1. INFORMACIÓN GENERAL

1.1 **Título**: REmoval of Parenchymal brain hematoma to Attenuate brain Injury and Reduce ICH-related damage (trial)

1.2 **Código del protocolo**:

1.3 **Versión**: Versión 1, Fecha (12/04/2026)

1.4 **Promotor:** FRCB-IDIBAPS

2. EQUIPO INVESTIGADOR

El estudio es multicéntrico, por lo que se detallan a continuación los investigadores principales de cada centro participante, así como de los colaboradores.

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2.7 **HOSPITAL DE BELLVITGE**

3. PROTOCOL SUMMARY

Primary Objective	To assess whether image-guided endoscopic evacuation of intracerebral hemorrhage within 24h of onset is effective at reducing secondary brain injury and blood-brain barrier disruption as compared to controls treated only with standard medical therapy
Primary Outcome	Volume of perihematomal edema and levels of blood-brain barrier permeability constant (Ktrans) at day 5±2 from randomization
Study Design	Multicenter phase III, prospective, randomized, open, blinded endpoint (PROBE) study. Six participating centers from Europe. Duration of 5 years, with a 3-year inclusion period and one year of follow-up.
Population	Inclusion criteria: 1. Age 18 to 75 years; 2. NIHSS ≥ 6 and/or GCS 8-14; 3. Supratentorial non-traumatic ICH confirmed by non-contrast CT (NCCT), without a CT angiography confirmed causative lesion; 4. Minimal hematoma volume of 20 mL; 5. Intervention can be started within 24h of symptom onset; 6. Written informed consent
Sample size	225 patients, randomized 2:1 to undergo image-guided endoscopic evacuation surgery plus standard medical treatment, or standard medical treatment alone
Data source	Primary source
Medical device being tested	ARTEMIS Neuro Evacuation Device (Penumbra, Inc.)
Artificial intelligence algorithm/machine learning	Artificial intelligence and machine learning techniques will be applied to analyze all retrieved data, developing predictive models of secondary brain injury in intracerebral hemorrhage
Additional procedures related to the study	Magnetic resonance imaging (day 5±2), blood sampling (baseline and day 5±2), interview and questionnaire (day 30, 90 and 360)

4. BACKGROUND AND RATIONALE

4.1 Minimally invasive surgery for intracerebral hemorrhage

Spontaneous primary intracerebral hemorrhage (ICH) is the second most common cause of stroke annually affecting 15/100,000 people in Europe. It carries the highest fatality rates and the heaviest burden of neurological disability of all strokes, by which half of these patients are dead at 1 year and only 12–39% of the survivors achieve long-term functional Independence. It thus represents a considerable health and economic burden. Despite several efforts in the acute medical management of ICH, there is a large unmet need in this field as outcomes remain poor, and most patients are left without any definitive treatment, raising the interest for an interventional action in selected cases.

Hematoma evacuation through conventional craniotomy has failed to improve patient outcomes for decades and across multiple trials. Yet, early hematoma evacuation using minimally invasive surgery (MIS) has emerged as a promising alternative, offering potential advantages, including reduced manipulation of healthy brain tissue, shorter operative times, and decreased risks of complications.

MIS with Thrombolysis in Intracerebral Haemorrhage Evacuation (MISTIE-III) was a pivotal trial demonstrating a significant reduction in mortality in the surgical group. Although the overall effect on functional outcome was neutral, cases with successful evacuations (i.e., residual clot ≤15 mL) had significantly better outcomes compared to medical therapy alone. These results led to a change in the American Heart Association/American Stroke Association (AHA) guidelines towards recommending MIS clot evacuation to reduce mortality and, reasonably, to improve functional outcomes. The Early Minimally Invasive Removal of Intracerebral Haemorrhage (ENRICH) trial evaluated a trans-sulcal parafascicular surgical approach where MIS evacuation resulted in better functional outcomes at 180 days than guideline-based medical management, a beneficial effect particularly attributable to lobar hematoma. Preliminary data from the MIND trial (NCT03342664): A Prospective, Multicenter Study of Artemis a Minimally Invasive Neuro Evacuation Device in the Removal of Intracerebral Haemorrhage, suggests evacuation of the hematoma using the Artemis neuroevacuation device has a high technical success rate with substantial hematoma reduction. Although there was early clinical improvement in disability scores compared with medical management alone, these were not sustained out to 6 months.

These trials differ significantly in selection criteria, in the proportions of lobar and basal ganglia hematoma location, and importantly in the therapeutic time window. Also, the different techniques employed for the evacuation of the clot differ in the diameter of the trans-cerebral working port being used, in the overall efficacy to reduce the hematoma volume and in the rapidness to achieve it. Yet, all of them revolve around the same idea: to reduce the intraparenchymal blood load to reduce secondary brain damage to ultimately accelerate and improve the neurological function. Importantly, nearly all of them use functional outcomes based on scale scores and/or fatality as the main objectives. Another common potential limitation of the available trials is the lack of standardization in the use of intraoperative imaging.

4.2 Intraoperative image-guided hematoma evacuation

Surgical performance seems paramount to maximizing the degree of clot evacuation while minimizing collateral damage to surrounding brain. In this sense, the addition of intraoperative imaging devices able to guide surgical steps and decision making at specific checkpoints during the procedure seems reasonable to guarantee both the safety and efficacy of the operative technique. Despite this, most trials have not systematically employed intraoperative imaging during surgical evacuation of the hematoma nor as a final control to rule out the presence of a clot residue. The emergence of new operating rooms with integrated imaging systems should be considered as an important factor in improving the outcomes for these patients.

In the original endoscopic Stereotactic IntraCerebral Underwater Blood Aspiration (SCUBA) technique described by Mocco and Kellner group the basic imaging systems required are a neuronavigation system and an endoscope. The restricted vision provided by the endoscope within the hematoma cavity is compensated using neuronavigation. However, several limitations can be encountered with this basic combination, primarily driven by the fact that neuronavigation is based on preoperative imaging and does not account for intraoperative changes such as brain shift and hematoma cavity collapse or hematoma expansion. Therefore, the addition of intraoperative imaging is a remarkable technical advance, particularly in the setting of new integrated operating rooms where imaging devices are part of the operative workflow.

