Middle Meningeal Artery (MMA) Embolization for cSDH: Rationale and Design for the STOp Recurrence of MMA Bleeding (STORMM) Randomized-Control Trial

Swiss ID: 2023-00848
NCT number: NCT06163547
Protocol date: September 25, 2024

Study Type:	Other Clinical Trial according to ClinO, Chapter 4
Risk Categorization:	Risk category B according to ClinO, Art. 61
Study Registration:	*Intended registries: Swiss National Clinical Trial Portal and WHO International Clinical Trials Registry Platform*

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Investigated Intervention:	Middle Meningeal Artery Embolization for Chronic Subdural Hematomas
Protocol ID	2023-00848
Version and Date:	Version 2.0 (25.09.2024)

CONFIDENTIALITY STATEMENT

PROTOCOL SIGNATURE FORM

Study Title	Middle Meningeal Artery (MMA) Embolization for cSDH: STOp Recurrence of MMA Bleeding (STORMM) Randomized-Control Trial
Study ID	2023-00848

The Sponsor has approved the protocol version 2.0 (dated 25.09.2024) and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines as well as the local legally applicable requirements.

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GLOSSARY OF ABBREVATIONS

AE	*Adverse Event*
ASR/DSUR	*Annual Safety Report / Development Safety Report*
BASEC	*Business Administration System for Ethical Committees*
ClinO	*Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)*
CRF	*Case Report Form*
cSDH	*Chronic Subdural Hematomas*
eCRF	*electronic Case Report Form*
GCP	*Good Clinical Practice*
GCS	*Glasgow Coma Scale*
GOS-E	*Glasgow Outcome Scale - Extended*
HRA	*Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)*
ICH	*International Conference on Harmonisation*
MMA	*Middle Meningeal Artery*
mRS	*modified Rankin Scale*
MGS	*Markwalder Grading Scale*
TDN	*Therapy-Disability-Neurology grading system*
SAE	*Serious Adverse Event*
SDV	*Source Data Verification*

1 STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	Prof. Karl Schaller Service de Neurochirurgie Département des Neurosciences Cliniques HUG Rue Gabriel-Perret-Gentil, 4 1211 Genève 14
Study Title	Middle Meningeal Artery (MMA) Embolization for cSDH: Rationale and Design for the STOp Recurrence of MMA Bleeding Randomized-Control Trial
Short Title / Study ID	STORMM
Protocol Version and Date	Version 2.0 (25.09.2024)
Study Registration	Intended registries: Swiss National Clinical Trial Portal and WHO International Clinical Trials Registry Platform
Study Category and Rationale	Category B
Background and Rationale	Chronic Subdural Hematomas (cSHD) are common, and due to cerebral compression, often result in neurological impairment and reduced consciousness. Surgery is typically performed once neurological symptoms develop. Recent studies suggest that arteries nourished by the middle meningeal artery (MMA) may be responsible for hematoma progression and that MMA embolization is clinically useful. There is less evidence, that embolization of MMA also may be a treatment option for individuals without surgical treatment. We propose a multicentre study to investigate both potentials: (1) Assessment of efficacy of embolization after surgery to reduce recurrence and improve outcomes by conducting a randomized trial (**randomization arms; Arms 1 and 2**), (2) Assessment of embolization-alone efficacy when surgery is contraindicated or refused (**embolization-only arm, Arms 3 and 4**).
Risk / Benefit Assessment	Evidence to support the benefit of MMA embolization remains limited and the risk-benefit balance remains unclear. Case series have shown that recurrence rates with embolization are much lower, and that embolization is generally very safe. Risks associated with neurointerventional procedures will be directly discussed with patients or their caretakers as part of the conventional consenting procedure. Risks include access site hematoma, radiation exposure, vascular injury, brain ischemia, death (theoretic and extremely unlikely) and typical risks associated with general or local anaesthesia. The potential efficacy of MMA embolization as a treatment therefore requires higher level evidence in the form of randomized control trials. The benefit of the embolization is a substantial reduction in recurrence of cSDH, which has been reported to be as high 1 in 3-4 patients. Recurrence of cSDH can lead to additional surgery and complications.
Objective(s)	**First objective**: Evaluate the recurrence rates of cSDH after combined surgical and MMA embolization treatments (Arm 2) versus surgery alone (Arms 1). **Second objective**: The second objective is to evaluate the stability and regression of cSDH after for all the Arms of the study at follow-up.
Endpoint(s)	**Primary endpoint:** Clinical finding of recurrence of cSDH: surgical reoperation, neurological deterioration due to a cSDH after evacuation, post-

