STATISTICAL ANALYSIS PLAN

EXTRACT-PE: A Prospective, Multicenter Trial to Evaluate the Safety and Efficacy of the Indigo® Aspiration System in Acute Pulmonary Embolism

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Protocol CLP-11373

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Contents

1 Overview

This is a prospective multi-center, single-arm study designed to evaluate the effectiveness and safety of the INDIGO™ Aspiration System for aspiration mechanical thrombectomy in patients with acute pulmonary embolism (PE).

Up to 150 adult patients will be enrolled from approximately 25 centers in order to provide 100 evaluable patients after attrition. Each site will be limited to a maximum enrollment of up to 30 patients (~20% of total enrollment). Depending on an interim sample size review, the number of patients enrolled may increase up to 300 patients in order to provide up to 200 evaluable patients (for further details please refer to section 3.1).

This Statistical Analysis Plan (SAP) will provide details to further elaborate statistical methods as outlined in the protocol and will describe analysis conventions. The SAP will be signed off prior to database lock.

2 Sample Size

A sample size of up to 150 enrolled patients was selected for this study in order to provide 100 evaluable patients. Assuming a mean change of 0.42 in the RV/LV ratio from baseline to 48 hours and a standard deviation of 0.36 the two-sided 95% normal distribution confidence interval for a sample size of 100 patients is (0.35, 0.49). The estimated mean and standard deviation are based on clinical data from the SEATTLE II study of pulmonary embolism treatment (Piazza 2015).

Assuming a 48 hour major adverse events rate of 15% (15/100), the two-sided 95% normal distribution confidence interval is (8.0%, 22.0%). This estimated rate is based on complications reported for interventional treatment (Piazza 2015, Kucher 2014, Kuo 2015, Stein 2012, Neely 2015, Aklog 2002, Greenlish, 2011).

To account for up to 33% attrition, the enrollment was increased to 150 patients. The effectiveness and safety sample size calculations support 150 enrolled patients (Table 1 and Table 2).

2.1 Effectiveness Power

The effectiveness hypothesis tested is that the mean change in RV/LV ratio from baseline to 48 hours, RV/LV_{change}, does not equal 0.2:

H_0: $RV/LV_{change} = 0.2$

vs H_a: $RV/LV_{change} \neq 0.2$,

under an observed mean of 0.42 and standard deviation of 0.36 at alpha = 0.05.

The power for a one-group, two-sided test for a single mean difference was calculated for the test using SAS v 9.4 (SAS Institute, Cary, NC). The SAS code and output are provided in Section 17.

Table 1. Effectiveness Sample Size Parameters

Alpha	0.05
Sides	2
Estimated mean	0.42
Estimated standard deviation	0.36
Null mean (μ_0)	0.2
N	100
Power	>.999
Attrition	33%
Total N	100 x 1/(1 - 0.33) = 150

2.2 Safety Power

The safety hypothesis tested is that the 48 hour rate of major adverse events, Major AE, does not equal 0.40:

H_0: Major AE = 0.40

vs H_a: Major AE ≠ 0.40.

under an observed Major AE of 15% at alpha = 0.05.

The power for a one-group, two-sided test for a single proportion was calculated for the test using SAS v 9.4 (SAS Institute, Cary, NC). The SAS code and output are provided in Section 17.

Table 2. Safety Sample Size Parameters

Alpha	0.05
Sides	2
Estimated proportion	0.15
Null proportion (p_0)	0.40
N	100
Power	>.999

2.3 Justification of Effectiveness and Safety Thresholds

Effectiveness: A prior study of fibrinolysis identified greater than 0.20 as an appropriate decrease in the RV/LV ratio (Piazza 2015, Fasullo 2011). In this trial a lower limit of 0.2 mean decrease in RV/LV diameter ratio represents a reasonable improvement in effectiveness for this patient population.

Safety: Patients with acute pulmonary embolism (PE) have limited alternatives for treatment. While most patients continue to be treated conservatively with anticoagulation alone, high fatality and bleeding rates have been noted. For submassive PE patients, the mortality rate for patients treated with anticoagulation alone was as high as 25% (Konstantinides 2002) and the risk of the major bleeding was less than 8% (Konstantinides 1997). When indicated, more intensive treatment escalation may be required. These include systemic fibrinolysis, emergent surgical embolectomy, and catheter-directed interventions with aspiration or mechanical embolectomy devices.

- **Systemic Fibrinolysis** is offered to patients who are refractory to anticoagulant therapy. However, systemic thrombolysis is associated with a 20% risk for major bleeding, including a 2 – 5% risk of hemorrhagic stroke and a mortality rate as high as 11% (Kuo 2015). The clinical deterioration rate for submassive patients treated with systemic fibrinolysis could be as high as 38% (Mehta 2003).