Among the available imaging devices, two of them have been proposed in the application of image-guided ICH evacuation, given their optimal balance between low exploration time and high anatomic resolution. Namely, intraoperative cone-beam CT scan with a C-arm and intraoperative ultrasound.

Routine use of CBCT imaging at the end of MIS for ICH procedure or after several passes of aspiration allows to assess surgical performance and offers the chance for immediate and targeted re-aspiration of clot remnants, which may optimize hematoma volume aspiration rates and reduce secondary revision rates. Flat panel detector CT can be combined with navigation to update the image used to recalculate the trajectory to gain reliable and safe access to the hematoma after several passes of aspiration. Therefore, a platform that uses flat panel detector CT imaging obtained on the angiography table combined with neuronavigation guidance software provides a high degree of accuracy, convenient and rapid re-imaging to assess navigation accuracy and the degree of hematoma evacuation during or immediately after the procedure.

On the other hand, intraoperative ultrasound (iUS) is more dynamic and offers real-time imaging when applied over the brain surface during hematoma evacuation using a bur-hole-type probe. Yet, iUS is very operator-dependent and requires a longer learning curve. To help in this sense, a navigated 2D-US or 3D-US have been developed, which fuse a live US image with the navigation CT by integrating a navigation localizer with US probe. It can help with the anatomical interpretation of the US images, and it can potentially compensate for brain shift during neuronavigation. Another important point of iUS is that it is more susceptible to artifacts derived from the presence of air within the evacuation cavity. To overcome this, a neuroendoscopic adaptation of intravascular ultrasound, has been developed as a intracavitary ultrasound (ICARUS) to be applied directly in the walls of the evacuation cavity, improving the imaging resolution and reducing the artifacts.

Either of them, CT or iUS, applied on its own seem to improve the safety and efficacy of the minimally invasive hematoma evacuation, yet when applied in combination they may provide a synergistic technical improvement. Their use provides an opportunity to evaluate whether the evacuation threshold has been achieved, and to continue the procedure if the surgeon feels that better evacuation is achievable. With evidence supporting to target a surgical evacuation goal during minimally invasive ICH evacuation, intraoperative imaging, such as CT and US, play an important role in achieving the surgical goal.

4.3 Endoscopic evacuation with ARTEMIS Neuro Evacuation Device

The landmark study in MIS surgery was the ENRICH trial, including patients with supratentorial ICH of 30-80mL in volume operated on within the first 24h by means of aspiration under direct vision through a trans-sulcal parafascicular endoport system BrainPath and the NICO Myriad aspiration device (NICO Corp., Indianapolis). For the first time in a randomized study, the authors were able to demonstrate a significant and clinically relevant benefit of surgery in terms of mortality and improvement of functional outcomes at 6 months, a beneficial effect particularly attributable to lobar hematomas.

In a recent case-series of 100 patients with supratentorial ICH treated with the Artemis Neuro Evacuation Device resulted in excellent evacuation rates of the hematoma (postoperative volume 6.2 mL (SD 10.7), evacuation percentage 88.2% (SD 20.3)). Postoperative bleeding occurred in five cases (symptomatic in one). At six months, 46% of patients had a good functional outcome and 16% had died. A separate report on the same cohort who underwent surgery within 72 hours of ictus, showed that for every hour a patient was operated on earlier, the odds of having a good outcome increased by 5%. The efficacy in terms of evacuation rates and security in terms of low rebleeding rates seen in this series were replicated in the Phase II stage of the DIST trial, with Phase III currently ongoing.

Currently, there are two devices approved in the European Union for the evacuation of intracerebral hemorrhage for minimally invasive endoscopy-guided hematoma evacuation, namely the NICO Myriad aspiration device (Nico Corp.) and the ARTEMIS Neuro Evacuation Device (Penumbra, Inc.). Multiple case series have shown that evacuation with minimally invasive endoscopy-guided surgery can be achieved safely and efficaciously in terms of hematoma volume reduction. Mean hematoma clearance varied from 77.8% to 94.5% and in the most recent cohort study, the median evacuation percentage was 96.9% (IQR 85.5-99.6). In terms of complications, 5% of the patients in this study had a rebleed after surgery, of which one needed reoperation. Mortality was 3% at discharge and 16% at three months. A recent non-randomized study suggested that hematoma clearance is better, and the risk of infections lower with endoscopy-guided surgery compared to stereotactic aspiration techniques.

4.4 Secondary brain injury after intracerebral hemorrhage

All the abovementioned published or ongoing trials revolve around the idea that an early evacuation of the clot through minimally transgressive devices would theoretically reduce secondary brain damage and consequently reduce mortality and improve functional outcomes. After the initial insult, several factors are thought to promote further brain damage, such as increased intracranial pressure, local compression of nearby structures with decreased cerebral

perfusion, haematoma expansion, inflammation due to the presence of blood degradation products and development of oxidative stress, blood-brain barrier (BBB) disruption and interstitial vasogenic oedema.

Although all this secondary brain damage process is potentially reversible or avoidable, there are no randomized trials demonstrating that it can be modified by MIS evacuation of the haematoma. The fundamental changes seen at this level of pathogenesis are of great interest to understand the response to treatment, to overcome its limitations, and to adequately define the optimal time window; yet their assessment requires advanced techniques. Indeed, these may provide even more valuable information than conventional gross clinical rankings, allowing to capture cerebral changes not detected with dichotomised or pondered functional status scores.

The REmoval of Parenchymal brain hematoma to Attenuate brain Injury and Reduce ICH-related damage (REPAIR-ICH trial) proposed in WP1 of the SEISMIC project has been designed to assess whether minimally invasive endoscopy-guided surgery with intraoperative imaging support within 24 hours of symptom onset in addition to standard medical management, reduces secondary brain damage in primary supratentorial haematomas when compared to standard medical management alone. Secondary brain damage will be measured by radiological and biological markers, based on a comprehensive analysis of blood samples, tissue and advanced imaging tests.

