# Early minimally invasive image guided endoscopic evacuation of intracerebral haemorrhage (EMINENT-ICH): a randomized controlled trial

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| Study Type: | Other Clinical Trial according to ClinO, Chapter 4 |
| Risk Categorisation: | B |
| Study Registration: | Intended primary study registry: ClinicalTrials.gov<br>Registration number: **NCT05681988**<br>SNCTP registration number: not yet known |
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| Investigated Intervention: | Early minimally invasive image guided endoscopic evacuation of intracerebral haemorrhage |
| Protocol ID | *not applicable* |
| Version and Date: | Version 1.2 (dated 02/08/2023) |

**CONFIDENTIALITY STATEMENT**

*Not applicable*

Universitätsspital Basel

**PROTOCOL SIGNATURE FORM**

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|---|---|
| Study Title | Early minimally invasive image guided endoscopic evacuation of intracerebral haemorrhage (EMINENT-ICH): a randomized controlled trial |
| Study ID | Not yet applicable |

The Sponsor Prof. Dr. med. Raphael Guzman has approved the protocol version **1.2 (dated 02/08/2023)** and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, as well as the local legally applicable requirements. This protocol was written in accordance with the SPIRIT guidelines and the SPIRIT-PRO Extension[1, 2].

**Sponsor:**

Name: Prof. Dr. med. Raphael Guzman

Date: _____ Signature: _____

**Principal Investigator Basel:**

Name: PD Dr. med. Jehuda Soleman

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## GLOSSARY OF ABBREVATIONS

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|---|---|
| *AE* | *Adverse Event* |
| *ASR/DSUR* | *Annual Safety Repot / Development Safety Report* |
| *BASEC* | *Business Administration System for Ethical Committees* |
| BMT | best medical treatment |
| *CC* | *Conventional craniotomy* |
| *cCT* | *cranial computed tomography* |
| *ClinO* | *Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)* |
| *CRF* | *Case Report Form* |
| *CTCAE* | *Common Terminology Criteria for Adverse Events* |
| *DOAC* | *direct oral anticoagulants* |
| *eCRF* | *electronic Case Report Form* |
| *EDC* | *electronic data capture* |
| *ES* | *Endoscopic surgery* |
| *FADP* | *Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)* |
| *FOPH* | *Federal Office of Public Health* |
| *GCP* | *Good Clinical Practice* |
| *GCS* | *Glasgow Coma Scale* |
| *CDMS* | *Clinical Data Management System* |
| *GFAP* | *Glial Fibrillary Acidic Protein* |
| *HRA* | *Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)* |
| *ICH* | *International Conference on Harmonisation* |
| *ICU* | *intensive care unit* |
| *IL* | *Interleukin* |
| *ISF* | *investigator site file* |
| *MIPS* | *minimally invasive puncture surgery* |
| *MIS* | *Minimally invasive surgery* |
| *MOCA* | *Montreal Cognitive Assessment* |
| *MRI* | *magnet resonance imaging* |
| *mRS* | *modified Rankin Scale* |
| *NfL* | *the light-chain neurofilament subunit* |
| *NIHSS* | *National Institute of Health Stroke Scale* |
| *NOAK* | *new oral anticoagulants* |
| *OAC* | *Oral anticoagulants* |
| *PPI* | *Patient and Public Involvement* |
| *RR* | *Relative Risk* |
| *S100B* | *S100 calcium-binding protein B* |
| *SA* | *Stereotactic aspiration* |
| *SAE* | *Serious Adverse Event* |
| *SIMOA* | *single-molecule array* |
| *SIV* | *site initiation visit* |
| *SSICH* | *spontaneous supratentorial intracerebral haemorrhage* |
| *VKA* | *Vitamin K antagonists* |

# 1 STUDY SYNOPSIS

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| **Sponsor / Sponsor-Investigator** | Prof. Dr. med. Raphael Guzman<br>Vice Chair, Head of Vascular and Pediatric Neurosurgery<br>Department of Neurosurgery, University Hospital Basel<br>Spitalstrasse 21, 4031 Basel<br>Raphael.guzman@usb.ch |
| **Study Title** | Early minimally invasive image guided endoscopic evacuation of intracerebral haemorrhage (EMINENT-ICH): a prospective randomized controlled trial |
| **Short Title / Study ID** | EMINENT-ICH EKNZ 2022-02216 |
| **Protocol Version and Date** | Version 1.2 (dated 02.08.2023) |
| **Study Registration** | SNCTP and Clinicaltrials.gov (NCT05681988) |
| **Study Category and Rationale** | B – Inclusion of vulnerable patients and more than minimal risk due to the underlying disease |
| **Background and Rationale** | Spontaneous supratentorial intracerebral haemorrhage (SSICH) is the second most common form of stroke and accounts for approximately 2500 cases in Switzerland annually. The prognosis is very poor with nearly half of the patients dying within one year after haemorrhage.<br>Treatment options for SSICH remain ambiguous and consist of either the current gold standard, best medical treatment, or surgical hematoma evacuation. Neither the best medical treatment nor the established surgical mainstay (conventional craniotomy) have shown relevant improvement of survival or functional outcome rates. We therefore propose a minimal invasive approach with early image-guided endoscopic surgery conducted within 24 hours. Endoscopic surgery was shown to be safe and effective, however large trials analyzing the benefits of endoscopic surgery are lacking. We therefore propose, that an earlier, more complet and more rapid hematoma evacuation will improve the functional outcome and mortality rates in these patients. |
| **Risk / Benefit Assessment** | This study carries relevant risk of death and disability for the included patients due to the underlying disease of SSICH, however if left untreated, outcome may be even worse with a 30-day mortality up to 45% reaching to 54% at one year. The mortality rates however can be attributed almost exclusively to the underlying disease rather than the procedure. Since this is a surgical procedure, risks like bleeding, wound infections, surgical site infection, and complications related to anaesthesiologic procedures may occur. Furthermore, the procedure might, in extremely rare cases, lead to the death of the participant. Also, due to the location of SSICH, important brain structures have to be passed to access the hematoma cavity and, despite all efforts to conserve them, might be damaged.<br>Overall, we acknowledge the possible risk accompanying the proposed surgical method, but it is our opinion that compared with the medical standard of care for SSICH alone or no treatment at all, these risks are acceptable and fairly balanced with the prospect of potential better survival and less morbidity as well as better functional outcome through the proposed surgical method. |
| **Objective(s)** | The primary objective of this two, armed, open-labelled, single centre randomised controlled trial is to show superiority of early minimally invasive image-guided hematoma evacuation additionally to BMT compared to BMT alone in functional outcome rates at 6 months in patients with SSICH.<br><br>Secondary objectives are:<br>• to show superior survival rates of patients in the ES arm<br>• to study patient reported quality of life after treatment for SSICH at different time points (3 and 6 months after intervention)<br>• to study patient satisfaction with the outcome after treatment for SSICH at different time points (7 days, 3 months and 6 months after intervention) |

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| | • to study cognitive outcome in patients after treatment for SSICH at different time points (7 days, 3 months and 6 months after intervention)<br>• to study the morbidity rates of patients in both treatment arms<br>• to study the efficacy of ES in reducing the hematoma volume<br>• to study the change in focal neurological deficits exhibited by the patients after treatment.<br>• to study the temporal evolution of serum biomarkers (Neurofilament light-chain subunit (NfL), Glial Fibrillary Acidic Protein (GFAP), S100 calcium-binding protein B (S100B), IL-1α and β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70 and TNF-α) and their change in relation to early hematoma ES. |
| **Endpoint(s)** | **Primary outcome:**<br>• Good functional outcome 6 months after treatment, measured by the mRS. Good functional outcome is defined as a mRS of ≤3 points and will be assessed as binary outcome (yes/no, final value) at 6 months (blinded) after treatment. The cut-off for good functional outcome is chosen at a mRS score of 3 points, as this reflects the turning point for a patient being able to live a partially self-dependent life or to live a severely disabled life. In this context, a mRS score of 3 points reflects the ability to walk unassisted and care for one's own bodily needs despite being moderately dependent on assistance, while a mRS score of 4 points describes a patient who is not able to walk anymore and needs assistance with all daily activities and thus marks a severe loss of patient autonomy.<br><br>**Secondary outcomes:**<br>• The mortality rate as measured by death of a participant (binary outcome (yes/no), final value) at 6 months after intervention.<br>• Patient reported outcome measures at 7 days (Patient satisfaction and cognition), 3 and 6 months after intervention, those being:<br>o Patient and caregiver quality of life as assessed by the PROMIS® questionnaire (continuous variable, final value)<br>o Patient Satisfaction as assessed by a short survey (Appendix 2) on a scale of 1-5 (continuous variable, final value)<br>o Patient cognitive outcome as assessed by the MOCA® Test (continuous variable, final value)<br>• The morbidity rate, meaning occurrence of:<br>o Ischemic stroke<br>o Recurrent SSICH (defined as any radiologically confirmed increase in hematoma volume postoperative/follow-up that is either asymptomatic or associated with a worsening of the focal-neurological deficit by ≥4 points on the NIHSS and/or a decrease in consciousness by ≥2 points on the GCS)<br>o Epileptic seizure<br>o Surgical site infection (intervention group only)<br>o Any need for open neurosurgical procedures<br>o Infections (i.e. pneumonia, urinary tract infection)<br>o Any other not defined complication that prolongs the hospital stay and/or leads to further treatment not envisaged in the original treatment plan.<br>The occurrence of any of these events 6 months after intervention (binary variable (occurrence/no occurrence), final value, proportion).<br>• The change of focal neurological deficit measured by the NIHSS, from baseline to 6 months after intervention as a continuous variable (continuous variable, change from baseline).<br>• The time to intervention, defined as the period from symptom onset/last seen well to start of surgery (start surgical measures, i.e. positioning of patient) or start of medical treatment (admission of first treatment of BMT) (continuous variable, time to event). |

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| | • The temporal evolution of serum levels of the prespecified biomarkers as continuous variable from start to 6 months after intervention (continuous variable, change from baseline).<br>• The total time spent on the intensive care unit (ICU)/stroke unit as a continuous variable from the first admission to the ICU/stroke unit to discharge from ICU/stroke unit at 7 days/discharge after intervention (continuous variable, final value).<br>• The total time spent in intubation measured in minutes from the start of intubation to extubation as specified in the anesthesiology report at 7 days/discharge after intervention (continuous variable, final value).<br><br>Outcomes/Measurements applying to the intervention group only:<br>• The proportion of hematoma volume reduction rate (goal ≤15% of its initial volume). The hematoma volume will be measured on serial cranial computer tomography (cCT) and the difference between the volume of the cCT used for surgery and the cCT directly after surgery will be calculated. The hematoma volume on the pre-operative cCT will be calculated using the (A * B * C)/2 method during screening and secondarily validated using the volumetric function of the navigation software. Hematoma on directly postoperative images will be calculated using the volumetric function of the navigation software. The hematoma volume reduction rate will be a binary variable (achieved reduction<15%/did not achieve reduction<15%, final value).<br>• The relative (percentage) reduction or increase of hematoma volume from baseline admission cCT to postoperative cCT directly after surgery as a continuous variable (final value). |
| **Study Design** | This is a national single-centre, two-arm, open labelled randomised controlled trial within the stroke units and stroke centres of the swiss stroke registry in a superiority fashion. |
| **Statistical Considerations** | The primary analyses are performed following the intention-to-treat principle. Additionally, per-protocol analysis will be performed for sensitivity analysis. We study the ratio of positive outcomes in both study arms by performing a Bayesian A/B test after every 40 additional patients, using the method described by Gronau et al.. Data collection (and the periodical analysis of these data) will continue until a Bayes Factor of 10 (or 1/10) is achieved. The odds ratio and its 95% credible interval will be reported.<br>Secondary analysis is performed on the secondary outcomes. For continuous variables, a Bayesian regression with normal error term is used, for time-to-event outcomes Bayesian cox-regression is used, and for binary variables Bayesian logistic regression is used adjusted for covariates. Statistical analysis is performed with R version 4.2.1 or higher (R core Team, 2022).<br>In parallel to the Bayesian primary analysis, we will perform a frequentist test of proportions comparing study arm for the first 100 patients per study arm. In the ES arm, a number of explorative analyses are performed, studying the relation between hematoma location, hematoma size, and treatment outcome. In particular, for parameters measured over time, figures are created illustrating the development over time at both the patient level and group level. |
| **Inclusion- / Exclusion Criteria** | Inclusion criteria:<br>• Patient age ≥ 18 and <85<br>• Spontaneous supratentorial intracerebral hemorrhage (SSICH), defined as the sudden occurrence of bleeding into the lobar parenchyma and/or into the basal ganglia and/or thalamus that may extend into the ventricles confirmed by imaging<br>• SSICH volume ≥20 mL <100 mL (measured using the formula $\frac{A*B*C}{2}$)<br>• Stable clot volume defined as absence of increase of >33% (as assessed using the formula (A * B * C)/2) of initial clot volume on follow-up imaging.<br>• A focal neurological deficit consisting of either<br>  ○ clinically relevant hemiparesis (≥4 motor points on the NIHSS for facial palsy, motoric upper and lower extremities combined) |