- **Emergency Surgical Embolectomy** with cardiopulmonary bypass has re-emerged as an effective strategy for managing patients with submassive PE with RV dysfunction who are not eligible for or are refractory to current standard of care. The mortality rate associated with the surgery is as high as 19% (Stein 2012) and in a case series, 3.6% of patients had a major bleeding event (Neely 2015).

- **Catheter-Directed Intervention** is a relatively new treatment option that includes catheter-directed fibrinolysis, aspiration or mechanical embolectomy. Early results showed this mode of therapy may have promise. According to the limited data available, the mortality rate was ~3% (Kuo 2015). The data available on clinical deterioration gives a rate of ~3% and ~7% for major bleeding.

In summary, patients with PE who are eligible for the EXTRACT PE trial have few treatment alternatives. These patients are at high risk of morbidity and mortality including those who failed current standard of care. A procedure that is highly effective and has a peri-procedural complications rate of Major Adverse Events with an upper limit of 40% represents a reasonable advance for this patient population. The limited reasonable alternatives justify the proposed safety study success parameter.

This upper limit of 40% was determined from the upper bound of the 95% confidence interval for an estimated major adverse event rate calculated from weighting the published data based on clinical assessment of the importance to the current study.

3 Interim Analysis

No interim analyses are planned for the purpose of stopping the study early for success or futility.

An interim sample size review to re-assess the size of the estimated mean and standard deviations of the primary effectiveness variables and the rate of the primary effectiveness safety variables will be performed after n_1 = 50 evaluable patients (i.e. treated only using the Indigo Aspiration System) have primary endpoint data. The sample size will be adjusted accordingly (see section 3.1).

3.1 Re-estimation of Sample Size

The initial sample size estimation provides statistical power to demonstrate effectiveness and safety among patients treated only using the Indigo Aspiration System. A potential sample size adjustment is to assure that this trial will have the intended precision. The decision of sample size adjustment will be made based on the estimates of 48 hour mean change in the RV/LV ratio from baseline and 48 hour rate of major adverse events that are calculated for the first 50 evaluable (i.e. treated only using the Indigo Aspiration System) patients with primary endpoint data. The Core Laboratory data and the CEC adjudicated data supersede the investigator-reported data in this sample size re-estimation. Sample size will not be decreased regardless of the results of this evaluation. To warrant the originally intended >80% power of the study at the 0.05 level (2-sided), the evaluable sample size may be increased to a maximum of 300 enrolled patients in order to provide 200 evaluable patients, given expected attrition including use of adjunctive treatments for the purpose of reducing clot burden in pulmonary artery or any use of thrombolytics. The sample size re-estimation will be evaluated for the efficacy endpoint based on the observed interim mean and standard deviation and for the safety endpoint based on the observed interim proportion.

The sample size re-estimation method is based on evaluation of conditional power in relationship to pre-specified decision rules defined by ranges of attainable conditional power values. Only an increase in sample size is possible under this approach when observed conditional power falls within the 'promising zone' as described below (Bhatt 2016, Chen 2004, Cui 1999, Mehta and Pocock 2011, Orloff 2009, PASS 2017).

The conditional power at the interim analysis ($CP_{\hat{\delta}_1}(z_1, \widetilde{n_2})$) can be defined by the following equation from Mehta and Pocock (2011) and PASS (2017):

$$CP_{\hat{\delta}_1}(z_1, \widetilde{n_2}) = 1 - \Phi\left(\frac{z_{\alpha/2}\sqrt{n_2} - z_1\sqrt{n_1}}{\sqrt{\widetilde{n_2}}} - \frac{z_1\sqrt{\widetilde{n_2}}}{\sqrt{n_1}}\right) + \Phi\left(\frac{-z_{\alpha/2}\sqrt{n_2} - z_1\sqrt{n_1}}{\sqrt{\widetilde{n_2}}} - \frac{z_1\sqrt{\widetilde{n_2}}}{\sqrt{n_1}}\right)$$

where $\widetilde{n_2} = n_2 - n_1$, $z_{\alpha/2}$ = $\Phi^{-1}(1-\alpha/2)$, and z_1 is the value of the cumulative Wald statistic as computed at the interim analysis of n_1= 50 evaluable patients. Define the estimated treatment difference, $\hat{\delta}_1 = \hat{\mu}_1 - \mu_0 \; or \; \hat{p}_1 - p_0$ at interim analysis, where $\hat{\mu}_1$ and $\hat{p}_1$ are mean and proportion at interim analysis and μ_0 and p_0 are the null hypothesis correspondingly.

