Statistical Analysis Plan (SAP)
SAP Revision: 3.0

Middle Meningeal Artery **EM**bolization for the Treatment of Su**B**du**R**al Hem**A**tomas with TRUFILL® **n**-BCA

Protocol Number: CNV_2020_01
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Su**B**du**R**al Hem**A**tomas with TRUFILL® **n**-BCA

Protocol Version: 4.0

The following individuals have reviewed this version of the Statistical Analysis Plan and are in agreement with the content:

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Revision History

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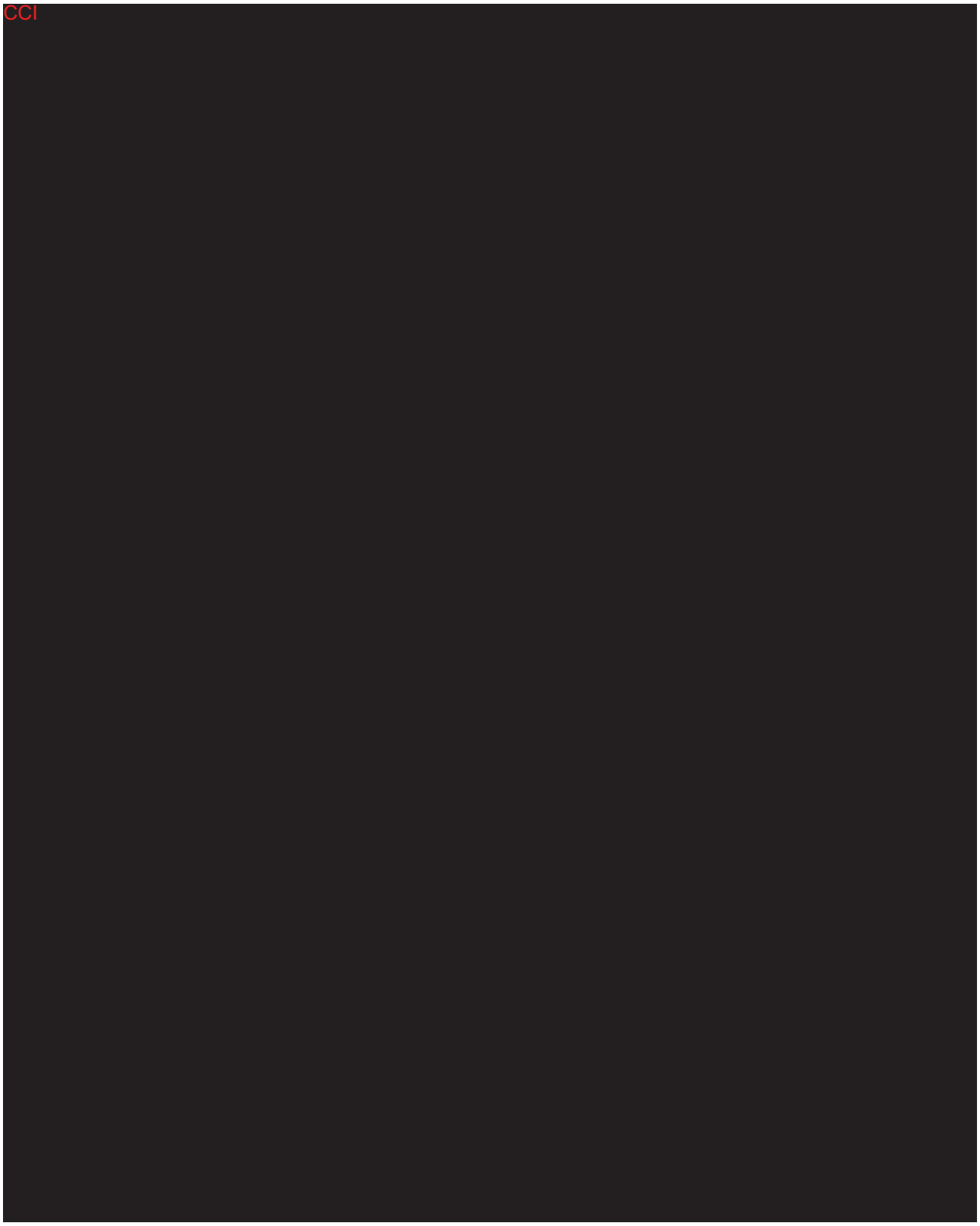

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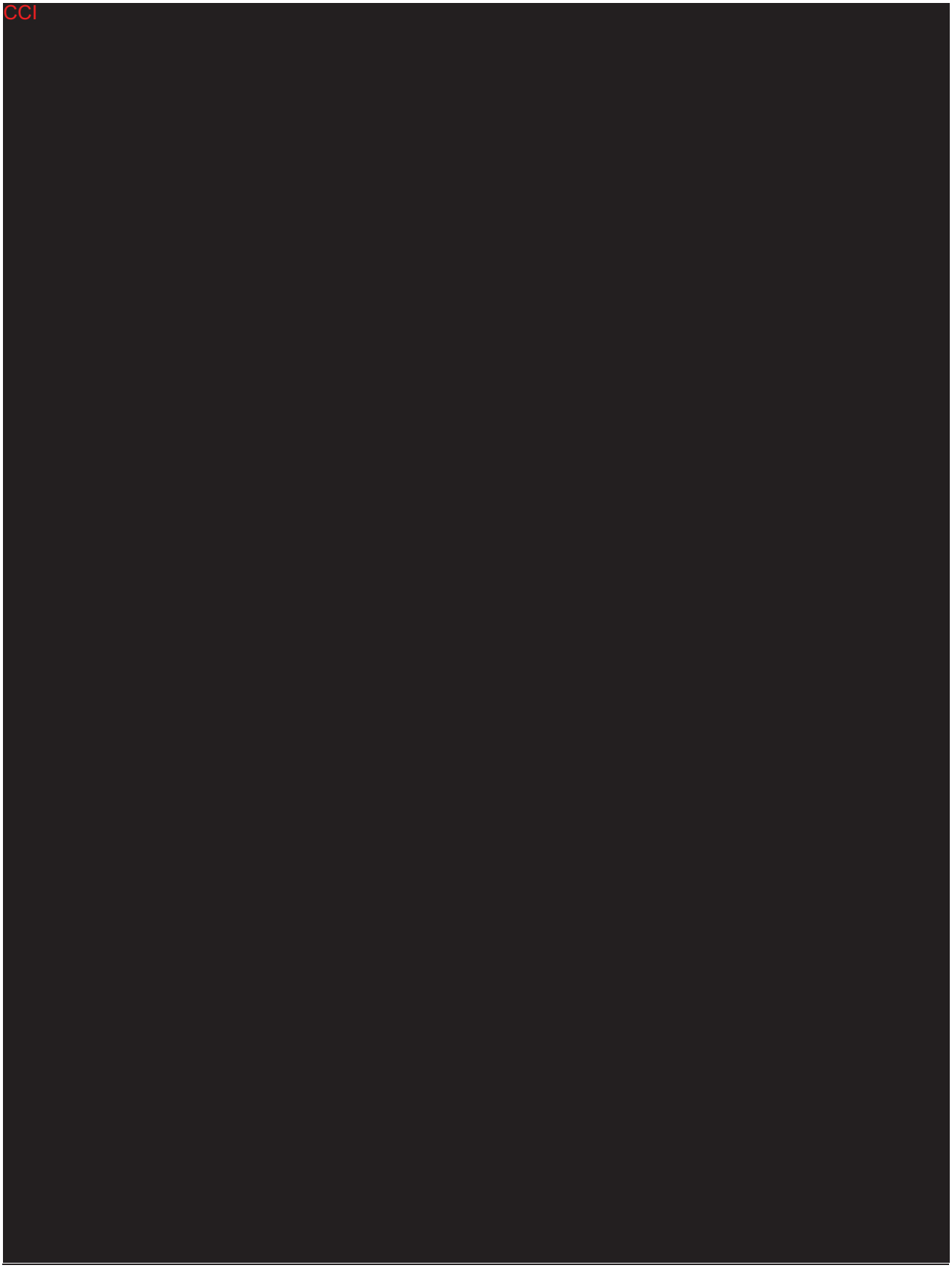


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1 Study Design

This is a prospective, multi-center, open-label, randomized controlled study in which up to 376 subjects will be enrolled and randomized 1:1 to receive standard of care alone or standard of care and TRUFILL n-BCA middle meningeal artery embolization (eMMA) for the treatment of chronic subdural hematoma (cSDH). The study is designed to evaluate the effectiveness and safety of eMMA in two cohorts – a surgical cohort and a non-surgical medical management (NSMM) cohort. Subjects will be followed at 1 month, 3 months, 6 months, and 1 year post-procedure. The primary endpoints will be evaluated at 6 months post-procedure.

