

Appendix 1 – PUFS Clinical Trial Protocol

IDE Clinical Study Investigational Plan

PUFS

Pipeline for Uncoilable or Failed Aneurysmsu

Protocol # / Version Date:	CLP-0005.C – Version: October 3, 2008
Study Sponsor:	Chestnut Medical Technologies, Inc. 173 Jefferson Ave. Menlo Park, CA 94025 <div style="background-color: black; width: 150px; height: 20px; margin-top: 5px;"></div> <div style="background-color: black; width: 450px; height: 20px; margin-top: 10px;"></div> <div style="background-color: black; width: 300px; height: 20px; margin-top: 5px;"></div>
Principal Investigator:	To be determined prior to start of study
Coordinating Investigator:	To be determined prior to start of study

A complete site list will be maintained and will be available upon request.

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Sponsor representative signature: _____

Sponsor representative name: _____

Date: _____

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1. Protocol Summary

Title:	Pipeline for <u>Uncoilable</u> or <u>Failed Aneurysms</u>
Name of Device:	Chestnut Medical Technologies, Inc. Pipeline™ Embolization Device (PED)
Study Design:	Prospective, multicenter, single-arm clinical trial
Purpose:	To determine the safety and effectiveness of Pipeline™ Embolization Device in the minimally invasive endovascular treatment of uncoilable intracranial aneurysms
Study Duration:	Each subject will participate for at least 5 years. Extended follow-up will occur in the post-market setting. Total trial duration will be approximately 6 years
Patient Population:	Patients with one wide-necked, large or giant intracranial aneurysm in the petrous, cavernous, or paraophthalmic regions of the internal carotid artery
Sample Size:	Up to 100 subjects
Number of Sites:	Up to 5 study sites
Patient Follow-Up:	Assessment prior to hospital discharge, and study visits at 30 days, 180, days and 1, 3 and 5 years after the procedure. Telephone contact at 90 days, 2 and 4 years after the procedure
Study Endpoints:	<p>Primary Endpoints:</p> <ul style="list-style-type: none"> • <u>Primary effectiveness endpoint</u>: index treatment success, defined as complete occlusion of target IA at 180-day angiography in the absence of additional treatments • <u>Primary safety endpoint</u>: occurrence of ipsilateral major stroke or neurologic death by 180 days <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • Complete occlusion of the target IA at 1, 3 and 5 years • Ipsilateral stroke at 180 days • Change in Modified Rankin Scale ≥ 2 points at 180 days • Change from baseline in neurologic signs/symptoms related to target IA at 180 days • Device-related adverse events at 180 days, 1, 3 and 5 years

2. Study Purpose

2.1. Name of Device

Pipeline™ Embolization Device (PED).

2.2. Purpose

The purpose of this document is to describe a clinical trial to be executed under Investigational Device Exemption.

2.3. Objectives

The objective of this study is to determine the safety and effectiveness of PED placement in the endovascular treatment of large or giant wide-necked intracranial aneurysms (IAs) in the petrous, cavernous or paraophthalmic (hypophyseal, ophthalmic, or paraclinoid) segments of the internal carotid artery

2.4. Duration

Each study subject will participate for at least 5 years. It is anticipated that long-term follow-up will occur in the post-market setting. The entire study duration is estimated to be 6 years.

3. Investigational Protocol

3.1. *Background*

Intracranial aneurysms (IAs) are common cerebrovascular abnormalities. The prevalence of IAs has been reported to be 0.8-2.0%.^{1, 2} The most common presentation of IAs is subarachnoid hemorrhage (SAH), the annual incidence of which varies by geographic region from 10 to 20 per 100,000.^{3, 4} SAH is a devastating injury with a case-fatality rate of 51%.⁵ Nearly half of its survivors are functionally incapacitated.⁶

Physicians treat IAs in order to reduce the incidence of spontaneous rupture or to alleviate symptoms of mass effect related to aneurysm growth. The anatomic goals of IA treatment are 1) to completely isolate the aneurysm sac from the circulation (i.e., complete occlusion) and, 2) to restore the morphologic integrity of the parent artery.

Common approaches to IA treatment include open neurosurgical and closed endovascular techniques. The most commonly used endovascular approach is coil embolization, in which small coils are placed inside the sac of an IA using a catheter inserted into the femoral artery. Thrombus forms on coils retained in the IA sac, resulting in isolation of the sac from the parent artery. The International Subarachnoid Aneurysm Trial (ISAT), a large randomized trial of endovascular coil embolization of IAs vs. neurosurgical clipping, showed that coil embolization had a lower rate of dependency or death in follow-up.⁷ Since the publication of ISAT, the use of endovascular therapy has grown markedly.

While coil embolization can be performed in many cases, complete occlusion of the IA and restoration of parent artery anatomy is surprisingly uncommon. Large (≥ 10 mm) and giant (≥ 25 mm) IAs are known to experience low rates of complete occlusion after coil embolization (acute complete occlusion rates of 40% in large IAs and 26% in giant IAs, respectively⁸). Achieving complete occlusion is important, since IA recurrence and re-bleeding are known to be associated with residual filling of the treated IA.⁹ Moreover, many patients with wide-necked saccular IAs cannot be treated with coil embolization because the geometry of the sac does not allow acute retention of placed coils. Coil embolization of non-saccular IAs (NSAs) is typically not attempted because the IA does not have a neck that can hold coils in place. In many cases, these patients cannot undergo neurosurgery for treatment of their IAs because of difficulty accessing the target IA or other surgical limitations. Thus, a substantial proportion of patients with IAs either has poor success rates with coil embolization or cannot undergo coil embolization for anatomic reasons. These IAs will be referred to as “uncoilable IAs.”

Chestnut Medical Technologies, Inc. (Menlo Park, CA) has developed a novel endoluminal device called Pipeline™ Embolization Device (PED). PED is specifically designed for placement into a parent artery affected by wide-necked

IAs or NSAs. PED is designed to slow flow into the aneurysmal portion of the artery in order to promote thrombosis of the IA while maintaining patency of the parent vessel. PED is also designed to allow endothelial regrowth, further limiting the potential for IA recurrence or recanalization.

In the investigation described herein, patients with IAs in the paraclinoid region of the internal carotid artery that are determined to be untreatable by standard coil-based methods alone (i.e., uncoilable) will undergo treatment with PED. Note that this study is being performed concurrently with another clinical study called COCOA (Complete Occclusion of Coilable Aneurysms using PED), a Chestnut Medical-sponsored study in which paraclinoid IAs determined to be coilable will undergo random assignment to treatment with either PED alone or coils alone.

3.2. Rationale for Study Design and Study Population

PUFS is a single-arm study of large and giant wide-necked IAs in which subjects will be treated with PED only. As described above, the long-term success rates for these IAs is low; thus these IAs are considered uncoilable. To date, no endovascular technology with FDA-accepted evidence of effectiveness is commercially available to address uncoilable IAs. For this reason, alternative minimally invasive treatments that could form a reasonable concurrent control group are not available. To put PUFS results into perspective, results will be compared with historical information derived from earlier cohorts in which subjects with similar IAs underwent coil embolization. It was this latter experience that led to our current understanding of the limitations of coil-based approaches to IA therapy.

The anatomic criteria for the PUFS target IAs were also selected based on results from PITA, a study of PED placement conducted in the EU and South America. In PITA, 24 of the 31 subjects treated with PED had IAs in the paraclinoid region and none experienced embolic stroke directly related to PED.* In a recent small (n=8) study conducted in Hungary, 4 subjects had IAs in the paraclinoid regions, all of which were considered uncoilable. Of these 4, one had a retinal artery thrombosis related to either coil embolization or PED (both devices were used in the procedure). In summary, prior clinical experience with PED provides strong evidence that the benefit of PED placement in the anatomic region targeted in PUFS outweighs the potential risks.

3.3. Prior Investigations

As of February 2008, PED has been used in 69 patients worldwide.

* One of these 24 patients required an emergency surgical intervention with ligation of the ICA at the level of the PCOM and experienced a hemispheric infarct post-operatively, not related to the PED, which had been removed.

PITA. PED was used in PITA (“Pipeline Embolization Device for Intracranial Treatment of Aneurysms”), a single arm study of IAs conducted in Europe and South America in 2007. Subjects were included if they had IAs with wide necks (> 4 mm or dome/neck ratio < 2) or IAs that had failed previous therapy. Many of the IAs in PITA would have been considered uncoilable. Thirty one patients were enrolled at four centers in the EU and South America and received a total of 47 implants. 46/47 PED placements were considered successful. Six-month follow-up angiography was performed in 30 patients and demonstrated complete IA occlusion in 28 patients (93.3%) with persistent IA filling in 2. Serious adverse events included periprocedural stroke in two patients (6.5%) and severe contrast reaction in one patient (3.2%).

Argentina. PED has also been used on a compassionate use basis in Argentina to treat complex IAs outside of PITA. Thirty-eight devices have been deployed in 28 patients to treat 29 aneurysms. Of the 18 patients that have returned for follow up (1-20 months), 14 (78%) showed complete IA occlusion, 2 showed a neck remnant (11%) and 2 (11%) have residual aneurysm. Many of the IAs treated in Argentina were considered uncoilable.

United States. Two patients with large, circumferential vertebral artery aneurysms have undergone PED treatment at Cleveland Clinic under compassionate use exemption by FDA. Both aneurysms were deemed untreatable by other open neurosurgical or conventional endovascular techniques by the referring neurosurgeons and an outside expert consultant. Both patients were treated without complications and remain without neurological symptoms. Both patients have had 1-year angiographic follow-up demonstrating durable anatomical reconstruction of their parent vessels and complete angiographic aneurysm occlusion.

An additional patient at Cleveland Clinic underwent PED placement under compassionate use exemption by FDA on April 11, 2008. This patient is a 13-year-old girl with a giant, partially thrombosed circumferential basilar trunk aneurysm. The aneurysm was determined to be untreated by neurosurgical approaches. A previous approach at coil embolization had failed. The PED placement procedure went well, with endovascular placement of 7 devices. Angiography at post-operative day 7 showed complete occlusion of the target IA.

