Improving the outcome of chronic subdural hematoma by embolization of the middle meningeal artery (ELIMINATE)

A multicenter, randomized controlled clinical trial

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ELIMINATE: Improving the outcome of cSDH by embolization of the middle meningeal artery

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PROTOCOL SIGNATURE SHEET

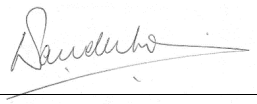
Name	**Signature**	**Date**
Head of Department: Prof.dr. W.P. Vandertop		116-063-202110
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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Event**
AR	**Adverse Reaction**
BHC	**Burr hole craniostomy**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CRF	**Case Report Form**
CRU	**Clinical Research Unit**
cSDH	**Chronic Subdural Hematoma**
DSMB	**Data Safety Monitoring Board**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
MMA	**Middle Meningeal Artery**
NFU	**Dutch Federation of University Medical Centers**
PIN	**Patient Identification Number**
QALY	**Quality Adjusted Life Year**
RCT	**Randomized Controlled Trial**
(S)AE	**(Serious) Adverse Event**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale:

Chronic subdural hematoma (cSDH) is a common neurological affliction which affects mostly frail and elderly patients. Surgical evacuation by using burr hole craniostomy (BHC) is the most frequently used treatment but carries a recurrence rate varying between 10-30% in the literature. Especially in this frail population re-operation is undesirable. Embolization of the middle meningeal artery is an adjuvant treatment which has been reported in multiple case reports and larger case series, showing a beneficial effect on recurrence rate, reducing it to <5%, with little chance on complications.

Objectives: Primary: To evaluate whether additional embolization of the middle meningeal artery after surgery for cSDH reduces the recurrent surgery rate. Secondary: to evaluate whether the use of middle meningeal artery embolization after surgical treatment in symptomatic cSDH patients increases quality of life (SF-36 and the EQ-5D-5L), performance in activities of daily living (Barthel index), functional outcome (mRS), cognitive functioning (MOCA/m-TICS) and reduces mortality, occurrence of complications, recurrence rate, size and volume of the hematoma, neurological impairment (mNIHSS, Markwalder score) and the use of care and health-related costs (iMCQ and iPCQ).

Study design: Multicenter, randomized controlled open-label superiority trial.

Study population: Patients diagnosed with a cSDH who require surgery.

Intervention: The intervention group will receive embolization in addition to standard surgical treatment. The control group will receive surgery only.

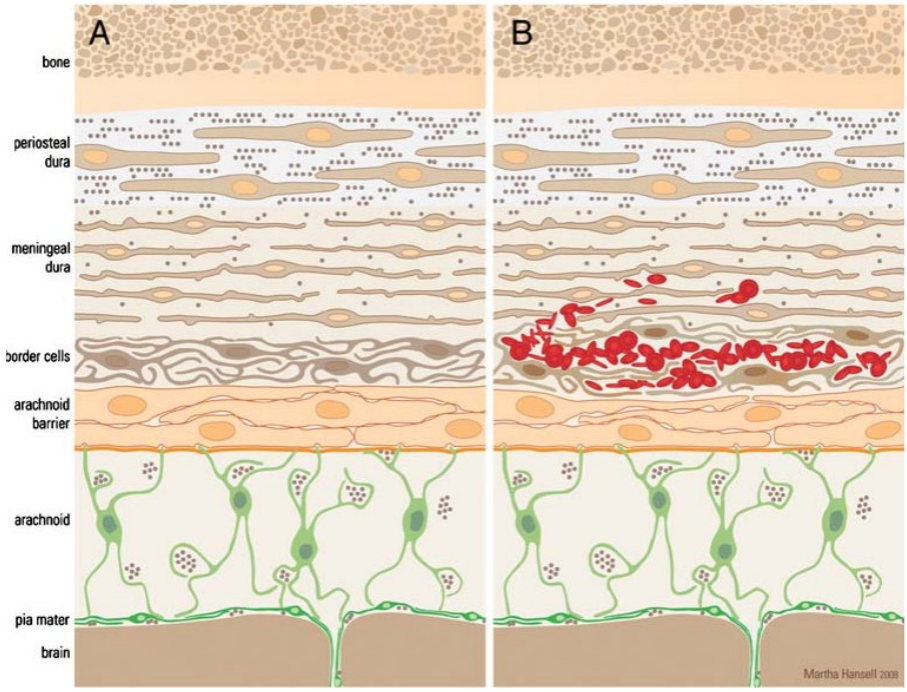
Main study endpoint: The number of patients who require reoperation within 24 weeks after the intervention.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Symptomatic cSDH patients will undergo peri-operative embolization of the middle meningeal artery until 72 hours after surgical treatment. Complications are monitored during hospital admission and follow-up. Radiological and clinical follow-up is at eight, 16 and 24 weeks post-intervention with a CT-scan of the head and assessment of mRS, MOCA/m-TICS, mNIHSS, Markwalder score, SF-36, EQ-5D-5L, Barthel index, iMCQ and iPCQ. Standard care after surgery entails outpatient follow-up with on average two CT-scans, indicated by clinical signs and symptoms. For this study a CT-scan will be performed routinely at eight, 16 and 24 weeks post-intervention; embolization, on average one CT-scan, and questionnaires are extra for this study. Potential complications of endovascular embolization are thromboembolic events which occur in <0.3%. Patients may benefit from the study if embolization proves to be effective to prevent recurrent surgery, thereby lowering the morbidity and mortality rate and increasing quality of life.

