Title	:	Managing Non-acute Subdural Hematoma Using Liquid Materials: a Chinese Randomized Trial of MMA Treatment
Protocol No.	:	MAGIC-MT
Version No.	:	V1.0
Effective Date	:	2023-12-02

Description:

- The purpose of this Statistical Analysis Plan (SAP) is to describe the planned analyses and presentation of results in the clinical study report corresponding to the study protocol MAGIC-MT .
- The purpose of this SAP is to describe the efficacy analysis and safety analysis required by the study protocol for middle meningeal artery (MMA) embolization using liquid embolic material for the treatment of non-acute subdural hematoma.
- This SAP will be provided to study team members to communicate the full delivery of the statistical analysis.

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Version History

This SAP is based on the MAGIC-MT study protocol version 3.0 version dated 2022-09-21 .

SAP Version	Effective Date	Author	Revision Description
1.0	2023-12-02	Zhou Liang	Original Version

CONTENTS

1. Summary of Protocol

1.1. Statistical Analysis Plan and Protocol Discrepancies

All changes to the content of the analyses originally specified in Protocol 3.0 (2022-09-21) are summarized in Table 1.

Table 1 Changes to the analysis plan defined in the protocol

Protocol	**Statistical Analysis Plan**	
Statistical description in the protocol	**Statistical description in statistical analysis plan**	**Reason for change**
• Section 7.3.1 For the primary endpoint, CMH chi-square analysis will be used to calculate the difference in the event rate between the two groups and its 95% confidence interval, and Kaplan-Meier method will be further used to estimate the event rate of the primary endpoint and its 95% confidence interval.	• Section 8.2.2 Primary analysis:90-day recurrence or progression rates will be summarized for each group using a two-sided 95% CI (Clopper-Pearson method). P-values for differences in recurrence or progression rates between the 2 groups will be compared between groups using the CMH chi-square test. The stratification factor is whether or not trepanation and drainage is performed. In addition, a two-sided 95% CI for the difference in recurrence or progression rates between the two groups will be calculated using the Miettinen-Nurminen method. • Sensitivity analysis: Generalized linear mixed-effects model will be used to calculate ORs and their 95% CIs for the comparison of recurrence or progression rates between the two groups for sensitivity analysis with group as a covariate, site as a random	• According to internal discussion as well as reference to the design of similar studies, time-to-event analyses were not included for the primary endpoint, and logistic regression analysis methods were added.

Protocol	Statistical Analysis Plan	
Statistical description in the protocol	**Statistical description in statistical analysis plan**	**Reason for change**
	effect. Multivariable analysis will also be provided to include group, sex, age, maximum thickness of hematoma on the enrolled side, baseline mRS score.	
• Section 7.3.2 The analyses of secondary endpoints will be the same as those for the primary endpoint, and comparisons between groups will be made using the Chi-square test (qualitative measure) or t-test (quantitative measure). For event endpoints, the Kaplan Meier method will be used.	• For two continuous secondary endpoints, Change of maximum hematoma thickness and hematoma volume between baseline and 90 days, a linear mixed effects model approach will be used to estimate the mean estimate (95% CI) of change from baseline for both treatment groups and mean estimate (95% CI) of difference between groups and p-value of difference between groups; Treatment group variables, sex, age, surgical treatment strata (trepanation/drainage vs. no trepanation/drainage), any usage of antiplatelet or anticoagulant therapy within one month before randomization(yes vs no), hematoma volume of baseline CT will be included in the model. The random effects will be site. For other continuous secondary endpoints, group comparisons will be performed using t-tests or Mann-Whitney U tests and 95% confidence intervals for	• According to internal discussion as well as reference to the design of similar studies, secondary endpoints do not include time-to-event analyses and linear mixed effects model analysis methods are added.

Protocol	Statistical Analysis Plan	
Statistical description in the protocol	**Statistical description in statistical analysis plan**	**Reason for change**
	the difference in means between groups will be calculated using normal approximation.	
• None	• Section 8.2.1 The results of central imaging assessment analysis of CT/MRI examinations required for the determination of the subject 's primary endpoint in this study will be presented in tables. Central image evaluation will be performed by the Independent Central Image Review Committee. Neurological symptoms and follow-up mRS scores were derived from OAC review data. • Section 9.3.2.1 CEC assessments for adverse events of special interest.	• Added central imaging assessments (CT/MRI examinations), CEC assessments (adverse events of special interest), and clarified data sources.

1.2. Study Objectives and Endpoints

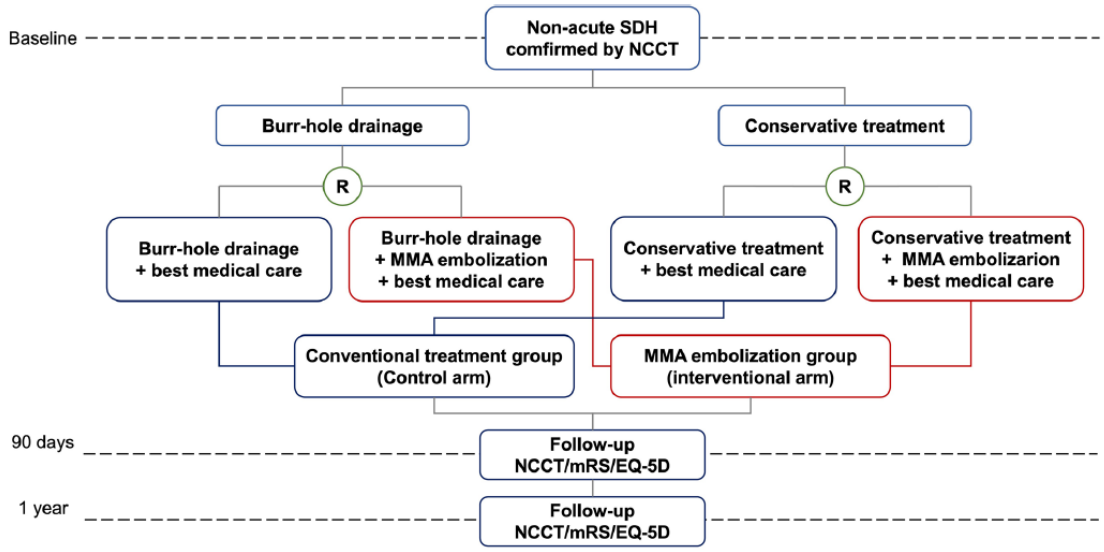
Study objectives	Study Endpoints
Primary objective	**Primary Study Endpoints**
• To validate that in patients with symptomatic non-acute subdural hematoma (SDH), MMA embolization with liquid embolic materials can reduce a) the incidence of symptomatic hematoma	• Incidence of symptomatic recurrence (in patients who undergo trepanation/drainage) or symptomatic progression of hematoma (in patients who do not undergo trepanation/drainage) within 90 days after randomization • Symptomatic hematoma recurrence is defined as maximum hematoma thickness >10 mm in patients in