Hungary. Eight patients with complex IAs not amenable to treatment with conventional coil embolization have been enrolled in a single center clinical study in Budapest, Hungary. Outcomes from this small study were generally very positive. Two patients had periprocedural strokes; one of these patients had not taken the pre-procedure antiplatelet medication according to the protocol. The other patient was treated with both PED and coils and experienced a retinal artery thrombosis. One patient died from a contralateral (untreated) IA. Six-month follow-up visits will begin in April 2008.

3.4. Design

This is a prospective, multicenter, single-arm clinical trial.

3.5. Number of Sites

Up to 5 study centers may participate in this trial.

3.6. Sample Size

The maximum sample size is 100 subjects who undergo study treatment and 180-day clinical and angiographic follow-up. The actual number of enrolled subjects is not known definitively and will depend on interim analysis (see **Section 3.20.3**).

3.7. Study Population

The target population for this study is patients with large or giant wide-necked or non-saccular intracranial aneurysms (IAs) in the petrous, cavernous or paraophthalmic (including paraclinoid, ophthalmic and hypophyseal segments) segments of the internal carotid artery. Patients may be included in the study if they meet all of the inclusion and none of the exclusion criteria shown in **Table 1**.

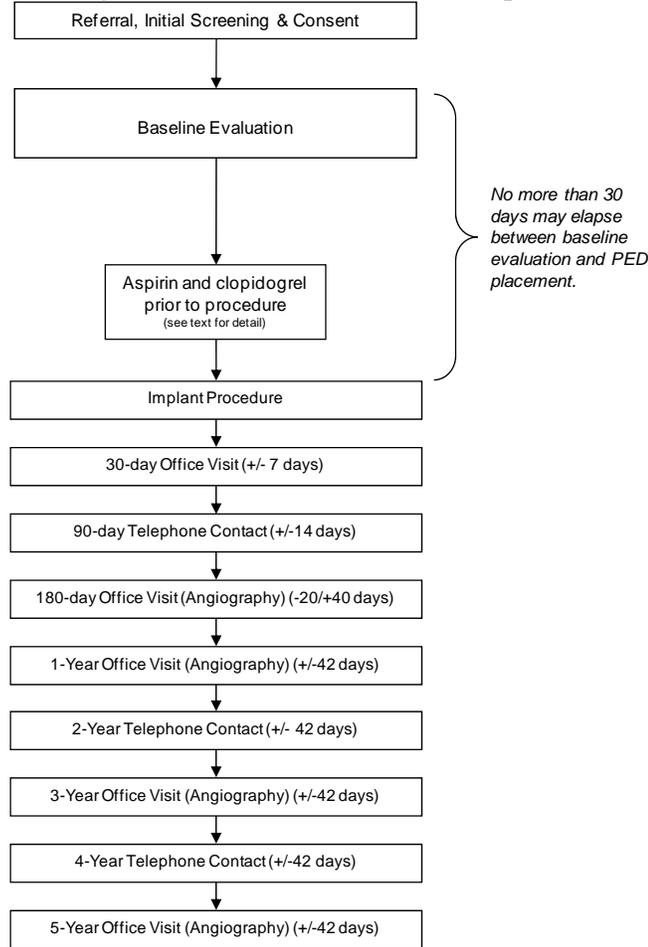
Table 1. Study inclusion and exclusion criteria. Patient must meet all inclusion criteria and have none of the exclusion criteria.

<p>Inclusion Criteria</p> <ul style="list-style-type: none"> a) Age 21 to 75 years, inclusive b) Patient has a single target IA that: <ul style="list-style-type: none"> 1) Is located in the following regions of the internal carotid artery: <ul style="list-style-type: none"> i. Petrous ii. Cavernous iii. Paraophthalmic (including paraclinoid, ophthalmic and hypophyseal segments) 2) Has a neck >4 mm or no discernible neck AND a size (maximum fundus diameter) >10 mm 3) Has a parent vessel with diameter 2.5 – 5.0 mm distal/proximal to the target IA c) Subject has provided written informed consent using the IRB-approved consent form d) Subject has the necessary mental capacity to participate and is willing and able to comply with protocol requirements
<p>Exclusion Criteria</p> <ul style="list-style-type: none"> a) More than one IA requires treatment in the next 6 months b) Subarachnoid hemorrhage in the past 60 days c) Any intracranial hemorrhage in the last 42 days d) Major surgery in the last 42 days e) Unstable neurologic deficit (i.e., any worsening of clinical condition in the last 30 days) f) History of irreversible bleeding disorder g) Platelet count < 100 x 10³ cells/mm³ or known platelet dysfunction h) Inability to tolerate, documented evidence of adverse reaction or contraindication to study medications i) Stent in place at the target IA j) Contraindication to CT scan or MRI k) Known allergy to contrast used in angiography that cannot be medically controlled l) Known severe allergy to [REDACTED] alloys m) Relative contraindication to angiography (e.g., serum creatinine > 2.5 mg/dL) n) Woman of child-bearing potential who cannot provide a negative pregnancy test o) Evidence of active infection at the time of treatment p) Other known conditions of the heart, blood, brain or intracranial vessels that carry a high risk of neurologic events (e.g., severe heart failure, atrial fibrillation, known carotid stenosis) q) Current use of cocaine or other illicit substance r) Any comorbid disease or condition expected to compromise survival or ability to complete follow-up assessments to 180 days s) Extracranial stenosis greater than 50% in the carotid artery Intracranial stenosis greater than 50% in the treated vessel

3.8. Overview of Study Flow

A diagram of study flow from referral through the study procedure is shown in **Figure 1**.

Figure 1. Diagram of study flow from referral to procedure.



3.9. Recruitment

Potential study participants will be identified by the study site Investigator or co-Investigator with assistance from qualified research staff. It is anticipated that referrals will be an important source of study candidates.

3.10. Screening

The Investigator or his/her designee will perform an initial evaluation of existing patient information to determine potential eligibility. This initial review of existing patient information may be performed prior to patient consent; however, no protocol-driven tests or procedures may be performed until after informed consent has been obtained.

3.11. **Informed Consent**

A member of the research team will explain the study's objectives to potential candidate patients, including describing standard treatment with coil embolization, treatment with PED, the requirements of the clinical investigation, and risks and benefits of participating. A patient must sign the informed consent prior to any procedures/tests that are protocol-driven or go beyond standard patient care for patients with IAs. All informed consent documents used under this study protocol will be consistent with applicable elements of ISO14155, Good Clinical Practice Guidelines and 21 CFR Part 50, and will be approved by the site's reviewing IRB prior to study initiation.

3.12. **Baseline Evaluation**

Once the site Investigator has determined that the patient meets all PUFS eligibility criteria, the patient is considered enrolled and is called a "study subject." The subject will undergo a focused physical examination, a blood draw for hematocrit, platelet count, serum creatinine, and a pregnancy test (if applicable). The baseline examination will include completing the NIH Stroke Scale. If the baseline evaluation requirements are available as part of the patient's routine examinations and medical history and are within 6 months, these tests need not be repeated after the patient's informed consent is obtained. A complete schedule of assessment for the study is shown in **Table 6**.

3.12.1. **Baseline Visual Examination**

Many patients with IAs in the paraclinoid region present clinically with eye findings, specifically cranial nerve III, IV and VI dysfunction (blown pupil, diplopia), loss of visual acuity or loss of visual fields. Therefore, all participating patients will undergo baseline examination by an ophthalmologist. The purpose of the baseline ophthalmologic examination (details in **Table 2**) is to document any pre-existing eye pathology.

Table 2. Description of baseline ophthalmologic tests.

Examination	Description
Fundus photograph	A photograph of the fundus will be taken at baseline only
Pupil function	Pupillary light (direct, consensual) and accommodation reflexes will be assessed clinically
Eye alignment	Alignment will be assessed at baseline only using the alternating cover test and prism diopters. Alignment will be collected with gaze center, left and right. In addition, eye movement during right and left gaze will be scored clinically on a 0-100 scale at baseline and during follow-up.

Examination	Description										
Visual acuity	<p>Visual acuity will be scored for each eye using a Snellen chart at baseline and follow-up. If visual acuity is impaired such that the subject cannot read the largest letter on the Snellen chart, visual acuity may be assessed according to the table below:</p> <table border="1"> <thead> <tr> <th>Abbreviation</th> <th>Definition</th> </tr> </thead> <tbody> <tr> <td>CF (count fingers)</td> <td>Ability to count fingers at a given distance</td> </tr> <tr> <td>HM (hand motion)</td> <td>Ability to distinguish a hand if it is moving or not in front of a patient's face</td> </tr> <tr> <td>LP (light perception)</td> <td>Ability to distinguish if the eye can perceive any light</td> </tr> <tr> <td>NLP (no light perception)</td> <td>Inability to see any light</td> </tr> </tbody> </table>	Abbreviation	Definition	CF (count fingers)	Ability to count fingers at a given distance	HM (hand motion)	Ability to distinguish a hand if it is moving or not in front of a patient's face	LP (light perception)	Ability to distinguish if the eye can perceive any light	NLP (no light perception)	Inability to see any light
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LP (light perception)	Ability to distinguish if the eye can perceive any light										
NLP (no light perception)	Inability to see any light										
Visual field	Visual field analysis (VFA) will be performed at baseline and follow-up with automated static perimetry (24-2 examination) using the Humphrey Field Analyzer. The primary measures of interest are mean deviation index and pattern standard deviation.										

3.13. Medical Regimen Before and After Procedure

The subject must take antiplatelet agents both prior to and after the placement procedure as defined below.

Clopidogrel. Subjects assigned to PED will take 600 mg “loading dose” of clopidogrel orally (loading dose) 1 day prior to the procedure OR 75 mg orally daily for at least 7 days prior the procedure. The subject will continue to take 75mg of clopidogrel by mouth daily for a minimum of 3 months following treatment.

