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

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PIVOTAL STUDY OF THE MICROVENTION FLOW RE-DIRECTION ENDOLUMINAL DEVICE STENT SYSTEM IN THE TREATMENT OF INTRACRANIAL ANEURYSMS

CLINICAL PROTOCOL NUMBER CL12001
REVISION 4.0, NOVEMBER 14, 2016

STUDY SPONSOR: MicroVention, Inc.

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SITE INVESTIGATOR
PROTOCOL AGREEMENT REV. 4 (NOVEMBER 14, 2016)

I have read this protocol and agree to adhere to the requirements of this protocol and conduct the study in compliance with Good Clinical Practices. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the investigational plan and the conduct of the study according to 21 CFR parts 50,54,56 and 812, ICH Good Clinical Practices Guidelines (E6) and Institutional Review Board (IRB) requirements. I will maintain a Delegation of Responsibility form defining the roles and duties I have delegated to include all study personnel involved in this study at my institution.

Clinical Site:

_____
Site Name

Site Investigator Signature:

_____ _____
Signature Date

_____
Print Name

CL120111, Revision 4.0 SUMMARY OF PROTOCOL CHANGES

CLINICAL PROTOCOL NUMBER CL12001, REVISION 4.0, EFFECTIVE DATE NOVEMBER 14, 2016	
Section	**Revision**
Study Overview	Changed address for PI who has relocated to another hospital Change of Sponsor Contacts (Clinical Study Management)
Section 4.0 Study Management Contacts	Changed address for PI who has relocated to another hospital
Section 5.0 Study Design:	Section 5.8 Inclusion Criteria Revised the inclusion criteria as follows: • Subject for whom existing endovascular options (coiling, stent-assisted coiling) would be ineffective because the aneurysm is predisposed to recurrence to having any of the following characteristics: a) Aneurysm has a maximum fundus diameter less than 10mm but ≥2mm. b) Aneurysm has any of the following morphologies: i. no discernible neck. ii. segmental parent artery dysplasia. iii. Aneurysm neck involving > 180degrees of parent artery circumference. iv. Complex lobulations limiting stent/coiling as a treatment option v. Neck > 4mm or dome/neck ratio ≤2. **OR** • Subject has a fusiform aneurysm of any size requiring treatment. **OR** • Subject is a poor candidate for open surgical treatment because of prior surgical procedures, comorbidities or location limiting conventional surgical options Follow Up Corrected the 30-day follow-up window to be consistent with all other references to 30-day follow-up in the protocol.

STUDY OVERVIEW

Study Device	MicroVention Flow Re-Direction Endoluminal Device (FRED®).
Study Title	Pivotal Study of the MicroVention Flow Re-Direction Endoluminal Device Stent System in the Treatment of Intracranial Aneurysms
Study Design	Prospective, multi-center, single arm study with follow-up at discharge, 30 days (± 7 days), 180 days (± 30 days), and 12 months (+ 60 days, -30 days).
Study Objective	To evaluate the safety and effectiveness of the MicroVention FRED System when used in the treatment of wide-necked intracranial aneurysms.
Target Treatment Indications	The FRED system is indicated for the endovascular treatment of adults (22 years of age or older) 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.
Enrollment	195 subjects at a maximum of 30 sites located in the United States and Japan
Study Hypothesis	The safety and effectiveness of the FRED meets similar performance goal as that which was identified from a comprehensive analysis of the peer-reviewed published literature reporting the safety and efficacy of endovascular treatment of intracranial aneurysms with flow-diverter devices.
Primary Endpoint	**Primary Safety Endpoint:** The primary safety endpoint is the proportion of subjects who experience one or more of the following: • death or major stroke within 30 days post procedure • 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:** • Proportion of subjects with complete occlusion (100%) 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 alternative treatment of the target IA had not been performed within 12 months. ➢ *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.*
Secondary Endpoints	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. Proportion of subjects with ≤ 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 successful delivery of the FRED System implant; 9. Incidence of successful deployment of the FRED flow-diverter Intra-cranial stent 10. Incidence of migration of the FRED System implant at 12 months; 11. Incidence of 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 or worsening of neurologic signs/symptoms, as measured by NIHSS at 12-months (and ophthalmic examination related to the target aneurysm if determined appropriate).
Sponsor & Study Device Manufacturer	MicroVention, Inc. 1311 Valencia Ave. Tustin, CA 92780 USA
Primary Investigator	Cameron McDougall, MD Swedish Neuroscience Institute 550 17th Ave. Suite 110 Seattle, WA 98122
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SUMMARY OF EVENTS (SoE)

	Pre-Procedure	Procedure	Post-Procedure	Discharge	30 days ± 7days	6 months ±30days	12 months + 60 days, -30 days
Medical History	X						
Physical Examination	X			X	X	X	X
Informed Consent[1]	X[1]						
Neurological Examination (including NIHSS and mRS)	X			X	X	X	X
Concomitant Medications	X			X	X	X	X
Laboratory Assessment[2]	X[2]						
Pregnancy Test	X[5]	X[5]				X[5]	X[5]
Intracranial Stent Procedure		X					
Procedural Medications		X	X				
Angiogram	X	X	X			X	X
Ophthalmic Exam at Baseline (only if applicable at F/U)[4]	X				X[4]	X[4]	X[4]
Clinical Eye Exam	X				X	X	X
Adverse Event		X	X	X	X	X	X
Serious Adverse Event[3]		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Unanticipated Adverse Event[3]		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Protocol Deviation	X	X	X	X	X	X	X
Death, or device related Adverse Event[3]		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Subject Disposition		X	X	X	X	X	X

[1] Informed consent must be signed before Subject is enrolled in the study. In case of an emergency, Protocol direction for obtaining a consent form should be followed.
[2] Preferably: CBC with differential, Blood Chemistry, PT/PTT, and blood sugar evaluation within 7 days from procedure; must conduct a pregnancy test (urine or serum) for women of childbearing age at time of enrollment and within 48 hours prior to procedure if >48 hours has elapsed since last pregnancy test.
[3] A Serious Adverse Event (e.g., death), protocol deviation, Unanticipated Adverse Device Effect or device related Adverse Event shall be reported to the Sponsor as soon as possible (i.e. within 24 hours) and no more than 10 working days from the date of becoming aware of the event or effect.
[4] Ophthalmic Exam is required within 30 days of procedure, a historical exam may be used. The ophthalmic exam is only required for follow up visits if there is an irregular baseline result or if concluded medically necessary due to changes in vision.
[5] Pregnancy testing may be completed through blood serum or urine testing. Pregnancy test shall be completed in accordance with standard practices at the institution prior to imaging. Pregnancy test will not be required if there is proof of hysterectomy or sterilization in the patient's medical record.

1.0 Study Title

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

2.0 Background

Intracranial Aneurysms (IAs) are common cerebrovascular abnormalities. The incidence of IAs has been reported to be 0.8% to 10% in the normal population. There are two distinct treatment strategies for the treatment of intracranial aneurysms. The first is the direct surgical exposure by a craniotomy followed by the placement of a surgical clip across the neck. This procedure secures the aneurysm as the clip opposes normal segments of the arterial wall and isolates the orifice of the aneurysm sac from the parent artery.[1-7] The second approach is an endovascular, intra-saccular approach. With this technique, a microcatheter is introduced via a transfemoral approach and manipulated into the cerebral aneurysm under fluoroscopic guidance. Following catheterization of the aneurysm, multiple detachable coils are placed within the aneurysm fundus, inducing aneurysm thrombosis and again isolating the aneurysm fundus from the parent artery circulation. Both treatment options are performed with the intention of preserving normal blood flow within the parent vessel harboring the intracranial aneurysm while completely occluding flow into the aneurysm itself. In a large study of ruptured aneurysms, endovascular therapy (EVT) was found to be superior to surgical clipping in achieving good patient outcomes.[6] At some centers, EVT is applied for the treatment of both ruptured and unruptured cerebral aneurysms when possible, with surgery reserved for lesions which are not amenable to EVT.

Wide-neck aneurysms are often the most anatomically challenging lesions to treat by either a surgical or an endovascular approach.[7, 8, 9,10,11] It is estimated that more than 25% of these intracranial aneurysms satisfy anatomical criteria for a "wide-neck. With a surgical approach, single or multiple aneurysm clips are sometimes required to reconstruct the parent vessel - aneurysm neck interface. With an endovascular approach, detachable coils placed within the aneurysm sac may protrude into the parent vessel and compromise normal blood flow. Thus, this anatomical configuration makes it difficult to achieve a thorough packing of the aneurysm with coils. As such, the rates of complete angiographic occlusion for these wide-neck aneurysms are often very low when standard microcatheter techniques are employed.[6]

For these reasons, a number of adjunctive techniques have been developed to facilitate the endovascular coiling of wide-neck aneurysms. In some cases, a temporary balloon assist technique is effective. While the balloon assist option[2, 12] is considered by some to be more technically demanding than unassisted coiling, it frequently allows the endovascular treatment of aneurysms which are not otherwise amenable to standard endovascular techniques using a microcatheter alone.[4] In some cases, if the aneurysm neck is too wide or the segment of vessel involved by the aneurysm is too long, a temporary balloon assist technique is insufficient to achieve aneurysm treatment. In these cases, intravascular stents may be implanted to provide a more durable support for endovascular coiling. With this "stent-assisted" technique, the neurovascular stent is placed across the aneurysm neck, to act as a bridge to prevent coils from protruding into the parent artery. Adjunctive use of stents may allow the operator to more safely achieve a higher packing density of coils. These more thoroughly packed aneurysms are likely better protected against future re-canalization and rupture. In addition, these devices also may produce an anatomical and physiological "remodeling" of the parent artery giving rise to the aneurysm. These effects may improve the rates of complete aneurysm occlusion and enhance the durability of the coiling treatment. [1 - 5, 48-50]

Alternatively, the sole use of flow diverting stents for the treatment of wide-necked aneurysms has been in practice since 2006. [13, 14] Flow diverting stents are designed with low porosity and high flexibility, resulting in a technology designed to preserve intraluminal blood flow through the parent artery and adjacent perforating vessels while occluding/redirecting blood flow away from the aneurysm, thus allowing thrombosis to occur in the aneurysm. [15, 16, 48-49]

Currently in the US, there is primarily one flow diverter commercially available, the Pipeline Embolization Device (PED) manufactured by Covidien, Irvine, CA (P100018 approved by FDA on April 6, 2011). There are currently three flow diversion devices available with CE Mark approval: the Pipeline (Covidien, United States), the SILK (Balt Extrusion, France), and the NeuroEndoGraft (Surpass Medical, Israel). It is estimated that over 6000 patients have been treated worldwide with a flow diversion device since 2007. The SILK device was the first flow diverter approved (CE Mark approval) in 2007(Houdart E, WFITN 2011).

The FRED System design is similar to other approved devices with the same or similar indications. The FRED System's inner stent is similar in design to the SILK and Pipeline devices which use 48 braided wires in a similar pore density to provide flow diversion characteristics, with the SILK and FRED comprised of nitinol. There have been cases reported of coil-assist stents being used successfully in conjunction with flow diverter stents in a layered fashion to treat aneurysms. This technique, placing a flow diverter device within a porous coil-assist stent, is mimicked in the dual layer design of the FRED System. The FRED System's outer stent is similar in design and materials to coil assist stent systems actually on the market, such as the Neuroform™, Boston Scientific, Fremont, CA; and Enterprise™ Vascular Reconstruction Device, Codman Neurovascular, Warren, NJ.