Study objectives	Study Endpoints
recurrence for patients receiving trepanation and drainage and b) the incidence of symptomatic hematoma progression for patients undergoing conservative treatment.	the trepanation group, combined with neurological symptoms, or that the patient needs to undergo re-operation • Symptomatic hematoma progression is defined as an increase of >3mm maximum thickness of SDH of patients in the non-trepanation group compared with baseline, or the need for surgery based on the assessment of the treating medical team
Secondary objectives	**Secondary Study End Point**
• To validate the efficacy of MMA embolization with liquid embolic materials	• Incidence of SDH symptomatic recurrence (in patients who undergo trepanation/drainage) and symptomatic progression (in patients who do not undergo trepanation/drainage) 360 days after randomization • Success rate of target vessel embolization in DSA imaging
• To validate the safety of MMA embolization with liquid embolic materials	• Serious Adverse Events (SAEs) within 90 days and 360 days • Death within 90 days and 360 days • Severe surgery-related complications within 30 days after surgery (including trepanation/drainage and MMA embolization): Symptomatic intracranial hemorrhage Surgery-related intracranial hemorrhage Surgery-related neurological deficits Surgery-related central nervous system infection Surgery-related arterial dissection, vascular wall injury and vascular rupture and perforation Surgery-related ischemia Access site hematoma Neuropathy at the puncture site Contrast allergy or contrast encephalopathy
• To validate the reduction of residual hematoma at 90 days after randomization in patients	• Changes of hematoma thickness on CT/MRI imaging at 90 days after randomization

Study objectives	Study Endpoints
undergoing MMA embolization	• Changes of hematoma volume at 90 days after randomization • Changes of midline shift in CT/MRI imaging at 90 days after randomization
• To validate the improvement in clinical outcome (mRS score) at 90 days and 360 days after randomization in patients undergoing MMA embolization	• Changes of Modified Rankin Scale (mRS) score at 90 days and 360 days after randomization • Proportion of patients with mRS score of 0 to 2 at 90 days and 360 days after randomization • Proportion of patients with mRS score of 0 to 3 at 90 days and 360 days after randomization
• To validate the improvement in health status (EQ-5D-5L scale) at 90 days and 360 days after randomization in patients undergoing MMA embolization	• Quality of life evaluated with EQ-5D-5L Scale at 90 days and 360 days after randomization
• To validate the reduction of readmission rate within 90 days after randomization in patients undergoing MMA embolization	• Total days of hospital stay, re-hospitalization times, destination for rehabilitation after discharge (going home vs rehabilitation hospital) and total hospitalization expenses

1.3. Study Design

Overview of Study Design and Key Characteristics



Design Features	• This is a multi-center, randomized, open-label, blinded evaluation endpoint, and parallel controlled clinical study. The study contents include: 1) Screening and baseline period: Confirm whether the patients are eligible for the study and make a record and decide whether trepanation and drainage should be performed by considering the condition of the disease and the imaging results, and then carry out randomization and therapy. Eligible subjects will be randomly assigned to the traditional treatment group or MMA embolization group at the ratio of 1:1. 2) Follow-up period: Assess patients for efficacy endpoints and safety endpoints at 30 days, 90 days and 360 days after randomization.
Study treatment	• MMA embolization: The surgery is performed under local anesthesia + analgesia, or general anesthesia, and the type of anesthesia is decided by the neurointerventionalists. Different types of catheters are chosen according to patients' anatomy. Arterial access is usually attained via femoral artery groin puncture, however radial or brachial artery access is also allowed. Angiography will usually show MMA dilatation and abnormal vascular staining on the affected side, and then embolic materials are slowly injected into the blood vessels, while avoiding reflux carefully. Investigators who use liquid embolic materials shall be qualified in corresponding training before they can perform the surgery. • Drug therapy: Drug treatment can be divided into the symptomatic treatment and treatment promoting hematoma absorption. Indications of drug treatment promoting hematoma absorption: 1) Confirmed diagnosis of non-acute SDH; 2) Patients complicated with multiple organ failure and coagulation dysfunction, etc. who are not suitable for surgery or refuse the surgery; and 3) To prevent postoperative recurrence after