Aspirin. Subjects assigned to PED will take at least 325 mg of aspirin daily for at least 2 days prior to the procedure. The subject will continue to take at least 325 mg of aspirin by mouth daily for a minimum of 6 months following treatment.

Aspirin and clopidogrel may be continued beyond the above regimen if medically indicated (e.g., aspirating for coronary artery disease prophylaxis).

3.14. Study Treatment Procedure

The study procedure is described briefly below. Full details are provided in the Instructions for Use document.

The study procedure will take place at least 3 days but no greater than 30 days following the end of the baseline assessment. The minimum delay prior to PED placement is required because subjects must take aspirin and clopidogrel prior to the procedure.

3.14.1. Patient Preparation for Procedure

The patient should be prepared for the PED placement according to standard hospital procedures. The vascular system is accessed via the femoral artery.

3.14.2. Medication during Treatment

The subject will undergo the PED placement under general anesthesia. Medications appropriate for general anesthesia will be administered using standard hospital practice. Heparin use will be required during PED placement as detailed in **Table 3**. In summary, a heparin bolus is required, with confirmation of anticoagulation via activated clotting time (ACT) prior to insertion of PED. Heparin may be administered for up to 24 hours after the procedure.

Table 3. Heparin use during both procedures.

During procedure	<ul style="list-style-type: none"> • Check baseline ACT • Bolus heparin at 50-100 U/kg • Prior to inserting study device into body, check ACT with goal of 2-3.5x normal • Adjust heparin as clinically appropriate to this target range • Check further ACTs per standard practice
After procedure	<ul style="list-style-type: none"> • Heparin may be used up to 24 hours after procedure. If medically indicated, heparin use may be continued after 24 hours, but the Investigator must document why.

3.14.3. Pre-Placement Angiography

On occasion, the status of the target IA may change between the end of baseline evaluation and the assigned study procedure, potentially increasing the risk of the study procedure. Therefore, angiography will be repeated just prior to the assigned treatment procedure in order to confirm that the study treatment can be performed safely, that no other adverse findings that might pose a risk to the patient are present, and to collect precise baseline images of the IA suitable for analysis by the core laboratory radiologist. In the unlikely event that a patient is excluded as a result of findings on the pre-treatment angiogram, the subject should undergo appropriate treatment of the target IA by the Investigator. The patient will be followed for the occurrence of adverse events up to hospital discharge.

If angiography shows that the patient remains eligible for study participation, the Investigator will perform PED placement and a Patient Implant Card will be completed.

The Investigator will submit electronic copies_of angiographic images on CD or other appropriate media to the study Sponsor. The Investigator will also prepare photo files containing images suitable for qualitative image analysis (QIA, see **Section 3.20.1**). The Investigator will ensure that subject identifiers are removed from all submitted images. Image files/CDs should be labeled with the subject's study ID number. Photo files are described in more detail in the study imaging manual.

3.14.4. Devices and Equipment

Optional coil placement with intravascular stents is commonly performed when treating large or non-saccular aneurysms. However, PED is designed to disrupt flow into the aneurysm sufficient to cause aneurysm thrombosis, obviating the need for additional coils. Therefore, optional coiling will not be allowed in this study.

In addition to the investigational device, devices that may be required for the study procedure include, but are not limited to, those shown in **Table 4**. All devices required to perform the procedure will be provided by the site and are available commercially for the indications for which they are proposed in this study.

Table 4. Other devices to be used during PED placement.

- | |
|---|
| <ul style="list-style-type: none"> • Access devices: Guiding catheter and sheath • Delivery catheters: Microcatheter, either Renegade Hi Flow (Boston Scientific), or Mass Transit (Cordis Neurovascular) are recommended • Non-ionic contrast • Guidewires • Any other adjunctive, approved/cleared device for IA treatment |
|---|

The placement procedure is described briefly in **Figure 2** and in more detail in the attached Instructions for Use (IFU) document.

NOTE: The Investigator should review and understand the complete IFU prior to performing any PED placement in this clinical study. The following is only a summary overview.

- | |
|---|
| <ol style="list-style-type: none"> 1. Using a standard radiographic technique, place a commercially available microcatheter past the distal edge of the IA. 2. Open the PED Introducer Sheath packaging. 3. Remove the wire from the packaging. 4. Push the wire and introducer sheath out of the packaging coil. 5. Insert the introducer sheath into the microcatheter hub. 6. Secure the introducer sheath to the hub. 7. Advance the PED into the microcatheter by pushing the delivery wire. 8. Thread the PED through the microcatheter until it lies in the parent artery distal to the target IA. 9. Unsheath the PED as recommended in the IFU by slowly retracting the catheter. 10. After the distal segment of the PED is exposed, deploy the distal end of the |
|---|

- PED per Instructions for Use.
11. Deploy the remainder of the PED by advancing the wire and maintaining forward motion on the catheter.
 12. After the entire PED is deployed, advance the microcatheter through the PED and retract the delivery wire into the microcatheter while rotating the delivery wire per the IFU to prevent entanglement with the fully deployed PED.

Figure 2. Summary of PED placement procedure.

3.14.5. Post-Treatment Angiogram

Post-treatment angiograms in the AP, lateral, and working positions will be obtained, and electronic copies will be submitted to the Sponsor. The Investigator will take necessary steps to ensure that pre- and post-placement angiograms are performed using similar views, magnifications and contrast amount so as to ensure valid “before-after” comparisons. However, these angiographic details will not be collected in case report forms (CRFs).

3.14.6. Recovery

The subject will be recovered from the procedure and discharged from the hospital as per standard practices. Prior to discharge, the Investigator will perform a neurologic examination and document any changes. The Investigator will also collect a modified Rankin Scale.

3.14.7. Disposal of Investigational Device

PEDs will either be returned to the study sponsor or disposed of per standard institutional practices. If the device is associated with a device-related adverse event, malfunction or failure, the device should be returned to Chestnut Medical for evaluation. For the return of biohazard product, Chestnut Medical must be contacted prior to product return for handling instructions.

3.15. Staged Treatment

In some cases, large IAs may require placement of multiple PEDs. On occasion, however, complex arterial anatomy may make it difficult or potentially risky for the Investigator to pass a second PED delivery system across a PED construct previously deployed in the parent artery earlier during the procedure. The Investigator may wish to use a staged approach, in which a second procedure is performed after a suitable healing period. Experience with other systems indicates that it is often easier to pass a second delivery system after the parent artery in which the initially placed implant has had time to undergo re-endothelialization.

Therefore, staged procedures will be allowed in this protocol, meaning that at any time up to 2 months after the initial PED placement procedure, the subject may

undergo a second PED placement procedure. To perform a staged procedure, the Investigator must specify at the end of the initial treatment procedure whether or not a second staged procedure will be attempted and why. A second procedure resulting from a failed initial procedure will be counted as a salvage procedure, not a staged procedure. Adverse events occurring after a second procedure will be captured and reported. In addition, stroke or death occurring within 180 days of second procedure will also “count” towards the primary safety endpoint (see **Section 3.20**).

Note: If the subject undergoes a second placement procedure as part of a staged approach, the 180-day angiogram will be performed 180 days after the second procedure.

3.16. Salvage Treatments

On occasion, it may be impossible for the Investigator to place even a single PED. Such failures will be called “primary treatment failures” and will be counted as failures for the study’s primary endpoint. The subject may undergo alternative treatments (called “salvage treatment”) at the discretion of the Investigator. Salvage procedures may include another PED placement attempt. The Investigator will document any salvage treatment and its outcomes. If a salvage procedure is required, the 180-day angiogram and 180-day follow-up schedule will be “reset” so that they occur 180 days after the salvage treatment. Post-treatment aspirin and clopidogrel use will be at the discretion of the Investigator and will depend on the intervention provided.

Note: A subject with a failed index procedure who undergoes salvage treatment should be followed to the study end (5 years after the salvage procedure). A salvage procedure should take place at least 5 days but not more than 60 days after the failed index procedure.

Note: A subject with successful PED placement who undergoes a second PED placement procedure as part of a “staged approach” is NOT considered a study treatment failure, and the second PED placement procedure is NOT considered a salvage treatment.

3.17. Progression of IA Symptoms

Some patients with paraclinoid aneurysms present with “mass effect” of the IA, causing cranial nerve deficits or visual field cuts. In many cases, endovascular treatment of such IAs causes regression of symptoms. On occasion, however, a subject with mass effect may experience initial relief of symptoms after IA treatment but then have worsened symptoms during follow-up. Worsened symptoms can occasionally be due to edema or inflammation of the “thrombosing” IA, which can often be treated with medical therapy. However, if the Investigator believes that a secondary endovascular or surgical procedure for the target IA is required because of worsening symptoms, the subject will be

deemed a delayed treatment failure, and may undergo any appropriate treatment (including PED if required). Subjects who undergo secondary treatments should be followed for safety purposes to the end of the study.

Table 5 summarizes terminology used for additional procedures that could be performed in study subjects.

Table 5. Summary of post-treatment events that may lead to alternative target IA treatments.

Term for second procedure	Reason for second procedure	Angiographic Follow-Up Required in Study
Staged procedure	First procedure successful, but Investigator wants to place additional PEDs in a second procedure to increase flow disruption	To 5 years after second staged procedure
Salvage procedure	Physician unable to place even 1 PED across target IA during index procedure. Salvage procedure performed to provide subject with treatment for IA. Salvage may include another attempt at PED placement.	To 5 years after salvage treatment
Secondary procedure	Despite successful PED placement, subject has symptom progression requiring additional procedure to treat symptoms. Since few other choices are available for these subjects, treatment with additional PEDs is allowed.	None. However, subject should be followed to 5 years after enrollment for safety purposes.

