SURF: A Prospective, Multicenter **S**tudy Assessing the Embolization of Intracranial Ane**u**rysms using WAVE™ Ext**r**a So**f**t coils, a part of the Penumbra SMART COIL® System

Protocol
CLP 13669.C

Date of Protocol
01 May 2020

Device Name
Penumbra SMART COIL® System including WAVE™ Extra Soft Coils

Sponsor
Penumbra, Inc.
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TABLE OF CONTENTS

CLP 13669.C Protocol Synopsis	
Study Title:	**SURF:** A Prospective, Multicenter Study Assessing the Embolization of Intracranial Aneurysms using WAVE™ Extra Soft coils, a part of the Penumbra SMART COIL® System
Study Objective:	The objective of this study is to demonstrate the safety and efficacy of the Penumbra SMART COIL® System, including the WAVE™ Extra Soft Coils (WAVE) as a fill and finish coil, in the treatment of intracranial aneurysms. Imaging will be analyzed by an independent core lab to assess aneurysm occlusion rates and perform a comparative analysis between imaging modalities.
Study Design:	Post-market, real world, prospective, multi-center study that will enroll approximately 800 subjects at up to 60 global sites
Indication:	Per Instructions For Use
Patient Population:	Patients with intracranial aneurysms treated with WAVE, as part of the Penumbra SMART COIL System
Study Device:	Penumbra SMART COIL System including WAVE Extra Soft Coils
Study Duration:	It is anticipated this study will take approximately 3 years. All subjects will be followed for approximately 1 year.
Follow-up:	Subjects will undergo follow-up at 7 days and/or discharge (whichever is first), as well as at 1-year post-procedure
Inclusion Criteria:	1. Patient age ≥ 18 years 2. Patient having embolization of intracranial aneurysms 3. WAVE Extra Soft Coil is the final finishing coil 4. Penumbra SMART COIL System accounts for at least 75% of total number of coils implanted 5. Informed consent obtained per IRB/EC requirements
Exclusion Criteria:	1. Life expectancy less than 1 year 2. Patient previously enrolled in the SURF Study 3. Known multiple intracranial aneurysms requiring treatment during index procedure 4. Patient is unwilling or unable to comply with protocol follow up schedule and/or based on the Investigator's judgment the patient is not a good study candidate 5. Participation in an interventional drug or device study that may confound the results of this study
Primary Endpoints:	**Efficacy:** • Adequate occlusion defined as Raymond-Roy Occlusion Class I and II at final follow-up

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Study Title:	**SURF:** A Prospective, Multicenter Study Assessing the Embolization of Intracranial Aneurysms using WAVE™ Extra Soft coils, a part of the Penumbra SMART COIL® System
	Safety: • SAEs within 24 hours post-procedure • Device-related SAE up to 7 days or discharge
Secondary Endpoints:	**Efficacy:** • Immediate post-procedure occlusion rate • Retreatment rate at final follow-up • Aneurysm Occlusion Raymond I post treatment • Aneurysm Occlusion Raymond I at final follow-up • Aneurysm recanalization or progressive thrombosis from post procedure to final follow-up **Safety:** • Major ipsilateral stroke • Device related SAE at final follow-up • All-cause morbidity and mortality
Sample Size Justification	Approximately 800 patients will be enrolled in this post market study with estimated 10% attrition at final follow-up. Assuming an observed rate of 89% (641/720) for the endpoint of Raymond-Roy I-II at follow-up, the sample size precision is greater than ± 3% for this endpoint (95% CI: 87%% to 91%). Assuming an observed rate of 2.8% (22/800) for the primary endpoint of device-related serious adverse events up to 7 days or discharge, the sample size precision is greater than ± 1.5% for this endpoint (95% CI: 1.6% to 3.9%). Assuming an observed rate of 8.9% (71/800) for the primary endpoint of serious adverse events at 24 hours post procedure, the sample size precision is greater than ± 2.5% for this endpoint (95% CI: 6.9% to 10.9%). These precision estimates are based on the normal approximation binomial 95% confidence intervals. Hence, the sample size provides an adequate level of precision for the primary endpoints.

1. Introduction and Rationale

Intracranial aneurysms are a significant health problem in the United States and Europe with an incidence rate as high as 6% [1-3]. If an intracranial aneurysm ruptures, blood leaks into the highly sensitive subarachnoid space around the brain, resulting in a subarachnoid hemorrhage (SAH). The annual risk of rupture of an intact intracranial aneurysm is estimated to be approximately 1.9% [4]. Of all SAH incidences, 85% are attributed to ruptured aneurysms [5] and approximately half of all ruptured aneurysms are fatal within the first six months [6]. Patients who survive the initial SAH are at significant risk of subsequent re-rupture as well. Various reports indicate that if left untreated, there is a re-bleeding rate of more than 50% within the first six months from initial presentation of a SAH [4]. In addition, permanent disability is reported to occur in 50% of patient's that survive a SAH and only one-third of patient's will have a positive outcome [7].

Neurosurgical clipping was the initial intervention for intracranial aneurysms (IA) prior to the introduction of alternative endovascular treatment options. The International Subarachnoid Aneurysm Trial (ISAT) was a randomized, prospective, multicenter trial that compared the safety and efficacy of endovascular coiling compared to neurosurgical clipping. The ISAT Trial enrolled 2143 subjects with ruptured IA and randomized them to endovascular detachable coil (n=1073) treatment or standard neurosurgical clipping (n=1070) [8]. The primary endpoint was the Modified Rankin Scale (mRS) of 3-6 (dependency or death) at one year. The clinical follow-up included assessment for rebleeding and death at 2 months and at one year. An interim analysis was conducted per the trial's steering committee and recruitment was stopped. The outcomes showed a statistically significant difference between the treatment arms in favor of the endovascular coiling arm (P=0.0019). Of the 801 subjects treated with endovascular coiling, 190 (23.7%) achieved an mRS of 3-6 at one year. Of the 793 subjects treated with neurosurgical clipping, 243 (30.6%) achieved an mRS of 3-6. The absolute risk reduction of dependency or death at one year was 6.9% (95% CI 2.5-11.3) and the relative risk reduction was 22.6% (95% CI 8.9-34.2) in favor of the endovascular coil arm. The risk of rebleeding from the ruptured aneurysm at one year was 2 per 1276 of the endovascular coil arm compared to 0 per 1081. The authors concluded that survival free disability at one-year post-treatment was significantly better with endovascular coiling.

The ISAT Trial demonstrated that coiling was a safe and efficacious alternative treatment option for IA. The trial has maintained long-term follow-up with 1644 subjects from 22 United Kingdom sites and collected clinical outcomes from 10-18.5 years post initial study procedure [9]. The mRS was collected annually from self-reported questionnaires and data on rebleeding and recurrent aneurysms were also collected by questionnaires and medical records. The rate of death was obtained from data provided by the Office of National Statistic. At a 10-year follow-up, 1003 subjects (n=435 coiling and n=370 clipping) had returned questionnaires and survival was higher for subjects that were initially treated with coiling (82%) compared to the surgical clipping arm (78%). Furthermore, subjects from the endovascular coiling arm were more likely to be alive and independent at 10 years compared to subjects from the clipping arm (OR 1.34, 95% CI 1.07-1.67). The durability

of endovascular coiling in the study provided level 1 evidence to support coiling for subjects with IA that are suitable for endovascular therapy.

Several factors influence which treatment the interventionalist selects, such as patient risk factors, rupture status, aneurysm neck diameter and width, as well as cerebral vessel location [10]. Current treatment options include bare metal coiling, stent assisted coiling, balloon assisted coiling, bioactive-hydrocoils, surgical clipping, flow diverters, and more recently, intrasaccular devices. Over the past decade, endovascular coiling has now been widely accepted for the treatment of both ruptured and unruptured aneurysms [9-17]. Coils that are considered to have 'stiff' properties are typically effective for the early stages of the aneurysm packing, while softer coils are more effective to complete the packing of residual empty spaces with 'finishing' coils. Finishing coils are beneficial to use at the end of the aneurysm packing process, because they are designed to fill-in the empty spaces to tighten the packing [18-21]. Earlier studies on coils demonstrated that there was a correlation between packing density and rates of recanalization [18, 20, 21]. Finishing coils were initially bare-metal, but the development of polymer or gel-coated coils have become available. The Hydrosoft and Hydroframe finishing coils (Microvention, Tustin, CA) were developed with a gel that expands when in contact with liquids[22].

The HELPS Trial was a randomized controlled trial comparing Hydrocoils to bare platinum coils and initial results showed a significantly higher rate of adverse outcomes in the bare platinum coil arm [23-25]. A subgroup analysis of the HELPS Trial further demonstrated that hydrocoils were associated with statistically significant lower rates of major recurrence for subgroups with recently ruptured aneurysms and medium-sized aneurysms[26-28]. There have been varying results published for hydrogel coils in the HELPS, PRET, and MAPS trials, but the recent results from the GREAT randomized trial showed favorable outcomes for the hydrogel coil arm [22]. The GREAT Trial enrolled 513 patients (hydrogel=256 and bare platinum=257 patients) in France and Germany. The investigators suggested that the significantly higher packing density observed in the hydrogel arm translated to better long-term angiographic results and lower retreatment rates.

The Hydrogel Endovascular Aneurysm Treatment Trial (HEAT) was a multicenter, randomized, controlled trial that evaluated the second-generation HydroCoil Embolic System (HES) compared to bare-platinum coils (BPC) for the treatment of intracranial aneurysms [29]. The primary endpoint was aneurysms recurrence over 24 months (defined by Raymond aneurysm scale). There were six hundred subjects enrolled at 46 sites with ruptured or unruptured intracranial aneurysms randomized to both arms (n=297 HES and n=303 BPC). The HES arm was superior to bare platinum coils at reducing the aneurysm recurrence rate. The recanalization rate was 4.4% for HES compared to 15.4% for BPC and no significant differences in adverse event rates.

