Post-Approval Study Outline

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1 Background

1.1 Regulatory History

Chestnut Medical began discussions of Pipeline Embolization Device (PED) with FDA in late 2007. The PUFS IDE was submitted in May 2008 and approved in June 2008. Version C of the PUFS protocol was submitted in September 2008 and Approved in October 2008. The vast majority of subjects in PUFS were enrolled using Version C.

PUFS is a 5-year study; however, FDA has agreed that the primary endpoint for PMA submission was at 180 days. From the start, the intent of long-term (5-year) follow-up in PUFS was to provide immediate and relevant post-market data while the PMA goes through its prolonged approval process.

Modules 1 (preclinical) and 2 (manufacturing) of the PED PMA were submitted to FDA in August 28, 2009 and Oct. 6, 2009. These modules are now closed. Module 3 (clinical) of the PED PMA was submitted to FDA in May 12, 2010. Expedited review was granted in June 16, 2010 with a filing date of May 18, 2010. FDA has informed Chestnut that an advisory committee meeting to discuss PED will occur on March 18, 2011.

In June 2010 FDA approved PUFS-CA (Continued Access). PUFS-CA is a continued access study, the purpose of which is to provide continued access of the device to investigators during the PMA approval period.[*] PUFS-CA is nearly identical to PUFS. The only differences between PUFS and PUFS-CA are:

- In PUFS-CA, the detailed neuro-ophthalmology examination by a site ophthalmologist was dropped. The reason for dropping the examination was that 1) the ophthalmologic examination performed by the neuroradiologist or neurosurgeon investigators was deemed sufficient and agreed in most cases with that performed by the neuro-ophthalmologist[†], and 2) the neuro-ophthalmology examination in PUFS provided sufficient information regarding changes in neuro-ophthalmologic function. It should be emphasized that PED is a tool for management of vascular disease, not ophthalmologic disease, and PED is not specifically designed to relieve aneurysm symptoms. However, because the device is not placed into the aneurysm fundus, the fundus can shrink over time, ameliorating symptoms in patients who present with symptoms due to aneurysm mass effect. (See the PUFS PMA study report for details on changes in aneurysm-related symptoms.)

- In PUFS-CA, electronic case report forms are used.

[*] See http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080260.htm (accessed December 9, 2010) and http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051345.htm#continuedaccess (accessed December 9, 2010).

[†] I will provide details of this analysis later.

As of December 2, 2010, 11 subjects have been enrolled in PUFS-CA.

1.2 Device Description

PED consists of a braided, multi-alloy, mesh cylinder shaped implant combined with a simple guidewire based delivery system. The PED is provided sterile (EtO) with the implant compressed inside an introducer sheath (**Figure 1**). The system is designed to be introduced into commercially available 3F neurovascular microcatheters (with an ID of 0.027" [0.69 mm]) for delivery to the target vessel adjacent to the intracranial aneurysm.

[redacted]

Figure 1. Pipeline Embolization Device.

1.3 Indications for Use

The proposed indications for use statement is:

- PED is indicated for the treatment of large or giant wide-necked intracranial aneurysms in the paraclinoid region of the internal carotid artery.

2 Study Name

The post-approval study will be called PUFS-PAS. This name clearly indicates that subjects in the study are those enrolled in PUFS (and PUFS-CA) and that the study concerns follow-up in the post-approval setting.

3 Study Purpose

The purpose of this post-approval study is to document the long-term safety and effectiveness of PED for the treatment of large and giant wide-necked aneurysms of the internal carotid artery.

4 Study Objectives

The objective of this protocol is to describe continued follow-up of PUFS study subjects in a post-approval setting.

5 Study Hypothesis

The primary study hypothesis is to show that the cumulative rate of the study's primary endpoint, ipsilateral stroke or neurovascular* death, is not 25% or greater . **Table 1** lists the pre- and post-approval goals. In the pre-approval study, FDA and Chestnut agreed that PED would be an approvable treatment if the pre-approval study's primary safety endpoint rate at 180 days (major ipsilateral stroke or neurologic death) was statistically <20%. As noted below, assuming a background 1% per year stroke rate from Day 180 to the end of the study (5 years), the study would also be considered a success from the very-long-term safety perspective, if the upper 95% confidence limit of the cumulative primary safety endpoint rate at 5 years is not 25% or greater. **Table 1** notes that the pre-approval safety goal has already been met. The post-approval study will focus on whether the combined outcome of late strokes or neurovascular death result in a cumulative primary safety endpoint rate that meets the 25% threshold.

It is emphasized that the primary safety endpoint in the post-approval aspect of the study is different from the primary safety endpoint used in the pre-approval portion of PUFS: the pre-approval portion counted major strokes only whereas the post-approval study will count <u>all strokes</u>. Also, the pre-approval study counted all neurologic death whereas the post-approval study will count only neurovascular deaths.

