STATISTICAL ANALYSIS PLAN

SMART – A prospective, multicenter registry assessing the embolization of neurovascular lesions using the Penumbra SMART COIL® System

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Protocol CLP 10023.B

January 11, 2017

Contents

1 Overview

SMART is a multicenter, single-arm prospective registry. Its primary objective is to acquire postmarket data on the use of the Penumbra SMART COIL® System (Smart) in the treatment of intracranial aneurysms and other malformations.

Approximately 1,000 subjects with intracranial aneurysms or other malformations treated by Smart will be enrolled across up to 100 sites. All subjects will be allocated to treatment with at least 75% Smart, Penumbra Coil 400™ (PC 400), or Penumbra Occlusion Device (POD®) coils as defined by the number of coils implanted.

The primary efficacy endpoint is the rate of retreatment through one year ± 6 months follow-up. The primary safety endpoint is the rate of procedural (within 24 hours of arterial puncture) device-related serious adverse events.

The secondary efficacy endpoints for the registry are the ability to achieve adequate occlusion at immediate post-procedure (Class I or II Raymond-Roy Occlusion Classification for aneurysms) and the number of times re-access with guidewire was required due to catheter kickout while using SMART/POD/PC 400.

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

2 Sample Size

The predetermined sample size of approximately n = 1000 subjects allows the primary efficacy and safety endpoints to be estimated with greater than ± 2% precision: re-treatment at one-year follow-up (95% CI: 6.6% to 10.0%) and procedural device-related serious adverse events (95% CI: 0.93% to 2.5%).

This analysis applies 95% two-sided binomial proportion confidence intervals using normal approximations to the binomial (SAS v 9.4; SAS Institute, Cary, NC).

These estimates assume 8.3% retreatment through one-year follow-up based on the mean rate observed in eight prior studies cited in the protocol, as weighted by their subject sample sizes. A 1.7% rate of procedural device-related serious adverse events is assumed based on data on file at the sponsor.

3 Interim Analysis

No interim efficacy analyses are planned for the purpose of terminating the registry early. However, interim analysis may be performed for the purpose of publication of SMART results.

4 Analysis Populations

4.1 Definitions

The ITT population will consist of all subjects who sign the informed consent and are enrolled in the registry with Smart, PC 400, or POD accounting for 75% or more of the total number of coils implanted. The ITT population will include only the first lesion treated for each subject. Summary statistics will be developed separately for additional lesions.

The PP population will be constructed by excluding subjects who have major protocol violations that impact endpoint evaluations. Subjects will be classified as screen failures if they are not consented or are consented and not enrolled due to failure to implant at least 75% Smart, PC 400, or POD coils or other reasons.

5 Statistical Methods

For this single-arm registry, results will primarily be presented as descriptive statistics and two-sided 95% confidence intervals.

Baseline, efficacy, and safety variables will be summarized using tables of descriptive statistics for continuous variables (n, mean, median, SD, and range) or frequency counts and percentages for categorical variables.

Confidence intervals will be developed using confidence bounds on the mean or mean change from admission for continuous variables or binomial proportion intervals under a normal approximation to the binomial for categorical variables.

For results developed using data from more than one visit, summaries will be reported for each visit from the full set of observed data available.

Staged procedures are not retreatments for the purposes of running all SMART registry analyses.

6 Baseline Characteristics

Baseline characteristics will be summarized using descriptive statistics for continuous variables or frequency counts and percentages for categorical variables. Two-sided 95% confidence intervals will also be presented.

A summary table will be reported with key baseline characteristics, including subject demographics, admission functional assessments, and lesion evaluation results.

7 Subject Disposition

The number of subjects in the following categories will be recorded:

- Enrolled subjects
- Completed and discontinued subjects
- ITT population
- PP population

Frequency counts and percentages will also be tabulated on the reasons for registry discontinuation: adverse events, death, exclusion for medical reasons, exclusion from registry by investigator, LTFU, withdrawal of consent, or other causes.

8 Effectiveness Analysis

8.1 Primary Effectiveness Analysis

The primary efficacy outcome is the rate of retreatment through one-year follow-up. Frequency counts and percentages will be reported for the subjects who required retreatment. A two-sided 95% binomial proportion confidence interval will be developed for the retreatment rate using a normal approximation to the binomial. All primary and secondary efficacy endpoint analyses will be run on both the intent-to-treat (ITT) population and the per-protocol (PP) population.

8.2 Secondary Effectiveness Analysis

Frequency counts and percentages will be reported for the two secondary efficacy outcomes:

- **Ability to achieve adequate occlusion at immediate post-procedure:** Defined as the proportion of subjects achieving adequate occlusion based on the investigator's assessment given anatomical and other considerations at immediate post-procedure.

This endpoint applies to the investigator's Yes/No assessment on whether adequate occlusion was achieved and not the Raymond-Roy Occlusion Scale. Frequency counts and percentages will be reported for this proportion. Two-sided 95% binomial proportion confidence intervals will be developed, using a normal approximation to the binomial.

