RESEARCH PROTOCOL

Dutch ICH Surgery Trial (DIST)

A prospective, multicenter, randomized, open clinical trial with blinded end-point assessment of minimally invasive endoscopy-guided surgery in patients with spontaneous, supratentorial intracerebral hemorrhage.

Version 2.0; December 2022

Dutch ICH Surgery Trial; minimally invasive endoscopy-guided surgery for spontaneous supratentorial intracerebral hemorrhage

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DOCUMENT HISTORY

Document version	Changes to protocol	Date
First METC submission Protocol version 1.0	-	February 13, 2022
Second METC submission Protocol version 1.1	Changes according to the suggestions of the Ethical Review Board of the Erasmus MC.	May 12, 2022
Third METC submission Protocol version 1.2	Changes according to the suggestions of the Ethical Review Board of the Erasmus MC.	July 11, 2022
First amendment Protocol version 2.0	Assessment of EQ-5D-5L added on day 6 (±1 day), changes in local principal investigator, names added to study committees, update of the common core data set, update of CTA acquisition protocol requirements.	December 22, 2022

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ADL	**Activities of Daily Living**
AE	**Adverse Event**
ALP	**Alkaline phosphatase**
ALT	**Alanine aminotransferase**
aPTT	**Activated partial thromboplastin time**
AST	**Aspartate aminotransferase**
AVM	**Arteriovenous malformation**
BI	**Barthel Index**
BIA	**Budget Impact Analysis**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CE	**Conformité Européenne**
CI	**Confidence Interval**
CONTRAST	**Collaboration for New Treatments of Acute Stroke**
CRP	**C-Reactive Protein**
CT	**Computed Tomography**
CTA	**Computed Tomography Angiography**
CTP	**Computed Tomography Perfusion**
CVST	**Cerebral Venous Sinus Thrombosis**
DAVF	**Dural Arteriovenous Fistula**
DOAC	**Direct Oral AntiCoagulants**
DIST	**Dutch Intracerebral Surgery Trial**
DSMB	**Data Safety Monitoring Board**
eGFR	**Estimated Glomerular Filtration Rate**
ENRICH	**Early MiNimally-invasive Removal of IntraCerebral Hemorrhage**
ER	**Emergency Room**
EudraCT	**European drug regulatory affairs Clinical Trials**
EQ-5D-5L	**EuroQol 5-dimensions 5-level**
EuroQol	**European Quality of Life**
FDA	**Food and Drug Administration**
GCP	**Good Clinical Practice**
IC	**Informed Consent**

ICER	**Incremental Cost-Effectiveness Ratio**
ICES	**Intraoperative Stereotactic Computed Tomography-Guided Endoscopic Surgery**
ICH	**Intracerebral Hemorrhage**
ICH-GCP	**International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – Good Clinical Practice**
ICH-GS	**Intracerebral Hemorrhage Grading Scale**
ICP	**Intracranial Pressure**
ICU	**Intensive Care Unit**
IL	**Interleukin**
iMCQ	**iMTA Medical Consumption Questionnaire**
INR	**International Normalized Ratio**
INVEST	**Single Arm, Feasibility Study of Minimally Invasive Endoscopic Surgical Treatment With Apollo for Supratentorial Intracerebral Hemorrhage**
iPCQ	**iMTA Productivity Cost Questionnaire**
IQR	**Interquartile range**
IVH	**Intraventricular Hemorrhage**
iVICQ	**iMTA Valuation of Informal Care Questionnaire**
LMWH	**Low-Molecular-Weight Heparin**
LOC	**Level Of Consciousness**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
MIND	**Prospective, Multicenter Study of Artemis a Minimally Invasive Neuro Evacuation Device, in the Removal of Intracerebral Hemorrhage**
MISTIE	**Minimally Invasive Surgery with Thrombolysis in Intracerebral hemorrhage Evacuation**
mRS	**Modified Rankin Scale**
NCCT	**Non-Contrast Computed Tomography**
NIHSS	**National institutes of Health Stroke Scale**
NSAID	**Non-Steroidal Anti-Inflammatory Drug**
NTR	**Netherlands Trial Register**
OR	**Operating Room**
PI	**Principal Investigator**

PIF	**Patient Information Form**
PRACTISE	**Promoting Acute Thrombolysis for Ischaemic Stroke**
PROBE	**Prospective, Randomized, Open, Blinded Endpoint**
PS	**Permeability surface-area product**
PTT	**partial thromboplastin time**
QALY	**Quality-Adjusted Life-Year**
RCT	**Randomized Controlled Trial**
RR	**Risk ratio**
(S)AE	**(Serious) Adverse Event**
SD	**Standard Deviation**
sICH	**Spontaneous Intracerebral Hemorrhage**
Sponsor	**The sponsor is the party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidizing party.**
SS-QOL	**Stroke-Specific Quality of Life scale**
STICH	**Surgical Trial in Lobar Intracerebral Haemorrhage**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
TIA	**Transient Ischemic Attack**
UN	**Untestable**
VAS	**Visual Analogue Scale**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Intracerebral hemorrhage (ICH) accounts for 16-19% of all strokes in Western Europe and contributes profoundly to mortality and disability. Thirty-day case fatality is 40% and of those surviving, only few gain independence. Except for stroke unit care and possibly early blood pressure lowering, there is currently no treatment of proven benefit. Surgical treatment, craniotomy, or minimally invasive surgery with the administration of alteplase, has so far not been proven effective. In the largest trials STICH I and II, and MISTIE III, the median time to treatment was more than 24 hours, which may be an important explanation for the lack of a treatment effect. A recent meta-analysis of randomized controlled trials showed that surgical treatment may be beneficial, in particular with minimally invasive procedures and when performed early. In the Dutch ICH Surgery pilot study, we showed that early minimally invasive endoscopy-guided surgical treatment performed within 8 hours of symptom onset in patients with supratentorial ICH is safe and technically effective. We hypothesize that early minimally invasive endoscopy-guided surgery improves the outcome in patients with supratentorial spontaneous ICH.

