ACE: An Aneurysm Coiling Efficiency Study of the Penumbra Coil 400 System

Protocol
CLP 4492.D

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Device Name
Penumbra Coil 400™ System

Sponsor
Penumbra, Inc.
1351 Harbor Bay Parkway
Alameda, CA 94502
USA

Contact Person
Malia McPherson
Telephone: 510-748-3294
Fax: 510-814-8305
E-mail: malia.mcpherson@penumbrainc.com

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Study Title:	**ACE: An Aneurysm Coiling Efficiency Study of the Penumbra Coil 400 System**
Objective:	The primary objective of this study is to gather post market data on the Penumbra Coil 400 (PC 400) System in the treatment of intracranial aneurysms, peripheral aneurysms and other malformations.
Study Design:	This study is a prospective, multi-center study of patients with intracranial aneurysms, peripheral aneurysms or other malformations who are treated by the PC 400 System. Data for each patient are collected up to 6 months post-procedure for the study. Long term follow-up to one year may also be conducted in accordance to the standard of care at each participating hospital at the discretion of the investigators.
Patient Population:	Approximately 2,000 patients with intracranial aneurysms, peripheral aneurysms or other malformations treated by the PC 400 System at up to 100 centers will be enrolled. Each center must have had prior experience with endovascular embolization by the PC 400 System before being able to enroll patients. This is defined as having treated at least 5 patients according to the cleared indication for use, either before or after IRB/EC approval (roll-in). Roll-in patients will not be part of the study.
Sample Size Justification:	Approximately 2,000 patients will be enrolled. With this sample size the precision is greater than ± 2.5% for the procedural device-related serious adverse event rate based on a binomial 95% confidence interval. Hence, the sample size provides a sufficient level of precision for the primary endpoint.
Inclusion Criteria:	Patients enrolled in this study must be those treated according to the cleared indication for the PC 400 System which is for the endovascular embolization of: 1. Intracranial aneurysms 2. Other neurovascular abnormalities such as arteriovenous malformations and arteriovenous fistulae 3. Arterial and venous embolizations in the peripheral vasculature
Exclusion Criteria:	Patients in whom endovascular embolization therapies other than Penumbra Coils are used will be excluded from this study. However, adjunctive use of balloon and stent are acceptable.
Primary Endpoint:	1. Packing density with the number of coils implanted 2. Time of fluoroscopic exposure 3. Procedural device-related serious adverse events at immediate post-procedure 4. Occlusion of the aneurysm sac at 6 months post-procedure
Secondary Endpoints:	1. Acute occlusion of the aneurysm sac at immediate post-procedure 2. Intracranial hemorrhage at discharge or 3 days post-procedure
Study Period:	It is anticipated patient enrollment will take 3 years. Patients will be followed up to 6 months after the procedure for the study, and it may be up to one year in accordance to the standard of care at each participating hospital at the discretion of the investigators.

2. INTRODUCTION

Intracranial aneurysms are a significant health problem in the United States with an estimated 1% to 6% of the adult population harboring cerebral aneurysms.[1,2] The annual risk of rupture of an intact intracranial aneurysm is estimated to be approximately 1.9%.[2] If an intracranial aneurysm ruptures, blood leaks into the highly sensitive subarachnoid space around the brain, resulting in a subarachnoid hemorrhage (SAH). SAH is known to be a major risk factor for a stroke due to the irritation of the outer layer of the nearby blood vessels surrounding the brain. This condition is associated with a high rate of mortality; close to half of ruptured aneurysms result in death within six months.[2-4] Patients who survived the initial SAH are at significant risk of subsequent re-rupture. 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.[4,5]

Even if an intracranial aneurysm does not rupture, it can lead to severe complications. As the aneurysm grows, it can press on nerves, put pressure on brain tissue, or interfere with other arteries or veins. Blindness, paralysis, and other morbidities often result. Thrombus can also form within the aneurysmal sac, break off, travel downstream, and cause an ischemic stroke. It has been reported that 2.2% to 23% of patients with unruptured aneurysms may eventually experience a rupture.[7,8] The International Study of Unruptured Intracranial Aneurysms evaluated the natural history of 1,937 unruptured aneurysms in 1,449 patients with a mean follow-up of 8.3 years.[8] It reported that 2.2% of these patients had a confirmed rupture during follow-up, but 66% of them were fatal. Juvela et al. reported on the long term natural history of unruptured intracranial aneurysms in a series of 142 patients.[7] With a median follow-up of 19.7 years, 23% of the patients experienced a SAH, which corresponds to an annualized rate of 1.3%. The cumulative rate of SAH tended to increase with time, with a rupture rate of 10.5% at 10 years, 23% at 20 years, and 30.3% at 30 years after diagnosis. Approximately half of the SAH patients did not survive. Thus, regardless of the rate of occurrence, fatality associated with this event is high in this cohort.[7, 8]