- **Re-access with guidewire due to catheter kickout:** This endpoint applies to catheter kickout while using SMART/PC 400/POD coils and not other adjunctive coils. Frequency counts and percentages will be reported for the proportion of subjects experiencing 0, 1, 2, and ≥ 3 kickout events. Two-sided 95% binomial confidence intervals with a normal approximation to the binomial will be presented for each frequency count.

9 Subgroup Analysis

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

- Actual adjunctive treatment used: Balloon, Stent, Other, None
- Age: < 65, ≥ 65
- Aneurysm location: Extradural ICA, ICA, ACA, MCA, Posterior Circulation, Venous Circulation, Other
- Aneurysm size: Small (Up to 10 mm in the largest diameter), Large (> 10 mm to 25 mm in the largest diameter), Giant (> 25 mm in the largest diameter)
- Aneurysm status: Ruptured, Unruptured
- Lesion nature: Aneurysm, Arteriovenous malformation, Fistula, Other
- Lesion treatment technique: Constructive, Deconstructive
- Neck width: Small neck (< 4 mm neck width), Wide neck (≥ 4 mm Neck Width or Dome-to-Neck ratio (defined as Dome Width / Neck Width) < 2)
- Vessel treatment at admission: Initial treatment, Retreatment

For re-access with guidewire due to catheter kickout, which is analyzed based on 0, 1, 2, and ≥ 3 kickout events, subgroup analyses will be performed using the Wilcoxon rank-sum test for subgroup variables with two levels and the Kruskal-Wallis test for subgroup variables with more than two levels. For the other three categorical endpoints, subgroup analysis will be performed using Fisher's Exact test.

10 Safety Analysis

10.1 Primary Safety Analysis

The primary safety endpoint is the proportion of subjects who experience at least one procedural (within 24 hours of arterial puncture) device-related serious adverse event.

Frequency counts and percentages of subjects experiencing a procedural device-related serious adverse event will be provided. A 95% two-sided binomial proportion confidence interval will be reported using a normal approximation to the binomial.

10.2 Analysis of Adverse Events

Only adverse events that are related to the procedure or device, unanticipated adverse device effects (UADE), and all serious adverse events (SAE) from consent through registry exit are reportable under the SMART protocol. Reported adverse event data will be presented for each subject, including actions taken, causality (if appropriate), outcome, seriousness, severity, and start and end dates. The onset of adverse events will also be shown relative (in number of days) to the day of treatment. All adverse events will be reported based on the assessment from the clinical study sites.

Rates of device or procedure related adverse events and serious adverse events will be calculated, broken down by category. These reports will count only the most severe adverse event for each subject and only those categories with at least 3% subjects included. Tabulations and descriptive statistics will be produced, including an analysis by time period: (1) intraprocedural or within 24 hours of procedure and (2) after 24 hours post-procedure.

10.3 Analysis of Deaths

Survival curves will be produced using the Kaplan-Meier product limit estimator. Survival will be tracked through registry completion at the one-year follow-up visit. In addition, 95% confidence intervals for the Kaplan-Meier survival curves will be computed and plotted at monthly time intervals.

A frequency table will also be presented containing one-year mortality rates, along with 95% two-sided binomial proportion confidence intervals using a normal approximation to the binomial.

11 Pooling Across Centers

To assess the validity of data pooling, heterogeneity across sites will be examined using relevant methods, such as ANOVA (continuous variables), contingency tables or binary logistic regression (categorical variables), or Cox proportional hazards (event time variables). Any sites containing fewer than ten subjects will be aggregated in this analysis.

All sites will conduct the registry according to a common protocol. Monitoring efforts will be allocated to assess whether sites are adhering to the protocol in a standardized manner to minimize the presence of heterogeneity across centers.

12 Lost to Follow-Up and Missing Data

Missing data are expected to arise on subjects who discontinue the registry early. For sensitivity purposes, the following additional analyses will be conducted on the primary efficacy endpoint:

- Analyze only subjects with complete one-year retreatment rate data
- For those subjects without any observations after treatment, missing one-year retreatment rate data will be imputed from baseline scores and included in an analysis

13 Changes to Planned Analyses

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

14 Programming Specifications

Statistical analyses will be programmed in SAS 9.4 or later (SAS Institute, Cary, NC) and presented in powerpoint, Word, or pdf format depending on whether a presentation or publication is required.

For Word or pdf output, one-inch margins will be used on all sides of the page, and the headers will be as follows. The left header will contain ‘Penumbra Inc.’ on the top line and ‘Protocol CLP 10023’ on the second line. The right header will contain pagination in the format ‘Page X of Y’. The left footer will contain a statement ‘Last run on DDMONYYYY using database version DDMONYYYY and program [program name.sas]’. The right footer will be blank.