An analysis of other coils available (Target Ultra Helical, MicroPlex Hypersoft, Axium Helix, ED Coil Extrasoft, and DeltaPlush) were evaluated by Ota et al. for area, perimeter, and circularity in an experimental model[30]. The authors suggested that Target Ultra Helical and MicrPlex may be more suitable for early procedure; Axium Helix and ED Coil Extrasoft for mid-procedure; and Deltaplush was better suited for finishing[30]. Therefore, coils with varying properties at different procedure times and stages may be beneficial.

Penumbra, Inc. (Alameda, CA) has developed the Penumbra SMART COIL® System to address the limitations of conventional embolization coil systems. SMART COIL is unique from other microcoils, because they do not have uniform stiffness, they have a tight conformational structure, and they have a robust stretch-resistance platform [32]. The SMART COIL system offers softer coil technology including the WAVE™ Extra Soft coil designed for filling and finishing. Penumbra SMART COIL System has been evaluated in multiple publications [31-38].

A multicenter retrospective review was performed by Spiotta et al.[31, 35] to capture data on all patients treated with at least one SMART Coil as part of an endovascular intracranial aneurysm (IA) embolization between July 2015 to January 2016. Fifty-nine patients underwent treatment for IAs with SMART Coils (44% were ruptured aneurysms). The mean aneurysm size was 5.9 ± 2 mm by 4.5 ± 2 mm. More than half (54.2%) of the patients underwent coiling with SMART Coils alone; the remainder used either framing or finishing coils of another type. About one-third (33.9%) of patients underwent balloon-assisted coiling, and 47.5% underwent stent-assisted coiling. Raymond I or II occlusion was achieved in 71.2% of patients. There were no device malfunctions or rebleeds observed. Six patients experienced a minor complication without clinical sequelae. Occlusion outcomes included 33.9% Class I, 37.3% Class II, and 28.8%. No rebleeds have been observed. The authors concluded that the SMART coil progressive design offered appreciable clinical advantages during deployment and demonstrated satisfactory safety and efficacy outcomes in treatment of a wide variety aneurysms, both ruptured and unruptured [31].

Another retrospective study was performed by Ilyas et al. to analyze baseline and initial outcomes data on consecutive patients treated by IA embolization from June 2016 to January 2017. Thirty-two patients with 33 aneurysms were included in the study; 15.2% presented with subarachnoid hemorrhage. Mean aneurysm diameter was 6.0 ± 2.5 mm, with 85% in the anterior circulation. Dome irregularity and fusiform aneurysm morphology were noted in 33% and 9% of aneurysms, respectively. Coiling was performed exclusively with SMART coils in 30 (90.9%) cases. Single- and dual-microcatheter techniques were utilized in 16 (48.5%) and one (3.0%) case, respectively. Balloon- and stent-assistance were used in three (9.1%) and 11 (33.3%) cases, respectively. The mean packing density was 25.2%. Raymond I or II occlusion was achieved in 75.8% of patients. No serious procedural complications were observed, and one device malfunction occurred in a patient with a wide-necked aneurysm (3.0%). The authors concluded that initial results showed a favorable risk to benefit profile of the SMART coil for the embolization of IAs [36].

Padmanadhan (2017) reported on a retrospective analysis of 75 consecutive patients treated in a single center for cerebral aneurysms with the SMART coil system [33]. There were 20 aneurysms treated exclusively with the SMART coil and 58 were treated with a combination of coils; 252 SMART coils were used (13 Standard, 27 Soft, and 212 ExtraSoft coils). Adjunctive devices were used in 57 cases (41 balloons and 16 stents). The results showed that no coil migration, coil stretching, premature detachment, or failure of coil detachment occurred with the SMART coils and three coils were retrieved and not detached. One event of intra-procedural rupture (controlled with balloon inflation) and 3

cases of intra-procedural thrombosis treated with IV Absciximab occurred. There three patient deaths of presenting subarachnoid hemorrhage and one case of delayed procedure related mortality (remote hemorrhage in stent assisted coiling case). The author reported that there was no change in the baseline modified Rankin score (mRS) for the remaining patients. In addition, the 6-month follow-up was available in 39/75 patients and showed complete aneurysm occlusion with no remnants in 32 patients and small neck remnants in 7 patients (under observation).The author concluded that the SMART (Penumbra, Inc.) coil system was safe, easy to use, and effective especially in the treatment of otherwise difficult to treat very small intracranial aneurysms [33].

A retrospective cohort study was recently completed by Sokolowski et al. is to assess the angiographic outcomes at interim follow-up after aneurysm embolization with SMART coils between June 2016 and August 2017 [38]. Baseline data and follow-up angiographic outcomes using the modified Raymond-Roy classification (MRRC) were reported from 33 patients with 34 aneurysms. The initial mean coil packing density was 26%, and the initial MRRC was I, II, IIIa, and IIIb in 24%, 26%, 35%, and 15%, respectively. The overall complication rate was 12%. At last follow-up (mean duration 7.7 ± 3.2 months), the retreatment rate was 14.7%, the MRRC was I, II, IIIa, and IIIb in 62%, 26%, 3%, and 9%, respectively. The authors reported that the majority of residual aneurysms after the initial embolization procedure would progress to complete or near-complete occlusion at interim follow-up [38]. In conclusion, they reported that the SMART coil was efficacious for the treatment of appropriately selected aneurysms and had an acceptable risk profile.

The SMART Registry is a prospective, multicenter registry sponsored by Penumbra, Inc. to assess the treatment of intracranial aneurysms and other neurovascular abnormalities. For eligibility, the intervention must have implanted at least 75% SMART COIL, Penumbra Coil 400™, and or Penumbra Occlusion Device (POD®) (Penumbra, Inc.). Study endpoints included retreatment through one-year follow-up, procedural device-related serious adverse events (SAE), occlusion status at immediate post-procedure, and at one-year follow-up.

The interim analysis from the first 500 consecutive subjects enrolled included cerebral aneurysms (90.6%, 451/498), of which 31.0% were ruptured; arteriovenous malformations (1.4%); fistulae (4.6%); and other lesions (3.4%)[39]. At admission, 70.8% of subjects were female, and the mean age was 60.0 ± 13.3 years. Aneurysms were small (87.7%), large (12.1%), and giant (0.2%), with 64.2% (265/413) having a wide neck.

The median time of fluoroscopic exposure was 36.5 minutes (IQR 24.0-56.0). Stent-assisted coiling was performed in 29.8% of patients, whereas balloon-assisted coiling was performed in 19.4% of patients. For all aneurysms, the median packing density was 29.5% (IQR 21.4-38.3). For all subjects, adequate occlusion at immediate post-procedure was achieved for 97.6% (483/495). In aneurysm subjects, Raymond I or II was achieved in 79.7% (354/444) of patients at immediate post-procedure, and 88.6% (124/140) at one-year follow-up. The retreatment rate through one-year follow-up was 3.8% (6/157).

Procedural device-related SAEs were observed in 3.2% (16/500) of patients. Mortality rates were 0.4% (2/496) within 24 hours of intervention and 11.4% (21/185) after 24 hours; no deaths were device-related. One-year follow-up data collection is ongoing.

Initial results suggest that the SMART COIL System achieves adequate embolization in a variety of neurovascular lesions. The clinical evidence has shown that coiling is a safe and durable alternative treatment option for suitable subjects. The SURF study will provide additional clinical evidence on the safety and efficacy of the WAVE™ Extra Soft coil (WAVE) for the treatment of cerebral aneurysms.

2. Penumbra SMART COIL System with WAVE Extra Soft Coil

The WAVE Extra Soft Coil is part of the SMART COIL System offered by Penumbra, Inc. and is specifically designed as a filling and finishing coil. WAVE may be used with other SMART Coils that have different sizes and properties: SMART Plus Standard, Standard, Soft, and Extra Soft. The specific coil that is most suitable is determined largely by the morphology of the aneurysm and coil properties needed at various packing stages. The SMART COIL System is designed for endovascular embolization in the neuro and peripheral vasculature. Intended users for this device are physicians who have received appropriate training in interventional radiology.

2.1 Coil

The coil is a bare platinum embolization coil constructed primarily out of 92% platinum, 8% tungsten alloy. The coil contains separate components conferring stretch resistance and secondary shape to the coil. The coil is available in five configurations of varying shape and softness: Smart Plus Standard, Standard, Soft, Extra Soft, and WAVE Extra Soft. A summary of all sizes of coil configurations is presented in Table 1.

Table 1: Coil Sizing Table

Trade Name	Catalog Number Prefix	Secondary Diameter (mm)		Length (cm)	
		Min	Max	Min	Max
Smart Plus Standard	400SMTSTD	9	18	20	60
Standard	400SMTSTD	3	8	4	60
Soft	400SMTSFT	1	14	2	45
Extra Soft	400SMTXSFT	1	6	1	15
WAVE™ Extra Soft	400SMTHXSFT	1	6	1	15

2.2 Detachment Pusher

The detachment pusher is a stainless steel and polymer 185 cm wire-like assembly used to advance and detach the coil at the target location. The coil is loaded onto the distal end of the detachment pusher via mechanical attachment to the distal detachment tip. The coil is detached from the pusher by actuating the detachment handle. The coil/detachment pusher assembly is provided sterile and is a single use device.