Prior to 1995, the traditional treatment for intracranial aneurysms was surgical clipping, in which the skull is surgically opened so metal clips can be applied to the aneurysm's neck to occlude it from the parent artery to prevent a rupture.[1] This treatment, while effective, is high risk, highly invasive, requires an extended hospital convalescence, and is technically difficult to perform in certain regions of the brain (such as the posterior circulation). Thus, this treatment modality is not a viable option for a significant number of patients, particularly during the acute phase of SAH, when the presence of cerebral edema and evolving thrombi formation render aneurysm access difficult, if not impossible.

In the early 1990's, an endovascular treatment technique for intracranial aneurysms was first introduced by Guido Guglielmi, who used electrolytically detachable platinum coils to pack and embolize the aneurysmal sac.[9, 10] The

rationale was to exclude the aneurysm from the circulation and thus reduce the risk of a rupture and SAH. The Guglielmi detachable coil (GDC) was not universally accepted at first but gained significant credibility after obtaining approval from the FDA for the intracranial aneurysm indication. Moreover, a few well-conducted, prospective, randomized studies of both ruptured and unruptured aneurysms have demonstrated that angiographic and clinical outcomes from this treatment modality were equivalent, if not better, than those obtained from surgical clipping.[6,8,11,12] Results were found to be similar for both treatments regardless of the inter-study differences in definitions for these outcome measures.[6,8,11,12] The most important landmark study was the International Subarachnoid Aneurysm Trial (ISAT) in which a total of 2,143 patients with ruptured intracranial aneurysms were randomized to either neurosurgical clipping or endovascular GDC coiling. The results showed that at one year follow-up, 30.6% of the patients treated by neurological clipping were either functionally dependent or dead as vs. 23.7% of those treated by GDC coiling, which resulted in a risk reduction rate of 22.6%. And thus, embolic coiling has now become the standard of care worldwide for endovascular occlusion for both incidental and ruptured intracranial aneurysms.

In light of the natural history of the disease, the primary focus for management of an intracranial aneurysm must be to prevent its rupture and sequelae.

The Penumbra Coil 400 (PC 400) System is a new generation of detachable coils developed by Penumbra Inc. It has recently received the CE Mark in Europe and is 510k cleared in the U.S. This coil system is specifically designed to promote aneurysm healing that is equivalent to standard platinum coils. This System consists of: an implantable Coil attached to a Detachment Pusher as well as a Detachment Handle. The Detachment Pusher is comprised of a shaft with a radiopaque positioning marker, a Distal Detachment Tip, and a pull wire. The Detachment Handle is used to detach the Coil Implant from the Detachment Pusher. The PC 400 is designed for endovascular embolization in the neural and peripheral vasculature. Intended users for this device are physicians who have received appropriate training in interventional radiology.

The Penumbra Embolization Coil is indicated for the endovascular embolization of aneurysms. The Embolization Coil functions to selectively embolize aneurysms by packing a sufficient quantity of soft platinum coils to achieve occlusion. The Coil Implant is constructed of 92% Platinum and 8% Tungsten round wire with a diameter approximately 0.0015in ± 0.0001in. The maximum primary diameter is 0.022in and the coil implant will have a semi-spherical atraumatic distal tip.

The Coil Implant is available in a standard *Frame* configuration, a soft *Fill* configuration, a *Soft Fill/Finish* configuration, and an *Extra Soft Fill/Finish* configuration.

The *Frame* Coil Implant is a three dimensional complex shape that follows the contours of the aneurysm surface and frames the inner surface of an aneurysmal sac when sized appropriately. The distal-most loop of a *Frame* Coil Implant is sized to prevent the coil from herniating into the parent vessel. The Implant is available in sizes to treat aneurysms in the 3-32mm diameter range and its stiffness must allow for atraumatic interaction with the aneurysm wall.

The *Fill* Coil Implant has a three dimensional complex shape that conforms to the size and shape of empty space within an aneurysm. The *Fill* Coil Implant is available in sizes to treat aneurysms in the 3-24mm diameter range. The *Fill* Coil Implant's stiffness must allow for atraumatic interaction with the aneurysm wall. The distal-most loop of a *Fill* Coil Implant is sized to prevent the coil from herniating into the parent vessel.