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5. HYPOTHESIS

Intracranial hematomas (ICH) cause a primary injury due to the disruption of the initial brain tissue and the mass effect. Secondary brain injury (SBI) begins during the first day in the healthy tissue surrounding the initial hematoma. Although new minimally invasive surgical (MIS) treatments significantly reduce the mass effect and the volume of residual blood, the risk of postoperative SBI remains. Measured as the volume of perihematomal or pericavity edema (PHE), the magnitude of SBI influences the clinical recovery of patients with ICH. However, the pattern followed by SBI in patients treated with MIS techniques is currently unknown. A better understanding of this pattern and of the underlying pathophysiological mechanisms could help in the design of new adjuvant therapies. In this context, our hypotheses are:

1. In patients treated with MIS, the main component of SBI is blood–brain barrier dysfunction (BBBd), which can be detected through advanced neuroimaging techniques such as Dynamic-Enhanced Magnetic Resonance Imaging (DCE-MRI). Likewise, the magnitude of SBI—PHE and BBBd—will be more significant in those patients with greater increases in biomarkers of neuronal damage, oxidative stress, markers of neuroinflammation, and a greater loss of cerebral autoregulation in the at-risk area.
2. The combination of clinical data and early neuroimaging using machine learning techniques will enable the development of predictive models of SBI in MIS surgery, facilitate the identification of new pathophysiological pathways in SBI, and allow the identification of potential therapeutic targets.

3. OBJECTIVES

Primary objectives:

1. To assess whether image-guided endoscopic evacuation of supratentorial ICH performed within 24h of symptom onset is effective at reducing secondary brain injury (SBI), defined as the reduction in perihematomal oedema (PHE) volume on CT scan performed at day 5 (±2 day), as compared to controls treated with standard medical therapy alone.

2. To assess whether image-guided endoscopic evacuation of supratentorial ICH performed within 24h of symptom onset is effective at reducing blood brain barrier disruption and cytotoxic damage, defined as the permeability constat (Ktrans) and the volume of restriction in DWI sequences of brain MRI performed at day 5 (±2 day).

Secondary objectives

1. As a secondary safety objective, to compare mortality rates from any cause at 30 and 365 days from randomization between surgically treated (image-guided endoscopic evacuation) patients and controls.

2. To compare good functional outcomes (defined as mRS 0-3) at days 30, 90 and 365 from randomization between surgically treated (image-guided endoscopic evacuation) patients and controls.

3. To determine the association between the degree of BBB disruption measured by DCE-MRI (day 5+/-2 from randomization) and ICH severity and outcome in surgical and non-surgical controls.

4. To evaluate the association of early (day 0 from randomization) biochemical and radiological biomarkers of BBB disruption with poor functional outcome (30, 90 and 365 days) in ICH patients (surgically treated and controls).

5. To compare serum neuroinflammatory and neurocytologic profiles over time (day 5+/-2 from randomization) in venous blood between surgically treated patients and controls.

6. In patients treated with MIS, to obtain samples of brain tissue at risk (peri-hematoma penumbra area) and samples of healthy tissue (entry point) in the same patient, and to compare the expression of mRNAs and SBI damage biomarkers between the two regions. To provide new knowledge of the cascades activated after an ICH and to find genes and biomarkers that correlate with the clinical outcome and PHE.

7. To establish correlations between in vivo neuroimaging findings and early circulating markers (neuroinflammation, oxidative stress, neuronal damage) and anatomopathological findings (tight junctions, immune cells, glial cells and oxidative stress) in post-surgical perihematomal tissue.

8. To integrate clinical, radiological and biochemical predictors data from all primary and secondary objectives, developing predictive models of SBI in ICH.

4. VARIABLES

Primary study parameter for efficacy

The primary effect parameter in terms of efficacy will be the decrease in secondary brain injury measured as the volume of perihematomal oedema determined on CT scan performed at day 5 (±2 days). Other primary parameters to measure SBI are the degree of blood-brain barrier permeability constant (Ktrans) and volume of cytotoxic damage in brain MRI performed at day 5 (±2 days). The treatment effect estimate will be adjusted for known prognostic factors, such as volume of initial hematoma, time to surgical intervention, age, pre-stroke mRS, systolic blood

pressure on admission, stroke severity (NIHSS), presence of IVH, known history of antiplatelet or oral anticoagulant use.

Secondary study parameter for safety

The key secondary parameter in terms of efficacy will be mortality from any cause at 30 days and at 365 days from randomization between surgically treated patients and controls.

Other key secondary objective would be the differences in good functional outcomes (mRS 0-3) between surgically treated patients and controls.

Other variables of interest

Other variables of interest that will be recorded during the study include:

1. Clinical variables
   TIME POINTS
   T0 baseline day 0 randomization: demographic and clinical data, CT and CTA data, blood biomarkers.
   T1 day 5 (+/-2) postrandomization: clinical data, MRI data and blood biomarkers.
   T2 day 30 postrandomization: clinical data.
   T3 day 90 postrandomization: clinical data.
   T4 day 365 postrandomization: Final follow-up.

   BASELINE CLINICAL VARIABLES:
   Demographic (age, sex)
   Cardiovascular risk factors
   Initial symptoms at presentation of the ICH
   Severity of neurological impairment (GCS and NIHSS)

   FOLLOW-UP CLINICAL VARIABLES
   mRS
   NIHSS

2. Radiological variables
   TIME POINTS AND VARIABLES
   T0 baseline CT and CTA: Hematoma volume, location, intraventricular bleeding, spot sign
   T24h CT: Hematoma volume
   T1 MRI: Vasogenic edema volume, Ktrans, ischemic lesions

5. STUDY DESING

REPAIR-ICH is designed as a multicentre phase III, prospective, randomized, open, blinded endpoint (PROBE) clinical trial in 225 patients with a spontaneous, supratentorial intracerebral haemorrhage. Patients will be recruited in 6 neurosurgical centres in Spain and in the Netherlands. In addition, local investigators in ~20 general hospitals without facilities for intracranial neurosurgery but with experience in clinical trials in stroke, will be part of the study

group and refer patients for inclusion, as a large number of patients with ICH is currently treated in these hospitals.