Table 1. Study hypotheses

Goal Type	Time point	Data Source	Safety Endpoint	Safety Rate Comparator	Conclusion
Original (pre-market)	180 days	PUFS	Occurrence of major ipsilateral stroke or neurologic death by 180 days after PED placement	<20%	Posterior prob = 0.999979
Post-approval	5 years	PUFS	Occurrence of ipsilateral stroke or neurovascular death by 5 years	<25%	TBD

6 Study Design

This study is a single-arm, prospective interventional clinical trial.

7 Study Population

The study population consists of subjects enrolled in the PUFS and PUFS-CA studies. For references purposes, study eligibility criteria are shown in **Table 2**. <u>Note that eligibility criteria for PUFS and PUFS-CA are identical</u>.

Table 2. PUFS and PUFS-CA eligibility criteria.

Inclusion Criteria
a) Age 21 to 75 years, inclusive
b) Patient has a single target IA that:

* The term neurovascular is used as opposed to neurologic. Death from brain cancer is a neurologic death but is obviously not attributable to PED.

1) Is located in the following regions of the internal carotid artery: 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
Exclusion Criteria 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 10^3 cells/mm^3 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 platinum or cobalt/chromium 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 t) Intracranial stenosis greater than 50% in the treated vessel

8 Primary Endpoint

The primary endpoint of this post-approval study is the occurrence of ipsilateral stroke or neurovascular death at 5 years after PED placement. Ipsilateral 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.

This is the same definition as used in PUFS. In PUFS, a clinical events committee (CEC) reviewed all serious adverse events and adjudicated whether a major stroke had occurred. In the post-approval study, the CEC will continue to evaluate SAEs and will confirm whether a stroke (of any severity) has occurred.

Neurovascular death is defined as death due to causes related to the neurovasculature. For example, death from arterial dissection or mycotic aneurysm would be considered neurovascular. Death from brain cancer, brain abscess, or meningitis would not be considered neurovascular.

We emphasize that the occurrence of an ipsilateral stroke in a patient with PED in place does not imply that stroke was due to PED. PUFS subjects are at risk for stroke due to underlying causes not related to aneurysm: age, hypertension (which was not surprisingly[*] common in the PUFS cohort), prevalent atherosclerotic disease, atrial fibrillation, etc.. Moreover, because of the presence of a baseline IA, PUFS subjects are obviously at risk to develop additional aneurysms, which, by themselves, can cause stroke. In addition to reporting the total number of strokes, we will report the number of strokes judged by the CEC to be probably or definitely related to PED. The CEC will use the same relatedness schema as used in PUFS, namely: unrelated, unlikely, possible, probably or definite relation to PED, the placement procedure, use of antithrombotic agents and underlying disease.

8.1 Subgroup Analysis

As per FDA's suggestions, subjects will be subgrouped into two types of aneurysms:

- **Group A: Aneurysms at or below the cavernous segment**. These aneurysms are "below the dura," such that rupture, if it occurs, is typically not fatal. Although the presence of symptoms was not required to be enrolled in PUFS, it should be noted that all subjects in PUFS with cavernous segment aneurysms were symptomatic (headache or cranial neuropathy). It should also be noted that some cavernous segment ICA aneurysms, especially giant ones, can extend above the dura, such that rupture can cause subarachnoid hemorrhage.

- **Group B: Aneurysms at the ophthalmic segment or above**. These are aneurysms that usually cause subarachnoid hemorrhage if they rupture.

In PUFS, subjects were divided approximately 50%/50% between the two subgroups.

9 Secondary Endpoints

Secondary endpoints in the proposed post-approval study are[†]:

[*] Hypertension is a known risk factor for aneurysms.

[†] Please note that PUFS included 3 additional secondary endpoints, all at 180 days, which were already reported in the PUFS PMA and are therefore not relevant to a PAS. These additional secondary endpoints are:

1. Ipsilateral stroke at 180 days
2. Change in Modified Rankin Scale > 2 points at 180 days
3. Change from baseline in neurologic signs/symptoms related to target IA at 180 days

- Complete occlusion of the target IA at 3 and 5 years
- Device-related adverse events at 3 and 5 years.

For complete occlusion, we will also report the number of subjects who undergo additional procedures to treat the target aneurysm. To date, three subjects have undergone additional treatment of the target aneurysm.* Angiographic outcomes are pending in these subjects.

Note that all adverse events occurring in PUFS subjects are captured on AE CRFs. It is likely that most neurologic adverse events can be easily handled by study investigators, who are interventional neuroradiologists or neurosurgeons and are qualified to handle such events. (In fact, most late adverse events in PUFS have been non-neurologic..) However, if the subject is evaluated by another consulting physician (e.g., neurologist, ophthalmologist, etc.), we will ask the site to provide copies of the medical records to substantiate information on the form. It should also be noted that all CRFs undergo monitoring; during the monitoring process monitors check to ensure that information on the CRF is reflected by information in the medical record.