The *Soft Fill/Finish* Coil Implant is a straight coil that will allow it to conform to empty space within an aneurysm with no preferential shape. The *Soft Fill/Finish* Coil Implant has a J-shaped tip to allow for atraumatic interaction with an aneurysm and its stiffness must allow for atraumatic interaction with the aneurysm wall. The *Soft Fill/Finish* Coil Implant fills small empty pockets within an aneurysm.

The *Extra Soft Fill/Finish* Coil Implant is either a helical shape or complex shape coil that will allow it to conform to empty space within an aneurysm. The *Extra Soft Fill/Finish* Coil Implant's stiffness allows for atraumatic interaction with the aneurysm wall.

3. STUDY OVERVIEW

The primary objective of this study is to gather post market data on the Penumbra Coil 400 (PC 400) System in the treatment of intracranial aneurysms, peripheral aneurysms and other malformations.

3.1 Study Design

This study is a prospective, multi-center study of patients with intracranial aneurysms, peripheral aneurysms or other malformations who are treated by the PC 400 System. Data for each patient are collected up to 6 months post-procedure for the study. It may also be collected up to one year in accordance to the standard of care at each hospital at the discretion of the investigators.

3.2 Study Objectives/Endpoints

The primary objective of this study is to gather post market data on the PC 400 System in the treatment of intracranial aneurysms, peripheral aneurysms, and other malformations.

Approximately 2,000 patients with intracranial aneurysms, peripheral aneurysms, or other malformations treated by the PC 400 System at up to 100 centers will be enrolled. Each center must have had prior experience with endovascular embolization by the PC 400 System before being able to enroll patients. This is defined as having treated at least 5 patients according to the cleared indication for use, either before or after IRB/EC approval (roll-in). Roll-in patients will not be part of the study.

3.2.1 The Primary Endpoints are:

- Packing density with the number of coils implanted
- Time of fluoroscopic exposure
- Procedural device-related serious adverse events at immediate post-procedure
- Occlusion of the aneurysm sac at 6 months post-procedure based on the classification by Roy, Milot and Raymond.[13]

3.2.2 The Secondary Endpoints are:

- Acute occlusion of the aneurysm sac at immediate post-procedure
- Intracranial hemorrhage at discharge or 3 days post-procedure

3.3 Study Population

Patients enrolled in this study must be those treated according to the cleared indication for the PC 400 System in the *Instructions for Use*. Each center must have had prior experience with endovascular embolization by the PC 400 System before being able to enroll patients. This is defined as having treated at least 5 patients according to the cleared indication for use, either before or after IRB/EC approval (roll-in). Roll-in patients will not be part of the study.

3.3.1. Inclusion Criteria

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

3.3.2. Exclusion Criteria

Patients in whom endovascular embolization therapies other than PC 400 System are used will be excluded from this study. However, adjunctive use of balloon and stent are acceptable.

4. STUDY PROCEDURES

All study procedures are to be conducted in accordance with the PC 400 System *Instructions for Use*.

SCHEDULE OF ASSESSMENTS

Assessment	Admission Evaluation	Immediate Post-Procedure	3 days Post-Procedure or Discharge[+]	6 months Post-Procedure**	1 year Post-Procedure**
History	√				
Imaging	√	√			
Physical Exam*	√		√		
Modified Rankin Scale	√			√	√[++]
Packing Density		√			
Aneurysm Occlusion[13]		√		√	√[++]
Procedure Time		√			
Adverse Events		√	√	√	√[++]
Retreatment				√	√[++]

* Includes blood pressure and heart rate.
[+] Whichever is sooner.
[++] At the discretion of the investigators in accordance to the standard of care at the participating hospitals.
** ± 30 Days

5. INVESTIGATOR RESPONSIBILITIES

5.1 Institutional Review Board Approval / 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. The IRB/EC shall approve all study documents, including the final protocol, amendments to the protocol, and the informed consent.

5.2 Informed Consent

The investigator is responsible for ensuring that the study is conducted according to this protocol and that a signed informed consent is obtained according to national and state requirements prior to inclusion of patients in the study.

5.3 Adherence to Protocol/Amendments

The investigator shall approve and adhere to this protocol and any amendments that arise during the course of the study. Any deviations to the protocol shall be discussed with Penumbra prior to implementation, where possible, and shall be documented on the appropriate case report form.

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 the confidentiality statement.