Patients will be randomly allocated to minimally invasive, image-guided endoscopic surgery, started within 24 hours of symptom onset in addition to standard medical management, or to standard medical management alone. The randomization procedure will be computer-based. Randomization is allowed when the presence of a spontaneous supratentorial ICH has been established by NCCT and an underlying vascular abnormality is ruled out by CTA, and further in- and exclusion criteria are met.

The treatment allocation will not be visible before the patient is registered in the study database, nor will it be possible to remove the patient from the database after the treatment assignment has become known. Both patient and treating physician will be aware of the treatment assignment. Information on the outcome at 90 and 180 days will be assessed through standardized telephone interviews using structured questionnaires by trained investigators unaware of treatment allocation. Imaging at baseline and during follow-up will be evaluated by assessors blinded for the baseline characteristics, outcome measures, and for the results of baseline imaging.

The study will run for 5 years, which includes a 6-month start-up phase, a 3-year inclusion period with a follow-up period of 12 months, and 6 months for analysis and reporting. The REPAIR-ICH trial will be performed under the approval of local Ethics Committees and in accordance with the Declaration of Helsinki, and national regulatory requirements. Data analysis will be performed by an independent statistician. It is planned as an intention-to-treat analysis. After randomization to any of the two groups, if patients require emergent intervention with conventional craniotomy as a life-saving procedure, they will be excluded from the analysis.

The investigational intervention is minimally invasive image-guided endoscopic surgery for hematoma evacuation. The investigational product is a device for minimally invasive, endoscopy-guided hematoma removal that is CE approved under the indication contemplated in the study: The Artemis Neuro Evacuation Device (Penumbra Inc, Alameda, California, USA) is available and CE approved for the evacuation of intracerebral hemorrhage.

The evacuation device is a surgical instrument designed to aid a surgeon in the removal of tissue and/or fluid during image-guided neurosurgery. It is compatible with the main endoscopic working ports regularly used in tertiary neurosurgical centers in Europe. The device is guided to the target location using intraprocedural image-guidance (intraoperative neuronavigation, ultrasound and/or CT scan). Inside the cannula there is a wire recessed proximally from the cannula's distal tip. Activation of the Powered Handle mechanically rotates the wire to facilitate continuous cannula patency during aspiration. The device is connected to a compatible Aspiration Pump and Collection Canister. The wand fits through the working channels of commercially available neuro-endoscopes.

With the neuronavigation software available at participating tertiary hospitals a trajectory will be selected that is considered safe and technically feasible, accessing the hematoma following its longest possible axis. The surgery is done under general anesthesia. A burr hole or mini-craniotomy is drilled at the planned entry point, the endoscope sheath of peel-away canula (19F) will be introduced to create a safe pass for the endoscope during the remainder of the

procedure. The Evacuation Device is then applied, and the hematoma is evacuated under direct endoscopic vision.

Intraoperative imaging (ultrasound and/or cone beam CT scan) is used to guide the hematoma evacuation. After each pass of aspiration, a control image is acquired, either with US and/or CT to determine the degree of evacuation and to detect remnants of the hematoma. With this exploration, the remnant of the hematoma is quantified, using the ABC/2 formula. If the residue is more than 15mL, a second pass of aspiration is directed towards the remnant. If the software is available at the participating center, after each image exploration, readjustments of the neuronavigation are allowed and recommended. Up to three passes of aspiration following the planned trajectory are allowed until the goal of evacuation is achieved (i.e., more than 70% of the initial clot volume or a remnant of less than 15mL). A final control CT scan image is acquired in all cases, preferably in the operating room, after the evacuation goal is reached or after three passes of aspiration have been completed. The type of intraoperative image-guiding device (ultrasound and/or CT) is left at the discretion of the operator.

The interventional treatment will be in addition to the standard medical management of ICH patients according to the latest guidelines of clinical practice and local institutional protocols available. Patients that are randomized to the control group will be treated with standard medical management alone.

6. SELECTION OF PARTICIPANTS

a. Recruiting phase

The study plans to include 225 patients with a spontaneous, supratentorial intracerebral hemorrhage. Patients will be recruited in 6 neurosurgical centres in Spain and in the Netherlands. Given the emergent nature of the disease being addressed, candidates will be recruited at the Emergency Department of the participating institutions. In addition, local investigators in around 20 general hospitals without facilities for intracranial neurosurgery but with experience in clinical trials in stroke, will be part of the study group and refer patients for inclusion, as a large number of patients with ICH is currently treated in these hospitals.
The study will run for 5 years, which includes a 6-month start-up phase, a 3-year inclusion period with a follow-up period of 12 months.

Patients will be screened in the Emergency Department of one of the six tertiary institutions or in one of the 20 associated secondary sites. Once the diagnosis of spontaneous supratentorial hematoma is made with NCCT, an angioCT will be immediately done per protocol at each center and evaluated by a radiologist to rule out secondary causes of bleeding. Next, a thorough revision of the patient baseline clinical and radiologic features will be done by a neurologist and neurosurgeon involved in the trial; if needed, the patient would be transferred from the secondary to the tertiary sites at this time, with priority level 1. If the patient is considered eligible for recruitment, information about the trial protocol and interventions will be given to either the patient and/or the family/legal representative, depending on the level of neurological impairment during the acute phase. If the patient is not competent to give the informed consent to participate in the trial, the family/legal representative will be asked to provide written consent in representation of the patient, and in all cases a deferred consent

will be obtained from the patient as soon as competency is regained. The patient or representative may, at any given time, withdraw informed consent, and an explanation is not needed. Participants will not receive any incentives or compensation.

Patient advocates and patient associations (Fundació Ictus) have been included to incorporate the perspectives of patients and their families in the development and delivery of REPAIR-ICH

- Study protocols, patient information sheets and informed consent and other relevant documents will be reviewed by patients
Patients will be involved in the set-up of the studies, including gaining study ethical approval and the initiation of study sites.
Patient advocate involvement will continue in the study follow-up phase, with continued valued support, particularly in relation to the use of samples and data to maximize scientific output.
In case of incomplete information or lack of responsive patients, specific surveys will be designed and disseminated among other patient networks.
We will prioritize trust building within patient populations by actively engaging with patients early on in the research process and establishing an ongoing dialogue between patients and researchers.
Patient feedback will also be used to translate research findings into key messages as well as identify potential barriers to communication.

