Managing non-acute subdural hematoma using liquid materials: a Chinese randomized trial of middle meningeal artery treatment (MAGIC-MT)—protocol

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Protocol Signature Page

Sponsor:	Signature	Date
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I have carefully read this trial protocol, and I agree that this protocol covers all the necessary contents required for the implementation of the trial. I will conduct the study according to the study protocol and complete the study within the specified time.

I will provide copies of this study protocol and all relevant materials to all personnel assisting me in this study. I will discuss these materials with them to ensure that they fully understand the relevant investigational products and how to conduct the trial.

Name	Signature	Date
[Principal Investigator]:		

Study Protocol Synopsis

Study Title	Managing non acute subdural hematoma using liquid materials: a Chinese randomized trial of middle meningeal artery treatment (MAGIC-MT)
Study Objectives	Primary objective: To validate that middle meningeal artery (MMA) embolization with liquid embolic materials, when compared to conventional treatments, can reduce the incidence of hematoma recurrence in patients receiving trepanation and drainage and the incidence of hematoma progression in patients undergoing conservative treatment in symptomatic non-acute subdural hematoma (SDH) patients. Secondary objectives: a. To validate the safety and efficacy of MMA embolization with liquid embolic materials; b. To assess change in residual hematoma size at 90 days post-procedure in patients undergoing MMA embolization; c. To assess improvement in clinical outcome (modified Rankin Scale [mRS] score) at 90 days and 360 days post-procedure in patients undergoing MMA embolization; d. To assess improvement in health status (EQ-5D scale) at 90 days and 360 days post-procedure in patients undergoing MMA embolization; e. To assess the readmission rate within 90 days post-procedure in patients undergoing MMA embolization.
Study Design	Multicenter phase III prospective randomized controlled trial with open-label treatment and blinded outcome assessment
Number of Study Sites	30-40 domestic hospitals
Statistical Considerations and Sample Size	Assuming that the incidence of events in the traditional treatment group is 12% and the embolization group is 5%, with a power of 90% and an estimated 8% drop-out rate, approximately 722 subjects should be enrolled with a ratio of 1:1 between the embolization group and the traditional treatment groups.
Inclusion Criteria	1. Patients with symptomatic non-acute SDH with mass effect (i.e., chronic or subacute SDH) Mass effect refers to a shift in midline structure or deformation of local cerebral cortex due to SDH. Symptomatic defined as neurological symptoms, such as headache, short-term cognitive dysfunction, language disorder or aphasia, gait instability, decreased muscle strength, sensory disturbances, epileptic seizure, etc. 2. Age ≥ 18 years; 3. Pre-morbid mRS score ≤ 2; 4. Informed Consent Form (ICF) signed by patient or guardian.
Exclusion Criteria	1. Radiographic imaging indicating massive cerebral infarction with corresponding symptoms; 2. Required craniotomy or craniotomy with small bone flap to remove SDH; 3. Emergency SDH removal/drainage; 4. Bilateral SDH with unknown origin of symptoms;

	5. Anatomical variations that may affect the safety of MMA embolization (e.g., prominent middle MMA-ophthalmic artery anastomosis); 6. Intractable coagulation dysfunction or abnormal platelet count and function (pre-operative International Normalized Ratio [INR] > 1.5 and/or platelet count < 80×10^{9}/L); 7. Contraindications to cerebral angiography, such as allergy to iodinated contrast agents, renal insufficiency (GFR < 30 ml/min), etc.; 8. Computed tomography (CT) or magnetic resonance imaging (MRI) showing intracranial space-occupying lesions; 9. Pregnancy or planning to become pregnant; 10. Serious or fatal coexisting disease that may prevent improvement of conditions or completion of follow-up; 11. Life expectancy < 1 year; 12. Recent operation unrelated to this study or investigators believe that they will be at higher risks if antiplatelet and/or anticoagulant drugs are discontinued; 13. Inability to complete follow-up as required by the protocol; 14. Patients participating in other clinical trials; 15. Prior surgery or interventional therapy on target SDH; 16. Inability to complete MMA embolization before trepanation and drainage.
Treatment Assignment	Eligible subjects will be randomly assigned to the traditional treatment group or MMA embolization group at a ratio of 1:1.
Primary Efficacy Endpoints	Symptomatic SDH recurrence and progression rate within 90 days post-procedure. Symptomatic SDH recurrence refers to the maximum thickness of hematoma exceeding 10 mm combined with neurological symptoms, or the patient requires re-operation (surgery group); Symptomatic SDH progression refers to the maximum thickness of hematoma increasing by more than 3 mm compared with baseline, or the patient requires operation (drug therapy group).
Secondary Endpoints	1. Efficacy Endpoints • Symptomatic SDH recurrence and progression rate at 360 days post-procedure • Success rate of target vessel embolization (MMA trunk and branch vessels) on digital subtraction angiography (DSA) imaging • Change in hematoma thickness on CT/MRI at 90 days post-procedure • Change in hematoma volume at 90 days post-procedure • Change in midline shift on CT/MRI at 90 days post-procedure • Change in mRS score at 90 days and 360 days post-procedure • Proportion of patients with mRS score ≤ 2 at 90 days and 360 days post-procedure • Proportion of patients with mRS score ≤ 3 at 90 days and 360 days post-procedure • Quality of life evaluated with EQ-5D Scale at 90 days and 360 days post-procedure • Total hospital length of stay, number of re-hospitalizations, discharge

	location, and total hospitalization expenses 2. Safety Endpoints • Serious Adverse Events (SAEs) within 90 days and 360 days; • SDH-related mortality within 90 days and 360 days; • Severe surgery-related complications within 30 days post-procedure (including surgery and intervention) o Symptomatic intracranial hemorrhage o Surgery-related intracranial hemorrhage o Surgery-related neurological deficits o Surgery-related central nervous system infection o Surgery-related arterial dissection, vascular wall injury, or vascular rupture and perforation o Surgery-related ischemia o Retroperitoneal/wrist hematoma o Neuropathy at the puncture site o Contrast allergy or contrast encephalopathy
Randomization	Subjects will be randomized into the control group or the study group using a stratified randomization method using SAS (version 9.4 or updated) to generate the randomization list.