Overview of Study Design and Key Characteristics	
	surgical treatment etc. The contraindications are: allergic to the drug used or having contraindications for the use of the drug. Atorvastatin calcium and dexamethasone are recommended. Atorvastatin calcium with small dose and long course of treatment can be used in combination with dexamethasone. The specific treatment is subject to the local clinical diagnosis and treatment specifications or corresponding clinical guidelines, and is not specified in this study. The application of hemostatic drugs will greatly increase the incidence risk of embolic diseases, so hemostatic drugs are not commonly used. • Surgical Treatment: Surgical treatment in this study refers to trepanation and drainage, and local anesthesia + analgesia or general anesthesia can be used for trepanation and drainage. Indications of trepanation and drainage: (1) There are clinical symptoms and signs of high intracranial pressure, with or without changes in consciousness and signs of cerebral hemisphere compression; (2) CT or MRI scan shows unilateral or bilateral subdural hematoma with thickness of > 10 mm, and midline shift of > 10 mm due to unilateral hematoma; (3) For those who have been treated with drugs for promoting hematoma absorption for 2 weeks or longer, and whose clinical manifestations and imaging examination have not improved significantly, or whose hematoma continues to increase or medication is intolerable, surgical treatment is recommended. If the subjects in the embolization group need surgery, the embolization will be performed before trepanation and drainage.
Assignment	• Eligible subjects will be randomized 1:1 to either conventional therapy (no MMA embolization) or MMA embolization.
Interim Analyses	• The study includes two formal interim analyses, and efficacy analyses will be performed when approximately one-third and two-thirds of patients completed the 90-day follow-up.
Sample Size	• 722 cases are expected to be enrolled in this study in China.
Study Duration	• In this study, it is estimated that the enrollment time will be from January 2021 to June 2023, that is, the enrolment period will be 30 months from the enrollment of the first subject to the enrollment of the last subject. After the completion of enrollment, the last subject will be followed up to 360 days after randomization.

2. Statistical Hypothesis

Hypothesis testing will be performed on hematoma recurrence or progression rates.

- Null hypothesis: there is no difference in the incidence of recurrence or progression of hematoma between the MMA embolization group and the control group at 90 days after randomization;

- Alternative hypothesis: there is difference in the incidence of recurrence or progression of hematoma between the MMA embolization group and the control group at 90 days after randomization.

The above hypothesis tests will be two-sided and statistical significance will be determined as a p-value of<0.05, and two-sided 95% confidence intervals will be reported.

3. Sample Size Considerations

The study hypothesizes that patients undergoing middle meningeal artery embolization may have lower symptomatic recurrence (in the trepanation/drainage group) and lower rates of symptomatic hematoma progression (in the non-surgical group) of subdural hematoma compared to patients who do not go MMA embolization. Two interim analyses will be conducted. With an expected symptomatic recurrence rate (trepanation/drainage group) / symptomatic progression rate (non-surgical group) after MMA embolization of 5% compared with 12% in the control group, and considering a loss to follow-up rate of 8%, a sample size of 722 cases with a two-sided alpha of 0.05 would yield 90% power.

4. Planned Analyses

4.1. Interim Analyses

Two formal interim analyses was planned to review data relating to treatment efficacy, participant safety and quality of trial conduct using an Haybittle-Peto stopping rule for efficacy. Given the conservative rule used and the negligible amount of type-I error rate spent at the interim analysis, the significance threshold will remain at 5% for the final analysis.

4.2. Final Analysis

The planned final analysis will be performed after the following steps are completed sequentially:

1. All subjects have completed the study as defined in the protocol.
2. The Statistical Analysis Plan (SAP) has been finalized and approved.
3. All required database cleaning is completed, and the head of Data Management department announces the final database release and database freeze.
4. Randomization codes are issued according to the unblinding process at the end of the trial.

Only blinded data will be reviewed prior to database lock. In addition, no database lock will occur prior to finalization of this SAP.

5. Analysis Population

Population	Definition/Criteria	Analyses Evaluated
All included Subjects Set	• All subjects who signed informed consent.	• Study Population
Intent-to-treat Analysis Set (ITT)	• Including all randomized subjects based on the intention-to-treat (ITT) principle, i.e. analysis of subjects based on initial treatment assigned by randomization	• Study Population • Efficacy
Per-Protocol Analysis Set (PPS)	• The PPS will include all subjects in the FAS who did not have any major protocol deviations. • Protocol deviations excluding subjects from the PPS are defined in Section 5.1 (Protocol Violations). • Analysis in PPS will be based on the treatment the participant assigned by randomization. • Additional efficacy analyses based on the PPS set will not be performed if the PPS set includes 90% or more of subjects in the FAS and the difference in analysis results between the two analysis sets is expected to be negligible.	• Study Population • Efficacy
Safety Set (SS)	• Includes all randomized subjects. • As treated • ITT analysis set	• Safety

5.1. Protocol Deviations

- Important protocol deviations, including those related to study inclusion/exclusion criteria, trial conduct, subject management, or subject assessment, will be summarized.

- Protocol deviations will be tracked by the study team during the course of the study according to relevant regulations in routine monitoring.
  - All data will be reviewed prior to database lock to ensure that all important protocol deviations and deviations that could lead to exclusion of subjects from the analysis can be captured and classified in the protocol deviation dataset.
  - This dataset will serve as the basis for summaries of protocol deviations.

6. Considerations for Data Analyses and Data Handling Conventions

Analyses will be performed using SAS ® System Version 9.4 or higher, and all tables, figures, and listings will be generated as RTF files.

For descriptive statistics, the number of observations (n), standard deviation, median, minimum, maximum，Q1 and Q3 will be presented for continuous variables and number and percentage of subjects will be presented for categorical variables, unless otherwise specified.

Table 2 provides an overview of the appendices in the SAP for outlining general rules for data analyses and data handling conventions.

Table 2 Overview of Appendix

Component
Appendix 1: Treatment Period and Study Period
Appendix 2: Data Display Standards and Handling Conventions
Appendix 3: Handling of Premature Withdrawals and Missing Data
Appendix 4: Abbreviations Table

7. Study Population Analyses

7.1. Overview of Planned Study Population Analyses

Unless otherwise stated, the analyses will be based on the ITT set.

Table 3 provides an overview of the planned study population analyses.