Moreover, the REPAIR-ICH trial protocol has been drawn from the cumulative experience of the investigators acquired throughout several levels in the clinical management and clinical research with patients suffering from ICH and their families and caregivers. First, an analysis of the outcomes and limitations seen with the previous institutional protocol (2020 and before) based on medical management as the gold standard and use of conventional craniotomy to evacuate the hematoma only as a life-saving procedure. The ability of the patients to recover after the stroke and the possibility to return home or to engage in an active rehabilitation program were noted.

Second, as preliminary data on early MIS for ICH became available, a pre-implementation study was performed to estimate the number of candidates potentially eligible for this procedure in our population, along with the expected changes in the working flows of secondary referral centers and emergency departments, the expected increase in the number of emergent procedures, and the changes in the length of hospital stay at the different levels of care units. To account for the socio-economic impact that the implementation of a protocol based on MIS for ICH, our group performed a cost-utility analysis, in which MIS seemed to be a cost-effective intervention in stroke care.

Third, as data from randomized trials became available and with the changes in the clinical practice guidelines contemplating the use of MIS procedures for ICH, a protocol was implemented in our center, and a pilot study was started to evaluate the changes in the surrounding brain after such intervention with advances neuroimaging. This pilot trial was done in two of the participating centers and is currently under analysis. This pilot phase was only exploratory, and it did not include a control group, yet I allowed us to establish a feasible workflow and to obtain valuable data to set off a randomized controlled phase.

b. Inclusion criteria:

To be eligible to participate in this study, a patient must meet all the following criteria:

1. Age 18 to 75 years;
2. NIHSS ≥ 6 and/or GCS 8-14;
3. Supratentorial non-traumatic ICH confirmed by non-contrast CT (NCCT), without a CT angiography confirmed causative vascular or other known underlying lesion;
4. Minimal hematoma volume of 20 mL;
5. Intervention can be started within 24 hours of symptom onset;
6. Written informed consent

c. Exclusion criteria:

A potential participant who meets any of the following criteria will be excluded from participating in this trial:

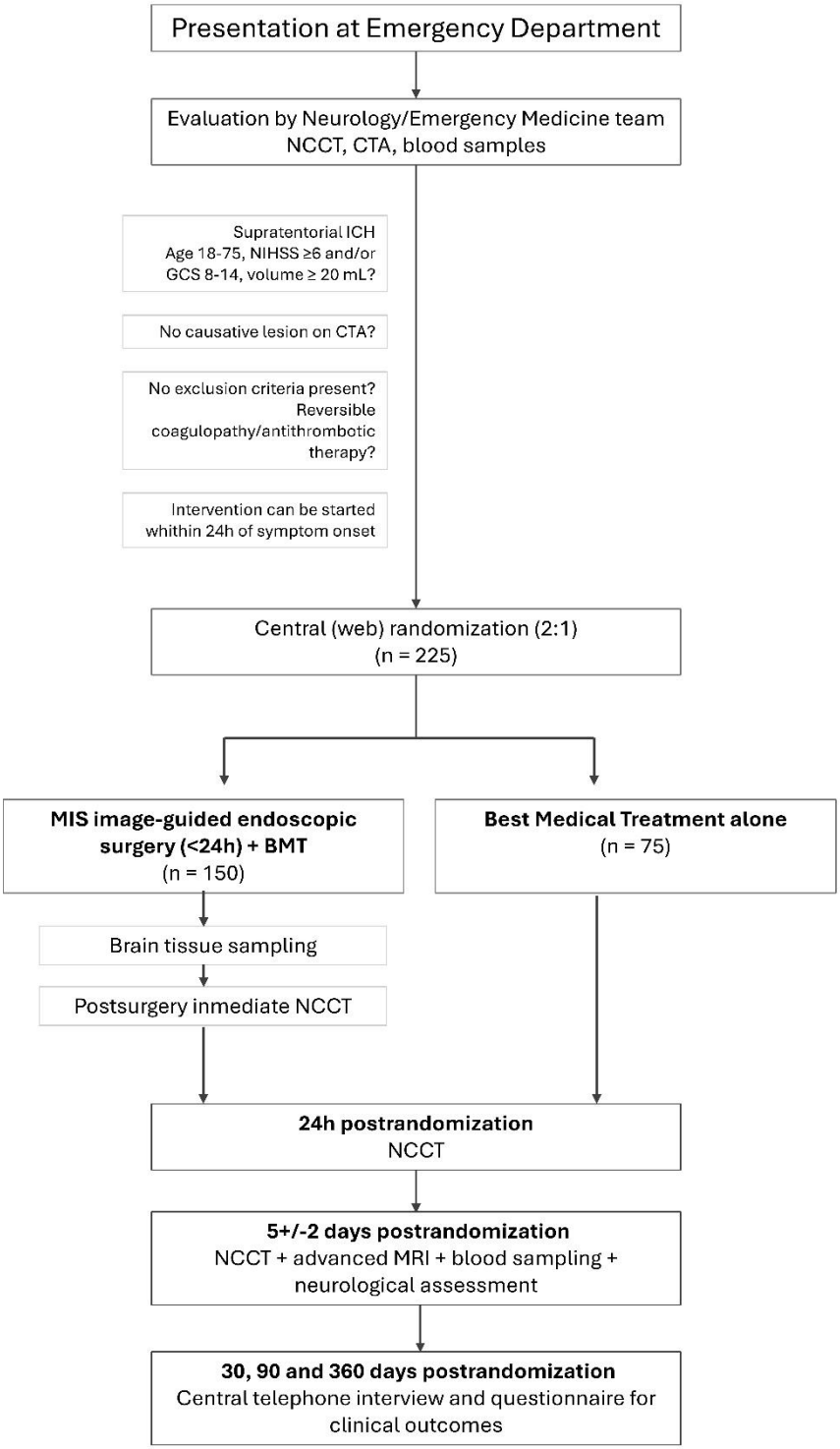
1. Considerable pre-stroke dependency in activities of daily living, defined as mRS ≥3;
2. GCS < 8 or signs of irreversible brainstem damage (i.e., coning, bilaterally dilated unresponsive pupils)
3. Hemorrhagic transformation of an infarct;
4. Untreated coagulation abnormalities, including INR >1.3, treatment with heparin and treatment with factor Xa inhibitors. Patients on vitamin K antagonist can be included after correction of the INR, patients on dabigatran (direct thrombin inhibitor) can be included after reversal of dabigatran with idarucizumab, and patients on antiplatelets can be included after administration of platelet transfusion;
5. Pregnancy;
6. Systemic disease conditioning a life expectancy inferior to 6 months;
7. Infratentorial hemorrhage;
8. Primary thalamic hemorrhage, or hemorrhage with significant brainstem extension;
9. Primary intraventricular hemorrhage, or hemorrhage with massive involvement of the ventricular system (> 50% of both lateral and third ventricles)