Objectives: 1. To study whether minimally invasive endoscopy-guided surgery, in addition to standard medical management, for the treatment of spontaneous supratentorial ICH performed within 8 hours of symptom onset, improves functional outcome in comparison with standard medical management alone; 2. Determine whether patients treated with minimally invasive surgery develop less perihematomal edema on non-contrast CT at day 6 (±1 day) than controls, and whether the CT perfusion permeability surface-area product around the ICH at baseline modifies this effect (DIST-INFLAME); 3. Compare immune profiles over time in peripheral venous blood between surgically treated patients and controls (DIST-INFLAME); 4. To assess the cost-effectiveness and budget-impact of minimally invasive endoscopy-guided surgery for the treatment of spontaneous supratentorial ICH performed within 8 hours of symptom onset.

Study design: A multicenter, prospective, randomized, open, blinded endpoint (PROBE) clinical trial.

Study population: We aim to include 600 patients of 18 years or older with a spontaneous supratentorial ICH with a minimal hematoma volume of 10 mL and a NIHSS of 2 or higher. Patients with an aneurysm, arteriovenous malformation, dural arteriovenous fistula, or cerebral venous sinus thrombosis as cause of their ICH will be excluded based on the admission CT angiography. Patients with a known tumor or cavernoma will also be excluded. For DIST-INFLAME (the second and third objective), we will include 200 patients; 100 randomized to intervention and 100 randomized to standard medical management.

Intervention: Patients will be randomized (1:1) to minimally invasive endoscopy-guided surgery performed within 8 hours of symptom onset in addition to standard medical management or to standard medical management alone.

Main study parameters/endpoints: The primary outcome parameter will be the modified Rankin scale (mRS) score at 180 days. This categorical scale measures functional outcome with scores ranging from 0 (no symptoms) to 6 (death). The treatment effect will be estimated with ordinal logistic regression analysis as common odds ratio, adjusted for prespecified prognostic factors. The adjusted common odds ratio will measure the likelihood that minimally invasive endoscopy-guided surgery will lead to lower mRS scores as compared to standard medical management alone. Secondary outcomes will include: the score on the mRS at 90 and 365 days; favorable outcome (defined as a mRS 0-2 and 0-3) and all other possible dichotomizations of the mRS at 90, 180 and 365 days; NIHSS at day 6 (±1 day); death, Barthel Index, EuroQol-5D-5L, SS-QOL, health economic evaluations (medical consumption, productivity loss and burden for the caregiver) , patient location and home time at 90, 180 and 365 days. Safety outcomes will be death within 24 hours, at 7 and at 30 days and procedure-related complications within 7 days. Technical effectiveness outcomes will be percentage volume reduction based on the baseline CT and CT at 24 hours (± 6 hours), percentage of participants with clot volume reduction ≥70%, and ≥80%, and with remaining clot volume ≤10mL, and ≤15mL, and conversion to craniotomy. In DIST-INFLAME, outcomes will include perihematomal edema at 6 days (±1 day), functional outcome at 180 days and immune and metabolomic profiles at 3 (± 12 hours) and 6 days (±1 day).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Minimally invasive endoscopy-guided surgery has been shown to carry limited risks and is of potential benefit to improve outcome, in particular when performed early. We therefore make use of deferred written informed consent. The main risks of surgery consist of persistent or recurrent intracranial hemorrhage, surgical site infection, intracranial infection and seizures. Besides the intervention for participants randomized to surgical treatment, the burden for all participants will consist of performing two additional non-contrast CT scans at 24 hours (± 6 hours) and 6 days (±1 day) after the baseline non-contrast CT, and a telephone interview for outcome assessment after 90, 180 and 365 days. Because patients with ICH may present with aphasia or decreased consciousness, we will include competent and non-competent patients (consent by proxy). In all participants in the surgical arm, a non-contrast CT immediately after surgery will be performed, to assess the achieved reduction in ICH volume. All participants will have blood samples drawn at baseline. In the participants in the DIST-INFLAME, a CT perfusion-scan will be performed at baseline and additional blood samples will be drawn on day 3 (± 12 hours) and day 6 (±1 day).

1. INTRODUCTION AND RATIONALE

Acute non-traumatic spontaneous intracerebral hemorrhage (sICH), accounts for 16 to 19% of all strokes in the Western population and 28 to 32% in low and middle income countries.[1,2] ICH is the deadliest stroke subtype with a 30-day case-fatality of approximately 40%.[3,4] Rapid identification and treatment are essential to facilitate recovery.[5] However, of the patients surviving, only few gain independence.[3,6] Besides the effect of stroke unit care[7] and early control of elevated blood pressure that may be beneficial,[8,9] there are no medical or surgical treatments with proven benefit.[5,10,11] A recent study with historical controls suggested that implementation of a hyperacute care bundle (anticoagulation reversal, intensive blood pressure lowering, neurosurgery in selected patients, access to critical care), may reduce case-fatality.[12]