Although relatively rare, there have been incidences of hemorrhagic events described in the literature with current flow diverters. This phenomenon is not yet fully understood, however, the majority of the literature suggests that anticoagulation/ therapy may play a primary role.

Based upon the similarity in design and materials with currently approved devices with the same indication for use, the extensive clinical experience of flow diversion devices with good success, the similarity in design to MicroVention's current LVIS® Device, the contraindications applied, and the demonstrated pre-clinical safety and performance results established, the risks associated with the use of the devices are acceptable when weighed against the benefits of the Subject..

3.0 Study Device

3.1 Device Name:

Flow Re-Direction Endoluminal Device (FRED)

3.2 Device Description

The FRED System consists of a self-expanding nickel titanium (nitinol) stent (implant) and a delivery pusher. The self-expanding implant is designed to expand to a pre-determined diameter when released from the delivery pusher. The implant is produced with outer diameters of 2.5mm to 5.5mm and in various lengths.

The nitinol implant consists of two concentric tubular woven meshes. Two radiopaque wires are woven along the outer implant in a helix configuration. There are four radiopaque markers at each end of the stent. Upon exiting the microcatheter at the target lesion, the implant expands to the vessel lumen diameter.

The delivery system is composed of an introducer and a delivery pusher. The introducer consists of a polymer tube with a tapered distal end. The introducer tube is used to protect the stent and helps facilitate stent introduction into the microcatheter hub. The delivery pusher is composed of a tapered nitinol mandrel. The distal end of the pusher has three radiopaque markers. A stainless steel outer coil is wound on the outside of the tapered portion of the nitinol mandrel. The delivery pusher is designed to secure the implant by mechanical means and release the implant at the lesion.

Table 1 below provides the FRED System models and dimensions. The implant and delivery system are depicted in **Figures 1 and 2** below.

Table 1 FRED System Models and Dimensions

FRED System Models (original series)			
MODEL NUMBER	Outer stent diameter, unconstrained (mm)	Stent total length (outer stent) constrained @ max. diameter (mm)	Stent working length (inner stent) constrained @ max. diameter (mm)
FRED3507-US	3.5	13.0	7.0
FRED3509-US	3.5	15.0	9.0
FRED3511-US	3.5	17.0	11.0
FRED3513-US	3.5	19.0	13.0
FRED3516-US	3.5	22.0	16.0
FRED3524-US	3.5	31.0	24.0
FRED3536-US	3.5	40.0	36.0
FRED4007-US	4.0	13.0	7.0
FRED4009-US	4.0	15.0	9.0
FRED4012-US	4.0	18.0	12.0
FRED4014-US	4.0	20.0	14.0
FRED4017-US	4.0	23.0	17.0
FRED4026-US	4.0	32.0	26.0
FRED4038-US	4.0	44.0	38.0
FRED4508-US	4.5	15.0	8.0
FRED4511-US	4.5	17.0	11.0
FRED4513-US	4.5	20.0	13.0
FRED4518-US	4.5	25.0	18.0
FRED4524-US	4.5	31.0	24.0
FRED4528-US	4.5	34.0	28.0
FRED4539-US	4.5	46.0	39.0
FRED5009-US	5.0	15.0	9.0
FRED5011-US	5.0	18.0	11.0
FRED5014-US	5.0	21.0	14.0
FRED5019-US	5.0	26.0	19.0
FRED5026-US	5.0	32.0	26.0
FRED5029-US	5.0	36.0	29.0
FRED5514-US	5.5	22.0	14.0
FRED5519-US	5.5	28.0	19.0
FRED5526-US	5.5	32.0	26.0

FRED Line Extension (2.5mm & 3.0mm)			
MODEL NUMBER[1]	Outer stent diameter, unconstrained (mm)	Stent total length (outer stent) constrained @ max. diameter (mm)	Stent working length (inner stent) constrained @ max. diameter (mm)
FREDJR2508-US	2.5	13.0	8.0
FREDJR2509-US	2.5	14.0	9.0
FREDJR2510-US	2.5	15.0	10.0
FREDJR2511-US	2.5	16.0	11.0
FREDJR2512-US	2.5	17.0	12.0
FREDJR2513-US	2.5	18.0	13.0
FREDJR2514-US	2.5	19.0	14.0
FREDJR2515-US	2.5	20.0	15.0
FREDJR2516-US	2.5	21.0	16.0
FREDJR2517-US	2.5	22.0	17.0
FREDJR2518-US	2.5	23.0	18.0
FREDJR2519-US	2.5	24.0	19.0
FREDJR2520-US	2.5	25.0	20.0
FREDJR2521-US	2.5	26.0	21.0
FREDJR2522-US	2.5	27.0	22.0
FREDJR2523-US	2.5	28.0	23.0
FREDJR2524-US	2.5	28.0	24.0
FREDJR2525-US	2.5	29.0	25.0
FREDJR2526-US	2.5	30.0	26.0
FREDJR3009-US	3.0	13.0	9.0
FREDJR3010-US	3.0	14.0	10.0
FREDJR3011-US	3.0	15.0	11.0
FREDJR3012-US	3.0	16.0	12.0
FREDJR3013-US	3.0	17.0	13.0
FREDJR3014-US	3.0	19.0	14.0
FREDJR3015-US	3.0	20.0	15.0
FREDJR3016-US	3.0	22.0	16.0
FREDJR3017-US	3.0	22.0	17.0
FREDJR3018-US	3.0	23.0	18.0
FREDJR3019-US	3.0	24.0	19.0
FREDJR3020-US	3.0	25.0	20.0
FREDJR3021-US	3.0	27.0	21.0
FREDJR3022-US	3.0	28.0	22.0
FREDJR3023-US	3.0	30.0	23.0
FREDJR3024-US	3.0	30.0	24.0
FREDJR3025-US	3.0	31.0	25.0
FREDJR3026-US	3.0	31.0	26.0
FREDJR3027-US	3.0	32.0	27.0

[1] The 2.5mm & 3.0mm FRED devices will be referred to as the "FRED Jr." for user clarification and for referencing the use of a 0.021" microcatheter within the labeling.

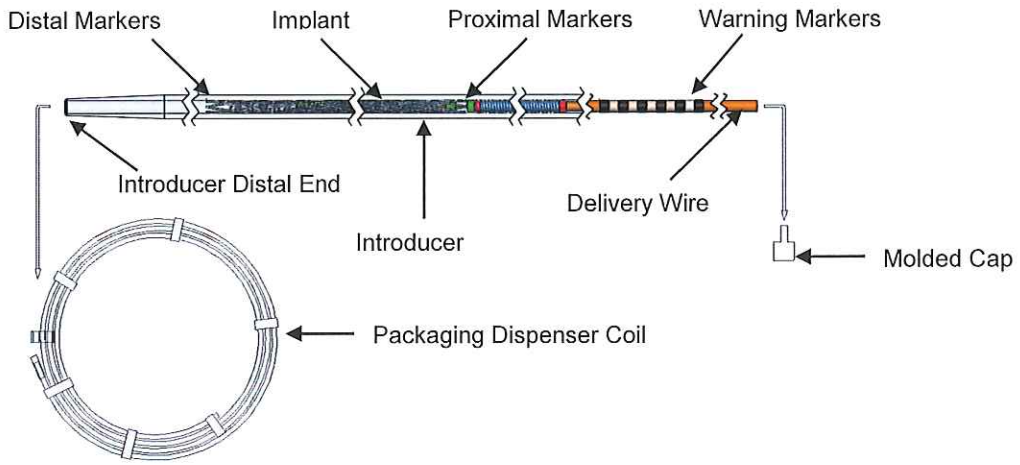

Figure 1: FRED Delivery System and Implant in Introducer

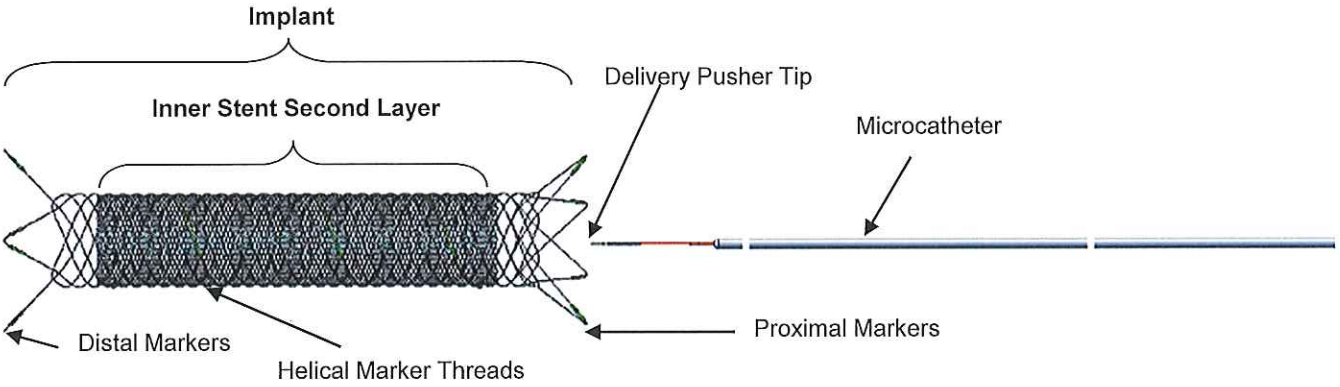

Figure 2: FRED System exited from microcatheter with implant fully expanded

3.3 Indications for Use

The FRED system is indicated for the endovascular treatment of adults (22 years of age or older) 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) of the petrous through communicating segments of the ICA, the proximal middle cerebral and anterior cerebral arteries, and the posterior circulation.

3.4 Contraindications

Use of the FRED System is contraindicated under these circumstances:

- Subjects in whom anticoagulant, antiplatelet therapy or thrombolytic drugs are contraindicated;
- Subjects with known hypersensitivity to metal, such as nickel-titanium and metal jewelry;
- Subjects in whom angiography demonstrates inappropriate anatomy that does not permit passage or proper deployment of the FRED System;
- Subjects with an active bacterial infection;

- Subjects with a pre-existing stent in place in the parent artery at the target aneurysm location.

4.0 Study Management and Contacts

4.1 Study Sponsor

MicroVention, Inc.
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Tustin, CA 92780. USA
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4.2 Study Contact

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4.3 Primary Investigator

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4.4 Image Core Laboratory

Steven Hetts, MD / Vivek Swarnakar, MD
185 Berry Street, Room 319
San Francisco, CA

5.0 Study Design

5.1 Study Objective

To evaluate the safety and effectiveness of the MicroVention FRED System when used in the treatment of wide-necked intracranial aneurysms.

MicroVention intends to demonstrate safety and efficacy of its flow diverter (FRED) in one-arm baseline controlled clinical study. Currently there is one similarly indicated device that is approved by FDA –Pipeline Embolization Device, PED (Medtronic, P100018).

The primary effectiveness endpoint of the Pipeline (Pipeline Embolization Device, PED) study, was the proportion (>50%) of subjects with complete (100%) occlusion of the and in the absence of major (i.e., >50%) stenosis of the parent vessel for the duration 180 days follow up period. The primary effectiveness endpoint of the FRED study is very similar: the proportion (>45%) of subjects with complete (100%) occlusion of the parent vessel in the absence of major (i.e., >50%) stenosis of the parent vessel. The slight reduction of acceptable proportion of 100%

occlusion is related to more challenging criteria – expanded anatomical areas of treated aneurisms (anterior and posterior vs. only anterior in Pipeline study) and extended observation period (12 months in FRED study vs. 6 months in Pipeline study). Additional success criteria in FRED study is the absence of additional alternative treatments for the same diagnosis within one year. An alternative treatment is defined as re-treatment of the target aneurysm with an alternative medical intervention including open repair, endovascular placement of an additional stent or treatment of In-stent Stenosis observed within 12 months follow-up visits.