10 Length of Follow-Up

Study subjects will be followed to 5 years after PED placement.

11 Follow-Up Schedule

The follow-up schedule includes phone calls at 2 and 4 years and clinic visits at 3 and 5 years. During the clinic visit, the patient will undergo a cerebral angiogram.

12 Description of Assessments

The following assessments will be completed at the 3- and 5-year clinic visits:

- Medical history
- Neurologic examination
- Modified Rankin Scale assessment
- Angiogram
- Concomitant medications

The following assessments will be completed at the 2- and 4-year telephone calls:

- Change in overall symptoms related to IA. If there is any worsening, an adverse event form should be completed.

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* ; in 2 cases, additional PEDs were placed when 1-year angiogram showed incomplete occlusion. In 1 case, coils were placed by a transvenous route to treat a carotid-cavernous fistula.

- Whether there were any adverse events
- Whether there were any procedures since last study contact
- Whether the subject is taking aspirin and/or clopidogrel (note: neither is required per protocol)
- Whether the subject is taking any other medication relevant to aneurysm (e.g., anticoagulants, steroids, etc.)

It should be noted that all subjects have already undergone baseline, 180 day and 1-year assessments. Two-year follow-up has recently begun. Also, it should be kept in mind that the study protocol does not require any antiplatelet medications after the 180-day time point.

13 Data Collection Procedures

Data are collected on paper case report forms (for PUFS subjects) and electronic case report forms (for PUFS-CA).

14 Minimizing Loss to Follow-Up

Loss to follow-up will be minimized by encouraging contact between study sites and subjects. Phone calls at 2 and 4 years will help to keep subjects involved with the study.

The original PUFS protocol included documentation requirements for subjects who become lost to follow-up, as shown in **Figure 2**. For any subject who cannot be contacted at 2 or 4 years by telephone, the site will make 3 documented attempts to contact the subject, by phone or letter. The protocol also requires that the site make concerted efforts to confirm that the subject is not dead, including, for example, search of death indices.

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).

Figure 2. Excerpt from PUFS protocol.

Chestnut will emphasize with the sites the importance of regular contact with the subject, including a discussion of upcoming visit schedules. Sites will also be asked to contact any subject who withdrew or has withdrawn to assess the reason for withdrawal. Sites will attempt

to contact withdrawn subjects at study-end to assess experience with the device. We will continue to report patient accountability in the PAS as we did in the PMA; this reporting rubric was taken from an FDA guidance document.*

15 Quality Assurance/Quality Control

Sites will continue to undergo periodic monitoring by study monitors. Study data entered into electronic CRFs are monitored in close to real-time by sponsor representatives, including a medical monitor.

16 Statistical Analysis

16.1 Primary Endpoint

The post-approval study described herein comprises long-term follow-up of subjects enrolled in PUFS. The pre-market goal for the primary safety endpoint was to show that the primary safety endpoint rate (major ipsilateral stroke/neurologic death) was <20% at 6 months. This threshold value was selected after review of literature showing high stroke/death rates in patients undergoing alternative treatments. The pre-market goal was achieved with a high degree of statistical certainty (posterior probability of 0.999979). The post-market goal of the study is to show that the long-term (5-year) primary safety endpoint rate (defined in **Section 8**) does not meet or exceed 25%. The 25% goal takes into account a background late stroke rate of approximately 1% per year.

A Bayesian approach was used for the pre-market aspect of the study; the Bayesian approach allowed use of an adaptive design in which enrollment could be ceased at early interim analyses if the predicted 180-day success rates were high. We do not propose to use interim analysis for the post-approval study; thus, a standard frequentist approach to analysis of the primary endpoint will be used. Because loss to follow-up is common in clinical trials with long time horizons, survival analysis using the Kaplan-Meier (K-M) approach to censoring is the most appropriate statistical method. The statistical goal of the study would be considered met if the upper 95% confidence limit of the 5-year K-M estimate of the cumulative primary safety endpoint rate does not meet or exceed 25%. In the calculations shown below we assume that most neurovascular deaths would occur as a result of stroke.

By definition, the K-M approach requires the following input:

- Timing for events meeting the primary safety endpoint that have already occurred, including minor strokes;
- Primary safety endpoint timing for any additional events, confirmed by the CEC, that may occur by 5 years of follow-up;
- Timing of last known contact among subjects who fail to attend a scheduled study visit (i.e., censor times)

* See http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072263.htm#4

Appendix 2 provides power calculations to show that the currently enrolled sample size is sufficient not only for the primary endpoint hypothesis but also for the same primary endpoint within individual subgroups.