The role of surgery in supratentorial sICH remains controversial, as reflected in the American and European guidelines that refrain from providing firm advice regarding the role of surgery in ICH.[13,14] As a result, there is large variation in clinical practice.[15] The landmark trials STICH and STICH II failed to demonstrate a beneficial effect of surgical treatment, mostly craniotomy. However, surgery was performed late, on average 30 hours after symptom onset in STICH,[16] and 27 hours in STICH II.[17] Additionally, both trials had high crossover rates from initial conservative treatment to surgical intervention in deteriorating patients (26% in STICH and 21% in STICH II). Increasing evidence suggests that minimally invasive procedures can avoid the potentially adverse effect of open surgery in patients with sICH and may achieve a beneficial effect on functional outcome. An individual patient data meta-analysis of randomized controlled trials (RCTs) published up to 2010 suggested that the effect of surgery may be modified by the clinical state of the patient and the timing of surgery, but in this analysis only a minority of patients was treated with minimally invasive techniques.[18] Recently, the MISTIE III trial showed that minimally invasive hematoma aspiration with local application of alteplase up to 72 hours after surgery could not be proven to be superior to standard medical care.[19] However, surgery in this trial was also performed late, on average 58 hours after symptom onset.[19] Our recent systematic review and meta-analysis of 21 RCTs of surgical treatment of supratentorial sICH aimed at clot removal, showed that any type of surgery (risk ratio (RR) 1.40, 95% confidence interval (CI) 1.22-1.60; I^2 46%; 20 studies) and minimally invasive surgery (RR 1.47, 95% CI 1.26-1.72; I^2 47%; 12 studies) improved good functional outcome.[20] In a meta-regression analysis, we found that surgery was more effective when performed earlier after symptom onset (p=0.004, 12 studies; median time to surgery 16.3 hours, interquartile range (IQR) 8.4; 28.9). Age, Glasgow Coma Scale, and hematoma volume did not modify the effect of surgery. Of note, 17 of the 21 studies included in de meta-analysis had a moderate or high risk of bias. In a sensitivity analysis of the four studies of high quality (two

assessing craniotomy[16,17] and two minimally invasive surgery[19,21]), the beneficial effect of surgical treatment was no longer statistically significant (RR for good functional outcome 1.10, 95% CI 0.98-1.25; I^2 0%). In a recent case-series of 100 patients with spontaneous supratentorial ICH (average volume 49.7 mL (standard deviation (SD) 30.6); mean age 62.2 years) treated with the Artemis™ Neuro Evacuation Device (or its first-generation version: the Apollo™ system), technical results were excellent (postoperative volume 6.2 mL (SD 10.7); evacuation percentage 88.2% (SD 20.3)).[22] Postoperative bleeding occurred in five cases, symptomatic in one. At six months, 46% of patients had a good functional outcome and 16% had died. Additionally, a separate report on the same patients who underwent surgery within 72 hours of ictus (90 patients), showed that for every hour a patient was operated on earlier, the odds of having a good outcome increased by 5%.[23] In a recent survey among neurologists and neurosurgeons in the Netherlands, 69% of neurosurgeons and 80% of neurologists were willing to randomize ICH patients in a RCT evaluating the effect of minimally invasive surgery on functional outcome.[15]

Approximately a quarter of patients with ICH show hematoma growth, with the highest probability of growth within the first 3 hours after symptom onset.[24] Besides the direct brain injury by compression and disruption of parenchyma, ICH elicits a secondary response.[25] This secondary brain injury results from toxicity due to blood degradation products (e.g. haem, iron) and plasma-derived components (e.g. thrombin), which starts within 3-4 hours after ICH, triggering an inflammatory response and the development of perihematomal edema.[26] Perihematomal edema increases rapidly over three days with a further slow increase up to 1-2 weeks after ICH onset.[27,28] Hematoma volume, hematoma growth, and possibly also perihematomal edema, are independent predictors of poor outcome.[29,30] Surgical treatment within 8 hours of symptom onset may not only lead to a reduction in hematoma volume, but also to a reduction of secondary brain injury.

The results of ultra-early surgery in patients with ICH have been contradictory, with some suggesting an increased rebleeding rate with surgery performed within four hours after symptom onset,[31] while others found no difference in rebleeding rates between stereotactic treatment performed within, or after six hours after symptom onset in patients without a CT angiography (CTA) spot sign.[32] In the Dutch ICH Surgery Trial (DIST) pilot study (www.dutch-ich.nl; NCT03608423), we recently showed that surgical treatment performed within 8 hours of symptom onset in patients with supratentorial sICH is safe and feasible (Sondag, submitted for publication). We included 40 participants with a mean age of 59.2 years (SD 13.6), 70% were male. Median ICH volume at baseline was 47.7 mL (IQR 29.4; 72.0). Median percentage volume reduction was 78% (IQR 50.3; 88.9). There were no technical complications with the device. Six participants experienced a primary safety outcome event of death (n=1) or an increase in neurological deficit (NIH Stroke Scale (NIHSS) increase ≥4 at 24 hours after

surgery; n=5). At 30 days, four participants had died (10%). Independent adjudication of the primary outcomes revealed that two of the five participants that experienced an increase in neurological deficit, already had deteriorated before surgery started; in one of these two, the NIHSS improved over time (at day 7 better than before surgery).

The aim of DIST is to assess whether minimally invasive endoscopy-guided surgery within 8 hours of symptom onset in addition to standard medical management, improves functional outcome after spontaneous supratentorial ICH when compared to standard medical management alone.

2. OBJECTIVES

2.1 Primary objective

To study whether minimally invasive endoscopy-guided surgery for treatment of supratentorial sICH performed within 8 hours of symptom onset, improves functional outcome at 6 months.

2.2 Secondary objectives

To determine whether patients treated with minimally invasive surgery develop less perihematomal edema on non-contrast CT at day 6 (±1 day) than controls, and whether CT perfusion (CTP) permeability surface-area product (PS) around the ICH at baseline modifies this effect (DIST-INFLAME).

To compare immune profiles over time in venous blood between surgically treated patients and controls (DIST-INFLAME).