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List of Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
APTT	Activated Partial Thromboplastin Time
AVM	Arteriovenous Malformation
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CEC	Clinical Event Committee
CMH	Cochran-Mantel-Haenszel
Cr	Creatinine
CRC	Clinical Research Coordinator
CRF	Case Report Form
CSDH	Chronic Subdural Hematoma
CT	Computed Tomography
CTA	Computerized Tomographic Angiography
DBP	Diastolic Blood Pressure
DSA	Digital Subtraction Angiography
DSMB	Data and Safety Monitoring Board
OAC	Outcome Assessment Committee
eCRF	Electronic Case Report form
EC	Ethics Committees
EDC	Electronic Data Capture System
EQ-5D	A standardized assessment instrument (developed by the EuroQol Group) that provides a simple descriptive measure of health outcome
g/L	Grams per Liter
GCS	Glasgow Coma Scale score
HCG	Human Chorionic Gonadotropin
IA	Intra-arterial
IAC	Imaging Assessment Committee
IC	Informed Consent
ICH	Intracranial Hemorrhage
INR	International Normalized Ratio
IRB	Institutional Review Board
ICA	Internal Carotid Artery
IV	Intravenous
KM	Kaplan Meier
MCA	Middle Cerebral Artery
MGS	Modified Graeb Scale score
MMA	Middle Meningeal Artery
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale

NBCA	n-butyl-cyanoacrylate
NCCT	Non-Contrast CT Scan
PI	Principal Investigator
RCT	Randomized Controlled Trial
REB	Research Ethics Board
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SAH	Subarachnoid Hemorrhage
SAP	Statistical Analysis Plan
SDH	Subdural Hematoma
SOP	Standard Operating Procedure

1. Introduction

Chronic subdural hematoma (CSDH), representing around 10% of intracranial hematomas, is a prevalent form of traumatic brain injury, with an annual incidence rate of 3─5.4 per 100,000 patients. The rise in craniocerebral trauma, particularly among the elderly, alongside increased use of antiplatelet and anticoagulant therapies, has amplified the risk of non-acute SDH, thereby intensifying the health challenges in this demographic.[1-3]. Current treatment methods for CSDH include conservative drug treatment, trepanation and drainage, and hematoma removal by craniotomy. Although treatment modalities like conservative pharmacotherapy, trepanation with drainage, and craniotomy for hematoma evacuation exist, the intricate pathophysiology of CSDH often obscures the bleeding source, complicating effective management. With recurrence rates ranging from 2 to 37%, the urgency for a safe, efficacious CSDH treatment protocol is paramount to decrease these rates and improve patient outcomes.[4-6].

The pathogenesis and resolution of CSDH remain partially understood. Research suggests its association with factors such as bridging vein laceration, osmotic pressure variations, hemorrhaging within the hematoma capsule, and localized hyperfibrinolysis. [7]. Additionally, recent insights highlight the significant role of inflammatory cells in the development and progression of subdural hematomas.[8,9]. In clinical practice, pharmacological interventions targeting inflammation, vascular leakage, and hematoma resolution are employed, with low-dose atorvastatin and dexamethasone being prevalent. A notable Chinese RCT indicated that low-dose atorvastatin (20 mg/day) over an 8-week course significantly enhances hematoma absorption and symptom improvement.[10] Despite these advancements, the complete efficacy and safety profiles of such treatments remain under exploration, as a significant patient cohort experiences hematoma progression post-medication, necessitating trepanation and drainage. Moreover, the recurrence rate for non-acute SDH post these procedures remains considerably high.

Current understanding suggests that the genesis and progression of CSDH predominantly involves the formation of an inflammatory pseudomembrane following subdural bleeding. This pseudomembrane's outer layer tightly adheres to the dura mater, incorporating newly formed, fragile vessels with heightened permeability. These vessels are susceptible to recurrent bleeding and leakage, potentially exacerbating hematoma growth and post-surgical recurrence. Notably, Tanaka et al.[11]'s selective angiography of the middle meningeal artery (MMA) in

CSDH patients revealed diffuse dilation and abnormal vascular networks, possibly representing large capillaries of the hematoma's adventitia. Histological examinations further identified diverse vascular structures (capillary-like vessels, venules, arterioles) penetrating the dura mater and connecting with MMA branches, underscoring the MMA's pivotal role in the blood supply to CSDH pseudomembranes and its significance in hematoma evolution.

MMA embolization, primarily utilized for treating dural arteriovenous fistulas and arteriovenous malformations, has emerged as a pivotal intervention in CSDH management. By obstructing the blood supply to the hematoma's adventitia, MMA embolization effectively mitigates the enlargement and recurrence of CSDH. Conventional treatments often report high recurrence and progression rates, particularly in patients on long-term antiplatelet or anticoagulant therapy. In cases of recurrent and refractory CSDH, MMA embolization has demonstrated significant efficacy in reducing hematoma progression and recurrence.[13,14 15-17]. Initially reported by Mandai in 2000, this technique gained prominence following its successful application in a patient with coagulation dysfunction and recurrent CSDH post multiple trepanations.[18] Neurosurgeons increasingly adopt MMA embolization for refractory CSDH, enhancing brain recovery, minimizing recurrence, and improving overall prognosis. Recent trends in endovascular treatment have positioned MMA embolization as a focal strategy in CSDH therapy. Systematic reviews indicate a mere 4.1% recurrence rate post-MMA embolization in newly diagnosed CSDH cases, highlighting its potential in mild cases to obviate surgical intervention[19]. Clinical studies also suggest that combining MMA embolization with traditional drainage can augment CSDH absorption rates, further lowering recurrence.[20] A 2019 meta-analysis reported significantly lower recurrence rates post-MMA embolization (2.1%) compared to traditional surgery (27.7%), underscoring its effectiveness in CSDH treatment[1].

Both liquid and solid embolics are employed in MMA embolization. Liquid options include Onyx and n-butyl-cyanoacrylate (NBCA) glues, whereas solid materials comprise coils, polyvinyl alcohol (PVA) particles, and gelatin sponge particles. For CSDH, solid embolics have been favored, as their size exceeds that of the MMA's risky anastomotic vessels (~100 μm), enhancing safety. Conversely, liquid embolics, by filling and effectively sealing target vessels, minimize recanalization risks and heighten permanent occlusion rates. Given their precise targeting and superior embolization capabilities, liquid embolics, particularly for cerebrovascular malformations, have gained preference over solids, which now often serve as adjuncts. Yet, in non-acute SDH treatments using liquid embolics, such as Onyx, reports

remain sparse and warrant further large-scale clinical studies for robust evidence.