1. INTRODUCTION AND RATIONALE

Chronic subdural hematoma

A chronic subdural hematoma (cSDH) is a collection of blood at the arachnoid-dura interface located in the dural border cell layer [1].



Subdural hematomas are one of the most common forms of hemorrhage affecting mostly elderly people. The estimated incidence in Western countries is 8.1 per 100,000 per year in patients aged 65 years or older, but increases to 58/100,000/year for those aged 70 years or older [2]. With the elderly population growing, the incidence of cSDH is expected to double by 2030 [3]. CSDH presents itself as an heterogeneous disease with various symptoms. Most common are gait disturbances, focal deficits, headaches and hemiparesis [3, 4]. Risk factors for occurrence are chronic alcoholism, male gender and anticoagulation and antiplatelet therapy [4, 5]. CSDH is a challenging disease of which the pathophysiology is not completely clear. Even though cSDH initially arises due to tearing of the bridging veins, its chronicity likely has an arterial origin. At first a subdural hematoma forms after a (minor) head trauma. The hematoma persists due to failure of the reparative and absorbing mechanisms. The current

hypothesis states that the inability of the human body to heal the hematoma is due to increased inflammation in the subdural fluid and neovascularization in the subdural membrane of the hematoma. This leads to repeated micro hemorrhages and further increase in inflammatory cells and fibrinolytic activity, which unables the body to stop recurrent microbleedings. Repeated micro hemorrhages are caused by collateral blood vessels originating from the middle meningeal artery [6, 7]. The correlation between the cycle of re-bleeding, fibrinolysis, inflammation and reabsorption of the subdural collection will determine whether the cSDH will resolve, persist or enlarge [8-13].

Treatment options

The first treatment option for mildly symptomatic cSDH is a conservative 'wait-and-scan' approach in which the patient is followed with CT-scans and outpatient clinic visits. The majority (75%) of these conservatively managed patients however, eventually still require surgery (own data). Medical treatment is a second non-surgical treatment option currently being studied in large RCTs, for instance with steroids (dexamethasone), mannitol, tranexamic acid, statins and ACE-inhibitors [14-19].

Surgical treatment is most frequently used in symptomatic patients with a cSDH as surgery provides instant decompression of the brain and rapid relief of (life-threatening) symptoms. However, surgery is costly and in these often frail patients with multi-morbidity, surgery comes with significant risks for future cognitive functioning and therefore loss of independence [20]. Furthermore, recurrence rates after surgery range from 9-30%, resulting in frequent re-operations [21, 22]. Therefore, the optimal treatment for cSDH remains a 'burning clinical question' for which neurologists and neurosurgeons do not have evidence-based answers. Multiple studies have described successful treatment with embolization of the middle meningeal artery as an adjunct to surgical evacuation [7, 23-25]. The goal of embolization is to devascularize the subdural membranes to a sufficient extent such that the balance is shifted from the continued rebleeding and accumulation of blood products towards reabsorption of the subdural effusion [26]. The use of embolization in cSDH patients was first reported in 2000 by Mandai et. al. [27] and since then multiple case reports, case series and cohort studies have been published investigating the safety and effectiveness [6, 7, 23-25, 27-39]. Ban et al. [23] published the largest cohort study in which they compared 72 patients with embolization (as sole treatment or with surgical treatment combined) to 469 (retrospectively) non-surgical treated patients. In this study no complications were reported and only one patient needed repeat surgery. A relatively large case series of 60 patients was reported by Link et al. [7], again with no complications and a success rate of 92% (patients who were able to avoid surgery). Recent systematic reviews on middle meningeal artery embolization highlight the

lower recurrence and complication rate in all embolization cases (<5% and 0%, respectively). Nevertheless, these results are based on non-randomized studies with moderate quality and a small sample size. The effect of embolization as an adjunct to surgical evacuation has never been evaluated in a randomized controlled trial.

In conclusion, although surgery is still the primary treatment option for the majority of patients with cSDH, it carries a significant risk of additional morbidity and mortality and has a relatively high risk of treatment failure. In the aging population, comorbidities are more frequent and the risk of peri-operative complications is acknowledged, limiting a favorable clinical outcome. Middle meningeal artery embolization appears to be a promising adjunct therapy to surgery, which might reduce the necessity for repeat surgical treatment and improve clinical outcome is this vulnerable patient group.

2. OBJECTIVES

Primary objective:

To evaluate whether patients treated with peri-operative embolization of the middle meningeal artery until 72 hours after surgical treatment compared to patients with surgical treatment alone:

1. require less reoperations for recurrent cSDH 24 weeks after intervention.

Secondary objectives:

To evaluate if patients treated with peri-operative embolization until 72 hours after surgical treatment compared to patients with surgical treatment alone have;

2. less hematoma volume at eight, 16 and 24 weeks on follow-up CT scan of the head;
3. less procedure-related complications;
4. less neurological impairment at eight,16 and 24 weeks after intervention, measured with the modified National Institutes of Health Stroke Scale (mNIHSS) score and Markwalder grading scale;
5. a better functional outcome 24 weeks after intervention, measured with the modified Rankin Scale (mRS) score;
6. a better cognitive functioning at eight, 16 weeks and 24 measured with the Montreal Cognitive Assessment (MOCA/m-TICS) test;
7. less mortality 24 weeks after intervention;
8. a better performance in activities of daily living at 24 weeks, measured with the Barthel index scale;
9. a better quality of life 24 weeks after intervention, measured with the:
    a. short Form Health Survey (SF-36) questionnaire (as the main secondary outcome);
    b. five dimensional EuroQol (EQ-5D-5L) questionnaire;
10. less care and health-related costs during the 24 week study period, measured with the:
    a. medical Consumption Questionnaire (iMCQ);
    b. Productivity Cost Questionnaire (iPCQ).