3.18. Follow-Up Examination

Subjects will undergo follow-up in the clinic at 30 days and 180 days after the index procedure, and also at 1, 3 and 5 years after the index procedure. (Note that if a second procedure is performed as a staged approach, or if the subject undergoes a salvage procedure, the 30-day visit and 180-day visit/angiogram should be performed 30 and 180 days after the second or salvage procedure, respectively.) At the 30-day, 180-day, and 1-, 3- and 5-year visits, the subject will undergo a neurologic examination and assessment of the modified Rankin scale. The Investigator will also document all medications currently being taken. At the 180-day visit only, the subject will undergo repeat ophthalmologic assessment by the ophthalmologist. The subject will also undergo angiography of the target IA at 180 days, and at years 1, 3 and 5 after the index procedure. If available, imaging should include rotational angiography with 3D reconstruction. Electronic images suitable for analysis will be sent to the Sponsor for review by the core laboratory radiologist. The final study visit will be at 5 years after the index (or salvage) procedure.

Study personnel will also contact the subject by telephone at 90 days, and at 2 and 4 years after the index (or salvage) procedure. The purpose of the telephone call is to encourage continued study participation and to assess for changes in clinical status. If the subject reports a change, an addition (i.e., unscheduled) visit may occur (if deemed necessary).

It is anticipated that long-term follow-up at years 1-5 will occur primarily in the post-market setting.

3.19. Schedule of Assessments

The study’s schedule of assessments, including allowed post-procedure visit date windows, is shown in **Table 6**.

Table 6. Schedule of assessments.

Assessments	Pre-procedure	Procedure, Second Procedure or Salvage Procedure	Post-procedure / Prior to Discharge	30-Days Follow-up (+/- 7 days)	†90 days (+/- 14 days)	180-Day Follow-up (day -+40/-20 days)	†2, 4 years (+/- 42 days)	1, 3, 5* years (+/- 42 days)
Inclusion/exclusion criteria	X							
Demographics and medical history	X							
Intercurrent medical history and medication use				X	X	X	X	X
Neurologic Exam	X		X	X		X		X
Fundus photograph	X							
Ophthalmologic examination	X					X		
Hematocrit/platelet count	X							
Pregnancy test	X							
Modified Rankin Scale	X		X	X		X		X
Angiogram		X				X		X
Adverse events review	X	X	X	X	X	X	X	X
Medications	X	X	X	X	X	X	X	X
Termination								X

*Termination at 5 years.

† Telephone contact

3.20. Study Primary Endpoints

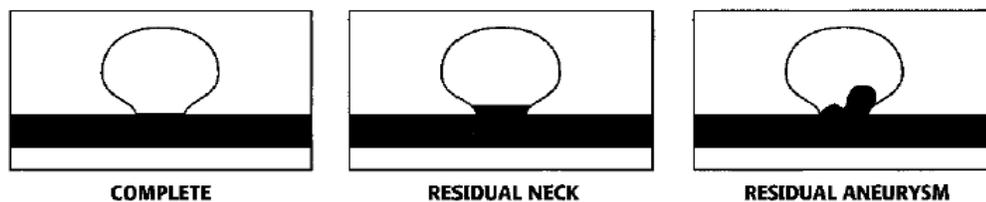
The study's **primary effectiveness endpoint**, called "PED treatment success," is the proportion of patients who show complete occlusion of the target IA and $\leq 50\%$ stenosis of the parent artery at the target IA location, as judged by the independent radiology committee (IRC, see **Section 4.20** below), on 180-day angiography in whom an alternative treatment on the target IA has not been performed. Note that use of additional PEDs in a second procedure as part of a staged approach is NOT considered alternative treatment. Note also that use of optional coiling during PED placement WILL BE considered an alternative treatment.

The study's **primary safety endpoint** is the proportion of subjects who experience either death due to neurologic reasons or major ipsilateral stroke (defined in **Section 3.25.1**) by 180 days after the last IA treatment procedure. While the primary safety endpoint is at 180 days, all adverse events occurring throughout follow-up will be assessed and tabulated. All safety endpoints will be adjudicated by an independent clinical events committee (CEC, see **Section 3.26**).

3.20.1. Qualitative Image Analysis of Primary Endpoint

The study's primary effectiveness endpoint relies on qualitative image analysis (QIA) performed by team of independent radiologist (independent radiology committee, IRC.) Each member of the IRC will be a qualified interventional neuroradiologist skilled in the interpretation of carotid angiograms. 3 IRC readers will participate. Images will be assessed according to the scale of Roy,¹⁰ shown in **Figure 3**. All readers will independently read all follow-up angiograms. The primary endpoint will be scored according to a "2 out of 3 majority wins" rule.

Figure 3. Criteria of Roy¹⁰ for judging IA endosaccular embolization success.



- **Complete** = complete occlusion, no flow of contrast seen in the sac
- **Residual Neck** = partial occlusion, some flow, or eddying flow, in the sac
- **Residual Aneurysm** = incomplete occlusion, apparent flow into the sac

A recent study showed that the reliability of individual radiologist raters in judging complete vs. incomplete post-treatment occlusion was very high (kappa = 0.96 and 0.99 for each rater).¹¹ Moreover, interrater reliability of the complete vs. incomplete judgment was also very high (kappa = 0.87).

An imaging manual will be developed to ensure reliable collection of images suitable for QIA. Investigators will be trained on image collection using the manual.

3.20.2. Analytic Perspective

Data analysis for the primary endpoints will use an intention-to-treat (ITT) approach with the following characteristics:

- For all primary and secondary endpoint analyses, the analysis population (i.e., “denominator” for rate calculations) will include only those cases in which the physician passed an access microcatheter distal to the IA for PED placement.
- The effectiveness of PED treatment alone will be assessed. That is, if a patient undergoes attempted PED placement with immediate failure, and subsequently undergoes an alternative therapy (e.g., neurosurgical clipping), and shows complete occlusion at the 180-day angiography, success cannot be attributed to the initial (failed) procedure.

Note that:

- If a subject has a missing angiogram at the 180-day visit or does not attend the 180-day clinical follow-up visit within the allotted window, the subject will be considered a primary effectiveness endpoint failure. Secondary analyses may be performed for subjects who had delayed follow-up angiograms. If required, multiple imputation methods will be used to assess the impact of missing data on the primary endpoint. Models may incorporate factors predictive of complete or incomplete occlusion using available data. Different assumptions for these models will be used as a type of sensitivity analysis.
- In the absence of data to suggest otherwise, a subject who does not attend the day 180 post-treatment visit in the allotted time window will not be considered a primary safety endpoint failure unless it is known that the subject experienced stroke or death.

3.20.3. Statistical Evaluation of Primary Endpoints

An adaptive Bayesian statistical approach will be used to evaluate the study’s primary endpoint and to potentially terminate enrollment before the maximum number of subjects (100). The statistical goal of the study is to show that complete occlusion of the target IA without stenosis of the parent artery (defined above) on 180-day angiography is at least 50% and the 180-day risk of major ipsilateral stroke or neurologic death is at most 20%. The approach utilizes pre-planned interim analyses and adjusts for overall risk of Type 1 error.

Modeling has shown that 100 subjects has ample statistical power to achieve the study's goals (non-inferiority for both safety and effectiveness to pre-defined thresholds). Details are available upon request.

3.20.4. Justification of Effectiveness and Safety Threshold

Effectiveness. All IAs in this study are uncoilable by virtue of being large and either wide-necked or having no discernible neck. Strong historical information from experience at University of California Los Angeles shows that the late complete occlusion rates with coil embolization alone for large (10-25 mm) and giant (≥ 25 mm) saccular IAs, most of which are wide-necked, are 36.4 and 27.7%, respectively. The complete occlusion rate for NSAs with coil embolization alone is zero, since coils typically cannot be retained in such IAs. Thus, 50% is a very conservative comparator for judging the effectiveness of PED for uncoilable IAs. An endovascular procedure with at least a 50% success rate would represent a marked advancement in therapy.

Safety. Patients with uncoilable IAs have limited alternatives for treatment. These alternatives include neurosurgical procedures, parent artery occlusion, and stent-assisted coiling.

- Various surgical procedures for uncoilable IAs can be performed. The death rate with surgery is 2.1-3.5%, and the perioperative morbidity rate is 15-25%. Roughly half of the perioperative adverse events are major strokes. Some authors have suggested that perioperative morbidity with neurosurgery is substantially underestimated.
- Deconstructive treatment (i.e., endovascular sacrifice of the parent artery with coils or detachable balloons) is tolerated by most, but not all, subjects. In published case series, stroke rates after parent artery occlusion are 8-18%.
- Stent-assisted coiling is a relatively new procedure. Intravascular stents are used to hold coils in place. Stroke occurs in approximately 9% of patients undergoing stent-assisted coiling. The target population in PUFS may be at higher risk for stroke because of the increased complexity of their target IAs compared to patients enrolled in stent-assisted coiling studies.

It should also be noted that patients with large/giant IAs or with NSAs have a very high rate of spontaneous rupture during follow-up. In the International Study of Unruptured Intracranial Aneurysms (ISUIA), patients with unruptured IAs were enrolled and followed forward in time.^{12,13} Compared to aneurysms <10 mm in diameter, IAs of 10-24 mm and >25 mm had relative risks of rupture of 11.6 and 59, respectively. Further follow-up from this cohort showed 5-year bleeding risks of 0%,

2.6%, 14.5%, and 40% for aneurysms less than 7 mm, 7–12 mm, 13–24 mm, and 25 mm or greater, respectively.¹⁴

In summary, patients eligible for PUFS have few reasonable alternatives. They face a high rate of often-fatal spontaneous bleeding without treatment. They also face a high rate of stroke or death with currently available treatments such as neurosurgery or parent artery sacrifice. A procedure with a high effectiveness rate and perioperative stroke/death rate whose upper confidence limit is <20% represents a significant advance for this patient population. The lack of reasonable alternatives justifies the proposed safety and effectiveness study success parameters.