	operative hematoma volume of more than 90% of the preoperative volume at follow-up. **Additional endpoints:** Glasgow Coma Scale (GCS), modified Ranking Scale (mRS), Markwalder Grading Scale (MGS), Glasgow Outcome Scale – Extended (GOS-E), Karnofsky Performance Score (KPS), Therapy-Disability-Neurology grading system (TDN), mortality rate, and re-hospitalisation for all causes.
Study Design	This study is a multicentre randomised-controlled trial.
Statistical Considerations	The incidence rates of cSDH recurrence is estimated at 20% and recurrence with MMA at 5%. With an alpha = 0.05 and a power of 80%, we estimate that a minimum of 156 patients (https://clincalc.com/stats/samplesize.aspx) need to be enrolled. Assuming a 15% loss of follow-up, 180 patients need to be enrolled in the study. It is therefore planned to enrol a total of 180 patients, with the aim of 60 patients per centre, however, this is flexible.
Inclusion- / Exclusion Criteria	**Inclusion Criteria: (Appendix 1)** - Age 18-100 years - Consent possible - cSDH located at the cerebral convexities - Patients with symptomatic cSDH - Patients with asymptomatic large chronic/subacute hematoma after 6 weeks of failed conservative treatment. **Exclusion Criteria:** - Consent not possible - Pregnancy - Prisoner - Angiography contraindication -Patient for whom follow-up is problematic (e.g. distant residency, homeless) - Previous surgery for cSDH **Exclusion for Randomization arms (Arms 1 and 2), but inclusion for embolization-only arms (Arms 3 and 4):** - Surgery not performed due to significant surgical contraindications - Refusal of surgical treatment
Number of Participants with Rationale	We estimate that a minimum of 156 patients need to be enrolled. Assuming a 15% loss of follow-up, a total of 180 patients needs to be enrolled in the study.
Study Intervention	Patients who undergo surgical treatment will be randomized into receiving embolization within 72 hours post-surgery (Arm 2) or no-embolization post-surgery (conventional management, Arm 1). Patients will be randomized at rate of 2 MMA embolization to 1 conventional management. Patients who are excluded for surgery due to significant medical contraindications (e.g. severe thrombocytopenia or double anti-thrombotic therapy without imminent danger of death) or patients who refuse surgery, will be considered for embolization only (Arms 3 and 4).
Control Intervention	Arm 1: conventional management
Study procedures	Patients who undergo surgical treatment will be randomized into receiving embolization within 72 hours post-surgery (Arm 2) or no-embolization post-surgery (conventional management, Arm 1). Patients will be randomized at rate of 2 MMA embolization to 1 conventional management. Patients who are excluded for surgery due to significant medical contraindications (e.g. severe thrombocytopenia or double anti-thrombotic

	therapy without imminent danger of death) or patients who refuse surgery, will be considered for embolization only (Arms 3 and 4). The details of study intervention are shown in the schedule assessments (Appendix 2). The recorded data to evaluate the recurrence of cSDH are surgical reoperation within 6 months but after 72 hours or after embolization, neurological deterioration due to a cSDH after evacuation, post-operative hematoma volume of more than 90% of the preoperative volume at follow-up. Additional outcomes such Glasgow Coma Scale (GCS), modified Ranking Scale (mRS), Markwalder Grading Scale (MGS), Glasgow Outcome Scale – Extended (GOS-E), Karnofsky Performance Score (KPS) and the Therapy-Disability-Neurology grading system (TDN) will be recorded (Appendix 3).
Study Duration and Schedule	The study will be undertaken at multiple trauma centres in Europe with the objective to enrol patients within an 18-24-month time-frame. With the last follow-up planned at 6 months, the combined study duration is expected to be no longer than 24-30 months. Planned 10/2024 of First-Participant-In. Planned 04/2027 of Last-Participant-Out.
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Study Center(s)	2 Swiss centres are involved in the study: Geneva and Lugano
Data privacy	Data privacy will be ensured through anonymization end encoding of all patients' data.
Ethical consideration	While it has been shown that the MMA embolization can reduce recurrence, this has not yet been demonstrated with high-level evidence. As low risks exist with the neuro-interventional procedures, there is a need for high level of evidence studies by randomizing patients to evaluate the potential benefits and to determine if these clearly outweigh the risks and costs of MMA embolization. Peer review publications and presentations of the results at international meetings are planned. The process of embolization requires another general anaesthesia, and while angiographic procedures are generally well tolerated, undertaking this procedure add a level of risk higher than the one of patients not undergoing embolization procedures. It is however believed based on data from previous case series and from expert opinion that the benefit of embolization will greatly outweigh the risks.
GCP Statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements.