2.3 Detachment Handle

The SMART COIL Detachment Handle is a plastic handle used to mechanically detach the Coil. The Detachment Handle is provided sterile and is intended for use in multiple coil detachments performed during a single procedure.

2.4 Indications

The Penumbra SMART COIL System is indicated for the embolization of:

- Intracranial aneurysms
- Other neurovascular abnormalities such as arteriovenous malformations and arteriovenous fistulae
- Arterial and venous embolizations in the peripheral vasculature

Embolization coils perform their intended function by volume filling of the aneurysm sac or target location. Achievement of aneurysmal occlusion is based on volume filling of the aneurysm, causing blood flow diversion from the aneurysmal sac to the parent artery, leading to secondary clot formation and organization within the target location.

The Penumbra SMART COIL System originally received the CE Mark in December 2014, FDA 510(k) clearance in March 2015, and Health Canada approval in October 2015.

3. Risk Analysis

A thorough risk analysis was performed as part of design control requirements of the Quality System Regulation (21 CFR 820). The current potential complications listed on the Instructions For Use (IFU) label include the following:

- acute occlusion
- air embolism
- allergic reaction and anaphylaxis from contrast media
- aneurysm rupture
- arteriovenous fistula
- coagulopathy
- infection
- intima dissection
- intracranial hemorrhage
- ischemia
- myocardial infarction
- neurological deficits including stroke
- parent artery occlusion

- coil herniation into parent vessel
- death
- device malfunction
- distal embolization
- emboli
- embolic stroke and other cerebral ischemic events
- false aneurysm formation
- hematoma or hemorrhage at access site of entry
- incomplete aneurysm occlusion
- peripheral thromboembolic events
- post-embolization syndrome
- premature device detachment
- recanalization
- renal failure
- respiratory failure
- revascularization
- thromboembolic episodes
- vessel spasm, thrombosis, dissection, or perforation

Potential complications associated with cerebral endovascular coiling procedures are similar to other angiographic and coiling procedures and may include:

- Allergic reaction to contrast agents
- Access site complications
- Infections
- Pseudoaneurysms
- Arterial dissection
- Parent vessel occlusion
- Thromboembolism (or other embolism)
- Aneurysm perforation (ruptured and unruptured)
- Rebleed
- Procedure-related morbidity
- Procedure-related mortality
- Coil migration

4. Study Overview

The objective of this study is to demonstrate the safety and efficacy of the Penumbra SMART COIL System including WAVE Extra Soft as a fill and finish coil in the treatment of intracranial aneurysms. Imaging will be analyzed by an independent core lab to assess aneurysm occlusion rates and perform a comparative analysis between imaging modalities.

4.1 Study Design

Post-market, real world, prospective, multi-center study that will enroll approximately 800 subjects at up to 60 global sites.

4.2 Study Objectives/Endpoints

4.2.1 Primary Endpoints

Efficacy:

- Adequate occlusion defined as Raymond-Roy Occlusion Class I and II at final follow-up

Safety:

- SAEs within 24 hours post-procedure
- Device-related SAE up to 7 days or discharge

4.2.2 Secondary Endpoints

Efficacy:

- Immediate post-procedure occlusion rates
- Retreatment rate at final follow-up
- Aneurysm Occlusion Raymond I post treatment
- Aneurysm Occlusion Raymond I at final follow-up
- Aneurysm recanalization or progressive thrombosis from post procedure to final follow-up

Safety:

- Major ipsilateral stroke
- Device related SAE at final follow-up
- All-cause morbidity and mortality

5. Study Population

5.1 Inclusion Criteria

1. Patient age ≥ 18 years
2. Patient having embolization of intracranial aneurysms
3. WAVE Extra Soft Coil is the final finishing coil
4. Penumbra SMART COIL System accounts for at least 75% of total number of coils implanted
5. Informed consent obtained per IRB/EC requirements

5.2 Exclusion Criteria

1. Life expectancy less than 1 year
2. Patient previously enrolled in the SURF Study
3. Known multiple intracranial aneurysms requiring treatment during index procedure
4. Patient is unwilling or unable to comply with protocol follow up schedule and/or based on the Investigator's judgment the patient is not a good study candidate
5. Participation in an interventional drug or device study that may confound the results of this study

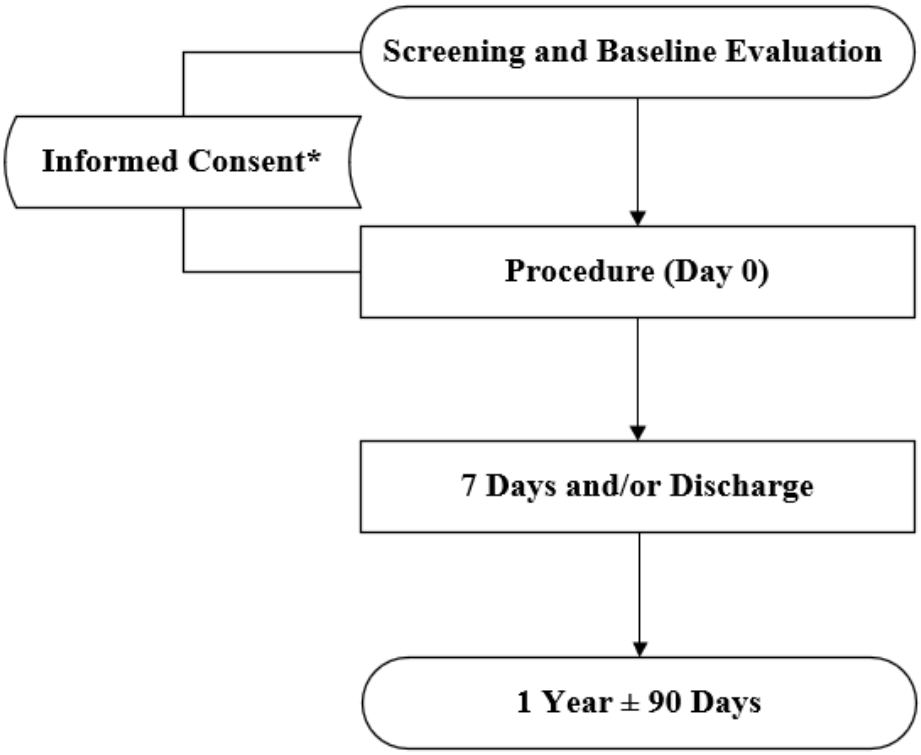
6. Study Procedures

6.1 Overview of Study Flow

Patients ≥18 years of age having embolization of intracranial aneurysms should be assessed for eligibility. All sites will keep a screen failure log of all potential study candidates who are screened and not enrolled or screened, consented, and not enrolled. Reason(s) for exclusion will be recorded. Screening information will be reported in Electronic Data Capture System (EDC).

Recruitment rates will be tracked over time for each site. The actual recruitment rates will be useful for planning further clinical trials and determining the widespread impact of the therapy.

Figure 1: Study Flow



*For sites in North America, ICF may be obtained up to 2 days post-procedure, but prior to discharge

6.2 Study Visits

Subjects enrolled in this study will follow the visit schedule below and will continue to receive routine practice/ standard of care treatment. Procedure is day 0 for determining follow-up visit dates.

- Screening & Baseline
- Procedure
- 7 Day and/or Discharge
- 1 Year Follow-Up ± 90 Days

6.3 Recruitment

The target population are subjects ≥18 years of age presenting with an intracranial aneurysm(s). No study specific screening tests or procedures are required for enrollment in the study. Standard of care evaluations will be used to confirm eligibility.

Potential study participants and/or their legal authorized representative (LAR) will be identified by the study team at each site to obtain consent and determine eligibility. The study allows for enrollment up to 800 subjects at up to 60 global sites.

6.4 Screening and Enrollment

The subject will be clinically evaluated in the same manner as any patient presenting with intracranial aneurysm(s). The medical history screen, available clinical/neurological exams obtained, and imaging information per institutional routine care will be evaluated to determine patient eligibility.

Pre-procedure angiography will be performed per institutional standard of care and will allow to define aneurysm location, size and best treatment strategy.

Patients will be considered enrolled once informed consent is obtained per IRB/EC, the index procedure is complete, and all eligibility is confirmed. Patients who fail to meet entry criteria pertaining to coil selection will be considered a screen fail.

6.5 Informed Consent

The Investigator or designee will obtain written informed consent from the subject or LAR using the current IRB/EC approved consent form per IRB/EC policy. For sites in North America, patients who have had an index procedure with SMART Coils and all eligibility is confirmed, may be consented up to 2 days post-procedure but prior to discharge. For sites outside of North America, the informed consent signature process will be described in Informed Consent Form and will be applied per local Ethics Committee approvals.

All informed consent documents used under this protocol will be consistent with applicable elements of EN ISO 14155:2011, Clinical investigation of medical devices for human subjects – Good Clinical Practice and 21 CFR Part 50, Protection of Human Subjects, and will be approved by the site's reviewing IRB/EC prior to study initiation.

Any modification to the sample informed consent form made by the study site must be approved by the Sponsor and the IRB/EC before use. Each study site will provide the Sponsor with a copy of the IRB/EC approved consent forms. Informed consent completion will be monitored regularly by the Sponsor.

6.6 Screening and Baseline Evaluation

All assessments are to be conducted in accordance with routine care at each participating hospital; the following data will be collected but is not limited to:

- Demographics
- Vital signs
- Review of medical history

- Baseline mRS
- If a patient has a SAH at baseline, the Hunt and Hess score will be collected

6.7 Procedure

All procedures are to be conducted in accordance with routine care at each participating hospital and the Instructions for Use for each device used.