Tables, Listings, and Figures will be titled in the format ‘Exhibit X.Y: [Name]’ on the first line with a subtitle of ‘Intent-to-Treat Population’ or ‘Per-Protocol Population’, as applicable, on the second line. The ITT analysis will be numbered ‘X.1’, and the PP analysis, if available, will be numbered ‘X.2’, where X denotes the number of the analysis being run. Pagination will reset to 1 for every new analysis, so that the ITT analysis is ‘Page 1 of Y’ and the PP analysis, if applicable, is ‘Page 2 of Y’. A Table of Contents will be presented in the form ‘Exhibit X.Y: [Name]……..[Page Number]’.

Tables and listings will be presented using left-justified data and a grid border around each cell. The respective column headers in the tables will contain the name of the table, ‘All Subjects (N = [number of subjects])’, and ‘95% CI’ unless otherwise specified in the mock TLFs. Column headers for the listings are presented in the shells.

Continuous variables will be presented as mean ± SD (min to max) with one decimal place precision, in the format ‘X.X ± X.X (X.X to X.X)’.

Categorical variables will be presented as percent (frequency/total) for each category with one decimal place precision in the format ‘X.X% (n/N)’. Individual categories will be indented four spaces. All categories will be listed out, and categories with zero observations will be reported in the format ‘0.0% (0/N)’. P-values will be presented to three decimal places.

Missing data will be presented in listings with dots (.) if the variable is continuous or blank cells if the variable is categorical.

The subgroup analysis table will be repeated in the format given in the mock shells for all subgroups and endpoints specified in the SAP section, ‘Effectiveness Subgroup Analysis’. The figure ‘Kaplan-Meier Estimates of Probability of Death in Subjects’ will present a plot of survival curves and confidence intervals at one-month intervals up to one year.

15 References

Agresti (2014). *Categorical Data Analysis*. John Wiley & Sons: New Jersey.

CLP SMART – A prospective, multicenter registry assessing the embolization of neurovascular lesions using the Penumbra SMART Coil® System. 10023 protocol, revision B, 23AUG2016.

Debrun GM, et al (1998). Selection of cerebral aneurysms for treatment using Guglielmi detachable coils: the preliminary University of Illinois at Chicago experience. *Neurosurgery*, 43(6), 1281-1295.

Hosmer, Lemeshow, and May (2008). *Applied Survival Analysis: Regression Modeling of Time-to-Event Data*. John Wiley & Sons: New Jersey.

Appendix: Mock Tables, Listings, and Figures

Part I. Mock Tables

Site Enrollment

Site Enrollment	All Subjects (N = N)
99999	X.X% (n/N)

Subject Follow-Up Visits

Subject Follow-Up Visits	All Subjects (N = N)
Admission Evaluation	X.X% (n/N)
Follow-Up	X.X% (n/N)

Analysis Populations

Analysis Populations	All Subjects (N = N)
Intent-to-Treat Population	X.X% (n/N)
Per Protocol Population	X.X% (n/N)

Subject Disposition

Subject Disposition	All Subjects (N = N)
Enrolled Subjects	X.X% (n/N)
Completed Subjects	X.X% (n/N)
Discontinued Subjects	X.X% (n/N)
Adverse Events	X.X% (n/N)
Deceased before Completion	X.X% (n/N)
Excluded for Medical Reasons	X.X% (n/N)
Excluded from Registry by Investigator	X.X% (n/N)
Lost to Follow Up	X.X% (n/N)
Withdrew Consent	X.X% (n/N)
Other	X.X% (n/N)

Demographics

Demographics	All Subjects (N = N)	95% CI
Age	X.X ± X.X (X.X to X.X)	(X.X, X.X)
Gender: Male	X.X% (n/N)	(X.X%, X.X%)

Medical History

Medical History	All Subjects (N = N)	95% CI
Previous Stroke	X.X% (n/N)	(X.X%, X.X%)
Headache	X.X% (n/N)	(X.X%, X.X%)
Migraine	X.X% (n/N)	(X.X%, X.X%)
Traumatic Brain Injury	X.X% (n/N)	(X.X%, X.X%)
Myocardial Infarction	X.X% (n/N)	(X.X%, X.X%)
Hypertension	X.X% (n/N)	(X.X%, X.X%)
Thyroid Disorder	X.X% (n/N)	(X.X%, X.X%)
Diabetes	X.X% (n/N)	(X.X%, X.X%)
Other Past Medical History	X.X% (n/N)	(X.X%, X.X%)
Family History of Aneurysms or Malformations	X.X% (n/N)	(X.X%, X.X%)
Polycystic Kidney Disease	X.X% (n/N)	(X.X%, X.X%)
Fibromuscular Dysplasia	X.X% (n/N)	(X.X%, X.X%)
Smoking	X.X% (n/N)	(X.X%, X.X%)
Cocaine Use	X.X% (n/N)	(X.X%, X.X%)