Our targeted conditional power at the first interim review is 80%, however we pre-specify a range of conditional power values below 80% that would deem our interim results promising and warrant a sample size re-estimation.

Table 3 provides cut-off values from Mehta and Pocock (2011) for the lower bound of the promising zone, CP_{min}, under some typical two-stage adaptive designs. CP_{min} is 0.36 (36%) for the parameter choices in this study (Table 5).

Table 3. CP_{min} cut-off values for some typical two-stage adaptive designs with no early stopping either for efficacy or futility

Sample size ratios		$\boldsymbol{CP_{min}}$ values for targeted conditional power	
Maximum allowed $(\boldsymbol{n_{max}/n_2})$	At interim look (n_1/n_2)	**80 per cent**	90 per cent
1.5	0.25	0.42	0.42
1.5	0.5	0.41	0.41
1.5	0.75	0.38	0.38
2	0.25	0.37	0.37
2	**0.5**	**0.36**	0.36
2	0.75	0.33	0.33
3	0.25	0.32	0.32
3	0.5	0.31	0.31
3	0.75	0.30	0.27
∞	0.25	0.32	0.28
∞	0.5	0.31	0.27
∞	0.75	0.30	0.25

Table 4 summarizes the sample size re-estimation decision based on the conditional power observed at interim analysis. The sample size is re-estimated when the interim conditional power falls within the promising zone of 0.36 to 0.80 (36% to 80%).

Table 4. Sample Size Re-Estimation Decision

Conditional Power	**Decision**
Less than 36%	"Unfavorable Zone" - No change to sample size
36% to 80%	"Promising Zone" - Increase sample size
At least 80%	"Favorable Zone" - No change to sample size

Table 5 provides the parameters used for the sample size re-estimation. We expect that enrollment of up to 300 enrolled patients will provide n_{max} = 200 evaluable patients. The number of evaluable patients and associated attrition rate including use of adjunctive treatments for the purpose of reducing clot burden in pulmonary artery or any use of thrombolytics will be monitored during the course of the trial until n_{max} = 200 evaluable patients are achieved.

Table 5. Sample Size Re-Estimation Parameters

Design Parameters	Value
Interim Sample Size, n_1	50
Cumulative Final Sample Size, n_2	100
Re-Estimated Cumulative Final Sample Size, n_2*	Derived Below
Pre-specified Maximum Allowable Sample Size, n_{max}	200
Sample Size Ratio – Maximum Allowed ($\boldsymbol{n_{max}/n_2}$)	**200/100 = 2**
Sample Size Ratio – At Interim Look ($\boldsymbol{n_1/n_2}$)	**50/100 = 0.5**
Incremental Sample Size, $\widetilde{n_2} = n_2 - n_1$	50
Re-Estimated Incremental Sample Size, $\tilde{n}_2'$	Derived Below
Estimated Attrition – Monitored during course of trial and adjusted as appropriate, including an estimated proportion of subjects receiving adjunctive treatments for the purpose of reducing clot burden in pulmonary artery or receiving any thrombolytics	33% (including an estimated 20% adjunctive treatment or thrombolytic use)
Significance Level (Alpha)	0.05

Targeted Conditional Power	80%

The re-estimated cumulative final sample size ($n_2{}^*$) is computed using the following equation (equation (9) from Mehta and Pocock (2011)) and will be increased by a factor based on a re-assessed attrition rate as per the initial sample size calculation:

$$n_2{}^* = \min(n_2{}', n_{max}), \text{where } \tilde{n}_2{}' \text{ satisfies the condition } CP_{\hat{\delta}_1}(z_1, \tilde{n}_2{}') = 1 - \beta, \beta = 80\%,$$

$$\text{and } n_2{}' \text{ is the estimated new sample size computed as } n_1 + \tilde{n}_2{}'.$$

Based on Mehta and Pocock (2011), this condition is satisfied by the function:

$\tilde{n}_2{}' = \left(\left[\frac{n_1}{{z_1}^2}\right]\left[\frac{z_{\alpha/2}\sqrt{n_2} - z_1\sqrt{n_1}}{\sqrt{n_2 - n_1}} + z_\beta\right]^2\right)$, where $z_{\alpha/2}$ = $\Phi^{-1}(1-\alpha/2)$, z_β = $\Phi^{-1}(1-\beta)$, and z_1 is the cumulative Wald statistic as computed at the interim analysis of n_1= 50 patients.