Onyx™ Liquid Embolic System, a leading liquid embolic, comprises an ethylene-vinyl alcohol (EVOH) copolymer, dimethyl sulfoxide (DMSO) solvent, and micronized tantalum powder. Its non-adhesive nature prevents microcatheter and vessel adhesion, facilitating safer post-embolization catheter retraction. Each application of Onyx™ propels preceding agents deeper into smaller vessels beyond microcatheter reach, enhancing dispersal. Onyx™ received CE certification in Europe in 1999 and was initially approved for cerebral AVM endovascular embolization. Notably, Rajah et al.'s case series utilizing Onyx for MMA embolization via the radial artery pathway underscored its safety and efficacy in CSDH treatment.[21]

Although various studies endorse MMA embolization as an effective treatment for CSDH, most are confined to single-center, prospective cohort designs with diverse patient inclusion criteria and intervention approaches. There's a notable gap in high-level evidence validating MMA embolization's efficacy. The MAGIC-MT study aims to bridge this gap by rigorously assessing the efficacy and safety of MMA embolization in comparison to conventional CSDH treatments. Furthermore, it seeks to contribute significantly to the standardization of clinical treatment protocols for CSDH.

2. Clinical Study Objectives and Endpoints

Primary objective:

To validate that MMA embolization with liquid embolic materials, when compared to conventional treatments, can reduce the incidence of hematoma recurrence in patients receiving trepanation and drainage and the incidence of hematoma progression in patients undergoing conservative treatment in symptomatic non-acute SDH patients.

Secondary objectives:

a. To validate the safety and efficacy of MMA embolization with liquid embolic materials;

b. To validate a reduction in residual hematoma size at 90 days post-procedure in patients undergoing MMA embolization;

c. To validate improvement in clinical outcome (modified Rankin Scale [mRS] score) at 90 days and 360 days post-procedure in patients undergoing MMA embolization;

d. To validate improvement in health status (EQ-5D scale) at 90 days and 360 days post-procedure in patients undergoing MMA embolization;

e. To validate a reduced readmission rate within 90 days post-procedure in patients undergoing MMA embolization.

The efficacy endpoints in this study include:

Primary efficacy endpoint:

- Symptomatic SDH recurrence and progression rate within 90 days post-procedure

  Symptomatic SDH recurrence refers to the maximum thickness of hematoma exceeding 10 mm combined with neurological symptoms, or the patient requires re-operation (surgery group);

  Symptomatic SDH progression refers to the maximum thickness of hematoma increasing by more than 3 mm compared with baseline, or the patient requires operation (drug therapy group).

Secondary efficacy endpoints:

- Symptomatic SDH recurrence and progression rate at 360 days post-procedure
- Success rate of target vessel embolization (MMA trunk and branch vessels) on digital subtraction angiography (DSA) imaging
- Change in hematoma thickness on computed tomography (CT)/magnetic resonance imaging (MRI) at 90 days post-procedure
- Change in hematoma volume at 90 days post-procedure
- Change in midline shift on CT/MRI imaging at 90 days post-procedure
- Change in mRS score at 90 days and 360 days post-procedure
- Proportion of patients with mRS score ≤ 2 at 90 days and 360 days post-procedure
- Proportion of patients with mRS score ≤ 3 at 90 days and 360 days post-procedure
- Quality of life evaluated with EQ-5D Scale at 90 days and 360 days post-procedure

- Total hospital length of stay, number of re-hospitalizations, discharge location (home vs. rehabilitation hospital), and total hospitalization expenses

The safety endpoints in this study include:

- Serious adverse events (SAEs) within 90 days and 360 days;
- SDH-related mortality within 90 days and 360 days;
- Severe surgery-related complications within 30 days post-procedure (including surgery and embolization)
    - Symptomatic intracranial hemorrhage
    - Surgery-related intracranial hemorrhage
    - Surgery-related neurological deficits
    - Surgery-related central nervous system infection
    - Surgery-related arterial dissection, vascular wall injury, and vascular rupture and perforation
    - Surgery-related ischemia
    - Retroperitoneal/wrist hematoma
    - Neuropathy at the puncture site
    - Contrast allergy or contrast encephalopathy

Note: Follow-up time at 30 days, 90 days, and 360 days post-procedure will be calculated based on the day of randomization in this study. Relevant endpoint events and safety events will be collected at these follow ups.

3. Study Design

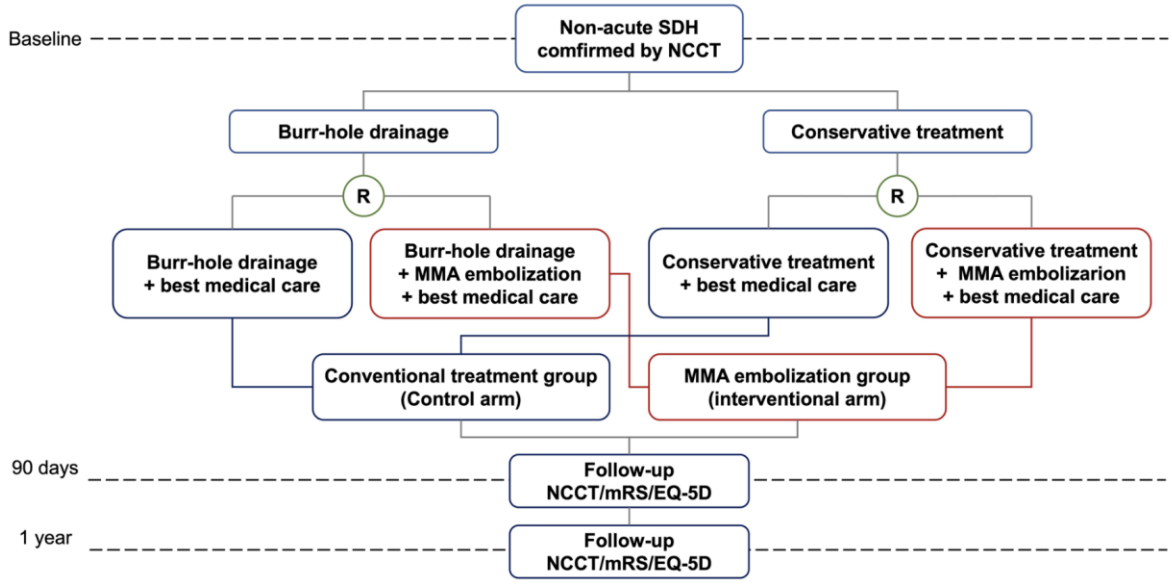
3.1 Overall Study Design

This is a multicenter, phase III, prospective, randomized, open-label, and parallel controlled clinical study with blinded outcome assessment. Approximately 722 cases will be included in this study in China, with a ratio of 1:1 for randomization into the MMA embolization and

traditional treatment groups.