5.4 Case Report Form Completion

The investigator and study staff shall complete the case report forms (CRFs) associated with this study. Patient numbers shall be used to identify individual patients in this study. The CRFs should be a complete and accurate record of patient data collected during the study consistent with Good Clinical Practices (GCP) requirements. It is the investigator's responsibility to ensure the quality of the data collected and recorded.

5.5 Reports

The investigator will be responsible for the following reports:

Protocol Deviation

If the medical condition of patients requires deviation from the protocol, the investigator must contact the Clinical Research Associate and/or Sponsor as soon as possible to obtain advice on whether or not the patient is to participate in the study. Any protocol deviation must be clearly documented.

Adverse Event Reporting

An ***Adverse Event*** is any undesirable clinical event occurring to a patient, during a clinical trial, whether or not it is considered related to the investigational product. This includes a change in a patient's condition or laboratory results which has or could have a deleterious effect on the patient's health or well-being.

Any Adverse Device Effect is any Adverse Event related to the investigational device. All Adverse Events or Adverse Device Effects should be recorded by the investigator in the Case Report Forms. They have to be carefully monitored during the entire study.

A ***Serious Adverse Event*** is an event that:

a) Led to death
b) Led to a serious deterioration in the health of the patient that:
   - Resulted in life-threatening illness or injury
   - 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

Minimum requirements of data to be recorded are: type of event, duration of adverse event or adverse device effects (start through end), severity, seriousness, action taken, outcome and, if appropriate, causality.

The Investigator will report any serious adverse event or adverse device effect to the Sponsor or its designee as soon as possible, but no later than 24 hours after the event is known. All serious adverse events or serious device effects must be documented on the Serious Adverse Events form along with an explanation of any medical treatment administered. The form must be completed, signed, and sent by fax or overnight courier to the Sponsor or its designee within five working days. This report must be followed by full written documentation.

An event need not be reported as a Serious Adverse Event if it represents only a relapse or an expected change or progression of the condition that was the cause of treatment without any other symptoms and signs than those present before treatment. This type of event need only be reported as an Adverse Event.

When appropriate, the IRB/EC shall be informed by the investigator about serious adverse events and adverse device effects associated with the use of the product, and Penumbra is responsible for informing the Health Authorities and other investigators of such events as appropriate.

5.6 Withdrawal of Approval

The investigator shall report to Penumbra immediately if, for any reason, the approval to conduct the investigation is withdrawn by the IRB/EC. The report will include a complete description of the reason(s) for which approval was withdrawn. The investigator shall submit all reports in a timely manner.

5.7 Records Retention

The investigator shall maintain the records associated with this study for a period of at least two years after the date on which the investigation is completed. These records include the following:

- Correspondence with the Sponsor or designee, the Medical Monitor, and other investigators.
- Patient Records, including Informed Consent Forms, copies of all completed CRFs, and supporting documents.
- Current study protocol with dates and details of reasons for any deviations from the protocol that could affect the scientific quality of the study or the rights, safety, or welfare of the patients.

- *Instructions for Use*
- Reports of any serious adverse event or adverse device effects.
- A copy of all approvals related to the clinical investigation.
- The approved, blank, informed consent form and blank CRFs.
- Certification that the investigational plan has been approved by the IRB/EC.
- Signed Agreements and current signed and dated *curriculum vitae* of the Study Investigator and all participating investigators.

6. SPONSOR RESPONSIBILITIES

6.1 Training

During study initiation, the Sponsor will train the investigator and study staff on the protocol for the study.

6.2 Investigator List

The Sponsor shall keep a list of the names, addresses, and professional positions of the investigators for the study.

6.3 Serious Adverse Event Reporting

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

6.4 Data Monitoring

Data monitoring will be performed remotely and on site when necessary. Standardized electronic CRFs will be used for queries and query resolution. A Penumbra employee or designate will conduct the following site visits:

- Site Initiation Visit

  This is conducted on site or remotely to train the study staff on study requirements, and other relevant training.

- Data Monitoring Site Visit

  Conducted as needed to ensure the study site is operating in compliance with this protocol, and completing the CRFs. Clinical monitoring will include review and resolution of missing or inconsistent data and source document checks to ensure the accuracy of the reported data. CRFs for all enrolled patients will be made available to the Sponsor for review and collection as agreed with the investigator. The Sponsor will evaluate and summarize the results of each site visit in written reports, identifying

repeated data problems with any investigator and specifying recommendations for resolution of noted deficiencies.

- Study Close-Out Site Visit

This visit is conducted at the termination of the study to resolve any outstanding data queries.