The primary safety endpoint composite between the FRED and Pipeline study is also more challenging, since the primary safety endpoint for Pipeline was the proportion of subjects who experienced either death due to neurologic causes or major ipsilateral stroke within 180 days whereas the primary safety endpoint for FRED is the proportion of subjects who experience one or more of the following: death or major stroke within 30 days post procedure & neurological death or major ipsilateral stroke within 12 months post procedure. The safety outcomes at 12 months in Pipeline studies are not published and no known.

The FRED study objective is to evaluate the safety and effectiveness of the MicroVention FRED System when used in the treatment of wide-necked intracranial aneurysms. Bayesian analyses will be performed to evaluate the primary efficacy and safety endpoints. The analysis objective is to test if the FRED System meets the OPC for efficacy (45%) and for safety (25%). Non-informative priors will be used for the assessment of both efficacy and safety endpoints. Bayesian approach to statistics is a principled approach for learning from evidence as it accumulates (FDA 2010). More details on the proposed analysis and details on the statistical analysis for secondary endpoints will be provided in the statistical analysis plan (SAP).

Pipeline Results:

The Pipeline SSED provides precedents for both efficacy and safety. Bayes analyses were performed. The PUFS study statistics follow for efficacy and safety.

For efficacy, of the 106 target IAs, complete IA occlusion without major stenosis was seen in 78 (73.6%, 95% posterior credible interval 64.4-81.0%). The posterior probability that the effectiveness rate exceeded 50% was 0.999999. An analogous frequentist statistical test, an exact binomial comparison of the observed 73.6% vs. a 50% threshold, yields a p-value of 0.0000006.

For safety, of the 107 subjects, six subjects (5.6%, 95% posterior credible interval CI 2.6 - 11.7%) were judged by the CEC to meet the primary safety endpoint. The posterior probability that the major safety endpoint rate was less than 20%, the predetermined safety success threshold, was 0.999979.

Literature Review Results:

The current supportive literature analysis document for safety and effectiveness clinical outcomes of flow diverters global provides a scientifically rigorous analysis of the relevant flow diverters' literature on patient cohorts that are applicable and directly comparable to the FRED IDE patient cohort. The literature review presents a combined OPC for safety and efficacy which includes a weighted average of 85% anterior vs. 15% posterior circulation that the distribution target for the FRED IDE cohort. The aneurysm population identified in the articles selected for analysis in the document is specifically aligned with the FRED patient population anatomically and physiologically.

A supplement analysis was also conducted to identify the in-stent stenosis rate (3.8%) to ensure that this event is not underreported across multiple publications. A 12% core lab adjustment was added when calculating the OPC for publications which did not include a core lab when reporting on aneurysm occlusion. The combined estimate for effectiveness for the anterior circulation (15 articles) was 56.2% (95% CI 42.8, 69.6) leading to a 45% one-sided lower 95% confidence limit for the anterior location. The combined estimate for effectiveness for the posterior location (9 articles) was 40.1% (95% CI 17.8, 62.3) leading to a 21.4% one-sided lower 95% confidence

limit for the posterior location. The sample size for the anterior circulation was 1120 vs. 81 for the posterior circulation.

Study Differences:

The current study will assess both anterior and posterior lesions following treatment. The combined anterior and posterior OPC from the FRED literature analysis document for both safety and efficacy is not directly comparable to that used for Pipeline since the PED was only used to treat ICA segments up to the superior hypopheseal segment whereas the FRED target is multiple vessel segments in the anterior and posterior circulation. The FRED study expects to up to 80% in the anterior circulation and up to 20% in the posterior circulation.

The Pipeline PUFS Study had a different primary safety endpoint which was the proportion of subjects who experienced either death due to neurologic causes or major ipsilateral stroke by 180 days after the last IA treatment procedure whereas the FRED Study primary safety endpoint is the proportion of subjects who experience one or more of the following: death or major stroke within 30 days post procedure and neurological death or major ipsilateral stroke within 12 months post procedure. Thus the primary safety endpoints are different. The 20% OPC used in the PUFS Study is likely too low given the longer duration.

OPC Selection Criteria:

The OPC for efficacy is motivated by our literature analysis where a 45% OPC was estimated to be the 95% lower bound determined from a series of qualifying publications. This estimate was based on a mixture of anterior and posterior lesions.

The OPC for safety is motivated by the Pipeline PUFS study where a 20% performance goal was used. However, the definition used in the PUFS study did not include all death and major stroke within 30 days, limited to deaths of neurologic cause and major ipsilateral strokes through 180 days instead of 12 months. For this reason, the 25% performance goal utilized here is slightly higher. For the purposes of the current study a conservative 5% adjustment is used, resulting in a 25% performance goal.

Conclusion

The FRED study success criteria are set to be similar to Pipeline study despite of more challenging safety and efficacy end points. It is understood that the actual safety and efficacy outcomes of the Pipeline study are exceeding the success criteria set in the Pipeline study protocol. MicroVention position is to use similar success criteria that were accepted by FDA for Pipeline study and we anticipate that the FRED study clinical outcomes will meet similar success criteria of the study pre-established in this protocol and, where comparable, will exceed these criteria to demonstrate similar comparable clinical outcomes of Pipeline Embolization Device (refer to Pipeline P100018 SSED).

5.2 Study Hypothesis

The safety and effectiveness of the FRED meets similar performance goal as that which was identified from a comprehensive analysis of the peer-reviewed published literature reporting the safety and efficacy of endovascular treatment of intracranial aneurysms with flow-diverter devices.

Efficacy hypotheses

The study is designed to compare the rate of the primary efficacy endpoint to a performance goal. The null and alternative hypotheses are:

Null hypothesis: $H_0: \pi_e \leq 45\%$

Alternative hypothesis: $H_A: \pi_e > 45\%$

where π_e is the proportion of subjects that are successes for the primary efficacy endpoint.

Safety hypotheses

The study is designed to compare the rate of the primary efficacy endpoint to a performance goal. The null and alternative hypotheses are:

Null hypothesis: $H_0: \pi_s \geq 25\%$

Alternative hypothesis: $H_A: \pi_s < 25\%$

where π_s is the proportion of subjects with primary safety endpoint events.

5.3 Study Description

The proposed study is a multi-center, prospective, single arm study with follow-up at 30 days (± 7 days), 180 days (± 30 days), and 12 months (+ 60 days, -30 days). The study includes five components:

- Screening period;
- Treatment period;
- 30-day clinical* follow-up visit;
- 180-day clinical* and angiographic follow-up visit;
- 12-month clinical* and angiographic follow-up visit.

* Clinical visit will include a physical and neurological exam. Ophthalmic examination will be performed if determined to be appropriate

5.4 Target Population

- Subjects with a single target intracranial aneurysm located along the internal carotid artery. The target aneurysm must have the following characteristics to be treated as part of the study:
  - Aneurysms with a neck ≥ 4mm or no discernible neck and a size (maximum fundus diameter) of > 10mm;
  - The parent artery must have a diameter of 2.0-5.0mm distal and/or proximal to the target intracranial aneurysm (IA)
  - Subject is a poor candidate for open surgical treatment because of prior surgical procedures, comorbidities or location limiting conventional surgical options and has a target aneurysm with a maximum fundus diameter less than 10 mm but > 7 mm with ANY of the following morphologies:
    - segmental parent artery dysplasia
    - aneurysm neck involving > 180 degrees of parent artery circumference
    - complex lobulations limiting stent/coiling as a treatment option
    - neck ≥ 4mm or no discernable AND dome/neck ratio < 2
- Fusiform aneurysms of any size requiring treatment;
- Subjects who have signed an informed consent form (ICF) and meet all the clinical and angiographic inclusion criteria set forth for this study

The treatment of aneurysms will be located in the following zones:

Zone	Anatomy Included	Additional Criteria
1	Petrous through superior hypophyseal segments of the ICA	• None
2	Communicating segment of the ICA through A1 or M1 segment	• exclude bifurcation aneurysms
3	Posterior Circulation including:	• exclude bifurcation aneurysms • exclude large or giant dolichoectactic aneurysms

5.5 Study Endpoints and Success Criteria

Primary Endpoint(s):

1. The primary safety endpoint will consist of a composite of any/all of the events list below:

   - death or major stroke within 30 days post procedure

   - neurological death or major ipsilateral stroke within 12 months post procedure, measured by mRS and NIHSS.

   NOTE: 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 minor stroke is defined as a new neurological event that persists for > 24 hours and results in an increase of < 4 points 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 an independent clinical events committee to have directly resulted from a neurologic cause

   Neurological and functional assessments will be measured by comparing baseline scores at 30 days, 180 days and 12 months post procedure.

2. The primary effectiveness endpoint is:

   Proportion of subjects with complete occlusion (100% occlusion) 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 alternative treatment of the target IA had not been performed. 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.

Secondary Endpoint(s):

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. 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.

2. Proportion of subjects in whom an 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 device

9. Incidence of unsuccessful deployment of the FRED device

10. Incidence of migration of the FRED device 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. Incidence of change in clinical and functional outcomes at 180 days and 1 year follow up, as measured by an ≥ 3 point increase in the modified Rankin Scale due to neurologic disability as 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)

The statistical analyses of the primary and secondary endpoints of the study will be based on imaging data that has been reviewed and assessed by an independent core lab and on trial clinical data that has been reviewed and adjudicated by the independent Clinical Events Committee (CEC).

Study Success Criteria:

The criterion for success is based on the posterior probability of the alternative hypotheses for both efficacy and safety (i.e. both efficacy and safety being met).

Efficacy Criterion

The FRED System will be declared efficacious if the posterior probability of the alternative hypothesis H_A based on the primary efficacy endpoint for is large, that is

$$P(H_A|Data) = P(\pi_e > 45\%|Data) > \pi^*$$

where π^* is the level of evidence we require to declare the efficacy alternative hypothesis true.

Safety Criterion

The FRED System will be declared safe if the posterior probability of the alternative hypothesis H_A based on the primary safety endpoint for is large, that is

$$P(H\_A|Data) = P(\pi_s < 25\%|Data) > \pi^*$$

where π^* is the level of evidence we require to declare the safety alternative hypothesis true.

For both safety and efficacy criterion, the posterior probability bound is

$$\pi^* = 0.95.$$

5.6 Subject Enrollment

195 subjects will be enrolled in the study at up to 30 investigational sites located in the United States and Japan. Additional subjects may be added to reach 155 subjects with a 12 month follow-up evaluation.