The study phases include: 1) Screening and baseline period: confirm whether patients are eligible for the study and create a record; decide whether trepanation and drainage should be performed by considering the condition of the disease and the imaging results; carry out randomized assignment and therapy. Eligible subjects will be randomly assigned to the traditional treatment group or MMA embolization group at a ratio of 1:1. 2) Follow-up period: visit patients for efficacy endpoints and safety endpoints at 30 days, 90 days, and 360 days post-procedure.

Figure 1. Schematic diagram of inclusion and randomization of subjects



3.2 Study Duration

In MAGIC-MT, the estimated enrollment time will be from January 2021 to June 2023, for a span of 30 months from the first to the last enrollment of subjects. After the completion of enrollment, the last subject will be followed up for 360 days post-procedure.

4. Study Population

4.1 Subjects must meet **all** the following inclusion criteria before they can participate in this study:

(1) Patients with symptomatic non-acute SDH with mass effect (i.e., chronic or subacute SDH);

Mass effect refers to a shift in midline structure or deformation of local cerebral cortex due to SDH.

Symptomatic defined as neurological symptoms, such as headache, short-term cognitive dysfunction, language disorder or aphasia, gait instability, decreased muscle strength, sensory disturbances, epileptic seizure, etc.

(2) Age ≥ 18 years;

(3) Pre-morbid mRS score ≤ 2;

(4) Informed Consent Form (ICF) signed by patient or his/her guardian.

4.2 Subjects who meet **any** of the following exclusion criteria are not eligible to participate in this study:

(1) Radiographic imaging indicating massive cerebral infarction with corresponding symptoms;

(2) Required craniotomy or craniotomy with small bone flap to remove SDH;

(3) Emergency SDH removal;

(4) Bilateral SDH with unknown origin of symptoms;

(5) Anatomical variations that may affect the safety of MMA embolization (e.g., prominent MMA - ophthalmic artery anastomosis);

(6) Intractable coagulation dysfunction or abnormal platelet count and function (pre-operative International Normalized Ratio [INR] > 1.5 and/or platelet count < 80×10^{9}/L);

(7) Contraindications to cerebral angiography, such as allergy to iodinated contrast agents, renal insufficiency (GFR < 30 ml/min), etc.;

(8) CT or MRI showing intracranial space-occupying lesions;

(9) Pregnancy or planning to become pregnant;

(10) Serious coexisting disease that may prevent improvement of conditions or completion of follow-up;

(11) Life expectancy < 1 year;

(12) Recent operation unrelated to this study or investigators believe that patient will be at higher risks if antiplatelet and/or anticoagulant drugs are discontinued;

(13) Inability to complete the follow-up as required by the protocol;

(14) Patients participating in other clinical trials;

(15) Prior surgery or interventional therapy on target SDH;

(16) Inability to complete MMA embolization before trepanation and drainage.

5. Treatment in the Study

In this study, patients were stratified based on initial clinical assessments into two primary categories: those designated for burr-hole drainage and those selected for conservative treatment. Each category was then subject to further randomization. Specifically, within the burr-hole drainage category, patients were allocated into either the 'burr-hole drainage + optimal medical care + MMA embolization' subgroup or the 'burr-hole drainage + optimal medical care' subgroup. Similarly, patients initially slated for conservative treatment were randomized into 'conservative management + optimal medical care + MMA embolization' and 'conservative management + optimal medical care' subgroups.

5.1 Best Medical Care

Optimal medical care in this context is tailored to alleviate symptoms and facilitate hematoma absorption, utilizing medications such as statins, steroids, and anti-epileptic drugs. The criteria for administering optimal medical care include: 1) a confirmed diagnosis of non-acute SDH; 2) patients presenting with multiple organ failure or coagulation dysfunction, who are unsuitable for or decline surgical intervention; and 3) as a preventative measure against post-operative recurrence. Contraindications for these medications encompass allergic reactions to the prescribed drugs or other relevant usage restrictions.

The protocol recommends Atorvastatin calcium and dexamethasone for pharmacotherapy, with a low-dose, prolonged regimen of Atorvastatin calcium potentially combined with dexamethasone. However, due to the heightened risk of embolic diseases associated with hemostatic drugs, their usage is generally discouraged. Ultimately, the specific treatment

approach is determined by the attending physician.

5.2 Burr-hole drainage

In this study, 'burr-hole drainage' encompasses the process of trepanation and drainage, which is conducted under local anesthesia with analgesia or under general anesthesia. The criteria for opting for trepanation and drainage include: (1) clinical manifestations of elevated intracranial pressure, potentially accompanied by altered consciousness and signs of cerebral hemisphere compression; (2) CT or MRI evidence of unilateral or bilateral SDH with a thickness exceeding 10 mm and a midline shift greater than 10 mm due to unilateral hematoma; (3) insufficient response to prolonged pharmacotherapy aimed at hematoma absorption (exceeding 2 weeks), with persistent clinical symptoms, imaging evidence of hematoma growth, intolerability to medication, or a recommendation for surgical intervention. Detailed protocols for perioperative assessment, surgical procedure, medication, and management of unique clinical situations are aligned with the established clinical pathway for CSDH.

In scenarios where participants in the embolization group necessitate surgical intervention, the protocol dictates that embolization precedes trepanation and drainage.

5.3 MMA Embolization

Participants allocated to the MMA embolization group will undergo cerebrovascular angiography followed by ipsilateral MMA embolization to address the SDH. Anesthesia, either general or monitored local, will be administered as per the procedural needs. The use of intravenous heparin during the procedure will be meticulously documented. Initially, femoral or radial artery access is established, followed by digital subtraction angiography (DSA) using a standard 5 French diagnostic catheter for cerebrovascular evaluation. Subsequently, a guiding catheter is positioned in the proximal external carotid artery, and a microcatheter is advanced into the main trunk of the MMA under roadmap guidance. Superselective angiography of the MMA is then performed to identify any hazardous collateral vessels, such as ophthalmic and petrous branches, prior to embolization. Absence of dangerous collaterals allows for embolization using ONYX-18 (Medtronic, USA) under blank fluoroscopic roadmap. Successful embolization is achieved when both frontal and parietal branches or the main trunk of MMA are selectively occluded. For comprehensive embolization, it is advised that the microcatheter navigates distally within the frontal and parietal branches, facilitating maximum penetration of embolic materials into the smaller vessels. In this trial, MMA embolization is

recommended to precede burr-hole drainage in patients assigned to the combined treatment group.