At a minimum, the following information will be captured in the Case Report Form (CRF) for the target aneurysm, data will not be captured for ancillary aneurysms treated during the index procedure:

- Sedation
- Type of aneurysm
- Size of aneurysm
- Aneurysm location
- Procedural information
- Devices used
- Aneurysm occlusion grade
- Adverse event review
- Angiography

Procedural angiography will be performed per institutional standard of care. Imaging will be uploaded and sent to an Imaging Core Laboratory to make a final determination on aneurysm occlusion rate.

6.8 7 Day and/or Discharge

The 7 day and/or discharge visit should be done within 1 day prior to discharge or at day 7, whichever occurs first. All assessments are to be conducted in accordance with routine care at each participating hospital, the following data will be collected but is not limited to:

- Vital signs
- mRS
- Adverse event review

In addition to the assessments above the following will be collected at discharge:

- The location that the subject is discharged to and the date of discharge
- If any adverse events occurred, it will be reported on the Adverse Event Form

6.9 Final Follow-Up (1 Year ± 90 Days)

All assessments are to be conducted in accordance with routine care at each participating hospital, the following data will be collected but is not limited to:

- Aneurysm occlusion grade
- Vital signs
- mRS
- Retreatment information
- Adverse event review
- Angiography*

*Angiography will be performed per institutional standard of care. DSA, CTA, or MRA are accepted for imaging modality. Images will be sent to an Imaging Core Laboratory to make a final determination on aneurysm occlusion rate. If both DSA and MRA are available, then both imaging modalities should be submitted for Core Laboratory review.

Table 2: Schedule of Assessments

ACTIVITY	SCREENING & BASELINE	PROCEDURE	7-DAY AND/OR DISCHARGE	FINAL FOLLOW-UP (1 YEAR ± 90 DAYS)
Written Informed Consent	X[1]			
Demographics	X			
Medical History	X			
Vitals	X		X	X
mRS	X[2]		X	X
Hunt & Hess	X[3]			
Procedure		X[4]		
Occlusion Grading		X		X[4,5,6]
Adverse Event Review		X	X	X

[1] For sites in North America, patients who have had an index procedure with SMART Coils and all inclusion/exclusion confirmed, may be consented up to 2 days post procedure but prior to discharge

[2] Baseline mRS is based on subject status prior to the index procedure

[3] For patients presenting with SAH

[4] Imaging should be uploaded into Image Management System within 14 days

[5] Occlusion Grading and other datapoints will be collected if retreatment occurs prior to study exit

[6] If both DSA and MRA are performed as part of standard of care follow-up, then both imaging modalities should be submitted for Core Laboratory review

7. Investigator Responsibilities

7.1 Institutional Review Board / Ethics Committee Approval

Prior to enrolling patients into the study, the investigator will ensure that proper Institutional Review Board (IRB)/Ethics Committee (EC) approval is obtained in accordance with applicable local laws and regulations. The IRB/EC shall approve all study documents as appropriate, including but not limited to the final protocol, amendments to the protocol, Instructions for Use (where applicable), Investigator Brochure (where required), and the informed consent.

The investigator will report to the Sponsor or designee immediately if the approval to conduct the investigation is withdrawn by the IRB/EC or Competent Authority. The report will include a complete description of the reason(s) for which approval was withdrawn.

7.2 Informed Consent

The investigator is responsible for ensuring that a signed and dated informed consent is obtained in accordance with Section 6.5 of this protocol and according to country and local requirements.

7.3 Adherence to Protocol/Amendments and Applicable Law

The investigator is responsible for overseeing, ensuring that the study is conducted, and completing the study according to this protocol and in accordance with the relevant aspects of EN ISO 14155:2011, Declaration of Helsinki, along with any conditions imposed by the reviewing IRB or EC, and all other applicable regulations. The investigator shall approve and adhere to this protocol and any amendments that arise during the course of the study.

It is the investigator's responsibility to ensure that the staff assisting with the study have the appropriate qualifications, are fully instructed on the study procedures, and will respect study confidentiality.

7.4 Case Report Form Completion

The Investigator and study staff shall complete the case report forms (CRFs) associated with this study. Subject numbers shall be used to identify individual participants in this study. The CRFs should be a complete and accurate record of subject data collected during the study according to relevant aspects of I.S. EN ISO 14155, 21 CFR 11, Electronic Records; Electronic Signatures and GCP requirements. It is the Investigator's responsibility to ensure the quality of the data collected and recorded is appropriate and collected in accordance with GCP and all applicable regulations. Data entry will be performed by the study site(s). Investigators are responsible for completion and timely submission of data to Penumbra, Inc. Every reasonable effort should be made to complete data entry within 7 business days of data collection.

7.5 Image Upload

Images from Immediate Post Procedure and Final Follow-Up visit may be uploaded to an image management system for Core Lab review. Instructions for image collection and upload will be provided. Study staff shall ensure that no images contain any personally identifying information about the subject or study site (e.g. Physician name, Institution name, patient name, etc.).

Sites will be provided with instructions for how images should be collected and submitted within 14 days of the acquisition of the required imaging. If the site is unable to provide the images within this time frame, the appropriate Sponsor contact should be notified.

7.6 Reporting

The investigator will be responsible for reporting the following:

7.6.1 Adverse Events

Adverse events (AE) must be recorded by the Investigator on the CRFs and will be monitored during the study. Only adverse events related to the procedure or device, and all SAEs will be collected starting at procedure through discharge for enrolled subjects. After discharge only neurological SAEs will be collected. Additional information for Symptomatic Intracranial Hemorrhage and Ischemic Stroke will be collected on Event of Interest CRFs.

Minimum requirements of data to be recorded are: Adverse event term, event start date, seriousness, action taken, outcome and procedure / device-relatedness or causality.

In order to ensure prompt reporting of AEs, all reportable AEs (as well as all related study data) are required to be entered into the EDC in a timely manner. Any suspected UADEs should be reported immediately by calling the Sponsor. All device related SAEs should be reported in the EDC within 72 hours of the site staff first being made aware of the occurrence of the SAE. If the EDC is unavailable, an email can be sent to Penumbra.

The Investigator must report adverse events to the IRB/EC according to local requirements. The investigator is responsible for reporting time frames and complying with local or national requirements. In addition, the investigator will report to the sponsor and IRB/EC any device deficiencies that could have led to a SAE, if required by national regulations or by local authorities.

For the purpose of reporting within this protocol, pre-existing conditions or planned procedures for pre-existing conditions are not reportable as AEs unless there is worsening of the condition with an increase in severity or frequency during the course of the study. All deaths will be reported regardless of causality. When reporting a death, the primary condition or diagnosis that contributed to the fatal

outcome should be reported as a SAE with an outcome of death. Only a single cause of death should be reported in EDC. If the cause of death is unknown, report "unknown cause of death" as a SAE.

7.6.2 Analysis of Adverse Events

A Medical Monitor will review events related to primary and secondary safety endpoints as they are reported. Events of Interest related to Symptomatic Intracranial Hemorrhage and Ischemic Stroke will also be reviewed by the medical monitor. Redacted source documents may be collected for events where the medical monitor deem necessary.

7.6.2.1 Definitions

- **Adverse Event (AE)**: any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the study medical device.

- **Adverse Device Effect (ADE):** An adverse event related to the use of the study medical device.

- **Definition of SAE**
  An SAE is an event that:
  - Led to death
  - Led to a serious deterioration in the health of the patient that:
    - Resulted in life-threatening illness or injury
    - Resulted in chronic disease
    - Resulted in permanent impairment of a body structure or a body function
    - Required in-patient hospitalization or prolongation of existing hospitalization
    - Resulted in medical or surgical intervention to arrest permanent impairment to body structure or a body function
    - Led to fetal distress, fetal death or a congenital abnormality or birth defect

- **Unanticipated Adverse Device Event (UADE):** An unanticipated adverse device effect is 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 protocol, or instructions for use. Unanticipated adverse device effect also includes any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.6.2.2 Relationship to the Study Device

An AE is considered to be device-related when it is reasonable to believe that the event may have been caused by or is related to the device. The following definitions will be used to assess the relationship of the adverse event to the use of study device. Grading for relatedness of 'probable' or 'definite' will be considered device related.

- **Definite:** The temporal sequence is relevant and the event abates upon device application completion/removal, or reappearance of the event on repeat device application

- **Probable:** The temporal sequence is relevant or the AE abates upon device application completion/removal or the AE cannot be reasonably explained by the subject's condition or comorbidities. The AE is related or most likely associated with the device

- **Possible:** The temporal sequence between the device and the AE is such that the relationship is not unlikely or there is no contradicting evidence that can reasonably explain the subject's condition. There is a possibility of a relationship between the AE and the device

- **Unrelated:** The AE is not associated with the device. There is no relation between the AE and the device

Similar grading will be used for assessing the relationship to index procedure, target aneurysm, and comorbidities.

7.6.3 Device Deficiencies

All device deficiencies related to the identity, quality, durability, reliability, safety or performance of the study device shall be documented and reported through the standard commercial process. Investigators must report all possible device deficiencies associated with the device observed during the study. This includes unexpected outcomes or device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention has not be made or c) if circumstances had been less fortunate.

Device manufacturers are required to report qualifying medical device incidents to the relevant national competent authorities. An incident is defined as "any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject or to a serious deterioration in their state of health." A deterioration in state of health is not considered unanticipated if the condition leading to the event was considered in a risk analysis.