2 Treatment Assignment

Subjects presenting with cSDH will be assessed by site physicians to determine whether the subject will undergo either surgery or NSMM. Once assigned to the cohort, subjects will be randomized.

- Surgical cohort

Eligible subjects will be randomized 1:1 after surgery to surgery + eMMA or surgery alone. Subjects randomized to surgery alone will follow standard of care (SOC) by site and receive no further intervention. “Standard of care” is defined as the best care for the individual subject including guideline-based care where clinical guidelines are available. Subjects randomized to surgery alone CANNOT undergo eMMA during the follow up period (i.e., no crossover).

- NSMM cohort

Eligible subjects will be randomized 1:1 to NSMM + eMMA or NSMM alone. Subjects randomized to NSMM alone CANNOT undergo eMMA during the follow up period (i.e., no crossover).

3 Randomization and Blinding Procedures

This is an open label study, subjects and treating physicians will not be masked to treatment assignment. Subjects presenting with a subdural hematoma will be assessed by site physicians to determine the appropriate treatment for each subject: surgical or NSMM, which thereby defines the cohort. Eligible subjects will then be randomized 1:1 to undergo SOC with eMMA vs SOC alone within each cohort. Randomization will be stratified by site within each cohort. Randomization will be assigned in permuted blocks within the site, and sites will not be aware of block sizes.

The Sponsor will remain blinded to summary outcomes by treatment until primary endpoint analyses.

Independent assessment of modified Rankin Score (mRS) and Markwalder Grading Scale (MGS) at 3, 6 and 12 months will be performed by a qualified independent evaluator who is not part of the interventional (embolization) treating team and not involved in patient care or data entry and is blinded to study treatment assignment.

4 Interval Windows

Study reports will be summarized by scheduled visits (as defined in Protocol Section 7), except for the following visit:

- 6 month follow-up (±45 days)

The study schedule is to be adhered to as closely as possible for all subjects. Measurements outside the interval windows will be treated as missing. In the case of repeated measurements taken at the same visit, the most recent non-missing measurement will be used unless specified otherwise.

5 Levels of Significance

The primary effectiveness endpoint will be tested at a one-sided significance level of 5%. Secondary endpoints will be tested using a gatekeeping strategy only if the primary effectiveness endpoint is successful. The familywise error-rate for hypotheses tests intended for labeling will therefore be controlled at 5%.

6 Analysis Sets

The following analysis sets are defined for this study:

- Intent-to-Treat (ITT) Analysis Set

The ITT analysis set consists of all enrolled subjects who are randomized in the study. Subjects will be analyzed as randomized regardless of treatment received.

A subject is considered enrolled in the study upon signing the informed consent form.

- Per Protocol (PP) Analysis Set

The PP analysis set is a subset of the ITT analysis set, excluding subjects with significant eligibility deviations, those who did not receive treatment as assigned and other major protocol deviations. Significant eligibility deviations and major protocol deviations may go to the physician Steering Committee for final decision. All subjects excluded from the PP analysis set will be documented in a separate listing with associated reason(s) before the final analyses take place.

- As Treated Analysis Set

The As Treated analysis set consists of all randomized subjects in the study who receive study treatment. Subjects will be analyzed by actual treatment they received.

Treatment with eMMA is defined as the injection of n-BCA into a blood vessel beyond the tip of microcatheter during index procedure.

Subjects randomized to treatment with eMMA, but who do not receive n-BCA as defined above and followed the standard of care regimen, will be analyzed in the control group, either surgery alone or NSMM alone based on cohort membership. If they received non n-BCA during the study follow-up beyond 10 days post

randomization or surgery, their data after the date of their embolic treatment will be excluded from the randomized treatment in the summary tables. Subjects randomized to treatment with eMMA, but who received non n-BCA instead of study embolic agent (n-BCA) within 10 days post randomization or surgery, will be excluded from the As Treated Analysis Set entirely. However, these subjects will be listed separately.

Subjects randomized to treatment without eMMA (SOC) are considered treated by their randomization assignment unless they received study embolic agent (n-BCA). If they received study embolic treatment within 10 days post randomization or surgery, they will be analyzed under surgery + eMMA or NSMM + eMMA based on cohort membership. If they received embolic treatment (n-BCA or non n-BCA) during the study follow-up beyond 10 days post randomization or surgery, their data after the date of their embolic treatment will be excluded from the randomized treatment in the summary tables. Subjects randomized to SOC, but who received non n-BCA within 10 days post randomization or surgery, will be excluded from the As Treated Analysis Set entirely, but listed separately.

7 Sample Size Justification

Cochran–Mantel–Haenszel (CMH) statistic will be used to test superiority in the primary effectiveness endpoint of SOC with eMMA over SOC alone. The CMH test will be performed with stratification by cohort (surgical vs. NSMM). A target of approximately up to 70% of subjects are expected to be allocated to the surgical cohort and the remaining subjects will be allocated to NSMM cohort. Subjects within each cohort will be randomized 1:1 to SOC alone or SOC with eMMA. Assuming a common odds ratio (Agresti, 1990) of 0.34, a total sample size of 376 subjects after accounting for 10% attrition will provide at least 80% power for the primary effectiveness endpoint at a one-sided significance level of 0.05.

Anticipated effectiveness rates for the primary effectiveness endpoint were derived from the literature (key articles include Rovlias et al., 2015; Kim, 2017; Brennan et al., 2017; Ban et al., 2018; Knopman et al., 2018; Fountas et al., 2019; Link et al., 2019; Shotar et al., 2020; Ng et al., 2020). The assumptions in Tables 1 and 2 below reflect the consensus of the Executive Steering Committee for the study.

For the secondary endpoint that evaluates a component of the primary effectiveness endpoint later in time (12 months), it is anticipated that the effect size will be at least as large for the primary effectiveness endpoint assessment.

Table 1 – Assumptions of event probability of primary effectiveness endpoint in surgical cohort

	SOC with eMMA	SOC alone
Event-free (success) probability	95.9%	88.5%
Event (failure) probability	4.1%	11.5%
Odds ratio	0.33	

Note: Odds ratio is calculated as the ratio of odds of failure over success in SOC with eMMA versus the odds of SOC alone.

Table 2 - Assumptions of event probability of primary effectiveness endpoint in NSMM cohort

	SOC with eMMA	SOC alone
Event-free (success) probability	90.9%	78.0%
Event (failure) probability	9.1%	22.0%
Odds ratio	0.35	

Note: Odds ratio is calculated as the ratio of odds of failure over success in SOC with eMMA versus the odds of SOC alone.

For the primary safety endpoint, we expect at least an 80% probability of observing adverse events (AEs) that occur at an incidence of at least 1% within each treatment group. This expectation pertains to approximately 188 participants receiving eMMA (surgery + eMMA and NSMM + eMMA) and 188 participants receiving standard of care (surgery alone and NSMM alone).

R code used to perform sample size calculations is included in the Appendix I.

8 Analyses to be Conducted

8.1 General Conventions

Unless indicated otherwise, summaries will be presented by treatment within each cohort.

The number of observations with data, the number of observations with missing data, mean, standard deviation, median, first quartile (Q1), third quartile (Q3), minimum and maximum will be provided for continuous data; and the number and percentage will be provided for categorical data. Percentages will be based on the number of subjects with non-missing data, unless specified otherwise.

All statistical analyses will be performed using SAS®, Version 9.4 or later, unless otherwise noted.

- Study Day

Study day will be calculated as the difference between the assessment date and reference date, i.e., assessment date - reference date.

According to the schedule of assessments in the protocol, study visits, visit-based assessments (e.g., CT scans/imaging, questionnaires etc.) will have the reference date be based on the date of index embolization procedure (or Day 0 phone/in person follow-up) to calculate study days. Specifically, the reference date is defined as follows by cohort and treatment.

- Surgery + eMMA (surgical cohort) and NSMM + eMMA (NSMM cohort)

The reference date is defined as the date of eMMA index procedure (Day 0).

- Surgery alone (surgical cohort)

The reference date is defined as the date of Day 0 visit. In the event Day 0 is missing due to reasons such as a subject is not discharged or cannot be contacted within 10 days of surgery, the date of Day 0 will be 10 days post-surgery.

