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Research Article

Chronic Subdural Hematoma Treatment with Embolization Versus Surgery Study (CHESS): Trial Rationale and Protocol

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Abstract

Background: Current treatment paradigms for Chronic Subdural Hematoma (CSDH) include either medical management for mildly symptomatic patients or surgical evacuation for severely symptomatic patients. Middle Meningeal Artery Embolization (MMAE) has demonstrated potential to reduce rate of recurrence and rescue surgery as an adjunctive or standalone treatment for CSDH. However, there currently lacks randomized trial data to support the safety and efficacy of standalone MMAE in CSDH patients. Objective: The objective of Chronic Subdural Hematoma Treatment with Embolization versus Surgery Study (CHESS) is to compare standalone MMAE to conventional surgery for treatment of moderately symptomatic CSDH. Methods: CHESS is a prospective, multi-center, open-label randomized controlled trial. Eligible CSDH patients will be randomized 1:1 to either conventional surgery (burr holes or craniotomy) or standalone MMAE with either polyvinyl alcohol particles or microspheres. The follow-up duration will be for 180 days following randomization. Results: The primary endpoint is a composite measure, comprising of the centrally-adjudicated need of rescue surgery and/or mortality, assessed from randomization through 180 days. Safety outcomes include symptomatic ischemic stroke, serious/life threatening adverse events, worsening neurological status, seizures, and cranial neuropathy. Exploratory endpoints include hematoma volume reduction (at least 50%), functional outcome, as well as changes in quality of life, cognition, and headache severity. Conclusions: CHESS is the first randomized controlled trial to characterize the safety and efficacy of standalone MMAE compared to conventional surgery in a moderately-symptomatic CSDH patient population. Results of this trial will further advance the role of endovascular approaches to CSDH treatment. Trial Registration Number: NCT06347796.

Keywords: Chronic subdural hematoma; Embolization; craniotomy; Endovascular procedures; Clinical trial; Trial protocol; Intention to treat analysis.

Introduction

Chronic Subdural Hematoma (CSDH) is associated with high rates of morbidity, mortality, and recurrence [1-4]. The clinical presentation of CSDH ranges from asymptomatic to significant neurological deterioration [5]. Severely symptomatic patients are treated with surgical evacuation, including burr hole drainage, craniotomy, or Subdural Evacuating Port System (SEPS). However, surgical evacuation has been associated with high rates of recurrence of up to 20% to 37%; these high rates of recurrence are likely related to localized neuroinflammation, leading to persistent neovascularization and recurrent microbleeds into the subdural space [6-9]. In contrast, mild or moderately symptomatic patients have been traditionally managed with close observation and pharmaceuticals, such as high-intensity statins, tranexamic acid, and corticosteroids [10-14]. There has been mixed evidence for safety and efficacy of these agents in managing CSDH, limited to a modest benefit when used adjunctively [14]. Hence, there is a strong need to identify a safer and more effective treatment approach.

Middle Meningeal Artery Embolization (MMAE) is a minimally-invasive approach to CSDH treatment that has demonstrated potential to lower rates of hematoma recurrence and reduce the need for rescue surgery. Randomized controlled trials evaluating adjunctive MMAE demonstrated potential benefit in the CSDH population [3,15-17]. Additionally, early evidence from case series and meta-analyses have suggested positive outcomes with both standalone and adjunctive MMAE, including lower rates of hematoma recurrence, reduced risk of requiring rescue surgery, and favorable rates of CSDH resolution [18-24]. However, there currently lacks evidence from randomized controlled trials to evaluate the safety and efficacy of MMAE as a standalone intervention for CSDH. The aim of the Chronic Subdural Hematoma Treatment with Embolization Versus Surgery Study (CHESS) is to compare standalone MMAE to surgical drainage in moderately-symptomatic CSDH patients.

Methods

CHESS is a prospective, multicenter, open-label randomized controlled trial comparing MMAE and conventional surgery for the treatment of moderately-symptomatic CSDH patients. Patients will be recruited from up to 45 sites in the United States, with 1:1 randomization of 394 total subjects. This trial is registered at ClinicalTrials.gov (NCT06347796), and is sponsored by the National Institute of Neurological Disorders and Stroke (NINDS; UG3 NS128397, UH3 NS128397). The study procedures described are based on Protocol Version 14 (approved on September 18, 2024) and the Manual of Procedures Version 1.0 (approved January 13, 2025).