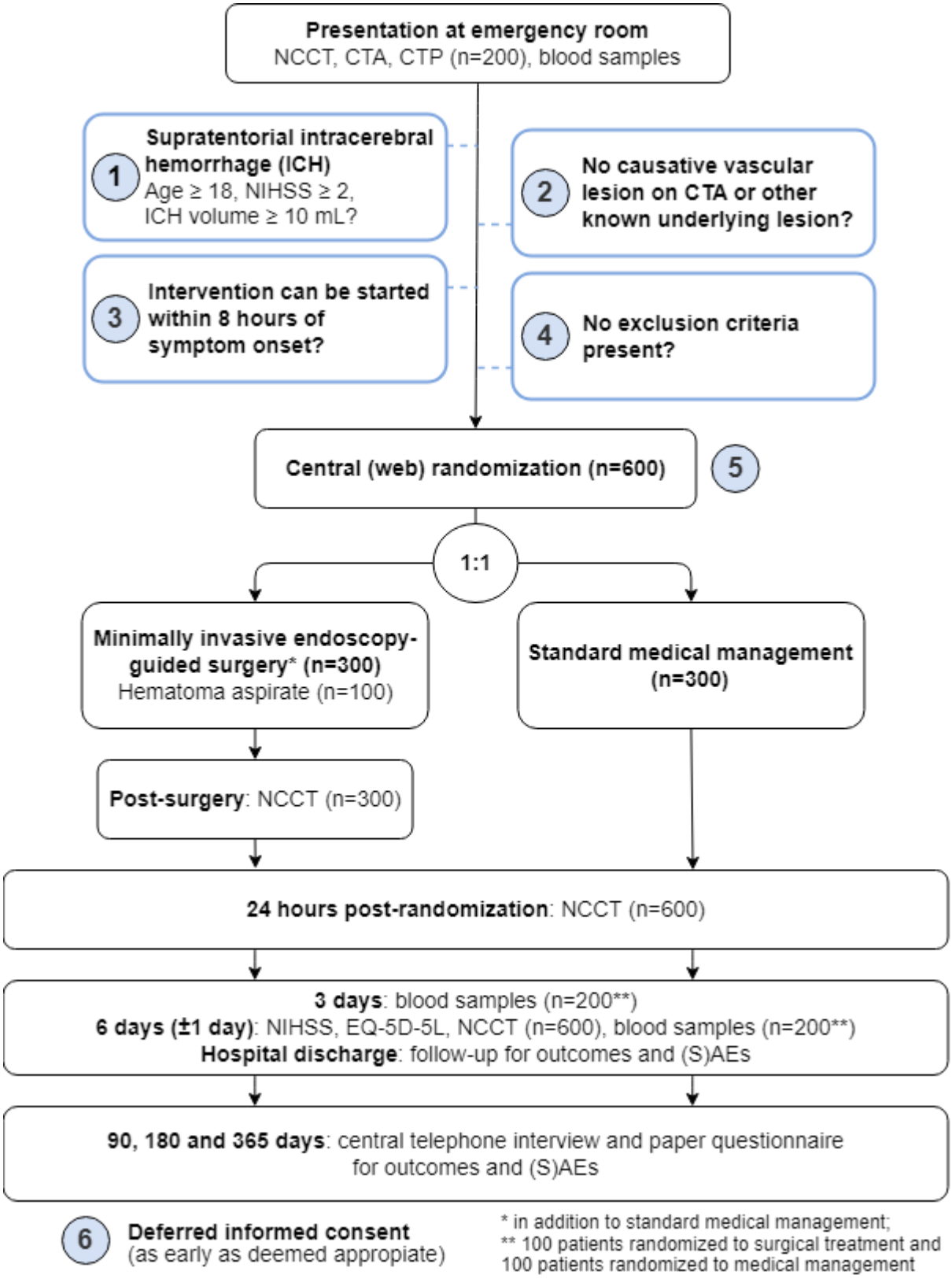
To assess the cost-effectiveness and budget-impact of minimally invasive endoscopy-guided surgery for the treatment of supratentorial sICH performed within 8 hours of symptom onset.

3. STUDY DESIGN

This is a multicenter phase III, prospective, randomized, open, blinded endpoint (PROBE) clinical trial in 600 patients with a spontaneous, supratentorial intracerebral hemorrhage (Figure 1). Patients will be recruited in 11 neurosurgical centers in the Netherlands. In addition, local investigators in ~33 general hospitals without facilities for intracranial neurosurgery but with experience in clinical trials in stroke, will be part of the study group and refer patients for inclusion, as a large number of patients with ICH is currently treated in these hospitals.