6. Study Process

This clinical study focuses on assessing the effectiveness of Middle Meningeal Artery (MMA) embolization in treating Chronic Subdural Hematoma (CSDH). It includes a detailed flowchart for the study process (Appendix 1), encompassing informed consent, enrollment, and various stages of evaluation. Key aspects involve obtaining written informed consent, medical history recording, vital signs monitoring, and a stringent randomization process using SAS software. The study also emphasizes comprehensive clinical examinations and evaluations, including routine blood tests, imaging (CT/MRI), and scoring assessments (mRS, EQ-5D) at multiple stages. Additionally, the study records hospitalization details, re-hospitalization rates, and surgery-related complications to ascertain the treatment's effectiveness and safety.

6.1 Study Flowchart

See Appendix 1.

6.2 Informed Consent and Enrollment

Subjects will be requested to provide written informed consent (IC) after receiving the study information. The investigators will explain the materials according to the requirements of subjects. Every subject (or his/her legal representative) and investigator must sign and date the IC form (ICF) approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC) before the subject can proceed with the qualification screening. Copies of the ICF will be provided to all subjects. Subjects who provide written IC will be screened and evaluated. Subjects who do not provide IC will receive further treatment according to the doctor's advice and/or the subject's willingness.

After obtaining IC from subjects, the investigators shall screen them according to the inclusion and exclusion criteria, confirming that subjects do not fall under any of the exclusion criteria. Only when a subject meets all inclusion criteria and does not meet any exclusion criteria can the investigators assign the subject into a group according to the random assignment instruction.

6.3 Medical History and Vital Signs

During the screening visit, the medical history of the subjects will be collected and recorded in

the eCRF. Baseline measurements, including blood pressure and heart rate, will be taken.

6.4 Randomization

The assignment for each subject into either the control group (no MMA embolization) or the study group (MMA embolization) will be determined by the randomization scheme. SAS (version 9.4 or updated) is used to generate the randomization list by a stratified randomization method. During screening, a unique identification number (screening number) is allocated to each subject who has provided the signed ICF. The annotation for the screening number includes a subject number and site number (e.g., the first subject in 01 site is 01001). This digital ID is allocated according to the order of entry into the study after the subject signs the ICF at the study site.

On day 0 of the trial, subjects obtain the corresponding randomization numbers and will be randomized to the study group or the control group at a ratio of 1:1.

The randomization number of subjects in all study groups is designated as #: D-ZZZ

D = representing the treatment group; expressed with Arabic numerals 1-X, where 1 represents the study group and 2 represents the control group.

ZZZ=Subject digital ID

Treatment allocation in this study is not blinded.

6.5 Clinical Examination and Evaluation

(1) Inspection items before randomization include:

Routine blood work (red blood cell count, white blood cell count, platelet count, and hemoglobin);

Coagulation (activated partial thromboplastin time [APTT], INR);

Hepatic and renal function (alanine aminotransferase [ALT], aspartate aminotransferase [AST], blood urea nitrogen [BUN], creatinine [Cr]), electrolytes (potassium, sodium, chlorine, and fingerstick blood glucose);

Cranial CT scanning;

DSA;

Cranial MRI (depending on the conditions);

Urine human chorionic gonadotropin (HCG) test (female of childbearing age).

(2) Assess mRS score and EQ-5D score at screening and during baseline period;

(3) Total length of hospital stay, destination for rehabilitation after discharge, and total hospitalization expenses are recorded at discharge;

(4) Record severe surgery-related complications of subjects in 30 days after any surgical procedure (including burr-hole drainage and MMA embolization);

(5) Re-examine cranial CT/MRI at 90 days after randomization and record total hospital stay, re-hospitalization times, destination for rehabilitation after discharge, and total hospitalization expenses;

(6) Assess mRS score and EQ-5D score at 90 days and 360 days after randomization;

(7) Record SAEs, SDH-related death events, and severe surgery-related complications, total hospital length of stay, number of re-hospitalizations, destination for rehabilitation after discharge, and total hospitalization expenses at 30 days, 90 days and 360 days after randomization.

7. Statistical Analysis

7.1 General Principle

A biostatistician will develop a statistical analysis plan according to the study protocol before data locking.

Continuous variables are expressed as mean ±standard deviation, with the number of cases, median, maximum, and minimum provided; categorical variables are described by frequency and constituent ratio.

7.1.1 Test level

Two-sided tests are performed for all hypothesis tests ($\alpha = 0.05$). The confidence level of all confidence intervals is 95%.

7.1.2 Hypothesis test

Original hypothesis: there is no difference in the incidence of recurrence or progression of hematoma between the MMA embolization group and the traditional treatment group at 90 days post-procedure;

Alternative hypothesis: there is a difference in the incidence of recurrence or progression of hematoma between the MMA embolization group and the traditional treatment group at 90 days post-procedure.

7.1.3 Estimation of sample size

This study hypothesizes that MMA embolization may reduce the recurrence (operation group) or progression (conservative treatment group) of SDH. The estimated recurrence or progression rate of hematoma in the MMA embolization group is 5%, while that of control group is 12%. When estimating bilateral 5% for the statistical significance level, 90% for power, and 8% for an acceptable rate of loss to follow-up, the total sample size is estimated to be 722 cases.

7.1.4 Estimation of missing values

Missing values are not imputed.

7.1.5 Subject disposition

Description of subjects' enrollment, drop-out cases, completion of expected follow-up, and early suspension presented as the number of cases and percentage;

Subject disposition by data set.

Descriptions for drop-out subjects are individually described, including treatment condition, reason for premature withdrawal from the trial, etc.

7.1.6 Protocol violation and deviation

Summarize and describe the subjects with protocol violations and deviations.

7.1.7 Demographics and baseline characteristics

Age, height, weight, vital signs, and other baseline characteristics are described by mean, standard deviation, median, maximum, and minimum; the constituent ratio is calculated for

gender, smoking status, drinking status, medical history, drug allergy history, physical examination, etc.

7.2 Safety Analysis

7.2.1 Adverse events

Adverse event (AE) data is described according to the current version of MedDRA and then statistically analyzed.

SAEs within 90 days and 360 days post-procedure and the incidence of serious surgery-related complications within 30 days after surgery are summarized. The incidence of AEs is recorded as 1 case if multiple AEs occur in one patient or the same AE occurs frequently in one patient.