The re-estimation will be conducted for both the effectiveness and safety endpoints and the highest calculated sample size will be utilized to adjust the study enrollment:

$$Re - Estimated\ Cumulative\ Final\ Sample\ Size = \max\{n^*_{2,Effectiveness}, n^*_{2,Safety}\},$$

subject to n_{max} = 200.

The SAS code for the calculation of conditional power and sample size re-estimation is provided in Section 17.3.

4 Analysis Populations

4.1 Definitions

All primary and secondary effectiveness endpoints will be performed for both the intent-to-treat (ITT) population and per-protocol (PP) population.

- **Target Population:** Patients presenting with symptoms of acute PE who meet other study entry criteria are eligible for this trial. Enrolled patients will be treated with aspiration thrombectomy by the Indigo® Aspiration System.

- **Intent-to-Treat Population:** All efficacy and safety outcome measures will be analyzed under the intent-to-treat (ITT) principle. Under this principle, the ITT population includes all patients who signed the informed consent and are enrolled in the study. The data from this population will be analysed even if the patient does not follow the protocol until completion.
- **Modified Intent-to-Treat Population:** In addition to the ITT analysis sample, a modified Intent-to-Treat (mITT) sample is defined as a subset of the ITT sample. This population is the primary population for all efficacy parameters. Patients receiving adjunctive treatments for the purpose of reducing clot burden in the pulmonary artery (intra-procedure and up to 48 hours post procedure) or receiving any thrombolytics during the procedure and up to 48-hours post-procedure will be excluded.

- **Per-Protocol Population:** In addition to the defined ITT analysis sample, a per-protocol (PP) sample is defined as a subset of the ITT sample. The per-protocol sample will include all enrolled patients who signed the informed consent and do not have significant protocol deviations (e.g. eligibility violation or missing primary endpoint assessment).

- **Safety Analysis (As Treated) Population:** For the safety analysis, a safety sample that is the same as the ITT sample will be examined in which patients will be analyzed according to the actual treatment received.

- **Consented but Device Not Introduced:** Patients who are consented and have venous puncture for the Indigo procedure, but with no component of the Indigo® Aspiration System entering the patient's body will be followed through discharge and their safety will be summarized separately in the clinical report.

The following additional population definitions apply to this study:

- **Screened:** All patients considered for participation in the study, regardless of whether they have a signed informed consent available.
- **Screen Failure:** All patients who were evaluated and do not meet the study entry criteria, who meet the entry criteria but decline to participate, or who meet the entry criteria but have no component of the Indigo System introduced into their body. Patients can be screen failed based on general or imaging criteria. These patients may or may not have signed an informed consent.

- **Enrolled:** All patients who have an informed consent form and HIPAA Authorization signed by the subject or LAR, and in whom the Indigo System has been introduced into their body. Informed consent must be obtained prior to enrollment.
- **Evaluable:** Enrolled patients without use of adjunctive treatments for the purpose of reducing clot burden in pulmonary artery (intra-procedure and up to 48 hours post procedure) and without use of any thrombolytics during the procedure and up to 48-hours post-procedure.
- **Completed:** All patients who were enrolled and completed the study Day 30 follow-up or were known to have died prior to Day 30.
- **Early Termination:** All patients who were enrolled but did not complete the study Day 30 follow-up and were not known to have died.

5 Statistical Methods

Summary tables (descriptive statistics and/or frequency tables) will be provided for all baseline variables, effectiveness variables, and safety variables, as appropriate. Continuous variables will be summarized with descriptive statistics (n, mean, standard deviation, range, and median). Frequency counts and percentage of patients within each category will be provided for categorical data. All 95% confidence intervals will be two-sided and presented using the asymptotic or exact intervals for continuous variables and the Wald or Clopper-Pearson intervals for categorical variables. All p-values presented will be two-sided.

6 Baseline Characteristics

Baseline data including, but not limited to demographics, clinical characteristics, and PE characteristics will be summarized using descriptive statistics and the associated 95% confidence intervals.

7 Patient Disposition

The number of patients for each of the following categories will be summarized.

- Screen failure patients
- Consented but device not introduced patients
- Enrolled patients

- Evaluable patients
- Patients completing the study; patients not completing the study
- Patients included in the intent to treat population
- Patients included in the modified intent to treat population
- Patients included in the per protocol population
- Patients included in the safety population

8 Effectiveness Analysis

8.1 Primary Effectiveness Analysis

The primary effectiveness variable is the change in RV/LV ratio at 48 hours. The primary efficacy analysis will be the difference between the baseline and the 48 hours RV/LV diameter ratio. The two-sided 95% confidence interval for the mean difference will be calculated. The primary effectiveness endpoint is met if the lower bound of the confidence interval is >0.2. The confidence interval will be used for testing the primary efficacy hypothesis that the mean change in RV/LV ratio from baseline to 48 hours, RV/LV_{change}, does not equal 0.2 at two-sided alpha = 0.05:

H_0: $RV/LV_{change} = 0.2$

vs H_a: $RV/LV_{change} \neq 0.2$.