16.2 Secondary Endpoint

The secondary endpoints for the post-approval study are:

- Complete occlusion of the target IA at 3 and 5 years
- Device-related adverse events at 3 and 5 years

Approach for complete occlusion. For complete occlusion, the following statistical approach will be taken. The approach is identical to that used to estimate 1-year complete occlusion rates in the PUFS PMA. The presence or absence of complete occlusion at 3 or 5 years is based on interpretation by the core radiographic laboratory of images from catheter angiograms. The analysis will take into account the following:

A. **Known failures**. Some subjects are known failures (e.g., postoperative death, aneurysm rupture, etc.).

B. **Complete occlusions**. These are subjects whose catheter angiograms show complete occlusion, as confirmed by the core laboratory.

C. **Withdrawals**. These are subjects who withdrew from the study prior to the 3- or 5-year angiogram.

D. **Refusers**. These are subjects who attend the 3- or 5-year clinic visit and who refuse catheter angiogram at 3 or 5 years. In most cases, these subjects will have had 3 prior angiograms (1 year, 180 days, baseline), two of which (180 days and 1 year) showed complete occlusion of the target aneurysm without stenosis. A subject might reasonably refuse a 3- or 5-year angiogram because she may believe that the stroke risk associated with a catheter angiogram outweighs the benefit (repeated confirmation of continued complete occlusion in the setting of a very high prior likelihood of continued complete occlusion).

The complete occlusion rate will be calculated in 4 ways as shown in **Table 3**.

Table 3. Analysis methods for complete occlusion rate.

Analysis	Formula	Description	Comment
Conservative	B/(A+B+C+D)	Intent-to-treat analysis	Most conservative analysis. Ignores prior information and assumes that subjects with 2 or 3 prior angiograms showing complete occlusion are effectiveness failures. This method is not commonly used in the reported medical literature.
Least Conservative	B/(A+B)	Optimistic approach	Method commonly used in published literature.
Survival analysis	Kaplan-Meier		Standard survival analysis approach
Fully predictive	$(B + C_{pred} + D_{pred})/(A + B + C + D)$	Predictive approach taking into account withdrawals	

D_{pred} is the predicted distribution of complete occlusions amongst refusers. C_{pred} is the predicted distribution of complete occlusions amongst subjects who withdrew from the study. We will use simple models as well as multivariate regression models in predictive computations. As noted previously, if a subject had complete occlusion at 180 days, there was a 97% chance that the subject would also show complete occlusion at 1 year; the two cases showing otherwise were rare exceptions. Confidence intervals for the 3- and 5-year occlusion rates will take into account standard sampling variation as well as variation of the predicted distribution. We believe that the number of refusers will be fairly low.

Both the "conservative" and survival analysis methods are considered the primary analyses, and the "least conservative" and "fully predictive" methods are considered sensitivity analyses.

Approach for device-related adverse events. Adverse events are characterized by study investigators as to relationship to device, procedure or underlying disease. Serious adverse events are also adjudicated by the CEC. We will report the number of events judged as probably or definitely related to PED divided by the number of subjects evaluated for adverse events.

17 Data Collection Forms

Data collection forms (case report forms) for PUFS-CA are included in **Appendix 1**. The case report forms for the 3-/5-year visits and 2-/4-year phone calls in PUFS are also included in the appendix.

18 Informed Consent Forms

A draft informed consent form template is included in **Appendix 1**. Sites typically modify these forms to conform to local IRB requirements.

19 IRB Approval Forms

All PUFS sites have IRB approvals/renewals for the PUFS study (**Table 4**). In addition, Mayo Clinic and NYU have approvals for PUFS-CA. A copy of IRB approvals is provided in **Appendix 3**.

Table 4. List of IRB approvals and renewals at PUFS sites.

Site	Approval Date	Renewal date
[redacted] - CINN	[redacted]	[redacted]
[redacted] – Rush	[redacted]	[redacted]
[redacted] – Stony Brook	[redacted]	[redacted]
[redacted] – NYU	[redacted]	[redacted]
[redacted] – BNI	[redacted]	[redacted]
[redacted] – Buffalo	[redacted]	[redacted]
[redacted] – WUSTL	[redacted]	[redacted]
[redacted] – Budapest	[redacted]	[redacted]
[redacted] – Hacettepe	[redacted]	[redacted]
[redacted] – CDH	[redacted]	[redacted]
[redacted] – Mayo Clinic	[redacted]	[redacted]

20 Reporting Requirements

The reporting clock begins at the time of device approval. An interim report will be sent to FDA every 6 months for the first 2 years of the study and annually thereafter. A final report will be sent no more than 3 months after the last subject follow-up visit.

21 Study Milestones

21.1 Study Initiation Date

The estimated PUFS-PAS initiation date is June 2011.

21.2 Monthly Number of Study Sites with IRB Approvals

10 centers are participating in PUFS. Of these 2 are also participating in PUFS-CA. No additional centers are in the process of getting approval for PUFS-CA. Two sites (Mayo Clinic, New York University) are currently enrolling subjects in PUFS-CA. The expected enrollment rate is 1-2 subjects per center per month. A copy of IRB approvals is provided in **Appendix 3**.