- NSMM alone (NSMM cohort)

The reference date is defined as the date of Day 0 visit. In the event Day 0 is missing due to reasons such as a subject cannot be contacted within 10 days of randomization, the date of Day 0 will be 10 days post randomization.

Unless specified otherwise, study days will be calculated with respect to Day 0. However, safety evaluations will have the reference date be based on the date of randomization.

- Baseline

Unless specified otherwise, the last non-missing measurement/imaging collected prior to randomization is considered as baseline. In the rare event that a subject (only applicable to subjects in surgical cohort) is randomized prior to the initial surgery (prior to Day 0), then the last non-missing measurement/imaging prior to Day 0 (on or after randomization) will be used as the baseline.

- Imaging data per Independent Core Lab

For categorical responses, the majority (yes/no) response will be used (i.e., if two Imaging Core Lab assessor values, the responses are the same; if three Imaging Core Lab assessor values, then the same response from two), unless a final reading from the consensus meeting is otherwise available.

For continuous data, the % difference will be calculated on the relative scale with respect to the average measurement using the following formula:

$$\% \text{ Difference} = \frac{|Measurement\ 1 - Measurement\ 2|}{Average\ (Measurement\ 1,\ \ Measurement\ 2)}\ x\ 100$$

If the first two readings are not within 5% difference, a third read will be required to resolve the discrepancy. If the third reader is not within 5% difference of either of the initial two readers, then a consensus meeting will be called to resolve the discrepancy.

Therefore, an average will be taken from the readings if the differences are within the 5% from the imaging core lab for analysis, unless a final reading from the consensus meeting is otherwise available.

In a rare case where the third reading is called and more than 1 pair of readings within 5% difference exists for a certain assessment, then the two readings of a larger % difference will be used.

In a rare case where the third reading is called and all pairwise differences of the 3 readings are within 5% difference, then the average of all three readings will be used for analysis.

- 6-month study endpoint analyses

For analysis purposes of study endpoints at 6 months, the 6-month data snapshot will include all subject data up to the last date of the following (i.e., cutoff date):

- 6-month clinical visit,
- 6-month CT,
- Possible re-treatment within the 6-month follow-up window; including re-operations or surgical procedure post randomization or unplanned embolic treatment, should there be any.

All data included in the 6-month data snapshot will be cleaned and monitored. All data will also be frozen prior to submission, except events ongoing (adverse event end date, adverse event resolution, discharge status, discharge date, concomitant medication end date) at the time of data cutoff. At the end of study, all cumulative data will be summarized after the database lock.

8.2 Disposition of Study Subjects

The number and percentage of subjects in each analysis set will be provided, together with a summary of study completion or discontinuation status with associated reasons. A flow chart describing the study disposition status will be provided as well.

Enrollment by site will be summarized for all enrolled subjects by analysis set. A summary of screen failures will be provided for each cohort by screen failure reason.

8.3 Demographic and Baseline Characteristics

Demographic profiles and baseline characteristics will be summarized by cohort and treatment for each analysis set, including but not limited to:

- Demographics: age (years), gender, ethnicity, race.
- Medical history: number of subjects with at least one medical history, and by type of historical events (e.g., brain atrophy, cardia arrhythmia etc.)
- Target subdural hematoma characteristics: symptoms associated with SDH, and location (parietal, frontal, occipital etc.) of target SDH.
- Baseline score via neurological and cognitive questionnaires, Markwalder Grading Scale (MGS), Glasgow Coma Scale (GCS) score, modified Rankin Score (mRS), Mini-Mental State Exam (MMSE) score, Quality of Life (EQ-5D-5L) score.

8.4 Medications and Medical Management Prescribed for cSDH

Medications and medical management will be summarized descriptively by cohort and treatment for each analysis set. Relevant data in the CRF will be listed as well.

- Medications

Medications that ended prior to date of randomization are considered as prior medications; otherwise they are considered as concomitant medications. Medications

with missing or incomplete end dates leading to unclear classifications are considered as concomitant medications.

Unless specified otherwise, only antithrombotic medications (e.g., antiplatelet, anticoagulant, fibrinolytics), statins, steroids and antiepileptic drugs will be summarized in the study. These medications of interest will be summarized as frequencies and percentages in the following categories.

- All medications
- All medications for medical management of cSDH
- Concomitant medications used during embolization procedure, excluding anesthesia

Missing medication dates will be imputed as follows:

- If a medication end date has year and month, without a day, it will be imputed as the earlier date of the following: last day of that month, or date of end of the study.

Compliance (%) will be summarized for each medication type as follows: percentage of subjects who completed regimen out of subjects who were prescribed with this medication.

All other types of medications collected per the clinical protocol (i.e., medications used during the study embolization procedure, medications to treat AEs) will be provided in listings.

- Medical management

The number and percentage of subjects will be summarized by the type of medical management they received.

- Concomitant procedures related to cSDH during study: by surgery type of percutaneous endoscopic gastrostomy, tracheostomy, shunt etc.
- Other medical management prescribed by type, e.g., ambulatory assistance, lifestyle modification etc.
- Compliance of medical management

  Compliance to the instructions of medical management from their study doctors will be summarized as frequencies and percentages based on subject report at each study visit.

8.5 Procedure Characteristics

Procedural data will be summarized by cohort and treatment for each analysis set, including but not limited to reason of procedure, procedural duration, anesthesia type, type of adjunctive devices, embolization technique, bilateral injection, ratios of Trufill system components used, etc. as reported from the site.

Procedure data evaluated by the core lab will also be summarized by cohort and treatment for each analysis set, including but not limited to injection location, distal penetration, reflux occurrence, etc.

8.6 Primary and Secondary Endpoints and Associated Hypotheses

8.6.1 Primary Effectiveness Endpoint and Associated Hypotheses

- **Residual or re-accumulation of the cSDH (>10 mm) at 6 months as assessed by an independent core laboratory OR re-operation or surgical procedure on the cSDH within 6 months post randomization**

  The primary effectiveness endpoint analysis will be conducted using the 6-month data snapshot in section 8.1 of general conventions, on the ITT analysis set. The same analysis will be repeated using the As Treated and PP analysis sets as supportive analyses.

  The null and alternative hypotheses for this endpoint are

  $$H_0: \theta_{CMH} \geq 1$$

  $$H_A: \theta_{CMH} < 1$$

  Where θ_{CMH} is the common odds ratio for primary effectiveness endpoint failure. Continuity corrected CMH test with stratification by cohort (surgical or NSMM) will be used to test the primary effectiveness endpoint at a one-sided significance level of 5%.

  The size of residual or re-accumulation of cSDH at 6 months will be assessed in terms of hematoma thickness per independent core lab. Subjects are considered as primary effectiveness endpoint failures if they have reported any of the following events:

  - Residual or re-accumulation of the cSDH (>10mm) at 6 months as assessed by the independent Imaging Core Lab.
  - Any re-operations or surgical procedures post randomization, as reported by the site, within 6-month follow-up window.

    In the rare event that a subject is randomized before the initial surgery procedure (only applicable to subjects in surgical cohort), the initial surgery (prior to Day 0) will not be considered as a re-operation for that subject.
  - Unplanned embolic treatment (n-BCA or non n-BCA) other than index procedure purpose prior to 6-month follow-up window.
  - Subjects with missing hematoma thickness at 6 months due to death prior to 6-month CT scan and the death is adjudicated by the CEC as due to study device related or due to the underlying disease state (i.e., lack of efficacy of study treatment).

Subjects who didn't satisfy above reasons, but with missing values on the primary effectiveness endpoint, will be imputed using multiple imputation, details are specified in section 8.7.

Event days are based on Day 0, however, re-operations or surgical procedures since randomization up till 6 months will all be counted towards events.

Estimates from the combined estimates across multiple imputed datasets will be reported. The number and percentage of subjects with events will be summarized by treatment and cohort. In addition, subjects of primary effectiveness failures will be summarized by reason (e.g., due to re-operations, hematoma thickness >10mm etc.). Estimates of odds ratio and associated two-sided 90% Wald confidence intervals will be presented for each cohort. The common odds ratio by Mantel-Haenszel method, corresponding two-sided 90% confidence interval, and p-value from continuity corrected CMH test will be presented as well. Odds ratios and the common odds ratio are both defined as the ratio of the odds of event (failure) probability to event-free (success) probability in subjects with eMMA (yes vs. no).

The study will be considered successful if the one-sided p-value from the combined estimate of the continuity corrected CMH test is significant at the 0.05 significance level.