2 BACKGROUND AND RATIONALE

Chronic Subdural Hematoma (cSDH) is one of the most frequently encountered pathologies in neurosurgery, presenting typically in the elderly population. The condition is often preceded by a history of a relatively minor trauma to the head, usually weeks before the onset of neurological symptoms. Patients can present with a wide set of neurological symptoms which typically include a reduced state of consciousness and confusion. The most important risk factors associated with cSDH development include anti-thrombotic medication use, male sex and craniocephalic disproportion often as a consequence of alcohol abuse, cerebral atrophy or both (1). Treatment for cSDH is typically undertaken once a patient becomes symptomatic and is classically performed by burr hole drainage of the hematoma, which resolves symptoms in a relatively rapid fashion.

cSDH are known for their frequent recurrence, with estimates in literature currently approximating a rate of between 9-33% (2-5). While the exact pathophysiology of the initial hematoma formation is not fully understood, it is believed that the shearing of veins at the dural cell layer is the initiating event, neovascularization in the ensuing inflammatory response is thought to be nourished by branches of the middle meningeal artery (MMA) (1). As a consequence, recent studies have shown that the embolization of the MMA can result in lower rates of recurrence, with a recent systematic review showing a composite recurrence rate of only 3.6% (6). The ramifications of such a drastic decline in rates of recurrence include a reduced need to re-operate individuals, often elderly, who often require anti-thrombotic medication for other medical conditions. However, evidence to support the benefit of MMA embolization remains limited and the risk-benefit balance remains unclear. The potential efficacy of MMA embolization as a treatment therefore requires higher level evidence in the form of randomized control trials.

In the present study, we outline the research protocol for a prospective multicenter randomized control trial wherein patients who undergo surgical treatment for cSDH will either receive post-operative MMA embolization or will be under observation following conventional management. It is hypothesized that MMA-embolization will reduce the recurrence of cSDH.

As a second focus, this study will also assess the potential benefit of MMA embolization for patients who have a surgical indication but cannot undergo surgery (due to personal or medical reasons). The objective of assessment of this cohort is to evaluate the capacity of MMA embolization to stop progression of cSDH. These patients as well as those choosing no treatment will not be randomized, but followed in the same manner as randomized patients. In this group it is hypothesized that MMA-embolization will prevent progression of the cSDH.

3 STUDY OBJECTIVES AND DESIGN

2.1 Hypothesis and primary objective

It is hypothesized that post-operative MMA embolization will reduce the recurrence of cSDH.

The primary objective is to evaluate the recurrence rates of cSDH at 6 months after combined surgical and MMA embolization treatment (Arm 2) versus surgery without embolization (Arm 1) (Appendix 1).

This study will also assess the potential benefit of MMA embolization-only treatment for patients who have a surgical indication but cannot undergo surgery (due to personal or medical reasons, Arms 3). The objective of assessment of this cohort is to evaluate the capacity of MMA embolization to stop progression of cSDH. These patients as well as those choosing no treatment (Arm 4) will not be randomized, but followed in the same manner as randomized patients (Arms 1 and 2). In this group it is hypothesized that MMA embolization will prevent progression of the cSDH. For patients included in the Arms 3 and 4, the follow-up schedule remains the same as for

the randomized cohort (Arms 1 and 2) (Appendix 2). Likewise, the same radiological parameters will be assessed (electronic Case Report Form (eCRF), Appendix 3). The second objective of our study is to evaluate the stability and regression of cSDH between all Arms of the study at follow-up.