Special consideration will be given to subjects initiating adjunctive treatments for the purpose of reducing clot burden in pulmonary artery (intra-procedure and up to 48 hours post procedure) or receiving any thrombolytics during the procedure and up to 48-hours post-procedure. Such treatments may mask study treatment effect and hence the outcome for these subjects will be conservatively considered an efficacy endpoint failure.

For the purpose of conducting primary effectiveness analyses in our study, the mITT subject data as observed (completer) will be used.

Sensitivity analyses of the primary efficacy endpoint will be performed. Subjects initiating adjunctive treatments for the purpose of reducing clot burden in pulmonary artery (intra-procedure and up to 48 hours post procedure) or receiving any thrombolytics during the procedure and up to 48-hours post-procedure will be analysed as follows for the primary efficacy analyses:

- The change in their RV/LV ratio at 48 hours will be imputed by the worst observed change in RV/LV ratio from the patient population with primary endpoint data
- The change in their RV/LV ratio at 48 hours will be imputed by the best observed change in RV/LV ratio from the patient population with primary endpoint data
- Their observed RV/LV results will be analyzed

For patients who are refractory to other PE treatments pre-procedure, such as EKOS, the change in RV/LV ratio from baseline to 48 hours will not be altered.

The Core Laboratory data supersede the investigator-reported data in all analyses of RV/LV diameter and will be applied to any interim and final primary effectiveness analyses. The primary effectiveness analysis will be performed in the ITT subject population. The analysis based on the Per Protocol (PP) population will be considered as supportive.

8.2 Handling of Multiplicity

There will be no adjustment on the primary effectiveness variable since the primary comparison is specified in the protocol. The six subgroup analyses will be considered secondary analyses and will be adjusted using the Bonferroni correction. In the event that the primary endpoint is not met, these subgroup analyses will only be considered as hypothesis generating for future studies.

9 Subgroup Analysis

To evaluate the impact of baseline conditions on treatment effect, subgroup analyses will be performed for the primary effectiveness variable, change in the RV/LV ratio, and the primary and secondary safety variables. The subgroups below will be used for these analyses:

- Age
- Gender
- Race/Ethnicity
- Use of IV or IA thrombolytics (tPA) for the purpose of reducing clot burden (intra-procedure and up to 48 hours post procedure)
- Use of IV or IA thrombolytics (tPA) at any time during study follow-up
- Clinical study center
- Operator (e.g. Physician A, Physician B, initial patients treated, subsequent patients treated)

Descriptive statistics will be presented for each subgroup. The subgroup analysis will be conducted using Fisher's exact test, Chi-square test, Wilcoxon rank sum, t-test, Kruskal-Wallis test or ANOVA for univariate analyses and logistic or linear regression for multivariate analyses. These analyses will be performed on the Per Protocol population. The Bonferroni p-value adjustment will be utilized for comparisons between subgroups.

10 Safety Analysis

10.1 Primary Safety Analysis

The primary safety endpoint is 48 hour major adverse events (device-related death, major bleeding, and peri-procedure device-related SAEs of clinical deterioration, pulmonary vascular injury, and cardiac injury). The proportion of patients who meet the safety endpoint based on this criterion will be calculated and analyzed as a binary variable with each subject counted only once. The two-sided 95% normal distribution confidence interval will be provided for the primary safety endpoint. The CEC data supersede the investigator-reported data in all analyses of adverse events and will be applied to any interim and final safety analyses. The CEC will have final adjudication to determine whether each adverse event satisfies the definition of the primary safety endpoint for the primary safety analysis.

The primary safety endpoint is met if the upper bound of the confidence interval is <40%. The confidence interval will be used for testing the primary safety hypothesis that the rate of 48 hour major adverse events, Major AE, does not equal 40% at two-sided alpha = 0.05:

H_0: Major AE = 40%

vs H_a: Major AE ≠ 40%.

Sensitivity analyses of the primary safety endpoint will be performed for subjects with missing primary endpoint data as described in Section 12.

