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The REpeated ASSEssment of SurvivorS in intracerebral haemorrhage: protocol for a multicentre, prospective observational study

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ABSTRACT

Background The REpeated ASSEssment of SurvivorS (REASSESS) study will conduct long-term cognitive, functional and neuropsychiatric performance assessments to determine whether evacuation of spontaneous intracerebral haemorrhage (ICH) reduces the risk of later cognitive decline in the ageing brain.

Methods and analysis This study will compare rates of cognitive decline under two treatment strategies for ICH. The first strategy is the use of minimally invasive surgery (MIS) with similar techniques as performed in (1) the Minimally Invasive Surgery plus rt-PA in the Treatment of Intracerebral haemorrhage Evacuation phase III (MISTIE III) trial, (2) the Early MiNimally-invasive Removal of IntraCerebral Haemorrhage (ENRICH) trial and (3) a single-centre cohort of consecutively treated patients with MIS. The second strategy is the current non-surgical standard of care using data from controls in MISTIE III and ENRICH and comparative data from The Ethnic/Racial Variations of ICH (ERICH) studyextended into the ERICH-Longitudinal study, which followed over 900 of ERICH cases with serial cognitive examinations. If successful, the REASSESS study could demonstrate that reduction of ICH volume is a critical target to reduce the risk of progressive cognitive decline, establish targets for residual haematoma volume reduction and determine if greater residual haematoma volume leads to a long-term inflammatory state.

Ethics and dissemination Approval of this study was obtained from the Johns Hopkins University Institutional Review Board (IRB00311985). The findings of the study will be published in academic peer-reviewed journals.

Trial registration number NCT05611918; ClinicalTrials.gov; registered on 23 May 2023.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a multicentre, prospective, observational study utilising patients from two large randomised controlled clinical trials and prospective cohorts.
⇒ Patients undergoing minimally invasive surgery for supratentorial intracerebral haemorrhage (ICH) require dedicated research to determine whether clinically effective clot reduction improves cognitive decline and functional dependence in the long-term compared with non-evacuated ICH.
⇒ This study assesses multiple outcomes including cognitive decline rates over 2 years, evaluation of a chronic inflammatory state in ICH survivors remote from the time of haemorrhage, and progression of MRI markers of cerebral small-vessel disease.
⇒ Blinding of the study participants and assessing clinicians may not be possible due to the nature of the intervention.
⇒ Major challenges include enrolment shortfall, loss to follow-up and unbalanced groups from the trial populations, which will be explored in subgroup analyses.

INTRODUCTION

Intracerebral haemorrhage (ICH) accounts for 15% of all strokes and has the highest disability rate among survivors.[1] ICH has a 40%–50% 30-day mortality rate, with only 27% of cases being functionally independent at 90 days. ICH survivors remain at high risk for negative outcomes including rebleeding, ischaemic stroke and progressive cognitive impairment. Post-ICH cognitive decline (PICD) is strongly associated with haematoma volume, white matter disease burden[2] and lobar location.[3] The current proposal addresses the hypothesis that reducing haematoma volume after ICH may reduce risk of progressive PICD. The preliminary data result from multiple NIH-funded studies. The Ethnic/Racial Variations of ICH (ERICH) study (NCT (National Clinical Trials Number) 01202864) began in 2010 and recruited 1000 white, 1000 black and 1000 Hispanic ICH cases across 19 centres and 41 sites along with 3000 matched controls. ERICH then extended into the ERICH Longitudinal study (ERICH_L), which followed

over 900 of the cases with serial cognitive examinations.[4] Results of this study found that 39% of ICH survivors develop progressive cognitive decline by 42 months, and that greater volume of ICH was associated with greater risk of decline. However, observational studies are unable to assess whether 'reducing' ICH volume can reduce the risk of progressive cognitive decline. The Minimally Invasive Surgery plus rt-PA in the Treatment of Intracerebral haemorrhage Evacuation phase III (MISTIE III) trial (2013–2018) (N=499)[5] and the Early MiNimally invasive Removal of IntraCerebral Haemorrhage (ENRICH) trial of minimally invasive surgery (MIS) for ICH (2018–2023) (N=300)[6] were large, prospective, randomised controlled trials, which compared MIS with standard non-surgical care. These studies offer a time-sensitive opportunity to evaluate the impact of haematoma reduction on the risk of cognitive decline. The average end-of-treatment (EOT) ICH volume among those surgically treated in MISTIE III was 12.5 mL compared with 43.7 mL in the standard care arm. ENRICH had a similar target population with median baseline ICH volume of 54 mL and a median EOT ICH volume of 7.2 mL in the MIS arm. We propose to leverage these valuable resources enriched by several similar cohorts of ICH patients to perform a detailed follow-up study of approximately 350 survivors of ICH recruited in these studies and combine them with data from up to 900 patients enrolled in ERICH_L, including detailed cognitive and functional outcome assessments to determine if surgical reduction of ICH volume leads to reduced risk of progressive cognitive decline.