Treatment Arms

Middle Meningeal Artery Embolization

Patients randomized to the MMAE treatment group will undergo unilateral endovascular embolization of the MMA ipsilateral to the CSDH collection with either Embosphere® Microspheres (Merit Medical Systems Inc., South Jordan, UT, USA) or CONTOUR™ Polyvinyl Alcohol (PVA) Embolization Particles (Boston Scientific Corporation, Marlborough, MA, USA). The following sizing variants are permitted: 100-300 micron microspheres; 300-500 micron microspheres; 150-250 micron PVA particles; 250-355 micron PVA particles; or 355-500 micron PVA particles. Type and sizing is per discretion of the treating neuro-interventionalist.

In the absence of prohibited anastomoses or collaterals, the target MMA will be selectively catheterized to infuse the particles until adequate devascularization in the MMA territory is achieved. Prior to embolization, selective angiography of the internal and external carotid arteries will be performed to assess for anatomical variants that would not be appropriate for MMAE (e.g., MMA origin from the ophthalmic artery) or may increase the risk of ischemia due to non-target embolization from unintended migration of embolic particles (e.g., collaterals, shunts, and anastomoses).

Conventional Surgery

Patients randomized to the conventional surgery treatment group will undergo either burr hole drainage or craniotomy. Routine cauterization of the MMA prior to dural opening will be prohibited unless required to control active bleeding, in order to minimize potential confounding due to MMA occlusion induced by cauterization versus endovascular embolization.

Study Workflow

Patient Population

Patients who present with a moderately-symptomatic CSDH will be screened per the inclusion and exclusion criteria summarized in Table 1.

Inclusion Criteria	Exclusion Criteria
Age 40-90 years, inclusively	Secondary cause apart from trauma for the qualifying SDH, such as an underlying vascular abnormality or tumor
Per CT of the head, one of the following:	Tentorial or interhemispheric SDH
• Unilateral convexity CSDH measuring at least 10 mm in thickness OR • Bilateral CSDH, if only one side is considered for treatment and the contralateral side is asymptomatic and <5mm in thickness	Previous craniotomy for the treatment of CSDH, if the craniotomy exceeds 7 cm at the maximal dimension on the baseline CT
CSDH is at least 2/3 isodense or hypodense, verified on the axial CT slice used to measure the thickness of the qualifying CSDH	mRS of 5 or higher
Qualifying baseline head CT performed within 7 days to randomization	Emergent surgical evacuation such as open craniotomy, burr hole drainage, or SEPS is required for the patient
Able to undergo assigned treatment within 48 hours of randomization	Unable to withhold all antiplatelet agents or oral anticoagulant agents for the first 7 days after randomization
Patient or legally authorized representative agrees to be randomized and provides written informed consent	Indication that withdrawal of care will be implemented for the qualifying SDH
	Prior surgical treatment for CSDH if the surgery is less than 30 days prior to randomization
	On tranexamic acid
	Platelet count of <100,000 per mL refractory to transfusion
	Coagulopathy that cannot be corrected to an INR of ≤ 1.5
	Known contraindications to angiography
	Known intolerance to occlusion procedures
	Known vascular anatomy (small artery size) or blood flow (high vascular resistance peripheral to the feeding arteries) that precludes catheter placement or embolic particle injection
	Known presence of collateral vessel pathways potentially endangering normal territories or cranial nerves during embolization
	Known large diameter arteriovenous shunt, i.e., where the blood does not pass through an arterial/capillary/venous transition but directly from an artery to a vein or presence of patent extra-to-intracranial anastomoses (where embolic particles could pass directly into the internal carotid artery, vertebral artery, or intracranial vasculature) that cannot be addressed with coil embolization
	Patient has a known active systemic infection or sepsis
	Patient is pregnant, planning to become pregnant, or lactating
	Life expectancy of less than 6 months due to comorbid terminal conditions

	Concurrent participation in another research protocol for investigation of an experimental therapy
	Known or suspected to not be able to comply with the study protocol
	No measurable deficit on the TUG, ASR, or MRC
Abbreviations: CT: Computed Tomography, CSDH: Chronic Subdural Hematoma, SDH: Subdural Hematoma, mRS: Modified Rankin Scale, SEPS: Subdural Evacuating Port System, INR: International Normalized Ratio, TUG: Timed Up and Go test, ASR: Aphasia Severity Rating test, MRC: Medical Research Council test for muscle strength.	