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| | ○ clinically relevant motor or sensory aphasia (≥2 points on the NIHSS)<br>○ clinically relevant hemi-inattention (formerly neglect, 2 points on the NIHSS)<br>○ decreased level of consciousness (GCS≤13)<br>• Presenting GCS 5 – 15 (in intubated patients GCS assessment will be performed after Rutledge et al. (Figure 2) or if impossible, the last pre-intubation GCS will be used)<br>• Endoscopic hematoma evacuation can be initiated within 24 hours after the patient was last seen well/symptom onset<br>• Informed consent of patient (only for patients able to consent)<br>Exclusion criteria:<br>• SSICH due to known or suspected structural abnormality in the brain (e.g. vascular malformation, aneurysm, AVM, brain tumor) and/or brain trauma and/or hemorrhagic conversion of an ischemic infarction<br>• Multiple simultaneous intracranial hemorrhages (e.g. multifocal ICH, cSDH, aSDH, SAH)<br>• Infratentorial hemorrhage or midbrain extension/involvement of the hemorrhage<br>• Coagulation disorder (including anticoagulation) with an INR of >1.5 which cannot be pharmacologically reverted until the planned time of evacuation<br>• Positive history of current pregnancy or breast-feeding<br>• Relevant disability prior to SSICH (mRS >2)<br>• Any comorbid disease or condition expected to compromise survival or ability to complete follow-up assessments through 180 days (e.g. bilateral fixed dilated pupils) |
| **Number of Participants with Rationale** | Based on the to-date available literature, our own meta-analysis and the data of 2020-2022 derived from the Swiss stroke registry we assume a favorable outcome around 50% for patients treated with BMT, while we anticipate a positive risk ratio of 1.6 towards favorable outcome for ES compared to BMT. Based on these assumptions, we explored sample sizes needed for achieving “compelling evidence”, as described by Schönbrodt & Wagenmaker.<br>Systematic reviews as well as data analyzed from the Swiss Stoke Registry over the last 2 years suggests that a plausible assumption for the proportion of positive outcomes in the control arm is 50% (0.5). Based on our calculations after collecting data of 70 patients per study arm, about 90% of trials will have achieved a BF of 10, being the “Bayesian equivalent” to a power of 90%. In addition, 50% of the simulated trials already achieve this level of evidence after the 40th hypothetical patient (per arm). Further, based on these calculation, it is extremely unlikely that the trial would take more than 130 patients per arm. Based on these results we assume that we will likely be able to stop collecting data before reaching **75 patients per arm (total of 150 patients) to reach a BF of 10**. |
| **Study Intervention** | Early minimally invasive image guided endoscopic hematoma evacuation as an add-on therapy to BMT performed within 24 hours after SSICH symptom onset. |
| **Control Intervention** | Best medical treatment i.e. active blood pressure control, seizure prophylaxis and care as according to the current guidelines. |
| **Study procedures** | 6 Visits in total, 4 of them during hospital stay, 2 of them as follow-up visits within the clinical routine. Each visit consists of assessing GCS, mRS and NIHSS, three visits include CT scans (before intervention, directly postoperative and during follow up) and blood sampling (before intervention, postoperative and during follow up). Three visits include assessing patient satisfaction and cognition, and two visits include patient quality of life assessments. |
| **Study Duration and Schedule** | Estimated duration for the main investigational plan is estimated to last 5 years<br><br>Planned 09/2023 of First-Participant-In<br>Planned 09/2028 of Last-Participant-Out |
| **Investigator(s)** | Principal Investigator:<br>PD Dr. med. Jehuda Soleman<br>Senior Neurosurgeon, Head of Clinical Research<br>Department of Neurosurgery, University Hospital Basel |

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| | Spitalstrasse 21, 4031 Basel<br>Jehuda.soleman@usb.ch<br><br>Sub-Investigators:<br>Prof. Dr. med. Urs Fischer<br>Chair of Neurology, Head of the Department of Neurology<br>Department of Neurology, University Hospital Basel<br>Petersgraben 4, 4031 Basel<br>Urs.fischer@usb.ch<br><br>Dr. med. Tim Hallenberger<br>MD PhD Candidate<br>Department of Neurosurgery, University Hospital Basel<br>Spitalstrasse 21, 4031 Basel<br>tim.hallenberger@usb.ch |
| **Study Center(s)** | Department of Neurosurgery<br>University Hospital Basel<br>Spitalstrasse 21<br>CH-4031 Basel<br>Switzerland |
| **Data privacy** | A unique patient identifier (i.e., patients study ID) will be used to identify patients and a password protected list will be maintained for traceability. The patient ID is generated when the patient is enrolled in the CDMS secuTrial® by consecutive automatic numbering (i.e., USB-NNN with NNN a tree digit number). Only the PI or delegated study personnel will have access to the encoding key. Enrolment and screening logs will be filed to ensure traceability. The Principal Investigator and, if applicable, delegates at the site will be authorized to do eCRF entries. The CDMS is accessible via a standard browser on devices with internet connection. Password protection and user-right management ensures that only authorized study investigators, monitors, data managers and local authorities (if necessary) will have access to the data during and after the study. An audit trail will maintain a record of initial entries and any changes made; time and date of entry; and username of person authorizing entry or change. Participant's identification logs will be stored as a password protected word files and saved on protected servers of the respective study site. On CRFs and other study specific documents, participants are only identified by the patient's study ID derived by secuTrial®. Completed paper CRFs will be kept locked in a drawer at the respective study site with access only to a very limited number of study team members. ECRFs will be secured in secuTrial®, only accessible by the study teams at the respective sites. The Investigators and the Sponsor endorse responsibility, that nobody else will have access to the confidential data and they guarantee protection against dissemination.<br>Biological material in this study (i.e., blood samples) are not identified by participant name but by the patient's study ID. Biological material is stored in an appropriate cooling system in a restricted area only accessible to the authorized personnel and handled under appropriate conditions. Biological material will be discarded after analysis as according to hospital regulations for biological waste. All study data, except blood samples, will be archived for a minimum of 10 years after study termination or premature termination of the clinical trial. |
| **Ethical consideration** | SSICH is a devastating disease affecting 2500 patients per year in Switzerland. As of today, nearly 60 years into the research of the ideal treatment of SSICH, effective treatment options improving not only mortality but more importantly functional outcome and HRQoL do not exist.<br>With the results of this multicenter, randomized controlled trial, we will generate highly relevant data, which will shape the future management of SSICH and lead to an improved treatment and outcome for patients. |
| **GCP Statement** | This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements. A clinical trial covered by ClinO Chapter 4 may be conducted in accordance with other rules than ICH-GCP guidelines, provided that such rules are |

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| | recognised in the specialty in question and the protection of participants and data quality and security are guaranteed (ClinO Art. 5, Abs 2). |

## 2 BACKGROUND AND RATIONALE

Spontaneous supratentorial intracerebral hemorrhage (SSICH) is the second most common form of stroke, accounting for roughly 9-27% of all strokes and affecting more than 5 million people worldwide annually (approx. 2500 cases in Switzerland annually)[3]. Mortality rates are high with a range of 40-45%[4]. Patients surviving an SSICH mostly have very poor Health Related Quality of Life (HRQoL) and serious neurological deficits resulting in great burdens for them, their relatives and the social system[5-7].
Primary brain injury in SSICH occurs due to intra-axial bleeding causing mass effect and destruction of brain tissue[8]. Secondary mechanisms of brain injury are the local decay of hemoglobin, causing further brain damage due to its toxicity and delayed brain edema[9]. As such, the hematoma volume plays a vital role, as larger hematoma volumes lead to poorer outcome[10].
Treatment options for SSICH aim to stop enlargement of the hematoma volume or evacuation of the hematoma volume itself[11]. They consist of either, best medical treatment (a combination of medical blood pressure control, intensive care and prevention of secondary complications, short BMT, considered the current gold standard of treatment, or open surgical hematoma evacuation. Both treatment arms, showed similarly low rates of good functional outcome and survival (Class of Recommendation 2a, Level of Evidence B)[11, 12]. Intensive blood pressure reduction to below 140mmHg showed minimal improvement of functional outcome (OR 0.87, p=0.04) and mortality rates (OR 0.75, p=0.06)[13, 14].
Surgical treatment options for SSICH can be divided into conventional craniotomy (CC) and minimally invasive surgery (MIS), including endoscopic surgery (ES) and stereotactic aspiration (SA)[11, 15]. The Surgical Treatment for Intracerebral Haemorrhage (STICH) I and II trials, failed to show significant superiority of open surgical removal of SSICH with CC compared to BMT for improved functional outcomes or mortality[16, 17].
MIS on the other hand seems to be a promising alternative to BMT and CC. Recent systematic reviews/meta-analysis suggested that MIS leads to markedly improved survival and favorable outcome rates compared to BMT, yet the most promising MIS technique remains elusive[18, 19].
The MISTIE (minimally invasive surgery plus rt-PA [alteplase] in intracerebral haemorrhage evacuation) I, II and III trials assessed the potential superiority of minimally invasive hematoma removal using SA (stereotactic insertion of a catheter into the hematoma cavity, repetitive irrigation of the blood clot using thrombolytic agents and subsequent hematoma drainage) compared to BMT[20-22]. MISTIE II demonstrated efficacy in reducing hematoma volume, clinical safety, and feasibility. MISTIE III evaluated good functional outcome after 1 year (modified Rankin Scale (mRS) ≤3 points) showing no significant difference between SA and BMT, while SA significantly reduced the all-cause mortality throughout the study period[21].
Recently, ES emerged as a safe and effective treatment option of SSICH[18, 23-26]. Meta-analysis showed decreasing mortality and higher favorable outcome rates after ES, compared to BMT. Further, compared to SA, more rapid hematoma evacuation and compared to CC lower morbidity rates were seen[18, 23, 24, 26]. We confirmed these results in our own meta-analysis, where we compared ES to BMT as a single comparator, which showed a significantly improved favorable outcome rate and an improved survival rate (p=0.02 and 0.01 respectively). Despite these promising findings, to date, large randomized controlled trials assessing the superiority of ES over BMT in SSICH are lacking[12, 27]. In the MISTIE III trial, evacuation of half the hematoma volume took two days on average with a median time between bleeding onset and randomization of 47 hours. Additionally, the optimal timing to hematoma evacuation remains elusive. A subgroup analysis of MISTIE III showed that patients receiving treatment within 36 hours after symptom onset profited more than those with later treatment onset (>36h)[22]. Likewise, a meta-analysis reports a 2.8 times greater likelihood of achieving functional independence if patients received hematoma evacuation within 24 hours after symptom onset[23]. This was confirmed by Kellner et al., stating that delayed treatment onset reduces the rate of favorable outcome by 5% per hour lost[28]. These findings suggest that early surgical hematoma evacuation is vital for the improvement of functional outcome and survival in SSICH.

Ultra-early hematoma evacuation (<7h) however, was associated with higher mortality rates and therefore, it seems that the optimal treatment window lies within the first 6-24 hours after bleeding onset[29, 30]. To this date, large randomized controlled trials analyzing this specific treatment window with ES are lacking.
Lastly, patient reported outcomes measures (PROMs) and cognitive outcomes in ES compared to BMT are currently underreported (if reported at all)[31]. Within the frame of the EMINENT trial these aspects will be evaluated in a standardized fashion.
Based on the pathophysiological considerations, the current literature and our own data, we are convinced, that evacuating SSICH in a minimal invasive endoscopic fashion, within 6-24 hours and achieving a fast and significant reduction of hematoma volume will result in superiority of good functional outcome and lower morbidity rates compared to BMT.

The present study aims to demonstrate efficacy of ES as add on therapy to BMT (henceforth simply referred to as ES) versus BMT alone in improving functional outcome and reducing death and dependency among patients with SSICH in a randomised controlled fashion. We further aim to contribute to the ongoing understanding of secondary neuronal damage involved in SSICH and their response to early hematoma evacuation, which leads to novel insights and possibly novel treatment modalities.

### 2.1 Explanation for the choice of comparator

Best medical treatment (a combination of medical blood pressure control, intensive care and prevention of secondary complications)[12], which is still considered the gold standard treatment of SSICH, acts as comparator in this randomized controlled trial. Therefore, we will be comparing ES with the standard of care (BMT) applied in all stroke centres and stroke units in Switzerland.

### 2.2 Benefits and Risks

This study carries relevant risk of death and disability for the included patients which is almost exclusively accountable to the underlying disease of SSICH, however if SSICH is left untreated, outcome may be even worse with a 30-day mortality up to 45% reaching to 54% at one year[32]. Since this study includes a surgical procedure, risks like bleeding, wound infections, surgical site infection, and complications related to anaesthesiologic procedures may occur. Furthermore, the procedure might, in extremely rare cases, lead to the death of the participant. Due to the location of SSICH, important brain structures might be damaged by accessing the hematoma cavity despite all efforts to conserve them.

Despite this, when compared to the potential damage inflicted by untreated SSICH, these complications are acceptable. If our hypothesis is correct, then the participants might benefit in form of better survival and functional outcome rates from the proposed intervention.

For further details, please refer to section 7.2 “Risk-Benefit Assessment”.

### 2.3 Justification of choice of the study population

The study population will include patients with spontaneous supratentorial intracerebral haemorrhage (SSICH). In accordance with our power analysis, we plan to enrol a total of 200 patients (100 patients in the intervention group, 100 patients in the control group). Vulnerable patients (i.e. not able to consent due to impaired consciousness) will be enrolled in this study. Since this study is partially based in an emergency setting, time is of vital importance. If unresponsive participants or participants incapable of judgement show sings that they are unwilling to participate in this study, then they will be excluded from this study. In case a patient is not able to consent, an independent physician will be asked to confirm that the interests of the patient are preserved.
For further details, please refer to sections 4.1 “Inclusion and Exclusion criteria, justification of study population” and 4.2 “Recruitment, screening and informed consent procedure”.

# 3 STUDY OBJECTIVES AND DESIGN

## 3.1 Hypothesis, primary and secondary objectives

The **Null hypothesis ($H_0$)** describes no difference in functional outcome rates of early minimally invasive image-guided endoscopic evacuation additionally to BMT for SSICH compared to BMT alone.
The **Alternative Hypothesis ($H_1$)** describes a difference (either improved or worsened [two-sided testing]) functional outcome rates of early minimally invasive image guided endoscopic evacuation additionally to BMT for SSICH compared to BMT alone.

The primary objective of this two, armed, open-labelled, single centre randomised controlled trial is to show superiority of early minimally invasive image-guided hematoma evacuation additionally to BMT compared to BMT alone in functional outcome rates at 6 months in patients with SSICH.

Secondary objectives are:

- to show superior survival rates of patients in the ES arm
- to study patient reported quality of life after treatment for SSICH at different time points (3 and 6 months after intervention)
- to study patient satisfaction with the outcome after treatment for SSICH at different time points (3 months and 6 months after intervention)
- to study cognitive outcome in patients after treatment for SSICH at different time points (3 months and 6 months after intervention)
- to study the morbidity rates of patients in both treatment arms
- to study the efficacy of ES in reducing the hematoma volume
- to study the change in focal neurological deficits exhibited by the patients after treatment.
- to study the temporal evolution of serum biomarkers (Neurofilament light-chain subunit (NfL), Glial Fibrillary Acidic Protein (GFAP), S100 calcium-binding protein B (S100B), IL-1α and β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70 and TNF-α) and their change in relation to early hematoma ES.

## 3.2 Primary and secondary outcomes

**Primary outcome:**

- Good functional outcome 6 months after treatment, measured by the mRS[33]. Good functional outcome is defined as a mRS of ≤3 points and will be assessed as binary outcome (yes/no, final value) at 6 months after treatment. The cut-off for good functional outcome is chosen at a mRS score of 3 points, as this reflects the turning point for a patient being able to live a partially self-dependent life or to live a severely disabled life. In this context, a mRS score of 3 points reflects the ability to walk unassisted and care for one's own bodily needs despite being moderately dependent on assistance, while a mRS score of 4 points describes a patient who is not able to walk anymore and needs assistance with all daily activities and thus marks a severe loss of patient autonomy.