5.7 Study Duration

The enrollment period is estimated to be 12 – 36 months from the date of study commencement. Data from 195 patients, who undergo treatment with the FRED Implant System with complete 12 month follow-up will be analyzed and summarized. It is anticipated that the data will be submitted to FDA in an original Premarket Approval Application (PMA). The duration of the clinical study from first enrollment through regulatory approval is estimated to be 36-42 months. MicroVention may also request enrollment of additional patients under a Continued Access Protocol, i.e., extended investigation, throughout the preparation of the PMA and regulatory approval process

5.8 Inclusion Criteria

Subjects for this study must meet ALL of the following criteria:

- Subject whose age is ≥ 22 and ≤ 75 years;
- Subject has a single target aneurysm located in the following zones:
  - Zone 1 - Petrous through superior hypophyseal segments of the ICA
  - Zone 2 - Communicating segment of the ICA through A1 or M1 segment
  - Zone 3 - Posterior Circulation
    - Basilar artery (not including the basilar bifurcation
    - Vertebral artery (distal to the PICA)
    - Vertebral artery (proximal to the PICA)

AND fit any of the following criteria:

- Subject for whom existing endovascular options (coiling, stent-assisted coiling) would be ineffective because the aneurysm is predisposed to recurrence to having any of the following characteristics:
  a) Aneurysm has a maximum fundus diameter less than 10mm but ≥2mm.
     i. To mitigate the risk for the treatment of subjects with small stable aneurysms that may not require treatment with respect to the possible risks and benefits associated with treatment, the treating clinician shall record a treatment justification (such as increased risk of rupture) for the aneurisms < 7mm that have been selected for treatment
  b) Aneurysm has any of the following morphologies:
     i. no discernible neck.
     ii. segmental parent artery dysplasia.
     iii. Aneurysm neck involving > 180degrees of parent artery circumference.
     iv. Complex lobulations limiting stent/coiling as a treatment option
     v. Neck > 4mm or dome/neck ratio ≤2.

  OR
- Subject has a fusiform aneurysm of any size requiring treatment.
  OR
- Subject is a poor candidate for open surgical treatment because of prior surgical procedures, comorbidities or location limiting conventional surgical options

The parent artery diameter must be 2.0 - 5.0mm distal and/or proximal to the target intracranial aneurysm;

Subject fulfills study requirements, and the subject or his/her Legally Authorized Representative provides a signed informed consent form;

Negative pregnancy test (serum or urine) in a female subject who has had menses in the last 18 months;

Subject commits to return to the investigational site for the 30-day, 180-day, and 12-month follow-up evaluations.

A subject is considered to be enrolled after signing the Informed Consent Form.

Given the epidemiology and clinical prevalence of intracranial aneurysms, it is expected that up to 80% of the patients treated will present with anterior circulation aneurysms and up to 20% of the patients will present with posterior circulation aneurysms.

5.9 Exclusion Criteria

Subjects **shall be excluded** from the study if **ANY** of the following conditions exist:

- Subject who suffers from a subarachnoid hemorrhage in the last 60 days
- Subject who suffers from any intracranial hemorrhage in the last 30 days
- Subject who presents with an intracranial mass or currently undergoing radiation therapy for carcinoma or sarcoma of the head or neck region;
- Subject with symptomatic extracranial or intracranial stenosis of the parent artery (>50%) proximal to the target aneurysm;
- Subject with an irreversible bleeding disorder, a platelet count of less than 100,000/ml < 100 x103 cells/mm3 or known platelet dysfunction or a contraindication to or inability to tolerate anticoagulants/antiplatelet agents;
- Active peptic ulcer disease, major systemic hemorrhage within 30 days, active bleeding diathesis, platelet < 100,000 or known platelet dysfunction, INR ≥ 1.5, clotting factor abnormality, current alcohol or substance abuse, uncontrolled severe hypertension (systolic pressure >180 mm Hg or diastolic pressure >115 mmHg), creatinine ≥ 3.0 mg/dL (unless on dialysis);
- Subject with contraindications or known allergies to anticoagulants or antiplatelets (aspirin, heparin, ticlopidine, clopidogrel, prasugrel or ticagrelor);
- Subject with known hypersensitivity to metal, such as nickel-titanium and metal jewelry
- Subject with documented contrast allergy, or other condition, that prohibits imaging.
- Evidence of active infection at the time of treatment;
- Presence of any of the following unequivocal cardiac sources of embolism; chronic or paroxysmal atrial fibrillation, mitral stenosis, mechanical valve, endocarditis, intracardiac clot or vegetation, myocardial infarction within three months, dilated cardiomyopathy, left atrial spontaneous echo contrast, ejection fraction less than 30%;
- Subject who has had a previous intracranial stenting procedure associated with the target aneurysm;
- Subject who is unable to complete the required follow-ups;
- Subject with life-threatening diseases;
- Subject who is pregnant or breastfeeding;
- Subject of childbearing potential, and unwilling to prevent pregnancy during their participation in the study

5.10 Angiographic Exclusion Criteria

- Subject has a cerebral diagnostic angiogram that demonstrates an aneurysm that is not appropriate for endovascular treatment;
- Subject has extracranial stenosis greater than 50% in the carotid artery of the target aneurysm;
- Subject has intracranial stenosis greater than 50% in the treated vessel;
- Subject has a mycotic or dissecting aneurysm;
- Subject has a bifurcation aneurysm for example at the bifurcation of the internal carotid artery, the middle cerebral artery or at the anterior communicating artery such that placement of the device would fail to satisfactorily cover the entire neck of the aneurysm or a major cerebral artery would be put at risk through "jailing";
- Subject has a posterior circulation aneurysm with the following morphology:
  - Placement of device would include basilar artery bifurcation
  - Large or giant dolichoectactic aneurysm;
- Subjects aneurysm has significant branch exiting from dome of aneurysm (for example, ophthalmic artery);
- Subject is harboring more than one aneurysm with both aneurysms requiring treatment at the same time;
- Subject has an arteriovenous malformation (AVM) in the area of the target aneurysm.

5.11 Follow-Up

All subjects enrolled into the study and treated with the FRED System shall be followed at 30 day (± 7 days), 180 days (± 30 days), and 12 months (+ 60 days, -30 days). The follow-up visits will include an examination by a study investigator, according to the criteria below:

30 Day Visit (+/- 7 days)

- A physical, functional, and neurological examination, using the NIH Stroke Scale Score and Modified Rankin Scale. The information shall be collected on the 30 Day Follow-up CRF worksheets

180 days Visit (+/- 30 days)

- A physical, functional, and neurological examination including the NIHSS Stroke Scale Score and Modified Rankin Scale. A neuro-ophthalmic examination may be requested if a baseline exam was performed. The information shall be entered on the 180 days Follow-up CRF worksheets
- Angiography (all required imaging to be sent to Core Laboratory to include AP, lateral and working positions angiograms. The investigator should take proper steps to ensure that follow-ups angiograms are performed using similar views.

12 Month Visit (+ 60 days, - 30 days)

- A physical, functional, and neurological examination including the NIH Stroke Scale Score and Modified Rankin Scale. The information shall be entered on the 12 Month Follow-up CRF worksheets
- Angiography (all required imaging to be sent to Core Laboratory to include AP, lateral and working positions angiograms). The investigator should take proper steps to ensure that follow-up angiograms are performed using similar views.

Unscheduled Visits

- Subjects shall be seen and assessed by members of the neurovascular team throughout the study period. If any events occur of if any imaging is performed outside the follow-up schedule, the information shall be captured and reported on the Unscheduled Visit CRF.

6.0 Statistical Methods

6.1 Analysis Population

The statistical analysis will use four populations:

1) The Intent to Treat (ITT) population will consist of all enrolled subjects who had an introduction of the FRED Implant System and were followed for 12 months or failing prior to 12 months. The ITT population will be used for all effectiveness analyses to test the efficacy hypothesis.

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.

3) The Per Protocol Population will consist of all subjects in the ITT Population for whom there were no major protocol deviations.*

   * Major protocol deviations include subjects who failed any of the inclusion/exclusion criteria, who were not evaluated within the study windows, or who received a treatment intervention impacting the ability to evaluate either safety or efficacy

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

6.2 Proposed Sample Size and Data Analysis

Upon FDA approval of CL12001 Rev 3.0, enrollment will be increased from 127 to 195 to allow for enrollment of subjects using FRED line extension. Sample size was determined through simulations. The sample size was chosen so that the Type I and the Type II error rates are bounded. With 155 subjects, there will be 80% posterior probability to reject the 45% OPC null hypothesis for efficacy and the 25% OPC null hypothesis for safety using one-sided tests with 5% Type I error.

Simulations were run in R statistical package (R citation) and OpenBUGS software, version 3.2.2. For each scenario, 10,000 datasets were generated in R. OpenBUGS was then used to obtain samples from the posterior distribution of each parameter and to calculate the probability of success. For each analysis, 50,000 samples were obtained from the posterior distributions after 1,000 samples were discarded.

Primary Efficacy

The primary efficacy endpoint in this study is complete occlusion 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 alternative treatment of the target IA had not been performed. 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 study is designed to compare the primary efficacy success percent to an independently derived performance goal, which is 45% for efficacy. The performance goal was obtained from a formal meta-analysis of results from studies of flow diverters during the first year after treatment. The methods and results of this meta-analysis are described in detail in the appendix. The null and alternative hypotheses are:

Null hypothesis: Pe ≤ 45%

Alternative hypothesis: Pe >45%,

where Pe is the proportion of subjects that are successes for the primary efficacy endpoint.

Allowing for up to 20% attrition through 12 months, a sample size of at least N=155 is expected at 12 months. Should the FRED percent equal 56.5%, then the sample size of 155 subjects would reject the null hypothesis with 80% power and one-sided 5% alpha level.

Primary Safety

The primary safety outcome is the percent of subjects who experience death or major stoke within 30 days of the implant or death due to a neurological cause or major ipsilateral stroke through 12 months post implant. The study is designed to compare the primary safety percent to an independently derived performance goal, which is 25% for safety. The null and alternative hypotheses are:

Null hypothesis: Ps ≥ 25%

Alternative hypothesis: Ps < 25%,

where Ps is the proportion of subjects with primary safety endpoint events.

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). Should the FRED primary safety endpoint percent equal 15%, then the sample size of N=155 subjects would reject the null hypothesis with >80% power and one-sided 5% alpha level.

Statistical Methods for Primary Endpoints

The primary safety and effectiveness endpoints will be analyzed using Bayes models (OpenBUGS).. The proposed model is a beta-binomial model that assumes that the outcome is a Binomial variable and a uniform prior on the probability of event.

Likelihood:

The likelihood is constructed based on distributional assumptions on the safety and efficacy results of the FRED system.

With N_e and N_s being the number of evaluable subjects for the Efficacy and Safety endpoints, respectively, the number of subjects that are successes for the primary efficacy endpoint, y_e, and the number of subjects with primary safety endpoint events are assumed to follow Binomial distribution with respective rates π_e and π_s. Thus,

$$y_e \sim Binomial(\pi_e, N_e) \text{ and } y_e \sim Binomial(\pi_s, N_s).$$

Prior Distributions:

Uninformative prior distributions are assumed for the efficacy and safety rates. More precisely,

$\pi_e \sim Beta(1,1)$ and $\pi_s \sim Beta(1,1)$.

For efficacy, if the one-sided 95% lower credible interval is at least 45%, then efficacy is established. For safety, if the one-sided 95% upper credible interval is no more than 25%, then safety is established. Bayes logistic models will be used to compute the credible intervals controlling for ae (<55, 55-64, ≥65) gender (male, female), zone (1, 2, 3), and region (Japan vs others), If both the safety and effectiveness null hypotheses are rejected, then the study goal will be considered to be met.

The primary effectiveness endpoint is defined, such that a subject will be considered a failure if the following occurs:

- A retreatment of the target aneurysm is required at any time prior to the 12-month follow-up evaluation, failure is considered to have occurred at the time of retreatment;
- The study device is deployed and properly positioned at the target site but fails to fully occlude the aneurysm by 12 months post-procedure;

Or if

- Presence of >50% stenosis of the parent artery at the target aneurysm at 12 months.

If a subject is a failure of this endpoint for multiple elements of the composite endpoint, then the subject is treated as a failure at the time of the earliest failure for the purposes of the statistical analysis.