Table 1: Inclusion and exclusion criteria.

In order to meet criteria for randomization, a patient will need to have a qualifying measurable deficit in one or more of the following scales: the Timed Up and Go (TUG), Aphasia Severity Rating (ASR), or Medical Research Council (MRC) muscle strength scores. To be considered moderately-symptomatic, a potential patient may have at least one or more of the following deficits attributable to the CSDH: TUG ≥ 11 seconds; and/or ASR 3-4; and/or MRC 4. However, if there is a severe deficit attributable to the CSDH per any of these scales (*i.e.*, ASR scores 0-2 and/or MRC <4 for any muscle group), then the patient will be deemed ineligible for CHESS, irrespective if they have a qualifying deficit or normal values on other scales. These severe CSDH patients requiring surgery lack equipoise for randomization, and consequently would fall outside of the target population for CHESS.

Randomization

After screening, the intervention (MMAE versus surgery) will be allocated 1:1 using WebDCU™, which is a central web-based randomization tool. At the point of randomization, the patient is considered as enrolled in the study, and will be followed until the conclusion of the study schedule (Figure 1). Treatment with MMAE or conventional surgery will occur within 48 hours of randomization.

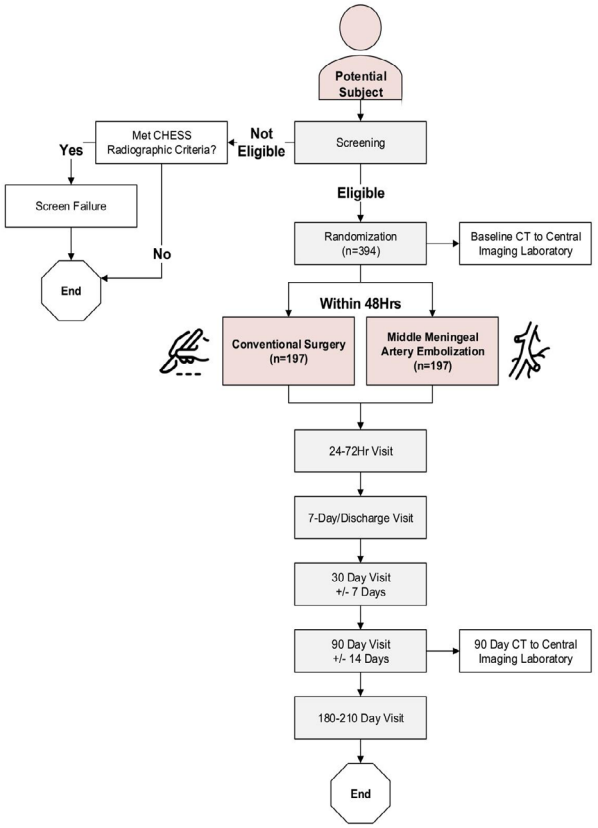

Figure 1: Flowchart demonstrating study design and key study events.

Follow-Up Visits

There are five pre-specified follow-up visits (Table 2). As CHESS is an open-label study, the treating provider will not be blinded to the treatment arm. To minimize bias, an independent assessor, who will be masked to the treatment arm, will ascertain key study endpoints at follow-up study visits.

Study Event	Screening	Treatment	24-72 Hours	7 Days or Discharge	30 Days	90 Days	180-210 Days	Rescue Surgery*
Consent	X							
Randomization		X						
Treatment		X						
Lab Work/Imaging								
Screening Lab Work	X							
Serum Creatinine	X		X					
Head CT	X		X			X	X	X
Clinical History Assessments								
Medical History	X							
Medications	X		X	X	X	X	X	
AE/SAEs		X	X	X	X	X	X	
Clinical Scale Assessments								
Markwalder Scale	X		X	X	X	X	X	
NIHSS	X		X	X	X	X	X	
MRC**	X		X	X	X	X	X	X
TUG**	X					X	X	X
ASR**	X					X	X	X
mRS	X						X	
EQ-5D-5L	X						X	
T-MOCA	X						X	
HIT-6	X						X	

Table 2: Schedule of study visits.

*This assessment must occur when meeting criteria for a rescue surgery assessment anytime from randomization until the end of the follow-up period.