10.2 Secondary Safety Analysis

The secondary safety variables are rates of AEs at 48 hours (device-related death, major bleeding, clinical deterioration, pulmonary vascular injury, and cardiac injury) and AEs at 30 days (any-cause mortality, device-related SAEs, symptomatic PE recurrence). Recurrent PE is defined as symptomatic PE objectively confirmed on contrast-enhanced chest CT, ventilation-perfusion lung scan, or invasive contrast pulmonary angiography. The proportion of patients

who experience a safety event based on these criteria will be calculated along with the associated two-sided 95% confidence interval.

10.3 Analysis of Adverse Events

Tabulations of adverse events will be presented with descriptive statistics at baseline hospitalization and follow-up visits. Adverse event incidence rates will be summarized by category and seriousness of the adverse event. Each subject will be counted only once within a category by using the adverse event with the highest seriousness within each category.

All information pertaining to adverse events noted during the study will be listed by subject, detailing verbatim given by the investigator, category, date of onset, date of resolution, causality and severity. The onset of adverse events will also be shown relative (in number of days) to the day of procedure.

A tabulation of Serious Adverse Events (SAEs) will be provided by subject.

The specific categories analyzed will be those that are reported by at least three (3) percent of the patients. The CEC adjudicated data supersedes the investigator reported data in all analyses of adverse events.

10.4 Handling of Multiplicity

There will be no adjustment for multiple comparisons on the primary safety variable since the primary comparison is specified in the protocol. The subgroup safety analyses will be considered secondary and will be adjusted using the Bonferroni correction.

10.5 Analysis of Deaths

The Kaplan-Meier product-limit method will be the primary method utilized to assess the mortality rate. With the date of procedure set at Day 0, any death occurring on or before calendar day 30 will be counted as a death. 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 30 will be censored at day 30. The time to death will be plotted with confidence intervals at monthly intervals.

Additionally, the death data will be presented as 30 Day binary deaths. The number of deaths will be presented with the 95% confidence interval.

11 Pooling Across Centers

The clinical study will be conducted under a common protocol for each investigational center with the intention of pooling the data for analysis. Every effort will be made to promote consistency in study execution at each investigational center. Analyses will be presented using data pooled across centers. Appropriate stratification and multivariate techniques, including random effects, contingency tables and logistic regression for binary outcomes, analysis of variance for continuous measures, and proportional hazards regression for time-to-event outcomes, will be used to assess differences between study centers to justify pooling data across centers. Centers with fewer than 10 patients may be combined and treated as one site in the pooling analysis, up to a limit of 30 patients per pooled site.

12 Lost to Follow-Up and Missing Data

For sensitivity purposes, the following additional analyses will be conducted for the primary efficacy endpoint:

- For those patients without any observations after procedure:
    - Their 48-hour post-procedure observations will be imputed by baseline scores and included in an analysis.
    - The change in their RV/LV ratio at 48 hours will be imputed using the worst observed change in RV/LV ratio from the patient population with primary endpoint data.
    - The change in their RV/LV ratio at 48 hours will be imputed using the best observed change in RV/LV ratio from the patient population with primary endpoint data.

Sensitivity analyses of the primary safety endpoint will be performed for subjects with missing primary safety endpoint at 48 hour follow-up as follows:

- The subjects will be excluded from analysis
- Their primary safety outcome will be imputed using the worst clinical scenario assuming the subject experienced a primary safety event
- Their primary safety outcome will be imputed using the best clinical scenario assuming the subject did not experience a primary safety event

- If needed, a tipping point analysis will be conducted in which the missing data will be replaced with values such that the upper bound of the confidence interval is greater than 40%

13 Blinding

The Penumbra Inc. clinical team responsible for the conduct of the study, the investigator, study center personnel, core laboratory and clinical events committee will not be blinded to each patient's treatment throughout the course of the study.

14 Committees

14.1 Clinical Events Committee (CEC)

A CEC will adjudicate adverse events for causality and attribution.

14.2 Data Safety Monitoring Board (DSMB)

The DSMB will review the overall safety of the trial.

14.3 Core Lab

An independent Core Lab will review and score imaging scans for RV/LV ratio.

15 Changes to Planned Analyses

All changes to the statistical analysis plan (SAP) will be documented in a revised SAP or the clinical study report.