21.3 Date of Initiation of Enrollment

Subjects in PUFS-PAS will be considered enrolled on the date of study initiation (see **Section 21.1**).

21.4 Expected Enrollment Rate

PUFS is fully enrolled. PUFS-CA continues to enroll. We expect an enrollment of 1-2 subjects/center/month at Mayo Clinic and New York University for the duration of the PUFS-CA enrollment period (period to be determined).

21.5 Date for Enrollment Completion

PUFS enrollment ended in July 2009. The expected date of enrollment completion for PUFS-CA is to be determined but most likely would be when Pipeline is approved by FDA.

21.6 Date to Complete Follow-Up of All Study Participants

PUFS enrollment ended in July 2009 and 5-year follow-up will be complete in July 2014. PUFS-CA continues to enroll, so study follow-up in these subjects will end later at some point in 2015 or beyond.

Appendix 1 – Risk Analysis

Adverse events potentially associated with PED use are shown in **Table 5**. Items marked with an asterisk are theoretically possible but were NOT seen in PUFS or compassionate use cases in the US.

Table 5. Adverse events potentially associated with PED use.

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

PUFS-CA case report forms are shown on the following pages. The PUFS informed consent form template is also included.

Appendix 2 - Sample Size Calculation

The statistical goal of this post-approval study is to show that the cumulative primary safety endpoint rate by 5 years is not 25% or greater. Kaplan-Meier (K-M) survival analysis will be used to determine event-free survival. The lower confidence limit of the event-free survival rate is equivalent to the upper confidence limit of the cumulative primary endpoint rate. The goal of the study will be assumed to be met if the upper confidence limit of the cumulative primary endpoint rate is <25%.

I used computer simulations to model hypothetical trials that take into account events that have already occurred in PUFS as well as predicted future events (e.g., future strokes, censoring). I ran 1000 simulations and calculated power as the proportion of modeled trials that met the study's pre-specified goals.

Events Already Occurred

In PUFS, 107 subjects were included in the safety cohort.* The following are relevant parameters to include in survival analysis simulations:

Subjects with events. To date, 10 subjects have had events meeting the primary endpoint (**Table 6**). Six subjects had major stroke and 4 had minor stroke.

Withdrawals. Three subjects ([redacted]) have withdrawn. They were event-free at the time of withdrawal.

Still participating. The remaining 107 – 10 – 3 = 94 subjects continue to participate and are event-free. Currently, these 94 subjects have approximately 1.5 years each of follow-up. If none withdraw, we would expect an additional 3.5 years of follow-up each, for a total of 3.5 x 94 = 329 subject-years of follow-up.

Table 6. Primary safety endpoint events to date in PUFS by location and type.

Location	Type	Patient ID	Stroke Day	Description
Cavernous	Major	[redacted]	~120	Thrombosis, possible medication non-compliance
Cavernous	Minor	[redacted]	1	Iatrogenic SAH
Cavernous	Minor	[redacted]	~200	Ipsilateral lacunar stroke
Cavernous	Minor	[redacted]	5	Intracranial hemorrhage
Petrous	Minor	[redacted]	4	Intracranial hemorrhage
Supraclinoid	Major	[redacted]	1	Thrombosis in PED
Supraclinoid	Major	[redacted]	4	Sudden cardiac death interpreted as neurologic death by CEC
Supraclinoid	Major	[redacted]	1	Intracranial hemorrhage
Supraclinoid	Major	[redacted]	62	Stenosis
Supraclinoid	Major	[redacted]	14	Intracranial hemorrhage

Events Not Yet Occurred

Two types of events can occur in the future: loss to follow-up and late events meeting the primary endpoint.

* One subject was excluded because she did not undergo a PED placement attempt.

Loss to follow-up. For modeling purposes, I assumed that 15% of subjects (15 subjects) will withdraw sometime between 1.5 and 3 years of follow-up, leaving 79 subjects at 3 years. I then assumed that an additional 10% (8 subjects) will withdraw between 3 and 5 years. If 23 subjects withdraw, we would lose approximately (5-2.25) × 15 + (5-1) × 8 = 73.25 subject-years of follow-up, leaving an accumulation of 329 – 73.25 = 255.75 subject-years of follow-up during which late events could occur.

Late stroke. The rate of late events meeting the primary safety endpoint after PED placement is not known. However, based on discussions I had with Dr. Tarver-Carr, and having observed 1 late minor stroke (subject [redacted]), I assumed a late annual risk of events meeting the primary safety endpoint of 1%. Assuming a 1% yearly risk of such events, the expected number of events is a binomial with parameters N = 256 and p = 0.01 (**Figure 3**).