**These assessments are performed by an outcome assessor masked to the study treatment.

Table 2 Abbreviations: CT: Computed Tomography, AE: Adverse Events, SAE: Serious Adverse Events, NIHSS: National Institutes of Health Stroke Scale, TUG: Timed Up and Go, ASR: Aphasia Severity Rating, MRC: Medical Research Council scale for muscle strength, EQ-5D-5L: EuroQol 5-Dimension 5-Level questionnaire, T-MOCA: telephone Montreal Cognitive Assessment, HIT-6: Headache Impact Test-6 questionnaire

Rescue Surgery

Rescue surgery may be indicated either due to lack of improvement or neurological worsening attributable to the CSDH in addition to SDH progression on imaging. Permitted rescue surgical evacuation procedures include craniotomy, burr holes, or SEPS.

For the purposes of endpoint determination, the need for rescue surgery in CHESS will be separately adjudicated when a patient either meets pre-specified clinical and radiographic criteria (irrespective of whether the patient received rescue surgery) or was emergently operated on (irrespective of whether the patient met clinical and radiographic criteria).

To meet clinical criteria, the patient will have had no improvement in a qualifying deficit measured at baseline per TUG, ASR, or MRC scales after ≥ 6 weeks from screening. Alternatively, a patient may also meet clinical criteria if scores worsen (i.e., MRC 0-2 in a muscle group contralateral to CSDH, ASR reduced by ≥ 1, or increase in TUG by ≥ 30%) at any time point that is otherwise not explained by another cause. To meet radiographic criteria, a patient would either need to have an increase in maximal hematoma thickness by ≥ 20% or an increase in midline shift by ≥ 3mm from baseline to any follow-up Computed Tomography (CT) imaging. Patients meeting any clinical symptom criteria and at least one radiographic criterion will be required to undergo central adjudication.

Study Organization

CHESS is led by four co-principal investigators from the University of Texas Medical Branch (Galveston, TX, USA), Medical University of South Carolina (Charleson, SC, USA), University of Missouri-Columbia (Columbia, MO, USA), and Cooper University Health Care (Camden, NJ, USA). The national coordinating center for the trial is at the University of Texas Medical Branch. The statistical and data management center is located at the Medical University of South Carolina. The Central Imaging Laboratory (CIL) and central Clinical Review Committee (CRC) is at the University of Missouri-Columbia.

Data Collection and Analysis

All data will be collected at the site and entered into a central electronic database (WebDCU™) maintained by the statistical and data management center. In addition to central and on-site monitoring, centralized data adjudication, and rigorous data checks, sites will maintain a contemporaneous screen failure log to describe reasons for not enrolling a patient who met radiographic inclusion criteria for CHESS. Upon conclusion of the trial and publication of the primary results, data related to this clinical investigation will be de-identified and made available in a public repository.

Central Imaging Laboratory

Masked to clinical information and treatment assignment, the CIL will conduct a standardized evaluation of hematoma size and volume from non-contrast head CTs obtained during the study. Head CT images for all randomized subjects obtained at baseline and 90-day follow-up will be transmitted to and analyzed by the CIL.

Clinical Review Committee

The CRC will review clinical information and imaging scans to centrally and independently adjudicate the need for rescue surgery. CRC review will entail assessments made by two independent reviewers, with disagreements in outcome assessments resolved by a consensus review. For quality control purposes, the first and second randomized subject at each site will be required to undergo CRC review at 90-day and 180-day follow-up visits. Additionally, any patient meeting criteria for rescue surgery evaluation will also undergo CRC review for primary endpoint adjudication.

Safety Monitoring

The Data and Safety Monitoring Board (DSMB) will consist of three physicians familiar with CSDH management, a statistician, and an ethicist. The DSMB will oversee patient safety through review of periodic safety reports summarizing all adverse events and making recommendations to ensure continued safety of participants. Additionally, an endovascular neurosurgeon with expertise in both CSDH evacuation and MMAE will be designated as an Independent Medical Safety Monitor (IMSM). The IMSM will contemporaneously review reported serious adverse events to identify emergent safety concerns.

Endpoints

Primary Endpoint

The primary endpoint is a composite outcome defined as the proportion of subject that need rescue surgery per CRC review or die within 180 days of randomization.