Note that a spot sign on CTA, or antiplatelet medication are NOT exclusion criteria. Please also note that patients using heparin or factor Xa inhibitors (apixaban, edoxaban and rivaroxaban) are not allowed to participate, irrespective of use of reversal agents.

7. STUDY INTERVENTIONS

The study will run for 5 years, which includes a 6-month start-up phase, a 3-year inclusion period with a follow-up period of 12 months, and 6 months for analysis and reporting.

A scheme of the main study procedures and the time of assessment is provided, and further information can be found in a tabular format.


Presentation at Emergency Department
Evaluation by Neurology/Emergency Medicine team
NCCT, CTA, blood samples
Supratentorial ICH
Age 18-75, NIHSS ≥6 and/or
GCS 8-14, volume ≥ 20 mL?
No causative lesion on CTA?
No exclusion criteria present?
Reversible
coagulopathy/antithrombotic
therapy?
Intervention can be started
whithin 24h of symptom onset
Central (web) randomization (2:1)
(n = 225)
MIS image-guided endoscopic
surgery (<24h) + BMT
(n = 150)
Best Medical Treatment alone
(n = 75)
Brain tissue sampling
Postsurgery inmediate NCCT
24h postrandomization
NCCT
5+/-2 days postrandomization
NCCT + advanced MRI + blood sampling +
neurological assessment
30, 90 and 360 days postrandomization
Central telephone interview and questionnaire for
clinical outcomes

Study Procedure	Recruitment/Screening Day 0	Enrolment/Baseline Day 0	Baseline CT + CTA Day 0	Surgical intervention (if applicable)	Initial control CT Day 2	Integral evaluation (CT+MRI + serum + clinical)	Integral clinical evaluation Day 30	Integral clinical evaluation Day 90	Final Site Visit Day 360
Obtain informed consent	X								
Demographics	X								
Medical history	X								
Randomization		X							
Administer study intervention				X					
Clinical and other assessments	X	X				X	X	X	X
Adverse events evaluation				X	X	X	X	X	X
Complete Case Report Forms (CRFs)		X		X	X	X	X	X	X

8. STATISTICS

a. Sample size calculation

Sample size estimations were based on available data on perihematomal oedema in patients treated medically and with minimally invasive surgery of spontaneous supratentorial ICH. Based on the distribution of the perihematomal oedema outcomes in the MISTIE II pilot trial and in the case series study from Horowitz, we assumed a mean decrease of 6mL in the surgical group and a mean increase of 2mL in the control group (ENRICH data) to an absolute risk difference of mortality of 9% and 10% at each time point. Providing a 90% power to detect a true treatment effect, with two-sided alpha=0.05, and an estimated loss of subjects of 10%, the analysis yielded a sample size of 225 subjects. Participants will be randomized (2:1) to undergo minimally invasive image-guided endoscopic evacuation surgery within 24 hours of symptom onset in addition to standard medical management, or to standard medical management alone. As planned, 150 patients who underwent surgery for ICH using new endoscopic MIS image-guided techniques (SCUBA technique) and 75 subjects with ICH but without any surgical treatment will be included.

b. Statistical analysis

Regarding statistical guidelines, the recommendations from scientific journals to improve the reliability of results will be followed. Specifically, the normal distribution of the defined variables will be evaluated with the Shapiro-Wilk test and the same variables will be expressed as mean and standard deviation or as median and interquartile range. Mean and standard deviation or median and inter-quartile range will be used to describe continuous variables depending on the shape of the distribution. Student-t test or Mann- Whitney U test will be used to compare results among the study groups planned in the study. Categorical variables will be described as proportions and the results in different study groups and subpopulations will be compared using a Chi-square test or Fisher's exact test when necessary. Likewise, paired T-tests will be carried out or Wilcoxon rank sum test. Bonferroni correction will be performed for multiple comparisons. The association between variables will be carried out with Spearman or Pearson correlation, univariate regressions or multivariate regressions as appropriate. A p value <0.05 will be considered significant.

9. ADVERSE EVENTS NOTIFICATION

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the trial procedure or the experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded in the medical record on site.

Serious adverse events is any untoward medical occurrence or effect that

- results in death;
- is life-threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or

- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention, but could have been based upon appropriate judgment by the investigator.

Serious adverse events that meet the aforementioned criteria should be reported to the sponsor, within 24 hours after coming to notice of the (local) investigator, by making use of the appropriate forms. The investigator of each participating center will report the following serious adverse events occurring in the study period to the sponsor without undue delay after obtaining knowledge of the events: Death from any cause, new symptomatic intracerebral hemorrhage, subdural/epidural hematoma, ischemic stroke, major cardiac event, pulmonary embolism.
Technical complications during surgery that do not lead to clinically detectable serious adverse events and neurological deterioration, will be recorded but not reported immediately.