All relevant data including hematoma thickness and subjects who received at least one re-operation or surgical procedure post-randomization will be listed. Subjects who failed the primary effectiveness endpoint will also be listed by reason.

8.6.2 Primary Safety Endpoint

- **Occurrence of all adverse events (AEs) through 6 months**

  All AEs through 6 months will be summarized descriptively using the As Treated analysis set in treatment with eMMA (surgery + eMMA and NSMM + eMMA) vs. treatment with SOC (surgery alone and NSMM alone). The same analysis will be repeated using the ITT and PP analysis sets as supportive analyses.

8.6.3 Secondary Endpoints and Associated Hypotheses

Hypothesis tests of secondary endpoints will be performed in a gatekeeping fashion and in the following order, only if the preceding null hypothesis is rejected. These hypotheses will be analyzed in the ITT analysis set.

1. **Good functional outcome at 3 months (mRS 0-2 or no worsening from baseline if baseline mRS ≥ 3)**

   The null and alternative hypotheses for the non-inferiority test on this endpoint are

   $$H_0: P_{SOC+eMMA} - P_{SOC} \leq -12\%$$
   $$H_A: P_{SOC+eMMA} - P_{SOC} > -12\%$$

where $P_{SOC+eMMA}$ and P_{SOC} are the proportions of success in subjects who reported good functional outcome at 3 months in the treatment of SOC+eMMA and SOC alone (across both cohorts), respectively. A subject is considered as success for this endpoint if mRS is 0-2 at 3 months, or there is no worsening from baseline mRS if their baseline mRS is ≥ 3.

Subjects with missing mRS scores due to death prior to 3 months will be considered to have a score of 6 in the analysis. Subjects with missing data at 3 months due to reasons other than death will be imputed with multiple imputation, details are specified in section 8.7. The risk difference between treatments for each imputed dataset will then be combined using Rubin's rule (1987). The combined estimate of the risk difference and corresponding two-sided 90% confidence interval will be reported.

The null hypothesis will be rejected if the one-sided 95% lower confidence bound of the combined estimate of the risk difference based on *t*-statistic is greater than -12%.

2. Subjects requiring a surgical procedure on the cSDH within 12 months

The null and alternative hypotheses for the superiority test on this endpoint are

$$H_0: \theta_{CMH \cdot sp} \geq 1$$

$$H_A: \theta_{CMH \cdot sp} < 1$$

where $\theta_{CMH \cdot sp}$ is the common odds ratio for surgical procedure endpoint failure. Continuity corrected CMH test with stratification by cohort (surgical vs. NSMM) at a one-sided significance level of 5% will be performed.

Subjects are considered as surgical procedure endpoint failures if they have reported any of the following events:

- Any re-operations or surgical procedures on the cSDH post randomization, as reported by the site, within 12-month follow-up window.

  In the rare event that a subject is randomized before the initial surgery procedure (only applicable to subjects in surgical cohort), the initial surgery, although post-randomization, will not be considered as a re-operation for that subject.
- Subjects of death within 12-month follow-up window and the death is adjudicated by the CEC as due to study device related or due to the underlying disease state (i.e., lack of efficacy of study treatment).

Event days are based on Day 0, however, re-operations or surgical procedures since randomization up till 12 months will all be counted towards events.

Subjects with unknown status on this endpoint due to death (or other than specified above) or early discontinuation from the study prior to 12-month follow-up window will be imputed using multiple imputation, details are specified in section 8.7.

Estimates from the combined estimates across multiple imputed datasets will be reported. The number and percentage of subjects with events (e.g., at least one

re-operation or surgical procedure post randomization) will be summarized by treatment and cohort. Estimates of odds ratio and associated two-sided 90% Wald confidence intervals will be presented for each cohort. The common odds ratio by Mantel-Haenszel method, corresponding two-sided 90% confidence interval and p-value from continuity corrected CMH test will be presented. The odds ratio and the common odds ratio are both defined as the ratio of the odds of event (failure) probability to event-free (success) probability in subjects with eMMA (yes vs. no).

The endpoint will be considered successful if the one-sided p-value from the combined estimate of the continuity corrected CMH test is less than at the 0.05. Subjects with at least one re-operation or surgical procedure since randomization will all be listed.

3. **Mean change in hematoma volume at 6 months compared to baseline as assessed by an independent core laboratory**

The null and alternative hypotheses for this endpoint are

$$H_0: \Delta \geq 0$$

$$H_A: \Delta < 0$$

where $\Delta = \mu_{SOC+eMMA} - \mu_{SOC}$ is the difference in mean change of hematoma volume (ABC/2 volume) at 6 months compared to baseline in subjects with SOC + eMMA vs. SOC alone. $\mu_{SOC+eMMA}$ is the mean change of hematoma volume at 6 months compared to baseline in SOC + eMMA (6-month volume – baseline volume); while μ_{SOC} similarly is the mean change of hematoma volume at 6 months compared to baseline with SOC alone. Identification of baseline imaging refers to 'baseline' considerations in section 8.1 of general conventions.

ANOVA (analysis of variance) will be performed to test this secondary endpoint. Change in hematoma volume at 6 months is the outcome variable. Main effects of cohort (surgical vs. NSMM), treatment (SOC + eMMA vs. SOC alone) and treatment by cohort interaction will be included in the model. Subjects with missing values of hematoma volume at baseline or 6 months will be imputed according to the strategy described in section 8.7. The ANOVA will be applied on each of these imputed datasets. The least square mean (LSMEAN) difference between treatments, standard error and corresponding two-sided 90% confidence interval from each imputed dataset will then be combined using Rubin's rule (1987) and reported.

The null hypothesis will be rejected if the one-sided combined estimate of 95% upper confidence bound on Δ is less than 0.

Hematoma volume and change from baseline at 6-month will be summarized by treatment and cohort. The imputed outcome will be included into the summary. All relevant data on hematoma volumes will be listed.

8.6.4 Other Secondary Endpoint Analyses

The remaining secondary endpoints are descriptive based on observed data.

For time to event endpoints, stratified Kaplan-Meier analyses (using product limit estimates) by treatment and cohort will be performed. Kaplan-Meier cumulative incidence rate and the corresponding two-sided 90% confidence intervals using log-log transformation will be reported, the estimate of standard error will be computed using Greenwood's formula. The cumulative incidence rate will be calculated as 1- survival rate at the specific timepoint of interest. The cumulative incidence rate will be reported at 90 days (i.e., for 3-month rate); 183 days (for 6-month rate) and 365 days (for 12-month rate) for respective timepoint of interest.

8.6.4.1. Other Secondary Endpoint Analyses – Effectiveness

Secondary effectiveness endpoints will be summarized by the planned treatment and cohort using the ITT. The supportive analyses will be using the PP analysis set. Only observed values will be included into the analysis, no missing data imputation will be performed. Identification of baseline imaging refers to 'baseline' considerations in section 8.1 of general conventions.

1. **Mean change in hematoma volume at 3 and 12 months compared to baseline as assessed by an independent core laboratory**

   Mean hematoma volume (ABC/2 volume) and change from baseline will be summarized at 3 and 12 months by treatment and cohort.

2. **Reduction of >50% hematoma volume at 3, 6 and 12 months as assessed by an independent core laboratory**

   Logistic regression will be used to analyze the proportion for reduction of >50% in hematoma volume (ABC/2 volume) at 3, 6 and 12 months. Subjects with missing values on the reduction of hematoma volume will be excluded from analysis. Reduction of hematoma volume in percentage will be calculated as follows,

$$Reduction\ (\%) = \frac{Post\_baseline\ volume - Baseline\ volume}{Baseline\ volume} \times 100\%$$

   Then reduction in percentage will be dichotomized into a binary variable based on a cutoff of 50% (yes if reduction >50%; no otherwise).

   To analyze the data at 3-month, reduction >50% (yes vs. no) at 3-month will be treated as the outcome variable. The logistic regression model will include treatment (SOC + eMMA vs. SOC alone) as the main effect, and baseline hematoma volume as a covariate. The same logistic regression model will be repeated for each cohort.

   The proportion of reduction >50% with associated 90% confidence interval at 3 months at the mean baseline volume within each cohort, will then be estimated from the model and summarized by treatment and cohort.

The same logistic regression will be repeated for other timepoints, where the reduction >50% (yes vs. no) at 6 and 12 months will be treated as the outcome variable, respectively. The proportion of reduction >50% at 6 and 12 months will then be summarized by treatment and cohort in a similar fashion.

The same logistic model will be applied to get the estimate of odds ratio of reduction >50% in hematoma volume in subjects treated with SOC + eMMA vs. SOC alone, together with 90% Wald confidence intervals by cohort at each time point of interest.