2.2 Primary and secondary endpoints.

Primary endpoint: The primary endpoint is cSDH recurrence at 6 months post-treatment. A recurrence is defined as a cSDH recurrence that requires surgical re-operation, a neurological deterioration due to a cSDH occurring 72 hours post-evacuation (or embolization) or thereafter, or a post-operative hematoma volume of more than 90% of the pre-operative volume at any follow-up.

The study will use a combination of clinical, radiological and functional measures to assess differences in recurrence between the primary objective, and secondary objectives. The radiological assessment includes hematoma volume, maximal coronal and sagittal hematoma size, and degree of mid-line shift for unilateral cSDHs, as measured on CT at 6-weeks and 6-months follow-up (Appendix 3). Recurrence of unilateral and bilateral hematomas will be recorded.

Radiological definition of hematoma “regression”, “stability” and “progression” are defined as >10% reduction in hematoma volume, +/-10% of previous hematoma volume, >10% increase in hematoma volume, respectively. Furthermore, the presence and proportion of “acute” components of the hematoma will be noted (acute component of >75%, 50-75%, <50% and >25%, 25% or less,0%) (Appendix 3).

Secondary endpoints: Additional outcomes such Glasgow Coma Scale (GCS), modified Ranking Scale (mRS), Markwalder Grading Scale (MGS), Glasgow Outcome Scale – Extended (GOS-E), Karnofsky Performance Score (KPS) and the Therapy-Disability-Neurology grading system (TDN) will be recorded (7-11) (Appendix 3). The occurrence of mortality and re-admission will likewise be monitored during the study period (Appendix 3). The recommencement of anti-thrombotic medication for patients under such treatment will be noted at time of discharge, and each follow-up period (Appendix 3).

2.3 Study design

We plan on recruiting all adult patients based on the inclusion and exclusion criteria outlines in Appendix 1. Patient demographic characteristics will be collected, as well as notable comorbidities (including COVID infection), the use of steroids, use of antithrombotic medication, smoking status, alcohol abuse, history of trauma, COVID vaccination status (and time of vaccination) (Appendix 3). In addition, a Charleston comorbidity index score will be attributed to all patients (7) (Appendix 3).

The study will be undertaken at the HUG and in the Lugano Neurocenter of the Southern Switzerland, and will in the future involved others trauma centres in Europe with the objective to enrol patients within an 18-24-month time-frame. With the last follow-up planned at 6-months, the combined study duration is expected to be no longer than 24-30 months.

Patients who undergo surgical treatment will be randomized into receiving embolization within 72 hours of surgery (Arm 2) or no-embolization (Arm 1) (Appendix 1). Patients will be randomized at rate of 2 MMA embolization to 1 conventional management. Depending on whether the consent can be obtained before surgery, and on the availability of neuro-interventional and anaesthesia staff, efforts will be made to undertake the embolization directly after surgery to avoid additional anaesthesia.

The choice for the randomisation rate of 2 MMA embolisation / 1conventional management is based on the three following points:
1) While there are no previous RCTs for this treatment, evidence seems to point to a consistent benefit of embolization with a low associated risk of complications.
2) As MMA embolisation is a relatively new procedure, allocating more patients to the intervention reduces the potential effect of the learning curve on the results.
3) As complications are rare, having more patients receiving MMA embolization permit to better evaluate this treatment.
Patients who are excluded for surgery due to significant medical contraindications (e.g. severe thrombocytopenia or double anti-thrombotic therapy without imminent danger of death) or patients who refuse surgery will be considered for embolization only (Arms 3 and 4) (Appendix 1).

2.4 Study intervention

Patients who undergo surgical treatment will be randomized into receiving embolization within 72 hours of surgery (Arm 2) or no-embolization (Arm 1). Patients will be randomized at rate of 2 MMA embolization to 1 conventional management.

Patients who are excluded for surgery due to significant medical contraindications (e.g. severe thrombocytopenia or double anti-thrombotic therapy without imminent danger of death) or patients who refuse surgery will be considered for embolization only (Arms 3 and 4).