3.21. Secondary Endpoints

Secondary clinical endpoints include:

- Rate of complete IA occlusion at 1, 3 and 5 years of follow-up
- Incidence of ipsilateral major stroke by 180 days
- Change in modified Rankin scale (MRS) at 180 days. MRS is a validated scoring system for neurologic status after stroke.¹⁵ The proportion of subjects with a change ≥ 2 at the 180-day visit compared to baseline will be determined. The modified Rankin Scale will be judged by the Investigator.
- Change from baseline in neurologic signs/symptoms related to target IA at 180 days
- Incidence of device-related adverse events at 180 days, 1, 3 and 5 years

3.22. Additional Statistical Analysis

Additional statistical analysis is described in the statistical analysis plan (available upon request). Subgroup analyses of the primary endpoints will be performed with the groupings shown in **Table 7**.

Table 7. Pre-planned subgroups.

<ul style="list-style-type: none"> • IA maximum dimension ≥ 25 mm vs. < 25 mm • IA neck size ≥ 6 mm vs. < 6 mm • IA partial thrombosed at baseline or not • Current/former smoker vs. never smoker
--

In addition, the following statistics will be calculated.

- Technical success, defined as the proportion of patients in whom at least one attempt was made to pass the access catheter distal to the target IA in whom the final locations of the PEDs placed are all within 5 mm of the desired location.

- Ranking of IA occlusion at all post-procedure timepoints using the three-tiered Raymond scale (i.e., incomplete, residual neck and complete occlusion).
- Proportion of subjects with complete occlusion of the target IA at 180 days, including salvage treatments, if provided
- Incidence of neurologic death by 180 days
- Change in mean deviation index (MDI) of the Humphrey Visual Field Assessment from baseline to 180 days after the index treatment. The MDI is the mean of the deviation from age-based normals in light sensitivity at pre-specified areas in the retina. MDI is measured in decibels (dB) and is a commonly accepted ophthalmologic endpoint. Since interpretation of visual fields requires clinical correlation, visual field assessments will be read by the site ophthalmologist and graded as to whether the subject is better, same or worse than prior to treatment. The minimally clinically important difference for MDI in patients with visual field defects due to IA is not known.
- Frequency of worsened eye alignment by clinical examination by the ophthalmologist
- Frequency of ≥ 2 lines lost in visual acuity by Snellen chart
- Frequency of ≥ 2 lines gained in visual acuity by Snellen chart
- Incidence of secondary treatments for the target IA
- Proportion of subjects in whom distal PED migration occurs. Distal migration is defined as distal movement of one or more PEDs of more than 5 mm in its parent artery location when comparing the 180-day angiogram with the post-placement angiogram.
- Proportion of PED subjects in whom more than mild stenosis at the PED occurs. IRC members will use the scoring system shown in **Table 8** to visually judge late stenosis of the treated parent vessel across the entire stent follow-up. A "2 out of 3" approach will be taken to score the category. If all members disagree (i.e., each assigns a different rating category), the middle value will be used. The proportion of subjects with each category of stenosis will be reported.

Table 8. Scoring system for stenosis.

Category	Degree of Stenosis
0	0 – 25%
1	>25 – 50%
2	>50 – 75%
3	>75 – 100%

For details of analytic approaches, see statistical plan.

3.23. Study Withdrawal

Subjects may be terminated or withdrawn from the study for the following reasons:

- Subject death
- Voluntary withdrawal – meaning that subject voluntarily chooses not to further participate in the study
- Loss to follow-up – meaning that the subject is more than one month late to a study visit and 3 documented attempts to contact the subject are unsuccessful.

NOTE: For those patients considered lost to follow-up (see definition above), the site will, at a minimum, make a concerted effort to confirm that the patient is not deceased (e.g., active search of death indices will be performed to ensure the patient remains alive).

All subjects enrolled (including those withdrawn or lost to follow-up) will be accounted for and documented.

3.24. Unattended Visits

Any study subject who does not attend a scheduled follow-up visit should be contacted by site personnel to determine the reason for the missed appointment(s). If the missed visit was due to an adverse event (AE), an AE Case Report Form (CRF) must be completed and any reporting requirements met.

3.25. Adverse Events

Adverse events (AEs) may occur after enrollment but prior to the index procedure, during the index procedure, or during the follow-up phase. Adverse events occurring prior to or during the baseline angiography assessment and/or other interventions prior to PED placement will be documented in the patient's medical record but will not count as study device- or study procedure-related, unless the adverse event is related to use of aspirin or clopidogrel. All adverse events will be reported to and reviewed by the study's Medical Monitor and by the Clinical Events Committee (CEC, see **Section 3.26**). Reporting of all adverse events will be handled per the applicable Sponsor Standard Operating Procedure (SOP).

Investigators will record characteristics of each adverse event on an Adverse Event CRF. Each adverse event will be judged by the Investigator as to its relationship and level of relatedness to the investigational devices and/or investigational procedure. Relatedness will be scored consistent with CTCAE 3.0* guidelines: unrelated, unlikely, possible, probably or definite relation to the study device or procedure. In addition, the Investigator will identify the date of onset, severity and duration. Severity will be judged using the scale noted in

* See http://ctep.cancer.gov/reporting/ctc_v30.html

Table 9. All adverse events will be monitored until they are adequately resolved or explained.

Table 9. Definition of event severity for judgment by Investigator.

Term	Definition
Mild	Patient is aware of a sign or symptom, but that sign or symptom does not interfere with normal activity <u>or</u> symptom is <u>both</u> transient and resolved
Moderate	Symptoms interfere with the subject's usual activity <u>or</u> symptoms require treatment
Severe	Symptom(s) cause <u>either</u> severe discomfort <u>or</u> have a significant impact of the subject's usual activity <u>and</u> symptoms require treatment

If a subject experiences a stroke (see **Section 3.25.1**), the Investigator will complete an NIH Stroke Scale assessment.

Definitions for adverse events are provided in **Section 4.10**.

3.25.1. Definition of Stroke

For the purposes of this study protocol, stroke is defined as:

A focal neurological deficit of presumed vascular origin persisting more than 24 hours AND a neuro-imaging study or other quantitative study that does not indicate a different etiology. The 24-hour criterion is excluded if the patient undergoes cerebrovascular surgery or dies during the first 24 hours. The definition includes patients presenting with clinical signs and symptoms suggestive of subarachnoid hemorrhage, intracerebral hemorrhage, or cerebral infarction. The definition also includes sudden loss or worsening of visual acuity due to retinal artery occlusion or retinal emboli. The definition excludes slowly progressive cranial nerve palsies or progressive visual field deficits due to continued aneurysm growth. The definition also excludes stroke events in cases of blood disorders such as leukemia or external events such as trauma.

Strokes will be categorized as ipsilateral or contralateral and peri-procedural (less than or equal to 30 days) or late (greater than 30-days from the procedure). Stroke severity will be graded by the Investigator as major or minor:

Major Stroke: A stroke, which is present after seven days and increases the NIH Stroke Scale of the patient by ≥ 4 .

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

Note: Item 3 of the NIH Stroke Scale describes visual field cuts as assessed by physical examination. Quantitative visual field analysis at the time of stroke may be substituted for physical examination, if available.

3.25.2. Anticipated Adverse Events

Table 10 shows a list of adverse events, some of which can be fatal, that are known to be associated with angiography, blood thinning medications, the PED implant and PED implant procedure as well as the use of general anesthesia.

Table 10. Anticipated adverse events related to PED, angiography and use of aspirin/clopidogrel.

Air embolism*	Ischemic stroke*
Anesthesia reaction	Loss of consciousness
Anxiety	Nausea
Arterial spasm*	PED stenosis*
Aspiration	PED thrombosis*
Back pain	Perforation or rupture of aneurysm sac*
Confusion, coma or other change in mental status	Perforation or rupture of parent artery*
Contrast reaction*	Peripheral thromboembolism*
Delivery system failure with premature or inaccurate device deployment*	Progressive neurologic symptoms related to IA*
Device fracture with embolism*	Pseudoaneurysm formation*
Device migration*	Reaction to radiation exposure
Device misplacement*	Renal failure
Dissection of the parent artery*	Retroperitoneal hematoma
Dizziness	Seizure
Fever	Stenosis of the parent artery*
Groin injury, including bleeding, pain, vessel or nerve damage	Subarachnoid hemorrhage*
Headache	Thromboembolism from PED or microcatheters*
Hemorrhagic stroke*	Thrombosis of branch vessel*
Hypertension	Thrombosis of parent artery*
Hypotension	Transient ischemic attack (TIA) *
Infection*	Vasospasm*
Intracerebral bleeding*	Vision impairment
	Vomiting

*Events listed with an asterisk could result in stroke, TIA or neurologic syndromes, including motor or sensory loss, loss of higher cortical function, loss of speech, visual loss, seizure or other syndromes.

Aspirin and clopidogrel must be taken by all subjects. Further details on anticipated side effects of these drugs are listed in **Table 11**.

Table 11. Anticipated side effects of aspirin and clopidogrel.

Aspirin*	Clopidogrel**
<ul style="list-style-type: none"> • Bleeding, including cerebral and gastrointestinal bleeding • Abdominal pain, nausea, vomiting, dyspepsia • Gastric ulcer, gastritis • Rash • Tinnitus 	<p>In trials of clopidogrel + aspirin vs. aspirin alone:</p> <ul style="list-style-type: none"> • Bleeding, including cerebral and non-cerebral bleeding <p>Other effects that occurred rarely in clinical trials included:</p> <ul style="list-style-type: none"> • Syncope, palpitation, weakness, fever, heart failure, nervous system disorders, constipation, vomiting, increased liver enzymes, rash, anxiety, insomnia • These symptoms were rare and did not occur more commonly in the clopidogrel+aspirin groups vs. the aspirin only groups. <p>Other post-market experience has included: neutropenia and thrombotic thrombocytopenia purpura (TTP).</p>

*Many of the effects listed for aspirin are known to occur only at high doses. The dose required for participation in this study is low (81 mg, 2 pills/day).