**Secondary outcomes:**

- The mortality rate as measured by death of a participant (binary outcome (yes/no), final value) at 6 months after intervention.

- Patient reported outcome measures at 3 and 6 months after intervention, those being:
  - Patient and caregiver quality of life as assessed by the PROMIS® questionnaire (continuous variable, final value)
  - Patient Satisfaction as assessed by a short survey (Appendix 2) on a scale of 1-5 (continuous variable, final value)
  - Patient cognitive outcome as assessed by the MOCA® Test (continuous variable, final value)
- The morbidity rate, meaning occurrence of:
  - Ischemic stroke
  - Recurrent SSICH (defined as any radiologically confirmed increase in hematoma volume postoperative/follow-up that is either asymptomatic or associated with a worsening of the focal-neurological deficit by ≥4 points on the NIHSS and/or a decrease in consciousness by ≥2 points on the GCS)
  - Epileptic seizure
  - Surgical site infection (intervention group only)
  - Any need for open neurosurgical procedures
  - Infections (i.e. pneumonia, urinary tract infection)
  - Any other not defined complication that prolongs the hospital stay and/or leads to further treatment not envisaged in the original treatment plan.

The occurrence of any of these events 6 months after intervention (binary variable (occurrence/no occurrence), final value, proportion).

- The change of focal neurological deficit measured by the NIHSS, from baseline to 6 months after intervention as a continuous variable (continuous variable, change from baseline).
- The change of disability measured by the mRS, from baseline to 6 months after intervention as a continuous variable (change from baseline, so called mRS shift analysis).
- The time to intervention, defined as the period from symptom onset/last seen well to start of surgery (start surgical measures, i.e. positioning of patient) or start of medical treatment (admission of first treatment of BMT) (continuous variable, time to event).
- The temporal evolution of serum levels of the prespecified biomarkers as continuous variable from start to 6 months after intervention (continuous variable, change from baseline).
- The total time spent on the intensive care unit (ICU)/stroke unit as a continuous variable from the first admission to the ICU/stroke unit to discharge from ICU/stroke unit at 7 days/discharge after intervention (continuous variable, final value).
- The total time spent in intubation measured in minutes from the start of intubation to extubation as specified in the anesthesiology report at 7 days/discharge after intervention (continuous variable, final value).

Outcomes/Measurements applying to the intervention group only:

- The proportion of hematoma volume reduction rate (goal ≤15% of its initial volume). The hematoma volume will be measured on serial cranial computer tomography (cCT) and the difference between the volume of the cCT used for surgery and the cCT directly after surgery will be calculated. The hematoma volume on the pre-

operative cCT will be calculated using the (A * B * C)/2 method during screening and secondarily validated using the volumetric function of the navigation software[34] Hematoma on directly postoperative images will be calculated using the volumetric function of the navigation software. The hematoma volume reduction rate will be a binary variable (achieved reduction<15%/did not achieve reduction<15%, final value).

- The relative (percentage) reduction or increase of hematoma volume from baseline admission cCT to postoperative cCT directly after surgery as a continuous variable (final value).

Additionally, we will collect baseline data of all patients such as age, sex, prior medical history and medication out of the electronic patient file.

Baseline factors acting as confounders and/or effect modifiers potentially influencing the primary and secondary endpoints are: age, existing comorbidities and use of oral anticoagulants (OAC, including Vitamin K Antagonists [VKA], New Oral Anticoagulants [NOAC], Direct Oral Anticoagulants [DOAC]). Correction in the primary outcome analysis will be conducted for; ICH volume, presence of intraventricular haemorrhage, do-not-resuscitate orders, location of haemorrhage and centre.

## 3.3 Study design

This is a national single-centre, two-arm, open labelled randomised controlled trial within the stroke units and stroke centres of the swiss stroke registry in a superiority fashion.

### 3.3.1 Potential problems associated with the trial desing

As no blinding of the surgeons or the patients is possible, potential bias can occur in this trial. Furthermore, the Hawthorne effect could be observed since the patients are aware of which treatment arm they received.

### 3.3.2 Methods of minimising bias

We plan to enrol a large enough sample to eliminate random error. Randomisation in 1:1 fashion should reduce any selection bias of patients due to the treating physician's expectation and possible confounders are well distributed among the groups. Randomisation will be done using a CDMS (SecuTrial®) by a trained member of the study personnel. All study personnel will be trained and instructed for the study procedures. The primary outcome evaluation is performed by blinded study personnel via telephone interviews, the primary outcome analysis is performed by our blinded trial statistician not involved the treatment plan of the patients. Other forms of reducing bias will be the use of prospective CRF Forms, the use of validated and commonly applied scores (mRS/NIHSS/GCS/PROMIS®/MOCA) for the outcome assessments and blinded laboratory personnel assessing the biomarker results, as the individuals analysing the biomarkers will have no information regarding the treatment plan of the patient. Lastly, regular quality control will take place to ensure that all procedure standards are met. Explorative stratified sub-group analysis accounting for possible confounders mentioned in 3.2 will be conducted.

### 3.3.3 Randomisation

Each eligible patient will be allocated to either the early ES or the BMT group in a 1:1 fashion, stratified for centre and with variable block length. This process will take place 1) after enrolment criteria were met, 2) the patient gave his/her consent or, if the patient is not able to consent, an independent physician confirmed that the interests of the patient are preserved and 3) within 24 hours after symptom onset have passed. A trained individual of the study team will implement the randomisation procedure within SecuTrial®. The allocation sequence is programmed in our CDMS SecuTrial®, which generates random block randomization algorithms

of variable length for a randomization in a 1:1 fashion. Randomisation is stratified for centre. It will also include a standard minimisation algorithm which will ensure that the treatment groups are balanced. The allocation sequence will be programmed in the CDMS by the data manager and, if necessary, a study-independent statistician. Patient ID and study arm will be generated by the randomization program and disclosed to the treating team electronically. Thus, the treatment allocation is concealed to the study team until randomization is conducted.

### 3.3.4 Blinding and Unblinding procedures (Code Break)

Since this is a surgical trial, blinding is not possible for primary care providers. However, the laboratory personnel analyzing the biomarkers as well as the statistician will be blinded as these are not directly involved in the patient care or outcome assessment. Laboratory personnel will be blinded to the allocation as only encoded material will be processed where patients are identified by their patient ID, which gives no hint to the allocation. Likewise, the study statistician responsible for the primary analysis will receive a blinded copy of the data sets. Furthermore, we will conduct blinded outcome assessment at 3 and 6-month follow-up trough study personnel blinded to the allocation of the patient in form of a standardized telephone assessment (Appendix 4)[35]. This form of assessment is highly comparable with face-to-face evaluation, is short and easy to implement[36].
Since no patient or care provider blinding is possible (due to the study design including a surgical treatment arm), no emergency unblinding is necessary.

## 3.4 Study intervention

### 3.4.1 Intervention group

The intervention group will first receive BMT (as described below) upon admission and early minimally invasive image guided endoscopic hematoma evacuation as an add-on therapy to BMT. Surgery will be performed within 6-24 hours after SSICH symptom onset. A detailed standardized presentation of the technique and all critical steps of the surgery including imaging, setup of image guidance and endoscopic equipment, as well as the exact process of aspirating the clot will be provided to all involved surgeons by a proctored workshop. Additionally, we published a technical note describing the technique with a video illustrating the steps of the surgery[37]. All individual parts of the procedure are standard neurosurgical practice. Regular training will be conducted to maintain and improve adherence.
The initial cCT scan or in case surgery is delayed more than 6 hours after the initial scan, a second cCT scan (stability scan), will be used for presurgical planning of the neuro-navigation. The entry point and trajectory to the hematoma will be determined on a routine presurgical BrainLab® neuro-navigation planning station (BrainLab®, Munich, Germany) or an equivalent neuro-navigation planning station (e.g. Medtronic Stealth planning station, Fig. 1a). The planned trajectory represents the shortest approach from the surface of the brain to the hematoma, ideally in adequate distance from functional (eloquent) areas of the brain. Surgery will be performed in an emergency operating theatre or a hybrid operation theatre equipped with intraoperative CT (in hybrid OR), neuronavigation, and neuro-endoscopy. Neuro-navigation will be used to mark the skin incision and the exact location of the entry burr hole (Fig. 1b). The burr hole will be drilled and a transparent trocar (ViewSite Brain Access System®, VycorMedical™, U.S.A or equivalent) will be used as a working channel for the endoscope and the suction device (regular suction device, Artemis®, Apollo®, or other suction devices, Fig. 1c and d). The position and progress of the trocar towards the hematoma cavity will be monitored with neuro-navigation. The endoscope (LOTTA® system, Karl Storz Endoscopes, Germany; Minop®, BBraun, Tuttlingen, Germany or equivalent) will be inserted into the trocar and tracked using neuro-navigation. Using the pre-planned trajectory, the hematoma will be entered. Using continuous suction and irrigation, the hematoma will be aspirated and wash out (Fig. 1e). Under visual control using the endoscope, the hematoma cavity will be continuously monitored and active bleeding areas will be irrigated or coagulated using the endoscopic coagulation device and Floseal®. After the hematoma cavity has been cleared, a final inspection under endoscopic visualization will be carried out (Fig. 1f). Thereafter, the wound is closed in standard neurosurgical fashion[37]. Directly after surgery, while

still intubated and sedated, patients will be transferred for a cCT in order to assess adequate hematoma evacuation. In a hybrid OR setting, the cCT will be performed directly in the operating theatre. If hematoma removal is found insufficient by the treating neurosurgeon, the patient will return to the operating theatre for further hematoma aspiration (using the same approach). After surgery patient's will be monitored and cared for in an intensive care/stroke unit. The patient will then be treated, according to the current guidelines for BMT in SSICH[12] (systolic BP <140mmHg, ICU care, controlling seizures and glucose levels).

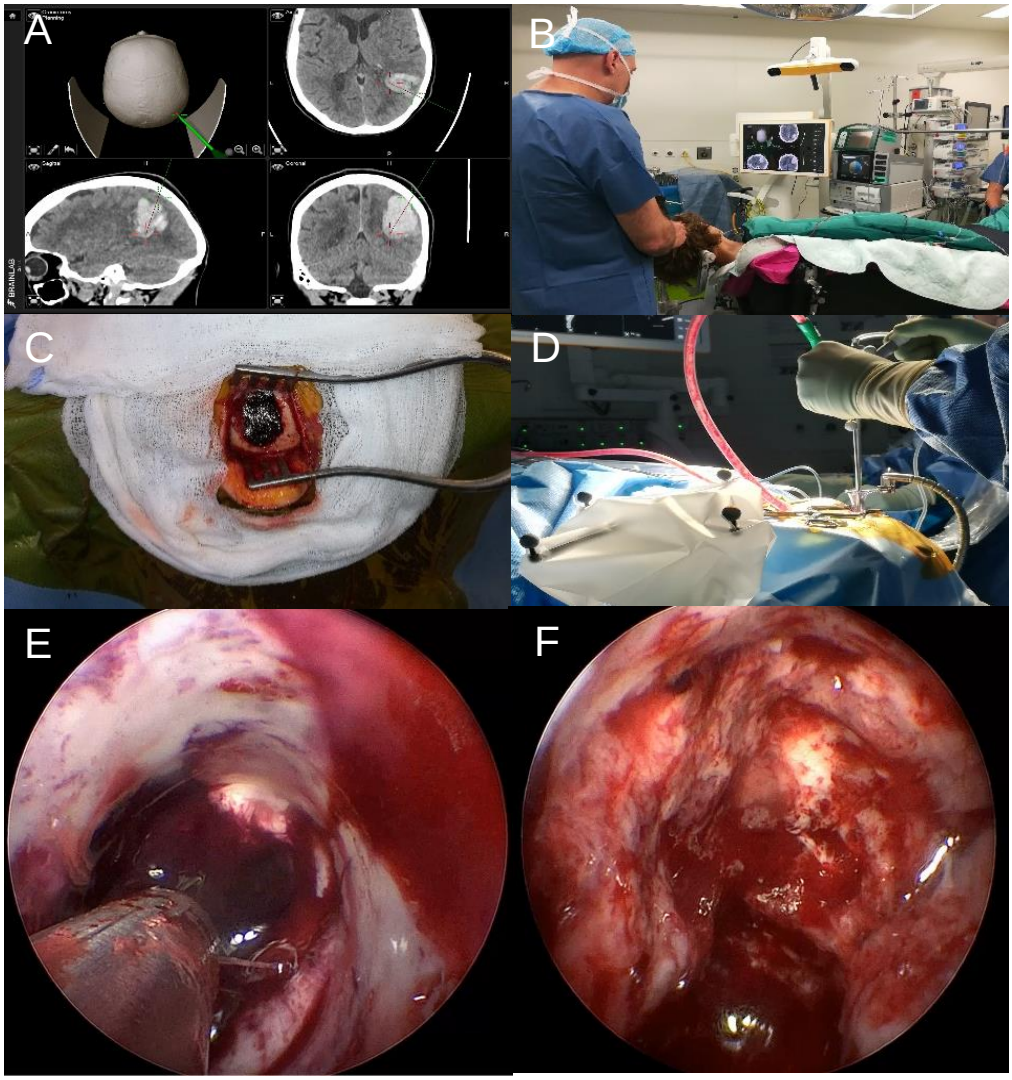


**Figure 1:** Steps of the surgery: A) Planning of the access; B) Confirming the entry point; C) The burr-hole access; D) Working with the suction device and the endoscope; E) suction of hematoma; F) completely evacuated hematoma cavity

### 3.4.2 Control group

The control group will receive the current gold standard treatment for SSICH according to the guidelines (BMT)[12]. This involves strict blood pressure control (SBP<140mmHg), if needed with intravenous or intraarterial blood pressure lowering agents, reversal of anticoagulation if applicable, intensive care surveillance and nursing on a ICU or stroke unit, control of seizures as well as glucose levels as needed and neurointensive monitoring if deemed necessary[12].

# 4 STUDY POPULATION AND STUDY PROCEDURES

## 4.1 Inclusion and exclusion criteria, justification of study population

The study population consists of patients with spontaneous supratentorial ICH (SSICH) defined by the following inclusion criteria upon screening. In accordance with our power analysis, we plan to enrol a total of 200 patients (100 patients in the intervention group, 100 patients in the control group). The recruitment procedure is described in 4.2 “recruitment, screening and informed consent procedure”.