7.6.4 Protocol Deviation

Deviations defined in this protocol should be clearly documented, if identified during monitoring or through other means. For this study, deviations should be reported for the following categories

- Inclusion/exclusion criteria deviation(s)
- Informed Consent deviation(s)

7.7 Records Retention

The Investigator shall maintain the records associated with this study for a period of at least two years after either the date on which the investigation is completed or the date that the records are no longer required for supporting a premarket approval/notification submission, whichever is later. A Trial Master File (TMF) will be used as the master repository for all site and Sponsor regulatory documents. These records include the following:

- Correspondence with the Sponsor or designee, the Medical Monitor, and other investigators
- Subject source records, including but not limited to: Informed Consent Forms, copies of all completed CRFs, and supporting documents (laboratory reports and reports of diagnostic tests, medical records, etc.)
- All versions of study protocol
- Documentation of protocol deviations
- Reports of any serious adverse event or serious device effects
- A copy of all approvals related to the clinical investigation
- The approved, blank, informed consent form and blank CRFs
- All approval/acknowledgment letters from the IRB/EC for all versions of the study protocol, ICF and other documents
- Clinical Trial Agreement
- Signed and dated curriculum vitae for all study personnel
- Medical licenses for the Principal Investigator and all participating sub-investigators
- Financial disclosure for the Principal Investigator and all participating sub-investigators
- All required regulatory documents such as Delegation of Authority and training logs
- Signed Protocol Signature Page(s)

8. Sponsor Responsibilities

8.1 Training

The Sponsor is responsible for providing training on the protocol, CRF completion, and image upload, as applicable for all study staff per delegation of authority log.

8.2 Investigator List

The Sponsor shall keep a list of the names and addresses of the clinical Investigators for the study.

8.3 Adverse Event Reporting

The Sponsor shall evaluate adverse event reports received from the study sites and found during data monitoring and shall report them to the appropriate regulatory bodies and other study sites as necessary.

8.4 Data Monitoring

Penumbra is responsible for ensuring that the study is conducted according to the appropriate regulations (US Food and Drug Administration 21 CFR §812, ISO 14155:2011). A Penumbra employee or designate will conduct the following site visits:

8.4.1 Site Qualification Visit

Conducted to ensure the study site has the appropriate staff, facilities, and expertise to participate in the study. Site Qualification can be waived under certain circumstances.

8.4.2 Site Initiation Visit

Conducted to train the study staff on use of the device, study requirements, and other relevant training.

8.4.3 Interim Monitoring Visit

Conducted as needed to ensure the study site is operating in compliance with this protocol, continues to have the appropriate staff and facilities, and is correctly completing the CRFs.

To ensure that investigators and their staff understand and accept their defined responsibilities, the Sponsor will maintain regular correspondence and perform periodic site visits during the course of the study to verify the continued acceptability of the facilities, compliance with the study plan, and maintenance of complete records. Clinical monitoring will include review and resolution of missing or inconsistent data and source document checks to ensure the accuracy of the reported data. Informed consent, CRFs and medical records for all enrolled and screen failed subjects will be made available to the Sponsor for review and collection.

8.4.4 Site Close Out Visit

Conducted to ensure all study, device, and regulatory-related activities have been completed prior to site closure.

8.5 Data Management

Case Report Forms (CRFs) will be used at all study sites. All study data will be entered into commercially available web-based electronic data capture system (EDC). Data entry will be performed by the study site personnel. Investigators are responsible for completion and timely submission of the data to the Sponsor. Every reasonable effort should be made to complete data entry within 7 days of data collection. This EDC system requires no on-site software installation or specific hardware to operate. Investigators, clinical coordinators, data managers, and Penumbra clinical personnel access project information and study data centrally via a web browser.

Automated data quality checks will display warnings for invalid data. Additionally, manual review of data listings may be used to identify data discrepancies or inconsistencies. The study site may be queried for clarification concerning CRF discrepancies or inconsistencies identified. If CRF corrections are necessary, they will be made by the Investigator or an authorized member of the Investigator's staff that is delegated to CRF/EDC. Questions or problems with submitted data will be addressed with the Principal Investigator via an electronic querying system, or through direct contact. The Investigator will review the CRFs for completeness and accuracy and provide his/her electronic signature and date to CRFs as evidence thereof. Any data items that have been changed will require reapplication of the electronic signature.

Study personnel will have individual login and password to access the clinical study information based upon each individual’s roles and responsibilities. The application provides hierarchical user permission data entry, viewing, and reporting options.

All data entry and data update information, including the date and person performing the action, will be available via the audit trail, which is part of the EDC system.

All CRFs and data files will be secured to ensure confidentiality. Investigators are required to maintain source documents required by the protocol, including laboratory results, reports, supporting medical records, and Informed Consent Forms. The source documents will be used during the regular monitoring visits to verify information entered on the CRFs.

9. Ethical Requirements

9.1 Declaration of Helsinki

The study will be performed in accordance with the applicable aspects of ISO 14155:2011, recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland (1964 and later revisions), ICH and US FDA GCP guidelines.

It is the responsibility of the investigator to obtain approval of the study protocol from the Institutional Review Board/Ethics Committee (IRB/EC) and to keep the IRB/EC informed of any serious adverse event, serious adverse device effects, and amendments to the protocol. All correspondence with the IRB/EC should be filed by the investigator and copies sent to the Sponsor or its designee.

9.2 Informed Consent

The Investigator is responsible for ensuring that a signed and dated informed consent is obtained in accordance with Section 6.5 of this protocol, as delegated by the site-specific Delegation of Authority, and according to country and local requirements.

9.3 Subject Data Protection

Each subject will be assigned a unique subject identification number at the time of enrollment. This subject identification number will be retained throughout the study. All case report forms (CRFs) will be tracked, evaluated, and stored using only the subject ID number. No personal identifying information will be included on the case report forms.

The informed consent form will notify subjects that study monitors, auditors, and representatives of government agencies and ethics committees will have access to personal identifying information to ensure that data reported on the CRFs corresponds to the person who signed the consent form and the information contained in the source documentation. Each subject must be informed that the data collected will be stored by computer and the applicable national regulations for handling of computerized data will be followed. Furthermore, each subject should be informed about the possibility of inspection of relevant parts of the hospital records by the Sponsor, or other Health Authorities, including the FDA.

10. Statistical Procedures

10.1 General Statistical Considerations

All statistical analyses will be descriptive in nature. Descriptive statistics will include the number of observations, mean, median, standard deviation, inter-quartile range, minimum and maximum for continuous variables and counts and percentages for discrete variables. All confidence intervals presented will be two-sided. Analyses will be conducted using SAS (SAS Institute, Cary, NC). The specific details of the planned analyses will be described completely in the statistical analysis plan.

10.2 Sample Size Estimation for the Primary Outcome

Approximately 800 patients will be enrolled in this post market study with estimated 10% attrition at final follow-up. Assuming an observed rate of 89% (641/720) for the endpoint of Raymond-Roy I-II at follow-up, the sample size precision is greater than ± 3% for this endpoint (95% CI: 87%% to 91%). Assuming an observed rate of 2.8% (22/800) for the primary endpoint of device-related serious adverse events up to 7 days or discharge, the sample size precision is greater than ± 1.5% for this endpoint (95% CI: 1.6% to 3.9%). Assuming an observed rate of 8.9% (71/800) for the primary endpoint of serious adverse events at 24 hours post procedure, the sample size precision is greater than ± 2.5% for this endpoint (95% CI: 6.9% to 10.9%). These precision estimates are based on the normal approximation binomial 95% confidence intervals and SMART Registry interim results (data on file at sponsor). Hence, the sample size provides an adequate level of precision for these primary endpoints.

10.3 Control of Systematic Error and Bias

The study will be conducted under a common protocol for each investigational site with the intention of pooling the data for analysis. Every effort will be made to promote consistency in study execution at each investigational site.

10.4 Missing Data and Imputation Methods

Every effort is to be made to keep all missing data, particularly the Final Follow-Up, to a minimum. Some data may be missing, mainly due to lost-to-follow-up subjects. The primary analysis will be data as observed. Sensitivity analysis will be performed.

10.5 Definition of Populations

10.5.1 Screened

Screened subjects are all subjects considered for participation in the study, whether or not they sign informed consent.

10.5.2 Screen Failure

Screen failure subjects are all subjects considered for participation in the study, who failed to meet inclusion criteria or met exclusion criteria. Patients can be screen failed based on general or procedure criteria. These patients may or may not have signed an informed consent form.

10.5.3 Enrolled

An eligible patient is considered enrolled once informed consent is obtained, index procedure is complete, and all inclusion criteria is confirmed.

10.5.4 Completed

Completed subjects are all subjects who were enrolled and completed the study follow-up or were known to have died prior to the follow-up timepoint are considered completed. The completed subject metric will be provided for Final Follow-Up.

10.5.5 Early Termination

Early termination subjects are all subjects who were enrolled but did not complete follow-up and were not known to have died are considered early termination subjects. The early termination subject metric will be provided for Final Follow-Up.

10.6 Definition of Analysis Populations

10.6.1 Intent to Treat Sample

As the primary analysis, all performance and safety outcome measures will be analyzed under the intent-to-treat (ITT) principle. Under this principle, the ITT sample includes all subjects who are enrolled. This population is the primary analysis population.

10.7 Interim Analysis

No interim analyses are planned for the purpose of stopping the study early. Interim analysis may be performed for regulatory submission or publication of study results. No adjustments will be made to the confidence bounds for the final analysis.

10.8 Statistical Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the rate of aneurysm occlusion at Final Follow-Up per Raymond-Roy classification. The proportion of subjects assessed as Raymond-Roy I or II will be provided along with the corresponding 95% confidence interval.