**See <http://products.sanofi-aventis.us/plavix/plavix.html#adverse>.

3.26. Clinical Events Committee

A clinical events committee (CEC) comprised of at least 2 non-Investigator neuroradiologists and 1 neurosurgeon will review all adverse events occurring in the study according to the CEC Charter. Any event meeting the definition of serious adverse event (SAE) must be reviewed by the CEC. The CEC will also be provided with listings of all events and may choose to adjudicate events that are not serious in nature. Members may discuss any event with the Investigator who was involved with the subject in question. The CEC will use the same rating scale for relatedness as shown in **Section 3.25**. The CEC will review and adjudicate the Medical Monitor's categorization of event type and severity using the CTCAE grade system (mild, moderate, severe, life-threatening, fatal). Adjudicated adverse events will be used in analysis of the primary safety endpoint.

3.27. Trial Operating Committee

This study will have a trial operating committee (TOC) whose goal is to oversee trial operations. The TOC will consist of the study's Principle Investigator, Medical Monitor, Consulting Statistician and Sponsor CEO. The TOC will review study progress and study conduct.

4. Study Management

As the study sponsor, Chestnut Medical Technologies, Inc. has the overall responsibility for the conduct of the study according to 21 CFR 812, 21 CFR Part 50, Good Clinical Practice (GCP) Guidelines (Guidance for Industry, E6 Good Clinical Practice Consolidated Guidance, ICH, April 1996), ISO 14155: Part 1 and 2, the Declaration of Helsinki, Medical Device Directive, *Annex X*, conditions imposed by the reviewing IRB/EC, FDA and all applicable regulatory requirements. For this study, Chestnut Medical will have certain direct responsibilities and will delegate other responsibilities to appropriate consultants and contract research organizations (CROs). Together, Chestnut Medical, consultants and CROs will ensure that the study is conducted according to all applicable regulations. All personnel to participate in the conduct of this clinical trial will be qualified by training, education and/or experience to perform his or her respective tasks.

NOTE: A complete list of participating investigators will be maintained and will be available upon request.

4.1. Investigator Responsibilities

The Investigator(s) shall be responsible for the day-to-day conduct of the investigation as well as for ensuring that the investigation is conducted according to all signed agreements, applicable elements of ISO 14155, the Clinical Investigational Plan, applicable FDA regulations, the principles that have their origin in the Declaration of Helsinki, and any conditions of approval imposed by the IRB/EC or FDA. The investigator is also responsible for having control of the device under investigation, for protecting the rights, safety and welfare of subject's under the investigator's care and for obtaining informed consent in accordance with 21 CFR Part 50. Each Investigator must sign the Investigator Agreement and Financial Disclosure prior to patient enrollment. No investigator will be added to the investigation until a signed Investigator Agreement is provided.

Responsibilities of the Investigator include, but are not limited to:

1. Ensuring that FDA and IRB approval are obtained prior the participation of a subject in a clinical trial. Such participation includes obtaining written informed consent
2. Ensuring that the Investigational device is used only under the supervision of a study investigator
3. Providing the study sponsor with accurate and complete financial information per 21 CFR Part 54
4. Returning or disposition of the study supplies at the sponsor's request
5. Ensuring that all personnel assisting with the clinical trial are adequately informed and understand their trial-related duties and functions

It is recommended that each site identify a study coordinator for this study. Working with and under the authority of the Investigator(s), the study coordinator

assures that all study requirements are fulfilled, and is the contact person at the site for all aspects of study administration.

The Investigator will allow direct access to source data/documents for trial related monitoring, audit, IRB/EC review and regulatory inspection. Also, the investigator will allow auditing of their clinical investigational procedure(s).

4.1.1. Required Documents from the Investigator

At a minimum, the following documents will be provided by the investigational site to the study sponsor:

- Signed Investigator Agreement
- Written and dated IRB/EC approval
- Written and dated IRB/EC approval for ICF document
- IRB/EC approval for any other written documents to be provided to the study subject (e.g., advertising)
- *Investigator and Co-Investigator's current Curriculum Vitae
- Any other relevant documents requested by the study sponsor or the reviewing IRB/EC or other regulatory authority(ies)
- FDA Form 3454 or 3455 (or equivalent) regarding financial interests

A site may not begin study participation until all of the above listed documents have been provided to the study sponsor.

** The study may begin once the CV of the site PI has been received. No additional Investigators may participate until a copy of their CV and a signed Investigator Agreement has been provided to the study sponsor.*

4.1.2. Investigator Records

The Investigator is responsible for maintaining medical and study records for every subject participating in the clinical study (including information maintained electronically such as digital imaging). The Investigator will also maintain *original* source documents from which study-related data are derived, which include, but are not limited to:

- all correspondence including required reports,
- records of receipt, use, or disposition of the investigational device,
 - type and quantity of device
 - date of receipt
 - batch number or code
 - name of person that received, used, or disposed of each device
 - why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of
- records of each subject's case history and exposure to the device which must include,

- signed and dated consent forms
- condition of each subject upon entering the study
- relevant previous medical history
- record of the exposure to the investigational device, including the date and time of each use and any other therapy
- observations of adverse device effects
- medical records (physician and nurse progress notes, hospital charts, etc.)
- results of all diagnostic tests
- case report forms
- any other supporting data
- the protocol and documentation (date and reason) for each deviation from the protocol.
- any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.

The Investigator must ensure that all study subject records are stored for at least 2 years after the end of the clinical study or the records are no longer required to support a PMA approval, whichever date is later. To avoid error, the study site should contact Chestnut Medical prior to the destruction of study records to ensure that they no longer need to be retained. In addition, Chestnut Medical should be contacted if the Investigator plans to leave the investigational site so that arrangements can be made for the handling or transfer of study records.

The Investigator will also maintain *original* source documents from which study-related data are derived, which include, but are not limited to:

- Clinic progress notes recording subject's medical history and medications
- Medical charts with operative reports and condition of subject upon discharge
- Medical records regarding AEs, including treatment and clinical outcome
- Results of diagnostic examinations
- Imaging (such as x-rays, MRIs), as well as the report of the radiologist's reading/interpretation of diagnostic imaging
- Notes of phone calls and/or correspondence indicating investigational site's attempts to follow study subjects at the required follow-up visits until subject's participation in the study is complete or terminated
- Records relating to patient death (e.g., death certificate, autopsy report/terminal medical records)
- Print-outs of source data generated by technical equipment (e.g., x-rays, MRIs) must be filed with the patient's records.

4.1.3. Data Collection

Study data will be collected using standardized Case Report Forms. The investigator is responsible for reviewing all CRF entries for completion and correctness. When changes are made on any CRF, the correct answer should be circled, the incorrect information lined through (neatly with a single line) and the change initialed and dated in an effort to not obscure the original or prior entry(ies). If necessary, an explanation for the change(s) may be provided and records of changes maintained. Procedures for correcting data collected and signed electronically will be consistent with 21 CFR 11.

4.1.4. Reporting of Adverse Events

All Serious Adverse Events (SAEs, see definitions in **Section 4.10**) must be reported to Chestnut (or designee) immediately, not to exceed **72 hours** after the investigator first learns of the event.

All SAEs need to be followed until the event is resolved (with or without sequelae). The Principal Investigator at the site will decide if more follow up information is needed in case the event is not resolved at study completion. In case of death, all possible information that is available, e.g. autopsy or other post-mortem findings, including the possible relationship to the device, should be provided.

The investigator must submit to Chestnut (or designee) any unanticipated adverse device effect (see **Section 4.10** for definition) **within 24 hours** after the investigator first learns of the effect. The investigator must also report the unanticipated adverse device effect to the EC/IRB within its pre-specified timeline.

The Investigator will report all of the above to the reviewing EC/IRB (*as applicable*) according to the local reporting requirements.

NOTE: Reports must identify subjects using the study's unique identifier to protect patient's confidentiality.

ADVERSE EVENT REPORTING [REDACTED]
EMERGENCY CONTACT: [REDACTED]

4.2. Sponsor Responsibilities

Chestnut Medical Technologies, Inc. is the manufacturer of the Pipeline™ Embolization Device and the Sponsor of this study. Chestnut Medical's responsibilities include but are not limited to:

1. Selecting qualified investigators (qualifications will be documented)
2. Providing investigators with the information necessary to conduct the investigation properly
3. Providing appropriate training to each study site and all study personnel (monitors), as necessary
4. Documenting training where appropriate
5. Selecting monitors qualified by training and experience to monitor the investigational study in accordance with FDA regulations (21 CFR 812.43(d))
6. Ensuring that the IRB approval is obtained
7. Submission of an IDE application to FDA
8. Ensuring that any reviewing IRB or FDA are informed of significant new information
9. Providing investigational product to qualified investigators
10. Obtaining signed Investigator Agreement for each investigator prior to their participation in the study
11. Obtaining sufficient and accurate financial disclosure information (21 CFR Part 54)
12. Reporting per 21 CFR 812.150 (b)

4.2.1. Training

The Pipeline™ Embolization Device is intended for use by interventional neuroradiologists or neurosurgeons who are trained in endovascular procedures and who have experience with embolization of IAs. All Investigators will undergo a standardized training program prior to study participation. As part of the training program, Chestnut Medical personnel or designee will provide hands-on training in the use of the device using a bench top model (or equivalent) to familiarize them with the use of the Pipeline™ Embolization Device. In addition, the investigator will attend PED placement cases performed at other medical centers or will undergo

proctoring of his first few cases by a physician experienced in PED placement. It is the responsibility of Chestnut Medical Technologies, Inc. to ensure that the investigator is thoroughly familiar with the appropriate use of the PED.

In addition to hands-on device training, each study center will undergo protocol initiation training which will include, but is not limited to, a review of the following:

- Device overview (for non-investigator research personnel)
- Clinical Investigational Plan (CIP)
- Regulatory files
- Consenting procedures
- Instructions for Use (IFU)
- Reporting requirements
- CRF completion and correction procedures
- Device handling procedures
- Protection of patient confidentiality
- Study supplies

Site training will be documented and training records maintained by the study sponsor.