Table 3 Overview of Planned Study Population Analyses

	Data Presentation Generated		
	Table	**Figure**	**Listing**
Subject Disposition [1, 3]			
Subjects who entered screening and failed screening	Y		Y
Randomized Subjects			
Subjects receiving any study treatment - Received burr hole drainage - Received MMA embolization - Received optimal medical therapy			
Completed Subjects			
Subjects who premature withdrew and reasons			
Entered Intent-to-Treat Set (ITT)			
Entered Per-Protocol Analysis Set (PPS)			
Entered Safety Set (SS)			
Protocol Deviations			
Important protocol deviations	Y		Y
Any protocol deviations	Y		Y
Demographic and Baseline Characteristics			
Sex [1]	Y		Y
Age (years) [2]			
Ethnic [1]			
Weight (kg) [2]			

	Data Presentation Generated		
	Table	**Figure**	**Listing**
Height (m) [2]			
BMI (kg/m [2]) [2]			
Smoking status [1]			
Alcohol status [1]			
Baseline mRS score[2]			
Prior medical history [1]			
Prior medical history	Y		Y
Prior medication history [1]			
Prior antiplatelet, anticoagulant use			
Prior statin use	Y		Y
Prior hormonal use			
Baseline cranial imaging diagnosis (CT/MRI)			
Massive cerebral infarction [1]			
Intracranial space-occupying lesion [1]			
Midline shift [1]			
If yes, shift distance [2]			
Subdural hematoma [1]	Y		Y
If yes, hematoma Side Positions [1]			
Maximum thickness of hematoma on the enrolled side [2]			
Volume of hematoma on the enrolled side [2]			

Notes:

1. Categorized data.

2. Continuous data.

3. Will be based on all screened sets of subjects.

Y = Plan Generation.

7.2. Description Of Study Population Analysis

7.2.1. Demographic and Baseline Characteristics

- Age (years) will be calculated as (date of informed consent – date of birth)/365.25 rounded down.
- BMI (kg/m^2) will be calculated as [weight(kg) / (height(cm)/100) ^^{2}].

8. Primary Efficacy Endpoints Analyses

8.1. Overview of Planned Primary Efficacy Endpoints Analyses

Unless otherwise stated, the primary efficacy endpoints analysis will be based on the Intent-to-Treat (ITT) and Per-Protocol (PPS) sets. Intent-to-Treat (ITT) set will be the primary analysis set.

Table 4 provides an overview of the planned primary statistical analyses.

Table 4 Overview of planned primary efficacy endpoints analyses

	Data Presentation Generated		
	Table	**Figure**	**Listing**
Incidence of recurrence (subjects with trepanation) or progression (subjects with no trepanation) of subdural hematoma within 90 days after randomization			
Number and percentage of subjects with event - Hematoma recurrence (in the trepanation/drainage group) in the MMA embolization and control arm respectively - Hematoma progression (in the non-surgical group) in the MMA embolization and control arm respectively - Death within 104 days (90 days + 14 days) in the MMA embolization and control arm respectively	Y		Y
Dichotomous data analyses:			Y

	Data Presentation Generated		
	Table	**Figure**	**Listing**
- Recurrence (in the trepanation/drainage group)/ progression rate (in the non-surgical group) with 95% CI - Difference in recurrence or progression rates between MMA embolization and control groups with 95% CI and CMH Chi-square P value - OR and its 95% CI for the comparison of recurrence or progression rates between treatment and control groups			

8.2. Specifications of Primary Efficacy Endpoints Analyses

8.2.1. Definitions and Derivations

- **Symptomatic** SDH recurrence (in the trepanation/drainage group) refers to a situation in which the maximum thickness of hematoma of patients exceeds 10 mm, combined with neurological symptoms, or the need for repeat surgery.
- Symptomatic SDH progression (in the non-trepanation/drainage group) refers to a situation in which the maximum thickness of increases by more than 3 mm compared with baseline, combined with neurological symptoms, or the need for surgery.
- The results of central imaging evaluation and analysis of CT/MRI examinations required for the determination of the subject 's primary endpoint in this study will be presented in tables and listings, respectively. Central image evaluation will be performed by the independent Core Lab. Evaluation of neurological symptoms will be derived from the Outcome Assessment Committee (OAC) review data.
- It should be noted that if there is a record of reoperation in participants who have undergone trepanation/drainage, and there is a record of surgical treatment in subjects who have received medical therapy without trepanation/drainage, the occurrence of the primary endpoint can be directly determined, and hematoma thickness or neurological symptoms are no longer required.
- In case of non-negligible amounts of missing data (>5%), we will use the MCMC method based on the Missing at random (MAR) assumption to impute missing data. The regression model will include group, sex, age, BMI, baseline mRS score and baseline maximum

hematoma thickness. The number of imputations is 10, seed=1234, nbiter=200. SAS code examples for multiple imputation will be provided in Appendix 3.

- Hematoma recurrence (trepanation/drainage group) or symptomatic hematoma progression (non-surgical group) at day 90 will be analyzed as follows. If there is any discrepancy between EDC and central imaging assessment scan date in the determination of visit window, the date determined by central imaging assessment shall prevail.

Table 5. Data Handling Rules for Primary Endpoint Analysis

Analyses	**Death within 104 days (90 days + 14 days)**	**Visit out of window**	**No 90-day (± 14 days) visit data**
Primary analyses	As if an event occurred	Observed measurements for out-of-window visits will be treated as 90-day results	Multiple imputation*
Sensitivity Analyses1	As if an event occurred	As No Event	As if an event occurred
Sensitivity Analyses 2	As if an event occurred	As No Event	As No Event

*If percentage of missing primary endpoint is less than 5%, multiple imputation will not be performed and missing data will be regarded as no event.

8.2.2. Analysis Methods

- The primary analysis will compare groups using the CMH chi-square test (the stratification factor is whether or not to perform trepanation/drainage was performed), summarize the 90-day recurrence (trepanation/drainage group) / progression rate (non-surgical group) for the MMA embolization group and the control group using the two-sided 95% CI (Clopper-Pearson method) and summarize the two-sided 95% CI for the difference in recurrence or progression rates between the two groups using the Miettinen-Nurminen method.

- Sensitivity analyses will use generalized linear mixed-effects model to calculate ORs and their 95% CIs for the comparison of recurrence or progression rates between the two arms, with group as fixed effect, site as random effect. Results of multivariable analysis will also be

presented, including treatment group, sex, age, surgical treatment strata (trepanation/drainage vs. no trepanation/drainage), any usage of antiplatelet or anticoagulant therapy, hematoma volume of baseline CT as covariates.