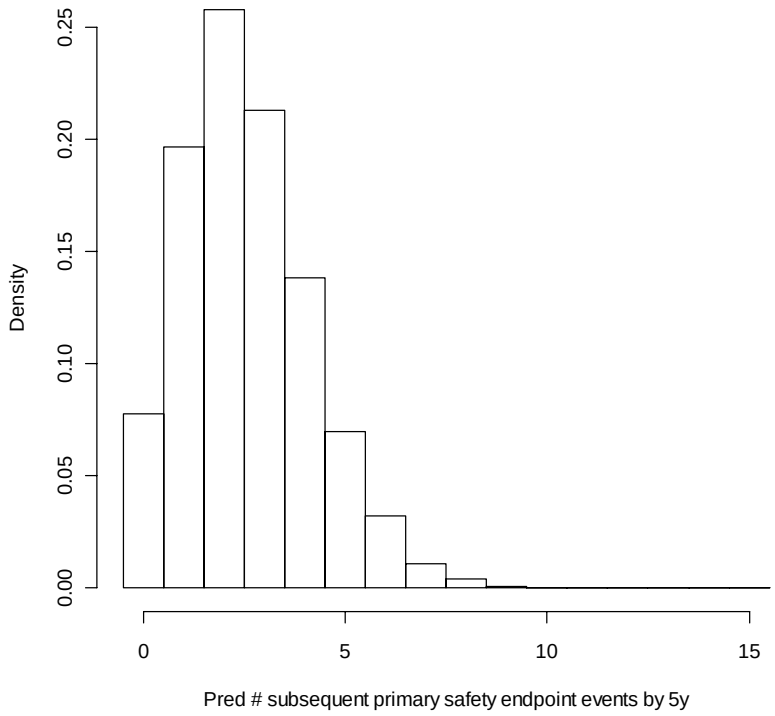

Figure 3. Predicted number of late events by 5 years, assuming 1% risk of stroke.

I entered this distribution of late primary safety events into a series of simulated, hypothetical clinical trials by modeling each event as occurring at a uniform random time between 1.5 and 5 years of follow-up. I also modeled loss to follow-up (i.e., censoring) as occurring at uniform random times between 1.5 and 5 years of follow-up.

Figure 4 shows a representative K-M plot from a hypothetical clinical trial simulated using modeling (R code shown at the end of this appendix). The plot shows the 10 "early" primary safety endpoint events, 3 subjects who were censored early, additional subjects censored between

1.5 years and 5 years and (in this simulation) two additional primary safety endpoint events. The 5-year event-free survival rate is 87% and the LCL is about 81%. Because the LCL is >75%, the trial would be considered to have met the pre-determined goals.

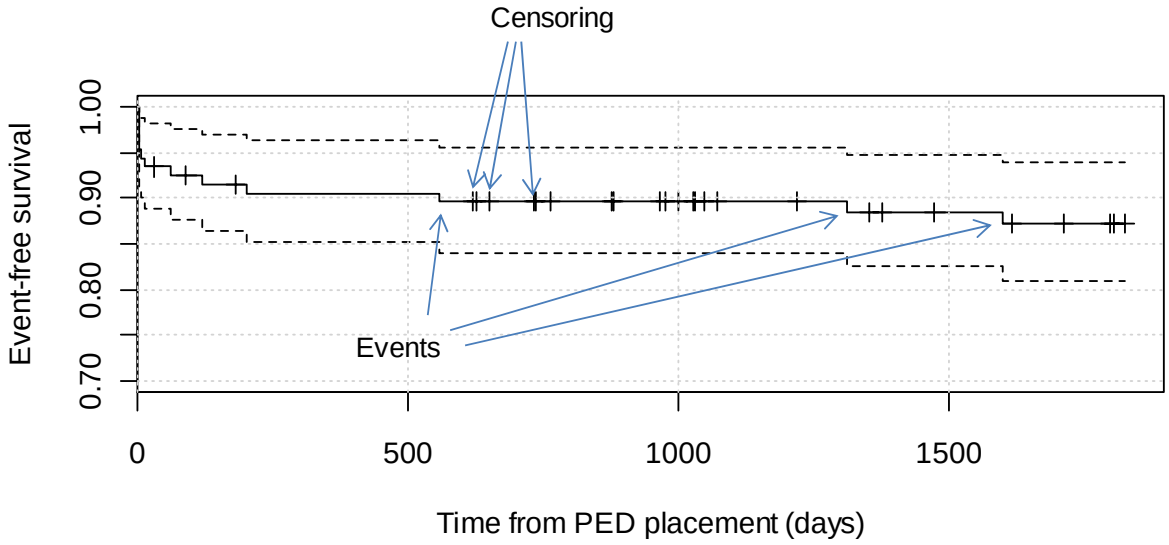

Figure 4. Hypothetical clinical trial showing early primary safety endpoint events occurring soon after PED placement, early censoring, late censoring and 1 late primary safety endpoint events. Follow-up occurs to 5 years (1825 days). Dotted lines show 95% CIs of K-M survival estimates.