10.9 Statistical Analysis of Primary Safety Endpoint

The primary safety endpoints are the following:

- SAEs up to 24 hours post-procedure
- Device-related SAE up to 7 days or discharge

The proportion of subjects experiencing each event will provided along with the corresponding 95% confidence interval.

10.10 Secondary Statistical Analysis

The secondary efficacy and safety endpoints will be assessed via proportions based on the endpoint criteria and 95% confidence intervals will be presented. Survival

estimates will also be utilized to evaluate the time-to-event using Kaplan-Meier methodology for deaths through 365 days. With the date of procedure set at day 0, any event occurring on or before day 365 will be included.

10.11 Analysis of Adverse Events

All adverse events will be summarized by showing the number and percent of subjects which report the event. Events will also be reported by relationship to the procedure or device. Adverse events judged as probably or definitely related to the SMART COIL System will be analyzed as device-related.

10.12 Imaging Outcomes Analysis

Aneurysm occlusion outcomes as assessed by the core lab will be evaluated for subjects that have both a DSA and MRA at follow-up. A sensitivity and specificity analysis will be conducted to evaluate the ability of MRA to detect residual flow in the coiled aneurysms.

10.13 Baseline Characteristics

Baseline data including, but not limited to demographics, clinical characteristics, and angiographic characteristics will be summarized using descriptive statistics.

10.14 Pooling Across Centers

Analyses will be presented using data pooled across centers. Key baseline and study endpoint variables will be presented by study site to assess any potential site effects.

10.15 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 Sponsor. Data may also be used for submissions to regulatory agencies as part of post-market clinical follow-up.

11. Core Lab

11.1 Imaging Core Lab

The Imaging Core Lab is composed of independent medical doctor(s) who are not participants in the study. The Core Lab is responsible for assisting in the development of specific criteria used for the categorization of clinical endpoints in the study. A

web-based electronic database will be provided for Core Lab to review and adjudicate images. Additional details related to the Core Lab are specified in the Core Lab Charter.

The independent imaging core lab will review images from the Immediate Post Procedure and Final Follow-Up to assess at minimum occlusion grading. An imaging core lab charter will provide procedure for core lab review. Penumbra is responsible for tracking images received and basic quality review.

12. Study Administration

12.1 Clinical Trial Termination/Withdrawal

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

- Voluntary withdrawal of consent— meaning that a subject voluntarily chooses not to participate further in the study. All data collected up to the withdrawal of consent will be maintained in the study database. Withdrawn subjects will not have any additional follow-up and will not be replaced.
- Lost to follow-up— a subject will be considered lost-to-follow-up when contact is not achieved at the last required follow-up visit window. At a minimum, the effort to obtain follow-up information will include three (3) attempts to make contact via telephone or e-mail. These efforts to obtain follow-up will be recorded in the subject's study files.
- Subjects may also be withdrawn at the Investigator's discretion if within their best interest. A subject's participation in the clinical study will be terminated if the Investigator believes that this is in the subject's best medical interest or if the subject no longer complies with the clinical study requirements

The sponsor may temporarily suspend or prematurely terminate the study at any time for the following reasons:

- Suspicion of risk to subjects
- If no positive IRB/EC decision is obtained or if the judgement of the IRB/EC is revoked
- If the applicable regulatory body has made an irrevocable objection
- If it transpires that continuation of study cannot serve any scientific purpose, and this is confirmed by the IRB/EC
- Business reasons

The Sponsor will document reasons for study suspension or premature termination and notify the PIs. The Sponsor will ensure that the IRB/ECs and regulatory authorities are notified in a timely manner.

The Sponsor will continue to provide resources to fulfil the obligations from the study protocol and existing agreements for following up the subjects enrolled in the study.

The Principal Investigators will promptly inform the enrolled subjects at his/her site, if appropriate.

If the Sponsor temporarily suspends the study and wishes to resume it, the Sponsor will inform the PIs, IRB/ECs, and (if appropriate) regulatory authorities. The Sponsor will provide a rationale for resuming the study. IRB/ECs must provide written approval before the study is resumed.

12.2 Missing Visits

Every effort should be made to bring subject in to scheduled follow-up visits. Any study subject who does not attend a scheduled follow-up visit should be contacted by site personnel to reschedule. If the missed visit was due to a reportable adverse event, an AE CRF must be completed.

12.3 Protocol Adherence and Amendments

Prior to beginning the study, the Principal Investigator must sign the protocol signature page documenting his/her agreement to conduct the study in accordance with this protocol. Deviations outlined in section 7.6.4 from the protocol must be documented and reported to Penumbra as soon as possible, and to the IRB/EC per local guidelines and government regulations.

12.4 Trial Registration

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

13. Publication of Information

All information and data generated in association with this study will be held in strict confidence and remain the sole property of the Sponsor. The Investigator agrees to use this information for the sole purpose of completing this study and for no other purpose without written consent from the Sponsor.

The results of this study may be offered for publication. The investigators and the Sponsor shall collaborate in the writing of the study to ensure accuracy. 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 Penumbra. The investigator agrees to use this information only in connection with this study and will not use it for other purposes without written permission from the Sponsor.

14. Contact Information

The address of Penumbra Incorporated is:

Penumbra, Inc.
One Penumbra Place
Alameda, CA 94502
Tel. (510) 748-3200
Fax (510) 814-8305

Key contacts for the Study include:

[redacted] [redacted] [redacted]
[redacted] [redacted] [redacted]

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16. Appendix

16.1 Acronyms and Abbreviations

Acronyms	Definition
ADE	Adverse Device Effect
AE	Adverse Event
BPC	Bare-Platinum Coils
CRF	Case Report Form
CTA	Computed Tomography Angiography
DSA	Digital Subtraction Angiography
EC	Ethics Committee
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practices
IA	Intracranial Aneurysms
ICH	Intracranial Hemorrhage
ID	Identifier
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	Intravenous
LAR	Legally Authorized Representative
mRS	modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
SAE	Serious Adverse Event
SAH	Subarachnoid Hemorrhage
UADE	Unanticipated Adverse Device Effect

16.2 Modified Rankin Scale

0	No Symptoms at all
1	No significant disability, despite symptoms; able to perform all usual duties and activities
2	Slight disability; unable to perform all previous activities but able to look after own affairs without assistance
3	Moderate disability; requires 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 requires constant nursing care and attention
6	Death

16.3 Hunt and Hess Grading Scale

Grade	Clinical Features
I	No symptoms or minimal headache and slight nuchal rigidity
II	Moderate to severe headache, nuchal rigidity, and no neurologic deficit other than cranial nerve palsy
III	Drowsiness, confusion, or mild focal neurologic deficit
IV	Stupor, moderate to severe hemiparesis, possible decerebrate rigidity, and vegetative disturbances
V	Deep coma, decerebrate rigidity, and moribund appearance

16.4 Definitions

16.4.1 Stroke

An acute episode of focal or global neurological dysfunction due to brain or retinal infarction, or from any intracranial hemorrhage inclusive of subarachnoid, intraventricular or intraparenchymal hemorrhages with signs and symptoms that persist for 24 hours or more. The 24-hour criterion is excluded if the patient undergoes cerebrovascular surgery or dies during the first 24 hours.

16.4.2 Major Ipsilateral Stroke

Major ipsilateral stroke is an acute episode of focal or global neurological dysfunction due to brain or retinal infarction, or from any intracranial hemorrhage (ICH) inclusive of subarachnoid, intraventricular or intraparenchymal hemorrhages in the same hemisphere of the target aneurysm and which is associated with an increase of 4 or more points on the NIHSS at 24 hours after stroke onset.

16.4.3 Intracranial Hemorrhage

Bleeding in the cranium of the brain inclusive of subarachnoid, intraventricular or intraparenchymal hemorrhages, symptomatic or asymptomatic. A symptomatic intracranial hemorrhage is associated with a 4 or more points increase on the NIHSS from baseline.

16.4.4 Morbidity

Defined as mRS 3 to 5 or worsening of mRS from baseline by 2 points

16.4.5 Perforation

The piercing or rupturing of a blood vessel; perforations can be detected or observed angiographically.

16.4.6 Dissection

Angiographic evidence of a tear in the arterial wall as defined by the occurrence of intramural hematoma.

16.4.7 Vasospasm

Spasm of a blood vessel, resulting in prolonged decrease in lumen diameter. Symptomatic vasospasm is defined as the development of new focal neurological signs, deterioration in level of consciousness, or both, when the cause was felt to be ischemia attributable to vasospasm after other possible causes of worsening (for example, hydrocephalus, seizures, metabolic derangement, infection, or oversedation) had been excluded.

16.4.8 Recanalization

Defined as an increase in size of the remnant in contrast filling of the aneurysm sac using results of immediate post-stent/embolization angiography as baseline.