3. STUDY DESIGN

Design

Multicenter, randomized controlled open-label superiority trial.

Duration

36 months

Setting

All potentially eligible patients for this study are either referred from another hospital to a participating center, or are already under the care of a neurosurgeon from a participating center. Whenever cSDH patients experience neurological symptoms for which an operation might be indicated, they are referred to a neurosurgeon. Therefore, no potentially eligible patients are missed. Whenever surgery is selected as the primary treatment, the attending neurosurgeon will check whether the patient: A) meets the inclusion criteria, B) does not meet the exclusion criteria, C) will try obtain informed consent from the patient or his/her legal representative. If it is not possible to contain informed consent before surgery it can be obtained before embolization. Follow-up will be with standard surgical follow-up and an additional outpatient clinic visit. For this study both mentally-competent patients and patients with a depressed level of consciousness are eligible for inclusion. In the case of patients who are mentally not-competent, including patients with a depressed level of consciousness, informed consent will be obtained from the patient's legal representative. As soon as the patient becomes mentally competent at a later instance during the 24 week follow-up period, he or she will be asked whether he or she agrees to continue the study participation and if so, to sign the informed consent form as well. This also applies when it is not possible to determine whether a patient meets an exclusion criterion at baseline by taking his/her history and/or when it cannot be derived from his/her medical file (other than the inability to obtain informed consent, see 4.3). When this is the case, the patient will be included in the study and this information will be checked as soon as possible with the patient or his/her legal representative. There are typically two settings in which patients will be eligible for inclusion. The first is a semi-emergency setting in which the patient has to be operated on promptly. In the event of a decreased level of consciousness after surgery, or other reasons of mental incompetence, such as severe aphasia or disorientation, informed consent will be obtained from a legal representative. If the patient becomes mentally competent after surgery, he/she will be asked to provide informed consent him/herself.

The second setting is a non-emergency one where the patient has significant cSDH symptoms for which an operation is indicated, but is still mentally competent. In this setting informed consent can be obtained from the patient before intervention.

Justification of the design

In order to relieve symptomatic cSDH patients from their (sometimes life-threatening) symptoms direct surgical intervention is needed. In this study, patients in both the control group and the intervention group receive surgical treatment. Embolization of the middle meningeal artery is only used an 'add-on' treatment to surgery in the intervention group, thus every subject will receive standard care and no patient will be withheld an operation.

Flowchart:

See appendix 15.1

Follow-up schedule

See appendix 15.2

4. STUDY POPULATION

4.1. Population (base)

The study population will be all symptomatic cSDH patients (as diagnosed by a neuroradiologist on CT-imaging of the head), who are in need of surgery due to their clinical status. The in- and exclusion criteria are described in paragraph 4.2.

Between 2012-2018, around 850 patients/year with a cSDH were operated in the Netherlands [40]. Using Open Data of the Dutch Health Authority (www.opendisdata.nl) an increase in operated cases can be seen from 766/yr in 2012 to 1107/yr in 2019, an increase of 44,5%. Each neurosurgical center treats about 50-70 cSDH patients per year with burr hole evacuation. Therefore, an inclusion rate of 20 patients per center/year seems realistic. We expect that Erasmus mc, Radboud umc and UMC Groningen are willing to participate. We plan to include 170 patients, which will take around three years. The Amsterdam UMC starts in year 1, the other centers in year 2 and 3 (year 1: 20 patients, year 2: 75 patients, year 3: 75 patients).

Gewijzigde veldcode

4.2. Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- CT-confirmed diagnosis of cSDH;
- Primary surgical treatment based on clinical symptoms (progressive neurological deficits).

4.3. Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Significant contraindication to angiography (eg. allergy for contrast);
- Structural causes for subdural hemorrhage, e.g. arachnoid cysts, cortical vascular malformations and a history of cranial surgery in the previous 365 days;
- Inability to obtain informed consent from the patient or legal representative (when the patient has a depressed level of consciousness), including language barrier;
- Monocular blindness on contralateral side of the hematoma.

4.4. Sample size calculation

Since embolization of the middle meningeal artery is an innovative treatment in cSDH, only scarce clinical data are available. Data from a systematic review of patients treated with burr hole evacuation and embolization showed a recurrent surgery rate of 3.6% [10]. A relatively conservative recurrent surgery rate of 17% was used for the burr hole evacuation group. In total 160 patients are needed (β:20%, α:5%), and anticipating on an attrition rate of 5%, 170 patients need to be included.

Although no data are available for our main secondary outcome, we assume that a reduction in recurrent surgery will result in a better QoL. We used a conservative estimate for the effect size (ES) of QoL (SF-36) (moderate ES: *d* = 0.50).8 In total 128 patients are needed (β:20%, α:5%).

5. TREATMENT OF SUBJECTS

5.1. Investigational product/treatment

Peri-operative embolization of the middle meningeal artery until 72 hours after burr hole evacuation. Embolization of the middle meningeal artery is a simple procedure. There is no learning curve and it is already used in treatment of epistaxis and preoperative embolization in meningioma resections.

Also, this procedure consists of embolization of extra cranial vessels only (the middle meningeal artery originates from the external carotid artery). Therefore, there is no involvement of intracranial vessels. This contributes to the safety of the procedure.