The details of study intervention are shown in the Appendix 1 and in the schedule assessments (Appendix 2).

4 STUDY POPULATION AND STUDY PROCEDURES

3.1 Inclusion and exclusion criteria, justification of study population

Inclusion Criteria (Appendix 1):

- Age 18-100 years, male or female
- Consent possible
- cSDH located at the convexities
- Patients with symptomatic cSDH
- Patients with asymptomatic large chronic/subacute hematoma after 6 weeks of failed conservative treatment.

Exclusion Criteria (Appendix 1):

- Consent not possible
- Pregnancy
- Prisoner
- Angiography contraindication
- Patient for whom follow-up is problematic (e.g. distant residency, homeless)
- Previous surgery for cSDH

Patients who will undergo surgical treatment (standard treatment of cSDH) and who will accept the STORMM consent will be randomized into receiving embolization within 72 hours post-surgery (Arm 2) or no-embolization post-surgery (conventional management, Arm 1). Patients will be randomized at rate of 2 MMA embolization to 1 conventional management.

Patients who are excluded for surgery, due to significant medical contraindications (e.g. severe thrombocytopenia or double anti-thrombotic therapy without imminent danger of death) or patients who refuse surgery, and who will accept the STORMM consent, will be considered for embolization only. Patients consenting embolization will be part of the Arm 3, and patients refusing embolization will be part of the Arm 4.

3.2 Recruitment, screening and informed consent procedure

We will proceed to a prospective recruitment in the Departments of Neurosurgery of the HUG and of the Lugano Neurocenter of the Southern Switzerland. All patients with inclusion criteria compatible will be enrolled for the different arms.

The investigators and research personnel will explain to each participant (or their caretaker) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits, and any discomfort it may entail. Each participant (or their caretaker) will be informed that the participation in the study is voluntary and that he or she may withdraw from the study at any time and that withdrawal of consent will not affect his or her subsequent medical assistance and treatment.

The participant (or their caretaker) will be informed that his or her medical records may be examined by authorised individuals other than their treating physician.

All participants (or their caretaker) for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study (Appendix 4 and 5). Patients (or caretaker) will be given at least 24 hours to decide whether to participate or not. However, patients can be included if they wish to give their consent before 24 hours. The formal consent of a participant, using the approved consent form, will be obtained before the participant is submitted to any study procedure (Appendix 4). In case of patient without discernment, the consent form could be signed by his/her representative (Appendix 5). The consent form will be signed and dated by the investigator or his/her designee at the same time as the participant sign. A copy of the signed informed consent will be given to the study participant. The consent form will be retained as part of the study records.

In case of emergency, if MMA embolization can be performed directly following the surgery, as this would reduce the risk associated with undergoing a second anaesthesia for the embolization sometime after the surgery, the patient could be recruited in emergency (Appendix 6 and 7). The anaesthesiologist involved in the care of the patient, but not involved in the project, will be consulted before the emergency inclusion of the patient in the study. The consent of the patient (Appendix 6) or of her/his legal representative (Appendix 7) will be requested *a posteriori*. If the patient or her/his legal representative refuses consent, the patient's data will not be included in the study.

Patients who decide not to participate in the study will be treated as per current standard of care.

3.3 Study procedures

The study will be undertaken at the HUG and in the Lugano Neurocenter of the Southern Switzerland, and will in the future involved others trauma centres in Europe with the objective to enrol patients within an 18-24-month time-frame. With the last follow-up planned at 6-months, the combined study duration is expected to be no longer than 24-30 months.Patients who undergo surgical treatment will be randomized into receiving embolization within 72 hours post-surgery (Arm 2) or no-embolization (Arm 1). Patients will be randomized at rate of 2 MMA embolization to 1 conventional management.
Patients who are excluded for surgery due to significant medical contraindications (e.g. severe thrombocytopenia or double anti-thrombotic therapy without imminent danger of death) or patients who refuse surgery will be considered for embolization only: Arm 3: Patients consenting embolization; Arm 4: Patients refusing embolization.

