistics are a principled approach for learning from evidence as it accumulates (FDA 2010, FDA guidance for industry and FDA staff guidance for the use of Bayesian statistics in medical device clinical trials, FDA CDRH CBER, February 5, 2010).

For the primary endpoints, the criterion for success is based on the posterior probability of the alternative hypothesis. The FRED device will be declared efficacious if the one-sided 95% lower

credible limit is at least 45%. The performance goal was obtained from a formal comprehensive literature review and meta-analysis of results from studies of flow diverters to treat patients matched to the FRED study subjects during the first year after treatment. Similarly, the FRED will be declared safe if the one-sided 95% upper credible limit is at most 25%. The performance goal used in the P100018 SSED of the Pipeline PUFS study was 20%.

However, the definition used in the PUFS study did not include all death and major stroke within 30 days, only death of neurologic cause and major ipsilateral strokes, and it was only evaluated through 180 days, not 12 months. For this reason, the performance goal utilized here is slightly higher. The primary safety endpoint in this study has not been used or reported as such previously, so the magnitude of the effect of this change is unknown. For the purposes of the current study a conservative 5% adjustment is used, resulting in a 25% performance goal (20% from above + 5% conservative adjustment).

6.3 ANALYSIS SOFTWARE

Statistical analyses will be performed using SAS version 9.3 or above (SAS Institute, Cary, NC, USA), R version 3.2 or above (R Foundation for Statistical Computing, Vienna, Austria) or other widely accepted statistical software. For Bayesian analyses of the primary endpoints, posterior estimates of modeled parameters will be reported along with the relevant one-sided and two-sided 95% credible intervals.

Descriptive statistics for continuous variables will include the mean, standard deviation, median, quartiles, and sample size for each treatment group. Categorical variables will be summarized using frequency distributions including counts and percentages. Proportions will be calculated using known non-missing values.

6.4 DISPOSITION OF SUBJECTS AND WITHDRAWALS

All subjects who provide written informed consent will be accounted for. The frequency and percentage of subjects who complete each scheduled assessment will be summarized in a tabular format including details on study exits with reason for exit.

6.5 PROTOCOL DEVIATIONS

Major protocol deviations will be summarized. This summary will include the number and percent of subjects with each major deviation type. A major protocol deviation is defined as a subject enrolled and treated, but who subsequently does not meet inclusion criteria or does meet exclusion criteria or have other deviations determined to impact the primary efficacy or safety endpoints analyses for this trial. Additionally, all protocol deviations, major and minor, will be

summarized. This summary will include the number and percent of subjects with each protocol deviation) and reason within each time interval.

6.6 MISSING DATA IMPUTATIONS

No safety data will be imputed whereas efficacy data may be imputed based on subject-specific situations. Regarding efficacy, for any subjects missing 12-month clinical, neurological and angiographic evaluations, the most likely 12-month efficacy outcomes at the subject-level will be imputed. For this purpose, all available 12-month data will be included. Additionally, for subjects not reporting 12-month occlusion data, results may be imputed from 6-month occlusion data along with available pre-treatment data. Safety data will not be imputed; 12-month contact will be sought to confirm stroke and survival status to confirm safety success. Subjects with no follow-up data will not be imputed for analysis of the primary effectiveness endpoint but alternative source-document verified data will be considered in judging 12-month efficacy.

In the event such imputations for the subjects with missing 12-month data cannot be made, then the other subjects with completed 6-month and 12-month safety and efficacy outcomes will be used to compute the respective probabilities of 12-month efficacy outcomes conditional on 6 month outcomes for the respective ITT, Safety, and PP populations.

6.7 MULTIPLE COMPARISONS AND MULTIPLICITY

The study requires both the primary safety and primary efficacy endpoints be met to declare study success, and therefore no multiplicity adjustment is required for declaring study success.

Also, given that the success standards are higher for both safety and efficacy for the supportive analyses than for the primary analyses, as long as statistical significance is achieved for the primary analyses, there is no statistical penalty required to make conclusions based on the more restrictive supportive analyses which are nested within the alternative hypotheses being tested.