5.2. Use of co-intervention (if applicable)

None.

5.3. Escape medication (if applicable)

None.

6. INVESTIGATIONAL PRODUCT

Not applicable.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable.

8. METHODS

8.1. Study parameters/endpoints

8.1.1.Main study parameter/endpoint

1. Number of patients who require a reoperation for recurrent cSDH at eight, 16 and 24 weeks after intervention.

8.1.2.Secondary study parameters/endpoints (if applicable)

2. Hematoma volume/size at eight, 16 and 24 weeks on follow-up CT scan.
3. Number of complications at hospital admission and eight, 16 and 24 weeks.
4. Neurological impairment at eight, 16 and 24 weeks, measured with the modified National Institutes of Health Stroke Scale (mNIHSS) score and the Markwalder grading scale.
5. Functional outcome at 24 weeks, measured with the modified Rankin Scale (mRS) score.
6. Cognitive functioning at eight, 16 and 24 weeks, measured with the Montreal Cognitive Assessment (MOCA) test and m-TICS.
7. Mortality at eight, 16 and 24 weeks.
8. Performance in activities of daily living at 24 weeks measured with the Barthel index.
9. Quality of life at 24 weeks, measured with the
   a. Short Form Health Survey (SF-36) questionnaire (as the main secondary outcome);
   b. EuroQol (EQ-5D-5L) questionnaire.
10. Care and health-related costs during the 24 week study period, measured with the
    a. Medical Consumption Questionnaire (iMCQ);
    b. Productivity Cost Questionnaire (iPCQ).

8.1.3.Other study parameters (if applicable)

1. Age at diagnosis;
2. Center of treatment;
3. Gender;
4. cSDH in history;
   a. When (date);
   b. What type of treatment received;
   c. Recurrence yes/no;

5. History of trauma;
6. History of smoking;
7. History of alcoholism;
8. History of hypertension;
9. Usage of antiplatelet/anticoagulation drugs;
    a. Which drug?
    b. Medication stopped before intervention;
        i. With which drug?
10. History of anticoagulation disease;
11. Liver disease;
12. Kidney function;
13. Allergies;
14. GCS-score, mNIHSS and mRS at admittance;
15. Symptoms (headache, motor/sensory deficit etc.) at admittance;
16. Date of diagnostic CT-scan;
17. Characteristics of cSDH at admittance (place, type, size, volume, midline shift);
18. Comorbidities such as hyperlipidemia, diabetes, atrial fibrillation, thyroid disease, cancer, dementia, thrombocytopenia;
19. Date of surgery;
20. Date of embolization;
21. Time between burr hole evacuation and embolization;

8.2. Randomisation, blinding and treatment allocation

Patients will be randomised to burr hole evacuation or burr hole evacuation + embolization in a 1:1 ratio using an online randomisation module (Castor Electronic Data Capture) and random blocks of size 2, 4 and 6 stratified for anticoagulation/antiplatelet use yes/no, bilateral cSDH yes/no and treatment center. Concealment of treatment allocation is not possible in this study. Both the treating physician and the patient know which treatment the patient receives. In the final analysis two neurosurgeons, both not involved and blinded for treatment allocation, will evaluate reasons for recurrent surgery.

8.3. Study procedures

After randomization patients receive either burr hole evacuation or burr hole evacuation and embolization. Embolization is performed peri-operative until 72 hours after surgery. The embolization procedure can be adapted to local standards~~will be as follows:.. first~~ Local

anesthesia of the puncture place. A femoral artery (or eventually a radial artery) access ~~will~~ can be obtained by using ~~a 5 French~~ a micropuncture or Seldinger puncture set~~kit~~ after which a 5 or 6 French vascular sheath is introduced. ~~And~~subsequently ~~common~~ the target (ipsilateral to subdural hematoma) internal ~~carotid~~ and external carotid arteries are catheterized. Contrast injections (injections rates and volumes according to local protocols) are performed with in at least lateral, but preferably also in PA projection through~~angiography is performed using a~~ a ~~standard~~ 5 or 6 French diagnostic or guiding catheter. When the ophthalmic artery has its usual origin from the ICA and the MMA originates from the maxillary artery ~~,~~embolization is possible with a very low procedural risk. A micro-catheter is then ~~advanced~~ introduced with selective~~l~~ ~~y~~ ~~under roadmap~~ catheterization~~guidance~~ under roadmap in~~to~~ the distal MMA. ~~, and~~ Contrast injection through the microcatheter in the distal MMA territory ~~angiography~~ is performed to evaluate the vascularization of the dura and to look for potential dangerous anastomoses such as the orbital branch to the ophthalmic artery. Embolization can be performed with a variety of embolic materials. First, it can be~~is~~ performed using polyvinyl alcohol (PVA) particles (100-300 microns in diameter) under blank fluoroscopic roadmap while carefully avoiding reflux. Particles are infused until lack of anterograde flow into the MMA branches is demonstrated on angiography, and the catheters are removed [33]. Second, an adhesive liquid embolic agent (glue: mixture of Histoacryl® and Lipiodol®), or a non-adhesive liquid embolic agent (Onyx®, Squid®, or Phil®) can be used for obliteration of the distal MMA territory. Third, occlusion can be achieved with micro coils (fibered / non-fibered, detachable / non-detachable) to obliterate the more proximal MMA. The procedure ~~is~~ can be performed under local anesthesia, but the condition of the patient might necessitate sedation or even general anesthesia.