6.5 Data Management

All study data will be entered into an electronic data capture (EDC) system provided by a vendor. Study personnel will have individual login and password to access the clinical study information based upon each individual's roles and responsibilities. For data security, the system operates within the Secure Socket Layer (SSL) 128-bit encryption protocol. This application is designed to fully support compliance with the following regulations and guidance documents:

- Guidance for Industry 21 CFR Part 11; Electronic Records; Electronic Signatures; Scope and Application [FDA];
- 21 CFR Part 820, also known as FDA Quality System Regulation (QSR);
- Guidance for Industry; E6 Good Clinical Practice: Consolidated Guidance;
- Guidance for Industry; Computerized Systems used in Clinical Investigations;
- General Principles of Software Validation; Final Guidance for Industry and FDA Staff;
- Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Data entry will be performed at the investigational sites. Standardized electronic Case Report Forms (eCRFs) will be provided for use at all investigational sites. Investigators are responsible for completion and timely submission of the data to Penumbra, Inc. 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. Incoming data are to be reviewed for quality & consistency before being locked for data export. Questions or problems with submitted data will be addressed with the principal investigator via an electronic querying system, or through direct contact.

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

7. CONTACT INFORMATION

The address of Penumbra Incorporated is:

Penumbra Incorporated
1351 Harbor Bay Parkway
Alameda, CA 94502
Tel. (510) 748-3200
Fax (510) 814-8305

Key contacts at the company include:

Malia McPherson, B.A.	Clinical Research Associate	510-748-3294
Siu Po Sit, Ph.D.	VP, Clinical Affairs	510-748-3221
Arani Bose, M.D.	Medical Monitor	510-748-3200
Adam Elsesser	CEO	510-748-3222

8. ETHICAL REQUIREMENTS

8.1 Declaration of Helsinki

The study will be performed in accordance with EN 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 IRB/EC and to keep the IRB/EC informed of any unexpected serious adverse events, 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.

8.2 Patient Information and Consent

It is the responsibility of the investigator to give each patient full and adequate verbal and written information regarding the objective and procedure of the study and the possible risks involved and to obtain signed informed consent from all patients prior to inclusion in the study unless the patient's health condition does not allow informed consent, in which case the state and national procedures will be applied. The original, signed consent is filed with the patient study records, and a copy is provided to the patient or legally authorized representative.

8.3 Patient Data Protection

The patients will be identified in the CRFs with patient number and initials. Only the investigator and the Sponsor or designee will have access to individual patient data. Furthermore, the patients should be informed about the possibility of inspection of relevant parts of the hospital records, including angiograms and

other imaging scans, by the Sponsor or other Health Authorities, including the US FDA.

9. STATISTICAL PROCEDURES

9.1 Sample Size Justification and Statistical Analysis

The primary objective of this post-market single center experience is to determine the safety and effectiveness of the Penumbra Coil System in a cohort of patients treated for intracranial aneurysm.

Approximately 2,000 patients will be enrolled. With this sample size the precision is greater than ± 2.5% for the procedural device-related serious adverse event rate based on a binomial 95% confidence interval. Hence, the sample size provides a sufficient level of precision for the primary endpoint.

This study is a single-treatment design. Hence, descriptive statistics will provide a basis for the majority of the analyses with a 95% two-sided confidence interval presented. For binary outcomes, the 95% two-sided confidence intervals will be calculated using exact binomial intervals. For numeric measures, a confidence bound for the mean or mean change from admission will be constructed.

Standard descriptive statistics for categorical endpoints will be the number and percent of patients with each level of the endpoint. For numeric endpoints, the standard descriptive statistics include the number of missing observations (n), the mean, the median, the standard deviation, the minimum value, and the maximum value.

Results collected at multiple visits will be summarized at each visit for which they are collected. Summaries for all measures will include all observed data for each visit.

9.2 Safety

All serious adverse events will be summarized by showing the number and percent of patients which report the event. Events will also be reported by relationship to the procedure or device. The denominator for the analyses is all enrolled patients.

The proportion of deaths for any reason through one year follow up will be calculated and a 95% confidence interval will be presented. The cause of death and time-to-death will be summarized. The proportion of patients with symptomatic intracranial hemorrhage will be summarized and reported.

Survival estimates will be generated to evaluate the time-to-death and time-to-event using Kaplan-Meier methodology for all events through one year. Peto's adjusted standard error estimates will be calculated.

10. PUBLICATION OF INFORMATION

The results of this study may be offered for publication and/or presentation. The investigators and the Sponsor shall collaborate in the writing of the study to ensure accuracy. 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.

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