Design

REpeated ASSEssment of SurvivorS (REASSESS) is a multicentre, prospective, observational study investigating change in cognitive function in ICH survivors from two randomised clinical trials and several prospective cohorts of ICH patients treated with or without MIS. The first patient was enrolled on 23 May 2023. The anticipated completion date is June 2027. The study design flowchart is shown in figure 1. This study is performed at the Johns Hopkins University (single IRB) and the University of Cincinnati. Each study site will be reactivated for completion of consent and the first patient encounter. All patients who fulfil the inclusion criteria and do not meet the exclusion criteria will be approached for participation. Written informed consent is obtained from all participants. The study will be approved by the Institutional Review Board of every site and is registered at Clinicaltrials.gov (NCT05611918).

Patient and public involvement

The initial research idea was proposed by the research team. The study protocol will be revised based on feedback to ensure the applicability of the intervention.

Objectives

Primary objective (main study):

1. To determine whether surgical clot reduction after ICH reduces the risk of progressive cognitive decline.

Secondary objectives (Main study):

1. To determine whether there is a long-term benefit in survival and functional outcome from MIS whether or not cognitive decline occurs.
2. To determine whether inflammatory gene pathway expression predicts the risk of cognitive decline.

MRI substudy:

Primary objective: to determine the effects of surgical clot reduction on MRI markers of cerebral small-vessel disease (CSVD) after ICH.

Secondary objectives:

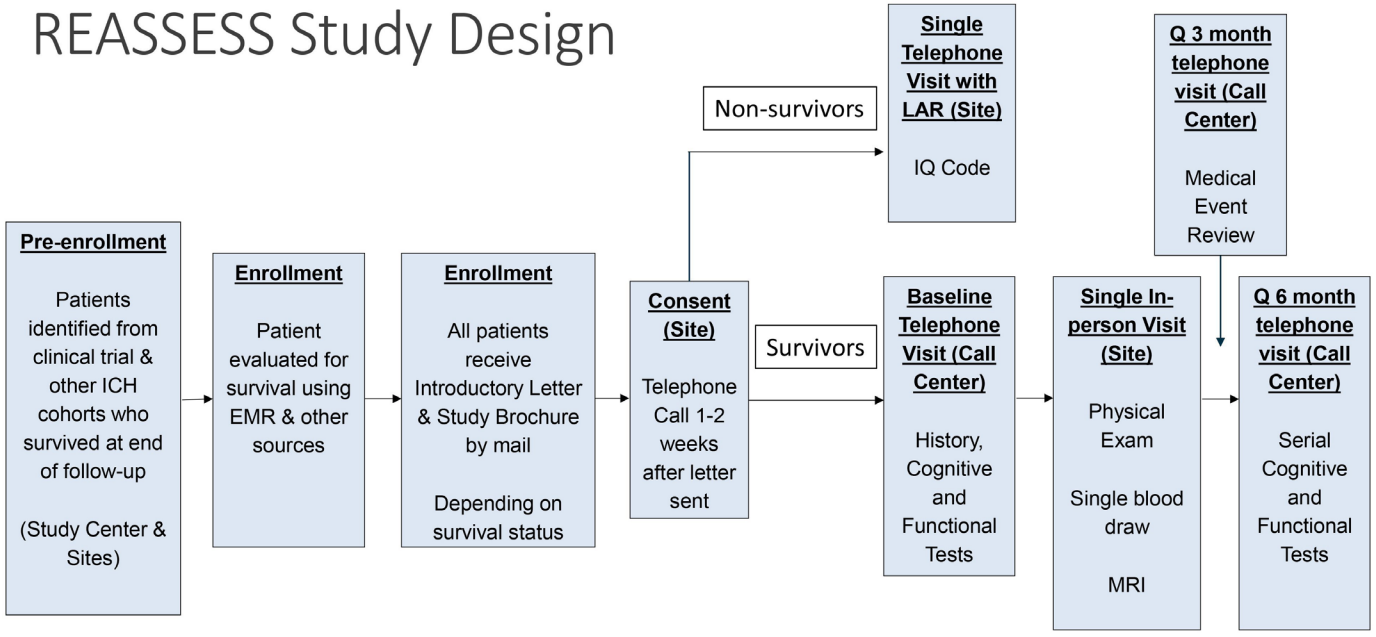

Figure 1 The flowchart for REASSESS. EMR, electronic medical record; ICH, intracerebral haemorrhage; LAR, legally authorised representative; REASSESS, REpeated ASSEssment of SurvivorS.