Process Times

Process Times	All Subjects (N = N)	95% CI
Total Fluoroscopic Time (Minutes)	X.X ± X.X (X.X to X.X)	(X.X, X.X)
Time from First Coil Deployed to Last Coil Detached (Minutes)	X.X ± X.X (X.X to X.X)	(X.X, X.X)
Time from Procedure to Retreatment (Days)	X.X ± X.X (X.X to X.X)	(X.X, X.X)

Lesion Evaluation

Lesion Evaluation	All Subjects (N = N)	95% CI
Lesions Treated		
1	X.X% (n/N)	(X.X%, X.X%)
2	X.X% (n/N)	(X.X%, X.X%)
≥ 3	X.X% (n/N)	(X.X%, X.X%)
Technique: Constructive	X.X% (n/N)	(X.X%, X.X%)
Previous Treatment with Coils	X.X% (n/N)	(X.X%, X.X%)
Lesion Nature		
Aneurysm	X.X% (n/N)	(X.X%, X.X%)
Fistula	X.X% (n/N)	(X.X%, X.X%)
Arteriovenous Malformation	X.X% (n/N)	(X.X%, X.X%)
Other	X.X% (n/N)	(X.X%, X.X%)
Lesion Side		
Right	X.X% (n/N)	(X.X%, X.X%)
Left	X.X% (n/N)	(X.X%, X.X%)
Midline	X.X% (n/N)	(X.X%, X.X%)
Lesion Location		
Extradural ICA	X.X% (n/N)	(X.X%, X.X%)
ICA	X.X% (n/N)	(X.X%, X.X%)
ACA	X.X% (n/N)	(X.X%, X.X%)
MCA	X.X% (n/N)	(X.X%, X.X%)
Posterior Circulation	X.X% (n/N)	(X.X%, X.X%)
Venous Circulation	X.X% (n/N)	(X.X%, X.X%)
Other	X.X% (n/N)	(X.X%, X.X%)

Adjunctive Treatment

Adjunctive Treatment	All Subjects (N = N)	95% CI
Adjunctive Technology Pre-Planned	X.X% (n/N)	(X.X%, X.X%)
Stent-Assisted Coiling	X.X% (n/N)	(X.X%, X.X%)
Balloon-Assisted Coiling	X.X% (n/N)	(X.X%, X.X%)
Other	X.X% (n/N)	(X.X%, X.X%)
Adjunctive Technology Used	X.X% (n/N)	(X.X%, X.X%)
Stent-Assisted Coiling	X.X% (n/N)	(X.X%, X.X%)
Balloon-Assisted Coiling	X.X% (n/N)	(X.X%, X.X%)
Other	X.X% (n/N)	(X.X%, X.X%)

Modified Rankin Scale

Modified Rankin Scale	All Subjects (N = N)	95% CI
Admission mRS	X.X ± X.X (X.X to X.X)	(X.X, X.X)
0 to 2	X.X% (n/N)	(X.X%, X.X%)
0	X.X% (n/N)	(X.X%, X.X%)
1	X.X% (n/N)	(X.X%, X.X%)
2	X.X% (n/N)	(X.X%, X.X%)
3	X.X% (n/N)	(X.X%, X.X%)
4	X.X% (n/N)	(X.X%, X.X%)
5	X.X% (n/N)	(X.X%, X.X%)
6	X.X% (n/N)	(X.X%, X.X%)
One-Year mRS	X.X ± X.X (X.X to X.X)	(X.X, X.X)
0 to 2	X.X% (n/N)	(X.X%, X.X%)
0	X.X% (n/N)	(X.X%, X.X%)
1	X.X% (n/N)	(X.X%, X.X%)
2	X.X% (n/N)	(X.X%, X.X%)
3	X.X% (n/N)	(X.X%, X.X%)
4	X.X% (n/N)	(X.X%, X.X%)
5	X.X% (n/N)	(X.X%, X.X%)
6	X.X% (n/N)	(X.X%, X.X%)

Hunt and Hess Grading Scale

Hunt and Hess Grading Scale	All Subjects (N = N)	95% CI
Admission Hunt and Hess	X.X ± X.X (X.X to X.X)	(X.X, X.X)
I	X.X% (n/N)	(X.X%, X.X%)
II	X.X% (n/N)	(X.X%, X.X%)
III	X.X% (n/N)	(X.X%, X.X%)
IV	X.X% (n/N)	(X.X%, X.X%)
V	X.X% (n/N)	(X.X%, X.X%)

Primary Effectiveness Analysis

Primary Effectiveness Analysis		
Primary Endpoint	**All Subjects (N = N)**	**95% CI**
Retreatment through Follow-Up	X.X% (n/N)	(X.X%, X.X%)