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17 SAS Code

17.1 Primary Efficacy Power Calculation

17.1.1 Code

```
title1 "Efficacy Power Calculation with mean of 0.42 and SD of 0.36";
proc power;
onesamplemeans
nullmean = 0.2
mean = .42
stddev = 0.36
power=.
ntotal = 100;
run;
```

17.1.2 Output

The POWER Procedure
One-Sample t Test for Mean

Fixed Scenario Elements	
Distribution	Normal
Method	Exact
Null Mean	0.2
Mean	0.42
Standard Deviation	0.36
Total Sample Size	100
Number of Sides	2
Alpha	0.05

Computed Power
Power
>.999

17.2 Primary Safety Power Calculation

17.2.1 Code

```
title1 "Safety Power Calculation with a safety proportion of 0.15 and a null proportion of 0.40";
proc power;
onesamplefreq test = Z method = normal
nullproportion = 0.40
proportion = 0.15
ntotal = 100
power = .;
run;
```

17.2.2 Output

The POWER Procedure
Z Test for Binomial Proportion

Fixed Scenario Elements	
Method	Normal approximation
Null Proportion	0.4
Binomial Proportion	0.15
Total Sample Size	100
Variance Estimate	Null Variance
Number of Sides	2
Alpha	0.05

Computed Power
Power
>.999

17.3 Sample Size Re-Estimation Calculation

```
/*****************************************************************************************************************
*****
macro for sample size re-estimation based on promising zone: for one sample mean variables;
mu0 = null mean
mu1_hat = observed interim mean
sigma1_hat = observed interim standard deviation
cp_min = minimum conditional power for promising zone
power = targeted conditional power
n1 = interim sample size
n2 = cumulative final sample size
nmax = pre-specified maximum allowable sample size
drop = estimated attrition
cp = conditional power
size = re-estimated cumulative final sample size
enroll = total enrollment including dropouts
test = z test value based on new sample size (if required to be increased)
new_alpha = p-value checked based on new n
*****************************************************************************************************************
***/

%macro simulation(mu0=,cp_min=,power=,n1=,n2=,nmax=,drop=);
  data a;
    length zone $30 estimate $50;
    alpha = 0.05;
    n2_tilde = &n2 - &n1;
            do mu1_hat = 0.225 to 0.8 by 0.01;
             do sigma1_hat = 0.3 to 0.95 by 0.01;
             za = quantile('NORMAL',1-alpha/2);
     zb = quantile('NORMAL',&power);
     se_delta1_hat = sigma1_hat / sqrt(&n1);
     delta1_hat = mu1_hat - &mu0;
     z1 = delta1_hat / se_delta1_hat;
     cp_u = 1 - cdf('NORMAL', (za * sqrt(&n2) - z1 * sqrt(&n1)) / sqrt(n2_tilde) - (z1 * sqrt(n2_tilde)) /
sqrt(&n1));
             cp_l = cdf('NORMAL', (-za * sqrt(&n2) - z1 * sqrt(&n1)) / sqrt(n2_tilde) - (z1 * sqrt(n2_tilde)) /
sqrt(&n1));
             cp = cp_u + cp_l;


             /*** conditions to check if value falls within promising zone ***/
             if cp ge &cp_min and cp le &power then do;
              zone = "Promising Zone";
              estimate = "Sample size should be increased";
              n2_tilde_prime  = ceil((&n1 / z1 ** 2) * ((za * sqrt(&n2) - z1 * sqrt(&n1)) / sqrt(&n2 - &n1) + zb) **
2);
      n2_prime = &n1 + n2_tilde_prime;
      size = min(n2_prime, &nmax);
      enroll = ceil(size/(1-&drop));
              test = delta1_hat/(sigma1_hat/sqrt(size));
      power1 = cdf('NORMAL',test-za) + cdf('NORMAL',-test-za);
      new_alpha = 2 * (1 - cdf('NORMAL', abs(test)));
             end;
              if cp gt &power then do;
              zone = "Favorable zone";
```

```
            estimate = "Sample size should not be increased";
            size = &n2;
            enroll = ceil(size/(1-&drop));
            test = delta1_hat/(sigma1_hat/sqrt(&n2));
            power1 = cdf('NORMAL',test-za) + cdf('NORMAL',-test-za);
            new_alpha = 2 * (1 - cdf('NORMAL', abs(test)));
            end;
            if cp lt &cp_min then do;
            zone = "Unfavorable zone";
            estimate = "Sample size should not be increased";
            size= &n2;
            enroll = ceil(size/(1-&drop));
            test = delta1_hat/(sigma1_hat/sqrt(&n2));
    power1 = cdf('NORMAL',test-za) + cdf('NORMAL',-test-za);
            new_alpha = 2 * (1 - cdf('NORMAL', abs(test)));
    end;
          output;
          end;
  end;
  keep  mu1_hat sigma1_hat za alpha size enroll zone estimate power1 new_alpha cp;

label