1. To determine the effects of CSVD burden on MRI on cognitive function after surgical clot reduction for ICH.
2. To determine the effects of inflammatory gene pathway expression on CSVD MRI markers.

Patient population

Inclusion criteria

Participants in the study will be recruited from three groups:

1. Participants enrolled in the MISTIE III or ENRICH trial who survived to the end of each trial's final follow-up (day 365 in MISTIE III and day 180 in ENRICH). Relatives of known survivors that are found to be deceased since the end of each trial will be contacted to capture relevant data.
2. Patients treated with MIS at the Mount Sinai Hospital since 1 January 2018, who survived to 6 months after initial ICH.
3. Patients from several other clinical trial or observational cohorts of consecutive ICH patients admitted since 1 January 2021, who survived at least 6 months from ictus.

All participants will meet the following criteria:

1. ≥18 years old.
2. Obtained informed consent.
3. Haematoma volume at baseline >30 mL.
4. Supratentorial ICH demonstrated on brain CT.
5. Glasgow Coma scale 5–14.
6. Historical Modified Rankin Scale 0–1.
7. Surgical treatment with only MIS initiated within 24 hours (ENRICH) and 72 hours (MISTIE III, Mount Sinai) of last known normal.

Exclusion criteria

1. Secondary cause of ICH on vascular imaging (ie, aneurysm, arteriovenous malformation, etc).
2. Surgical drainage via open craniotomy.
3. National Institutes of Health Stroke Scale (NIHSS) ≤5.
4. Intraventricular hemorrhage (IVH) > 50% of lateral ventricles (ENRICH) or casting of ventricles (MISTIE III).
5. Clinical herniation signs.
6. Uncorrected coagulopathy or clotting disorder.
7. No reasonable expectation of recovery, do-not-resuscitate or comfort measures or life expectancy <6 months.

REASSESS intervention

Site investigators will search survival status of study patients meeting inclusion criteria using the electronic medical record and other resources.

For survivors, following consent, site researchers will conduct a single in-person exam with each patient, which will include vital signs, the NIHSS, motor assessment scale, Mini-Mental Status Examination (MMSE), Western aphasia battery and a single blood draw for RNA sequencing to evaluate for chronic inflammation and genotyping. Dr Sansing's laboratory at Yale will perform transcriptional profiling of leukocytes from the blood samples of patients by RNA-seq. Drs Carl Langefeld and Timothy Howard at Wake Forest University School of Medicine will oversee genotyping of the Apolipoprotein E (APOE) haplotype and the genome-wide assays (Genome Screening Array, Illumina) and contribute to bioinformatic analyses. Each participant will be asked to participate in an optional MRI substudy, which includes a standardised brain MRI stroke protocol including susceptibility weighted imaging or gradient echo sequences during or after the in-person visit. Dr Vagal's imaging core lab will provide blinded central reads for CSVD burden.

The telephone call centre at the Johns Hopkins University (JHU) or University of Cincinnati (UC) will then perform:

1. A baseline telephone interview to assess medical events of interest, demographics and social history since first occurrence of ICH as well as cognitive function.
2. Up to four follow-up telephone interviews from the call centre at 6-month intervals (±30 days) from study enrolment to reassess cognitive function serially.
3. Up to four 10 min telephone calls from the call centre, each at 3 months from each telephone interview to maintain contact with the subject/surrogate.

For non-survivors, the site will obtain consent from the legally authorised representative and will complete the Short Form of the Informant Questionnaire on Cognitive Decline by telephone or mail.

Primary outcome

The primary outcome measure is the rate of cognitive decline, which is based on a composite measure of global cognition using the National Institute on Aging Genetics Initiative for Late Onset Alzheimer Disease Battery, a seven-measure cognitive testing battery to assess change in episodic, semantic and working memory in community-dwelling older persons with broad ability levels.[7 8] Clot reduction levels defining comparison groups will be obtained from automated or semiautomated computerised volumetrics using OsiriX or other validated software comparing baseline to EOT CT scans. We will compare rate of cognitive decline in patients with EOT volume <20 mL versus >20 mL.