Secondary Effectiveness Analysis

Secondary Effectiveness Analysis		
Secondary Endpoints	**All Subjects (N = N)**	**95% CI**
Adequate Occlusion at Immediate Post-Procedure	X.X% (n/N)	(X.X%, X.X%)
Raymond Scale Class I	X.X% (n/N)	(X.X%, X.X%)
Raymond Scale Class II	X.X% (n/N)	(X.X%, X.X%)
Raymond Scale Class III	X.X% (n/N)	(X.X%, X.X%)
Re-Access Attempts with Guidewire due to Catheter Kickout (Smart/PC 400/POD)		
0	X.X% (n/N)	(X.X%, X.X%)
1	X.X% (n/N)	(X.X%, X.X%)
2	X.X% (n/N)	(X.X%, X.X%)
≥ 3	X.X% (n/N)	(X.X%, X.X%)
Additional Analyses		
Re-Access Attempts with Guidewire due to Catheter Kickout (Other Adjunctive Coils)		
0	X.X% (n/N)	(X.X%, X.X%)
1	X.X% (n/N)	(X.X%, X.X%)
2	X.X% (n/N)	(X.X%, X.X%)
≥ 3	X.X% (n/N)	(X.X%, X.X%)
First Framing Coil Conformed to Lesion Morphology		
Completely Conformed	X.X% (n/N)	(X.X%, X.X%)
Partially Conformed	X.X% (n/N)	(X.X%, X.X%)
Compartmentalized	X.X% (n/N)	(X.X%, X.X%)
N/A	X.X% (n/N)	(X.X%, X.X%)
Packing Density	X.X% (n/N)	(X.X%, X.X%)
Occlusion at One Year (Aneurysms)		
Class I	X.X% (n/N)	(X.X%, X.X%)
Class II	X.X% (n/N)	(X.X%, X.X%)
Class III	X.X% (n/N)	(X.X%, X.X%)
Occlusion of Lesion at One Year (Non-Aneurysms)		
Better (Progressive Occlusion)	X.X% (n/N)	(X.X%, X.X%)
Stable	X.X% (n/N)	(X.X%, X.X%)
Worse (Recanalization)	X.X% (n/N)	(X.X%, X.X%)

Safety Analysis

Primary Endpoint		
Safety Analysis	**All Subjects (N = N)**	**95% CI**
Procedural Device-Related Serious Adverse Events	X.X% (n/N)	(X.X%, X.X%)

Subject Deaths

Subject Deaths	**All Subjects (N = N)**	**95% CI**
One-Year Death Rate	X.X% (n/N)	(X.X%, X.X%)

Serious Adverse Events

Serious Adverse Events	All Subjects (N = N)	95% CI
Serious Adverse Events	X.X% (n/N)	(X.X%, X.X%)
SOC 1	X.X% (n/N)	(X.X%, X.X%)
PT 1	X.X% (n/N)	(X.X%, X.X%)
PT 2	X.X% (n/N)	(X.X%, X.X%)
…		
SOC 2	X.X% (n/N)	(X.X%, X.X%)
PT 1	X.X% (n/N)	(X.X%, X.X%)
PT 2	X.X% (n/N)	(X.X%, X.X%)
…		

Device or Procedure Related Serious Adverse Events Within 24 hours

Device or Procedure Related Serious Adverse Events Within 24 hours	All Subjects (N = N)	95% CI
Device or Procedure Related Adverse Events	X.X% (n/N)	(X.X%, X.X%)
Device Related Adverse Events	X.X% (n/N)	(X.X%, X.X%)
SOC 1	X.X% (n/N)	(X.X%, X.X%)
PT 1	X.X% (n/N)	(X.X%, X.X%)
PT 2	X.X% (n/N)	(X.X%, X.X%)
…		
SOC 2	X.X% (n/N)	(X.X%, X.X%)
PT 1	X.X% (n/N)	(X.X%, X.X%)
PT 2	X.X% (n/N)	(X.X%, X.X%)
…		
Procedure Related Adverse Events	X.X% (n/N)	(X.X%, X.X%)
SOC 1	X.X% (n/N)	(X.X%, X.X%)
PT 1	X.X% (n/N)	(X.X%, X.X%)
PT 2	X.X% (n/N)	(X.X%, X.X%)
…		

Device or Procedure Related Serious Adverse Events Greater than 24 hours

Device or Procedure Related Serious Adverse Events Greater than 24 hours	All Subjects (N = N)	95% CI
Device or Procedure Related Adverse Events	X.X% (n/N)	(X.X%, X.X%)
Device Related Adverse Events	X.X% (n/N)	(X.X%, X.X%)
SOC 1	X.X% (n/N)	(X.X%, X.X%)
PT 1	X.X% (n/N)	(X.X%, X.X%)
PT 2	X.X% (n/N)	(X.X%, X.X%)
…	X.X% (n/N)	(X.X%, X.X%)
Procedure Related Adverse Events	X.X% (n/N)	(X.X%, X.X%)
SOC 1	X.X% (n/N)	(X.X%, X.X%)
PT 1	X.X% (n/N)	(X.X%, X.X%)
PT 2	X.X% (n/N)	(X.X%, X.X%)
…		