16.4.9 Aneurysm Size

Aneurysm size should be reported in millimeters in 3 dimensions as well as categorical taxonomy:

- Small Neck: < 4 mm
- Wide Neck: ≥ 4 mm or a dome to neck ratio of less than 2 mm
- Small Aneurysms: ≤ 5 mm at its largest diameter
- Medium Aneurysms: 6 – 14 mm at its largest diameter
- Large Aneurysms: 15 mm – 24 mm at its largest diameter
- Giant Aneurysms: ≥ 25 mm at its largest diameter

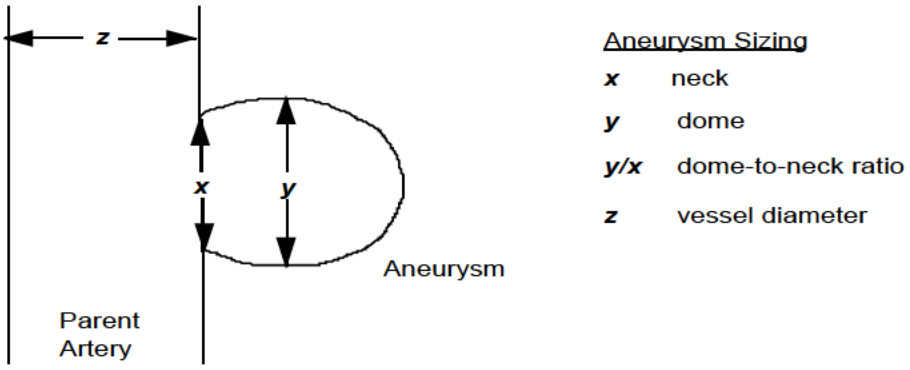


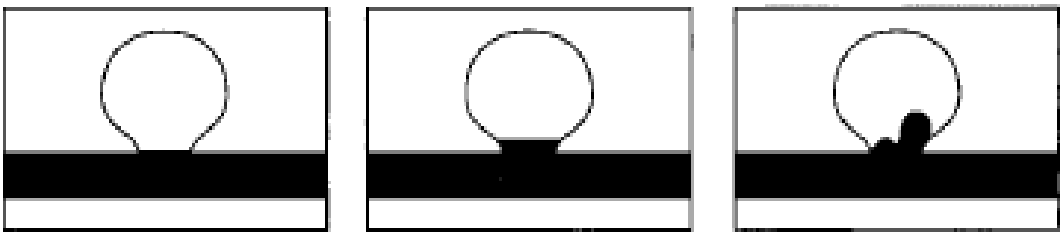
Figure 2. Aneurysm Sizing

16.4.10 Angiographic Outcome

The primary effectiveness endpoint is occlusion of the treated aneurysms. This is defined as the proportion of aneurysms with Class 1 and 2 occlusion as described by Roy et al (*Stroke 2001;32:1998-2004)*:

- Class 1 – Complete occlusion
- Class 2 – Residual neck
- Class 3 – Residual aneurysm

Figure 3: Classification of Angiographic Results



Class 1
Complete Obliteration

Class 2
Residual Neck

Class 3
Residual Aneurysm

Adopted from Roy, Milot and Raymond. Stroke 2001;32:1998-2004

STATISTICAL ANALYSIS PLAN

SURF: A Prospective, Multicenter Study Assessing the Embolization of Intracranial Aneurysms using WAVE™ Extra Soft coils, a part of the Penumbra SMART COIL® System

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Protocol CLP 13669

Version 3.0

Contents

1 Overview

SURF is a postmarket, real-world, prospective, multicenter single-arm study. Its objective is to demonstrate the safety and efficacy of the Penumbra SMART COIL® System, including the WAVE™ Extra Soft Coils (WAVE) as a fill and finish coil, in the treatment of intracranial aneurysms. An independent core lab will read images to assess aneurysm occlusion rates, facilitating an analysis on the sensitivity and specificity of MRA imaging to detect residual aneurysm blood flow at final follow-up as compared to DSA (Section 8.3 of this document).

Approximately 800 patients will enroll at up to 60 global sites. Each site will be limited to a maximum enrollment of 120 patients (15% of total enrollment). An estimated 10% of enrolled patients will experience attrition by final follow-up.

This Statistical Analysis Plan (SAP) elaborates on statistical methods outlined in the study protocol and presents analysis conventions. The SAP will be signed off prior to database lock.

2 Sample Size

Approximately 800 patients will enroll in this post-market study, resulting in 720 patients who achieve final follow-up after 10% anticipated attrition. This sample size provides adequate precision to estimate the primary effectiveness and safety endpoints.

Primary Endpoint	**Assumption for Observed Rate[1]**	**95% CI[2]**	**Precision**
Adequate occlusion defined as Raymond-Roy Occlusion Class I and II at final follow-up	89% (320/360)	86% to 92%	Greater than ±3.5%
	89% (401/450)	86% to 92%	Greater than ±3%
	89% (481/540)	86% to 92%	Greater than ±3%
	89% (561/630)	87% to 91%	Greater than ±3%
	89% (641/720)	87% to 91%	Greater than ±3%
Device-related SAE up to 7 days or discharge	2.8% (11/400)	1.1% to 4.4%	Greater than ±2%
	2.8% (14/500)	1.4% to 4.2%	Greater than ±1.5%
	2.8% (17/600)	1.5% to 4.2%	Greater than ±1.5%
	2.9% (20/700)	1.6% to 4.1%	Greater than ±1.5%
	2.8% (22/800)	1.6% to 3.9%	Greater than ±1.5%
SAEs within 24 hours post-procedure	9.0% (36/400)	6.2% to 11.8%	Greater than ±3%
	9.0% (45/500)	6.5% to 11.5%	Greater than ±2.5%
	8.8% (53/600)	6.6% to 11.1%	Greater than ±2.5%
	8.9% (62/700)	6.8% to 11.0%	Greater than ±2.5%
	8.9% (71/800)	6.9% to 10.9%	Greater than ±2.5%

[1] Set at SMART CLP 10023 Registry interim observed results (data on file at sponsor)
[2] Two-sided 95% Wald normal approximation binomial proportion confidence interval

3 Interim Analysis

As there will be no interim analyses for the purpose of terminating the study early for success or futility, alpha adjustments will not be made to the confidence intervals in the final analysis. However, interim analysis may be performed for the purpose of publication or regulatory submission of SURF results.

4 Analysis Populations

4.1 Definitions

The following analysis population definitions apply to this study:

- **Screened:** All patients considered for participation in the study, whether or not they sign informed consent.
- **Screen Failure:** All screened patients who failed to meet inclusion criteria or met exclusion criteria. Patients can be screen failed for general or procedure criteria.
- **Enrolled:** All eligible patients who obtained informed consent, completed the index procedure, and have inclusion-exclusion criteria confirmed.
- **Intent-to-Treat (ITT):** All enrolled patients. The primary analysis, including all effectiveness, safety, and subgroup reporting, will be run on this population.
- **Completed:** All enrolled patients who completed the study follow-up or were known to have died prior to the follow-up.

5 Statistical Methods

Continuous variables will be summarized using the following descriptive statistics: N, Mean (SD), Median [IQR], Range (Min, Max). Categorical variables will be summarized using frequency counts and percentages of patients within each category. Confidence intervals will be reported for the following analyses only: effectiveness, safety, sensitivity, and change from baseline. Two-sided 95% confidence intervals will be reported using asymptotic intervals for continuous variables and Wald normal approximation binomial proportion intervals for categorical variables.

6 Baseline Characteristics

Baseline characteristics, including demographics, clinical characteristics, and angiographic characteristics, will be summarized using descriptive statistics for continuous variables and using frequency counts and percentages for categorical variables.

7 Patient Disposition

To summarize patient disposition outcomes, the number of patients in the following analysis populations will be recorded:

- Screen Failure
- Enrolled
- Intent-to-Treat (ITT)
- Completed

The number of patients who do not complete the study will be reported as well, broken down by their reasons for discontinuation.

8 Effectiveness Analysis

8.1 Primary Effectiveness Analysis

For the primary effectiveness endpoint, frequency counts, percentages, and two-sided 95% Wald confidence intervals will be reported using the ITT population:

- **Adequate occlusion defined as Raymond-Roy Occlusion Class I and II at final follow-up:** The percentage of patients assessed as Raymond-Roy Class I or II out of patients who had a Raymond-Roy evaluation done (Class I, II, or III) at the time of final follow-up. Retreatments at final follow-up will be modelled as Raymond-Roy Class III.

The core lab data supersede the investigator-reported data in primary and secondary effectiveness analyses.

8.2 Secondary Effectiveness Analysis

For the secondary effectiveness endpoints, frequency counts, percentages, and two-sided 95% Wald confidence intervals will be reported using the ITT population:

- **Immediate post-procedure occlusion rate:** The percentage distribution of patients assessed as each of Raymond-Roy Class I, Class II, and Class III out of patients who had a Raymond-Roy evaluation done (Class I, II, or III) at immediate post-procedure.
- **Retreatment rate at final follow-up:** The percentage of patients who had the target aneurysm retreated since the index procedure out of patients who have data on this question (Retreatment, No Retreatment) at the time of final follow-up. Staged procedures are not retreatments for the purposes of running all SURF study analyses.
- **Aneurysm Occlusion Raymond I post treatment:** The percentage of patients assessed as Raymond-Roy Class I out of patients who had a Raymond-Roy evaluation done (Class I, II, or III) at immediate post-procedure.
- **Aneurysm Occlusion Raymond I at final follow-up:** The percentage of patients assessed as Raymond-Roy Class I out of patients who had a Raymond-Roy evaluation done (Class I, II, or III) at the time of final follow-up. Retreatments at final follow-up will be modelled as Raymond-Roy Class III.
- **Aneurysm recanalization or progressive thrombosis from post procedure to final follow-up:** The percentage of patients who experienced a deterioration in Raymond-Roy Occlusion Grading (aneurysm recanalization; Class I becoming II or III, or Class II becoming III) or improvement in Raymond-Roy occlusion (progressive thrombosis; Class II becoming I, or Class III becoming I or II) out of patients who had a Raymond-Roy evaluation done at both time points. Retreatments at final follow-up will be modelled as aneurysm recanalization.