Secondary outcomes

Secondary outcomes are (1) survival; (2) poor functional outcome (Modified Rankin Score 4–6); (3) Barthel Index[9]; (4) De Jong Gierveld Loneliness Scale[10]; (5) EuroQOL EQ-5D[11–13]; (6) Activities of daily living and fall history[14] ;(7) Telephone Interview for Cognitive Status.[15 16]

Exploratory outcomes

We will determine if a chronic inflammatory state is identifiable through RNA-sequencing of leukocytes remote from time of haemorrhage and test the association with cognitive decline.

We will develop and test polygenic risk scores (PRS), which may be included as covariates in the RNA-seq analyses. PRS provide a measure of the genetic load an individual carries for a particular outcome (disease, trait). We will compute the PRS for dementia, Alzheimer's, type 2 diabetes, hypertension and atrial fibrillation using established loci from the Genome Wide Association Study catalogue.[17] PRS will also be directly tested for association with cognitive decline including standard regression methods.

MRI substudy

The REASSESS MRI Ancillary Substudy will examine the effects of surgical clot reduction on imaging markers of CSVD after ICH and for progression where MRI has been previously obtained during the clinical trial. The primary outcome for the MRI study is the total burden of CSVD and individual CSVD features (white matter hyperintensities (WMHs) of presumed vascular origin, cerebral microbleeds (CMBs), recent subcortical infarcts, perivascular spaces, cortical superficial siderosis, enlarged perivascular spaces, lacunes of presumed vascular origin and atrophy).[2]

Sample size estimation

As a reference, the pilot ICH cohort demonstrates a risk of cognitive decline of 39% at a mean of 42 months from ICH. MISTIE III results suggest that lowering ICH volume may be associated with less dementia with an approximate 30% reduction in risk at 1 year for EOT volume <20 mL versus >20 mL. The residual ICH volume in the MISTIE III surgical cohort of survivors was 11.6 mL, compared with 40.8 mL in the non-surgical survivors, resulting in two distinct residual volume groups. Assuming an approximate 30% effect size, and that clot volume reduction to <20 mL is similar to a baseline ICH volume of <20 mL in ERICH, we would anticipate a risk of cognitive decline of 33% in the surgical cohort with <20 mL residual volume (vs 46% in cases with >20 mL volume).

Under a projected 10% annual mortality attrition from MISTIE III/ENRICH and based on 1-year survival rates of 46% (SOC, standard of care): 54% (MIS) in North America, we anticipate recruiting up to 350 patients (190 MIS and 160 SOC). We will augment the non-surgical group with cases from ERICH. Based on a difference of 13% (30% reduction) in risk of cognitive decline, we will have 80% power to statistically detect this effect size with a minimum sample size of 135 MIS survivors, and 750 non-operated patients, assuming a two-sided alpha of 0.05.

Data monitoring, collection and analysis

The data monitoring committee (DMC) consists of the co-PIs, and members of the research division, with responsibility for maintaining the data management plan and monitoring data collection and entry. All data pertaining to the study will be entered into a Research Electronic Data Capture (REDCap) database. Full access to the dataset will be limited to the members of the DMC.

Statistical analyses

The analysis will include all patients based on the per protocol principle in each study. All data in this study will be statistically analysed using STATA V.17 (StataCorp. 2021. Stata Statistical Software: Release V.17. College Station, Texas).

We will use mixed-effects models to characterise person-specific trajectories of change in cognitive function and to test the hypothesis that post-ICH rate of cognitive decline is more rapid in non-operated ICH survivors with greater than 20 mL baseline ICH volume compared with ICH survivors who underwent MIS with less than 20 mL EOT ICH volume. Volume effects will be examined irrespective of surgical intervention but are highly correlated with surgical treatment. As a sensitivity analysis, we will evaluate the effect of volume as a continuous variable.

We will create a composite measure of global cognition using all cognitive data and specific measures of episodic, semantic and working memory (1–3), converting raw scores on individual tests to z scores and averaging z scores of component tests to get the composite score (1–3). We will use mixed models to characterise change in each composite cognitive measure and to examine the relation of MIS (vs no MIS) to annual rate of change. We will evaluate various confounding factors associated with the primary outcome variable.