All hematoma volumes, change (%) from baseline and flags if reduction >50% will be listed.

3. **Complete resolution of the cSDH at 3, 6 and 12 months assessed by an independent core laboratory**

   Logistic regression will be used to report the proportion of complete resolution at 3, 6 and 12 months. Complete resolution (yes vs. no) will be treated as the outcome variable. The model will include treatment (SOC + eMMA vs. SOC alone) as the main effect. The same logistic regression model will be repeated for each cohort. The odds ratio of complete resolution in subjects with SOC + eMMA vs. SOC alone with corresponding 90% Wald confidence intervals at 3-month, 6-month and 12-month will be estimated for each cohort.

   Subjects with or without complete resolution will all be listed, together with their last follow-up days in the study and end of study status (completed or discontinued by reason).

4. **Median time to achieve complete resolution of the cSDH**

   A GEE (generalized estimating equation) model with log link function will be fit to the data. The model will include complete resolution of cSDH (yes vs. no) as outcome, treatment (SOC + eMMA vs. SOC alone)as the main effect, and time to complete resolution (in days, since Day 0) as a covariate. Exchangeability will be assumed for the working correlation matrix. The same logistic regression model will be repeated for each cohort.

   Median time (days) to achieve complete resolution of the cSDH will be obtained by inverse prediction at the proportion of 0.50 for each treatment and cohort.

5. **Subjects that develop an acute component of their existing cSDH or a new cSDH at 3, 6 and 12 months as assessed by an independent core laboratory**

   Stratified Kaplan-Meier analyses by treatment and cohort will be used to summarize the cumulative incidence of event rate. Development of an acute component of existing cSDH or a new cSDH is considered as a composite endpoint; and the event date is the date of first event of any component (development of acute component of an existing cSDH or a new cSDH). Event days and survival days will be calculated with respect to Day 0. Subjects without events will be censored at the date of last study follow-up. The cumulative incidence rate at 3, 6 and 12 months will be reported with associated two-sided 90% confidence intervals.

Subject status on cSDH by time will all be listed.

6. **Subjects requiring a surgical procedure on the cSDH within 3 and 6 months post randomization**

   Stratified Kaplan-Meier analyses by treatment and cohort will be used to summarize the cumulative incidence of event rate. The earliest occurrence is defined as the event, which includes re-operation or surgical procedure on the cSDH post randomization (excluding unplanned embolic treatment other than index procedure). And the event date is the date of first event. Subjects without events will be censored at the date of last study follow-up. Event days and survival days will be calculated with respect to the date of randomization. The cumulative incidence rate at 3 and 6 months will be reported with associated two-sided 90% confidence intervals.

   In the rare event that a subject is randomized before the initial surgery procedure (only applicable to subjects in surgical cohort), the initial surgery, although post-randomization, will not be considered as a re-operation for that subject.

   Subjects who received at least one event post-randomization will be listed.

7. **Subjects requiring greater than one surgery on the cSDH within 3, 6 and 12 months post randomization**

   The number and percentage of subjects who require greater than one (i.e., two or more) event of re-operations, surgical procedures on the cSDH post-randomization (excluding unplanned embolic treatment other than index procedure) within 3, 6 and 12 months will be summarized by treatment and cohort. Event days are based on Day 0, however, any event since randomization up to 12 months will be counted.

   In the rare event that a subject is randomized before the initial surgery procedure (only applicable to subjects in surgical cohort), the initial surgery, although post-randomization, will not be considered as a re-operation for that subject. The odds ratio of receiving more than one surgery (yes vs. no) in subjects with SOC + eMMA vs. SOC alone will be summarized by cohort, with associated two-sided 90% exact confidence intervals.

8.6.4.2. Other Secondary Endpoint Analysis – Safety

Secondary safety endpoints will be summarized using As Treated analysis set, supportive analyses will be based on ITT and PP analysis sets. Analyses under As Treated analysis set for subjects who received unplanned embolic treatment (n-BCA or non n-BCA) other than randomization assignment, assessments post the date of embolic treatment will be excluded from summary tables; but their all-visit data will be listed separately.

1. **mRS Distribution change in mRS Score at 3, 6 and 12 months**

   A shift table describing the change from baseline at 3, 6 and 12 months will be summarized. Subjects with missing mRS scores post-baseline due to all-cause

death will have a score of 6 in the analysis, subjects with missing mRS scores due to reasons other than all-cause death will be excluded from the analysis.

All mRS data will be listed by visit.

2. **Death, stroke, myocardial infarction or thromboembolic complications within 3, 6 and 12 months as assessed by the Clinical Events Committee**

   Death, stroke, myocardial infarction (MI), thromboembolic complications are considered as a composite endpoint, where death is based on site reported data and others are based on the assessments from CEC.

   Stratified Kaplan-Meier analyses by treatment and cohort will be performed to summarize the cumulative incidence of the event rate.

   Incidence of any events as defined within this composite endpoint is considered as the event of interest, and the event date is the date of the first event of any component. Subjects without any events will be censored at the date of last study follow-up. Subjects from SOC (i.e., surgery alone or NSMM alone) without events, but received unplanned embolic treatment beyond 10 days post randomization or surgery, will be censored at the date of embolic treatment under randomization assignment in the As Treated analysis set.

   Event days and survival days will be calculated with respect to the date of randomization. The Kaplan-Meier cumulative incidence rates at 3, 6 and 12 months will be reported with associated two-sided 90% confidence intervals.

   All relevant subject data satisfying this composite endpoint will be listed.

3. **Development of new onset of seizures within 3, 6 and 12 months as assessed by the Clinical Events Committee**

   Stratified Kaplan-Meier analyses by treatment and cohort will be performed to summarize the cumulative incidence of the event rate.

   New onset of seizures are considered as events; and the event date is date of the first onset of such events. Subjects without events will be censored at the date of last study follow-up. Subjects from SOC (i.e., surgery alone or NSMM alone) without events, but received unplanned embolic treatment beyond 10 days post randomization or surgery, will be censored at the date of embolic treatment under randomization assignment in the As Treated analysis set.

   Event days and survival days will be calculated with respect to the date of randomization. The Kaplan-Meier cumulative incidence rates at 3, 6 and 12 months will be reported with associated two-sided 90% confidence intervals.

   Subjects with at least one event will all be listed.

4. **Change in Markwalder Grading Scale (MGS) at 3, 6 and 12 months compared to baseline**

   A shift table describing the change from baseline to 3, 6 and 12 months will be summarized. Subjects with missing scores will be excluded from analysis.

MGS scores by visit and changes from baseline will all be listed.

5. **Change in MMSE Score at 6 months compared to baseline**

   MMSE scores will be categorized as severe cognitive impairment (MMSE score between 0-17), mild impairment (MMSE score between 18-23), and normal (MMSE score between 24-30). A shift table describing the change (shift in above categories) from baseline to 6 months will be presented. Subjects with missing scores will be excluded from analysis.

   MMSE scores and changes from baseline will all be listed.

8.6.4.3. Other Secondary Endpoint Analyses – Health Economics

1. **Hospital days and ICU days**

   Hospitalization data will be summarized using the PP analysis set.

   If discharge date is missing or incomplete so that the calculation of length of stay (LOS) cannot be performed, then the discharge date will be imputed per the algorithm in section 8.7, additional missing data will be excluded from LOS calculation.

   LOS will be calculated as follows,

   - LOS (days) = date of discharge – date of admission + 1

   Total LOS and LOS at ICU of hospitalizations for index procedure will be summarized by cohort. Discharge location will be summarized in subjects discharged alive from eMMA index procedure. The number of subjects who died during index procedure will be noted separately.

   All-cause hospitalizations during follow-up will be summarized separately by treatment arm and cohort. The number of all-cause hospitalizations (including hospitalizations without discharge due to death or early withdrawal), the number and percentage of subjects who received at least one hospitalization, and the maximum LOS per subject will be summarized separately. The maximum LOS is taken to be the longest stay across all-cause hospitalizations during follow-up at the subject level.

2. **Change in EuroQol 5-dimension 5-level (EQ-5D-5L) score at 6 months compared to baseline**

   EQ-5D-5L observed total heath score at baseline and change from baseline at 6 months will be summarized by treatment and cohort.

8.6.5 Additional Safety Analyses – Adverse Events (AEs)

AEs will be summarized, by treatment and cohort in As Treated analysis set.