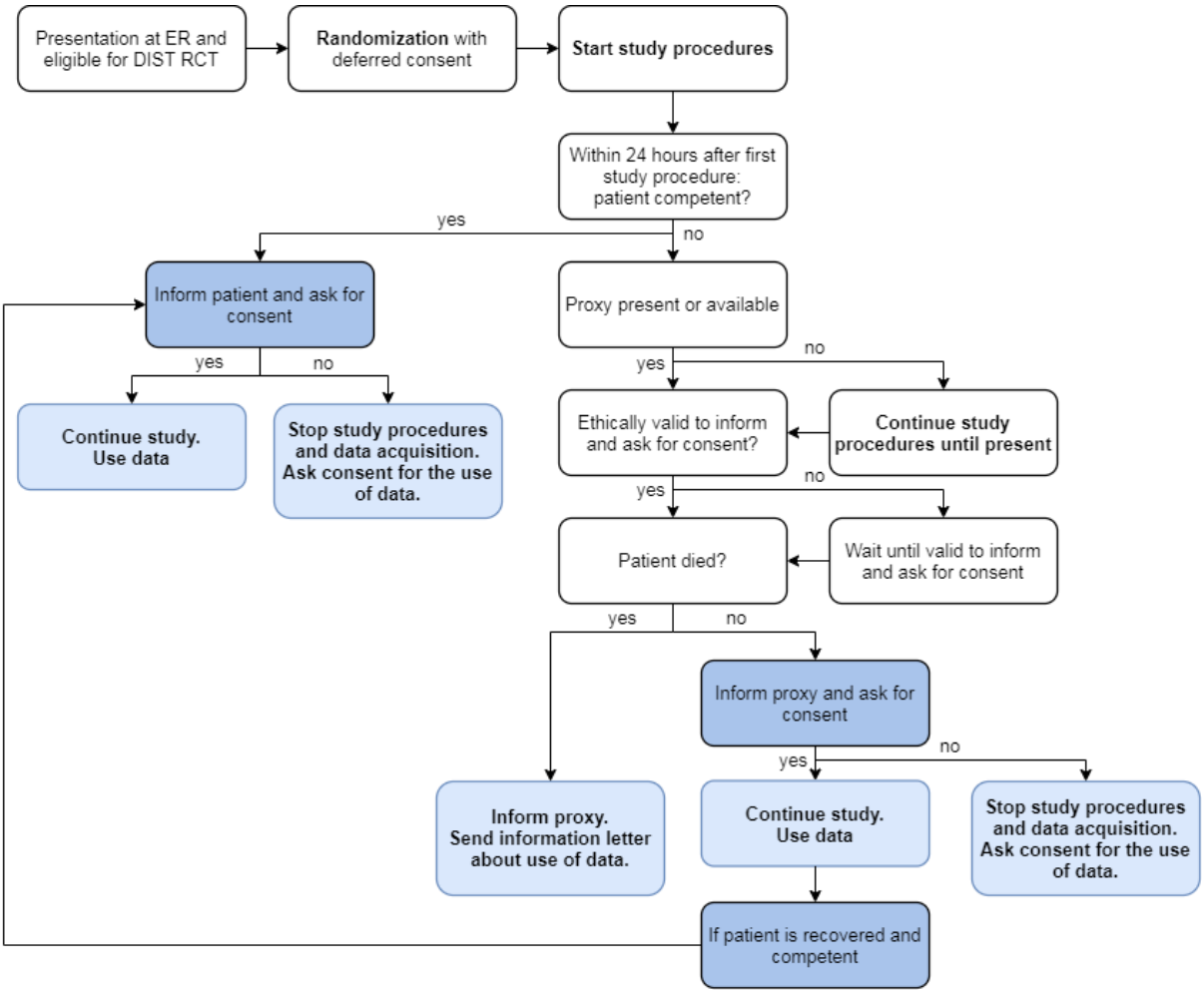
The study will run for 5 years, which includes a 6-month start-up phase, a 3-year inclusion period with a follow-up period of 12 months, and 6 months for analysis and reporting. The DIST is part of the 'Collaboration for New TReatments of Acute Stroke' (CONTRAST, see Appendix 3). The trial will be performed according to the ICH-GCP principles, the Declaration of Helsinki, and national regulatory requirements. An overview of the study and main procedures that participants will undergo and the deferred consent procedure is provided in Figure 1, Figure 2 and Appendix 5.

Figure 1. Flow chart of study procedures



CTA: Computed tomography angiogram; CTP: CT Perfusion; EQ-5D-5L: EuroQol 5-dimensions 5-level; ICH: intracerebral hemorrhage; NCCT: Non-contrast computed tomography; NIHSS: National Institutes of Health Stroke Scale; (S)AEs: (Serious) Adverse Events.

Figure 2. Flow chart of deferred consent procedure for the DIST. Based on the flow chart for use of proxy-deferred consent in emergency critical care research.[33]



4. STUDY POPULATION

4.1 Population (base)

We will include 600 patients with non-traumatic, spontaneous, supratentorial ICH, with or without intraventricular hemorrhage (IVH) or subarachnoid extension, without a causative lesion on admission CTA (e.g. arteriovenous malformation (AVM), dural arteriovenous fistula (DAVF), cerebral venous sinus thrombosis (CVST)) in 11 neurosurgical centers (Appendix 1). Participants will be randomized to undergo minimally invasive endoscopy-guided surgery within 8 hours of symptom onset in addition to standard medical management, or to standard medical management alone. In addition to these 11 neurosurgical centers, ~33 general hospitals will identify and refer eligible patients for inclusion.

In the Netherlands, over 6,000 people per year experience an ICH of whom 50% present to the hospital within 3 hours of symptom onset.[34] The 11 neurosurgical centers and their network of 33 additional participating centers combined admit between 2,000 and 3,300 patients with ICH annually (200-300 patients per neurosurgical center and three referring hospitals). Inclusion of 600 patients in 3 years will require each of the 11 neurosurgical centers to include 55 patients in 3 years, equivalent to approximately 18 patients per year. The inclusion of 18 patients from 200-300 patients per year admitted to one neurosurgical center and three referring hospitals, is less than 10%, which is certainly feasible. Experiences from the DIST pilot study support these numbers.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all the following criteria:

1. Age 18 years or older;
2. NIHSS ≥ 2 (Table 2);
3. Supratentorial non-traumatic ICH confirmed by non-contrast CT (NCCT), without a CTA confirmed causative vascular lesion (e.g. aneurysm, AVM, DAVF, CVST), or other known underlying lesion (e.g. tumor, cavernoma);
4. Minimal hematoma volume of 10 mL;
5. Intervention can be started within 8 hours of symptom onset;
6. Written informed consent (deferred).