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

The trial will be monitored by an independent safety monitoring board. The safety committee will have a direct link to the study coordinator at each site, who is entitled to provide all the required information about the course of the trial. The safety monitoring board will visit each center at least every 6 months and a monitoring report will be drawn up at the end of each monitoring visit by the board. The last monitoring visit will also be the close-out visit. In addition, continuous remote monitoring with telephone and web-based monitoring will be performed to ensure the resolution of all queries. The primary investigator will submit a summary of the progress of the trial once a year, including the serious adverse events/reactions, other problems, and amendments to the trial protocol. The study coordinator will be entitled to bilateral interaction between the study's safety monitoring board and the local regulatory committees, including the Ethics Committee for Biomedical Research and Clinical Practice at the corresponding participating institution. This organization will ensure access to documentation requirements concerning the ethical regulations.

10. ETHICAL AND LEGAL ASPECTS

The consortium will ensure access to regulatory expertise as well as adherence to the highest ethical standards through each member's own institutional ethics committee. This study will be conducted in accordance with international ethical standards from the Declaration of Helsinki (2024) regarding principles for medical research involving human subjects. Furthermore, all study documents required by the ethics committee will be approved before study initiation. Each study protocol and all study-related materials will be approved by the ethics committee prior to engagement of study subjects. Any changes to the protocol will be submitted and reviewed by the ethics committee prior to implementation, as any substantial amendment of the protocol needs to be approved also by the ethics committee.

Applicable national regulations in Spain (the country of the sponsor) include:

- Reglamento (UE) 2017/745 del Parlamento Europeo y del Consejo de 5 de abril de 2017.
- Real Decreto 192/2023, de 21 de marzo, por el que se regulan los productos sanitarios.

- Real Decreto 1716/2011 por el que se regula la utilización de muestras biológicas en investigación.

a. Information to the patients and consent for aprticipation in the study

If a patient is considered eligible for recruitment, information about the trial protocol and interventions will be given to either the patient and/or the family/legal representative, depending on the level of neurological impairment during the acute phase. If the patient is not competent to give the informed consent to participate in the trial, the family/legal representative will be asked to provide written consent in representation of the patient, and in all cases a deferred consent will be obtained from the patient as soon as competency is regained. The patient or representative may, at any given time, withdraw informed consent, and an explanation is not needed. Participants will not receive any incentives or compensation.

b. Evaluation of the risk-benefit for participation in the study

The expected benefit from endoscopy-guided surgery compared to standard care may amount to 11% relative risk reduction for death or dependence (Akhigbe et al. 2015; Zhou et al. 2012). Patients from the control group will be given the usual treatment according to international, national and local guidelines, including treatment of high blood pressure in the acute phase and monitoring for hyperglycemia and treatment thereof.

Because outcome after ICH is generally poor, with 40% of patients dead at one month, and because a large proportion of patients with ICH present with dysphasia or impaired consciousness that may incapacitate them, it is essential to also include the incapacitated patients in this trial and not restrict the trial to capacitated patients only. We therefore expect that the potential benefit of minimally invasive endoscopy-guided surgery performed within 24 hours after symptom onset outweighs the risk of harm in this study treatment.

c. Equal inclusion and sex/gender perspective

The present study considers the principle of equity in research, avoiding sex and/or gender-related biases and promoting the appropriate inclusion of both. Participation will not be restricted by sex.

When relevant, results will be analyzed in a sex-stratified manner, and proportional representation will be encouraged to allow the detection of potentially meaningful differences, particularly in circulating levels of biomarkers of secondary brain injury. These considerations reflect the principles of responsible research and the commitment to scientific validity and fairness in the distribution of the benefits derived from knowledge.

11. DATA SOURCE AND MANAGEMENT

a. Data source

Data will be primarily collected from the participants by the researchers at each participating institution.

The following type of data will be collected at the designated timepoints:

T0 baseline day 0 randomization: demographic and clinical data, CT and CTA data, blood biomarkers.
T1 day 5 (+/-2) post randomization: clinical data, MRI data and blood biomarkers.
T2 day 30 post randomization: clinical data.
T3 day 90 post randomization: clinical data.
T4 day 365 post randomization: Final follow-up.

Clinical variables: Demographic (age, sex), cardiovascular risk factors, initial symptoms at presentation of the ICH, severity of neurological impairment (GCS and NIHSS).

Radiological variables: CT and CTA at baseline location, initial volume of hematoma, presence of spot sign. CT on day 5, volume of hematoma. MRI on day 5, volume of hematoma, volume of vasogenic oedema, volume of infarction in DWI, permeability constant Ktrans in DCE.

Blood sample variables at baseline and at 5 days: metalloproteinase MMP-2, 3, 7, 9, 13 , uric acid, alantoine and 8-epi-prostaglandine F2a, interleukin IL-1α/1β/2/4/6/8/10, IFNγ/TNFα, light chain neurofilaments (NF-L) and Tau protein, and miRNAs.

Data entry will be performed at each clinical site by a locally designated staff member. Medical records, Picture Archiving and Communication Systems and laboratory reports available at each clinical site will be the primary source for data collection. The collected database will be made available and possibly shared with other European clinical network databases and integrated into an online CRF data sharing platform.

b. Data management

The study will be held in strict adherence to international ethical guidelines and data management regulations in biomedical human research. The primary investigator will be responsible to guarantee that the study follows such recommendations. The Research Ethics Committee in each center will review and approve the study protocol, including the information that is given to the patients included in the trial and the document of informed consent regarding the study procedures and the treatment of personal data. Any given patient can only enter the study after the consent form has been signed by the proper patient or the family/legal representants.

Data confidentiality will follow the European Regulation 2016/679 and the related national laws tailored to each participating country to guarantee the protection of personal data and digital rights of the patients. All data will be entered into a web-based database by local research personnel. Subject records are coded with a unique study number. The local investigators will keep a list showing codes and names. Unique documents with identifying information will be stored separately from the study database in digital files, categorized by study number on a secure drive system, accessible only by the study coordinator.