          mu1_hat = "Observed Interim Mean"
          sigma1_hat = "Observed Interim SD"
          za = "Za"
          alpha = "Alpha"
          size = "Re-Estimated Cumulative Final Sample Size"
          enroll = "Re-Estimated Cumulative Final Enrolled Sample Size (To Accommodate Dropout)"
          zone = "Zone"
          estimate = "Decision"
          power1 = "Power"
          new_alpha = "Interim P-Value with this Scenario"
          cp = "Conditional Power";
 run;
%mend;

%simulation(mu0=0.2,cp_min=0.36,power=0.8,n1=50,n2=100,nmax=200,drop=0.33);

/*************************************************************************************************************************
*****
macro for sample size re-estimation based on promising zone: for one sample proportion variables;
p0 = null proportion
p1_hat = observed interim proportion
sigma1_hat = observed interim standard deviation
cp_min = minimum conditional power for promising zone
power = targeted conditional power
n1 = interim sample size
n2 = cumulative final sample size
nmax = pre-specified maximum allowable sample size
drop = estimated attrition
cp =  conditional power
size = re-estimated cumulative final sample size
enroll = total enrollment including dropouts
test = z test value based on new sample size (if required to be increased)
new_alpha = p-value checked based on new n
```

```
*************************************************************************************************************************
***/

%macro psimulation(p0=,cp_min=,power=,n1=,n2=,nmax=,drop=);
  data a_prop;
    length zone $30 estimate $50;
    alpha = 0.05;
    n2_tilde = &n2 - &n1;
           do p1_hat = 0.1 to 0.7 by 0.025;
            sigma1_hat = sqrt(p1_hat*(1-p1_hat));
     za = quantile('NORMAL',1-alpha/2);
     zb = quantile('NORMAL',&power);
     se_delta1_hat = sigma1_hat / sqrt(&n1);
     delta1_hat = p1_hat - &p0;
     z1 = delta1_hat / se_delta1_hat;
     cp_u = 1 - cdf('NORMAL', (za * sqrt(&n2) - z1 * sqrt(&n1)) / sqrt(n2_tilde) - (z1 * sqrt(n2_tilde)) /
sqrt(&n1));
           cp_l = cdf('NORMAL', (-za * sqrt(&n2) - z1 * sqrt(&n1)) / sqrt(n2_tilde) - (z1 * sqrt(n2_tilde)) /
sqrt(&n1));
           cp = cp_u + cp_l;

           /*** conditions to check if value falls within promising zone ***/
           if cp ge &cp_min and cp le &power then do;
            zone = "Promising Zone";
            estimate = "Sample size should be increased";
            n2_tilde_prime  = ceil((&n1 / z1 ** 2) * ((za * sqrt(&n2) - z1 * sqrt(&n1)) / sqrt(&n2 - &n1) + zb) **
2);
     n2_prime = &n1 + n2_tilde_prime;
     size = min(n2_prime, &nmax);
     enroll = ceil(size/(1-&drop));
     test = delta1_hat/(sigma1_hat/sqrt(size));
            power1 = cdf('NORMAL',test-za) + cdf('NORMAL',-test-za);
            new_alpha = 2 * (1 - cdf('NORMAL', abs(test)));
           end;
            else if cp gt &power then do;
            zone = "Favorable zone";
            estimate = "Sample size should not be increased";
            size =&n2;
            enroll = ceil(size/(1-&drop));
            test = delta1_hat/(sigma1_hat/sqrt(&n2));
            power1 = cdf('NORMAL',test-za) + cdf('NORMAL',-test-za);
            new_alpha = 2 * (1 - cdf('NORMAL', abs(test)));
           end;
           else if cp lt &cp_min then do;
            zone = "Unfavorable zone";
            estimate = "Sample size should not be increased";
            size= &n2;
            enroll = ceil(size/(1-&drop));
            test = delta1_hat/(sigma1_hat/sqrt(&n2));
            power1 = cdf('NORMAL',test-za) + cdf('NORMAL',-test-za);
     new_alpha = 2 * (1 - cdf('NORMAL', abs(test)));
           end;
                    output;
    end;
            keep  p1_hat sigma1_hat za alpha size enroll zone estimate power1 new_alpha cp;
```

```
label
        p1_hat = "Observed Interim Proportion"
        sigma1_hat = "Observed Interim SD"
        Za = "Za"
        alpha = "Alpha"
        size = "Re-Estimated Cumulative Final Sample Size"
        enroll = "Re-Estimated Cumulative Final Enrolled Sample Size (To Accommodate Dropout)"
        zone = "Zone"
        estimate = "Decision"
        power1 = "Power"
        new_alpha = "Interim P-value with this Scenario"
        cp = "Conditional Power";
 run;
%mend;

%psimulation(p0=0.4,cp_min=0.36,power=0.8,n1=50,n2=100,nmax=200,drop=0.33)
```