4.3 Exclusion criteria

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

1. Considerable pre-stroke dependency in activities of daily living, defined as a pre-stroke mRS ≥3 (Table 1);
2. ICH-GS score ≥11 (Table 3);
3. Hemorrhage due to hemorrhagic transformation of an infarct;
4. Untreated coagulation abnormalities, including INR >1.3 (point of care measurement allowed), treatment with heparin and treatment with factor Xa inhibitors. Patients on vitamin K antagonist can be included after correction of the INR, and patients on dabigatran (direct thrombin inhibitor) can be included after reversal of dabigatran with idarucizumab;
5. Moribund (e.g. coning, bilateral dilated unresponsive pupils), or progressively deteriorating clinical course with imminent death;
6. Pregnancy (note: most patients will be beyond childbearing age);
7. DIST-INFLAME: patients that use immunosuppressive or immune-modulating medication.

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

4.4 Center eligibility

To be fully eligible for participation in the trial and to include patients in the trials, neurosurgical centers must meet the following criteria:

1. The center should have continuous availability of a neurosurgeon with expertise in minimally invasive endoscopy-guided surgery;
2. The center should have neuronavigation equipment readily available;
3. The neurosurgeon should adhere to the surgical protocol (See Appendix 6; Surgical Protocol, version 1.0, dated February 4th 2022).

Referring hospitals must meet the following criteria:

1. Experience in clinical stroke trials;
2. Principal investigator GCP certified.

4.5 Sample size calculation

Sample size estimations were based on the distribution of the outcomes in the MISTIE III trial,[19] and the preliminary data from the DIST pilot study. We assumed a distribution of the mRS in controls of mRS 0: 0%; mRS 1: 5%; mRS 2: 15%; mRS 3: 20%; mRS 4: 25%; mRS 5: 15%; mRS 6: 20%, and a favorable treatment effect with a common odds ratio of 1.49, corresponding to an absolute risk difference of mRS 0-3 of 11%. In a simulation in a Monte Carlo model with 5000 runs, we computed the proportion of positive trials, for a given sample size. This yielded a sample size of 800, providing a 90% power to detect a true treatment effect, with two-sided alpha=0.05. In the analysis we will use covariate adjustment, which reduces the sample size by 25%.[35,36] Therefore the aim is to included 600 patients, 300 in each arm.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

The investigational treatment is minimally invasive endoscopy-guided surgery. The investigational product is: any device for minimally invasive, endoscopy-guided hematoma removal that is CE approved and admissible by the steering committee. Currently, the Artemis^{TM} Neuro Evacuation Device (Penumbra Inc, Alameda, California, USA) is available and CE approved. If more devices become CE approved and have been granted admission for us by the steering committee during the course of the trial, the choice for any particular device will be left to the discretion of the neurosurgeon.

The treatment will be in addition to the standard medical management of ICH patients. Patients that are randomized to the control group will be treated with the standard medical management alone.

5.2 Use of co-intervention

Not applicable. No standard co-medication is advised by the steering committee.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

The devices allowed into the trial are minimally invasive neuronavigation integrated endoscopy-guided devices. At present, this includes only the Artemis™ Neuro Evacuation Device, manufactured by Penumbra, Inc., which is CE marked (Appendix 8).

The Artemis™ Neuro Evacuation Device is a surgical instrument designed to aid a physician in the removal of tissue and/or fluid during image-guided neurosurgery. The Artemis™ Neuro Evacuation Device is guided to the target location using intraprocedural image-guidance. Inside the Artemis™ Neuro Evacuation Device cannula is a wire recessed proximally from the cannula's distal tip. Activation of the Powered Handle mechanically rotates the wire to facilitate continuous cannula patency during aspiration. The Artemis™ Neuro Evacuation Device is designed to be used in conjunction with a compatible Penumbra Aspiration Pump and Collection Canister. The wand fits through the working channels of commercially available neuro-endoscopes. With the neuronavigation software available at the acquiring hospitals a trajectory will be selected that is considered technically feasible and safe, and allows access to the longest possible axis of the hematoma. After obtaining intracranial access through a burr hole, a peel-away sheath will be introduced to create a safe pass for the endoscope during the remainder of the procedure (see Appendix 6; Surgical Protocol, version 1.0, dated February 4th 2022).

6.2 Summary of findings from non-clinical studies

The minimally invasive, endoscopy-guided device that will be applied (Artemis™ Neuro Evacuation Device) is CE-marked and FDA-approved for clinical use.

Information of non-clinical studies is otherwise not applicable.

6.3 Summary of findings from clinical studies

The role of surgery to improve outcome of patients with spontaneous ICH remains controversial. This is reflected in the European and American guidelines for the management of spontaneous ICH that refrain from firm advice regarding the role of surgery in spontaneous ICH.[13,14] The theoretical rationale revolves around the concepts of decreasing the impact of the hematoma on the surrounding tissue and preventing increased intracranial pressure with or without herniation. The landmark trials STICH and STICH II failed to demonstrate a beneficial effect of surgical treatment, mostly craniotomy. However, surgery was performed late, on average 30 hours after symptom onset in STICH,[16] and 27 hours in STICH II.[17] Additionally, both trials had high crossover rates from initial conservative treatment to surgical