3.4 Withdrawal and discontinuation

Patients will be able to withdraw from the study at any given time by notifying the investigators (Appendix 8 and 9). Patients will have to choose whether she/he wants that her/his data will be stored coded or anonymized. Anonymised information regarding patients' sex and age will be kept in a separated, encoded file to test for selection biases (internal quality control of the study).

5 STATISTICS AND METHODOLOGY

4.1. Statistical analysis plan and sample size calculation

Randomized Arms: Arms 1 and 2:

The incidence rates of cSDH recurrence is estimated at 20% and 5% without and with MMA embolization, respectively. For an alpha = 0.05 and a power of 80%, we estimate that a minimum of 156 patients need to be enrolled. Assuming a 15% loss of follow-up, a total of 180 patients need to be enrolled in the study. It is therefore planned to enrol 180 patients.

Comparison of recurrence rate between the groups will be assessed via logistic multivariate analysis where recurrence is the dependent variable. Sex, presence of unilateral/bilateral cSDH, treatment of anti-thrombotic medication, alcohol abuse, age and cerebral atrophy will be considered as independent variables.

The random assignment of participants to conventional treatment (Arm 1) or MMA embolization (Arm2) will be achieved using a block randomization method stratified by centre (Geneva, Lugano). Random block sizes will be used. To maintain the concealment of allocation principle, block sizes will only be revealed once enrolment is ended.
For each centre, the randomization list will respect a 1:2 ratio (1 conventional management for 2 MMA embolization). Expecting a higher capacity of patient enrolment in Geneva, the randomization lists will be of different size:

- The randomization list will be of size n=120 in Geneva (n=40 in arm1, n=80 in arm2);
- The randomization list will be of size n=60 in Lugano (n=20 in arm1, n=40 in arm2).

Randomization will be computer generated with R software. The seed allowing to reproduce the randomization plan will be stored in the programming file of the software (r script).

Embolization-only Arms: Arms 3 and 4:

This part of the study is inherently exploratory, and it is not possible to estimate how many people will fall into this category as this is not yet a standardized treatment. The benefits of embolization (Arm 3) will be compared to patients who are eligible for embolization only but do not receive this treatment (the patient or his/her caregivers do not wish) and are only followed clinically (Arm 4). Enrolment for this portion of the study will terminate once the recruitment goal of the randomized portion of the study is attained. If the cohort size permits, changes in outcomes (changes in volume progression, mortality and readmission) between these 2 groups will be assessed with univariate and multivariate analysis.

4.2. Handling of missing data and drop-outs

Data obtained until the dropout will be kept unless the patient refuses. If interpretable, they will be analysed. Missing data will not be imputed or replaced; patients with missing data will be excluded from analyses for the primary objectives, however, this data may be used for subsequent secondary analyses if interpretable.

6 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements (12-17).

5.2 (Serious) Adverse Events and notification of safety and protective measures

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation subject which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavorable or unintended finding, symptom, or disease temporally associated with a trial procedure, whether or not related to it.

A Serious Adverse Event (SAE) (ClinO, Art. 63) is any untoward medical occurrence that

- Results in death or is life-threatening,
- Requires in-patient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity, or
- Causes a congenital anomaly or birth defect.

Both Investigator and Sponsor-Investigator make a causality assessment of the event to the trial intervention (see table below based on the terms given in ICH E2A guidelines (16)). Any event assessed as possibly, probably or definitely related is classified as related to the trial intervention.

Relationship	**Description**
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Both Investigator and Sponsor-Investigator will make a severity assessment of the event as mild, moderate or severe. Mild means the complication is tolerable, moderate means it interferes with daily activities and severe means it renders daily activities impossible.

Reporting of SAEs (see ClinO, Art. 63)

All SAEs will be documented and reported immediately (within a maximum of 24 hours) to the Sponsor-Investigator of the study (Appendix 10).

If it cannot be excluded that the SAE occurring in Switzerland is attributable to the intervention under investigation, the investigator will report it to the Ethics Committee via BASEC within 15 days.

If the SAE occurs at one of the study sites, the coordinating investigator will report the events to the Ethics Committee concerned, within 15 days.