Figure 5 shows the distribution of the UCL for the predicted 5-year K-M estimate for the cumulative event rate. UCLs were calculated with alpha set at the standard 0.05. Most of the values are <20% and nearly all are <25%. Power, the proportion of UCLs <25%, is >99%.

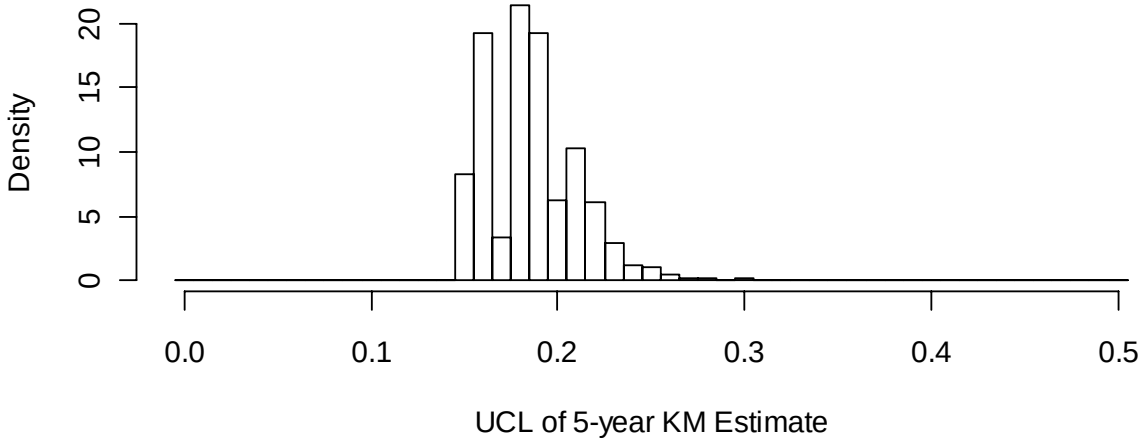

Figure 5. Distribution of UCL of the predicted 5-year K-M estimate for cumulative primary endpoint event rate.

As noted above, FDA is interested in results by subgroup. Conveniently, the two anatomic areas of interest in the internal carotid artery (cavernous segment and below vs. ophthalmic segment and above) divide the PUFS cohort approximately 50%/50%. Moreover, 5 strokes occurred in each subgroup. I therefore repeated the simulations described above considering 107/2 = 53 subjects as the target population. Taking into account similar degrees of loss to follow-up (8 subjects lost during years 1.5-3 and an additional 4 subjects lost during years 3-5), I calculated an expected 138.5 years of subject follow-up to accrue by 5 years. Taking into account the predicted number of primary safety endpoint events, power to conclude that the UCL of the cumulative primary safety endpoint event rate is <25% is >80%.

Note that the approach I've described is conservative because:

- It counts stroke of any type, including stroke types that are unlikely to be related to placement of a neurovascular implant (e.g., lacunar stroke, stroke due to hypertension, embolic stroke related to atrial fibrillation, etc.). Clearly, these strokes are not due to PED; however, clinically it is often difficult to discern the cause of stroke.

- Intracranial aneurysm is known to have a genetic component and multiple aneurysms are fairly common. Thus, PUFS subjects are likely to be at risk for developing new aneurysms in other locations that, either spontaneously or with treatment, may rupture or thrombose and cause stroke. If stroke is determined to be due to a cause completely separate from the target aneurysm, additional analyses may be performed removing these observations as unrelated to PED.

- It excludes PUFS-CA subjects. Including these subjects will increase study power.