Statistical Methods for Secondary Endpoints

The timing of the primary efficacy component failures (incomplete occlusion of the target aneurysm, >50% stenosis of the parent artery at the target IA at 12 months as assessed by angiography, an alternative treatment of the target IA was performed), primary safety components (death or major stoke within 30 days of the implant, death due to a neurological cause, major ipsilateral stroke through 12 months post implant) as well as the secondary endpoint proportions and incidences will be presented using standard summary statistics including the incidence and 95% credible intervals. No hypothesis tests will be performed for the primary or secondary endpoint components or secondary endpoints.

Adverse Events

Additionally, other safety endpoints will also be assessed based on Adverse Events. The number of subjects and the number of adverse events per subjects will be presented for Adverse Events, unanticipated Adverse Events, Serious Adverse Events, and unanticipated Serious Adverse Events. The results will be provided by system organ class and preferred term. Narrative case summaries will be provided for each Serious Adverse Event. Two-sided 95% credible intervals will be presented for each adverse event with ≥5% incidence.

Technical Failures

Technical failure subjects will be presented separately but will be excluded from the ITT and Per Protocol populations if they did not receive the device. They will be included in the Safety population.

A FRED procedure will be categorized as a technical failure if the following occurs:

- Failed FRED Device Deployment Due to Technical Issues with the FRED Device
    - 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. The Subject will be monitored for any Adverse Event for one (1) week

following the failed deployment due to a technical issue related to the FRED Device. Unless medically necessary to pursue treatment sooner, it is recommended that further attempts to treat the target aneurysm be deferred for a minimum of one (1) week so that any potential procedural Adverse Events may be monitored.

- Failed Device Deployment Due to Issues Related to the Procedure
  - If the FRED Device cannot be deployed due to any other issues related to the procedure, the Subject will be counted as enrolled but not treated and will not be considered a secondary endpoint failure. The Subject will be maintained within the study for one (1) week. Thereafter, the Subject may be replaced in the study. The Subject will be monitored for any Adverse Event for one (1) week following the failed deployment due to issues related to the procedure. If the Subject has an Adverse Event, that Subject will also have 30-day, 6-month and 12-month clinical follow-ups. An angiographic follow-up will not be required unless the clinician believes it is medically necessary. Unless medically necessary to pursue treatment sooner, it is recommended that further attempts to treat the target aneurysm be deferred for a minimum of one (1) week so that any potential procedural Adverse Events may be monitored.

Subgroup Analysis

Results for the primary and secondary endpoints will be stratified by the following subgroups:

- Location (anterior, posterior)
- Age (<55, 55-64, ≥65)
- Gender: results will be stratified by gender
- Anatomic location (zone 1, 2 and 3)
- Region (Japan, other countries)

Since it is not possible to determine any observed differences are truly due to a difference in treatment effect, any observed significant differences in outcomes ($p<0.1$) across subgroups will be examined and compared to available literature regarding known risk effects for the subgroups.

Missing Data

In general, all analyses will be performed using the ITT analysis set, which constitutes all available cases and all available visits. Every effort will be made to get 12 month follow-up for all study patients. The primary endpoints will be analyzed first without imputing missing or incomplete data. Multiple sensitivity analyses will be performed in order to better understand the potential effect of missing or incomplete data on the conclusions for the primary endpoints. These sensitivity analyses will impute values for subjects who are event free (for the specific primary endpoint), but do not have complete data. The analysis method used on the imputed datasets will use the binary result (i.e. simple event percents).

Methods will be endpoint specific. For example, to determine the rate of major strokes, all subjects followed with major strokes reported or no major strokes observed during the defined time period will be counted in the analysis. A lifetable analysis of time to major stroke using the nominal visit will be constructed to use all available data. Other similar endpoints will be analyzed using this strategy.

Other endpoints can be imputed using Expected Mean algorithms. In general, when missing data exists, it is important to assess the impact of missing data on a statistical estimation and testing result; therefore, in addition to analyses based on all observed cases, sensitivity analyses will be performed on the primary endpoints. Multiple imputation method using logistic regression on selected demographic and baseline disease characteristics will be applied.

The best and worst case imputation approach will also be calculated. If under the worst-case approach the study hypotheses are upheld, no further imputation analyses will be performed. Additionally, a multiple imputation approach will be used. We construct a logistic regression model for the probability of failure based on baseline characteristics thought to be predictive of the event and/or of missingness. Imputed datasets will be generated and the results combined to re-test the primary study hypotheses.

Analysis by Center

In this single arm study it is not possible to assess a treatment by center interaction, given there is only one treatment. However, results will be summarized by center for the primary efficacy and safety endpoints. Additionally, an analysis will be performed to assess site homogeneity for these two endpoints.

To facilitate analysis, sites with fewer than 10 subjects may be lumped into a "virtual" or "pseudo" site. If the number of subjects in this pseudo site is large (e.g. greater than 20 subjects), then an attempt will be made to combine the small sites into multiple small sites variables based on geographic location, such that small sites in a similar geographic location are combined but that each pseudo site level created contains at least 10 subjects.

Both endpoints to be compared are will be analyzed using a logistic regression model. If there are any global site differences found at the two-sided $p<0.1$ level, then an additional analysis will be performed to assess the effect of any differences in baseline characteristics across sites. Baseline characteristics will be compared across sites and any that are out of balance at the two-sided $p<0.1$ will also be included in the analysis of the primary endpoints across sites to assess the effect of their inclusion. This analysis is intended to help assess prognostic factors associated with the performance of the study device.

Statistical Bibliography

- 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.
- R Development Core Team (2012). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/
- Lunn D, Spiegelhalter D, Thomas A, Best N. The BUGS Project: Evolution, Critique and Future Directions. *Stat Med* 2009;283049–3067.
- Thomas A, O Hara, R, Ligges U, Sturtz S. Making BUGS Open. R News 6: 12-17

7.0 Informed Consent

Each subject shall review, understand, and sign an informed consent form (ICF) that has been approved by the investigational site's Institutional Review Board (IRB) for use in this study. The consenting process must be done in accordance to the policies and procedures of that specific investigational site, and as specified in this protocol.

The original signed informed consent form shall be retained in the subject's study files. A copy of the informed consent form shall be provided to the subject.

Any amendments made to this protocol that result in a change in the informed consent must be submitted to the IRBs. It is left to the discretion of each IRB whether previously enrolled subjects must sign the new version of the consent form at the next study encounter, according to the IRB policies in place at that institution.

8.0 Site Responsibilities, Reporting and Recordkeeping

The Principal Investigator has the following responsibilities:

- Submit the Clinical Investigation Plan/Protocol and the informed consent form to the Investigation Site IRB/EC for approval. A formal, written approval to participate in the study from the IRB/EC shall be provided to the Sponsor prior to any patient enrollment.
- Protect the rights, safety and welfare of subjects;
- Conduct the study in accordance with the signed investigator agreement with the Sponsor, the Clinical Investigation Plan/Protocol, the IDE regulations and any other requirements imposed by the FDA and IRB/EC;
- While waiting for approval of the IDE application, the Principal Investigator may determine whether or not potential subjects would be interested in participating in the study, but cannot request written informed consent or allow any subjects to participate before obtaining IRB/EC and FDA approval;
- Obtain informed consent per the IDE requirements of 21 CFR Part 50 (Protection of Human Subjects) and the standard of care at the Investigation Site;
- Ensure that the investigational device is only used for subjects under his/her supervision in this study and shall not supply the investigational devices to any person not authorized to receive it;
- Complete the CRF forms, (copies of the Case Report Forms are provided by MicroVention) for each Subject enrolled in the study per the requirements of the Clinical Investigation Plan/Protocol and the Manual of Operating Procedures;
- Upon completion or termination of the study or the investigator's participation in the study, or at the request of the Sponsor, the Principal Investigator shall return to the Sponsor any remaining supply of the investigational devices, or dispose of them as the Sponsor directs;
- The Principal Investigator shall disclose to the Sponsor sufficient accurate financial information to allow the Sponsor to submit certification or disclosure of financial interests under 21 CFR Part 54 (Financial Disclosure by Clinical Investigators). The Principal Investigator shall update the information if any relevant changes occur during the course of the study and for one year following completion of the study.

The Principal Investigator shall provide the following reports in a timely manner:

- A written report shall be submitted to the Investigation Site IRB/EC and Sponsor of any Unanticipated Adverse Device Effect as soon as possible (i.e. within 24 hours) but no later than 10 working days after the investigator first learns of the effect;
- A written report shall be submitted to the Sponsor regarding a withdrawal of study approval from the IRB/EC within 5 working days;
- A progress report shall be submitted to the Sponsor, Monitor and IRB/EC at regular intervals but no less than on a yearly basis. The report to the IRB/EC shall include a request for approval to continue the study. The status of the study shall be shared with the IRB/EC and Sponsor upon request.

- If a FRED System is used without obtaining informed consent, a report shall be provided to the IRB/EC and Sponsor within 5 working days after the use occurs.

- The Sponsor shall be notified of any deviation from the Clinical Investigation Plan/Protocol to protect the life or physical well-being of a Subject in an emergency. The notice shall be provided as soon as possible (i.e. 24 hours) but no later than 5 working days after the emergency occurred. If it is not an emergency, prior approval from the Sponsor shall be required for changes in or deviations from the protocol.

- Any proposed amendments to the protocol or informed consent form that have IRB/EC approval shall be submitted in written form to the Sponsor.

- The IRB /EC shall be notified of any changes to the status of the study including completion, termination or other necessary changes, according to the IRB policies in place at that institution.

- A letter of notification of the completion, termination or discontinuation of the study shall be submitted to the IRB/EC.

- A final report shall be submitted to the IRB/EC and Sponsor within 3 months after termination or completion of the study.

The Principal Investigator shall maintain accurate and complete records relating to the study. These records shall include:

- The Clinical Investigation Plan/Protocol and any documentation (date and reason) for each deviation from the protocol

- All correspondence including required reports

- Records of receipt, use and disposition of the investigational device

- Records of each Subject's case history and exposure to the investigational device

A detailed description of the responsibilities of the investigational sites is found in the study Manual of Operating Procedures. The site Principal Investigator is responsible for site adherence to these expectations.

9.0 Sponsor Led Device Training

The FRED® device is intended to be used by interventional neuro-radiologists or neurosurgeons who are trained in endovascular procedures and who have experience with embolization of intracranial aneurysms.

All investigators and co-investigators will undergo standardized training prior to study participation. As part of the training program, MicroVention personnel or designee will provide hands-on training in the use of the device using a bench top model (or equivalent) to familiarize the investigator with the use of the FRED System. In addition, the investigators will attend didactic sessions to cover the directions for use, preparation of the FRED System and procedure planning.

In addition to didactic sessions and hands-on training, the study personnel at each study site will undergo protocol training and site initiation visit. Site training and initiation will be documented and the records maintained by the study sponsor.

10.0 Medications

10.1 Pre-Procedure

- Aspirin (ASA) 81-325 mg/day per oral for a minimum of 5-7 days prior to the procedure
- Clopidogrel (Plavix) 75 mg/day per oral for a minimum of 5-7 days prior to the procedure. If the Subject has an intolerance or documented contraindication to clopidogrel, another antiplatelet agent; such as P2Y12 receptor inhibitors (prasugrel or ticagrelor) may be prescribed.

If the subject has not been on dual antiplatelets (aspirin and clopidogrel) for a minimum of 5-7 days prior to the procedure, a single loading dose of aspirin 325 mg and clopidogrel 600 mg should be given at least 6 hours (but no more than 24 hours) prior to the procedure.