The effectiveness endpoints will be reported using only the Raymond-Roy Occlusion Grading Scale. However, frequency counts, percentages, and two-sided 95% Wald confidence intervals will also be provided for the Meyers Consensus Grading Scale Grades 0, 1, 2, 3, 4, and 5 at immediate post-procedure and final follow-up, using the ITT population and core lab data.

Aneurysm packing densities will be reported as the coil volume of all Penumbra and non-Penumbra coils implanted divided by the aneurysm volume as measured by the core lab, based on two-dimensional geometric modeling as the primary analysis and the ABC method as a supplemental analysis.

8.3 Imaging Outcomes Analysis

DSA is the reference standard imaging modality for aneurysm assessment after coiling, but MRA imaging is safer for patients and less expensive. Therefore, an imaging outcomes analysis will assess how successfully MRA scans detect residual aneurysm blood flow at final follow-up as compared to DSA scans, based on sensitivity, specificity, and related summary measures.

For each of Raymond-Roy Class II to III (any residual flow), Class II (residual neck), and Class III (residual aneurysm) at the time of final follow-up, the following statistics will be reported using the ITT population and core lab data:

- **Sensitivity:** The proportion of true positives (patients belonging to each of the three Raymond-Roy groups above on DSA) that are correctly identified as such on MRA as well. The percentages of patients assessed as each of Raymond-Roy (1) Class II to III, (2) Class II, and (3) Class III on MRA and DSA out of patients with the same Raymond-Roy group assessed on DSA at the time of final follow-up will be computed.
- **Specificity:** The proportion of true negatives (patients not belonging to each of the three Raymond-Roy groups above on DSA) that are correctly identified as such on MRA as well. The percentages of patients assessed as each of Raymond-Roy (1) Class I, (2) Class I or Class III, and (3) Class I to II on MRA and DSA out of patients with the same Raymond-Roy group assessed on DSA at the time of final follow-up will be computed.
- **Positive likelihood ratio (LR):** Sensitivity divided by (1 - Specificity).
- **Negative likelihood ratio (LR):** (1 - Sensitivity) divided by Specificity.
- **Cohen's κ:** Summary measure of agreement between DSA and MRA in detecting each of Raymond-Roy Class II and III, Class II, and Class III.

As a secondary comparison, this analysis will be repeated using each of Meyers Consensus Grading Scale Grades 1 to 5 (any residual flow), Grade 1 (90% or greater aneurysm occlusion), Grade 2 (70-89% aneurysm occlusion), Grade 3 (50-69% aneurysm occlusion), Grade 4 (25-49% aneurysm occlusion), and Grade 5 (Less than 25% aneurysm occlusion).

8.4 Economic Analysis

Frequency counts and percentages will be reported for the following healthcare utilization data:

- Devices used: Access guide catheters, microcatheters, and Penumbra coils
- Follow-up and additional follow-up clinic and office visits

- Follow-up and additional follow-up DSA, MRA, and CTA scans

The healthcare utilization information will be used to estimate healthcare costs.

8.5 Handling of Multiplicity

There will be no adjustment for multiplicity in SURF study reporting.

9 Subgroup Analysis

The following subgroup analyses will be performed for all primary and secondary effectiveness and safety endpoints using the ITT population:

- **Adjunctive technology used during treatment:** Balloon, Stent, Other, None
- **Age at time of informed consent (years):** < 65, ≥ 65
- **Sex:** Female, Male
- **Ethnicity:** Hispanic or Latino, Not Hispanic or Latino
- **Race:** American Indian or Alaska Native, Asian, Black or African American, White, Other
- **Site country:** North America (US/Canada), Europe
- **Target aneurysm location:** Extradural ICA, ICA, ACA, MCA, Posterior Circulation, Other
- **Target aneurysm size:** Small (≤ 5 mm at its largest diameter), Medium (6 to 14 mm at its largest diameter), Large (15 to 24 mm at its largest diameter), Giant (≥ 25 mm at its largest diameter)
- **Target aneurysm status:** Ruptured, Unruptured
- **Target aneurysm anatomical location:** Bifurcation, Sidewall, Other
- **Neck width:** Small-Neck (< 4 mm Neck Width), Wide-Neck (≥ 4 mm Neck Width or Dome-to-Neck Ratio (defined as the maximum of dome width, depth, and height divided by neck width) < 2)
- **Target aneurysm previously treated:** Previous Treatment at Admission, No Previous Treatment at Admission

Descriptive statistics and two-sided 95% Wald confidence intervals will be presented for each subgroup.

10 Safety Analysis

10.1 Primary Safety Analysis

For the primary safety endpoints, frequency counts, percentages, and two-sided 95% Wald confidence intervals will be reported using the ITT population:

- **SAEs up to 24 hours post-procedure:** The percentage of patients who experience serious adverse event(s) with start date on the date of procedure (day 0) or the next calendar day.
- **Device-related SAE up to 7 days or discharge:** The percentage of patients who experience serious adverse event(s) with probable or definite relationship to the SMART Coil System from the date of procedure (day 0) through the date of discharge or seven calendar days from the date of procedure, whichever occurs earlier.

10.2 Secondary Safety Analysis

For the secondary safety endpoints, frequency counts, percentages, and two-sided 95% Wald confidence intervals will be reported using the ITT population:

- **Major ipsilateral stroke:** The percentage of patients who experience major ipsilateral stroke adverse event(s), as defined in the SURF study protocol.
- **Device related SAE at final follow-up:** The percentage of patients who experience serious adverse event(s) with probable or definite relationships to the SMART Coil System from the date of procedure (day 0) through the final follow-up visit at 1 Year ± 90 Days from the date of procedure.
- **All-cause morbidity and mortality:** The percentage of patients who experience either of the following events:
    - **All-cause morbidity:** mRS 3 to 5 at the final follow-up evaluation or worsening of mRS by 2+ points the date of procedure (day 0) through the final follow-up visit at 1 Year ± 90 Days from the date of procedure. If the final follow-up mRS is missing, mRS as assessed at the 7-day and/or discharge visit will be substituted.
    - **All-cause mortality:** Death for any reason from the date of procedure (day 0) through calendar day 365

Adverse events occurring after the final follow-up visit at 1 Year ± 90 Days and deaths occurring after day 365 will be separately tabulated and not included in endpoint and adverse event rates.

10.3 Analysis of Adverse Events

In the SURF study, only device-related or procedure-related adverse events and serious adverse events (SAEs) will be collected from procedure through discharge. After discharge, only neurological SAEs will be collected. Additional information for Symptomatic Intracranial Hemorrhage and Ischemic Stroke will be collected on Event of Interest case report forms.

Frequency counts and percentages will be provided for all reportable adverse events and broken down as well based on relationships to the device and procedure. Reportable adverse event data will be listed for each patient, including the type of event/verbatim term, start date, seriousness, action taken, outcome, and causality (if appropriate). The onset of adverse events will also be shown relative (in number of days) to the date of procedure.

The specific categories analyzed will be those that are reported by at least three (3) percent of the patients. As there is no CEC for this study, all adverse events will be reported based on the assessment from the clinical study sites.

10.4 Analysis of Deaths

Survival estimates will be used to evaluate the time-to-event using the Kaplan-Meier product-limit method for deaths through 365 days. With the date of procedure set at day 0, any event occurring on or before day 365 will be included. If clinical assessment is missing for a patient who has not died, the patient will be censored at the last follow-up date. Patients who are alive at day 365 will be censored at day 365. The time to death will be plotted with 95% confidence intervals.

Additionally, the frequency and percentage of deaths for any reason (all-cause mortality) will be presented with the two-sided 95% Wald confidence interval.

11 Pooling Across Centers

Analyses will be presented using data pooled across centers. The primary and secondary effectiveness and safety endpoints will be presented by study site to assess any potential site effects.

Pooling analyses will be conducted across study sites on the primary effectiveness and primary safety endpoints. Fisher's exact test (univariate analysis) and stepwise binary logistic regression

on study site, adjusted for key baseline and other appropriate variables (multivariate analysis), will be used. The multivariate results will take precedence in testing for site heterogeneity.

To assess the validity of pooling North America (US/Canada) and Europe sites, logistic regression models will be used for the primary effectiveness and primary safety endpoints. Stepwise multivariate binary logistic regression models with geographic location (North America (US/Canada versus Europe), study site, and a subset of key baseline and procedural predictors will be used for each primary endpoint to test for heterogeneity across geographic locations.

Wald odds ratios of the treatment effects for geographic location and study site will be presented with two-sided p-values to test whether the odds ratios equal 1. Centers enrolling three or fewer patients will be eliminated from all pooling analyses.

12 Missing Data and Imputation Methods

The primary analysis will be data as observed, in which results are reported using the data that are available without imputing missing values.

As sensitivity analyses, the primary effectiveness and primary safety endpoints will be recomputed using the ITT population after imputing missing data:

- Imputation using baseline scores (run for primary effectiveness only)
- Imputation using the worst clinical scenario, assuming the subject was assessed as Raymond-Roy Class III at the time of final follow-up (effectiveness) or experienced a primary safety event (safety)
- Imputation using the best clinical scenario, assuming the subject was assessed as Raymond-Roy Class I and II at the time of final follow-up (effectiveness) or did not experience a primary safety event (safety)

13 Changes to Planned Analyses

All changes to this Statistical Analysis Plan (SAP) will be documented in a revised SAP or the clinical study report.

14 References

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15 Revision History

Version	Prepared By	Description of Changes
1.0	Sam Watcha	Initial Release
2.0	Sam Watcha	Updated number of sites, subgroup analysis, and pooling analysis to reflect global site enrollment under protocol revision C Updated sample size and endpoint definitions
3.0	Sam Watcha	Added sample size scenarios to Section 2. Sample Size