**Inclusion criteria:**

- Patient age ≥ 18 and <85
- Spontaneous supratentorial intracerebral hemorrhage (SSICH), defined as the sudden occurrence of bleeding into the lobar parenchyma and/or into the basal ganglia and/or thalamus that may extend into the ventricles confirmed by imaging
- SSICH volume ≥20 mL <100 mL (measured using the formula $\frac{A * B * C}{2}$)
- Stable clot volume defined as absence of increase of >33% (as assessed using the formula (A * B * C)/2) of initial clot volume on follow-up imaging.
- A focal neurological deficit consisting of either
    - clinically relevant hemiparesis (≥4 motor points on the NIHSS for facial palsy, motoric upper and lower extremities combined)
    - clinically relevant motor or sensory aphasia (≥2 points on the NIHSS)
    - clinically relevant hemi-inattention (formerly neglect, 2 points on the NIHSS)
    - decreased level of consciousness (GCS≤13)
- Presenting GCS 5 – 15 (in intubated patients GCS assessment will be performed after Rutledge et al.[38] (Figure 2) or if impossible, the last pre-intubation GCS will be used)
- Endoscopic hematoma evacuation can be initiated within 24 hours after the patient was last seen well/symptom onset
- Informed consent of patient (only for patients able to consent)

**Exclusion criteria:**

- SSICH due to known or suspected (on CT-A scan) structural abnormality in the brain (e.g. vascular malformation, aneurysm, AVM, brain tumor) and/or brain trauma and/or hemorrhagic conversion of an ischemic infarction
- Multiple simultaneous intracranial hemorrhages (e.g. multifocal ICH, cSDH, aSDH, SAH)
- Infratentorial hemorrhage or midbrain extension/involvement of the hemorrhage
- Coagulation disorder (including anticoagulation) with an INR of >1.5 which cannot be pharmacologically reverted until the planned time of evacuation
- Positive history of current pregnancy or breast-feeding in premenopausal women
- Relevant disability prior to SSICH (mRS >2)

- Any comorbid disease or condition expected to compromise survival or ability to complete follow-up assessments through 180 days (e.g. bilateral fixed dilated pupils)

| GCS Motor Score | GCS Eye Score | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| 1 | 1 | 1 | 1 | 2 |
| 2 | 1 | 1 | 1 | 1 |
| 3 | 1 | 1 | 1 | 2 |
| 4 | 2 | 1 | 2 | 2 |
| 5 | 3 | 2 | 3 | 3 |
| 6 | 4 | 4 | 4 | 5 |



**Figure 2:** GCS score in intubated patients after Rutledge et al.

### 4.1.1 Rationale for the inclusion of vulnerable patients

Concerning vulnerable patients, which we might have to include in this study due to the nature of SSICH being a medical emergency, the following applies:
These participants can be included in this study according to the above-mentioned inclusion and exclusion criteria. Since this study is based on an emergency setting, time is of vital importance. For participants not able to consent, an independent physician (not involved with the study) will be consulted to confirm that the interest of the patient are preserved by participating in this study.. As soon as the participants are able to consent again, they will be retrospectively informed according to the process described in 4.2 and can decide upon further participation in this study. Likewise, in the case that an independent physician was asked to confirm that the interest of the patient were preserved and the patient remains unable to consent, a legal guardian or a relative will be informed and can decide upon further participation. Information process will be the same for the legal guardian or relatives as described in 4.2 “Recruitment, screening and informed consent procedure”.
If unresponsive participants or participants incapable of judgement show any sign that they are unwilling to participate in this study, they will be excluded from this study.

## 4.2 Recruitment, screening and informed consent procedure

The recruitment will take place at either the emergency department or the Stroke Centre of the University Hospital Basel. Participants will be recruited by a member of the study team in the form of consecutive ongoing enrolment in daily practice as well as recruitment through a referring family physicians or peripheral hospitals to the emergency department in daily practice.

Initial screening according to the eligibility criteria pre-specified above will be performed upon admission. Some of the inclusion measurements are used in daily practice (e.g. NIHSS, GCS score evaluation, admission-imaging scan) and must be applied before informed consent is given as this is necessary to determine an underlying disease and assess study eligibility of the respective participant. These measurements serve only for the standard clinical examination used in daily emergency room practice and for testing inclusion criteria for the present study. A specific clinical examination will be performed after informed consent by the patient, a legal guardian or an independent physician was given. The investigators, a member of the study team or the attending neurosurgeon in case none of the previously named persons is available, will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that the participant may withdraw from the study at any time and that withdrawal of consent will not affect the participant’s subsequent medical assistance and treatment.
The participants will be informed that the participants medical records may be examined by authorised individuals other than their treating physician.

All participants will be provided with a participant information sheet and a consent form describing the study and providing sufficient information for the participants to make an informed decision about the participation in the study. Enough time needs to be given to the participant to decide whether to participate or not, even in the setting of an emergency. However, since rapid evacuation is a vital asset of this study, we will limit this timeframe depending of the acuteness of the individual situation. The formal consent of a participant using the approved consent form, will be obtained before the participant is submitted to any study procedure aside the already mentioned necessary routine examinations of daily practice at our institution.

The consent form will be signed and dated by the investigators, a member of the study team or the attending neurosurgeon at the same time as the participants. A copy of the signed informed consent will be given to the study participants. The consent form will be retained as part of the study records and the informed consent process will be documented in the electronic patient file. All further study procedures will be commenced after the participants consented to participate in this study.

In case the patient is unable to consent due to impaired consciousness (i.e. due to the hematoma), an independent physician (who is not participating in the trial) will be asked to confirm whether the interests of the patient are preserved in the study or not. As soon as the patient regains the ability to consent, he will be retrospectively informed about the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort the study may entail. The patient will then retrospectively be asked to provide informed consent to further participate in the study. In case a patient remains unable to consent or becomes permanently unable to consent, a legal guardian or relative will be informed about the study and will be asked to provide retrospective consent as proxy for the patient.

There will be no compensation for the participants in this study.

### 4.3 Study procedures

The planned overall study duration including recruitment period and follow-up for each participant is limited to 6 months after first admission to the hospital ending with visit 6. The study schedule consists of 6 study visits (V1-V6), which follow the regular in- and outpatient visit schedule in patients with SSICH (clinical routine), including the following procedures with the respective time period mentioned. All data collection for this study will begin after informed consent was given.

All imaging studies, study visits, the neurological examinations (GCS, NIHSS, MOCA) and the clinical examination are part of the daily clinical practice routine for SSICH, while the study specific examinations will consist of mRS evaluation, assessing the quality of life, patient satisfaction (Appendix 2) and acquiring blood samples. Blood sample will consist of collecting an aliquot of approximately 2 x 5 ml blood serum at each indicated visit. The additional blood samples for the study will be taken, if possible, during daily routine while the patient will be in the hospital (V1 & V3). For the Follow-Up visit (V6), an additional puncture will be necessary to obtain the blood samples. The PROMs Quality of Life and patient satisfaction will be assessed additionally by providing a paper-form questionnaire to the patients and their relatives. If patients are not able to complete the questionnaire, relatives will be asked to provide data.

Collected data will be preserved in encoded form to be used in future studies, patients will be informed about the encoded retention of data and given a separate informed consent. All blood samples will be discarded after analysis and will not be used for future studies.

We designed this trial together with affected patients, caregivers and patient organization representatives (EUPATI-CH) in the scope of PPI as pragmatic as possible, meaning that all visits and procedures were meticulously evaluated. With this we are convinced, that patients will remain in the trial as it is only little, if any at all, expenditure more than what would be the standard of care. From patients that drop out, we will analyse the data until the point of drop-out (last visit present) in an intention-to-treat fashion. Likewise, if any deviation from intervention protocol should occur, the results will be analysed as intention-to-treat. Outcome data collected for drop-

outs will consist of all study data collected to the last visit.

#### 4.3.1 V1: Study inclusion, baseline assessment and treatment: up to 24 hours after symptom onset

Study eligibility criteria are confirmed and written informed consent is obtained from the patient. After informed consent was given, randomisation to the intervention or the control group will be conducted by a member of the study team through the CDMS SecuTrial®.

A clinical examination is performed including vital signs (resting blood pressure and heart rate, height, and weight), NIHSS, GCS, and mRS. Blood sampling for biomarkers will be obtained. Patient baseline data is acquired.

In the intervention group a study baseline CT scan (stability scan) is obtained 6 hours after the admission scan if surgical hematoma evacuation is started >6 hours after the admission scan. Endoscopic hematoma evacuation must be initiated within 24 hours according to the procedure described in 3.4.1 “Intervention group”. Surgical Baseline data is acquired.

Patients randomised to the control group will receive standard medical care according to the current guidelines as described in 3.4.2 “control group”.

#### 4.3.2 V2: Day 1 assessment: 24 ± 6 hours after start of treatment

Clinical examination is performed as detailed for V1 except for body weight and height. All patients (control and intervention group) will receive a CT scan to assess the evolution of the hematoma volume (recurrent haemorrhage or postoperative hematoma reduction in case of the intervention group).

#### 4.3.3 V3: Day 3 assessment: 72 ± 12 hours after treatment

Clinical examination is performed as detailed for V1 except for body weight and height. Blood sampling for biomarkers will be obtained.

#### 4.3.4 V4: Day 7 assessment: 7±1 days after treatment or at hospital discharge

Clinical examination is performed as detailed for V1 except for body weight and height.

#### 4.3.5 V5: Month 3 assessment: 3 months ± 14 days after treatment

Clinical examination is performed as detailed for V1 except for body weight and height and mRS. A MOCA Test is performed. Additionally, a questionnaire regarding patient satisfaction will be filled-out whenever possible through a relative or otherwise together with a member of the study team and patients and their relatives will be asked to fill out a questionnaire together with a member of the study team regarding quality of life. Additionally, patients are telephonically contacted by a study-team member (blinded to the allocation) to assess the mRS according to the form in Appendix 4.

#### 4.3.6 V6: Month 6 assessment: 6 months ± 7 weeks after treatment

Clinical examination is performed as detailed for V1 except for body weight and height and mRS. Blood sampling for biomarkers will be obtained. A cCT will be performed for all patients (control and intervention group) to evaluate possible rebleeding, hematoma resorption and the shape of the hematoma cavity. A MOCA Test is performed. Additionally, a questionnaire regarding patient satisfaction will be filled-out whenever possible through a relative or otherwise together with a member of the study team and patients and their relatives will be asked to fill out a questionnaire together with a member of the study team regarding the quality of life. Additionally, patients are telephonically contacted by a study-team member (blinded to the allocation) to assess the mRS according to the form in Appendix 4.

| **Study period** | **Treatment Period** | | | | **Follow-Up** | |
|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** |

| Time (hour, day, week) | <24 hours of symptom onset | 24 hours after treatment onset | 72 hours after treatment onset | 7 days after treatment onset | 3 months after treatment onset | 6 months after treatment onset |
|---|---|---|---|---|---|---|
| **Eligibility** | X | | | | | |
| **Study consent** | X | | | | | |
| **Asses vital signs (BP,HR,height)** | X | X | X | X | X | X |
| **Acquire NIHSS score** | X | X | X | X | X | X |
| **Acquire GCS score** | X | X | X | X | X | X |
| **Acquire mRS score** | X | X | X | X | X** | X** |
| **Acquire blood samples (NfL, GFAP, S100B, IL)** | X | | X | | | X |
| **Conduct Stability CT scan*** | X | | | | | |
| **Conduct directly postoperative CT scan†** | | X | | | | |
| **Conduct postinterventional CT scan‡** | | X | | | | X |
| **Quality of Life** | | | | | X | X |
| **Patient Satisfaction** | | | | | X | X |
| **Cognition** | | | | | X | X |

**intervention group only; only required if surgery cannot be initiated within 6 hours after the first cCT scan*
*†intervention group only; the directly postoperative cCT is conducted directly after surgery to assess hematoma evacuation and differentiate potential recurrent hemorrhage*
*‡all patients; the postinterventional cCT scan is conducted 24 hours and 6 months after the treatment start to assess potential recurrent/enlarged hematoma and defect size*
***blinded telephone assessment*

### 4.3.7 Additional material, storage, cocomitant care as well as methods and tests used for sample collection and analysis

The imaging analysis, the additional materials and biomarkers used for this study and the procedure to reverse oral anticoagulation are explained in the following section.

#### 4.3.7.1 Imaging analysis

In this study we will conduct cCT scans:

- At admission (clinical routine, both groups)
- 6 hours after the admission scan if surgery is started >6 hours after the admission scan (clinical routine stability scan, intervention group only)
- Directly postoperative (clinical routine in this procedure, intra-operative or directly after surgery, intervention group only)
- At the first day after start of treatment (clinical routine in SSICH, both groups)
- At the visit after 6 months (clinical routine, both groups)

The cCT scans serve to assess the hematoma volume and to provide information about the hematoma reduction rate or increase in hematoma volume and possible rebleeding after surgery.

The pre-operative hematoma will be assessed with the $\frac{A*B*C}{2}$ formula for screening purposes due to its fast and broad applicability in emergency room settings and will then, in a second step, be validated with the neuronavigation software later on[34]. To analyse the often irregular-shaped and small postoperative hematoma volume (cCT scan directly after surgery (intervention)/ 24 hours after treatment onset(control)), the hematoma will be segmented, and its volume calculated manually on a BrainLab® planning station (or equivalent) by a trained member of the study team. Both hematoma volumes as calculated on the BrainLab® planning station (or equivalent) from cCTs at admission and directly postoperative/after 24 hours after treatment onset will be compared to assess the evolution of the hematoma volume. This increases the comparability as the $\frac{A*B*C}{2}$ formula struggles with small irregular shaped hematoma volumes.

#### 4.3.7.2 Questionnaires

The questionnaires used in this study are the Montreal Cognitive Assessment, the PROMIS Scale v1.2 Global Health, and a questionnaire for patient satisfaction derived in our Patient and Public involvement meetings (Appendix 2 and 3). Both, MOCA and PROMIS are well established and validated questionnaires to assess cognition and quality of life respectively and were deemed the most effective and patient friendly by our PPI representatives[39, 40]. Further, the timepoint of assessment was discussed and decided upon with the PPI representatives. The questionnaire regarding patient satisfaction was created together with the PPI representatives by first collecting the most important aspects of patient satisfaction, which were then in a next step condensed to the 5 most important questions. This questionnaire is not validated in clinical trials, but a reflection of important PROMs and a product of intense collaboration with PPIs.