Enter Analysis Methods and Results Presentation

8.2.3. Model Specifications

8.2.3.1. Model Specifications of Primary Analysis

Statistical analysis of binary categorical variables
Endpoints and parameters

• Endpoint: recurrence or progression rate of hematoma at 90 days after randomization
• Parameters:
  − Proportion estimate and 95% CI
  − Risk difference, p-value and 95% CI

Input Variables
• AVAL: response variable • TRTAN: groups • COUNT: number of subjects per level per group • COVARIATES: adjustment Variables
SAS Code Sample

Example code for Clopper-Pearson 95% CI calculation:
proc freq data = adeff;
  table aval/binomial (cl = exact) alpha = 0.05 ;
  weight count;
  by trtan;
  ods output binomialcls = binomialcl;
run;
 	
Example code for risk difference and 95% CI calculation:
proc freq data = adeff;
  table trtanaval/riskdiff (cl = mn) chisq alpha = 0.05;
weight count;
  ods output pdiffcls = diff chisq = pvalue1;

run;

Example code for CMH chi-square:

```
proc freq data = adeff;
    table stratatrtanaval/chisq alpha = 0.05;
weight count;
    ods output chisq = pvalue1;
run;
```

Presentation of Results

- Estimates of rates and 95% CIs were available for BinomialCL.
- Risk difference and 95% CI are available from diff.
- Chi-square P values are available from PVALUE1.

8.2.3.2. Model Specifications of Sensitivity Analysis

Statistical analysis of binary categorical variables

Endpoints and parameters

- Endpoint: hematoma recurrence (trepanation/drainage group) or symptomatic hematoma progression (non-surgical group) rate of hematoma at 90 days after randomization
- Parameters:
  - OR and 95% CI

Input Variables

- AVAL: response variable
- TRTAN: groups
- SITEID: subject site number
- COUNT: number of subjects per level per group
- COVARIATES: adjustment Variables

SAS Code Sample

Generalized Linear Mixed-effects Model Example Code:

```
proc glimmix data=adeff descending;
    class site trtan;
    model aval/count = trtan covariates / solution;
    random intercept / subject=site;
   ods output oddsratio= odds ratio estimates；
```

run;
Presentation of Results
• The OR and 95% CI for the ratio can be obtained from Odds Ratio Estimates.

8.3. Subgroup Analyses

The primary efficacy endpoint point will be analyzed in the following subgroups:

- Age group(<70 vs ≥70)
- Sex (male vs female)
- Surgical treatment strata (trepanation/drainage vs. no trepanation/drainage)
- Smoking status(yes vs no)
- Medical history of brain trauma (yes vs no)
- Any usage of antiplatelet or anticoagulant therapy before randomization(yes vs no)
- Any usage of statins within one month before randomization(yes vs no)
- Midline shift of baseline CT (<10 mm vs ≥10 mm)
- Hematoma thickness of baseline CT (<10 mm vs ≥10 mm)
- Hematoma volume of baseline CT (<Q3 of combined hematoma volume data, ≥Q3 of combined hematoma volume data)
- Bilateral SDH (yes vs no)
- Embolized branches of MMA (main trunk only, distal only, main trunk & distal)

Subgroup analysis will use the same statistical analysis methods as described in Section 8.2.2.

9. Secondary Statistical Analyses

9.1. Secondary Efficacy Endpoint Analyses

9.1.1. Overview of Planned Analyses for Secondary Efficacy Endpoints

Unless otherwise stated, analyses of secondary efficacy endpoints will be based on the intent-to-treat analysis set (ITT) and per-protocol (PPS) set.

Table 6 Planned Overview of Secondary Efficacy Endpoint Analyses

	Data Presentation Generated		
	Table	**Figure**	**Listing**
Incidence of recurrence or progression of SDH at 360 days after randomization: Same as Table 4 Overview of planned primary statistical analyses			
Categorical secondary endpoints: Success rate of target blood vessel embolization in DSA imaging Change in mRS score at 90 days and 360 days after randomization compared to baseline Proportion of patients with mRS score of 0 to 2 at 90 days and 360 days after randomization Proportion of patients with mRS score of 0 to 3 at 90 days and 360 days after randomization Destination for rehabilitation after discharge (going home vs rehabilitation hospital)			
Statistical description of categorical data: Number (n) and percentage of subjects in each category	Y		Y
Dichotomous data analysis: - Proportion and its 95% CI - Difference in sample rate between MMA embolization and control groups, p-value and 95% CI - OR for MMA embolization and control groups with 95% CI			
Continuous Secondary Endpoints: Changes of hematoma thickness in CT or MRI imaging at 90 days after randomization compared to baseline Changes of hematoma volume at 90 days after randomization Changes of midline shift in CT or MRI imaging at 90 days after randomization Changes of mRS score at 90 days and 360 days after randomization Quality of life evaluated with EQ-5D-5L Scale at 90 days and 360 days after randomization Total hospital stay (number of days) Re-hospitalization times Total hospitalization expenses			
Statistical description of continuous data: - Number of non-missing cases (n) - Mean (standard deviation)	Y		Y

	Data Presentation Generated		
	Table	**Figure**	**Listing**
- Median - Min, Max - Q1,Q3			
Continuous data analysis: - Estimate of mean and 95% CI for MMA embolization and control groups - Difference in means and 95% CI between MMA embolization and control groups - P value for difference in means between MMA embolization and control groups			

9.1.2. Specifications of Secondary Efficacy Endpoint Analyses

9.1.2.1. Definitions and Derivations

- Change from 90 days/360 days post study treatment will be calculated as 90 days/360 days measurement – baseline measurement
- Total days in hospital = Date of discharge - Date of hospitalization + 1 (Hospital information page)
- Other definitions and derivations are the same as in Section 8 .2.1