During hospital admission procedure-related complications are registered (extra for this study). At discharge the patient will be provided with questionnaires for outcome assessment at week eight (extra for this study). An outpatient clinic visit is scheduled at eight, 16 and 24 weeks after the patient has received intervention. The visit eight weeks post-intervention is standard care. The visits after 16 and 24 weeks are extra for this study.

During the visits after eight and 16 weeks the following will be assessed :

- Head-CT scan without contrast (standard care);
- The presence of radiological recurrence and/or reoperation necessity (standard care);
- The presence of complications from the intervention (extra for this study);
- mRS, MOCA/m-TICS, mNIHSS, Markwalder (extra for this study);
- Health-care related costs: iMCQ and iPCQ (extra for this study);

- questionnaires provided for outcome assessment at week 16/24 (extra for this study).

During the visit after 24 weeks the following will be assessed:

- Head-CT scan without contrast (extra for this study);
- The presence of radiological recurrence and/or reoperation necessity (extra for this study);
- The presence of complications from the intervention (extra for this study);
- mRS, MOCA/m-TICS -and mNIHSS, Markwalder (extra for this study);
- ADL: Barthel index scale (extra for this study);
- QoL: SF-36 and EQ-5D-5L (extra for this study);
- Health-care related costs: iMCQ, iPCQ (extra for this study).

Appendix 15.2 provides a complete overview of registration of outcome measures and study procedures.

8.4. Withdrawal of individual subjects

Subjects, or their legal representatives who approved the authorization for inclusion in the study, can leave the study at any time for any reason if they wish to do so without any consequences. This is in accordance with the WMO, article 6. Acquired patient data until that moment will be used for data analyses. Only if the patient wants to have the acquired data removed from the database, these data will not be used for the outcome analyses.

The investigator can decide to withdraw a subject from the study for urgent medical reasons.

If it is revealed after inclusion, that one of the exclusion criteria was present in a certain patient on admission, this patient will remain included in the study and this will be recorded as a protocol violation. These patients will remain included for the outcome assessments to ensure an adequate intention-to-treat analysis.

8.4.1.Specific criteria for withdrawal (if applicable)

Not applicable.

8.5. Replacement of individual subjects after withdrawal

It is not possible to replace individual subjects after withdrawal.

8.6. Follow-up of subjects withdrawn from treatment

If a patient or their legal representative decide to withdraw from the study the reasons for withdrawal will be documented. After withdrawal the patient will be treated by the standards of normal cSDH care.

8.7.Premature termination of the study

Reasons for premature termination are:

- When the number of inclusions is insufficient due to non-provided informed consent;
- If treatment with embolization results in an unexpected high number of SAE's.

The collected data from up until the moment of termination will be analysed. The investigators want to stress that both of these reasons for termination are not anticipated in this study.

9. SAFETY REPORTING

9.1. Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2. AEs, SAEs and SUSARs

9.2.1.Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to embolization. All adverse events related to the study procedures and with clinical relevance, reported spontaneously by the subject or observed by the investigator or his staff will be recorded. For example, an asymptomatic hyponatremia of 134 managed without treatment will not be reported. On the other hand, a hyponatremia of 125 with clinical symptoms for which a sodium drip is started will be recorded as an AE. For this study AEs are defined according to the definition stated above but not many AEs are expected. Most of the AEs are expected to occur during hospital admission.

During the 24 week study period, at each follow-up moment as described in paragraph 8.3, occurrence of AEs will be monitored. Each AE will be reported in the CRF. Follow-up of AEs is described in paragraph 9.4.

9.2.2.Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

In this study a SAE is defined according to the abovementioned definition. The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following SAE:

- Hospital admission for the treatment of diseases that can be attributed to being an elderly patient, such as delirium, infections, constipation and an exacerbation of a pre-existent disease (excluding cSDH).
- Any admission unrelated to an AE, e.g., for labour/delivery, cosmetic surgery, social and/or convenience admissions to a hospital.
- Elective hospitalisation (planned before the subject consented for study participation) for pre-existing conditions that did not exacerbate during the study period as judged by the clinical investigator and where admission did not take longer than anticipated.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present at the start of the study that do not worsen.
- Pneumocephalus caused by burr hole evacuation.
- Post-operative wound infection or leakage.
- Hospital admission and, if necessary, surgery for recurrent cSDH.

These SAEs will be reported in a twice-yearly line listing until the follow-up of the last patient is completed.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

If there are any SAEs during this study, the majority of them are expected to become evident during hospital admission. Therefore the investigators can monitor SAEs closely the first period of the study. After discharge the biggest part of the 24 week study period takes place at home, so SAEs will not directly be observed by the investigator or his staff. Getting knowledge of SAEs depends on spontaneous reporting by the subject or other treating physicians to the investigator or his staff. The reported SAE will be documented in the patients' medical file.

During the 24 week study period, at each follow-up moment as described in paragraph 8.3, occurrence of SAEs will be monitored. Each SAE will be reported in the CRF. Follow-up of AEs is described in paragraph 9.4.

9.2.3.Suspected unexpected serious adverse reactions (SUSARs)

Not applicable.

9.3. Annual safety report

Not applicable.

9.4. Follow-up of adverse events

All AEs will be followed until they have abated, or until the end of study. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.5. Data Safety Monitoring Board (DSMB)

The DSMB consists of two members who are clinicians with medical expertise in neurosurgery/neuroradiology experienced in the (statistical) methods for clinical research. All members are independent of the study.