7 ENDPOINT ANALYSES

7.1 PRIMARY EFFICACY VARIABLE

The primary efficacy endpoint is the percent of subjects in the ITT population with complete occlusion (defined as Raymond class I) without clinically significant stenosis (defined as ≥50% stenosis) of the parent artery at the target IA based on core lab evaluations at the 12-month follow-up angiography and in whom an alternative treatment of the target IA had not been performed post-FRED placement. An alternative treatment is defined as re-treatment of the target aneurysm with an alternative treatment modality including open repair, endovascular

placement of an additional stent or treatment of In-stent Stenosis observed at the 180-day or 12 month follow-up time-points or at an unscheduled study follow up visit.

The primary efficacy hypotheses are:

$$H_{\mathrm{E0}}: \pi_E \leq 0.45$$

$$H_{\mathrm{E1}}: \pi_E > 0.45$$

The null hypothesis (H_{E0}) for this endpoint states that the true proportion of subjects treated with the FRED Device who achieve complete occlusion (Raymond class I) without clinically significant (≥ 50%) stenosis of the parent artery 12 months post-treatment and without any subsequent alternative treatment is no higher than 45%. The alternative hypothesis the FRED trial aims to demonstrate is that the true proportion of subjects who achieve effectiveness success at 12 months is greater than 45%.

Using the prior

$$\pi_E \sim Beta(1,1)$$

the posterior distribution for the primary efficacy endpoint rate will be

$$\pi_E \mid E, n \sim Beta(1 + E, 1 + n - E)$$

where n is the number of evaluable subjects and E is the number of subjects who meet the efficacy endpoint. The point estimate of the posterior distribution of the primary efficacy endpoint will be presented with its lower 95% credible bound, as well as the posterior probability of the alternative hypothesis H_{E1}. If the posterior probability exceeds 0.95, the primary efficacy endpoint will have been met.

7.2 PRIMARY SAFETY ENDPOINT

The study's primary safety endpoint is the proportion of subjects in the Safety Population who experience either major stroke or death within 30 days, or major ipsilateral stroke or neurological death 31 days through 12 months post procedure. CEC-adjudicated data will be used for this analysis.

The primary safety hypotheses are:

$$H_{\mathrm{S0}}: \pi_S \geq 0.25$$

$$H_{\mathrm{S1}}: \pi_S < 0.25$$

The null hypothesis (H_{S0}) for this endpoint states that the true proportion of subjects treated with the FRED Device who experience neurologic death or major ipsilateral stroke one-year post-treatment is equal to or higher than 25%. The alternative hypothesis the FRED trial aims to demonstrate is that the true proportion of subjects treated with the FRED Device who experience neurologic death or major ipsilateral stroke one-year post-treatment is actually lower than 25%.

Using the noninformative prior

$$\pi_S \sim Beta(1,1)$$

the posterior distribution for the primary safety endpoint event rate will be

$$\pi_s \mid S, n \sim Beta(1 + S, 1 + n - S)$$

where n is the number of evaluable subjects and S is the number of subjects who meet the safety endpoint. The point estimate of the posterior distribution of the primary safety endpoint will be presented with its lower 95% credible bound, as well as the posterior probability of the alternative hypothesis H_{S1}. If the posterior probability exceeds 0.95, the primary safety endpoint will have been met

The supportive analysis (second OPC set) will be conducted for both primary efficacy and primary safety using more restrictive performance goals identified from a revised set of literature analysis and presented to FDA on 16 February 2017. The format of this analysis will be a Bayesian design identical in form to the above except that the performance goals will be 0.46 for efficacy and 0.15 for safety. Details of the resulting analyses and associated power are as below, from which it can be seen that the study is sufficiently powered at the final enrolled and treated count of 140.

	Efficacy		Safety	
	Original	Revised	Original	Revised
Significance level, alpha	0.05	0.025	0.05	0.025
1 or 2-sided test	1	1	1	1
Null: OPC, p_0	0.45	0.46	0.25	0.15
Alternative: FRED, p_A	0.58	0.60	0.15	0.06
Power (%)	90	90	90	92
N	140	140	140	140

7.3 MISSING DATA ANALYSES

Subjects are expected to comply with the follow-up schedule. Efforts to prevent missing data include, but are not limited to, a reminder for the scheduled 30-day, 180 days and 12-month follow-up, obtaining additional phone numbers or contact information for all subjects at the time of the procedure along with requesting permission to contact the subject's family members or care-givers, and collecting only necessary data to reduce the burden to subjects and investigators. In-depth site training and regular monitoring will also help to minimize missing data, and collaborating with the Investigators to ensure the subjects are committed to complying with all scheduled follow-up visits.