Data monitoring will include the verification of the availability of informed consents and the exclusion and inclusion criteria. Sample's associated data will be further curated before data extraction. Data on name and date of birth will be correlated with sample data, including associated electronic health records.

c. Data base

Data will be entered into a database compliant with EU guidelines for data protection and management (General Data Protection Regulation - GDPR - 2016/679). The Clinical Trial Unit of IDIBAPS will be engaged and able to create and maintain the study database, also providing technical support throughout the study and long-term data storage. Patient data generated by this study will be maintained in confidence and protected (through pseudonymization, key-code data creation), following regulatory requirements.

Moreover, REPAIR-ICH will use an electronic data management system based on an electronic case report form (eCRF). The eCRF will be designed and implemented in RedCap. The system complies with international standards and provides the data management activities with a consistent, auditable and integrated electronic environment.

The Clinical Trial Unit of IDIBAPS will be responsible for the creation and maintenance of the study database as well as providing technical support throughout the study and long-term storage of the data. In accordance with regulatory requirements. Study records will be maintained in a confidential manner (pseudonymization, key-code data creation). All access to the data will be managed by and restricted to study investigators. In compliance with ethical requirements, study records will be maintained for 10 years after completion of study. Paper and electronic records will be destroyed or erased per institutional/University policy. Data will be retained in aggregate form to enable easy retrieval for publication purposes. Electronic data will not be entered with direct identifiers. Electronic data will be managed using a secure, web-based system that has user-level access control (RedCAP). Analytical datasets will be stored on secure servers that also limit access to the investigator team. Data will be analyzed and reported in a de-identified, aggregate form.

d. Access to data

Data will be entered into a web-based database, as mentioned above, by local research personnel. Subject records are coded with a unique study number. The local investigators will keep a list showing codes and names. Unique documents with identifying information will be stored separately from the study database in digital files, categorized by study number on a secure drive system, accessible only by the study coordinator.

12. PROCESSING OF DATA AND RECORD STORAGE. DATA CONFIDENTIALITY

The purpose of data collection is to study the impact of minimally invasive surgery for endoscopic evacuation of primary cerebral hematomas on the natural progression of secondary brain injury, specifically in terms of perihematomal edema and blood–brain barrier permeability.

The processing, communication, and transfer of personal data of all participants will comply with EU Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons regarding the processing of personal data and the free movement of such data, as well as Spanish Law 3/2018 of 5 December on the Protection of Personal Data

and the Guarantee of Digital Rights. The legal basis that justifies the processing of your data is the consent you provide at this time, in accordance with Article 9 of EU Regulation 2016/679.

The data collected for these studies will be identified only by a code, so no information that could identify the participants will be included. Only the study physician and collaborators with authorized access to source data (medical records) will be able to link the data collected in the study to the patient's clinical history.

The identity of participants will not be accessible to anyone else except in cases of medical emergency or legal requirement.

Health authorities, the Research Ethics Committee, and personnel authorized by the study sponsor may access identifiable personal information when necessary to verify study data and procedures, but confidentiality will always be maintained according to applicable law.

Only coded data will be transferred to third parties or to other countries, and under no circumstances will such data contain information that could directly identify the participant (such as full name, initials, address, social security number, etc.). Should such transfer occur, it will be for the same purpose described in the study and with confidentiality guaranteed.

If a transfer of coded data outside the EU is carried out—whether to entities related to the hospital, service providers, or researchers collaborating with us—the participants' data will be protected through safeguards such as contracts or other mechanisms established by data protection authorities.

As project sponsors, we commit to processing the data in accordance with EU Regulation 2016/679 and therefore to maintaining a record of processing activities and conducting a risk assessment of the processing we perform, in order to determine which measures must be applied and how to apply them.

In addition to the rights already recognized under the previous legislation (access, modification, objection, and cancellation of data, deletion under the new Regulation), participants may now also restrict the processing of data collected for the project if it is incorrect, request a copy, or request that the data be transferred to a third party (portability). To exercise these rights, they must contact the principal investigator of the study or the Data Protection Officer (DPO) of Hospital Clínic de Barcelona at protecciodades@clinic.cat. They also have the right to contact the Data Protection Agency if they are not satisfied.

The data cannot be deleted even if a patient withdraws from the study, in order to guarantee the validity of the research and comply with legal obligations and medication authorization requirements.

The Investigator and the Sponsor are required to retain the data collected for the study for at least 10 years after its completion. Afterwards, personal information will only be retained by the center for your healthcare, and by the sponsor for other scientific research purposes if the patient has given consent and if permitted by law and applicable ethical requirements.

13. MANAGEMENT OF BIOLOGICAL SAMPLES

a. Origin of the samples: Samples will be prospectively collected from the participants during the trial.

b. Sample number and type: Biological samples that will be collected include a) peripheral blood samples, obtained at baseline and on day 5; b) brain tissue samples, obtained intraoperatively.

c. Designated location for analysis: The blood samples will be transferred at the end of the study to the biological sample collection of the Functional Unit of Cerebral Vascular Pathology at Hospital Clínic de Barcelona (R121004093), where the corresponding biomarker studies will be carried out. The preparation of the paraffin block and the freezing of the brain tissue samples will be performed through the biobank of each center. Subsequent immunohistochemistry and immunofluorescence analyses will be conducted at Center 1 (Cerebral Vascular Pathology Laboratory, CELLEX). The shipment of samples from Center 2 to Center 1 for processing will require the mandatory Material Transfer Agreement (MTA).

d. Responsible for the management of the samples: The primary investigators will be directly responsible for the management of the samples.

e. Destination of the samples at the end of the study: Once the study is completed, the samples will be destroyed.

14. FUNDING

The project will be funded by the EU's Innovative Health Initiative (IHI) grant awarded to the SEISMIC consortium to Pioneer next-generation minimally invasive brain treatments.

An economic report is attached as a separate document detailing the allocated resources.

Direct payments to the investigators are not contemplated in this study.

15. RESULTS COMMUNICATION AND PUBLICATION POLICY

The relevant results obtained from this research project, whether positive or negative, will be communicated to the scientific community through peer-reviewed scientific journals, institutional repositories, and professional conferences or symposia. The published data will be available for use in future academic research by the participating centers or by other interested institutions. Additionally, given the public interest and concern surrounding hemorrhagic stroke, an adapted dissemination of the results will be provided to the general public through the media and patient forums.