Platelet inhibition function tests should be performed prior to the procedure (using platelet counts or point of care assays) such as Verify Now ® (Accumetrics, US) or others. Instructions and threshold levels of platelet inhibition is provided in the Manual of Operating Procedures.

10.2 Intra-Procedure

- Heparin: A bolus of intravenous heparin should be given that is weight-adjusted to maintain the activated clotting time (ACT) near 250-300 seconds throughout the procedure. **ACT should be checked throughout the procedure at 60 minute intervals.**
- If a Glycoprotein IIb – IIIa receptor antagonist (abciximab/ReoPro®, tirofiban/Aggrastat®, or eptifibatide/Integrilin®) is used during the procedure, then ACT should be maintained at less than 220 seconds to avoid hemorrhage.

10.3 Post-Procedure

- For at least 6 months post-procedure: Aspirin (ASA) 81-325 mg/day per oral
- Clopidogrel 75 mg/day per oral or equivalent

After the initial 6 month period, 1 antiplatelet agent only should be considered and taken for lifetime. Aspirin is preferred if no contraindication.

10.4 Medication Log

Documentation of other medications that the subject takes during their participation in the study shall be collected, as described in the Manual of Operating Procedures.

11.0 Procedure

11.1 Subject Screening and Enrollment

Potential study subjects shall be assessed using the Screening Form. This includes a review of the inclusion/exclusion criteria and confirmation they are met.

For women of childbearing potential (any menses within the last 18 months unless surgically sterilized), pregnancy test (serum or urine) should be done at the time of screening.

When all items have been completed and the Screening Form has been signed by a site study physician, the subject should be given the informed consent to review and to sign. The subject shall have the opportunity to speak to a study physician regarding any questions they may have about the study. The consenting process shall be documented in the medical record according to the study site policies.

As part of standard diagnosis for neurovascular aneurysms, the subject shall be evaluated by the neurovascular team. The subject shall have an appropriate clinical evaluation (utilizing the NIHSS and mRS) performed by a qualified/certified person, a laboratory evaluation and a cerebral vascular imaging (CTA, MRA, or conventional angiography). Vascular imaging shall be evaluated for aneurysm location, aneurysm size and morphology, aneurysm neck width, and parent artery size, making sure it fulfills the angiographic inclusion criteria. The images of the aneurysm will be accessed by the Principal Investigator of the Study to confirm the patient meeting angiographic criteria.

A baseline clinical eye and ophthalmic exam must be performed by an ophthalmologist on all subjects and must be conducted within 30 days of the FRED procedure. A historical exam that was previously conducted by an ophthalmologist at most at 30 days before the procedure is acceptable. The clinical eye exam shall be performed at every visit and can be conducted by the Principal Investigator, Research Nurse, or an appropriate and delegated designee. However, an ophthalmic exam shall be performed during the screening process or if any visual deficits occur during the study, by an ophthalmologist. If any visual deficits are found at a follow-up evaluation or an adverse event of visual impairment occurs, another clinical eye and ophthalmic exam shall be conducted by an ophthalmologist and followed until the deficit has resolved.

11.2 Pre-Procedure

The pre-procedure antiplatelet medications should be prescribed as stated in section 11.1.

11.3 Intra-Procedure – FRED System Deployment

The subject shall be brought to the neurovascular angiographic suite for diagnostic cerebral angiography and endovascular aneurysm treatment with the FRED System. While the diagnostic portion of the procedure may be performed under local anesthesia and/or conscious sedation, **treatment with the FRED System must be performed under general anesthesia.**

Arterial access shall be gained using standard techniques via either a femoral, brachial or radial artery approach. A vascular sheath shall be inserted according to standard angiographic techniques. Following sheath placement, IV Heparin shall be administered to achieve an ACT between 250-300 seconds.

ACT shall be monitored at least hourly and the measurement recorded.

Initial diagnostic cerebral angiography shall be performed to accurately define the aneurysm fundus size, neck size and parent artery diameter. These measurements must be made to verify that the dimensions of the aneurysm and the size of the parent artery are compatible with the study inclusion criteria. If the measurements result in exclusion of the Subject from the study, the subject shall be withdrawn from the study and considered enrolled but not treated. The reasons for withdrawal of all Subjects shall be documented. Appropriate treatment using standard of care should proceed at the discretion of the clinician.

For complete procedure instructions, refer to the Instructions for Use (IFU) that is included in each device package.

11.4 Withdrawal Criteria

A subject can withdraw their consent to participate in the study at any time. Each site must follow their institutional policies and procedures for withdrawal of consent by a research subject.

Available data for any subject who withdraws from the study will be included in the final data analysis.

11.5 Subject withdrawal/Lost to Follow-Up

A subject can stop his/her participation in the study by withdrawing their consent. In such cases, the subject shall not be penalized for such action. Meanwhile, the subject shall be treated according to the standard practice of the institution. The reason for withdrawal shall be documented on the CRF.

Available data for subjects who withdraw from the study shall be included in the final data analysis. The same criteria shall be used for those subjects who are lost to follow-up.

11.6 Follow-Up of Subjects enrolled but not treated

A subject that is considered enrolled but not treated with the FRED System shall be closely monitored for one (1) week.

If the subject experiences a neurological event that is determined to be probably or definitely related to the FRED device by the independent Clinical Events Committee (CEC) , or if the CEC is unable to determine relatedness, that subject will be followed at 30-days, 180-day and 12-months.

A subject that is considered enrolled but not treated because of a failure to continue meeting the inclusion criteria or subsequently meet the exclusion criteria, or because of a failed FRED System deployment, and who did not have an Adverse Event, will not have 30-day;180-day and 12-month follow-up.

Prior to study enrollment, careful consideration should be given to the likelihood of a subject's ability to complete all study follow-up requirements. Names and phone numbers for additional contact persons should be recorded in the subject's study file. Attempts should be made promptly to locate a study subject after a missed visit and any barriers to ongoing participation should be discussed and remedied if possible.

Available data for any subject who has become lost to follow-up will be included in the final data analyses.

12.0 Angiographic Requirements

Qualitative Image Analysis shall be performed by a team from the imaging core lab. It is the role of the Core Laboratory to assess the angiographic outcomes including aneurysm occlusion status and parent artery patency.

12.1 Core Laboratory Angiography Assessment Methods

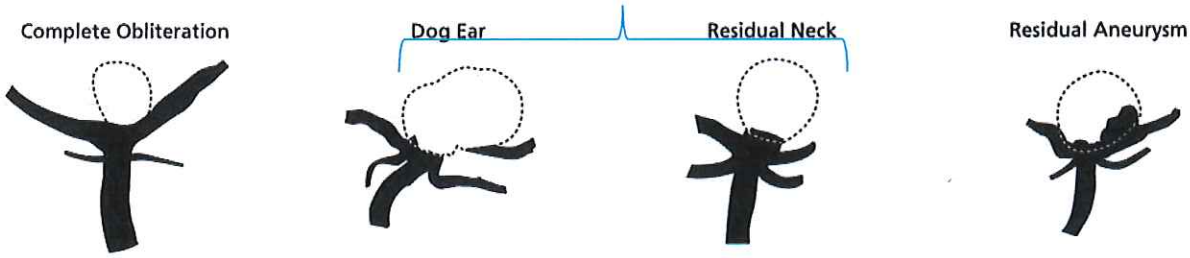
12.1.1 Aneurysm Occlusion

Angiographic assessment of the anatomic occlusion of the aneurysm shall be performed using the Roy and Raymond's Classification at the following time points:

- Immediately post-procedure
- 180-day follow-up
- 12-month follow-up

The angiographic assessment shall be performed by independent, blinded reviewer(s). The following occlusion characterization shall be used for reference:

Raymond Scale 1 Raymond Scale 2 Raymond Scale 3



- Complete(100%) = complete occlusion, no flow of contrast seen in the sac;
- Near Complete (>90-99%-residual neck) = partial occlusion, some flow in the neck or sac;
- Incomplete aneurysm (≤90%- residual aneurysm) = incomplete occlusion, apparent flow into the sac;

Reference: Roy D, Milot G, Raymond J. Endovascular treatment of unruptured aneurysms. Stroke 2001;32:1998-2004. [47]

12.1.2 Parent Artery Patency

Stenosis shall be assessed using the WASID criterion which is defined as greater than 50% luminal loss at angiographic follow up using the WASID method:

$[1(D_{stenosis}/D_{normal})] \times 100$

Where $D_{stenosis}$ is the diameter of the artery at the site of the most severe stenosis and D_{normal} is the diameter of the proximal normal artery.

12.2 Site Requirements – Angiographic Imaging

Images shall be sent as DICOM electronic files uploaded onto digital media (example CD) to the Core Laboratory for analysis. The Digital Media must be labeled using the subject's FRED Study Number instead of Subject Name, for confidentiality purposes.

12.2.1 Initial Angiography

Sites shall send the following images (at a minimum):

- AP ,Lateral and working projections;
- Working projections selected for FRED deployment (pre-deployment);
- Working angles (post-FRED deployment);
- If available, imaging should include 3D reconstruction;

12.2.2 Angiography at 180 days and 12 months post-procedure

Sites shall send the following images (at a minimum):

- AP, Lateral and working projections;

- Working projections selected for FRED deployment (pre-deployment);
- Working angles (post-FRED deployment);
- If available, imaging should include 3D reconstruction;
- The investigator should take proper steps to ensure that follow-ups angiograms are performed using similar views.

13.0 Adverse Events

13.1 Definitions

- **Adverse Event (AE)**:

  Any unfavorable and unintended sign (including laboratory findings), symptom or disease that occurs to a subject while enrolled in this clinical investigation. Medical conditions that exist at study enrollment are not considered an AE unless condition worsens after use of the study device or antithrombotic medications.

- **Serious Adverse Event (SAE):**

  A serious adverse event is any medical experience regardless of its relationship to the study treatment that occurs during subject enrollment in this trial that results in any of the following: (1) inpatient hospitalization or prolongation of a hospitalization; (b) persistent or significant disability/incapacity; (c) death of the study subject, or (d) necessitates an intervention to prevent a permanent impairment of a body function or permanent damage to a body structure.

- **Unanticipated Adverse Device Effect (UADE):**

  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 IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety or welfare of subjects.

The common terminology criteria for adverse events (CTCAE) will be utilized for Adverse Event (AE) reporting. The CTCAE v.4.0 incorporates certain elements of the MedDRA terminology and the list is incorporated into the Manual of Operating Procedures.

Table 2 Adverse Event Reporting and Device Malfunction

Classification	Reporting time	Type of report
Unanticipated Adverse Device Effects (UADE)	Within 24 hours of learning of event; no more than 10 working days from learning of event	Adverse Event Reporting Form to be submitted to the sponsor, CRO and IRB according to the IRB policies in place at that institution. [1]
Serious AE (SAE)	Within 24 hours of learning of event; no more than 10 working days from learning of event	Serious Adverse Event Reporting Form to be submitted to the sponsor, CRO and IRB according to the IRB policies in place at that institution. [1]
Non-serious AE	Within 30 working days of event.	Adverse Event Reporting Form in EDC
Device Malfunctioning With or Without Adverse Event	Within 5 working days of learning the event	Investigational Clinical Device Product Complaint and Return Form to be submitted to the sponsor, CRO and IRB according to the IRB policies in place at that institution. In case of death, it should be submitted to the FDA, Sponsor, CRO and IRB according to the IRB policies in place at that institution. [1]
[1] Note: Participating clinical sites have different IRBs that sometimes have varying Adverse Event reporting policies. Some request that all AEs be reported; others only request that only the SAEs and UADEs be reported. Regardless of this direction by site specific IRBs, MicroVention and its associated CROs require sites to report all AEs (including UADE reporting, serious AE, Non serious AE, Device Malfunction with or without AE) in an appropriate timeframe. No limitation of the reporting of adverse events are made by the sponsor (MicroVention), CRO and FDA.		