RNA sequencing measurements will be used to generate inflammatory gene expression patterns and variability metrics. We will perform interaction analyses between ICH severity metrics and inflammatory gene expression patterns. EOT ICH volume for association with gene expression, and interaction terms will be entered in separate multivariable models for incident cognitive decline as outcome variables. Adjustments for multiple testing will be used to modify significance thresholds based on number of multivariable models being tested.

The MRI study hypothesis that the burden of CSVD on MRI will correlate with the EOT volume of ICH in operated and non-operated ICH survivors will be tested via generalised linear models relating the total CSVD scores to EOT volume. We will also: (1) analyse actual progression of CSVD scores and WMD in patients who have both a baseline and follow-up MRI as a sensitivity analysis, (2) evaluate the association between the total burden of CSVD on end-study MRI and cognitive function, quantified by the MMSE and Telephone Montreal Cognitive Assessment using generalised linear mixed effects models and (3) perform interaction analyses between CSVD MRI metrics and inflammatory gene expression patterns generated from RNA sequencing measurements.

Missing data

We estimate loss to follow-up at 10%. Additionally, data may be missing due to participants missing one or more data collection telephone visits during the study period. Missing data will be handled using a linear mixed effect model in the main analysis. Additional sensitivity analyses will be conducted using multiple imputation models to

assess the robustness of the results to different missing data assumptions. Patients who do not participate in any longitudinal data collection visits will be excluded from the analysis.

Data availability

Anonymised individual data will be made available after publication of the study's findings and will be uploaded to the NIH data repository after completion of the study.

DISCUSSION

Published evidence suggests ICH and dementia are closely related, and that 14.2%–19% of ICH patients develop new-onset dementia 1 year after ICH.[3] This very high rate of progressive cognitive decline may be secondary to progression of the underlying pathophysiologic mechanisms that led to the ICH, such as CSVD and cerebral amyloid angiopathy (CAA). Alternatively, progression could be related to chronic inflammation triggered by the ICH itself that may cause progressive decline or acceleration of the underlying causes. Both haemorrhage size and location impact the risk of developing cognitive decline and/or depression among ICH survivors.[18] The risk of dementia is two times as high in patients with lobar ICH compared with non-lobar ICH.[19] The APOE gene is also robustly associated with CSVD and with ICH risk; APOE variants E2 and E4 represent the most potent genetic risk factors for ICH[20–22] and have an established role in risk for Alzheimer's disease and CAA.[23] Patients with ICH often have varying degrees of underlying microvascular lesions on MRI and the presence of CMBs, WMHs and total burden of CSVD are associated with significantly lower odds of achieving functional independence after ICH.[24–27] Pre-existing CSVD burden at time of initial ICH appears to modify outcomes after MIS for ICH[28] although the impact of MIS on the progression of CSVD has not been studied.

Thus, while radiographically, ICH may resolve over weeks to only a thin cavity, substantial damage due to mass effect, acute inflammation and pre-existing CSVD contributes to increased risk of cognitive decline that may be mitigated by early surgical evacuation. This innovative study will, for the first time, evaluate if effective evacuation of supratentorial spontaneous ICH reduces the risk of later cognitive decline years after the original haemorrhage. While several outcome studies of long-term cognitive impairment after ICH have been reported, no studies in which haematoma removal or reduction was performed have completed long-term assessments of risk of later cognitive decline. If successful, the current proposal could (1) demonstrate that reduction of ICH volume is a critical target to reducing the risk of progressive cognitive decline, (2) establish targets for residual haematoma volume reduction, (3) determine whether greater residual haematoma volume leads to a long-term inflammatory state and (4) investigate the effects of surgical clot reduction on MRI markers of CSVD and determine the effects of CSVD burden on cognitive function after surgical clot reduction, and the effects of inflammatory gene pathway expression on CSVD MRI markers. Non-demonstration of these hypotheses would be an important finding that would refocus efforts to reduce cognitive impairment via mitigation of other risk factors.

ETHICS AND DISSEMINATION

The parent studies have been approved by the institutional review boards of all participating centres and written informed consent of all patients was obtained prior to enrolment. Approval of this study was obtained from the Johns Hopkins University Institutional Review Board (Single IRB) and all participating centres. This study will be performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting observational studies.[29] The results will be disseminated in peer-reviewed journals and in conference reports.

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Contributors WZ and DW contributed to the trial design and originated the study idea. MLF, DH and LS contributed to the study design based on their respective areas of expertise. LS, KL, RH, AV and NW assisted in implementing certain procedures. NO, KT, LG, KL and NM collaborated on revision of the protocol. All authors reviewed and approved the final manuscript. WZ acted as guarantor.

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