Follow up of (Serious) Adverse Events

The patient population on average is considered very old (70-80 years) and present with a condition requiring surgery. Therefore, the possibility of SAE regardless of embolization is considered high. We will note the record cases of mortality, re-operation within 6 months, and embolization related complications, and undertake an interim analysis after 50% of study enrollment. As this would result in an estimated 60 patients (30 of 90 enrolled) receiving embolization, this number will likely provide sufficient to determine if there is a significant increase of adverse events. Monitoring for adverse events will be undertaken continuously, and if it is deemed that there is a disproportionate number of adverse events that are occurring prior to the interim analysis, an earlier case-analysis may be sought under such an exceptional circumstance. The management of and reporting of adverse events will be guided by the center of clinical research at HUG.

Notification of safety and protective measures (see ClinO, Art 62, b)

If immediate safety and protective measures have to be taken during the conduct of the study, the investigator will notify the Ethics committee of these measures, and of the circumstances necessitating them, within 7 days.

5.3 (Periodic) safety reporting

An annual safety report (ASR/DSUR) will be submitted once a year to the local Ethics Committee by the Investigator (ClinO, Art. 43 Abs). In international multicentric studies, the ASR/DSUR contains information from all sites including information from sites outside of Switzerland. The Sponsor-Investigator distributes the ASR/DSUR to all the participating Investigators.

5.4 Radiation

The radiation exposure from conventional cerebral angiograms has been reported to range between 350 to 4100 mGy, with the wide range being due to numerous factors including body habitus, anatomy and technical factors (18). This dose in the context of radiology is high and the risks and benefits of the neuro-interventional procedure which includes radiation exposure will be discussed as part of the standard consent practices.

5.5 Pregnancy (if applicable)

Pregnant women are excluded from the present study.

5.6 Amendments

Substantial changes to the study setup and study organization, the protocol and relevant study documents will be submitted to the Ethics Committee for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Ethics Committee. Such deviations shall be documented and reported to the Ethics Committee as soon as possible.

A list of all non-substantial amendments will be submitted once a year to the competent EC together with the ASR.

5.7 (Premature) termination of study

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, e.g.

- Ethical concerns,
- Insufficient participant recruitment,
- When the safety of the participants is doubtful or at risk (e.g. when the benefit-risk assessment is no longer positive),
- Alterations in accepted clinical practice that make the continuation of the study unwise,
- Early evidence of harm or benefit of the experimental intervention.

Upon regular study termination, the Ethics Committee will be notified via BASEC within 90 days (ClinO, Art. 38). Upon premature study termination or study interruption, the Ethics Committee is notified via BASEC within 15 days (ClinO, Art. 38).

At the end of the study, all health-related data and data analysis will be anonymized and will be kept in an encoded document available to the Principal Investigator during a duration of 10 years.

5.8 Insurance

In the event of study-related damage or injuries, the liability of the institution HUG provides compensation, except for claims that arise from misconduct or gross negligence.

6 FURTHER ASPECTS

6.1 Overall ethical considerations

The study protocol, the documents intended for the patients, and the list of investigators have been submitted to the Cantonal Commission of Ethics for Research on human beings (CCER) for approval. During the course of the study, the investigators will be obliged to submit to the CCER for review any changes to these documents, to inform the CCER of the progress of the study, of the occurrence of SAEs and of any new relevant facts concerning the investigational product.

6.2 Risk-benefit assessment

Evidence to support the benefit of MMA embolization remains limited and the risk-benefit balance remains unclear, although preliminary evidence seems to suggest a significant benefit.

The potential efficacy of MMA embolization as a treatment therefore requires higher level evidence in the form of randomized control trials.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

The interview of the patient will be done by a clinician of the clinical care team via the use of computerized data entry of the hospital's patient records interface.

Health-related personal data captured during this project are strictly confidential. Data generation, storage and analyses of health-related personal data within this project will strictly follow the current Swiss legal requirements for data protection and will be performed according to the Ordinance HRO Art. 5. Only authorized personnel will have access to health-related data. Information about study subjects will be kept confidential and managed according to the requirements of the Authorities.

For quality assurance the sponsor, the Ethics Committee or an independent trial monitor may visit the research sites. Direct access to the source data and all study related files is granted on such occasions. All involved parties keep the participant data strictly confidential.