AEs will be summarized by system organ class (SOC) and preferred term (PT) in a frequency table. The incidence is calculated by systems and symptoms/signs (count of cases: the number of subjects with at least one AE).

Severity of AEs: When the same subject has the same AE several times, the most serious one is used to analyze the severity of the AE.

A list of subjects experiencing AEs will be provided.

7.2.2 Death

Mortality within 90 days and 360 days post-procedure is summarized, and a list of cases is provided.

7.2.3 Concomitant medication (during the study)

Summarize the usage of concomitant medication during the study (including any changes in concomitant medication during screening, new concomitant medication after screening, and drugs for treating AEs), and the frequency of use of each drug.

7.3 Efficacy Analysis

7.3.1 Primary efficacy analysis

Summarize the incidence of the primary endpoint event.

Primary endpoint event: incidence of recurrence (surgery group) or progression (drug therapy

group) of SDH within 90 days post-procedure

Hematoma recurrence refers that the maximum thickness of hematoma exceeding 10 mm, combined with neurological symptoms, or the patient needs to undergo re-operation (surgery group);

Symptomatic CSDH progression refers that the maximum thickness of hematoma increasing by more than 3 mm compared with baseline, or the patient requires operation (drug therapy group).

Note: The primary endpoint event is considered to have been met for any patient who died from any cause within 90 days post-procedure.

Cochran-Mantel-Haenszel (CMH) chi-square analysis will be used for primary endpoints. The difference in event incidence between the two groups and its 95% confidence interval will be calculated. The Kaplan-Meier (KM) method is further used to estimate the incidence of primary endpoint events and its 95% confidence interval.

SAS code to be used in CMH analysis is as follows:

```
ods output CMH=CMH_out;

proc freq data=FatComp order=data;

    tables Layer*Exposure*Response /CMH ALPHA=0.05;

    weight count;

    output out=cmh_ci cmh;

run;
```

Sas code to be used for KM estimation is as follows:

```
proc lifetest data=TTE alpha=0.05;

    time avalm*cnsr(1);

    strata /group=trtg;

    ods output Quartiles = Quartiles
```

```
    ProductLimitEstimates=Estimates;
run;
```

7.3.2 Secondary efficacy analyses

Summarize the following indicators:

- Recurrence or progression rate of SDH at 360 days post-procedure
- Success rate of target blood vessel embolization (MMA trunk and branch vessels) on DSA imaging
- Change in hematoma thickness on CT/MRI at 90 days post-procedure
- Change in hematoma volume at 90 days post-procedure
- Change in midline shift on CT/MRI at 90 days post-procedure
- Change in mRS score at 90 days and 360 days post-procedure
- Proportion of patients with mRS ≤ 2 at 90 days and 360 days post-procedure
- Proportion of patients with mRS ≤ 3 at 90 days and 360 days post-procedure
- Quality of life evaluated with EQ-5D Scale at 90 days and 360 days post-procedure
- Total hospital length of stay, number of re-hospitalizations, destination for rehabilitation after discharge (home vs. rehabilitation hospital) and total hospitalization expenses

Same as primary endpoint analysis, Chi-square test (qualitative indicator) or t-test (quantitative indicators) is used for inter-group comparison in secondary endpoint analysis.

For time event endpoints, such as incidence of recurrence or progression of SDH at 360 days post-procedure, the KM method will be used.

7.3.3 Sub-Group analysis

In the evaluation of both primary and secondary outcomes, pre-specified subgroup analyses were conducted, focusing on distinctions between patients undergoing burr-hole drainage and those receiving optimal medical management. For safety assessments, the analysis encompasses all patients who were randomized and subsequently underwent the study

treatment.

8. Data Management

8.1 Filing of Case Report Form

The design of the Case Report Form (CRF) shall guarantee the collection of all data which are specified in the study protocol and meet the needs of statistical analysis. Electronic Case Report Form (eCRF) is an electronic form of CRF, which is used to record the data of each subject during the trial. The eCRFs must be filled in and completed for all included cases.

Electronic Data Capture System (EDC) for clinical trials is adopted for data collection management. The clinical trial investigator or Clinical Research Coordinator (CRC) shall fill in the eCRF accurately, timely, completely, and standardly according to CRF filing instructions.

8.2 Data Verification and Query

In order to ensure the integrity, consistency, and accuracy of data, automatic logic verification and manual logic verification are adopted. The EDC system performs real-time automatic logic verification on the filled data, such as the range and logical relationship of data values. The data administrator will send a manual Query in EDC.

8.3 Database Locking

After completing all data filling and query clearing, the PI, statistical analyst, Sponsor representative, clinical research associate (CRA) representative, and data administrator complete the final definition and judgment of the analysis population, and approve database locking in writing, and then the data administrator locks the database.

Generally, the locked database cannot be unlocked. If unlocking is needed, the unlocking conditions and procedures must conform to the corresponding SOP, and the unlocking process must be carefully controlled and recorded.

9. Ethical Protection and Informed Consent of Clinical Study

9.1 Ethical Considerations

The clinical study shall be conducted in compliance with the codes of ethics set forth in the *Declaration of Helsinki* by World Medical Association and *Good Clinical Practice for Medical*

Device Clinical Trials. Before the study begins, the Ethics Committee (EC) shall strictly deliberate the study protocol and related documents from the perspective of protecting the rights and interests of subjects, and the study can be implemented only after obtaining the written approval of the EC. All parties involved in the study shall bear corresponding ethical responsibilities according to their respective responsibilities in the study.

9.2 Approval of Study Protocol

Before the clinical study, the investigators need to submit the clinical study protocol, ICF and other related documents to the EC of hospitals where the clinical study site is located. The clinical study can only be started after approved by the EC. Any amendment to the study protocol must be approved by the EC before it can be implemented.

9.3 Informed Consent Process and Informed Consent Form

Before including a subject, the investigator must explain details of the clinical study to the subject:

The subject voluntarily participates in the clinical study and has the right to withdraw from the clinical study at any stage;

The personal data of the subject will be kept confidential. The EC, the drug regulatory authority and the implementer may consult the information of the subject, but shall not disclose the contents;

During the clinical study, the medical institution has the obligation to provide the subject with information related to the clinical study;

The subject is informed about the contents, objectives, and possible AEs of this study, and can only be included after fully understanding this study and signing the ICF;

The ICF is jointly signed by the investigator and the subject in duplicate, each copy for each party.

10. Provisions on Aes

10.1 Adverse Events

10.1.1 Definition of AE

An AE is defined as any untoward medical occurrence in the process of the clinical study, regardless of its relationship to the investigational medical device.