intervention in deteriorating patients (26% in STICH and 21% in STICH II). Increasing evidence suggests that with minimally invasive procedures the potentially adverse effect of open surgery in patients with spontaneous ICH can be avoided,[37] and a beneficial effect on functional outcome may be achieved. An individual patient data meta-analysis of randomized controlled trials published up to 2010 suggested that the effect of surgery may be modified by the clinical state of the patient and the timing of surgery, but in this analysis only a minority of patients was treated with minimally invasive techniques.[18] Recently, the MISTIE III trial showed that minimally invasive hematoma aspiration with local application of alteplase up to 72 hours after surgery did not seem to be superior to standard medical care.[19] However, surgery in this trial was performed late, on average 58 hours after symptom onset.[19] Our recent systematic review and meta-analysis of 21 RCTs of surgical treatment of supratentorial spontaneous ICH aimed at clot removal, showed that any type of surgery (RR 1.40, 95% CI 1.22-1.60; I^2 46%; 20 studies) and minimally invasive surgery (RR 1.47, 95% CI 1.26-1.72; I^2 47%; 12 studies) improved good functional outcome. In a meta-regression analysis, we found that surgery was more effective when performed earlier after symptom onset (p=0.004, 12 studies; median time to surgery 16.3 hours, IQR 8.4; 28.9). Age, Glasgow Coma Scale, and hematoma volume did not modify the effect of surgery in this meta-regression. Of note, 17 of the 21 studies included in de meta-analysis had a moderate or high risk of bias. In a sensitivity analysis of the four studies of high quality (two assessing craniotomy[16,17] and two minimally invasive surgery[19,21]), the beneficial effect of surgical treatment was no longer statistically significant (RR for good functional 1.10, 95% CI 0.98-1.25; I^2 0%). In addition, retrospective as well as randomized studies have suggested that minimally invasive aspiration may be more beneficial than craniotomy with hematoma evacuation.[37-44] These results have triggered multiple randomized controlled trials to investigate the effect of minimally invasive (endoscopy-guided) surgery in addition to standard medical management in comparison with standard medical management alone: MIND (NCT03342664), EVACUATE (NCT04434807), and ENRICH (NCT02880878). Currently, the Artemis™ Neuro Evacuation Device is available for minimally invasive endoscopy-guided hematoma evacuation. Multiple case series (with a total of 585 patients) have shown that evacuation with minimally invasive endoscopy-guided surgery can be achieved safely and efficaciously.[37,45-52] In contemporary studies mean hematoma clearance varied from 77.8% to 94.5%.[37,44,49-53] In the largest (n=100) and most recent retrospective cohort study, the median evacuation percentage was 96.9% (IQR 85.5-99.6).[22] Five percent of the patients in this study had a rebleed after surgery, of which one needed reoperation. Forty-six patients were independent, defined by a mRS of 0-3, at three months. Mortality was 3% at discharge and 16% at three months. A recent non-randomized study suggested that hematoma clearance is better and the risk of infections lower with endoscopy-guided surgery compared to stereotactic aspiration techniques.[24]

Timing of surgery remains controversial with some advocating to perform surgery only after demonstration of the absence of hematoma growth at least six hours after symptom onset. Our systematic review and meta-analysis suggested that earlier surgery may be more beneficial than surgery performed late.[20] In addition, a recent study showed that for every hour that patients were operated on earlier, they had a 5% increase in the odds of having a good functional outcome at 6 months.[23] However, a previous pilot study of 'ultra-early' surgery within 4 hours after sICH aiming to include 20 patients, was terminated early after a planned interim analysis in 11 patients due to post-operative bleeding in four patients (median time to surgery 180 minutes), which in three of them were fatal.[31] Others found no difference in rebleeding rates between stereotactic treatment within (mean 4.8 hours; 32 patients; 1 rebleed) or after six hours (mean 13.8 hours; 27 patients; 2 rebleeds) after symptom onset in CTA spot sign negative patients, suggesting that early surgery may be safe in patients with ICH in the absence of a spot sign.[32] However, it should be noted that in a recent individual patient data meta-analysis of 5,435 patients assessing prediction of hematoma growth, the addition of the CTA spot sign to a prediction model with time from symptom onset, ICH volume, anticoagulant use and antiplatelet use, improved the C-index only slightly (from 0.78, 95% CI 0.75-0.82; to 0.83, 95% CI 0.80-0.86).[24] Another study comparing endoscopy-guided and aspiration surgery suggested that patients operated within six hours (28 of 39 in the endoscopy group and 27 of 42 in the aspiration group) had better outcomes ($p<0.05$) than those operated between 6-24 hours, but details of patient characteristics of these groups and of the analysis were not provided.[51]

In the DIST pilot study (NCT03608423), we recently showed that surgical treatment performed within 8 hours of symptom onset in patients with supratentorial ICH is safe and feasible (Sondag, submitted for publication). We included 40 participants with a mean age of 59.2 years (SD 13.6), 70% were male. Median ICH volume at baseline was 47.7 mL (IQR 29.4; 72.0). Median percentage volume reduction was 78% (IQR 50.3; 88.9). There were no technical complications with the device. Six participants experienced a primary safety outcome event of death (n=1) or an increase in neurological deficit (NIHSS increase ≥4 at 24 hours after surgery; n=5). At 30 days, four participants had died (10%). Independent adjudication of the primary outcomes revealed that two of the five participants that experienced an increase in neurological deficit had already deteriorated before surgery started; in one of these two, the NIHSS improved over time (at day 7 better than before surgery). Four participants (10%) had a rebleed within 30 days, of whom two within 7 days. Surgery was started within 4 hours after symptom onset in three participants (7.5%), and within 6 hours in 21 participants (52.5%). None of the three participants in whom surgery was started within 4 hours after symptom onset had a rebleed, and only one of 21 participants in whom surgery was started within 6 hours. Twelve

participants had a CTA spot sign, of whom five had active bleeding during surgery. The other 14 participants with active bleeding during surgery, did not have a CTA spot sign at baseline.

6.4 Summary of known and potential risks and benefits

We refer to the structured risk analysis in Chapter 13.

The potential risks of the minimally invasive endoscopy-guided aspiration of the ICH include postoperative site infection, intracranial infection, intracranial hemorrhage/rebleeding, and seizures. Nevertheless, several studies have shown that minimally invasive endoscopy-guided surgery for ICH is feasible and safe.[37,45-49,54] Rebleeding was reported in 2 to 6.7%.[37,49] Seizures and pulmonary infections appear less frequent than after craniotomy,[37] and intracranial infections are rare.[37,51,52] In the non-randomized DIST pilot study (Sondag, submitted for publication), eight participants experienced a pulmonary infection within 30 days. An intracranial infection was reported in four participants (one confirmed with positive cerebrospinal fluid culture, and three suspected intracranial infections) within the first 30 days. Of these, three participants had been treated with an external ventricular drain for hydrocephalus. One of these patients experienced epileptic seizures at the time of the suspected intracranial infection. No seizures were observed in other participants.