All AEs collected in the study since randomization will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number of events, the number

and percentage of subjects with at least one AE will be summarized overall and by following category. CEC adjudicated data will be presented whenever available.

- All AEs
- Serious AEs (SAEs)
- Study device and/or eMMA procedure (with n-BCA) related AEs (composite)
- Study device related AEs
- eMMA procedure (with n-BCA) related AEs
- SDH medication related AEs
- Surgical procedure on SDH related AEs
- AEs by severity
- AEs by outcome
- Unanticipated adverse device effects (UADEs)

8.7 Handling of Missing Data

Missing data for the primary and secondary endpoints with hypothesis tests will be imputed using multiple imputation. Unless specified otherwise, multiple imputation will be implemented within each treatment and cohort.

- Primary analysis for the primary effectiveness endpoint: missing data of primary effectiveness endpoint either due to subdural hematoma thickness at 6 months or unknown status on re-operations or surgical procedures on the cSDH within 6 months

  Step 1 Auxiliary variables for multiple imputation:

  Subject treatment (with or without eMMA procedure), cohort (surgical or NSMM cohorts), and hematoma thickness at baseline and post-baseline visits from the independent core lab, will be included into data imputation. Additional auxiliary (predictor) variables will be identified using the following method.

  To examine the association of the predictor with the outcome variable (binary success or failure), a logistic regression modeling will be performed, a p-value < 0.1 from the Wald test or Likelihood Ratio test will be used to indicate if the predictor is associated with the outcome, thus, to be included as an auxiliary variable into the multiple imputation for this endpoint.

  - For continuous predictors, the predictor will be categorized into four categories based on quartiles. Three indicator variables corresponding to the highest quartiles will be used in the model. A Wald test or Likelihood Ratio test will be used to assess the statistical significance of the association between the predictor and the outcome comparing the model with the three indicators to a reduced version of the model excluding the indicators.

- For binary predictors, the model will include a single indicator variable for the predictors. Similar to the models for continuous predictors a Wald test or Likelihood Ratio test will be used to assess association between the predictor and the outcome by comparing to a reduced model that excludes the indicator variable for the predictor.
- For categorical predictors with more than two categories, in cases where the categorical variable has 3-4 categories with sufficient data in each category, indicator variables will be created for each category and the lowest category will be left out of the model as the reference group. In cases where the number of categories is greater than 4, either quartiles will be used to divide the predictor into 4 categories similar to the continuous case, or a categorization based on clinically meaningful cut-offs will be used. As before, a Wald test or Likelihood Ratio test will be used to assess the association of each predictor with the outcome.

Step 2 Data generation stage:

Assuming an arbitrary data missing pattern, a fully conditional specification (FCS) logistic regression method (for classification variables) will be used to impute the missing values for the primary effectiveness endpoint (success or failure) at 6 months. Auxiliary variables identified above will be included into data imputation.

Five imputed datasets (M=5) will be generated using a pre-specified seed number. The imputation number may be further refined in case of convergence issues or the stability of model estimates is not observed.

Step 3 Analysis stage:

A continuity corrected CMH test will then be applied on each of these imputed datasets.

Step 4 Combination stage:

The results from each set of imputed datasets will be combined using Rubin's rule (1987) to incorporate both within and between imputation variability, assuming the estimates are asymptotically normally distributed. Before pulling the results together, the following transformation will be applied.

4.1) Wilson-Hilferty transformation (1931) will be applied on the CMH test statistic per Appendix II, before the pooled analysis across multiply imputed datasets. A one-sided p-value from the combined CMH test will be reported.

4.2) The common odds ratio from CMH test is based on a chi-square distributed statistic, hence, logarithm transformation, per Van Burren (2012), on the common odds ratio will be applied before the pooled analysis across multiply imputed datasets per Appendix III. A combined common odds ratio and associated confidence interval will be reported.

- Secondary endpoint: missing mRS scores due to death prior to 3 months will be considered to have a score of 6; missing data at 3 months due to reasons other than death will be imputed using multiple imputation in a similar way as the primary effectiveness endpoint.

  Step 1 Auxiliary variables for multiple imputation:

  Subject treatment (with or without eMMA procedure), cohort (surgical or NSMM cohorts), and baseline mRS score will be included into data imputation. Additional auxiliary (predictor) variables will be identified using the following method.

  To examine the association of the predictor with the outcome variable (binary data), a logistic regression modelling will be performed, a p-value < 0.1 from the Wald test or Likelihood Ratio test will be used to indicate if the predictor is associated with the outcome, thus, to be included into the multiple imputation for this endpoint.

  The way to handle the continuous, binary or categorical predictors will be the same as introduced earlier in the multiple imputation section for the primary effectiveness endpoint.

  Step 2 Data generation stage:

  Assuming an arbitrary data missing pattern, a fully conditional specification (FCS) logistic regression method (for classification variables) will be used to impute the missing values for the secondary endpoint (success or failure) at 3 months. Auxiliary variables identified above will be included into data imputation.

  Five imputed datasets (M=5) will be generated using a pre-specified seed number. The imputation number may be further refined in case of convergence issues or the stability of model estimates is not observed.

  Step 3 Analysis stage:

  Estimates of risk difference will be calculated for each imputed dataset.

  Step 4 Combination stage:

  Estimates from these imputed datasets will then be combined using Rubin's rule (1987). Combined estimate for the risk difference and associated two-sided 90% confidence interval based on a *t*-statistic will be reported.

- Secondary endpoint: missing data for surgical procedures on the cSDH within 12 months will be imputed using multiple imputation in a similar way as the primary effectiveness endpoint.

  Step 1 Auxiliary variables for multiple imputation:

  Subject treatment (with or without eMMA procedure), cohort (surgical or NSMM cohorts), hematoma thickness at baseline and post-baseline visits, from the independent core lab will be included into data imputation. Additional auxiliary (predictor) variables will be identified using the following method.

To examine the association of the predictor with the outcome variable (binary data), a logistic regression modelling will be performed, a p-value < 0.1 from the Wald test or Likelihood Ratio test will be used to indicate if the predictor is associated with the outcome, thus, to be included into the multiple imputation for this endpoint.

The way to handle the continuous, binary or categorical predictors will be the same as introduced earlier in the multiple imputation section for the primary effectiveness endpoint.

Additional multiple imputation steps will be implemented in the same way as the primary effectiveness endpoint.

- Secondary endpoint: missing data for change in hematoma volume at 6 months will be imputed using multiple imputation.

  Step 1 Auxiliary variables for multiple imputation:

  Subject treatment (with or without eMMA procedure), cohort (surgical or NSMM cohorts), and hematoma volume at baseline and post-baseline visits, from the independent core lab will be included into data imputation. Additional auxiliary (predictor) variables will be identified using the following method.

  To examine the association of the predictor with the outcome variable, linear regression models using maximum likelihood estimation method will be performed (when the normality assumption is met). If model assumptions are violated, additional transformation of the outcome (or link functions) and functional forms may be considered. A p-value < 0.1 from the Wald test or Likelihood Ratio test be used to identify the predictors to be associated with the outcome, thus included into the multiple imputation for this endpoint.

  The way to handle the continuous, binary or categorical predictors will be the same as introduced earlier in the multiple imputation section for the primary effectiveness endpoint.

  Assuming an arbitrary data missing pattern, Markov chain Monte Carlo (MCMC) method will be applied for this continuous endpoint. Auxiliary variables identified above will be included into data imputation. Five imputed datasets (M=5) will be generated using a pre-specified seed number. The imputation number may be further refined in case of convergence issues or the stability of model estimates is not observed.

  ANOVA test will be applied on each of these imputed datasets and estimates from these imputed datasets will then be combined using Rubin's rule (1987).

- Health economic endpoints: missing discharge dates from hospitalization

  Hospitalized subjects with missing or incomplete discharge date for whom the calculation of LOS cannot be performed will be imputed via following methods:

  - Applicable to incomplete discharge date regardless of reasons

If only day is missing, while the month and year of discharge are available, then it will be imputed to be the earlier date of day 30 of that month and year, or end of study completion/discontinuation date.

- Applicable to hospitalized subjects without discharge due to all-cause mortality

  To account for competing risks with all-cause mortality, LOS will be imputed by random drawing from the upper 90th percentile of the distribution of LOS from all other live subjects with non-missing values by cohort and treatment.

  Remaining subjects with missing or incomplete discharge date that could not be imputed will be excluded from LOS summaries.