Subgroup Analysis: Actual Adjunctive Treatment Used

Subgroup Analysis	Balloon	95% CI	Stent	95% CI	Other	95% CI	None	95% CI	P-Value
Retreatment through Follow-Up	X.X% (n/N)	(X.X%, X.X%)	X.X% (n/N)	(X.X%, X.X%)	X.X% (n/N)	(X.X%, X.X%)	X.X% (n/N)	(X.X%, X.X%)	X.XXX
Adequate Occlusion at Immediate Post-Procedure	X.X% (n/N)	(X.X%, X.X%)	X.X% (n/N)	(X.X%, X.X%)	X.X% (n/N)	(X.X%, X.X%)	X.X% (n/N)	(X.X%, X.X%)	X.XXX
Re-Access Attempts with Guidewire due to Catheter Kickout									
0	X.X% (n/N)	(X.X%, X.X%)	X.X% (n/N)	(X.X%, X.X%)	X.X% (n/N)	(X.X%, X.X%)	X.X% (n/N)	(X.X%, X.X%)	X.XXX
1	X.X% (n/N)	(X.X%, X.X%)	X.X% (n/N)	(X.X%, X.X%)	X.X% (n/N)	(X.X%, X.X%)	X.X% (n/N)	(X.X%, X.X%)	X.XXX
2	X.X% (n/N)	(X.X%, X.X%)	X.X% (n/N)	(X.X%, X.X%)	X.X% (n/N)	(X.X%, X.X%)	X.X% (n/N)	(X.X%, X.X%)	X.XXX
≥ 3	X.X% (n/N)	(X.X%, X.X%)	X.X% (n/N)	(X.X%, X.X%)	X.X% (n/N)	(X.X%, X.X%)	X.X% (n/N)	(X.X%, X.X%)	X.XXX

Pooling Across Centers

Pooling Across Centers	Adjunctive Treatment Used (Yes/No)	Age ≥ 65	Aneurysm Location: ICA	Aneurysm Size: Small	Aneurysm Status: Ruptured	Lesion Nature: Aneurysm	Lesion Treatment Technique: Deonstructive	Neck Width: Wide neck	Vessel Treatment at Admission: Retreatment
99999	X.X% (n/N)	X.X% (n/N)	X.X% (n/N)	X.X% (n/N)	X.X% (n/N)	X.X% (n/N)	X.X% (n/N)	X.X% (n/N)	X.X% (n/N)
99999	X.X% (n/N)	X.X% (n/N)	X.X% (n/N)	X.X% (n/N)X	X.X% (n/N)	X.X% (n/N)	X.X% (n/N)	X.X% (n/N)	X.X% (n/N)
…									
P-value	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX

Major and Minor Protocol Deviations

Major and Minor Protocol Deviations	All Subjects (N = N)
Major Deviations	
Subject does not Meet Inclusion Criteria	X.X% (n/N)
Subject was not Treated for Intracranial Aneurysms/ Other Neurovascular Abnormalities according to the Cleared Indications for SMART/PC 400/POD	X.X% (n/N)
Informed Consent not Obtained	X.X% (n/N)
Subject Meets Exclusion Criteria	X.X% (n/N)
Minor Deviations	
Improperly Signed or Incomplete Informed Consent	X.X% (n/N)
Out of Window Visit	X.X% (n/N)
Missing Visit	X.X% (n/N)
Out of Window Assessment	X.X% (n/N)
Assessment Not Done	X.X% (n/N)
Delayed Reporting of Serious or Procedure/Device Related Adverse Event	X.X% (n/N)
Registry Assessment/Procedure Done by Non Registry Staff or Registry Staff not Delegated to Task	X.X% (n/N)
Other	X.X% (n/N)

Enrollment and Screening

Enrollment and Screening	All Subjects (N = N)
Consented and Not Enrolled	X.X% (n/N)
Less than 75% of Total Number of Coils Implanted are SMART, PC 400, or POD	X.X% (n/N)
Other	X.X% (n/N)
Not Consented and Not Enrolled	X.X% (n/N)
Did not Want to Participate	X.X% (n/N)
Life Expectancy less than 1 Year	X.X% (n/N)
Subject Already Enrolled in SMART	X.X% (n/N)
Participating in Another Clinical Investigation that could Confound the Evaluation of the Registry Device	X.X% (n/N)
Other	X.X% (n/N)