4.2.2. Adverse Event Review

The study sponsor will immediately conduct an evaluation of any unanticipated adverse device effect (21 CFR 812.46(b)) and will ensure the necessary reporting of the event(s) to regulatory authorities, investigators and reviewing IRBs/ECs as necessary.

If an investigation shows that an unanticipated adverse device effect presents an unreasonable risk to subjects, the sponsor will terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the sponsor makes this determination and not later than 15 working days after the sponsor first receives notice of the effect (21 CFR 812.46(b)(2)).

The sponsor will only resume a terminated investigation after obtaining IRB and FDA approval (21 CFR 812.150(b)).

4.3. Ethical Considerations

The rights, safety and well-being of clinical investigation subjects shall be protected consistent with the ethical principles laid down in the Declaration of Helsinki. This shall be understood, observed and applied at every step in this clinical investigation.

It is expected that all parties will share in the responsibility for ethical conduct in accordance with their respective roles in the investigation. The Sponsor and the Investigator(s) shall avoid improper influence or inducement of the subject, monitor, the clinical investigator(s) or other parties participating in or contributing to the clinical investigation.

4.3.1. Protection of Patient Confidentiality

At all times throughout the clinical investigation, confidentiality will be observed by all parties involved. All data shall be secured against unauthorized access. Privacy and confidentiality of information about each subject shall be preserved in study reports and in any publication. Each subject participating in this study will be assigned a unique identifier. All CRFs will be tracked, evaluated, and stored using only this unique identifier.

The Investigator will maintain a confidential study subject list identifying all enrolled subjects. This list will contain the assigned study subject's unique identifier and name. The Investigator bears responsibility for keeping this list confidential. This list will not be provided to the study sponsor and is only to be used at the study center.

Monitors and auditors will have access to the study subject list and other personally identifying information of study subjects to ensure that data reported in the CRF corresponds to the person who signed the ICF and the information contained in the original source documents. Such personal identifying information may include, but is not limited to the subject's name, address, date of birth, gender, race and medical record number.

NOTE: The subject's name, medical record number or address will NOT be recorded in the monitor's visit report or the database; demographic data that may be recorded include date of birth, race, and gender.

Any source documents copied for monitoring purposes by the Sponsor will be identified by using the assigned patient's unique identifier in an effort to protect subject confidentiality.

4.3.2. Ethics Committee/Institutional Review Board Approval

Institutional Review Board (IRB) / Ethics Committee (EC) approval is required prior to study commencement. The Investigator must also obtain renewal of IRB/EC approval as dictated by local requirements during the entire duration of the study. The Investigator is responsible for fulfilling any conditions of approval imposed by the reviewing IRB/EC, such as regular reporting, study timing, etc. The Investigator will provide the study sponsor with copies of such approvals and reports.

Withdrawal of IRB/EC approval must be reported to the study sponsor immediately (*not more than 5 working days*) following the investigator's knowledge of the withdrawal.

The reviewing Independent Review Board (IRB) / Ethics Committee (EC) must review and approve an Informed Consent Form (ICF) specific to this study. Chestnut will provide each study center with an example ICF. The study center, to meet specific requirements, may modify this example ICF; however, the ICF must contain all of the elements required by Chestnut. Each investigational site will provide Chestnut with a copy of the IRB/EC approved ICF and renewed approvals and consents as appropriate for the duration of the study. The original, signed and dated ICF should be retained by the investigational site for monitoring, and a copy provided to the subject.

The written informed consent (and any other written information to be provided to the study subject) should be updated whenever new information becomes available that may impact the patient's consent. Any such revision or update must be approved by the reviewing IRB/EC before being provided to the study subject. Should it be necessary that such information is verbally provided to the study subject (in the case that the information may impact the patient's willingness to continue study participation), communication of the information must be documented.

If informed consent is not obtained, the investigational site must notify Chestnut Medical Technologies, Inc. or designee within 5 working days of knowledge of the event.

NOTE: A complete list of reviewing IRBs will be maintained and will be available upon request.

4.3.3. Quality Assurance and Supervision by Authorities

All documents and data shall be produced and maintained in such a way to assure control of documents and data to protect the subject's privacy as far as reasonably practicable. The Sponsor and representatives of the FDA or other regulatory authorities are permitted to inspect the study documents (e.g., study protocol, CRFs, and original study-relevant medical records/files) as needed. All attempts will be made to preserve subject confidentiality.

All clinical sites are subject to audit by study sponsor personnel or designee for protocol adherence, accuracy of CRFs and compliance with applicable regulations. Any evident pattern of non-compliance with respect to these standards will be cause for the site to be put on probation until appropriate corrective action is taken.

The study protocol, data-recording procedures, data handling as well as study reports are subject to an independent clinical Quality Assurance audit by Chestnut Medical Technologies, Inc., its designee, or health authorities.

4.4. Data Collection and Data Management

Study data will be collected using standardized Case Report Forms. Each CRF will be designed to accommodate the specific features of the trial design. Modification of a CRF will only be made if deemed necessary by the study sponsor.

4.4.1. Database for Data Storage

Data Management will employ a full featured, relational database. Conventional data verification routines will be performed. Data Management will be performed according to the Data Management Center's data handling, database security and other applicable SOPs.

To ensure proper tracking of CRFs and angiograms, a master tracking system will be utilized.

4.4.2. Data Entry

Data entry will be performed as the completed CRF pages are received by Data Management. The data entry screen will be similar to the CRF, which reduces transcription errors by data entry personnel. Data entry will be performed by qualified personnel that have undergone appropriate training.

4.4.3. Data Cleaning

All CRF pages will be subject to initial inspection for omitted data, gross data inconsistencies, illegible data and deviations. Any deficiencies or deviations will be reviewed and any necessary action determined (e.g., data query, communication to the study center).

Intermittent data review will be performed and any discovered errors will be reported to the study site using the data correction and query process (as necessary). The study site will be expected to review the query, make any necessary corrections or comments, and return to Data Management where the correct response will be entered into the database. The data cleaning cycle will be repeated until all data are considered clean.

4.4.4. Data Back-up

Incremental computer data back-up will be performed on a regular basis. All hard copies of Case Report Forms and media will be stored in a secure location.

4.4.5. Confidentiality and Security

Passwords will be issued to appropriate personnel to insure confidentiality and protection of data by allowing variable levels of access to Data Management's computer systems.

4.5. Study Suspension or Early Termination

The study can be discontinued at the discretion of the study Sponsor for reasons including, but not limited to, the following:

- Occurrence of adverse events unknown to date in respect to their nature, severity, or duration, or the unexpected incidence of known adverse events
- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary
- Insufficient recruitment of subjects
- Unanticipated adverse device effect (UADE) presenting an unreasonable risk to subjects
- Persistent non-compliance with the protocol
- Persistent non-compliance with EC/IRB or regulatory requirements

If the study is discontinued or suspended prematurely, the Sponsor shall promptly inform all clinical investigator(s)/investigational center(s) of the termination or suspension and the reason(s) for this. The EC/IRB will also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the clinical investigator/investigation center(s). Regulatory authorities and the personal physicians of the subjects may also need to be informed if deemed necessary.

4.6. Protocol Deviations

A protocol deviation is defined as any study action taken by the clinical Investigator or site personnel in conflict with the Study Protocol.

Investigators must obtain prior approval from Chestnut clinical study management before initiating *major* deviations from the investigational plan, except where necessary to protect the life or physical well being of a subject in an emergency. Such approval shall be documented in writing and maintained in clinical study management and Investigator files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, (e.g. subject was not available for scheduled follow-up office visit, blood sample lost by laboratory, etc.); however, the event is still considered a deviation and will be reported on the appropriate CRF.

Deviations must be reported to Chestnut regardless of whether medically justifiable, pre-approved by Chestnut or taken to protect the subject in an emergency. Subject specific deviations will be reported on the Protocol Deviation

case report form. Non-subject specific deviations, (e.g. unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a physician who has not signed an Investigator agreement or not been trained in the use of the device, etc.), will be reported to Chestnut. Investigators will also adhere to procedures for reporting study deviations to their IRB/EC in accordance with their specific IRB/EC reporting policies and procedures.

Regulations require that Investigators maintain accurate, complete and current records, including documents showing the dates of and reasons for each deviation from the protocol. For reporting purposes, Chestnut classifies study deviations as major and minor:

Major deviation: Any deviation from subject inclusion and exclusion criteria, subject informed consent procedures or unauthorized device use.

Minor deviation: Deviation from a protocol requirement such as incomplete/inadequate subject testing procedures, follow-ups performed outside specified time windows, etc.

Minor Deviations that continue to occur at an investigational site may be classified as Major Deviations if corrective action is not taken to secure future compliance to the protocol.

4.7. Final Report

A final report will be completed, even if the study is prematurely terminated. At the conclusion of the trial, a multi-center abstract reporting the results will be prepared and may be presented at a major meeting(s). A multi-center publication may also be prepared for publication in a reputable scientific journal. **The publication of results from any single center experience within the trial is not allowed until the aggregate study results have been published, unless there is written consent from the study sponsor.**

4.8. Information Confidentiality

All information not previously published concerning the test device and research, including patent applications, manufacturing processes, basic scientific data, etc., is considered confidential and should remain the sole property of Chestnut Medical Technologies, Inc. All information and data generated in association with this study will be held in strict confidence and remain the sole property of Chestnut Medical Technologies, Inc. The Investigator agrees to use this information for the sole purpose of completing this study and for no other purpose without written consent from Chestnut Medical Technologies.

4.9. Trial Registration

The study will be registered in a publicly accessible trial database (e.g., clinicaltrials.gov) prior to study initiation.

4.10. Definitions and Acronyms

The following terms and acronyms are herein defined.

Adverse Event (AE) - any untoward medical occurrence in a subject (ISO 14155).

Note: This definition does not imply that there is a relationship between the adverse event and the device under investigation.