Safety Endpoints

Safety will be characterized by assessing the proportion of patients who experience the following events from randomization to the end of the follow-up period:

- Symptomatic ischemic stroke
- Serious/life threatening adverse events
- Worsening neurological status or new, disabling neurological symptom (e.g., ≥ 1 decline on the Markwalder Scale)
- Seizures
- Cranial neuropathy

Exploratory Endpoints

Additional exploratory endpoints include:

- Proportion of patients with ≥ 50% hematoma volumetric reduction on CT between screening and 90-day follow-up
- Change in quality of life (assessed with the EQ-5D-5L questionnaire) between screening and 180-day follow-up.

- Change in cognitive outcome (assessed with T-MOCA tool) between screening and 180-day follow-up.
- Change in headache severity (assessed with HIT-6 questionnaire) between screening and 180-day follow-up.
- Proportion of patients with favorable functional outcome, defined as an improvement in mRS score, between screening and 180-day follow-up. If baseline mRS is 0, a favorable outcome is defined as a stable mRS of 0.

Sample Size Calculation

The sample size for this superiority trial was determined by assuming that the proportion of patients meeting the primary endpoint (requiring rescue surgery or mortality) within 180 days is 25% in the conventional surgery (control) group and 12% in the MMAE group [25]. With Type I and Type II error probabilities of 0.05 and 0.15, respectively, the total sample size required is 319. To account for approximately 10% loss to follow-up and crossover among treatment groups, the target sample size for randomization was increased to 394. No more than 520 patients will be consented to be screened for the study, to account for patients who may become ineligible for CHESS after completing post-consent screening procedures.

Statistical Analysis Plan

For analysis of all primary, safety, and exploratory outcomes, regression models will be performed. For binary outcomes (inclusive of the primary endpoint), log-binomial generalized linear models will directly estimate the relative risk given the treatment assignment, adjusting for age and CSDH type (i.e., de novo CSDH or recurrent CSDH) as covariates. For outcomes assessing changes in assessment score values, linear regression analyses will be performed between the outcome and treatment group adjusting for baseline score, age, and CSDH type. For each of these outcomes, adjusted treatment effect and 95% confidence interval will be reported.

The primary outcome analysis will be further expanded to also characterize the effect of using PVA particles versus microspheres. The primary outcome will similarly be analyzed across the following subgroups pertinent to the CSDH population, if the subgroup size is sufficient: baseline hematoma volume (⟦<120 cm⟧ ^3 *vs.* ≥ 120⟦cm⟧^3); de novo versus recurrent CSDH patients; recurrent CSDH patients with either prior burr holes versus craniotomy; and the use of conscious sedation versus general anesthesia in the MMAE-treated group. To account for heterogeneity due to clinical sites, a secondary mixed effects model for the primary outcome will be performed, with clinical site and a site-by-treatment interaction term as random effects.

An additional pre-specified subgroup analysis will extend the primary analysis to additionally adjust for sex/gender and race/ethnicity, in addition to interactions with treatment, to explore heterogeneity of the treatment effect across subgroups and to characterize subgroup-specific treatment effects.

All efficacy and safety will use an intention-to-treat sample, including all subjects who are randomized in the study. Missing data will be imputed by a multiple imputation method accounting for baseline covariables.

Discussion

CHESS is the first randomized control trial in the United States intended to compare standalone MMAE versus conventional surgical evacuation. Enrollment has started in November 2024 and is ongoing. Enrollment is expected to occur over 53 months, with conclusion of study-related follow-up at 60 months. The findings of CHESS will advance current understanding of the role of MMAE in CSDH treatment.

Three recently-completed randomized controlled trials have provided evidence for the role of MMAE in CSDH treatment. The Embolization of the Middle Meningeal Artery with ONYX™ Liquid Embolic System for Subacute and Chronic Subdural Hematoma (EMBOLISE, NCT04402632) was a multicenter, open-label, randomized controlled trial across 39 sites in the United States consisting of two arms: 1) comparing observation versus MMAE in mild CSDH patients; and 2) surgery versus adjunctive MMAE with surgery for moderate or severe CSDH patients [8,17]. The primary efficacy outcome was reoperation due to hematoma recurrence or progression in 90 days. Although the results of the observational arm of EMBOLISE is forthcoming, the surgical arm has been reported; the adjunctive MMAE cohort (n=197) had significantly lower rates of reoperation than surgery alone (n=203) (MMAE + surgery: 4.1% v. surgery only: 11.3%; p=0.0081) [17]. The rate of serious safety events was comparable between cohorts. Hence, the results of the surgical arm of EMBOLISE support use of MMAE adjunctively to surgical evacuation in moderate or severe CSDH patients for reducing the odds of hematoma recurrence or progression.