Sensitivity Analysis

Sensitivity Analysis	All Subjects (N = N)	95% CI
Analysis of All Subjects with Follow-Up Complete		
Retreatment through Follow-Up	X.X% (n/N)	(X.X%, X.X%)
Adequate Occlusion at Immediate Post-Procedure	X.X% (n/N)	(X.X%, X.X%)
Re-Access Attempts with Guidewire due to Catheter Kickout (SMART/PC 400/POD)		
0	X.X% (n/N)	(X.X%, X.X%)
1	X.X% (n/N)	(X.X%, X.X%)
2	X.X% (n/N)	(X.X%, X.X%)
≥ 3	X.X% (n/N)	(X.X%, X.X%)
Procedural Device-Related Serious Adverse Events	X.X% (n/N)	(X.X%, X.X%)
Analysis of Complete Datasets with Missing Data Imputed		
Retreatment through Follow-Up	X.X% (n/N)	(X.X%, X.X%)
Adequate Occlusion at Immediate Post-Procedure	X.X% (n/N)	(X.X%, X.X%)
Re-Access Attempts with Guidewire due to Catheter Kickout (SMART/PC 400/POD)	X.X% (n/N)	
0	X.X% (n/N)	(X.X%, X.X%)
1	X.X% (n/N)	(X.X%, X.X%)
2	X.X% (n/N)	(X.X%, X.X%)
≥ 3	X.X% (n/N)	(X.X%, X.X%)
Procedural Device-Related Serious Adverse Events	X.X% (n/N)	(X.X%, X.X%)

Part II. Mock Listings

Subject Follow-Up Visits

Subject	Visit	Visit Date
99999-999	Admission Evaluation Follow-Up	DDMONYYYY

Analysis Populations

Subject	Intent-to-Treat	Per Protocol
99999-999	Yes No	Yes No

Subject Disposition

Subject	Completed	If Yes, Date of Registry Completion	If No, Reason	Other, Specify
99999-999	Yes No	DDMONYYYY	Adverse Events Deceased before Completion Excluded for Medical Reasons Excluded from Registry by Investigator Lost to Follow Up Withdrew Consent Other	<Specify text>

Demographics

Subject	Age	Gender
99999-999	X	Female Male

Medical History

Subject	Medical History
99999-999	Previous Stroke Headache Migraine Traumatic Brain Injury Myocardial Infarction Hypertension Thyroid Disorder Diabetes Other Past Medical History Family History of Aneurysms or Malformations Polycystic Kidney Disease Fibromuscular Dysplasia Smoking Cocaine Use

Process Times

Subject	Total Fluoroscopic Time (Minutes)	Time from Arterial Puncture to First Coil Deployed (Minutes)	Time from Arterial Puncture to Last Coil Detached (Minutes)
99999-999	X	X	X

Lesion Evaluation

Subject	Technique	Previous Treatment with Coils	Lesion Nature	Other, Specify	Lesion Side	Lesion Location	Other, Specify	Arterial Access Site	Other, Specify
99999-999	Constructive Deconstructive	Yes No	Aneurysm Fistula Arteriovenous Malformation Other	<Specify text>	Right Left Midline	Extradural ICA ICA ACA MCA Posterior Circulation Venous Circulation Other	<Specify text>	Right Femoral Left Femoral Right Radial Left Radial Other, Specify	<Specify text>

Adjunctive Treatment

Subject	Adjunctive Technology Pre-Planned	Planned Adjunctive Treatment	Adjunctive Technology Used	Actual Adjunctive Treatment
99999-999	Yes No	Stent-Assisted Coiling Balloon-Assisted Coiling Other	Yes No	Stent-Assisted Coiling Balloon-Assisted Coiling Other

Modified Rankin Scale

Subject	Admission mRS	One-Year mRS
99999-999	X	X

Hunt and Hess Grading Scale

Subject	Admission Hunt and Hess
99999-999	X

Primary Effectiveness Analysis

Subject	Retreatment through Follow-Up
99999-999	Yes No Unknown

Secondary Effectiveness Analysis

Subject	Was Adequate Occlusion Achieved?	Occlusion of the Aneurysm	Re-Access with Guidewire due to Catheter Kickout while Using SMART/PC 400/POD	Re-Access with Guidewire due to Catheter Kickout while Using Other Adjunctive Coils	First Framing Coil Conformed to Lesion Morphology	Packing Density	Occlusion of the Aneurysm at One Year	Occlusion Grading of Lesion at One Year (Non-Aneurysm)
99999-999	Yes No	Not Applicable (no aneurysm treated) Class I Class II Class III Not done, explain:	Yes No	Yes No N/A	Completely Conformed Partially Conformed Compartmentalized N/A	X%	Not Applicable (no aneurysm treated) Class I Class II Class III Not done, explain:	Better (Progressive Occlusion) Stable Worse (Recanalization) Not Applicable (aneurysm treated) Not done, explain:

Safety Analysis

Subject	SOC / PT / Name of Event	Date of Onset	Time Period	Outcome	Date Resolved or Other, Specify	Severity	Relationship to Disease State/Angiographic Procedure	Relationship to SMART / PC 400 / POD Coil System	Action Taken	Other, Specify
99999-999	X	DDMONYYYY	Intraprocedural or within 24 hours of Procedure After 24 Hours Post Procedure	Resolved Unresolved (Event Continuing) Death due to this event Unresolved (Death Due to Other Event) Unresolved (at time of registry exit/study closure) Other	DDMONYYYY or <Specify text>	Mild Moderate Severe	Unrelated Possible Probable Definite / Unrelated Possible Probable Definite	Unrelated Possible Probable Definite N/A / Unrelated Possible Probable Definite N/A / Unrelated Possible Probable Definite N/A	None Remedial Therapy Medical Procedure Hospitalization Other	<Specify text>