Subject compliance with required follow up will be tabulated and reported as proportions. Subjects who withdraw from the study will be tabulated with the reasons for the withdrawal.

For subjects not reporting 12-month occlusion data, the 180-day efficacy outcomes will be used to impute 12-month efficacy results. A conditional analysis will be performed to determine the probability of 12-month efficacy (success, failure) based on 180-day efficacy (success, failure).

Tipping point analyses will be performed to include data on subjects without the primary safety or efficacy endpoints (missing data or subjects lost to follow-up).

7.4 CENTER HETEROGENEITY

To assess consistency of treatment effect size across study centers, any study center with less than 5 subjects will be pooled with other such study centers prior to carrying out this assessment.

A number of measures have been taken to assure center heterogeneity:

- the study sites were monitored for protocol compliance,
- the same data gathering instrument and method were used in every site.
- investigators are selected for their experience and ability in performing interventional neurovascular procedures
- investigational sites are required to follow the same detailed protocol with explicit inclusion and exclusion criteria
- the primary safety and efficacy endpoints of this study are objective events determined by a central CEC and independent angiographic core laboratory.

An analysis of comparability across study sites will be carried out to determine the similarity of study sites with respect to important demographic and other variables, either known or suspected to have an influence on the outcome variables.

Individual data, for individual k will be assumed to follow a Bernoulli distribution:

$$Y[k] \sim dbern(p[center[k]])$$

where center is an index variable that indicates the center that the individual k was recruited in. Statistical testing will be performed using Pearson's chi-square test.

7.5 SUBGROUP ANALYSIS

Subgroups for secondary analysis of primary endpoints (safety and efficacy) include:

- Location (anterior, posterior)
- Age (<60, 60-69, ≥70)
- Gender: results will be stratified by gender
- Anatomic location (zone 1, 2 and 3)
- Vascular risk factor: Hypertension (Yes, No)
- Vascular risk factor: Hyperlipidemia (Yes, No)
- Vascular risk factor: Tobacco Use (Yes, No)

The success percents for primary endpoints will be presented descriptively within each subgroup and global tests of significance on the endpoints will be performed to check the heterogeneity of differences in the primary endpoint success percents for safety and efficacy across all subgroups.

The purpose of this analysis is not to formally assess success within each subgroup, but simply to assess consistency of results across the various subgroups.

7.6 SECONDARY ENDPOINT VARIABLES

A Bayesian analysis will be employed in assessment of secondary endpoints.

For all dichotomous secondary endpoints, the model employed to summarize the rate (π) of secondary endpoint will be similar to the model employed for the analysis of the primary endpoints. More specifically, under the prior for the rate

$$\pi \sim Beta(1,1)$$

the posterior distribution for the secondary endpoint event rate will be

$$\pi \mid Y, n \sim Beta(1 + Y, 1 + n - Y)$$

where n is the number of evaluable subjects and Y is the number of subjects with events. The rate of the endpoint with a 95% credible interval will be reported; both one-tailed and two-tailed intervals will be computed to be consistent with the two OPC sets. In addition to the results based on the model, raw counts and proportions will be reported.

For all continuous secondary endpoints, the Bayesian model employed to summarize the mean outcome (μ) and standard deviance (σ) of secondary endpoint will use a conjugate analysis where the point and interval estimates are numerically the same as the sample mean and sample standard deviation. More specifically, the prior for the mean and variance will be

$$p(\mu, \sigma^2) \propto \sigma^{-2}$$

the posterior distribution for the secondary endpoint mean (μ) and variance (σ^2) will be

$$\mu \mid Y_1, Y_2, \ldots, Y_n, \sigma^2, n \sim Normal\left(\bar{Y}_n, \frac{\sigma^2}{n}\right)$$

$$\frac{(n-1)S^2}{\sigma^2} \mid Y_1, Y_2, \ldots, Y_n, n \sim \chi^2(n-1)$$

where n is the number of evaluable subjects and $Y_1, Y_2, \ldots, Y_n$ are the data collected on the n subjects and S^2 is the sample variance. The mean and standard deviation rate of the posterior distribution of the mean and variance of the secondary endpoint with an equitailed 95% credible interval will be reported.