R code for the above simulations is shown in **Figure 6**. We conclude that PUFS as designed has adequate power for the 5-year safety hypothesis.

```
library(survival)

majorstroke=c(1,1,3,14,62,120) #6 major strokes already occurred in (respectively) BRABE, CICZU, BURGE, TOPMA, KARGU, ZARPE
minorstroke=c(1,4,5,200) #4 minor strokes in (respectively) ACELI, SANEV, PATRH, PACKA
stroke=c(majorstroke,minorstroke)
numstrokesalreadyoccurred=length(stroke)

#model predicted distribution of future strokes
sims=10000
par(mfrow=c(1,1))
s5y=rbinom(sims,256, 0.01)
hist(s5y,xlab='Pred # subsequent primary safety endpoint events by 5y', freq=FALSE, breaks=seq(-.5,15.5,1))

sims=1000 #model 1000 clinical trials
par(mfrow=c(2,1))  #set plot window to 2 x 1
results=NULL
for (i in 1:sims){
        stroketimes=floor(runif(s5y[i],min=365*1.5,max=365*5)) #model new stroke occurring between years 1.5 and 5
        withdrew=c(30,90,180) #3 subjects already withdrew
        censor3=floor(runif(15, min=365*1.5, max=365*3)) #model censoring of 15 subjects between 1.5 and 3 years
        censor5=floor(runif(8,min=365*3, 365*5)) #model censoring of additional 8 subjects between 3 and 5 years
        time=c(stroke,stroketimes,withdrew, censor3,censor5,rep(1825,110)) #vector of event times, which includes old and new strokes
and censored observations
        event=c(rep(1,numstrokesalreadyoccurred),rep(1,length(stroketimes)), rep(0,110))
        psurv=Surv(time[1:107],event[1:107])  #survival on first 107 observations of vector
        pfit=survfit(psurv~1)
        KMsum=summary(pfit)
        if (i %% 50 == 0) { #every 50 sims, print some results
                print(i)
                print(paste(time[1:107],event[1:107]))
                plot(pfit,main=paste('Sim: ', i), ylim=c(.7,1),
                        ylab='Event-free survival', xlab='Time from PED placement (days)')
                grid(nx=NULL, ny=NULL,col="lightgray")
        }
        UCL=1-KMsum$lower  #vector of UCLs of stroke rate at event times
        times=KMsum$time   #vector of event times
        timepoint3=max(times[times<=1095]) #largest time point <3 years
        timepoint5=max(times[times<=1825]) #find largest time point <5 years
        UCL3=UCL[times==timepoint3] #UCL of KMest at 3 years
        UCL5=UCL[times==timepoint5] #UCL of KMest at 5 years
        totalnumstrokes=sum(event[1:107]) #total number of strokes in dataset
        results=rbind(results,c(totalnumstrokes,timepoint3,UCL3,timepoint5,UCL5))  #store simulation result in an array "results"
}

numstrokes=results[,1]
UCL5=results[,5]
hist(UCL5, breaks=rg, xlab='UCL of 5-year KM Estimate',freq=FALSE)
hist(numstrokes,breaks=seq(0-.5, 25+.5, 1),xlab='Pred # events by trial end',freq=FALSE)
mean(UCL5<.25)
```

```
#Repeat analyses for the supraclinoid subgroup

sims=1000
stroke=c(1,1,4,14,62) #BRABE BURGE CICZU KARGU TOPMA
numstrokesalreadyoccurred=length(stroke)

sims=10000
par(mfrow=c(1,1))
s5y=rbinom(sims,139, .01)
hist(s5y,xlab='Pred # subsequent primary safety endpoint events by 5y', breaks=0:10, freq=FALSE)

sims=1000
par(mfrow=c(2,1))
results=NULL
for (i in 1:sims){
        stroketimes=floor(runif(s5y[i],min=365*1.5,max=365*5)) #model new stroke occurring between years 1.5 and 5
        withdrew=c(30,90) #Model 2 subjects as having withdrawn
        censor3=floor(runif(8, min=365*1.5, max=365*3)) #model censoring of 8 subjects between 1.5 and 3 years
        censor5=floor(runif(4,min=365*3, 365*5)) #model censoring of additional 4 subjects between 3 and 5 years

        time=c(stroke,stroketimes,withdrew, censor3,censor5,rep(1825,110)) #create vector of event times, which includes old and new
strokes and censored observations
        event=c(rep(1,numstrokesalreadyoccurred),rep(1,length(stroketimes)), rep(0,110))
        psurv=Surv(time[1:53],event[1:53])  #survival on first 107 observations of vector
        pfit=survfit(psurv~1)
        KMsum=summary(pfit)
        if (i %% 50 == 0) {
                print(i)
                print(paste(time[1:107],event[1:107]))
                plot(pfit,main=paste('Sim: ', i), ylim=c(.7,1))
                grid(nx=NULL, ny=NULL,col="lightgray")
        }
        UCL=1-KMsum$lower  #UCL of stroke rate
        times=KMsum$time   #vector of KM estimates
        timepoint3=max(times[times<=1095]) #largest time point <3 years
        timepoint5=max(times[times<=1825]) #largest time point <5 years
        UCL3=UCL[times==timepoint3] #UCL of KMest at 3 years
        UCL5=UCL[times==timepoint5] #UCL of KMest at 5 years
        totalnumstrokes=sum(event[1:54]) #total number of strokes in dataset
        results=rbind(results,c(totalnumstrokes,timepoint3,UCL3,timepoint5,UCL5))
}

numstrokes=results[,1]
UCL5=results[,5]
hist(UCL5, breaks=rg, xlab='UCL of 5-year KM Estimate',freq=FALSE)
hist(numstrokes,breaks=seq(0-.5,25+.5,1),xlab='Pred # events by trial end',freq=FALSE)
mean(UCL5<.25)
```

Figure 6. R code for predictive calculations.

Appendix 3 – IRB Approvals

The following pages provide copies of IRB approvals for PUFS.

Omitted for brevity.