#### 4.3.7.3 Biomarker analysis

Blood sampling will consist of collecting an aliquot of approximately 2 x 5 ml blood serum at the visits as indicated above. The additional blood samples for the study will be taken, if possible, during daily routine while the patient will be in the hospital (V1 & 3). For the Follow-Up visit (V6), an additional puncture will be necessary to obtain the blood samples. The blood samples will be labelled with the patient study ID and sent to the laboratory for processing. Afterwards they will be sent to the laboratories of Prof. Dr. Jens Kuhle and Prof. Dr. Raphael Guzman at the Department of Biomedicine, University Hospital Basel for biomarker analysis. The biomarkers assessed in this study are mentioned in 3.1 “Hypothesis and primary objective”. The biomarkers analyzed are validated and can be used to monitor brain injury in SSICH[41-43]. NfL are highly specific structural proteins of neurons released by the disruption of axonal membranes and associated with the severity, activity, and treatment response in neuronal injury[44-46]. S100B is a non-specific marker for neuronal injury and the disruption of the blood-brain barrier which correlates with the infarction volume and clinical outcome in ischemic stroke and SSICH[47, 48]. GFAP is an intermediate filament protein expressed by astrocytes. GFAP levels are specifically higher among patients with SSICH than among patients with ischemic stroke when measured early after symptom onset[49].

We will use a novel assay to measure NfL which was developed in our Laboratory of Clinical

Neuroimmunology (Prof. Dr. med. Jens Kuhle). The test is based on single-molecule array (SIMOA) technology for digital immunoassays, using the capture monoclonal antibody (mAB) 47:3, and the biotinylated detector mAB 2:1 from UmanDiagnostics (Umeå, Sweden), transferred onto the SIMOA platform. SIMOA has been shown to be more sensitive than conventional ELISA or ECL based assays to quantify NfL in serum[50].

S100B and GFAP will be measured in the laboratory of Prof. Dr. med. Guzman (S100B) and Prof. Dr. med. Kuhlen (GFAP) using a standardized immunoassay from frozen plasma samples via electrochemiluminescence (Roche Cobas Elecsys, Roche, Switzerland).

Interleukins (IL-1α and β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, TNF-alpha) will be measured in the laboratory of Prof. Dr. med. Guzman with electrochemiluminescent (ECL) immunosorbent assays (Meso Scale Discovery, Maryland 20877, U.S.A.). This platform allows for testing of multiple biomarkers in limited sample volumes.

The blood samples and aliquots are stored in an appropriate cooling system in a restricted area only accessible to the authorised personnel and handled under appropriate conditions.

#### 4.3.7.4 Concomitant care

All additional treatment deemed necessary by the treating physician to address potential complications of SSICH are allowed. This includes antibiotics for any kind of infection (pulmonary, wound infection), antipsychotics in case of delirium, pain medication when needed, gastric acid inhibitors as addendum to pain medication, reversal of anticoagulation according to the guidelines but also re-surgery or secondary surgery if deemed necessary. All occurrences of such treatment will be documented within the clinical research file (CRF)/electronic CRF (eCRF).

#### 4.3.7.5 Medical reversal of oral anticoagulation

Oral anticoagulation will be pharmacologically reverted according to the guidelines at the University Hospital Basel and the current guidelines for ICH treatment.

- Heparin and low molecular weight heparin will be reverted with protamin.
- Vitamin K antagonists will be reverted with 4-factor prothrombin complex concentrate and/or vitamin K.
- Rivaroxaban, Apixaban, Edoxaban and Fondoparinoux (DOACS) will be reverted with 4-factor prothrombin complex concentrate.
- Dabigatran (DOAC) will be reverted with Idarucizumab.

Based on our clinics standard operation procedures, after surgery anticoagulation is restarted if no new bleeding is demonstrated in the postoperative CT scan at the 3$^{rd}$ postoperative day. DOACS and VKA will be resumed on the 3$^{rd}$ or 4$^{th}$ postoperative day (depending on the patients GFR, if the GFR is >30 we restart on the 2$^{nd}$ day after surgery or if the GFR is <30 we restart on the 3$^{rd}$ day after surgery) if the patient is clinically stable and no new bleeding is seen on the postoperative CT scan.

Antiplatelet drugs (Aspirin/Clopidogrel/Prasugrel or Ticagrelor) will be handled as follows:

- Aspirin will be discontinued if used as primary prophylaxis and reinstated at the 3$^{rd}$ postoperative day. If Aspirin is used as secondary prophylaxis, no discontinuation is required.
- Clopidogrel will be discontinued before surgery and pharmacologically reverted if necessary with platelet concentrate or Desmopressin and then reinstated at the 3$^{rd}$ postoperative day.
- Prasugrel will be discontinued before surgery and pharmacologically reverted if necessary with platelet concentrate and then reinstated at the 3$^{rd}$ postoperative day.
- Ticagrelor will be discontinued before surgery and then reinstated at the 3$^{rd}$ postoperative day.

#### 4.3.8 Expected biases to the study and measures taken to reduce them

Expected biases are mentioned under 3.3.2 “Methods of minimising bias”. All involved personnel will be trained for the procedures and conduct of the protocol, its interventions and visits.

### 4.4 Withdrawal and discontinuation

Participants, their respective legal guardian or next of kin in case the patient remains unable to consent, can withdraw informed consent for this study whenever they want. They are withdrawn from this study if they do not meet the inclusion criteria mentioned under 4.1 “Inclusion criteria”. If patients of childbearing age get pregnant during the course of this study, they will be converted to MRI imaging instead of CT imaging but will not be ruled out.

The data of participants withdrawing prematurely (e.g. withdrawal of informed consent) is vital for the validity of the results of this trial. Currently, no sufficiently powered studies have been published on the potential benefits of ES in SSICH and it will be crucial to analyse every last patient so that the conclusion drawn from this trial is based on best possible evidence from our sample. With that, we can guarantee that future patients receive treatment based on the best possible data. The data and biological material of patients withdrawing prematurely will remain coded and used for the final outcome analysis according to the intention-to-treat principle. Participants lost that way will be marked as lost to follow-up.

## 5 STATISTICS AND METHODOLOGY

### 5.1. Statistical analysis plan and sample size calculation

The involved and responsible statistician is:

Dr. Gilles Dutilh
Senior Statistician
Department Klinische Forschung
University Hospital Basel
Spitalstrasse 12
CH-4031 Basel

#### 5.1.1 Hypothesis

The **Null hypothesis ($H_0$)** describes no difference in functional outcome rates of early minimally invasive image-guided endoscopic evacuation additionally to BMT for SSICH compared to BMT alone.
The **Alternative Hypothesis ($H_1$)** describes a difference (either improved or worsened [two-sided testing]) functional outcome rates of early minimally invasive image guided endoscopic evacuation additionally to BMT for SSICH compared to BMT alone.

#### 5.1.2 Sample size estiamation

##### 5.1.2.1 Derivation of assumptions for analysis of power

The power analysis is based upon the results from our own systematic review with meta-analysis, which assessed the effects of endoscopic surgery on functional outcome and mortality rates compared to BMT and CC in existing RCTs. A total of 591 patients with 312 in the control group (216 CC and 96 BMT) and 279 in the treatment group (ES) were analysed.

Favourable outcome, defined as mRS 0-3, Barthel Index ≥70, Glasgow outcome scale 4-5 or an Activity of Daily Living score 1-3, 6 months after treatment was assessed as primary outcome. Favourable outcome of ES compared to BMT could be assessed in 2 studies yielding 23/64 for ES and 18/92 for BMT. This results in a cumulative Relative Risk (RR) of having a favourable outcome of 1.93 [1.12;3.33] (p=0.02) in favour for ES compared to BMT with insignificant heterogeneity (0%, p=0.92). However, we also looked at the sparse literature regarding ES in

SSICH treatment.

Yao et al. conducted the first review with meta-analysis on RCTs and cohort studies clarifying the therapeutic effects of ES in SSICH compared to a combined control of CC and BMT[24]. The primary outcome was all cause mortality while secondary outcomes were poor functional outcome (mRS 4-6, Glasgow Outcome Scale 1-3 or corresponding clinical presentation) among others.

Poor functional outcome was observed in 197/348 cases in ES and 271/373 in the control resulting in a RR of having poor outcome of 0.78 [0.70;0.87] ($p<0.001$) with an insignificant heterogeneity (0%, $p=0.60$) in favour of ES. The reciprocal value of this would correspond to a RR of having a favourable outcome of 1.28 in favour of ES.

We also included a work by Sondag et al., who compared all surgical treatment (craniotomy, craniopuncture, stereotactic aspiration, MISTIE and ES) to BMT in RCTs regarding favourable functional outcome and death[19]. Favourable functional outcome was defined as good outcome, described as mRS 0-3, Glasgow Outcome Scale 4 and 5, BI ≥60 and an extended Glasgow Outcome scale of 5-8 points or, if none of this scores was reported, according to the definition of favourable outcome defined by the authors of the included studies. If available, the outcome assessed at 6-month follow-up was assessed, if not available the 3- or 12-month follow-up was assessed together with the 6-month outcome for the meta-analysis. A subgroup analysis comparing MIS (stereotactic aspiration, MISTIE and ES) versus BMT alone showed an RR of 1.47 to achieve favourable outcome in favour of MIS (MIS events: 575/1056, BMT events: 378/989).

When combined, the RRs of our, Yao et al.'s and Sondag et al.'s work results in a RR of 1.56 or roughly **RR of 1.6**. Additionally, we analysed the favourable outcome rates (mRS 0-3 after 3 months) of BMT from 2020-2022 from the swiss stroke registry and found, that the rate of favourable outcome of the last two years was approximately 65%. However, all patients, even those with minimal bleeding and minimal impairment alongside patients with bleedings of >100 mL and very poor outcome, are included in the swiss stroke registry, potentially diluting the functional outcome in favour of good outcomes rather than worse outcomes. In consideration of that aspect, a plausible assumption for the proportion of positive outcomes in the control arm is 50% (0.5).

#### 5.1.2.2 Bayesian Sequential analysis

Based on the to-date available literature[19, 23, 24], our own meta-analysis and the data of 2020-2022 derived from the Swiss stroke registry we assume a favorable outcome around 50% for patients treated with BMT, while we anticipate a positive risk ratio of 1.6 towards favorable outcome for ES compared to BMT. Based on these assumptions, we explored sample sizes needed for achieving "compelling evidence", as described by Schönbrodt & Wagenmakers[51]. Compelling evidence is defined as finding a Bayes Factor (BF) that points with a certain strength at favoring the null hypothesis or the alternative hypothesis i.e. hypothetical experiments, expressing how much more likely the data were generated from a model where both study arms have the same probability of a positive outcome, compared to a model where there is a difference in the probability of a positive outcome. Simply put, it essentially measures the evidence between the two hypothesis. The BF expresses how likely the data originates from one hypothesis vs. the other (For an introduction into the interpretation of Bayes Factors as indices of evidence, please refer to Jarosz & Wiley[52]). Often used verbal interpretations are "substantial" or "positive" for BFs around 10, and "strong" to "very strong" for BFs over 100
Of all the strengths when using BF as opposed to p-values for inference, two stand out:

- A BF may quantify evidence against or in favor of the null-hypothesis.
- BFs may be monitored continuously as the data is generated and collected without the need of correction schemes as needed in a classical null-hypothesis significance testing procedures.

Both strengths described above are exploited in the sample size analysis performed here: we peak at the data at any moment to see whether we have enough evidence, to allow to decide in favor of either the alternative, or the null hypothesis. Note that it does not make sense to additionally calculate a p-value at the finally achieved n. Such a p-value will, by nature, be biased towards “significance”.

#### 5.1.2.3 Bayesian A/B Test

We calculated the BF using the method presented by Gronau et al.[53] as implemented in the R package `ab_test`. For these first exploratory simulations, we used the default parameter priors supplied by the R package. The Bayes Factor calculated in this way, quantifies how much more likely the data originate from a “truth” where the probability in both arms is equal, vs a truth where both probabilities are different.

#### 5.1.2.4 Stopping rule

The evidence is regularly calculated until either a pre-set level of evidence threshold, is achieved in favour of either of the hypotheses, or when the maximum sample size is reached. For the current study, we chose to set the maximum total sample size at 200, and the evidence threshold at a Bayes Factor of 10, which is generally considered as strong evidence. In the simulations below, however, we show the expected evidence up to 170 patients per arm.

#### 5.1.2.5 Sample size analysis results

Figure 3 shows the results of a simulation, in which for various proportions of positive outcome for BMT (0.4, 0.5, 0.6, different panels) and various assumed positive risk ratios in favor of ES over BMT (1.2, 1.3, 1.4, 1.5, 1.6, differently colored lines), a large number of hypothetical trials were simulated, collecting up to 170 observations per study arm. The lines indicate the proportion of such simulated trials that reached the BF threshold of 10 in favor of either the null or the alternative hypothesis at each sample size.
Comparing the panels, one can see that, the higher the probability in the control arm, the quicker the percentage of trials that achieved the BF-threshold rises. In other words: the higher the baseline proportion of good outcome in the BMT arm, the lower the expected sample size.
Comparing differently colored lines within panels, one can see that with higher risk ratios, the expected n decreases.
Systematic reviews as well as data analyzed from the Swiss Stoke Registry over the last 2 years suggests that a plausible assumption for the proportion of positive outcomes in the control arm is 50% (0.5) (Figure 2b). The pink line indicates the anticipated risk ratio of 1.6 in favor of ES. Based on our calculations after collecting data of 70 patients per study arm, about 90% of trials will have achieved a BF of 10, being the “Bayesian equivalent” to a power of 90%. In addition, 50% of the simulated trials already achieve this level of evidence after the 40th hypothetical patient (per arm). Further, based on these calculation, it is extremely unlikely that the trial would take more than 130 patients per arm. Based on these results we assume that we will likely be able to stop collecting data before reaching **75 patients per arm (total of 150 patients) to reach a BF of 10**.