7.6.1 PROTOCOL DEFINED SECONDARY ENDPOINT VARIABLES

Secondary endpoints as defined in Section 4.4 will be summarized and reported. No formal hypothesis testing for success is planned for these endpoints.

7.7 MEDICAL HISTORY

Medical history will be summarized. For each condition, the number and percent of subjects with the condition will be presented. In addition, previous aneurysm treatments and current status of aneurysm will be summarized.

7.8 LABS

Laboratory values obtained at baseline will be summarized. The number of subjects who completed each lab and the number and percent of subjects with clinically abnormal values for each lab will be summarized. This summary will be purely descriptive in nature. A listing of subject lab values will be compiled and included in an appendix to the CSR.

7.9 PROCEDURE

FRED device utilization will be presented, including number of devices and percent of subjects within each category. Other procedural information including procedural technique and medications (anti-coagulants and anti-platelets) utilized intra-procedurally will be similarly summarized.

8 ADVERSE EVENTS

Adverse events will be adjudicated by the CEC in accordance with the CEC Manual of Procedures (MOP) presented accordingly. The results of CEC adjudication will serve as the basis for the summary tabulations of all adverse events in this trial. Analyses and displays will be based on CEC findings.

8.1 ALL ADVERSE EVENTS

Summaries of incidence rates, seriousness and relationship to the investigational device of individual AEs and SAEs will be presented. Because a subject may experience more than one AE, summaries will provide both the number of subjects and the number of events. Percentages provided will be the percent of subjects experiencing one or more adverse events.

AE summaries will be conducted using the CEC adjudicated assessments. AE summaries will be presented for serious and non-serious adverse device effects, serious and non-serious adverse events to be categorized into neurologic vs non-neurologic.

Additionally, separate CEC and site listings will be generated to include the subject number, AE number, days since FRED Device implant, whether or not the AE is classified as an SAE, and the relationship of the AE to the investigational device or procedure as determined by the CEC.

8.2 SERIOUS ADVERSE EVENTS

Summaries of incidence rates and relationship to the investigational device of individual SAEs will be included in the CSR. Summaries will provide both the number of subjects and the number of events. Percentages provided will be the percent of subjects experiencing one or more serious adverse events. SAE summaries will be conducted using the CEC adjudicated assessments. A data listing of SAEs will also be provided, displaying details of the event(s) captured in the database.

8.3 DEATHS

For any deaths occurring during the course of the FRED study, a full narrative will be provided and relevant information will be supplied. All deaths will be summarized separately including cause, device, and procedure relatedness per CEC determination.

9 OTHER PLANNED ANALYSES

9.1 CONCOMITANT MEDICATIONS

Medications are to be reported in the concomitant medications log. A listing of all medications used will be created and included as an appendix to the CSR. Anti-coagulants, and anti-platelet medication usage will be tabulated.

9.2 DEVICE OBSERVATIONS

A description of any device observations will be provided in the CSR. The summary will include the number of observations and the percentage. Additionally, all device observations will be provided in a listing for further detail.

9.3 ADDITIONAL INTERVENTIONS AND REINTERVENTIONS

A summary of retreatment the target aneurysm through 12-month follow up will be prepared. In addition, a Kaplan-Meier curve showing the time to retreatment will be included in the CSR. Retreatment will be timed as soon as a subject undergoes an additional (at time of initial intervention) or subsequent intervention of the treated aneurysm.

9.4 STATISTICAL ANALYSIS PLAN REVISIONS

The SAP will be approved prior to analysis of outcomes from the database. The final report may contain additional tables, footnotes or statistical tests if warranted by the data obtained. These analyses will be clearly described as post hoc analyses.