The Managing Non-Acute Subdural Hematoma Using Liquid Materials: A Chinese Randomized trial of MMA Treatment (MAGIC-MT, NCT04700345) was a multicenter, open-label randomized controlled trial across 31 centers in China assessing adjunctive MMAE with standard of care (either burr-holes, medical management, or a combination) or standard of care alone; patients were stratified into surgical and non-surgical cohorts, and then randomized into adjunctive MMAE or no-MMAE treatment groups [16]. The patient population consisted of symptomatic CSDH patients with mass effect not otherwise requiring emergency evacuation. The primary efficacy outcome was rates of symptomatic recurrent or residual hematoma within 90 days. Rate of serious adverse events was significantly lower in patients treated with MMAE as an adjunct to surgical or non-surgical care (n=360) compared to patients who were not embolized (n=362) (adjunctive MMAE: 6.7% v. no MMAE: 11.6%, p=0.02) [16]. Rates of symptomatic recurrence or progression were not statistically different (MMAE: 6.7% v. no MMAE: 9.9%, p=0.10) [8,16]. Thus, the data from MAGIC-MT suggest that MMAE with standard of care may have similar efficacy but improved safety outcomes compared to standard management alone.

The SQUID Trial for the Embolization of the Middle Meningeal Artery for Treatment of Chronic Subdural Hematoma (STEM, NCT04410146) was a multicenter, open-label, randomized controlled trial across 33 United States sites assessing MMAE as an adjunct compared to standard treatment alone (either surgical or nonsurgical care) for symptomatic CSDH [15]. The primary efficacy outcome, which was a composite of the rates of recurrent or residual hematoma, rescue surgery, or major stroke or death from neurological cause within 180 days, occurred in 16% of the adjunctive MMAE group (n=149), compared to 36% of the comparator group (n=161) [15]. Although the rate of hematoma recurrence or progression was significantly lower in patients treated with MMAE and non-surgical care versus non-surgical care alone (p=0.0001), there lacked a statistically significant difference in these rates when comparing patients treated with adjunctive MMAE and surgical evacuation versus surgical care alone (p=0.058) [8,15]. Rates of mortality and disabling stroke were similar across subgroups. Consequently, the results of STEM suggest that adjunctive MMAE reduces the likelihood of hematoma recurrence or worsening without increasing risk of serious complications.

Given that the design of CHESS differs from other trials by examining standalone MMAE, the results from CHESS will augment the findings of these other trials by specifically exploring MMAE's potential beyond being an adjunct intervention in CSDH care. Moreover, CHESS contrasts to most of the completed and ongoing randomized controlled trials in the choice of embolic material; CHESS exclusively uses particles for embolization, while all the other trials above have used liquid embolic agents. Early evidence from a case series suggests that the performance and safety of particles is similar to liquid embolic agents, but CHESS will specifically provide randomized data to validate the safety and efficacy of particles for MMAE [26]. The cost of particles is a small fraction of that of liquid embolics. Additionally, CHESS will include enrollment of both de novo CSDH and specific recurrent CSDH. Previous and ongoing trials have exclusively enrolled patients with de novo CSDHs; consequently, CHESS will provide further evidence to help guide approaches to management within an understudied CSDH subpopulation [8].

In addition to the primary CHESS study, a complementary biorepository will be established. BIO-CHESS will be a prospectively maintained bank of CSDH patients randomized in CHESS to undergo surgical evacuation at a BIO-CHESS participating site. During surgery, samples of the dura, subdural membrane, CSDH fluid, and peripheral blood will be collected and centrally stored at the Biospecimen Exchange for Neurological Disorders (BioSEND) center at Indiana University School of Medicine (Indianapolis, IN, USA). This repository will facilitate biological, clinical, and radiographic correlations to facilitate future proteomic and genetic analyses, aimed at supporting additional studies identifying potential biomarkers and elucidating the underlying pathophysiology of CSDH.

Conclusion

The CHESS trial is a randomized controlled trial comparing standalone particle MMAE and surgical evacuation in moderately-symptomatic CSDH patients. The findings of this trial will advance understanding of safe and effective treatment approaches in this patient population.

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Ethics Approval

This study was approved by Biomedical Research Alliance of New York (BRANY; Melville, NY, USA) central institutional review board (#24-02-066).

Conflict of Interest

All other authors do not have disclosures to declare related to this work.

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