9.1.2.2. Statistical Analysis Methods

- 360 days recurrence or progression of SDH after randomization will be analyzed in the same way as the primary endpoint (Section8.2.2)
- Ordinal logistic regression will be used for intergroup comparison of mRS scale scores at 90 and 360 days after randomization, with treatment group, sex, age, surgical treatment strata (trepanation/drainage vs. no trepanation/drainage), any usage of antiplatelet or anticoagulant therapy within one month before randomization(yes vs no), hematoma volume of baseline CT as covariates.
- Other categorical secondary endpoints will be analyzed in the same way as the primary endpoint (**Error! Reference source not found.Error! Reference source not found.**Section)

- The linear mixed effects model approach will be used to estimate the mean estimate (95% CI) and the mean estimate (95% CI) of the differences between groups as well as the P values of the differences between groups for the change in maximum hematoma thickness at 90 days after randomization compared to baseline and the change in hematoma volume at 90 days after randomization compared to baseline; Treatment group variables, sex, age, surgical treatment strata (trepanation/drainage vs. no trepanation/drainage), any usage of antiplatelet or anticoagulant therapy within one month before randomization(yes vs no), hematoma volume of baseline CT , visit variables, and visit by treatment group variable interactions will be included in the model and site as the random effect.
- For other continuous secondary endpoints, T tests will be used to compare groups, and 95% confidence intervals for the difference in means between groups will be calculated using normal approximation.

9.1.2.3. Model Specifications

Statistical analysis of binary categorical variables
Endpoints and parameters
• Endpoint: Change of mRS scale score at 90 and 360 days after randomization compared to baseline • Parameters: – Ordinal OR and 95% CI
Input Variables
• AVAL: response variable • TRTAN: groups • SITEID: subject site number • COUNT: number of subjects per level per group • COVARIATES: adjusted Variables
SAS Code Sample

Logistic Regression Example Code:
proc glimmix data=adeff descending;
class siteid trtan;
model aval/ count = trtan covariates / solution;

random intercept / subject= siteid;

run;

Presentation of Results

- The OR and 95% CI for the ratio can be obtained from Odds Ratio Estimates.

Statistical analysis of continuous variables

Endpoints and parameters

- Endpoint:
  Changes of hematoma thickness in CT or MRI imaging at 90 days after randomization compared to baseline
  Changes of hematoma volume at 90 days after randomization compared to baseline
  Changes of midline shift in CT or MRI imaging at 90 days after randomization compared to baseline
  Quality of life evaluated with EQ-5D-5L Scale at 90 days and 360 days after randomization compared to baseline
  Total hospital stay (number of days)
  Re-hospitalization times
  Total hospitalization expenses
- Parameters:
  - Mean and 95% CI
  - Difference in means and 95% CI with P-value

Input Variables

- AVAL: response variable
- TRTAN: group
- SITEID: subject site number
- AVISITN: visit variables
- COVARIATES: adjusted variables

SAS Code Sample

Linear Mixed Effects Model Method Example Code:

```
proc mixed data = adeff;
class trtan siteid avisitn;
   model aval = trtan covariates avisitn avisitn avisitn trtan/solution ddfm = kr;
   random siteid /type = cs;
lsmeans trtanavisitn/diff cl alpha = 0.05 e;
ods output lsmeans = lsmeans diffs = diffs;
run;
```

T-Test Example Code:

```
ods otput conflimits = conflimits ttests = ttests;
proc ttest data = adeff dist = normal sides = 2 ci = equal alpha = 0.05;
class trtan;
var aval;
run;
```

Presentation of Results

Linear mixed effects model approach:

- Estimation of mean and 95% CI for both groups:
  - Point Estimate: Estimate Variable in lsmeans dataset
  - Corresponding 95% CI: Lower vs. Upper variables in lsmeans dataset
- Estimate and 95% CI for difference in means between groups:
  - Filtered all TRT A N ≠ TRT A N and AVISITN = AVISITN records in Diffs dataset and output:
    - Point Estimate: Estimate Variable in Diffs Post-Screening Dataset
    - Corresponding 95% CI: Lower versus Upper Variables in Diffs Post-Screening Dataset
- P-value: Probt variable in filtered dataset Diffs

T-Test:

- The difference in means and 95% CI are available from CONFLIMITS.
- P-values for t-tests are available from TTESTS.

9.2 Safety analyses

9.2.1 Overview of Planned Safety Analyses

Unless otherwise stated, safety analyses will be based on the Safety Analysis Set.

Table 7 provides an overview of the planned safety analyses.

Table 7 Planned Safety Analysis Overview

	Data Presentation Generated		
	Table	**Figure**	**Listing**
Adverse events (within 90 days/360 days after surgery) [1]			
All Adverse Events	Y		Y
Serious Adverse Events (SAEs)			
Moderate and severe adverse events			
Procedure-related serious complications within 30 days after randomization (including surgical and interventional procedures) [1, 2]			
Major complications associated with drilling or MMA embolization	Y		Y
Major complications associated with drilling			
Major complications associated with MMA embolization			
Adverse events of special interest [1]			
Adverse events of special interest	Y		Y
Serious adverse events of special interest			Y
Death (within 90 days/360 days after randomization) [1]			
Death from any cause	Y		Y
Concomitant medications [1]			
Antiplatelet or anticoagulant therapy	Y		Y
Other concomitant medications			

Notes:

1. Categorical data.

2. Postoperative serious complications include: symptomatic intracranial hemorrhage, surgery-related intracranial hemorrhage, surgery-related neurological dysfunction , surgery-related central nervous system infection , surgery-related arterial dissection, vessel wall injury, and vessel rupture and perforation , surgery-related ischemic events , retroperitoneal/wrist hematoma , puncture site neuropathy , contrast agent allergy, or contrast agent encephalopathy

Y = Plan Generation.