10.1.2 Classification of adverse events

Mild: The subject can tolerate, without effecting the treatment. No special treatment is required. There is no impact on the health of the subject.

Moderate: The subject cannot tolerate, with the need of device removal or special treatment. There is direct impact on the health of the subject.

Severe: It endangers a subject's life, leading to disability or death. Device removal or an emergency treatment needs to be done immediately.

10.1.3 Correlation between Aes and investigational devices

1) Definitely related: The type of Aes has been confirmed as the type of reaction that must occur in investigational medical device, which accords with the reasonable chronological order after treatment, and this AE cannot be explained by other reasons.

2) Probably related: The occurrence of Aes may be caused by the use of investigational medical device, and there is a reasonable chronological order between the occurrence of events and the use of investigational medical device.

3) Possibly related: The occurrence of Aes may be caused by the investigational medical device, and other factors cannot be ruled out. There is a reasonable chronological order between the occurrence of Aes and the use of investigational medical device, and the causality between the events and the use of investigational medical device cannot be ruled out.

4) Possibly unrelated: The occurrence of Aes is more likely related to other factors. Or the occurrence time of the AE indicates that it is unlikely to have causality with the use of investigational medical device.

5) Not related: There is no correlation between the occurrence of Aes and the use of investigational medical device.

6) Unable to determine: The correlation between the occurrence of Aes and the use of investigational medical device cannot be determined.

10.2 SAEs

SAEs are the following events occurred during the clinical study:

1) Death;

2) Fatal disease or injury;

3) Permanent impairment of a body structure or a body function;

4) Resulting in hospitalization or prolonged hospitalization;

5) Medical or operative intervention is required to avoid any permanent impairment in the physical structure or physical function;

6) Fetal distress, fetal death or congenital anomalies, congenital defect, etc.

10.3 Possible Adverse Events and Plans

1) Cerebral vasospasm: during embolization, cerebral vasospasm may be induced due to repeated operations and embolization and stimulation of contrast media on the vessel wall. Intravenous or transarterial administration of antivasospasm drugs such as Nimotop injection, Fasudil injection, and Papaverine injection can be used during the surgery, to improve cerebral vasospasm in patients in the embolization group.

2) Mistaken embolization: because there are communicating branches between intracranial and extracranial arteries (dangerous anastomosis), embolic agents are easy to mistakenly enter into communicating branches, so it is necessary to master the injection dose and speed of embolic agents during embolization to prevent mistaken embolization. Circulating nurses shall closely observe the swallowing, pronunciation, vision and limb activities of patients, and find out special discomfort symptoms as early as possible.

3) Contrast agent allergy: although nonionic contrast agents are widely used at present, allergic reactions may still occur during endovascular interventional therapy, especially in patients with high risk factors of allergy. When the patient is found to have facial flushing, nausea, vomiting, headache, blood pressure drop, dyspnea, convulsion, shock and coma, allergic reaction shall be considered and anti-allergic treatment shall be given promptly.

11. Management Considerations

Coordinating Investigators:	Professor Mao Ying Huashan Hospital, Fudan University No. 433 Huashan Road, Jing'an District, Shanghai 200040 Professor Liu Jianmin First Affiliated Hospital of the Second Military Medical University (Changhai Hospital of Shanghai) No. 168 Changhai Road, Yangpu District, Shanghai 200082
Steering Committee	China: Mao Ying, Liu Jianmin, Gu Yuxiang, Yang Pengfei; Foreign country: Mayank Goyal (CAN), Charles Majoie (NED)
Statistician:	Professor Zhao Naiqing
Chairman of Data and Safety Monitoring Board (DSMB):	Prof. Craig Anderson (Aus)
Contract Research Organization:	Cardiovascular Chinese Research Center

11.1 Subject confidentiality All information, medical records, and laboratory data of subjects must be kept confidential. The discussion, analysis and report of information and data are only for the purpose of this clinical study. In the eCRF and any report, the number will be used to distinguish the subject's identity, and the subject's identity will be kept confidential.

11.2 Study monitoring The Sponsor's representatives or its designated personnel are allowed to visit the study site regularly, to assess the quality of data and the integrity of study. The representative will review the study records of the study site and directly compare these records with the original documents, discuss the implementation of the study with the investigators, and confirm the rationality of study implementation. In addition, the study can be evaluated by internal auditors of the Sponsor and government inspectors who must be allowed to view eCRFs, original documents, and other study documents. The Sponsor's audit report will be kept confidential.

During the monitoring visit, the investigator or the designated personnel under the investigator must be present at some times to review the data, answer any queries, and be allowed to directly access to subject records (such as medical records, office documents, hospital documents, and study-related documents) for validation of original data. Before each visit, the eCRF must be filled in and provided to the Sponsor's representative for checking its accuracy and integrity.

11.3 CRF and study records: All records will be kept confidential. Personal information of subjects, including names, shall not be disclosed at any time. Subjects' clinical/experimental data shall not be disclosed to any party other than the Sponsor

or its designated personnel and relevant competent government agencies. In all cases, the information must be kept confidential with caution for subjects. In the eCRF and other study-related documents, the number will be used to represent the subject's identity.

The study site staff will collect data electronically. Initially, data will be collected on the original documents, and then transcribed to the eCRF. The eCRFs will not be used as the primary medium for collecting any data. The data in eCRF is sourced from original documents, and must be consistent with original documents. Any deviation between eCRF and original documents must be explained and recorded. All necessary information must be recorded in the blank space provided in the eCRF. If certain data are not available or not applicable, they must be recorded as Not Available or Not Applicable; no blank space can be left.

Each subject participating in the study must have a complete eCRF, and each page in the form must be reviewed and approved by the PI. The PI will confirm that he/she has reviewed the recorded data by electronic signature in the electronic data collection page. The PI may entrust the review and confirmation to a qualified doctor who may be appointed as an assistant investigator. Investigators must keep a copy of the eCRF, including records of changes and corrections.

11.4 Data and Safety Monitoring Board: An independent Data and Safety Monitoring Board (DSMB) will be established to regularly review and analyze all safety data. The effect data generated by the study will be evaluated by DSMB for potential risks and benefits of the treatment. DSMB will be composed of independent professional doctors (at least 2 persons) who will not undertake the recruitment of subjects in this study and a biostatistician whose identity is not disclosed. DSMB will keep SAEs under review. DSMB will review the frequency and severity of all aEs as well as demographic data, etc. Specific meetings may be held for any safety reasons during the study. Based on results of data review, if any termination criterion is met, DSMB will give suggestions on whether to continue, adjust or terminate the study. Other responsibilities and details of DSMB will be included in the DSMB Charter.