Serious Adverse Event (SAE) - an adverse event that (ISO 14155):

- led to a death,
- led to a serious deterioration in the health of the subject,
- resulted in a life-threatening illness or injury,
- resulted in a permanent impairment of a body structure or a body function,
- required hospitalization or prolongation of existing hospitalization,
- resulted in medical or surgical intervention to prevent permanent impairment to body structure or function,
- led to fetal distress, fetal death, a congenital abnormality, or birth defect.

Adverse Device Effect (ADE) - any untoward and unintended response to a medical device (ISO 14155)

Note: This includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. This definition also includes any event that is a result of user error.

Serious Adverse Device Effect (SADE) - an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune (ISO 14155).

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 application (including a supplementary plan or application), or any other unanticipated serious problem associated with a

device that relates to the rights, safety, or welfare of subjects (21CFR812.3.s) and (ISO 14155).

Note: The occurrence of a diagnostic or elective surgical procedure for a pre-existing condition, unless the condition becomes more severe or increases in frequency, would not be considered procedure or device-related.

Aneurysm size

Maximum dimension across aneurysm

Applicable Regulatory Requirement(s)

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products of the jurisdiction where trial is conducted (E6, GCP Guidance)

Case Report Form (CRF)

A printed, optical or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each subject (E6, GCP Guidance)

Cavernous

Area near the cavernous sinus, a cavity bordered by the sphenoid bone and the temporal bone of the skull

Contract Research Organization (CRO)

A person or an organization (commercial, academic or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions (E6, GCP Guidance)

Documentation

All records, in any form (including, but not limited to, written electronic, magnetic, and optical records; and scans, X-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial and the actions taken (E6, GCP Guidance).

Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected (E6, GCP Guidance)

Informed Consent

The process by which the subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to

participate. Informed consent is documented by means of a written, signed, and dated informed consent form.

Informed Consent Form (ICF)

Institutional Review Board (IRB)

IRB is synonymous with Ethics Committee (EC)

An independent body (a review board or a committee, institutional, regional, national or supranational), constituted of medical/scientific professionals and nonmedical/nonscientific members, whose responsibility is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favorable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and materials to be used in obtaining and documenting informed consent of the trial subjects (E6, GCP Guidance).

Instructions for Use (IFU)

Intracranial Aneurysm (IA)

Investigator /Principal Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator (E6, GCP Guidance). All other investigators at the trial site not assuming the lead role will be referred to as either sub- or co-investigators.

Mean deviation index

Mean of the deviation in light sensitivity from age-matched normals

Modified Rankin Scale

Scale for measuring general neurologic function. See below.

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Monitor

When used as a noun, it means the individual designated by a sponsor or contract research organization to oversee the progress of an investigation. The monitor may be an employee of the sponsor, or a consultant to the sponsor or an employee or consultant to a contract research organization (21 CFR 812.3)

Monitoring

Monitor when used as a verb means to oversee an investigation (21 CFR 812.3). Monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, GCP and the applicable regulatory requirements (E6, GCP Guidance).

Neck

Width of the opening of the aneurysm where it meets the parent vessel

Paracaloid

Area near the clinoid portion of the sphenoid bone

Pattern standard deviation

Deviation in light sensitivity from normals accounting for global eye problems (e.g., cataracts)

Petrous

Canal inside the temporal bone which the internal carotid artery traverses

Pipeline™ Embolization Device (PED)**Qualitative image analysis (QIA)****Salvage treatment**

Treatment used when index treatment is not possible

Secondary treatment

Treatment provided if index treatment is a clinical failure despite placement/retention of devices

Source Data

All information in original and identified records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation. Source data are contained in source documents (E6 GCP Guidance, ISO 14155).

Source Documents

Original documents, data and records (ISO 14155).

Note: This may be, for example, hospital records, laboratory notes, pharmacy dispensing records, copies or transcriptions certified after verification as being accurate copies, photographic negatives, radiographs, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical investigation.

Standard Operating Procedure (SOP)**Subarachnoid Hemorrhage (SAH)**

Bleeding into the subarachnoid space surrounding the brain. The bleeding may occur spontaneously, usually from a cerebral aneurysm, or may result from trauma.

Termination

Termination means a discontinuation, by sponsor or by withdrawal of IRB or FDA approval, of an investigation before completion (21 CFR 812.3).

Transient Ischemic Attack (TIA)

A focal ischemic neurological deficit of abrupt onset and of presumed vascular etiology that resolves completely within 24 hours of onset.

Unanticipated Adverse Device Effect (UADE)

See Adverse Events.

5. Risk Analysis

A thorough risk analysis was performed as part of design control recommendations of the Quality System Regulation (21 CFR 820). Results of prior investigations on PED were included in the risk analysis. The risk analysis is described in the Investigator's Brochure. In summary, the benefits of Pipeline use in the patient population to be included in this study outweigh the risks.

6. Device Description

The PED is a [REDACTED] endovascular implant. The [REDACTED] configuration results in approximately [REDACTED] coverage of the arterial wall [REDACTED]). The implant is fabricated from [REDACTED] and [REDACTED] wires. [REDACTED] is radiopaque and both [REDACTED] and [REDACTED] are known to be biologically inert, making them ideal metals for a permanent endovascular implant. Moreover, [REDACTED] has a long history of usage as a neurological embolization material in the form of detachable coils.

The PED delivery system is a 175cm guidewire-based technology. The primary component is a [REDACTED]. The tip and protective coils are a [REDACTED] alloy, the proximal marker [REDACTED] alloy, and the distal, mid and proximal [REDACTED] are a [REDACTED] mixture. The PED delivery system is manufactured by [REDACTED] the components into place with the proximal marker position varying based upon PED implant length.

The delivery system is compatible with commercially available microcatheters with an ID of 0.027".

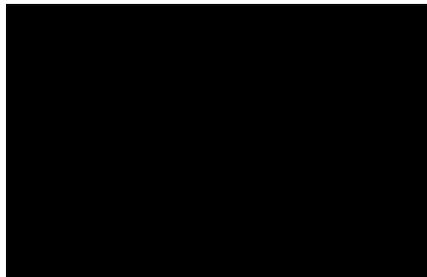
PED Materials Table w/ Patient Contact	
Component	Material
IMPLANT	Blood Path Contact
Braid	[REDACTED]
DELIVERY SYSTEM	Blood Path
Core Wire	[REDACTED]
Tip Coil	[REDACTED]
Protective Coil	[REDACTED]
Proximal Marker	[REDACTED]
PACKAGING	No Patient Contact
Introducer Sheath	[REDACTED]
Device Handle	[REDACTED]
Packaging Hoop	[REDACTED]
Pouch	[REDACTED]
Packaging Box	[REDACTED]
Labels & IFU	[REDACTED]

Note: The PED may create local field inhomogeneity and susceptibility artifacts which may degrade the diagnostic quality of MRI images. Based on the non-clinical testing of the 5.0 mm device using standard views, the worst case maximum artifact was < 3mm when subjected to 3.0 Tesla.

7. Monitoring Procedures

7.1. Monitor Responsibilities

Study site monitoring will be performed by [REDACTED] (or designee).



NOTE: A complete list of study monitors and their qualifications will be maintained and will be available upon request.

Each site will be visited regularly in an effort to ensure that the study is conducted in compliance with the Clinical Investigational Plan and all applicable guidelines, laws and regulations. The monitor will also review data reported in the Case Report Form for accuracy and consistency with the information found in the subject's medical records (source data verification). Monitoring will also include the assessment the site's overall progress, including but not limited to the site's ability to keep accurate records and to report study related data to the study sponsor in a timely fashion. Monitoring of each site will be performed according to Chestnut Medical's Monitoring SOP and the Monitoring Plan. In order to appropriately monitor the progress of the study, the monitor will have access to the source documents and other information necessary to ensure Investigator compliance with the Investigational Plan and applicable rules and regulations and to assess the progress of the clinical investigation.

The study monitors will conduct a pre-investigational visit. Monitors will ensure that the protocol is thoroughly understood. Monitors will maintain personal contact with the Investigator and staff throughout the study by phone, e-mail, mail and on-site visits. The monitor will compile and file a monitoring report for each visit. Monitoring will ensure continued protocol compliance, adequate patient enrollment and accurate data reporting and device accountability.

The monitor shall verify, at a minimum, that:

1. The rights and well-being of the study subjects are being protected
2. The site is conducting the study in compliance with the CIP and applicable regulations and guidelines
3. Any major deviation from the CIP is discussed with the Investigator(s), documented and reported to the Sponsor. Minor deviations will also be documented and reported on an aggregate basis, as necessary.
4. The device is being used according to the CIP, and if modifications are required either to the device or its method of use or to the CIP, this need is reported to sponsor management
5. The Investigator(s) have and continue to have staff and facilities to conduct the investigation safely and effectively
6. The Investigator(s) have and continue to have access to adequate number of subjects and devices
7. Signed and dated ICFs have been obtained from each subject at the time of enrollment and before any study-related procedures have been performed
8. The data in the CRF are complete, are recorded in a timely manner and are consistent with the source data
9. The procedures for recording and reporting adverse events and adverse device effects to the Sponsor are being followed
10. There is a process in place for device accountability and traceability that is maintained

11. Subject withdrawal and / or non-compliance is documented

Findings of non-compliance or required modifications shall be reviewed with the Investigator(s) and disclosed in a written monitoring report. The monitor will report to the sponsor any noncompliance with the signed Investigator's Agreement, conditions imposed by the IRB or FDA, and the requirements of the IDE. The sponsor shall then either secure compliance, or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation (21 CFR 812.46(a)).

7.2. Source Data Verification

Source data verification will be performed on all data collected on study-related Case Report Forms (100% source data verification).

7.3. Site Close-out

At the time of the site close-out visit, the site monitor or designee will collect all outstanding study documents, ensure that the Investigator's files are accurate and complete, review record retention requirements with the Investigator, make a final accounting of all study supplies, and ensure that all applicable requirements are met for the study (this visit will be conducted according to the study sponsor's SOP for close-out visits). The observations and actions made at this visit will be documented in a final report.

8. References

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