The DSMB will act in an independent, expert and advisory capacity to monitor participant safety, and evaluate the overall conduct of the clinical trial. Further specifications on the responsibilities, the meetings, and the decision making of the DSMB are documented in the DSMB charter.

The advice(s) of the DSMB will only be sent to the Steering Group of the study. Should the sponsor decide not to (fully) implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

10. STATISTICAL ANALYSIS

Statistical analyses will be based on the intention-to-treat principle. Baseline assessments and outcome parameters will be summarized using simple descriptive statistics. Continuous, normally distributed variables will be expressed as means and standard deviations; continuous, non-normally distributed and ordinal variables as medians (25th – 75th percentiles), and categorical variables as counts and percentages. Normality of data will be explored by a Normal Q-Q Plot and tested by the Shapiro-Wilk test. Where necessary we will use multiple imputations for handling missing data. In all analyses statistical uncertainty will be expressed in two-sided 95% confidence intervals. A two-sided p value less than 0.05 is considered statistically significant. We will not correct for multiple testing.

10.1. Primary study parameter(s)

The difference in the proportion of patients requiring surgery for cSDH within 24 weeks after embolization will be analyzed using Fisher's exact test. In addition, logistic regression will be performed including treatment groups and the stratification variables (anticoagulation/antiplatelet use yes/no and treatment center, see also paragraph 8.2) as independent variables. The effect size will be expressed in an adjusted odds ratio.

10.2. Secondary study parameter(s)

Differences in volume and size reduction of cSDH, neurological impairment (mNIHSS), and cognitive function (MOCA/m-TICS) between the treatment groups and over all time points will be analyzed using a linear mixed model with treatment group membership as a fixed-effect and an appropriate random-effect structure. Mortality and complication rate during the 24 weeks follow-up will be analyzed using Fisher's exact test.

Ability to do basic and complex activities of daily living (Barthel Index) and functional outcome score (mRS) at 24 weeks will be compared with the two-sample t-test or Mann-Whitney test, where appropriate.

Differences in the mean changes in level of quality of life (SF-36) from baseline to 24 weeks will be analyzed using the two-sample t-test. In addition, we will analyze these treatment effects by performing multivariable linear regression with 24-weeks observations as the dependent variable, and treatment groups, the baseline values and the stratification variables as the independent variables.

10.3. Economic evaluation

The economic evaluation will be performed from a societal perspective, set up as a cost-effectiveness analysis, cost-utility and a budget impact analysis. The rationale for this economic evaluation is that lower rates of recurrent surgery for cSDH following the addition of embolization will result in major reduction in costs for surgery, associated hospital admissions, as well as a cost reduction related to dependency within 6 months follow-up. Although the addition of embolization also incurs costs (extra procedure), this is not expected to offset this cost-reduction.

The costs per quality-adjusted life year (QALY) are the primary outcome. The incremental cost-utility ratio reflecting the extra costs per QALY is calculated. In addition the incremental costs/ prevented case of recurrent surgery is calculated as secondary outcome. Additional costs as a result of comorbid conditions will be excluded. No discounting will be applied (study horizon: 6 months).

The mid- and long-term budget impact of implementing the new treatment strategy will be assessed from governmental, insurer and provider perspectives. We will extrapolate the outcomes of the economic evaluation nationwide. Therefore the budget-impact analysis will be designed and executed according to the ISPOR guidelines [41, 42].

We will differentiate between direct medical costs (surgical procedures, embolization, CT-scans, hospital stay, outpatient care, admissions to nursing home and other primary and paramedical health care following discharge), direct non-medical costs (travel to and from health care providers) and indirect costs (lost productivity due to absence from paid work). Health care utilisation during the index hospitalisation will be documented in the clinical report form. Health care and other resource use following discharge will be collected with the iMTA Medical Consumption questionnaire and the Productivity Costs Questionnaire at eight, 16 and 24 weeks. Unit costs for health care use will be estimated according to the Dutch guideline for economic evaluation research [43]. Health-related QoL will be collected at 24 weeks with the EQ-5D. Utility values for EQ-5D scores will be based on Dutch estimates [44]. Utility scores will be uniformly interpolated, assuming constant health state between subsequent assessments.

10.4. Interim analysis

The DSMB will perform an interim analysis for safety when follow-up is completed of the first 42 (25% of total inclusions) included participants. Additionally, the DSMB will monitor

safety data when follow-up is completed of the first 85 and 120 participants. Efficacy is monitored after follow-up of the first 85 participants is completed. Efficacy monitoring is based on the primary outcome: between-group difference in proportion of patients requiring recurrent surgery within 24 weeks after start intervention.
After considering the information in the interim report, the DSMB could give the following recommendations:

- continue the study according to the study protocol;
- continue the study with modifications to conduct, design or sample size;
- discontinue the study due to clear harm;
- discontinue the study due to clear benefit;
- discontinue the study because completion of the study is not feasible.

The justifications for a recommendation to terminate the study due to clear harm will be based on data showing a notably increase of (serious) adverse events in the intervention group. No pre-specified statistical stopping rule for safety is formulated.

The justifications for a recommendation to terminate the study due to clear benefit will be based on pre-specified stopping boundaries for the primary endpoint of the study (proportions of patients requiring recurrent surgery within 24 weeks after intervention). As a stopping rule the Haybittle-Peto method will be used:

- interim efficacy analysis 1 (n=85) p = 0.001;

Further details are described in the DSMB charter.