13.2 Anticipated Adverse Device Effects

The following potential risks and complications are known to be associated with cerebral angiography, intracranial catheterization, intracranial stent/ flow diverters placement and would not be considered as UADEs:

- Allergic reaction, including but not limited to, imaging contrast dye, nitinol metal, and any other medications used during the procedure;
- Aneurysm rupture;
- Aneurysm growth;
- Bleeding including intracerebral, retroperitoneal or in other locations (Note: reportable events involving bleeding are not limited to those related to the procedure);
- Blindness;
- Cardiac arrhythmias;
- Cranial neuropathy;
- Device fracture, migration or misplacement;
- Device thrombosis;
- Diplopia;
- Dissection or perforation of the parent artery;
- Emboli;
- Failure to deliver the device;
- Failure to deploy the device at the intended target site;
- Headache;
- Hemorrhage;
- Hematoma / Hypoperfusion;
- Infection;
- Injury to normal vessel or tissue;
- Ischemia;
- Mass effect;
- Myocardial Infarction;
- Neurological deficits;
- Occlusion of non-target side branches;
- Pseudoaneurysm formation;
- Renal failure;
- Stenosis of stented segment;
- Seizure;
- Stenosis or thrombosis of the parent artery or a side branch vessel;
- Stroke or TIA (Transient Ischemic Attack);
- Thromboembolic event;

- Total occlusion of treated parent vessel segment;
- Vasospasm;
- Vessel perforation;
- Visual impairment.

13.3 Reporting of Adverse Events by Subjects

All subjects shall be instructed to report any adverse events to the Principal Investigator or Study Coordinator at hospital discharge and during the following 12 months.

Details and criteria regarding the procedure and the site's responsibility for reporting adverse events are described in the Manual of Operating Procedures.

13.4 Device Malfunction

If a device does not meet the specific performance requirements, per the provided Instructions for Use, the issue/incident must be reported. Reporting directions are described in the Manual of Operating Procedures. Another device shall be available to the physician to complete the procedure.

If the device malfunction results in an adverse event, it must be reported according to the directions in the Manual of Operating Procedures.

13.5 Post-Procedure Management of Adverse Events

Subjects will be evaluated at the scheduled follow-up visits. If any adverse events occur outside the follow-up schedule, additional follow-up should occur. The procedure for this is described in the Manual of Operating Procedures.

13.6 Data & Safety Monitoring Board (DSMB)

The purpose of the DSMB is to evaluate the relative treatment effects based on protocol-specified endpoints to determine if the trial is meeting its objectives. The DSMB will periodically assess the clinical trial data including but not limited to enrollment, device performance, mortality and major morbidity clinical outcomes, and make recommendations to MicroVention accordingly. The DSMB, which is referred to herein as The Board will provide these recommendations to ensure consistency with the objectives of the trial and appropriate ethical requirements.

The Board shall be formed prior to commencing the study. The Board shall have direct communication with the Primary Investigator of the study.

Each member of The Board shall have no financial or proprietary interest in the investigational device or the study itself. The Board will meet with the Primary Investigator prior to study initiation to review this Protocol and the Manual of Operating Procedures.

The Board will meet and review trial data at

- the earlier of three (3) months or after approximately 20 subjects (+/- 5) have been enrolled in the study and their data is available
- approximately every three (3) months thereafter depending on and commensurate with the rate of enrollment, and
- as needed if specific concerns arise.

The DSMB will provide recommendations to the Sponsor consistent with the objectives of the study and appropriate ethical requirements.

The primary objectives of the DSMB will include:

- Protect subject welfare
- Preserve study integrity by providing an independent review of data relating to safety and efficacy
- Review study data and make recommendations to stop, suspend, continue or modify the study based on serious concerns about subjects' safety, inadequate performance or rate of enrollment or observed beneficial or adverse effects of the treatment under the study
- Review risk/benefit profile of the device based on ongoing clinical study results
- Evaluate the progress of the trial, including periodic assessments of the data quality, participant risk verses benefit and other factors that can impact study outcomes
- Provide corrective actions for study centers that do not comply with study protocol or that perform unsatisfactorily
- Make recommendations, when appropriate, to increase the number of study centers or extend the enrollment period and/or study duration
- Ensure the outcomes of the meetings are based upon unbiased and comprehensive evaluation of the data
- Communicate findings, other recommendations or concerns as appropriate.

The DSMB may be asked to review final study results and recommend to the Sponsor modifications for future studies.

To minimize bias of its members, The Board shall be blinded to subject identities, Principal Investigators and investigational sites, to the extent possible.

Members of The Board shall include leading experts in neurology, interventional neuroradiology, and/or endovascular neurosurgery. None of the members of The Board shall be Principal Investigators in this study. The membership of The Board is contained in the appendix of the DSMB Charter.

Stopping Rules have been written and The Board will evaluate safety based on these rules. Any Board recommendations for study modification or termination because of concerns over patient safety, or issues relating to the data monitoring or quality control, shall be submitted immediately in writing and by verbal communication to the Primary Investigator for consideration and final decision.

14.0 Data Management

14.1 Data Quality Assurance

The sponsor (or designee) shall be responsible for training the appropriate personnel at each investigational site.

The sponsor (or designee) shall review the method of identifying and enrolling the appropriate subjects into the study.

The sponsor (or designee) shall provide the necessary documents and forms to assist each investigational site on subject recruitment, procedural follow-up, and the completion of forms for the study.

Each site shall be responsible for assuring uniform data collection and protocol compliance as required by the Clinical Investigation Plan/Protocol and associated documents.

14.2 Data Accuracy and Verifiability

All CRFs and other study documentation shall be filled out completely and clearly, copies of which shall be submitted to the sponsor upon request. CRFs and other study documents that are incomplete, or for which data is unclear, shall be replaced or completed upon request of the sponsor and then resubmitted to the sponsor upon request. A detailed description of the CRF completion and submission process is provided in the Manual of Operating Procedures.

It is the responsibility of the Principal Investigator from each investigational site to ensure that all data pertinent to the study be collected and entered into the study's secure data sharing website. The website will be maintained by an independent data management company and the sponsor shall have "view only" access. All data entered must be backed up by source documents. Copies of these documents will be stored in the site's study files and made available as requested by the sponsor for monitoring purposes.

15.0 Monitoring

The Sponsor shall select a Monitor(s) qualified by training and experience to monitor the study. A Monitor may be an employee of the Sponsor or an organization contracted by the Sponsor. The Monitor shall assure that the investigators are complying with the signed investigator agreement, the Clinical Investigation Plan/Protocol, IDE regulations and any conditions of approval imposed by the Investigation Site IRB/EC or FDA. Routine monitoring will occur to:

- verify that subject enrollment is being achieved;
- verify that the inclusion/exclusion criteria has been met at enrollment;
- verify that the correct version of the informed consent has been signed by the subject;
- review the medical records of all enrolled subjects to ensure all adverse events have been captured and properly reported;
- verify that the data and imaging are accurate, complete and backed up by source documents;
- verify that all contracts, certifications, and medical licenses for each site are valid through the duration of the study.

16.0 Protocol Adherence

The approved Clinical Investigational Plan/Protocol for the FRED study shall be followed without deviation. If the Principal Investigator and/or sponsor believe that an amendment or modification to the protocol is necessary, such amendment or modification shall be presented, in written form, to the study Primary Investigator, Dr. McDougall, and The Board for review and approval.

The process for handling protocol violations/deviations is described in the Manual of Operating Procedures.

17.0 Protocol Amendments and Modifications

Administrative changes which do not affect the risk/benefit ratio to the Subject shall be presented to the Investigation Site IRB/EC for abbreviated approval, according to the IRB policies in place at that institution. Any such changes shall be submitted to the Sponsor for record-keeping purposes. Material amendments or modifications shall require the full review and approval of the Primary Investigator, The Board, the IRB/EC at each Investigation Site, the FDA and the Sponsor prior to any implementation.

Any amendments or modifications, whether deemed administrative or material, to the original Clinical Investigation Plan/Protocol shall be shared with all Investigation Sites.

18.0 Risks and Benefits

As stated in the background section of this protocol, there are clinical challenges in treating intracranial wide neck aneurysms and there are several alternatives for the treatment of wide-neck intracranial aneurysms. Surgical approaches include clipping and trapping or wrapping. Endovascular treatment of intracranial aneurysms with detachable coils, which was introduced in 1996, allowed for an alternative therapeutic option to surgical clip ligation. Despite the introduction of improved coils as well as stent and balloon assisted coiling, there still some limitations: incomplete aneurysm occlusion as well as recurrence in complex large and giant aneurysms. If left untreated, aneurysms can rupture, causing death or significant permanent morbidity.

With an endovascular approach, detachable coils placed within the aneurysm sac of wide-neck aneurysms may protrude into the parent vessel and compromise normal blood flow. Thus, this anatomical configuration makes it difficult to achieve a thorough packing of the aneurysm with coils. As such, the rates of complete angiographic occlusion for these wide-neck aneurysms are often very low when standard techniques are employed.

With the stent-assisted technique, the neurovascular stent is placed across the aneurysm neck, to act as a bridge to prevent coils from protruding into the parent artery. Stenting may allow the operator to more safely achieve a higher packing density of coils. These more thoroughly packed aneurysms are likely better protected against future re-canalization and rupture. In addition, these devices placed in the parent vessel may produce an anatomical and physiological "remodeling" of the parent artery giving rise to the aneurysm. These effects may improve the rates of complete aneurysm occlusion and enhance the durability of the treatment.

The FRED System is designed as an alternative to embolization by coiling alone, stent-assisted coiling, or clipping of wide-necked aneurysms. Based on the concept of flow diversion stents, the FRED System is designed to preserve intraluminal blood flow through the parent artery and adjacent perforating vessels while occluding/redirecting blood flow into the aneurysm, allowing thrombosis to occur in the aneurysm. Adjunctive use of embolic coils may also be practiced. Due to its smaller cell size resulting from a higher metal-to-surface area ratio, the FRED is typically used without the adjuvant therapy of coils placed within the aneurysm sac of the parent artery, normally associated with a coil assist stenting techniques.

Some of the potential adverse events and risks/complications that may be associated with intracranial stenting with the FRED System include those listed in the Adverse Events section of this protocol. Mitigation activities including mechanical, performance, biocompatibility and sterilization testing have been performed with the FRED System and all tests met the applicable acceptance

criteria. Animal testing showed that the FRED System could be safely deployed and implanted in rabbit carotid arteries.

The efficacy of the FRED System for use with embolic coils for the treatment of unruptured, wide neck (neck $\geq$ 4 mm or dome to neck ratio < 2), intracranial, aneurysms arising from a parent vessel with a diameter $\geq$ 2.0 mm and $\leq$ 5.0 mm has not been demonstrated. However, the benefit of using the flow diversion stenting technique to prevent aneurysm rupture may outweigh the identified risks.

19.0 Control of Investigational Devices

The investigational devices (FRED System) shall be the sole responsibility of the Principal Investigator at the investigational site.

They shall be stored in a secure location that is separate from any other devices.

The investigational devices shall only be utilized in accordance to the FRED study protocol.