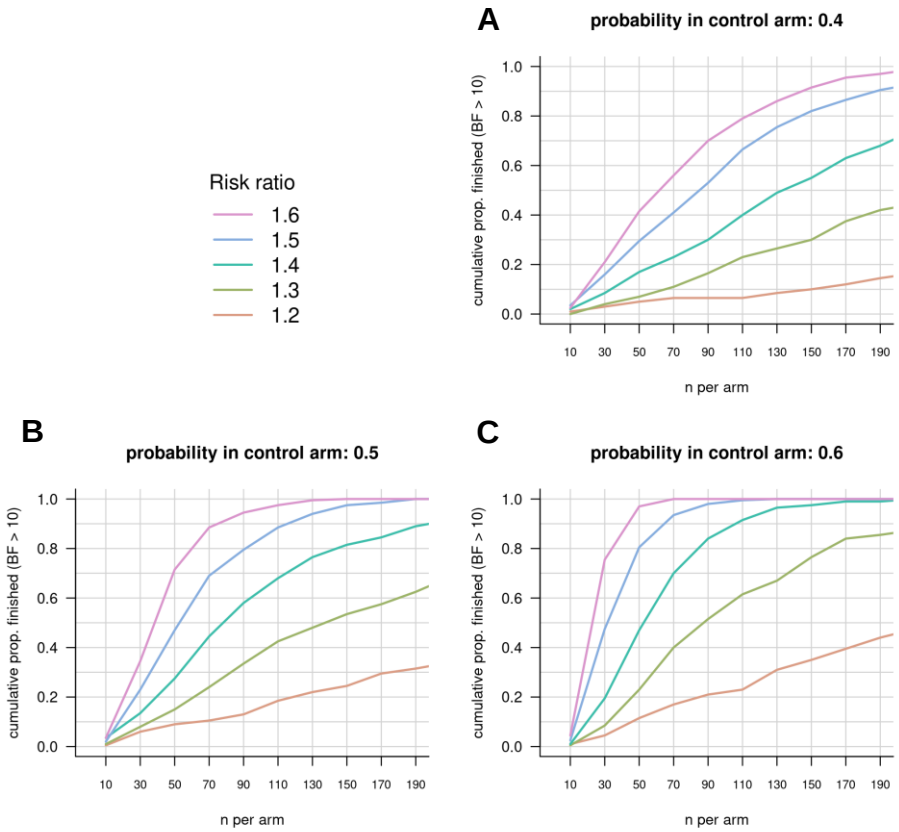


**Figure 3:** Results of the simulation for SSE at different probabilities and Risk Ratios. A) For a probability of favorable outcome in BMT of 40%; B) for a probability of 50% and C) for a probability of 60%

#### 5.1.2.6 Conclusion of sample size estimation

Based on these results we assume that we will likely be able to stop collecting data before reaching **75 patients per arm (total of 150 patients) to reach a BF of 10**. We aim to collect a minimum of 40 patients per study arm. From that point on, we will perform the abovementioned BF test after every 40 new patients (about 20 per arm, exact number subject to randomization). The evidence is regularly calculated until either a pre-set level of evidence threshold is achieved in favor of either of the hypotheses (BF of 10 or 1/10 respectively, considered as strong evidence), or when the maximum sample size is reached. For the current study, we chose to set the maximum total sample size at 200 (as deemed sufficient based on a frequentist sample size estimation for the same assumptions). If this threshold is not reached, a new cost-benefit analysis of continuing to collect data will be performed. However, as described above, this is highly unlikely. After data collection is deemed completed and follow-ups at 6 months are complete, all secondary and sensitivity analyses will be performed. For the data collected up to 40 per arm, a p-value may be calculated (sensitivity analysis) and used for a classical hypothesis test.

### 5.1.3 Planned statistical methods

The primary analyses are performed following the intention-to-treat principle. Additionally, per-protocol analysis will be performed for sensitivity analysis. We study the ratio of positive outcomes in both study arms by performing a Bayesian A/B test after every 40 additional patients, using the method described by Gronau et al.[53]. Data collection (and the periodical analysis of these data) will continue until a Bayes Factor of 10 (or 1/10) is achieved. The odds

ratio and its 95% credible interval will be reported. Covariates ICH volume, presence of intraventricular bleeding, do-not-resuscitate orders, location of hematoma and centre will be included in a Bayesian logistic regression model
Secondary analysis is performed on the secondary outcomes. For continuous variables, a Bayesian regression with normal error term is used, for time-to-event outcomes Bayesian cox-regression is used, and for binary variables Bayesian logistic regression is used. Statistical analysis is performed with R version 4.2.1 or higher (R core Team, 2022)[54]. A complete mRS shift analysis will be calculated.

In parallel to the Bayesian primary analysis, we will perform a frequentist test of proportions comparing study arm for the first 100 patients per study arm. In the ES arm, a number of explorative analyses are performed, studying the relation between hematoma location, hematoma size, and treatment outcome. In particular, for parameters measured over time, figures are created illustrating the development over time at both the patient level and group level.

### 5.1.4 Interim analysis

As described under “5.1.2.6. Conclusion of sample size estimation”, the data may be inspected any time, but we plan to perform the primary analyses after every 40 patients (20 per arm), and will stop data collection if the BF, in favor of either the null, or the alternative hypothesis is over 10.

### 5.1.5 Stratification for outcome analysis

Explorative stratified subgroup analysis for potential confounders (ICH volume, presence of intraventricular bleeding, do-not-resuscitate orders, location of hematoma and centre) will be conducted using Bayesian logistic regression models. An analyses of gender differences is planned.

### 5.1.6 Deviations from statistical analysis plan

If substantial deviations of the analysis as outlined in these sections are needed for whatever reason, the protocol will be amended. All deviations of the analysis from the protocol or from the detailed analysis plan will be listed and justified in a separate section of the final statistical report.

## 5.2. Handling of missing data and drop-outs

If missing data occurs, we will try to obtain the respective data needed from either the participant, their next of kin or their treating physician. If acquiring the respective missing data is not possible, we will mark the data as missing. In case of missing laboratory values, we will aim to achieve them, if this proves to be impossible, the data will be marked as missing. In case more than 5% of patients show missing data for the primary outcome across arms, multiple imputation is performed.

# 6 REGULATORY ASPECTS AND SAFETY

## 6.1 Local regulations / Declaration of Helsinki

This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements.

## 6.2 (Serious) Adverse Events and notification of safety and protective measures

A Serious Adverse Event (SAE) (ClinO, Art. 63) is any untoward medical occurrence that

- Results in death or is life-threatening,
- Requires in-patient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity, or
- Causes a congenital anomaly or birth defect

Both Investigator and Sponsor-Investigator make a causality assessment of the event to the trial intervention, (see table below based on the terms given in ICH E2A guidelines). Any event assessed as possibly, probably or definitely related is classified as related to the trial intervention.

| **Relationship** | **Description** |
|---|---|
| Definitely | Temporal relationship<br>Improvement after dechallenge*<br>Recurrence after rechallenge<br>(or other proof of drug cause) |
| Probably | Temporal relationship<br>Improvement after dechallenge<br>No other cause evident |
| Possibly | Temporal relationship<br>Other cause possible |
| Unlikely | Any assessable reaction that does not fulfil the above conditions |
| Not related | Causal relationship can be ruled out |
| *Improvement after dechallenge only taken into consideration, if applicable to reaction | |

Both Investigator and Sponsor-Investigator make a severity assessment of the event as mild, moderate or severe. Mild means the complication is tolerable, moderate means it interferes with daily activities and severe means it renders daily activities impossible.

**Reporting of SAEs** (see ClinO, Art. 63)

All SAEs are documented and reported immediately (within a maximum of 24 hours) to the Sponsor-Investigator of the study.

If it cannot be excluded that the SAE occurring in Switzerland is attributable to the intervention under investigation, the Investigator reports it to the Ethics Committee via BASEC within 15 days.

If the SAE occurs at one of the study sites, the coordinating Investigator reports the events to the Ethics Committee concerned, within 15 days.

Exemptions from expedited reporting may be possible if the SAE is either a clear result of the underlying disease or well-known. These are defined below:

- Death
- Haemorrhagic transformation to an ischemic stroke
- Recurrent ICH
- Epileptic seizure
- Infection of any kind (i.e. surgical site infection, pneumonia, UTI etc.)
- Persistent focal neurological impairment

**Follow up of (Serious) Adverse Events**

These patients will be followed according to the normal procedures of follow up in case of (S)AE

within our clinic. These patients are followed periodically in an ambulatory setting until the (S)AE stabilizes or resolves.

**Notification of safety and protective measures** (see ClinO, Art 62, b)

If immediate safety and protective measures have to be taken during the conduct of the study, the investigator notifies the Ethics committee of these measures, and of the circumstances necessitating them, within 7 days.

### 6.3 (Periodic) safety reporting

An annual safety report (ASR/DSUR) is submitted once a year to the local Ethics Committee by the Investigator (ClinO, Art. 43 Abs).

### 6.4 Radiation

There will be no additional radiation for this study other than the planned cCT-scans, which are in accordance with routine clinical practice for SSICH. Every one of these cCT-scans will have an approximate radiation dose of 4.5 mSV. If the permitted dose guidance value (5 mSv per year if no direct benefit is expected for the participants) is exceeded at any time, the local Investigator notifies the Ethics Committee via BASEC within 7 working days of it becoming known (see ClinO, Art. 44).

### 6.5 Pregnancy

We plan to assess pregnancy or a possible pregnancy in women of childbearing age before inclusion. If the patient's history is positive for a pregnancy or a possible pregnancy, the patient will be excluded. If a participant gets pregnant during the study, they will receive an MRI instead of a CT scan and can continue with the study procedures. In case of pregnancy during the course of the study, the Sponsor-Investigator will be notified within a maximum of 24 hours and the outcome of the pregnancy will be followed up. The patient will be informed, that she has to contact the study team in case of pregnancy and after birth.

### 6.6 Amendments

Substantial changes to the study setup and study organization, the protocol and relevant study documents are submitted to the Ethics Committee for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Ethics Committee. Such deviations shall be documented and reported to the Ethics Committee as soon as possible.
Substantial amendments are changes that affect the safety, health, rights and obligations of participants, changes in the protocol that affect study objective(s) or central research topic, changes of study site(s) or of study leader and sponsor (ClinO, Art. 29).
A list of all non-substantial amendments will be submitted once a year to the competent EC together with the ASR.

### 6.7 (Premature) termination of study

The Sponsor-Investigator may terminate the study prematurely according to the following circumstances:

- Arising ethical concerns
- Insufficient participant recruitment
- When the safety of the participants is doubtful or at risk (e.g. when the benefit-risk assessment is no longer positive)

- If alterations in accepted clinical practice that make the continuation of the study unwise arise
- Presence of early evidence of harm or benefit of the experimental intervention

Upon regular study termination, the Ethics Committee is notified via BASEC within 90 days (ClinO, Art. 38).

Upon premature study termination or study interruption, the Ethics Committee is notified via BASEC within 15 days (ClinO, Art. 38).

Biological materials collected until premature termination of the study will be evaluated according to the study protocol as will all acquired data to this point. The study will be published with the data collected until the point of premature termination while mentioning in the publication that a premature termination according to whatever reasons applied was chosen.

### 6.8 Insurance

Insurance for this study will be supplied by Helvetia Schweizerische Versicherungen AG. A contract was issued between the Helvetia Schweizerische Versicherungs AG and the Sponsor Prof. Dr. med. Raphael Guzman.

## 7 FURTHER ASPECTS

### 7.1 Overall ethical considerations

SSICH is a devastating cerebrovascular disease with currently insufficiently available effective treatment options. Our proposed approach of endoscopic evacuation of SSICH is based on pathophysiological and clinical evidence on the importance of early reduction in hematoma volume, as well as lessons learned from previous surgical trials. It is vital to evaluate new surgical methods to ameliorate patient's survival rate and to lower the social burden for the respective families. Conventional craniotomy has failed to show a significant impact on the functional outcome and mortality rates, minimally invasive surgical techniques however showed promising results. Especially ES has proven to inflict less damage to the surrounding brain tissue compared to the open surgical approaches due to its minimally invasive nature. Therefore, we plan to assess this surgical method in comparison to the current gold standard of treatment for SSICH (BMT) in a randomised controlled fashion to generate valid data on the best treatment modality for SSICH. Both are accepted treatment options for SSICH.

If ES fails to show significant effects on the specified outcome measures in the planned "interim analysis", the study will be prematurely terminated and BMT for ICH will be applied immediately for all patients.

All patients have the right to voluntarily participate in this study. Every participant, his legal guardian or his relatives have the right of information about the study and their study data.

Vulnerable populations may be included in this study as described in 4.2 "Recruitment, Screening and informed consent procedure". They might not be addressable at the time of inclusion, however, as soon as they are addressable again, they will be informed about the study according to the process in 4.2.

Overall, we consider this study to be fairly balanced between risk for the patients due to their initial condition compared to possible SAEs occurring through the surgical method proposed in this study.

### 7.2 Risk-benefit assessment

This study aims to prove the superiority of ES and BMT compared to BMT alone for a devastating disease with currently insufficient effective treatment. However, potential risk and SAEs can be anticipated.

This study carries relevant risk of death and disability for the included patients due to the underlying disease of SSICH, however if left untreated, outcome may be even worse with a 30-day mortality up to 45% reaching to 54% at one year. The mortality rates however can be attributed almost exclusively to the underlying disease rather than the procedure. Since this is a surgical procedure, risks like bleeding, wound infections, surgical site infection, and complications related to anaesthesiologic procedures may occur. Furthermore, the procedure might, in extremely rare cases, lead to the death of the participant. Also, due to the location of SSICH, important brain structures have to be passed to access the hematoma cavity and, despite all efforts to conserve them, might be damaged.

When compared to the potential damage inflicted by untreated SSICH however, these complications are acceptable. If our hypothesis is correct, then the participants might benefit in form of better survival and functional outcome rates from the proposed intervention.

To minimise the risk of complications, two of the senior neurosurgeons at our institution, one of them being the chief of cerebrovascular neurosurgery, have prepared a standardised surgical procedure which will be taught to all involved surgeons via proctor workshop training. The surgical procedure itself will be carried out adhering to the highest neurosurgical standards. Careful preoperative planning with BrainLab® neuronavigation (or an equivalent neuronavigation system), the minimally invasive nature of the proposes surgical method, the shorter duration of surgery, a more complete hematoma evacuation under full sight and irrigation of active bleeding sites will contribute to reducing the risk of possible AEs for the participants.

Furthermore, participants will receive the medical standard of care before and after the surgical intervention as well as in the control group and are closely monitored during their stay at our institute.

If our hypothesis proves to be true, then surgical evacuation for SSICH may ameliorating mortality and functional outcome for future patients suffering from this devastating disease.