Subject Deaths

Subject	Date of Death
99999-999	DDMONYYYY

Serious Adverse Events

Subject	SOC / PT / Name of Event	Date of Onset	Time Period	Outcome	Date Resolved or Other, Specify	Severity	Relationship to Disease State/Angiographic Procedure	Relationship to SMART / PC 400 / POD Coil System	Action Taken	Other, Specify	Classification of Event	Did event cause the subject to withdraw from registry?
99999-999	X	DDMON YYYY	Intraprocedural or within 24 hours of Procedure After 24 Hours Post Procedure	Resolved Unresolved (Event Continuing) Death due to this event Unresolved (Death Due to Other Event) Unresolved (at time of registry exit/study closure) Other	DDMON YYYY or <Specify text>	Mild Moderate Severe	Unrelated Possible Probable Definite / Unrelated Possible Probable Definite	Unrelated Possible Probable Definite / Unrelated Possible Probable Definite / Unrelated Possible Probable Definite	None Remedial Therapy Medical Procedure Hospitalization Other	<Specify text>	Death Permanent impairment or damage Requires hospitalization or prolongation of existing hospitalization Life threatening Medical or surgical impairment to prevent permanent impairment or damage	Yes No

Device or Procedure Related Adverse Events Within 24 hours

Subject	SOC / PT / Name of Event	Date of Onset	Time Period	Outcome	Date Resolved or Other, Specify	Severity	Relationship to Disease State/Angiographic Procedure	Relationship to SMART / PC 400 / POD Coil System	Action Taken	Other, Specify
99999-999	X	DDMONYYYY	Intraprocedural or within 24 hours of Procedure After 24 Hours Post Procedure	Resolved Unresolved (Event Continuing) Death due to this event Unresolved (Death Due to Other Event) Unresolved (at time of registry exit/study closure) Other	DDMONYYYY or <Specify text>	Mild Moderate Severe	Unrelated Possible Probable Definite / Unrelated Possible Probable Definite	Unrelated Possible Probable Definite / Unrelated Possible Probable Definite / Unrelated Possible Probable Definite	None Remedial Therapy Medical Procedure Hospitalization Other	<Specify text>

Device or Procedure Related Adverse Events Greater than 24 hours

Subject	SOC / PT / Name of Event	Date of Onset	Time Period	Outcome	Date Resolved or Other, Specify	Severity	Relationship to Disease State/Angiographic Procedure	Relationship to SMART / PC 400 / POD Coil System	Action Taken	Other, Specify
99999-999	X	DDMONYYYY	Intraprocedural or within 24 hours of Procedure After 24 Hours Post Procedure	Resolved Unresolved (Event Continuing) Death due to this event Unresolved (Death Due to Other Event) Unresolved (at time of registry exit/study closure) Other	DDMONYYYY or <Specify text>	Mild Moderate Severe	Unrelated Possible Probable Definite / Unrelated Possible Probable Definite	Unrelated Possible Probable Definite / Unrelated Possible Probable Definite / Unrelated Possible Probable Definite	None Remedial Therapy Medical Procedure Hospitalization Other	<Specify text>

Enrollment and Screening

Subject	Status	Date of Consent	Reason Subject Not Enrolled	Other, Specify	Not Consented and Not Enrolled Reason	Other, Specify
Subject not Consented	Consented and Enrolled Consented and Not Enrolled Not Consented and Not Enrolled	DDMONYYYY	Less than 75% of total number of coils implanted are SMART, PC 400, or POD Other, Specify	<Specify text>	Did not want to participate Life expectancy less than 1 year Subject already enrolled in SMART Participating in another clinical investigation that could confound the evaluation of the registry device Other	<Specify text>

Major and Minor Protocol Deviations

Subject	Timepoint	Protocol Deviation Codes	Inclusion-Exclusion Criteria Not Met	Other, Specify
99999-999	Baseline/Procedure Discharge Follow Up Other (specify):	Subject does not Meet Inclusion Criteria Subject Meets Exclusion Criteria Improperly Signed or Incomplete Informed Consent Out of Window Visit Missing Visit Out of Window Assessment Assessment Not Done Delayed Reporting of Serious or Procedure/Device Related Adverse Event Registry Assessment/Procedure Done by Non Registry Staff or Registry Staff not Delegated to Task Other (specify):	Patient was not treated for intracranial aneurysms/ other neurovascular abnormalities according to the cleared indications for SMART/PC 400/ POD Informed consent not obtained Life expectancy is less than one year Participation in another clinical investigation that could confound the evaluation of the registry device Subject already enrolled in SMART registry	<Specify text>

Part III. Mock Figures

Kaplan-Meier Estimates of Probability of Death in Subjects