11. ETHICAL CONSIDERATIONS

11.1. Regulation statement

This study will be conducted in full accordance with the principles of the "Declaration of Helsinki" (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and Medical Research Involving Human Subjects Act (WMO).

11.2. Recruitment and consent

All patients admitted to a participating center for which surgical treatment is selected as the primary treatment strategy are potentially eligible for inclusion. Whether surgery or conservative management is selected as primary treatment depends on the clinical status of the patient.

After the decision whether to operate or not the neurosurgeon will check whether the patient is eligible for inclusion. When the patient is eligible the neurosurgeon will inform the patient about the study and ask for informed consent. If it is not possible to obtain informed consent because the patient is incapacitated (due to a decreased level of consciousness or severe aphasia), a legal representative of the patient will be informed and asked to provide informed consent. The patient or legal representative will decide whether they or the person they represent, want to participate in the study. As soon as the patient is able to provide informed consent, he/she will be asked to do so.

11.3. Objection by incapacitated subjects

Minors are excluded from the study. A significant part of the study subjects might be incapacitated at moment of inclusion. In those cases, a legal representative will be asked to provide informed consent on behalf of the study subject. However, as stated in the WMO, mentally incompetent study subjects cannot be forced to undergo a treatment against their will. If resistance to the treatment is suspected, this will be evaluated according the Code of Conduct: *The expression of objection by incapacitated (psycho)geriatric patients in the context of the WMO [45]*. If objection by the study subject is obvious, treatment will be stopped.

11.4. Benefits and risks assessment, group relatedness

The beneficial effect for subjects of this study would be that if embolization is indeed effective as an adjuvant treatment, the chance to develop a recurrent cSDH and having to receive recurrent surgery is reduced greatly. Especially in a frail patient population this is

advantageous. Cerebral angiography is a procedure that is used in clinical practice since its introduction in 1927. Numerous studies have investigated the safety of these procedures and the consensus is that these are relatively safe. The most common complication of cerebral angiography is an access site hematoma (2.5%). Other less common complications are nausea/vomiting (1.2%), a headache (0.8%) or a stroke (0.14%) [46-48]. For embolization of the middle meningeal artery it is not necessary to catheterize the internal carotid artery, only the external carotid artery, thereby minimizing cerebral complications.

In existing literature almost 200 cases in which specifically embolization of the middle meningeal artery is used to treat cSDH are described. In none of these cases complications due to embolization have been reported. Potential serious complications of embolization of the middle meningeal artery are monocular blindness and transient facial nerve palsy. However, this can be prevented during the procedure. Monocular blindness is attributable to embolizing anastomoses between the middle meningeal artery and ophthalmic artery. This can be seen on the angiography prior to the embolization. Whenever this is seen the radiologist will make sure that the ophthalmic artery is saved by advancing the tip of the microcatheter distally in order to avoid reflux and embolization of the ophthalmic branch collaterals [49]. Transient facial nerve palsy can occur when the petrosal branch of the MMA supplies the vasa nervous of the facial nerve. This can also be seen on the angiogram. If this is the case, the interventionalist must prevent embolizing the branch by advancing the tip of the microcatheter past its origin [12]. These small risk complications do not outweigh the risks that accompany receiving re-operation for recurrent cSDH. Therefore, this study is classified as a moderate risk according to the NFU criteria for human research.

As discussed in paragraph 8.3, the subjects receive peri-operative embolization until 72 hours after burr hole evacuation. Embolization is not painful and in order to obtain femoral artery access local anesthesia is sufficient. Patients have to be admitted to the hospital while awaiting embolization. The timing of embolization depends on availability of the interventional radiologist and angiography suites, but is aspired to be as soon as possible after burr hole evacuation. During the follow-up period only the questionnaires after eight weeks and the outpatient clinic visits at 16 and 24 weeks after intervention are extra. Therefore, it is expected that the potential benefits of this study outweigh its potential risks and (minimal) burden.

Chronic SDH is a heterogeneous disease where some patients are admitted to the hospital with a decreased level of consciousness and in urgent need for surgery, where others with a similar hematoma only experience a light headache or other mild symptoms. The decision

whether to operate depends mostly on the clinical status of the patient, and logically patients with a decreased level of consciousness are prime candidates for surgery. Exclusion of these patients would lead to selection bias and then the study population would not reflect the patient population correctly. For this reason it is necessary to also include incapacitated or mentally-incompetent adults in this study.

11.5. Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6. Incentives (if applicable)

None.

13. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

13.1. Handling and storage of data and documents

The executing investigator will set up a Trial Master File at the beginning of the study. The list of essential documents will be in accordance with the GCP-guidelines. The essential documents that make up the file will be stored in a secure but accessible manner. All essential documents will be legible and accurate. For each included patient a digital Case Record Form (CRF) will be completed. The CRF consists of a sequential set of instructions with provision for data recording. Part of the data registered at the CASTOR database will be done as direct entry during the study visit, this will comprehend the mRS, MGS, mNIHSS and m-TICS. Also the relation of the SAE with the study procedure and its severity is directly entered in the database. All randomized patients are identified by a Patient Identification Number (PIN). The investigators will ensure that patients' anonymity is maintained. On screening forms, digital or paper CRF's or other documents, patients will only be identified by a PIN. The subject identification code list will be safeguarded by the investigator. Data will be stored for 15 years. All patient information is handled following the requirements of the Algemene Verordening Gegevensbescherming (AVG). Therefore, this study meets the criteria of Dutch law regarding handling personal data.