11.5 Clinical Event Committee (CEC): The CEC will independently and impartially evaluate the safety events, including at least all protocol-specified safety endpoints of the subjects. The CEC should be composed of at least three independent physicians, one of whom will act as CEC President. Details regarding the responsibilities of CEC

members and clinical events that require CEC review will be included in the CEC constitution.

11.6 Imaging assessment committee (IAC): The primary and secondary endpoints of the trial involve quantitative imaging assessments, which will be reviewed by the IAC with data including at least: CT/MRI (screening period/baseline, 90-day follow up [V4], 360-day follow up [V5]), and DSA imaging (target vessels [MMA main and branch vessels]).

11.7 Outcome Assessment Committee (OAC): The OAC is responsible for evaluation of multiple subjective data, including at least clinical symptoms and mRS score (90-day follow up [V4] and 360-day follow up [V5]).

11.8 Financial disclosure: The financial affairs of the study must be recorded in the agreement between the Sponsor and the investigators.

12. Confidentiality Principle

The investigator must strictly keep confidential the study results, protocol, and other materials and shall not publish any information spontaneously without the written authorization of the Sponsor. Any citation must also be made with the Sponsor's prior written authorization.

The personal data of the subject participating in the study is confidential; however, the EC, National Medical Products Administration (NMPA), competent department of health and family planning or the Sponsor may look up the personal data of the subject participating in the study for the demand of work according to the established procedure.

13. Agreement on the Publication of Study Results

The Sponsor and investigators shall agree on the final study report.

The study results can be published as scientific literature or submitted to authorities. The following terms are made to protect the commercially confidential data.

All the information about the investigational device (e.g. patent application, the previously unpublished manufacturing process and basic scientific data provided by the Sponsor to the investigator) is considered confidential and is the property of the Sponsor. The investigator shall not use the information for other purposes without the written permission of the Sponsor.

Before the study results are published or released, the investigator shall allow the Sponsor to review the results and put forward opinions within 30 days to confirm that the confidential information is not disclosed and supplement the relevant information. According to the general accepted principles of scientific research cooperation, the investigator shall discuss with the relevant personnel of Sponsor about the results, and reach an agreement before the publication of the results.

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Appendix 1.Study Flowchart

Study procedure	Screening period[a]	Baseline	Follow-up period			
Visit time[b]	V0	V1	V2	V3	V4	V5
	Day -14 to Day 0	Day 0	Discharge	Day 30	Day 90	Day 360
Informed consent	X					
Demographic data	X					
Inclusion/exclusion criteria		X				
Medical history and previous medication	X					
Vital signs	X			X	X	X
Admission examination[c]	X					
CT/MRI[d]	X				X	X
DSA[e]		X				
Randomization and treatment		X				
Total hospitalization expenses			X		X	X
Efficacy endpoints					X	X
SAEs			X			
SDH-related death events			X			
Severe surgery-related complications			X			
Concomitant medication/treatment			X	X	X	X
mRS score	X				X	X
EQ-5D scale	X				X	X

[a] Screening visit and baseline visit can be conducted on the same day

[b] The visit time window is ±7 days for V3, ±14 days for V4, and ±30 days for V5

[c] Blood routine (red blood cell count, white blood cell count, platelet count, hemoglobin), coagulation (APTT, INR), hepatic and renal function (ALT, AST, BUN, Cr), electrolytes (potassium, sodium, chlorine), random blood glucose; urine HCG test is required for female of child-bearing potential

[d] CT is mandatory and MRI is optional. The doctor should decide whether MRI is necessary based on the condition of the patient

[e] This item is conducted only in MMA embolization group

Appendix 2. EQ-5D Scale

Your name: ☐

By placing a tick "√" in **one** box in each group below, please indicate which statements best describe your own health status **today**.

Mobility

I have no problems in walking about (1 point) ❑

I have slight problems in walking about (2 points) ❑

I have moderate problems in walking about (3 points) ❑

I have severe problems in walking about (4 points) ❑

I am unable to walk about (5 points) ❑

Self-care

I have no problems washing or dressing myself (1 point) ❑

I have slight problems washing or dressing myself (2 points) ❑

I have moderate problems washing or dressing myself (3 points) ❑

I have severe problems washing or dressing myself (4 points) ❑

I am unable to wash or dress myself (5 points) ❑

Usual Activities (e.g., work, study, housework, family or leisure activities)

I have no problems doing my usual activities (1 point) ❑

I have slight problems doing my usual activities (2 points) ❑

I have moderate problems doing my usual activities (3 points) ❑

I have severe problems doing my usual activities (4 points) ❑

I am unable to do my usual activities (5 point) ❑

Pain /Discomfort

I have no pain or discomfort (1 point) ❑

I have slight pain or discomfort (2 points) ❑

I have moderate pain or discomfort (3 points) ❑

I have severe pain or discomfort (4 points) ❑

I have extreme pain or discomfort (5 points) ❑

Anxiety or Depression

I am not anxious or depressed (1 point) ❑

I am slightly anxious or depressed (2 points) ❑

I am moderately anxious or depressed (3 points) ❑

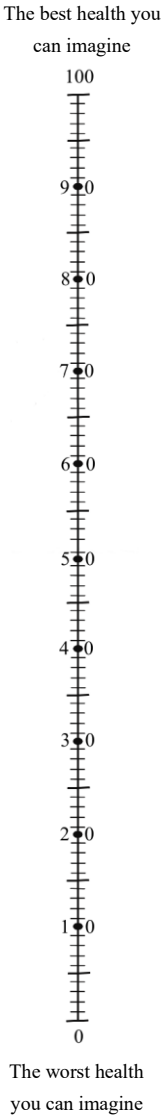
I am severely anxious or depressed (4 points) ❑

I am extremely anxious or depressed (5 points) ❑

Please mark the point that best represents your health today:

100 means the best health you can imagine

0 means the worst health you can imagine



Appendix 3. Modified Rankin Scale (mRS score)

Patient symptoms	Score
No symptoms	0
No significant disability despite symptoms; able to carry out all usual works and live	1
Slight disability, unable to carry out all previous activities, but able to look after own affairs without assistance	2
Moderate disability; requiring some help, but able to walk without assistance	3
Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance	4
Severe disability; bedridden, incontinent and requiring constant nursing care and attention	5