9.2.2 Specifications Of Safety Analyses

9.2.2.1 Adverse Events

- An untoward medical occurrence during a clinical investigation, whether or not related to the investigational medical device, is an adverse event (AE).
- AEs will be coded using MedDRA version 24.0 or higher. System Organ Class (SOC) and Preferred Term (PT) will be reported.
- The investigator will grade the severity of the AE (mild, moderate, severe). AEs with missing severity will not be imputed.
- Adverse events will be summarized using frequency tables in descending order of incidence by SOC and PT unless otherwise specified. If a subject has the same AE reported more than once, the highest severity of this AE for that subject will be reported.
- For adverse events of special interest, the CEC assessment and investigator assessment will be performed, and the results of the two assessments will be presented separately.

9.2.2.3 Concomitant medication

- Concomitant medications are defined as medications that were taken by the patient until or until after randomization.
- Concomitant medications will be summarized by treatment group and the number and percentage of subjects will be listed by medication name.

10. References

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12. APPENDICES

1 2.1 Appendix 1: Treatment Period and Study Period

Treatment Period and Study Period

Study Day

Day 0 is defined as the day of Randomization.

Study duration after Day 0 is calculated as the number of days relative to randomization date:

- Reference Date = Missing Value → Study Day = Missing Value
- Reference Date < Randomization → Study Day = Reference Date – Randomization Date
- Reference Date ≥ Randomization → Study Day = Reference Date – randomization Date + 1

Time points and assessment windows

Study Flow Chart

STUDY PROCEDURES	Screening [a]	Baseline	Follow-up Period			
Visit Time [b]	V0	V1	V2	V3	V4	V5
	-14 to Day 0	Day 0	At discharge	Day 30	Day 90	Day 360
Informed Consent	X					
Demographics	X					
Inclusion/Exclusion Criteria		X				
Medical History and Prior Medications	X					
Vital signs	X			X	X	X

Treatment Period and Study Period						
Admission examination [c]	X					
CT/MRI [d]	X				X	X
DSA [e]		X				
Randomized and treated		X				
Treatment and nursing costs			X		X	X
Efficacy Endpoints					X	X
Serious Adverse Events			X			
SDH-related death events			X			
Procedure-related serious complications			X			
Concomitant medication/treatment			X	X	X	X
MRS scale	X				X	X
EQ-5D Scale	X				X	X

A Screening visit and baseline visit may be on the same day

B V3 visit window is ± 7 days, V4 visit window is ±14 days, and V5 visit window is ±30 days

C Blood routine (red blood cell count, white blood cell count, platelet count, hemoglobin), coagulation function (APTT , INR), liver and kidney function (ALT , AST , BUN , Cr), Electrolytes (potassium, sodium, chloride, calcium), fasting blood glucose; Women of childbearing potential will need a negative urine HCG test to be enrolled. Those women of childbearing potential with positive or missing pregnancy test will not be included.

D CT is mandatory, MRI optional, and MRI examination may be performed at the physician 's discretion according to the patient' s condition

E Performed only in the MMA embolization group

Acceptable Time Windows for Follow-up Period

Treatment Period and Study Period	
Time Point	**Acceptable Time Window**
V3	±7 days
V4	±14 days
V5	±30 days

12.2 Appendix 2: Data Display Standards and Handling Conventions

Data Display Standards and Handling Conventions

Criteria for Data Presentation

- Numerical data will be reported with precision collected in the eCRF.
- Precision reported from non-eCRF sources will follow dMed 's statistical principles but may be adjusted to clinically interpretable decimal places (dp.).
- Derived data and their statistics will be 1 decimal place more than the original data and the corresponding statistics. For example, if the raw data collected contains 1 decimal place, derived data in the listings will be presented to 2 decimal places. Therefore, the average number of derived data will be presented with 3 decimal places, minimum and maximum with 2 decimal places, standard deviation with 4 decimal places, and so on.
- Precision validity and display utility will be considered in determining the number of decimal places displayed. Therefore, if the number of decimal places is too large to add additional information, the reported data will retain the appropriate number of decimal places. The maximum number of decimal places reported for any summary statistic should be 4, unless otherwise specified.
- The maximum number of decimal places can be directly applied to the ADaM dataset.

Data Display Standards and Handling Conventions

Precision

Name	Description	Decimal place (dp)	
N	Number of subjects in treatment group	Always shown as 0 dp.	
N	Number of subjects with non-missing results	Always shown as 0 dp.	
%	Percent	Categorical data shown as 1 dp.	
Mean	Arithmetic mean	1 dp. more than original data	
SD	Standard deviation	2 dp. more than original data	
Median	Median	1 dp. more than original data	
Min.	Minimum value	Corresponds to raw data	
Max.	Max	Corresponds to raw data	
SE	Standard Error	1 dp. more than statistical parameters	
95% CI	95% confidence interval	1 dp. more than statistical parameters	
P value	P value	3 dp., or < 0.001	

Baseline Definitions and Derivations

The last non-missing measurement/assessment prior to the randomization date will be used as the baseline measurement unless specified.

Measurements/assessments will be considered (if not missing) at baseline if performed on the same day as randomization.

- Change from baseline = value at post-treatment visit – baseline if there is no specific formula or medical requirement in the protocol.
- Percent change from baseline = 100% * (treatment value at post visit – baseline)/baseline

General Data Display Standards and Handling Conversion

Data Display Standards and Handling Conventions
Planned and Actual Time ● Unscheduled visits and visits outside protocol-specified windows (ie, documented as protocol deviations) will be included in listings only, unless otherwise specified. **Proportion Calculation** ● Percent of zero counts will not be shown. ● Percentages will be calculated based on the number of participants in the analysis population of interest, unless specifically stated. Missing observations will also be included in the denominator calculation. **Time Transition of segments** ● 1 year = 365.25 days ● 1 month = 30.4375 days ● 1 week = 7 days

12.3 Appendix 3: Handling of Early Withdrawals and Missing Data

Handling of Early Withdrawals and Missing Data			
Subjects Withdrawn Early			
Subject substitution: Subjects will not be replaced regardless of withdrawal from the trial for any reason.			
Handling of missing data			
For the analysis of the primary endpoint, no 90 day (±14 days) visit data subjects w ill be handled as described in the table below.			
Analysis	Death within 104 days (90 days + 14 days)	Visit out of window	No 90-day (± 14 days) visit data

Handling of Early Withdrawals and Missing Data			
Primary analysis	As if an event occurred	Observed measurements for out-of-window visits will be treated as 90-day results	Multiple imputation*
Sensitivity 1	As if an event occurred	As No Event	As if an event occurred
Sensitivity Analysis 2	As if an event occurred	As No Event	As No Event

*If percentage of missing primary endpoint is less than 5%, multiple imputation will not be performed and missing data will be regarded as no event.