- Concomitant medications: missing data imputation in medication dates are specified in Section 8.4.
- Adverse events: missing data imputation in adverse event dates for secondary safety endpoints using Kaplan-Meier analyses are as follows:
  - If an AE start date has year and month, without a day, it will be imputed as the later date of the following: first day of that month, or date of randomization.
- No other missing data imputation is planned in the study.

8.8 Sensitivity Analyses

The following analyses will be performed to assess sensitivity to analysis sets and missingness of the primary effectiveness endpoint.

- The primary effectiveness endpoint analysis (section 8.6.1) will be repeated using the ITT, As Treated, and PP analysis sets with observed data only. No data imputation methods will be applied.
- For the primary effectiveness endpoint analysis, a Gail-Simon test (1985) will be performed to examine a potential qualitative interaction between treatment and cohort using the observed data at an alpha level of 0.15 using the ITT analysis set. A p-value <0.15 on the Gail-Simon test is indicative of a significant qualitative treatment by cohort interaction.
- A logistic regression will be fit by taking treatment (with or without eMMA procedure), cohort (surgical or NSMM cohorts) and treatment by cohort interaction as fixed effects, the binary outcome of the primary effectiveness endpoint will be included as the outcome variable using ITT analysis set. Missing data will be excluded. P-value of the interaction term will be reported.
- Worst-case scenario

  To examine the potential impact of worst-case scenario, subjects with missing data on the primary effectiveness endpoint will be imputed as follows using ITT analysis set.

Subjects randomized to eMMA procedure (e.g., surgery + eMMA or NSMM + eMMA) will be considered as failures on the primary effectiveness endpoint (e.g., 6-month hematoma thickness >10mm); subjects randomized to SOC (e.g., surgery alone or NSMM alone) will be considered as success.

- Best-case scenario

  To examine the potential impact of best-case scenario, subjects with missing data on primary effectiveness endpoint will be imputed as follows using ITT analysis set.

  Subjects randomized to eMMA procedure (e.g., surgery + eMMA or NSMM + eMMA) will be considered as success on the primary effectiveness endpoint; subjects randomized to SOC (e.g., surgery alone or NSMM alone) will be considered as failures (e.g., 6-month hematoma thickness >10mm).

8.9 Subgroup Analysis

The primary effectiveness endpoint will be analyzed by subgroup with clinically meaningful risk factors based on subjects with non-missing values in the ITT analysis set. Descriptive statistics will be presented by cohort, treatment and subgroup.

8.9.1 Sex Specific Analysis

A logistic regression using the ITT analysis set will be performed, including sex (female vs. male), cohort (surgical vs. NSMM), treatment (SOC + eMMA vs. SOC alone) and sex by treatment interaction will be included into the model as fixed effects. Non-significant p-value of sex by treatment interaction (i.e., p-value >0.15) will support poolability of outcomes by sex.

If males and females are not poolable, summary statistics will be presented for the primary effectiveness endpoint by cohort, treatment and sex.

8.9.2 Other subgroup analyses

No formal inference will be made on other subgroup analyses. Descriptive statistics, odds ratio and associated two-sided exact 90% confidence intervals will be provided for each subgroup by treatment and cohort as applicable, unless instructed otherwise.

- Age (<75 vs. ≥75 years old)
- Race
- Ethnicity

8.9.3 Assessment of Site and Region Homogeneity

Homogeneity of odds ratios of primary effectiveness endpoint will be assessed in the ITT analysis set based on the non-missing values.

- Sites with less than 5 subjects will be combined based on geographic location, region (US vs. outside US [OUS]) within cohort (see Appendix V for details): the site with least number of subjects will be combined with the next smallest site, until the pre-specified minimum subject count is reached by subregion, region and cohort. Subjects with missing values of the primary effectiveness endpoint will be imputed with multiple imputation using the same method as described in Section 8.7 for the primary effectiveness endpoint.. After sites have been combined per above rule, then homogeneity assessment on site will be performed as follows: A logistic regression will be fit by taking region, cohort, treatment (SOC + eMMA vs. SOC alone), region by treatment interaction as fixed effects, the binary outcome of the primary effectiveness endpoint will be included as the outcome variable.
- A separate logistic regression will be fit in a similar way, by taking sites (after combination), cohort, treatment (SOC + eMMA vs. SOC alone), site by treatment interaction as fixed effects.

  Then a Holm-Bonferroni multiplicity adjustment method will be used to control the Family-wise error rate at 0.15 for the hypothesis tests of primary effectiveness endpoint. The p-values of the interaction terms (region by treatment interaction and site by treatment interaction from above models) will be sorted from low to high and will be compared to alpha levels of 0.075 and 0.15, respectively.
- If regions are not poolable, summary statistics will be presented for the primary effectiveness endpoint by region, treatment and cohort.

  The OUS enrollment is small (50) and is expected to be distributed between the two treatments and two strata. If there are convergence issues in any of the logistic models performed on any of the imputed datasets, descriptive statistics by region will be provided.
- If sites are not poolable, summary statistics will be presented for the primary effectiveness endpoint by site, treatment, and cohort. If there are convergence issues in any of the logistic models performed on any of the imputed datasets, descriptive statistics by site will be provided.

8.10 Additional Analyses

The following analyses will be summarized using observed values by treatment and cohort using ITT, PP and As Treated analysis sets, unless noted otherwise.

- Study device deficiencies: frequency of device deficiency will be summarized based on the data collected from CRF using the ITT analysis set only.
- Protocol deviations: the number of deviations, the number and percentage of subjects with at least one protocol deviation will be summarized using ITT analysis set. Summaries of protocol deviations due to COVID will be presented as well.
- Re-operations or surgical procedures post randomization: frequency of events, the number of subjects who receive at least one re-operation or surgery by type (burr

hole, craniotomy, etc.), and location (parietal, frontal, occipital and temporal) will be summarized based on the data collected from CRF.

- Assessment outcomes

  Descriptive statistics will be summarized for the following data by treatment and cohort at each follow-up for each analysis set, unless noted otherwise. Missing scores will be excluded from summaries unless noted otherwise.

  1. mRS

  Frequency by mRS score (in categories of 0, 1, …, 6 and 0-2 or no worsening from baseline if baseline mRS ≥ 3) will be summarized by treatment and cohort at each visit. Individual mRS scores will be plotted by treatment and cohort at each visit. Subjects with missing mRS score due to all-cause death will be managed in the same way as section 8.6.3.2. Odds ratio of subjects achieving mRS 0-2 or no worsening from baseline if baseline mRS ≥ 3 in the treatment of SOC + eMMA vs. SOC alone will be presented by cohort at each post-baseline visit.

  2. MMSE score

  MMSE score (0-30) will be summarized numerically at each visit. Frequency of MMSE scores by categories of 0-17 (severe cognitive impairment), 18-23 (mild impairment), 24-30 (normal) will be summarized at each visit by treatment and cohort.

  3. MGS score

  Frequency of MGS scores (0-4) will be summarized descriptively at each visit.

  4. Quality of Life (EQ-5D-5L) score

  The frequency of functional scores (by categories of no problems, slight problems, moderate problems, severe problems, unable to function and not rated in the 5 dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) will be summarized at each visit using PP analysis set only. Change from baseline to 1 year and change from 6 months to 1 year will also be summarized.

- Imaging data per independent core lab

  Descriptive statistics will be summarized for the following data by treatment and cohort at each follow-up using observed data. Changes from baseline will be presented for numerical data as well.

  1. Hematoma volume (cm^3) in terms of ABC/2 volume
  2. Thickness of SDH (mm)
  3. Midline shift (mm)
  4. Presence of new SDH compared to the pre-randomization CT (yes, no)
  5. Presence of an acute component of SDH compared to the pre-randomization CT (yes, no)

6. Complete resolution of SDH (yes, no)

9 Data Monitoring Committee (DMC)

An independent DMC will be responsible for monitoring the accumulated interim data as the study progresses to ensure subject safety. All safety review procedures will be established and agreed upon in the DMC Charter.

Once the study begins, the DMC will meet periodically to review safety data. The DMC may request more frequent meetings if necessary to fulfill its charge. The responsibility to accept, reject or further clarify the DMC recommendations resides with the study sponsor.