The accountability of each device that is delivered to the Investigation Site, including size, length, expiration date, lot number, and quantity, shall be solely the responsibility of the Principal Investigator.

The Principal Investigator shall not provide the investigational devices assigned to the FRED study to any other person, under any circumstances.

The process for maintaining investigational device accountability is found in the Manual of Operating Procedures.

20.0 End of Study

20.1 Expected Study End

The study will close once the desired number of subjects has been enrolled and the 12 months follow-up period or primary endpoint has been reached for all subjects. Study duration is estimated to be approximately 36 months from the enrollment of the first subject.

20.2 Early Study End

The study may be terminated early for any of the following reasons:

- New findings invalidate the positive risk-benefit assessment;
- The time schedule and recruitment phase cannot be met, secondary to low recruitment;
- In response to recommendations by the Data Safety Monitoring Board (DSMB);
- The sponsor decides to terminate the study, secondary to device related issues.

20.3 Termination of a Site by the Study Sponsor

The study may be terminated at an individual investigational site due to significant lack of compliance to the approved Clinical Investigational Plan/Protocol. The site may also be closed due to lack of enrollment. This will be determined by the study sponsor in consultation with The Board.

20.4 Resumption of Terminated Sites

The sponsor shall not resume the study at a terminated investigational site without prior IRB/EC and FDA approvals.

21.0 Publication

Any potential journal publications about the FRED study shall be provided to the sponsor for review prior to submission for publication consideration, as stated in the Site Investigator Protocol Agreement. The FRED study will be posted on the clinicaltrials.gov website.

22.0 Bibliography

1. Lee YJ, Kim DJ, Suh SH, et al. Stent-assisted coil embolization on intracranial wide-necked aneurysms. Neuroradiology 2005; 47: 680-689.

2. dos Santos Souza MP, Agid R, Willinsky RA, et al. Microstent-assisted coiling for wide-necked intracranial aneurysms. Can J Neurol Sci 2005; 32: 71-81.

3. Katsaridis V, Papagiannake C, Violaris C. Embolization of acutely ruptured and unruptured wide-necked cerebral aneurysms using the Neuroform2 stent without pretreatment with antiplatelets: a single center experience. AJNR Am J Neuroradiol 2006; 27: 1123-1128.

4. Mocco J, Snyder KV, Albuquerque FC, et al. Treatment of intracranial aneurysms with the Enterprise stent: a multicenter registry. J Neurosurg 2009; 110: 35-39.

5. Akpek S, Arat A, Morsi H, et al. Self expanding stent – assisted coiling of wide-necked intracranial aneurysms: a single-center experience. AJNR Am J Neuroradiol 2005; 26: 1223-1231.
6. Molyneux A, Kerr R, Stratton I, Sandercock P, Clarke M, Shrimpton J, Holman R. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet 2002: 360: 1267-74.

7. Wakhloo A. Intracranial Stenting: Applications and Techniques. International Symposium on Endovascular Therapy, January 23-27, 2000.

8. Guterman L, Hopkins LN. Endovascular treatment of giant intracranial aneurysms. Techniques in Neurosurgery Vol 4 No 2:179-184, June 1998.

9. Szikora I, Guterman L, Wells K, Hopkins LN. Combined use of stents and coils to treat experimental wide-necked carotid aneurysms: Preliminary results. AJNR 15: 1091-1102, June 1994.

10. Geremia G, Brack T, Brennecke L, Haklin M, Falter R. Occlusion of experimentally created fusiform aneurysms with porous metallic stents. AJNR 21:739-745, April 2000.

11. Lanzino G, Wakhloo A, Fessler R, Mericle R, Guterman L, Hopkins LN. Intravascular stents for intracranial internal carotid and vertebral artery aneurysms: Preliminary clinical experience. Neruosurg Focus 5(4): Article 3, 1998.

12. Berge J., Tourdias T., Moreau JF et al. Perianeurysmal brain inflammation after flow diversion treatment. AJNR 2011; 32: 1930-34.

13. Lylyk P. Miranda C., Ceralto R et al. Curative endovascular reconstruction of cerebral aneurysms with the pipeline embolization device: The Buenos Aires experience. Neurosurg 2009; 64: 632-643.

14. Szikora I., Berentei Z., Zulcsar Z et al. Treatment of intracranial aneurysms by functional reconstruction of the parent artery: the Budapest experience with the pipeline embolization device. AJNR 2010; 31:1139-47.

15.

16. Cebral JR., Mut F., Raschi M et al. Aneurysm rupture following treatment with flow-diverting stents computational hemodynamic analysis of treatment. AJNR 2010; 32:27-33.

17. Kelly CJ., Krings T., Fiorella D. et al. A novel grading scale for the angiographic assessment of Intracranial Aneurysms treated using Flow diverting stents.Interv Neuroradiol 2010:16:133-37.

18. Cekirge HS, Yavuz K., Geyik S et al. A novel « Y » stent flow diversion technique for the endovascular treatment of Bifurcation aneurysms without endovascular coiling. AJNR 2011; 32:1262-68.

19. Consoli A., Nappini S, Renieri L et al. Treatment of two blood blister-like aneurysms with flow diverter stenting. J NeuroIntervent Surg 2011; 10.

20. Dai D., Ding YH., Kadirvel R., et al. Patency of branches after coverage with multiple telescoping flow-diverter devices: An in vivo study in rabbits. AJNR 2012:33: 171-74.

21. D'Urso PI, Lanzino G., Cloft HJ and al. Flow diversion for intracranial aneurysms: a review. Stroke 2011; 42:2363-68.

22. Fiorella D., Kelly ME., Albuquerque FC et al. Curative reconstruction of giant mid-basilar trunk aneurysm with the Pipeline embolization device. Neurosurg 2009; 64:212-17.

23. Fiorella D., Albuquerque F., Gonzalez F. et al. Reconstruction of the right anterior circulation with the Pipeline embolization device to achieve treatment of a progressively symptomatic, large carotid aneurysm. J NeuroInterv Surg 2010; 2:31-37.

24. Fiorella D., Woo HH., Albuquerque FC et al. Definitive reconstruction of circumferential fusiform intracranial aneurysms with the pipeline embolization device. Neurosurgery 2008; 62: 1115-20

25. Gaughen JR Jr, Hasan D., Dumont AS et al. The efficacy of the endovascular stenting in the treatment of supraclinoid internal carotid artery blister aneurysms using a stent-in-stent technique. AJNR 2010; 31:1132-38.

26. Jahromi BS, Mocco J., Bang JA. Et al. Clinical and angiographic outcome after endovascular management of giant intracranial aneurysms. Neurosurg 2008; 63: 662-75.

27. Kamran M., Yarnold J., Grunwald IQ, et al. Assessment of angiographic outcomes after flow diversion treatment of intracranial aneurysms: a new grading schema. Neuroradiology 2010; 53: 501-8.

28. Kallmes DF, Ding YH, Dai D et al. A new endoluminal, flow-disrupting device for treatment of saccular aneurysms. Stroke 2007; 38:2346-52.

29. Klisch J., Turk A., Turner R., et al. Very Late Thrombosis of Flow-Diverting Constructs after the Treatment of Large Fusiform Posterior Circulation Aneurysms. AJNR 2011; 32:627-32.

30. Kulcsar Z., Houdart E., Bonafe A., et al. Intra-aneurysmal thrombosis as a possible cause of delayed aneurysm rupture after flow diversion treatment. AJNR 2011; 32:20-25

31. Kulczar Z., Ernemann U., Wetzel SG et al. High-profile flow diverter (Silk) implantation in the basilar artery: efficacy in the treatment of aneurysms and the role of the perforators. Stroke 2010; 41:1690-6.

32. Lopes DK., Johnson AK., Evaluation of cerebral artery perforators and the pipeline embolization device using optical coherence tomography. J. NeuroIntervent Surg 2011;10: 102

33. Lubicz B, Collignon L, Raphaeli G et al. Flow-diverter stent for the endovascular treatment of intracranial aneurysms: a prospective study in 29 patients with 34 aneurysms. Stroke 2010; 41: 2247-2253.

34. McAuliffe W., Wycoco V., Rice H. et al. Immediate and Midterm Results following Treatment of Unruptured Intracranial Aneurysms with the Pipeline Embolization Device. AJNR 2012; 33:164-170.

35. Meyers PM., Schumacher HC., Higashida RT et al. Reporting standards for endovascular repair of saccular intracranial cerebral aneurysms. Stroke 2009:40; 366-79.

36. Nelson PK., Lylyk P., Szikora I., and al. The Pipeline Embolization Device for the Intracranial Treatment of Aneurysms Trials. AJNR 2011; 32:34-40.

37. Pistocchi S., Blanc R., Bartolini B et al. Flow diverters at and beyond the level of the circle of Willis for the treatment of intracranial aneurysms. Stroke 2012; 43:1032-1038.

38. Puffer RC, Kallmes DF., Cloft HJ et al. Patency of the ophthalmic artery after flow diversion treatment of paraclinoid aneurysms. J Neurosurg 2012; January 6.

39. Raymond J., Guilbert f., Weill A et al. Long-term angiographic recurrences selective endovascular treatment of aneurysms with detachable coils. Stroke 2003; 34:1398-1403.

40. Raymond J., Darsaut TE., Guilbert F et al. Flow diversion in aneurysm trial: the design of the FIAT study. Interv Neuroradiol 2011;17: 147-53.

41. Sadasivan C, Cesar L., Seong J et al. An original flow diversion device for the treatment of intracranial aneurysms: Evaluation in the rabbit elastase-induced model. Stroke n2009; 40:952-58.

42. Shehab N., Sperling I.S., Kegler SR., National estimates of emergency department visits for hemorrhage-related adverse events from clopidogrel plus aspirin and from warfarin. Arch Intern Med 2010; 170:1926-1933.

43. Siddiqui AH., Kan P., Abla AA., et al. Complications following Treatment with Pipeline Embolization for Giant Distal Intracranial Aneurysms with or without coil embolization. Neurosurg 2012.

44. Sluzewski M., van Rooij WJ., Beute GN et al. Balloon-assisted coil embolization of intracranial aneurysms: incidence, complications, and angiography results. J Neurosurg 2006; 105:396-99.

45. Velat GJ., Fargen KM., Lawson MF et al. Delayed intraparenchymal hemorrhage following pipeline embolization device treatment for a giant recanalized ophthalmic aneurysm. J NeuroInterv Surg 2011; 4(5):e24.

46. Wong GKC., Kwan MCL., Ng RYT et al. Flow diverters for treatment of intracranial aneurysms: Current status and ongoing clinical trials. J Clin NeuroSc 2011; 18:737-40.

47. Yang P., Liu J., Huang Q et al. Endovascular treatment of wide-neck middle cerebral artery aneurysms with stents: a review of 16 cases. AJNR 2010; 31:940-46.

48. Roy D, Milot G, Raymond J. Endovascular treatment of unruptured aneurysms. Stroke 2001;32:1998-2004.

49. Lin, L. , Colby, G., Kim, J., Huan, J., Tamargo, R., Coon, A. Immediate and follow-up results for 44 consecutive cases of small (<10 mm) internal carotid artery aneurysms treated with the pipeline embolization device. Surg Neurology International, 2013, 4:114.

50. Diaz, O., Gist, T., Manjarez, G., Orozco, F., Almeida, R. Treatment of 14 intracranial aneurysms with the FRED system. J NeuroIntervent Surg 2013, 0:1–4.

51. Chalouhi, N., Starke, R., Yang, S., Bovenzi, C. Tjoumakaris, S., Hasan, D., et al. Stroke 2014; 45:54-58.