SAS Code Sample:

```
proc mi data=im1 seed=1234  nimpute=20 out=im2
round=. . . . . 1
min=. . . . . 0
max=. . . . . 1;
;
   by trtan;
   var sex age bmi basemrs basemth aval;
mcmc chain=multiple nbiter=200 niter=100;
run;


proc sort data=im2;
   by _imputation_ trtan usubjid siteid;
run;


proc transpose data=im2 out=im2_t(rename=(_name_=avisit col1=aval));
```

```
    by _imputation_ trtan usubjid siteid;
    var v1 v2;
run;

proc sql noprint;
    create table im2_count as
    select distinct
    _imputation_,
    trtan,
    avisit,
    aval,
    count(*) as count
    from im2_t
    group by _imputation_,trtan,avisit,aval
    order by _imputation_,trtan,avisit,aval
    ;
quit;

/*clopper-pearson 95%ci*/
ods select none;
proc freq data= im2_count;
    by _imputation_ trtan avisit;
    table aval / binomial (cl=exact) alpha=0.05;
    weight count;
```



```
    ods output binomial=binomial;
run;
ods select all;


proc transpose data=binomial out=binomial_t;
    by _imputation_ trtan avisit;
    var nvalue1;
    id label1;
quit;


proc sort data=binomial_t;
    by trtan avisit _imputation_;
run;


ods select none;
proc mianalyze data=binomial_t;
    by trtan avisit;
    modeleffects proportion;
    stderr ase;
    ods output parameterestimates=binomial_t_pool;
run;
ods select all;
```

```
/*mn*/
proc freq data=im2_t;
   by _imputation_ ;
   tables trtan *aval / commonriskdiff (cl=score test=score) riskdiff (cl=mn);
   ods output commonpdifftests=commonpdifftests1 commonpdiff=commonpdiff1
            pdiffcls=pdiffcls1 riskdiffcol1=riskdiffcol11;
run;

data riskdiffcol11;
set riskdiffcol11(where=(row="difference"));
run;
proc sort data=riskdiffcol11;
   by _imputation_;
run;

proc mianalyze data=riskdiffcol11;
   modeleffects risk;
   stderr ase;
   ods output parameterestimates=pest1_pool;
run;

/*cmh*/
*** perform cmh test;
proc freq data=im2_t;
```



```
 tables strata*trtan*aval/cmh;
 ods output cmh=cmh;
 by _imputation_;
run;
*** apply wilson-hilferty transformation to the cmh statistic and
 standardize the resulting normal variable;

data cmh_wh;
set cmh(where=(althypothesis="general association"));
 cmh_value_wh=((value/df)**(1/3) - (1-2/(9*df)))/sqrt(2/(9*df));
 cmh_sterr_wh = 1.0;
run;

*** combine results;
proc mianalyze data=cmh_wh;
 ods output parameterestimates=mian_cmh_wh;
 modeleffects cmh_value_wh;
 stderr cmh_sterr_wh;
run;

proc sql noprint;
    create table im2_count2 as
    select distinct
    _imputation_,avisit,siteid,trtan,aval,
```



```
    count(*) as count
    from im2_t
    group by _imputation_,avisit,siteid,trtan,aval
    order by _imputation_,avisit,siteid,trtan,aval
    ;
quit;

ods select none;
proc glimmix data=im2_count2;
    by _imputation_ avisit;
    class siteid trtan aval;
    model aval/count=trtan / solution;
    random intercept / subject=siteid;
    ods output parameterestimates=parameterestimates;
run;
ods select all;

proc sort data=parameterestimates(where=(trtan=1)) out=parameterestimates1;
    by trtan avisit _imputation_ ;
run;

ods select none;
proc mianalyze data=parameterestimates1;
    by trtan avisit;
```

```
    modeleffects estimate;
    stderr stderr;
    ods output parameterestimates=parameterestimates1_pool;
run;
ods select all;
```

Prior/concomitant medications/treatments

Prior medications/therapies are those that ended prior to randomization.

Concomitant medications/therapies are medications/therapies other than study treatment or premedication with study treatment taken at any time during the study (on or after randomization), including medications/therapies started and continued prior to randomization.

Incomplete dates for prior/concomitant/post-study medications/treatments recorded in the CRF will not be imputed and will be classified according to the following rules:

Date Started	End date	Actions
Not missing/partially missing/missing	Not missing	• Prior medication/therapy if end date < randomization date • Concomitant medication/treatment if end date ⩾ randomization date
	Partially missing, but known to partially show that it cannot occur on or after the date of randomization	• Prior Medications/Therapies
	Partial missing, unclear relationship to randomization date	• Assumed concomitant medication/treatment
	Complete absence	• Assumed concomitant medication/treatment

Note: "<" refers to "earlier than" and "≥" refers to "same day or later".

12.4 Appendix 4: Abbreviations Table

Abbreviation	Description
AE	Adverse Event
CRF	Case Report Form
CT	Computed Tomography
DSA	Digital Subtraction Angiography
EQ-5D-5L	A standardized assessment instrument (developed by the EuroQolGroup) that provides a simple descriptive measure of health-related quality of life
MMA	Middle Meningeal Artery
MRI	Magnetic Resonance Imaging
MRS	Modified Rankin Scale
PT	Preferred Term
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDH	Subdural Hematoma
SOC	System Organ Class