10 Reference

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Appendices:

Appendix I: Sample size calculation for the primary effectiveness endpoint

Sample size for the primary effectiveness endpoint was calculated in R, version 4.2 with the following codes. The calculated effect size N=334. A 10% attrition rate is applied on top on the effect size, leading to a final sample size of 376 in total.

```
library(samplesizeCMH)
sample_size_corrected<-power.cmh.test(p2=c(0.885, 0.78), s=0.5, theta=2.89, power=0.9, t=c(0.3, 0.7), alternative="greater", sig.level=0.05, correct=TRUE)
print(sample_size_corrected)
```

Appendix II: R code for One-Sided CMH Test

One-sided CMH test can be impleted in R via the following code; where alpha is set to be 0.05, continuity correction is applied and the alternative hypothesis will be set to the direction of ‘less’.

```
mantelhaen.test(data.test, correct = TRUE, alternative ="less", conf.level =0.95)
```

Appendix III: Pulling Results of the CMH Test using Wilson-Hilferty Transformation from Multiply Imputed Dataset

PharmaSUG203 – Paper SP03 by Ratitch, Lipkovich and O'Kelly (2003)

The CMH general association statistic, under the null hypothesis of no association, has an asymptotic chi-square distribution with $(C1-1)(C2-1)$ degrees of freedom where $C_1$and $C2$ represent the number of categories assumed by each of the two categorical variables. The chi-square distribution is highly skewed for smaller degrees of freedom, thus obtaining a combined result of the CMH test from multiply imputed data requires a Wilson-Hilferty transformation (Wilson & Hilferty, 1931; Goria, 1992) that would normalize the CMH statistic.

$$wh\_cmh^{(m)} = \sqrt[3]{\frac{cmh^{(m)}}{df}} \quad (1)$$

where $cmh^{(m)}$ is the CMH statistic computed from the m^{th} imputed dataset, df is the number of degrees of freedom associated with the CMH statistic, and $wh\_cmh^{(m)}$ is the transformed value. The transformed statistic is approximately normally distributed with mean $1-\frac{2}{9\times df}$ and variance $\frac{2}{9\times df}$ under the null hypothesis. Thus, the statistic (1) can be transformed to a variable of normal distribution:

$$st_{wh\_cmh}{}^{(m)} = \frac{\sqrt[3]{\frac{cmh^{(m)}}{df}}-\left(1-\frac{2}{9\times df}\right)}{\sqrt[2]{\frac{2}{9\times df}}} \quad (2)$$

where $st_{wh\_cmh}{}^{(m)}$ is the transformed variable of normal distribution, with a mean 0 and variance 1.

Pooling the results from multiply imputed datasets will be implemented as follows,

Step 1: Perform CMH test for every imputed dataset (PROC MI).

Step 2: Apply Wilson-Hilferty transformation to the CMH statistic and standardize the resulting variable, per formula (2).

Step 3: Apply Rubin's rule using the transformed values to get a combined CMH test result (PROC MIANALYZE).

Step 4: Report one-sided p-value for the combined CMH test, which is obtained as the upper-tailed p-value from the normal test produced by PROC MIANALYZE on the transformed statistic.

Appendix IV: Pulling Common Odds Ratios using Log Transformation from Multiply Imputed Dataset

PharmaSUG203 – Paper SP03 by Ratitch, Lipkovich and O'Kelly (2003)

Rubin's pooling methodology (1987) is based on the assumption that the estimates are asymptotically normally distributed. The Mantel-Haenszel estimate of the common odds ratio for categorical variables are not normally distributed. Hence, normalization, e.g., logarithm transformation, need to be applied to the statistics estimated from each imputed dataset before the application of Rubin's combination rule, noted from Ratitch et. al. (2013).

The transformation of the estimates will be implemented as follows,

Step 1: Obtain the Mantel-Haenszel estimate of the common odds ratio for every imputed dataset (PROC MI)

Step 2: Apply logarithm transformation on the estimates of the common odds ratio and standard error for each imputed dataset:

$$log\_value = log(commonOR)$$

$$log\_se = (\log(upperCL) - log(lowerCL))/(2 * Z_{0.95})$$

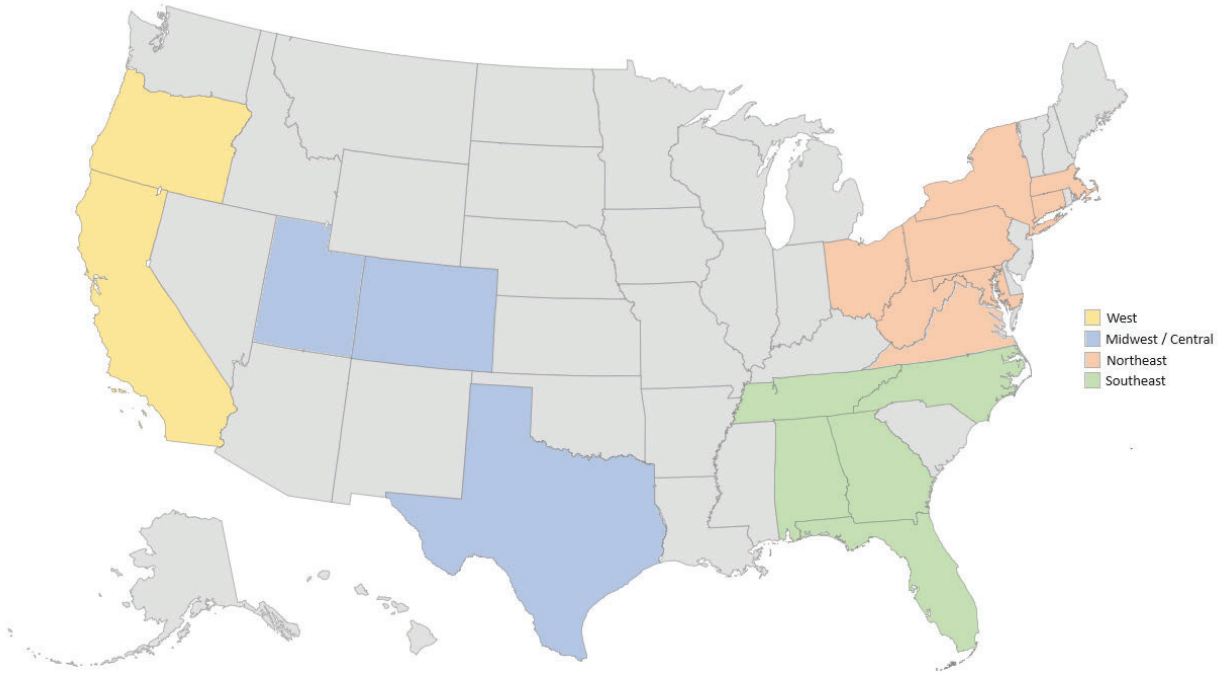
where log is the logarithm function and Z is the normal distribution. From each imputed dataset, we denote $commonOR$ as the estimate of common odds ratio from the continuity corrected CMH test; $upperCL$ and $lowerCL$ as the upper and lower confidence limits of the estimated common odds ratio based on 90% significance level; log_se as the standard error after transformation from each imputed dataset, obtained from the log-transformed lower and upper confidence limits for the estimate of common odds ratio.

Step 3: Apply Rubin's combination rule to pool together the estimated statistics (after log-transformation) across multiply imputed datasets (PROC MIANALYZE).

Step 4: The combined estimate of common odds ratio and confidence intervals then will be transformed back to its original scale and report them for the estimated common odds ratio and its confidence interval based on the multiple imputation.

Appendix V: Geographic Subregions within United States

Sites with less than 5 subjects will be combined into one of the 4 subregions as indicated below based on their geographic location.



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Challenge: The user clicked on the signature field: 'Signature Field 1'.

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Document e-signed by PPD [redacted]

Signing reason: I am approving this document

Signature Date: 2024-10-01 - 6:58:13 PM GMT - Time Source: server- PPD [redacted]

Email viewed by PPD [redacted]

2024-10-01 - 10:09:26 PM GMT- PPD [redacted]

PPD [redacted] authenticated with Adobe Acrobat Sign.

Challenge: The user clicked on the signature field: 'Signature Field 4'.

2024-10-01 - 10:21:47 PM GMT

Document e-signed by PPD [redacted]

Signing reason: I am approving this document

Signature Date: 2024-10-01 - 10:21:56 PM GMT - Time Source: server- PPD [redacted]

Email viewed by PPD [redacted]

2024-10-01 - 11:31:12 PM GMT- PPD [redacted]

PPD [redacted] authenticated with Adobe Acrobat Sign.

Challenge: The user clicked on the signature field: 'Signature Field 2'.

2024-10-01 - 11:31:47 PM GMT

Document e-signed by PPD [redacted]

Signing reason: I am approving this document

Signature Date: 2024-10-01 - 11:32:19 PM GMT - Time Source: server- PPD [redacted]

Agreement completed.

2024-10-01 - 11:32:19 PM GMT