13.2. Monitoring and Quality Assurance

Academic Medical Center's Clinical Monitoring Center (CMC) will provide independent monitoring. An independent monitor will monitor the study data according to Good Clinical Practice (GCP). For this study moderate monitoring is required conform the NFU risk classification. Therefore monitor frequency will be twice a year (at least one on-site visit). During these visits patient flow, Trial Master File integrity, informed consent, in- and exclusion criteria, Source Data Verification and SAEs are monitored. The monitoring of informed consent presence takes place in 50% of the study objects. The monitoring of the informed consent procedure, in- and exclusion criteria, Source Data Verification and SAEs takes place in 25% of the study subjects.

13.3. Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;

- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC.

Non-substantial amendments will not be notified to the accredited METC, but will be recorded and filed by the sponsor.

13.4. Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

13.5. Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC of the end of the study within a period 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

13.6. Public disclosure and publication policy

The study will be registered in an international trial registry (http://www.clinicaltrials.gov) and Het Nederlands Trial Register (https://www.trialregister.nl/) .After completion of the study, the authors aim to publish the results in high-impact peer-reviewed journals and present the results in the usual international fora of relevant specialist societies, regardless of either positive or negative results. Authorship will be

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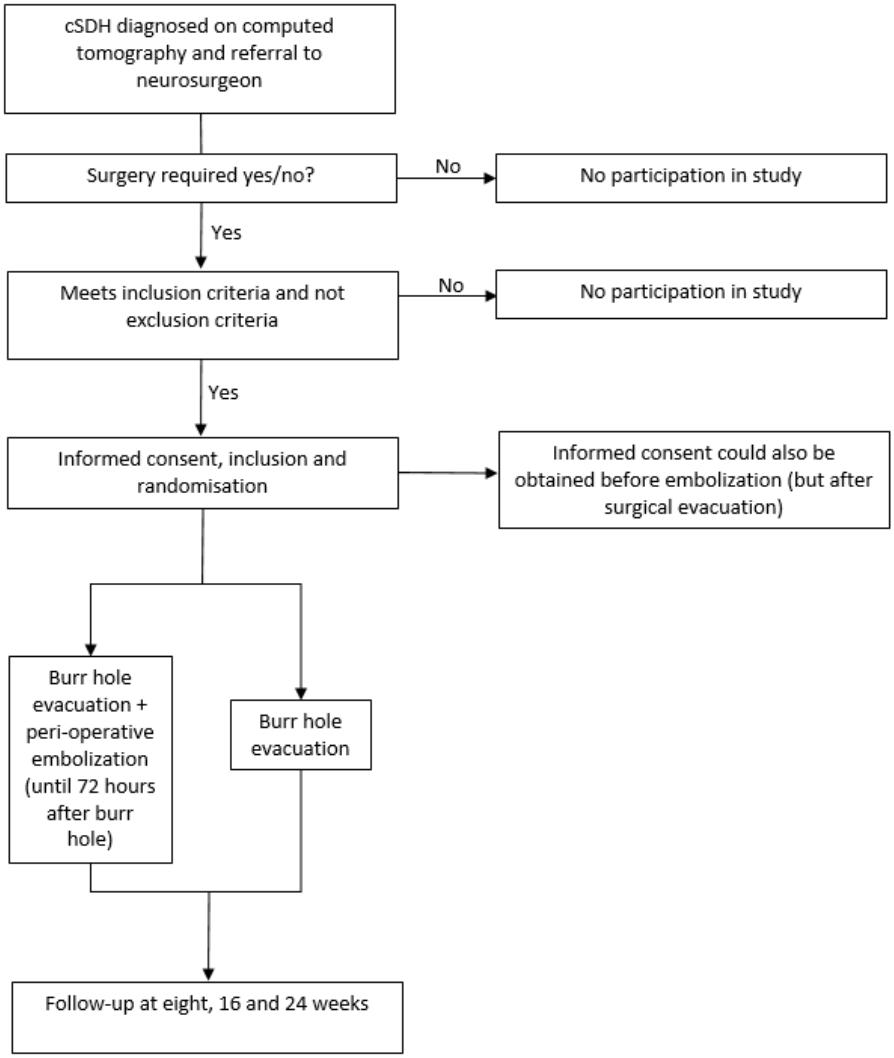
granted using the Vancouver definitions and depending on personal involvement. The first, second and last author names will be decided by the principal investigator and project leader. Besides the first, second and last author, the steering group members, site investigators and additional names are mentioned in alphabetical order. Participating centers will be entitled to one name in the author list (site investigators).

14. STRUCTURED RISK ANALYSIS

Not applicable.

15. Appendices

15.1. Flowchart



15.2. Follow-up schedule

	Inclusion	Treatment	Hospital admission after intervention	Week 8: outpatient visit	Week 16: outpatient visit	Week 24: outpatient visit
Baseline data						
Inclusion and exclusion criteria	X					
Baseline characteristics	X					
Treatment						
Burr hole or burr hole +embolization		X				
Primary outcomes						
1. Reoperation for recurrence?			X	X	X	X
Secondary outcomes						
2. cSDH volume & size	X			X	X	X
3. Complications			X	X	X	X
4. mNIHSS	~~X~~			X	X	X
5. mRS	X					X
6. MOCA/m-TICS	~~X~~			X	X	X
7. Mortality				X	X	X
8. Markwalder score	X			X	X	X
9. Barthel Index	~~X~~					X
10. A) SF-36	~~X~~					X
B) EQ-5D-5L	~~X~~					X
11. A) iMCQ				X	X	X
B) iPCQ				X	X	X

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