7.2 Data recording and source data

The investigators will manage the data which will be treated confidentially according to the rules of medical secrecy. The data of each patient will be reported in a dedicated eCRF (Appendix 3) and encoded. The same code will be assigned to the source data containing the patient's parameters. The CRFs will be kept in the Neurosurgery Departments until the end of the study. For security and storage issues, data will be transcribed and coded in a REDCap database that will be created especially for this study. The principal investigator and secondary investigators will keep the code key.

7.3 Confidentiality and coding

Study data will be collected from the CRFs. Patient names will be replaced by a study participation number (code). Only investigators actively involved in the study will know the identity of the patient. Subjects will be informed that their personal data may be made available in the event of an audit or inspection by regulatory authorities, in a confidential manner and for the purpose of verifying the application of the ethical principles of Good Clinical Practice in the context of a research protocol. In case of publication, the results will be expressed in a collective manner and no patient will be identifiable.

The type of coding is quantitative. Software used for coding and archiving will be the REDCap database, a swiss CTDMS (Clinical Trials Data Management system) already widely used in our institution.

7.4 Retention and destruction of study data

All study data are archived for 10 years after study termination or premature termination of the study.

8 MONITORING AND REGISTRATION

For the Geneva University Hospitals, the institution that will perform the monitoring duties of this study is the Clinical Research Center of the HUG (Appendix 11).

Performed monitoring will be:
- site initiation visit,
- routine visit at 5% patient's inclusion: full source data verification (SDV),
- routine visit at 50% of remaining patients: partial SDV-key data,
- close-out visit.

For the Neurocenter of the Southern Switzerland, the institution that will perform the monitoring duties of this study is the Clinical Trial Unit of the EOC (Appendix 12).

Performed monitoring will be:
- site initiation visit,
- Routine Monitoring Visit 1: Once 5 participants are enrolled,
- Routine Monitoring Visit 2: Once 21-24 participants are enrolled,
- Routine Monitoring Visit 3: Once 37-42 participants are enrolled,
- Routine Monitoring Visit 4: Once 53 participants are enrolled - last visit of the 60th,
- Routine Monitoring Visit 5: Once 69 participants are enrolled,

- Routine Monitoring Visit 6: Once 86 participants are enrolled,
- Routine Monitoring Visit 7: Once 103 participants are enrolled,
- Routine Monitoring Visit 8: After last participant last visit,
- Close-Out Visit: After database lock except in case of premature site closure

The study is registered in a national language in the Swiss National Clinical trial Portal (SNCTP via BASEC): SNCTP000005765 | NCT06163547 | BASEC2023-00848. In addition, the study is registered in a registry listed in the WHO International Clinical Trials Registry Platform (ICTRP; http://www.who.int/ictrp/en/): Clinicaltrials.gov: NCT06163547.

9. FUNDING / PUBLICATION / DECLARATION OF INTEREST

The authors declare no competing interest.

Currently the project is funded by the “Fond de Service de Neurochirurgie (HUG)”, and the “Fondation Privée des HUG”, and financial support are regularly submitted to private foundations and public funding agencies.

Results will be disseminated via several ways:
- Research reports for the financial supporting foundations,
- Scientific article(s) in peer-reviewed international journal(s).

All data or biological samples collected from patients in this study are public but remain protected and access gated under the responsibility of the HUG and the project leader.

All data resulting from the processing of information remains the intellectual property of the individual or group of individuals that developed the data processing method and remain under the responsibility of the individual or group of individuals that generated the processed data.

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APPENDIX

Appendix 1: Inclusion and exclusion criteria - Study arms
Appendix 2: Schedule of assessment
Appendix 3: Case report form
Appendix 4: Information letter and informed consent form for patients
Appendix 5: Information letter and informed consent form for representative
Appendix 6: Information letter and informed consent form for patients recruited in emergency
Appendix 7: Information letter and informed consent form for representative of patients recruited in emergency
Appendix 8: Consent withdraw for patients
Appendix 9: Consent withdraw for representative
Appendix 10: SAE report
Appendix 11: Monitoring plan for Geneva
Appendix 12: Monitoring plan for Lugano