Overall, we acknowledge the possible risk accompanying the proposed surgical method, but it is our opinion that compared with the medical standard of care for SSICH alone or no treatment at all, these risks are acceptable and fairly balanced with the prospect of potential better survival and less morbidity as well as better functional outcome through the proposed surgical method.

### 7.3 Patient and Public involvement

Some of the aspects of this study were designed and developed in collaboration with representatives of the public. Aspects covered in the Patient and Public involvement were identification of patient relevant endpoints and choosing the most appropriate patient friendly tools to assess these, critically assessing, and optimising the patient visit schedule, helping to improve the comprehensibility patient ICFs and the lay summary for a broad audience. Further involvement is planned in the assessment of risk-benefit for patients during monitoring visits, consultancy regarding dissemination of the results and input to evaluate and improve further PPI involvement. For further details, please consult Appendix 2 “PPI Plan”.

## 8 QUALITY CONTROL AND DATA PROTECTION

### 8.1 Quality measures

Every assessor will be trained on how to complete the CRFs and the conduct of the questionnaires. An audit trail will maintain a record of initial entries and any changes made; time and date of entry; and username of person authorizing entry or change in the CDMS. The eCRF will be implemented by the Data management group at the DKF of the University Hospital Basel using the CDMS secuTrial®. Data managers at the DKF Basel will implement validation rules in

the CDMS. When data gets saved in an eCRF, it will be validated for completeness and discrepancies (i.e., using mandatory fields and active missing value handle). Data will be reviewed by the responsible investigator as well as an independent monitor. The monitor will raise queries using the query management system in secuTrial®. Designated investigators have to respond to the query and confirm or correct the corresponding data. Thereafter the monitor can close the query. Range checks for scores will be implemented.
The blood samples and aliquots collected by trained personnel and are stored in an appropriate cooling system in a restricted area only accessible to the authorized personnel and handled there under appropriate conditions. The statistical analysis will be performed completely independent by the involved statistician at the DKF Basel. The final data set will be available in an encoded and anonymized form in accordance with the data transparency guidelines of the SNSF. For quality assurance the sponsor, the Ethics Committee or an independent trial monitor may visit the research site. Direct access to the source data and all study related files is granted on such occasions. All involved parties keep the participant data strictly confidential.

## 8.2 Data recording and source data

### 8.2.1 Data recording

All data like scores (NIHSS, GCS, mRS, MOCA, PROMIS®, patient satisfaction), patient history and surgical baseline data will be collected or observed in daily clinical routine and transcribed to a paper CRF referring to the patient's study ID. The study ID is generated when the patient is randomized in the CDMS secuTrial® by consecutive automatic numbering (i.e. USB-NNN with NNN a tree digit number). Information on radiological imaging or laboratory values will be extracted from the respective system. Data from radiological images will be directly transcribed to the paper CRF. Vital parameters (BP, HR, Temperature, Weight, Height) will be directly transferred from the electronic patient file located in the hospital information system to the paper CRF. Laboratory values (encoded) will be provided per mail to the investigators by our laboratories (Clinical Neuroimmunology and Brain Ischemia) and transcribed to the paper CRF. Study data will be transferred from the paper CRF to an eCRF captured via an online Clinical Data Management System (CDMS) secuTrial®, based at the IT-department of the University Hospital Basel. The data collected is entered into the study eCRF. Additional storage capacity can be added as needed. For each enrolled study participant, a eCRF is maintained.

### 8.2.2 Source data

Source data for this study will be all data collected within the paper CRF, namely scores of the mRS, NIHSS, GCS, PROMIS®, MOCA, patient satisfaction, patient and surgical baseline data and findings of the clinical examination except for the vital sings and radiological assessments as they are documented in daily practice in the electronic patient file or radiology program respectively and can be found there for monitoring purposes. Morbidity will be noted in the CRF. Source data will be available and may be found in paper or electronic form.

## 8.3 Confidentiality and coding

A unique patient identifier (i.e., patients study ID) will be used to identify patients and a password protected list will be maintained for traceability. The patient ID is generated when the patient is enrolled in the CDMS secuTrial® by consecutive automatic numbering (i.e., USB-NNN with NNN a tree digit number). Only the PI or delegated study personnel will have access to the encoding key. Enrolment and screening logs will be filed to ensure traceability. The Principal Investigator and, if applicable, delegates at the site will be authorized to do eCRF entries. The CDMS is accessible via a standard browser on devices with internet connection. Password protection and

user-right management ensures that only authorized study investigators, monitors, data managers and local authorities (if necessary) will have access to the data during and after the study. User administration and user training is performed by the DKF Basel according to predefined processes. An audit trail will maintain a record of initial entries and any changes made; time and date of entry; and username of person authorizing entry or change. For each patient enrolled an eCRF must be completed. The principal investigator will be responsible for assuring that the data entered the eCRF is complete, accurate, and that the entry and updates are performed in timely manner. If a patient withdraws from the study, the reason must be noted on a dropout form of the p and eCRF. Participant's identification logs will be stored as a password protected word files and saved on protected servers of the respective study site. On CRFs and other study specific documents, participants are only identified by the patient's study ID derived by secuTrial®. Completed paper CRFs will be kept locked in a drawer at the respective study site with access only to a very limited number of study team members. ECRFs will be secured in secuTrial®, only accessible by the study teams at the respective sites. The Investigators and the Sponsor endorse responsibility, that nobody else will have access to the confidential data and they guarantee protection against dissemination. Trial and participant data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the study.

Biological material in this study (i.e., blood samples) are not identified by participant name but by the patient's study ID. Biological material is stored in an appropriate cooling system in a restricted area only accessible to the authorized personnel and handled under appropriate conditions. The material will be sent coded by the patient's study ID to 1) the laboratory of Prof. Dr. med. J. Kuhle (NfL, GFAP) or 2) to the laboratory of Prof. Dr. med. R. Guzman (S100B, Interleukins). The results will be provided by mail to the study investigators and will not show in the hospitals electronic record system. A back-up copy will be kept at the archives of the hospital's laboratory. The material's location is tracked by a laboratory log which is kept in the sites investigator site file (ISF). Biological material will be discarded after analysis as according to hospital regulations for biological waste. All study data, except blood samples, will be archived for a minimum of 10 years after study termination or premature termination of the clinical trial.

### 8.4 Retention and destruction of study data and biological material

The study protocol and the informed consents for further usage of the collected data will be archived for an undefined time after study termination or premature termination of the study to be able to prove that informed consent for further usage was given. Biological material will be kept for a duration of 1 week after obtaining the final analysis. Disposal of the biological material will be in accordance with the hospital regulations concerning body fluids and blood samples from patients. The collected study data might be used in encoded form for future trials. If no consent for further usage of the data is given, the collected study data will be destroyed after 10 years and not be used for further studies.

#### 8.4.1 Dissemination of study results

The documentation accompanying the data will consist out of the Data Record Table (DRT) exported from the CDMS secuTrial®, therefore containing all data collected on paper CRF. It is an Excel file summarizing the questions and variables collected in the eCRF. The Excel file consists out of the following sheets:

- **Configuration:** An overview sheet of the internal project's name, eCRF version and which extended features of secuTrial® have been activated.
- **Form overview:** In this sheet, all available forms of the eCRF will be listed and the full visit plan (name, day of visit, type of visit, possible deviations in days) will be shown. For each form the visits in which it is available (or whether it is visit independent) and the name of the .csv table when exported will be given.

There will be one sheet for each form, containing the names of the form and a .csv table. All

variables stored in a table will be listed in separate rows, with the following metadata:

- Question and description text as shown in the eCRF, caption of the variable in the eCRF, type of the variable (e.g. text field with maximal number of characters, date, number item with maximal number of digits, radio button or drop down selection with list of available answers, check box, date), name of the variable in the exported .csv tables and if applicable any additional rules (e.g. mandatory item, optional item, “hide item if” with corresponding conditional)

The metadata variables (e.g. patient-ID, visit number, date of last edit, person entering data) and potential details regarding processing and analysis saved with the eCRF data in the exported tables will be specified in an additional Excel file. The patient-ID will serve as the persistent identifier. During the conduct of the study, we plan to consult patient organization representatives to discuss possibilities to best disseminate the results of the trial. Thus the following are only tentative plans. We plan to disseminate the results over 1) our trial website, 2) over the SNSF platform and 3) with the help of PO representatives to the respective patient organizations, 4) by publishing the results open-access in a peer-reviewed journal 5) social media (linked-in, twitter etc.).

### 8.4.2 Reproducibility

The Ordinance of 20 September 2013 on Clinical Trials in Human Research (Clinical Trials Ordinance, ClinO) ordains that handling of health-related personal data in connection with a clinical trial must be restricted to those persons who require this data to fulfil their duties. The Federal Act of 30 September 2011 on research involving Human Beings (Human Research Act, HRA) requires an informed consent of the person, the legal representative or next of kin for reuse of personal data. Personal data may only be disclosed to third parties provided the person has given written consent in each case. In exceptional cases, further use of data for research purposes may be made if informed consent is absent (HRA Art. 34). Researchers who wish to reuse the data will have to obtain authorization of the responsible ethics committee as ordained in the Ordinance of 20 September 2013 on Human Research with the exception of clinical Trials (Human Research Ordinance, HRO). The definition of “further use” in the HRO in particular includes the storage in databases and making accessible or available or transferring of health-related personal data already collected. A transfer of research data to a data repository would therefore violate national law. Although some repositories allow storing data none publically and restricting data access to specific users, they do not support restricted access to a subset of stored variables. Since the responsible ethics committee can exclude certain variables from reuse in a specific project application, restriction to subsets is a required feature.

The only way to circumvent the HRA would be an anonymization of the data, i.e. the masking or deleting of all items which, when combined, would enable to identify a patient without disproportionate effort. Health-related personal data are considered correctly coded in accordance with the HRA if, from the perspective of a person who lacks access to the key, they are to be considered anonymized (HRO Art. 26). Since the investigator must retain all documents required for the identification and follow-up of participants for at least ten years after the completion of a clinical trial (ClinO Art. 45), data may appear anonymized to third parties, while in fact the HRA considers them coded and forbids reuse without the persons’ consents. Additionally, an anonymization would make the combination of these data with routine data and data from other clinical trials impossible, which is the most important and most common reason for reuse of data in clinical research. Furthermore, it would counteract the efforts of the government-funded Swiss Personalized Health Network (SPHN), which has given priority to effective exchange of patient data.

Instead of transferring the data on a repository, the Department of Clinical Research (DKF) of the University of Basel will act as an independent Data Access Committee (DAC) and store the data at time of publication on secure servers, maintained and backed-up by the IT-Department of the University Hospital Basel. Researchers who wish to reuse data may submit a project synopsis to the DKF.
The DKF as independent DAC will answer formal request of applicants, review and submit the project documents to the responsible ethics committee(s) and (upon approval) securely transfer the requested data to the applicants.
Metadata describing the type, size and content of the datasets will be shared along with the study protocol and case report forms on the public repository dataverse.harvard.edu.
Additionally, the CRFs will be uploaded on medical-data-models.org and all variables will be annotated by their Unified Medical Language System Concept Unique Identifier (UMLS CUI) to improve findability for other clinicians. With the metadata registered on a public repository together with a reference to the DAC, this procedure will adhere to the FAIR principles to the best of the legal limitations for clinical research in Switzerland.
The results of this study will be published in a peer-reviewed medical journal, independent of the results and the statistical code is made available upon request. A data sharing statement referring researchers to the DKF for data access will be contained in the study protocol and publication.

# 9 MONITORING AND REGISTRATION

Monitoring duties will be provided by the Clinical Trial Unit of the University Hospital Basel. The study site will be initiated with a site initiation visit and then regularly checked during the course of the study as defined in the monitoring plan. All informed consents, source data, e.g. CRF, eCRF and laboratory results, the trial master file and the investigator site file will be monitored. All source data and all documents will be made accessible to monitors and questions will be answered during monitoring through the study staff. The data and safety monitoring committee is independent from the investigator team and consists of an expert in the field, a statistician, a monitor and a data analyst. Additionally, a Patient expert with experience in regulatory affairs will be member of the DSMB, responsible for assessing risk and benefits for the patients during this trial.

This study will be registered in the Swiss National Clinical Trial Portal and in the Clinicaltrials.gov Registry Platform.

# 10. FUNDING / PUBLICATION / DECLARATION OF INTEREST

## 10.1 Funding

This study is funded by the Swiss National Science Foundation (SNSF), grant number 33IC30_213916. Additionally, applications to ProPatient and the Bangerter-Rhyner Foundation are planned. A preparatory grant from the SNSF (33IC30_213916) for thPatient and Public Involvement was received and funded the PPI during the set-up phase. The funders will have no involvement in the planned study design and will not have any role during its execution, analysis and interpretation of data or decision to submit results.

## 10.2 Publication

The results of this study are expected to be published in a peer reviewed journal of neurosurgery or neurology with all following persons authorized to access, listed as authors. We confirm that if gender effects are observed, they will be published in the final study report. If an analysis is performed but no gender effects are observed, this will also be published.

Authors will be:

- Prof. Dr. med. Raphael Guzman, Sponsor, *Vice-Chairman, Department of Neurosurgery, Chief of cerebrovascular neurosurgery, University Hospital Basel, Switzerland*
- PD Dr. med. Jehuda Soleman, Principal-Investigator Basel, *Senior Neurosurgeon, Head of Clinical Research Department of Neurosurgery, University Hospital Basel, Switzerland*
- Prof. Dr. med. Urs Fischer, Sub-Investigator, *Chair of Neurology, Head of the Department of Neurology, University Hospital Basel, Switzerland*
- Dr. med. Tim Jonas Hallenberger, Sub-Investigator, *MD PhD Student, Department of Neurosurgery, University Hospital Basel, Switzerland*
- Dr. Gilles Dutilh, Senior Statistician, *Clinical Trial Unit, University Hospital Basel, Switzerland*

Associates will be:

- Prof Dr. med. Jens Kuhlen, Analysis of NfL, *Head of Multiple Sclerosis research, Department of Neurology, University Hospital Basel, Switzerland*

Patient and Public Involvement representatives will be:

- Andrea Sarti Vogt, Individual Patient, Identification of relevant PROMs, Organisation (Protocol design, ICF forms), Lay summary, Evaluation of PPI Involvement
- Claudia Böni, Caregiver, Identification of relevant PROMs, Organisation (Protocol design, ICF forms), Lay summary, Evaluation of PPI Involvement
- Rosine Mucklow, Patient organization representative and Patient Expert, Identification of relevant PROMs, Organisation (Protocol design, ICF forms), Lay summary, Monitoring, Evaluation of PPI Involvement

The clinical trial unit of the University Hospital Basel will be involved in data management, statistical calculations, monitoring and PPI involvement. An independent data and safety monitoring board will be responsible for conducting the planned “interim analysis”.

Contribution:

RG, JS, LB, UF and TJH conceived the study protocol and all authors drafted the protocol. RG is expected to be the grant holder. RG, JS, TJH and UF implemented the study. TJH designed the PPI aspects of this study. RG and JK will provide the laboratory material and locations for biomarker analysis. GD will perform statistical analysis. All authors critically revised the protocol before submission to the local ethics committee.

### 10.3 Declaration of interest

The authors declare no conflict of interest for the present study. Mr Tim Hallenberger discloses, that he receives a MD PhD scholarship jointly by the SNSF and the Swiss Academy of Medical Sciences.

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**Background and rationale**


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## Appendix 1: Schedule of assessments

| Study period | Treatment Period | | | | Follow-Up | |
|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** |
| **Time (hour, day, week)** | **<24 hours of symptom onset** | **24 hours after treatment onset** | **72 hours after treatment onset** | **7 days after treatment onset** | **3 months after treatment onset** | **6 months after treatment onset** |
| **Eligibility** | X | | | | | |
| **Study consent** | X | | | | | |
| **Asses vital signs (BP,HR,height)** | X | X | X | X | X | X |
| **Acquire NIHSS score** | X | X | X | X | X | X |
| **Acquire GCS score** | X | X | X | X | X | X |
| **Acquire mRS score** | X | X | X | X | X** | X** |
| **Acquire blood samples (NfL, GFAP, S100B, IL)** | X | | X | | | X |
| **Conduct Stability CT scan*** | X | | | | | |
| **Conduct directly postoperative CT scan†** | | X | | | | |
| **Conduct postinterventional CT scan‡** | | X | | | | X |
| **Quality of Life** | | | | | X | X |
| **Patient Satisfaction** | | | | | X | X |
| **Cognition** | | | | | X | X |

**intervention group only; only required if surgery cannot be initiated within 6 hours after the first cCT scan*
*†intervention group only; the directly postoperative cCT is conducted directly after surgery to assess hematoma evacuation and differentiate potential recurrent hemorrhage*
*‡all patients; the postinterventional cCT scan is conducted 24 hours and 6 months after the treatment start to assess potential recurrent/enlarged hematoma and defect size*

***blinded telephone assessment*

## Appendix 2: Patient and Public Involvement Plan

| **Activity** | **What was the role of the PPI contributor(s)?** | **What was the objective?** | **How did it influence the study submitted? Please describe the benefit of the involvement.** |
|---|---|---|---|
| Include an individual patient, a caregiver and a patient organization representative to identify and prioritize patient relevant outcome measures (PROMs) as secondary outcome measures. | The PPI contributors participated in a group meeting and gave input and advice on identifying important PROMs from the patient's perspective. | Ensuring that relevant PROMs are identified as secondary outcome measures | With the help of the PPIs we identified patient satisfaction, cognitive outcome of patients as well as patient's quality of life as new and underreported secondary outcomes. We further worked together to choose the optimal questionnaires and arrived at the PROMIS® questionnaire for Quality of Life, the MOCA for cognition and devised together the most important aspects of patient satisfaction in the hospital and follow-up setting. We also determined together at which time points these outcomes should be assessed and what would be reasonable from a patients perspective. |
| Include an individual patient, a caregiver and a Patient Organization representative to identify and advice on potential weak spots in the study procedures, to optimize the study design and procedures to patient friendly design and procedures and to | In a first step, the PPI contributors were required to read and understand the study protocol in advance of the group meeting. Then, they participated in a group meeting and gave advice on identified weak spots in the study and procedures to help optimize the study | To identify possible weak spots in the study procedures and to optimize the study design and conduct into a patient friendly design to ultimately improve enrolment rates and study retention | Together with the PPIs, we improved and simplified our visit schedule. Specifically, we reduced the blood sampling to the most essential number of samples, thought about training tools to improve psychological patient care (i.e. on ICU), developed the idea |

| | | | |
|---|---|---|---|
| find the correct follow-up time | schedule for involved patients. | | to also include patients relatives for assessing the patient satisfaction as this would yield more valid results, changed the timing of follow-up visits and confirmed 6 month as optimal endpoint of the study from a patients perspective |
| Include an individual patient and a caregiver to give advice and input for formulating an easily understandable patient informed consent form.<br>As our PO Representative was very experienced, we didn't want to miss her opinion in this process despite being not initially planned | In a first step, the PPI contributors were required to read and critically assess the informed consent form regarding understandability, clearness and which expectations are addressed and which are not. In a second step, they were required to give their assessment/feedback to the investigators and advise on potential improvements to the informed consent form | To create a easily understandable and appealing informed consent form for potential patients and their relatives to correctly address the patient expectations | With the help of the PPIs we established an easy to understand patient informed consent form (ICF). We further clarified aspects of the ICF such as the benefit of the study and the concept of the two treatment methods. We further added more explanation on the surgical technique and the best medical treatment. Lastly we improved the visual design of the ICF as some aspects were confusing and not easy to grasp. |
| Consulting an individual patient or caregiver to review the lay summary of the study and its goals for the grant proposal and later publication on our website.<br>With this we had again the help from all our PPIs as the opinions of a caregiver and a Patient Organization representative were very valuable. | The individual patient or caregiver was required to have required to read the lay summary to assess and give feedback whether it is clearly understandable or not. | To ensure the lay summary of the proposed project is easily understandable for the general public | We identified and removed wording problems, potentially making the summary less suggestive while we also determined that the summary reflected the important aspects of the study and is easily understandable. |

| Phase | Activity | What is the role of the PPI contributor(s)? | What is the objective? |
|---|---|---|---|
| Management and study process | Consulting a patient expert to be part of the data and safety monitoring board and conducting risk-benefit assessment and patient safety aspects within the DSMB. | The patient expert is required to have experience in safety and regulation procedures. The PE is expected to actively participate in the DSMB and faithfully complete his appointed task of assessing risk and benefits for the involved participants. | Ensure patient perspective is taken into consideration for all questions and issues (i.e. safety) that arise during the study. Providing a patient relevant perspective to risks and benefits of the study and potential safety aspects. |
| Data analysis/Management and study process | As member of the DSMB, the Patient Expert will inadvertently be confronted with results from the regular interim analysis due to the nature of Bayesian modelling. The Patient Expert assesses the risk-benefit ratio according to these results together with the trial statistician | The patient expert is required to have experience in safety and regulation procedures and basic statistic knowledge. The PPI is expected to actively participate in the DSMB and faithfully complete his appointed task together with the trial statistician. | Ensure that important trends in the risk-benefit assessment are detected and that patient safety is maintained in collaboration with the rest of the DSMB. |
| Dissemination and implementation | Consulting patient an organization representative (i.e. EUPATI-CH or Fragile Suisse) and a caregiver and a patient regarding dissemination and communication of the study results to a broad audience in a patient friendly manner. | The PPI team is expected to collaborate and actively participate in preparing the study results in an appealing and easily understandable fashion together with the study team. The PPI team is required to understand the meaning of the results and its impact on the community they represent. | Ensure that the study results are clear, in lay language and appealing to effectively disseminate them in the relevant population so that the affected patients are addressed and aware of the results |
| Evaluation | Consulting the PPI Team involved in the study to evaluate the impact of PPIs at different study phases/milestones | The PPIs are expected to attend a debriefing and to actively participate in evaluating the impact of PPI, giving | Gaining important insights into the benefits and the impact PPI had on different phases/milestones of |

| | | | |
|---|---|---|---|
| | (i.e. Ethics approval etc.)., assessing "lessons learned" and potential improvements for future PPI involvement. | feedback regarding PPI involvement in the project and discuss potential improvements for future PPI activities/involvement. For that the PPI is required to have participated in previous PPI activities. | the study, discussing "lessons learned" and potential improvements for future PPI involvement in the present or future studies |

**Appendix 3 – Patient satisfaction Questionnaire**

# Questionnaire Patient Satisfaction

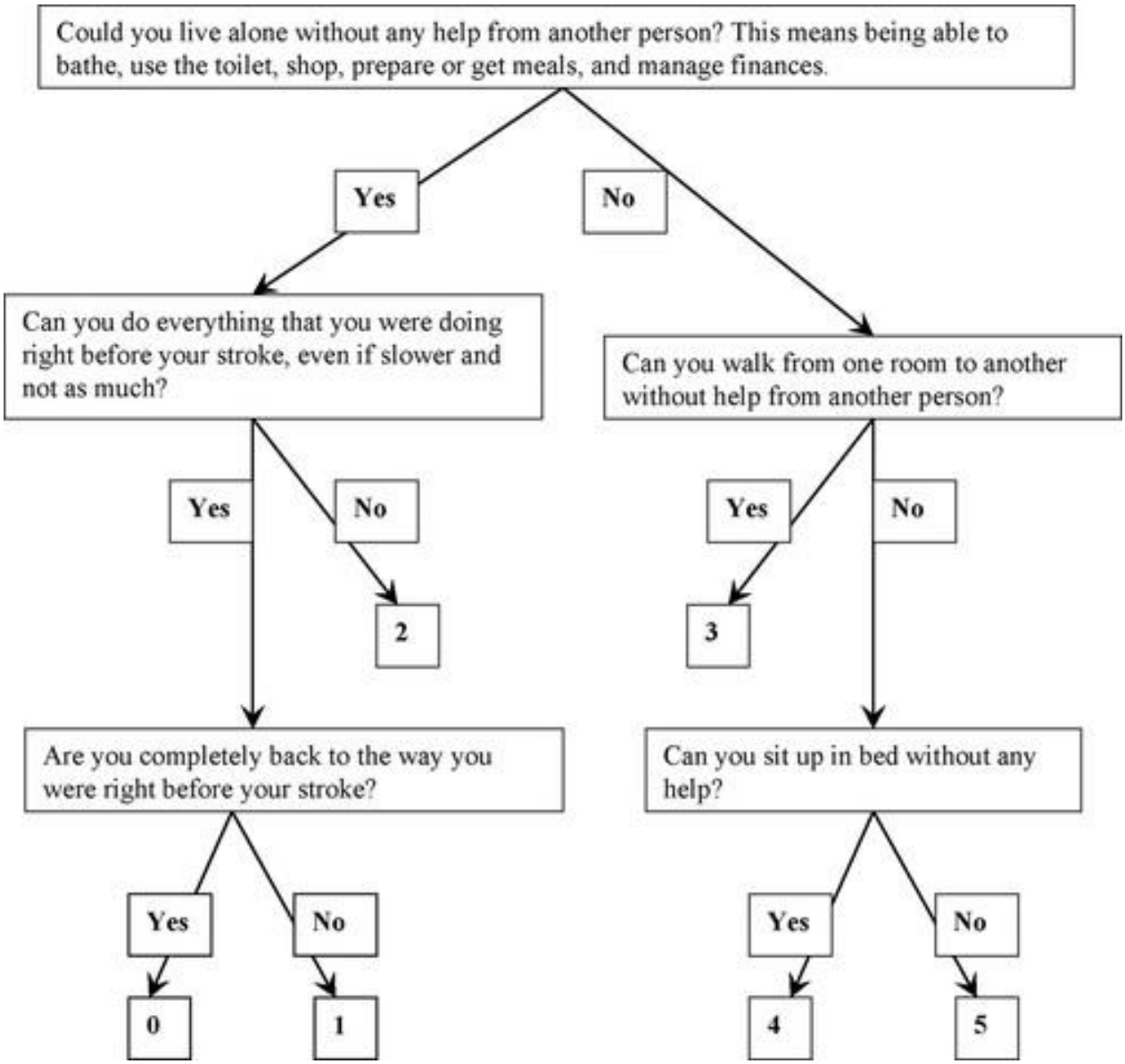
VISIT 5

| Question | Score (1=worst, 5=best) | |
|---|---|---|
| **1. Did you have the impression that you were well looked after?** | ☐ 1 point<br>☐ 2 points<br>☐ 3 points<br>☐ 4 points<br>☐ 5 points | ☐ not known |
| **2. Were all of your questions answered properly (i.e. what the further problems of the disease could be, what happens in the future) and did you have the impression that you were taken serious?** | ☐ 1 point<br>☐ 2 points<br>☐ 3 points<br>☐ 4 points<br>☐ 5 points | ☐ not known |
| **3. Did you have the impression that enough time was allocated for you during your in-patient visit?** | ☐ 1 point<br>☐ 2 points<br>☐ 3 points<br>☐ 4 points<br>☐ 5 points | ☐ not known |
| **4. How satisfied are you with the treatment outcome (i.e. functional outcome, disability etc.)?** | ☐ 1 point<br>☐ 2 points<br>☐ 3 points<br>☐ 4 points<br>☐ 5 points | ☐ not known |
| **5. How satisfied are you with your treatment overall?** | ☐ 1 point<br>☐ 2 points<br>☐ 3 points<br>☐ 4 points<br>☐ 5 points | ☐ not known |
| **Total points** | | |

VISITE 6

| Question | Score (1=worst, 5=best) | |
|---|---|---|
| **1. Did you have the impression that you were well looked after?** | ☐ 1 point<br>☐ 2 points<br>☐ 3 points<br>☐ 4 points<br>☐ 5 points | ☐ not known |
| **2. Were all of your questions answered properly (i.e. what the further problems of the disease could be, what happens in the future) and did you have the impression that you were taken serious?** | ☐ 1 point<br>☐ 2 points<br>☐ 3 points<br>☐ 4 points<br>☐ 5 points | ☐ not known |
| **3. Did you have the impression that enough time was allocated for you during your in-patient visit?** | ☐ 1 point<br>☐ 2 points<br>☐ 3 points<br>☐ 4 points<br>☐ 5 points | ☐ not known |
| **4. How satisfied are you regarding the information received for the future after the trial?** | ☐ 1 point<br>☐ 2 points<br>☐ 3 points<br>☐ 4 points<br>☐ 5 points | ☐ not known |
| **5. How satisfied are you with your treatment overall?** | ☐ 1 point<br>☐ 2 points<br>☐ 3 points<br>☐ 4 points<br>☐ 5 points | ☐ not known |
| **Total points** | | |

**Appendix 4 - Standardized telephone assessment for the primary outcome**




*As presented in „Simplified Modified Rankin Scale Questionnaire*
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