The potential benefit lies in a better functional outcome and a decrease in case fatality as a result of the reduction in hematoma volume and possibly reduction of secondary brain injury by the surgery.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The primary outcome is the score on the modified Rankin Scale (mRS) at 180 days (± 14 days) (see paragraph 8.3.4).[55] The mRS is the preferred disability parameter of clinical trials in stroke. The mRS is an ordinal hierarchical scale incorporating a total of seven categories from 0 up to and including 6, and describes the range of disability encountered post stroke with 'Death' assigned a score of 6 (Table 1). Assessment of outcome on the mRS will be performed by independent assessors, blinded to the allocated and actually received treatment. Their assessment will be based on standardized reports of a telephone interview by trained research personnel who are not aware of treatment allocation. The blinded assessors are members of the outcome assessment committee.

8.1.2 Secondary study parameters/endpoints

- The score on the mRS at 90 days (± 14 days) and 365 days (± 14 days);
- Favorable outcome, defined as a mRS of 0-2 at 90 days (± 14 days), 180 days (± 14 days) and 365 days (± 14 days);
- Favorable outcome, defined as a mRS of 0-3 at 90 days (± 14 days), 180 days (± 14 days) and 365 days (± 14 days);
- All other possible dichotomizations of the mRS at 90 days (± 14 days), 180 days (± 14 days) and 365 days (± 14 days)
- Neurological deficit, as assessed with the NIHSS (Table 2) at 6 days (±1 day) after randomization, or at discharge;
- Death at 90 days (± 14 days), 180 days (± 14 days) and 365 days (± 14 days);
- Performance in activities of daily living assessed with the score on the Barthel Index (Table 5) at 90 days (± 14 days), 180 days (± 14 days) and 365 days (± 14 days);
- Quality of life assessed with the EuroQol 5D-5L (Table 4) at 6 days (±1 day), 90 days (± 14 days), 180 days (± 14 days) and 365 days (± 14 days);
- Quality of life assessed with the Stroke-Specific Quality of Life scale (Table 6) at 90 days (± 14 days), 180 days (± 14 days) and 365 days (± 14 days);
- Resource use measured with a questionnaire based on the iMTA Medical Consumption Questionnaire (iMCQ) and iMTA Productivity Cost Questionnaire (iPCQ) at 90 days (± 14 days), 180 days (± 14 days) and 365 days (± 14 days);

- Burden for the caregiver assessed with the iMTA Valuation of Informal Care Questionnaire (iVICQ) at 90 days (± 14 days), 180 days (± 14 days) and 365 days (± 14 days);
- Home time: the number of nights among the first 90, 180 and 365 days since stroke onset that are spent in the patient's own home or a relative's home;
- Patient location over the first 90, 180 and 365 days: hospital, rehabilitation service, chronic nursing facility, home.

The safety outcomes are:

- Death within 24 hours;
- Procedure related complications within 7 days;
- Case-fatality at 7 and 30 days.

The technical effectiveness outcomes are:

- Percentage volume reduction based on baseline CT and CT at 24 hours (± 6 hours);
- Percentage of participants with hematoma volume reduction ≥70%;
- Percentage of participants with hematoma volume reduction ≥80%;
- Percentage of participants with remaining hematoma volume ≤10mL;
- Percentage of participants with remaining hematoma volume ≤15mL;
- Conversion to craniotomy.

For the DIST-INFLAME sub-study, outcomes are:

- Perihematomal edema assessed on NCCT at 6 days (±1 day), or discharge (if earlier);
- The score on the mRS at 180 days (± 14 days);
- Immune and metabolomic profiles in venous blood assessed at 3 days (± 12 hours) and 6 days (±1 day) (see paragraph 8.3.5).

8.1.3 Other study parameters

Baseline parameters, assessed at the time of hospital admission:

- Demographics: age; sex; ethnicity;
- Weight; height;
- Vital signs: systolic and diastolic blood pressure, heart rate and temperature;
- Neurological examination: NIHSS (see paragraph 8.3.3. and Table 2), Glasgow Coma Scale;
- Pre-stroke functionality: pre-stroke mRS (Table 1);
- Comorbidities/medical history: comorbidity influencing mRS, premorbid cognitive complaints, falls in the past year, known hypertension, known hyperlipidemia,

peripheral artery disease, diabetes mellitus, atrial fibrillation or flutter, previous ischemic or hemorrhagic stroke, TIA, myocardial infarction, chronic heart failure, deep venous thrombosis, pulmonary embolism, known renal disease (serum creatinine >200micromol/L, dialysis or renal transplant), known liver disease (bilirubin > 2x upper normal limit (UNL) with AST/ALT/ALP >3x UNL, or cirrhosis), labile INR, history of major bleeding, predisposition to bleeding, mechanical heart valve replacement;

- Medication: use of antiplatelet agents, vitamin K antagonists, direct oral anticoagulants (DOACs), therapeutic heparin, antihypertensives, statins, NSAIDs, and immunosuppressant and immunomodulatory drugs;
- Intoxications: use of alcohol, smoking status, use of drugs;
- Laboratory examinations (see paragraph 8.3.5);
- Imaging results: ICH location (deep versus lobar),[56] ICH volume, IVH extension (modified Graeb score),[57] subarachnoid extension, subdural extension, hydrocephalus, CTA spot sign, other predictors of hematoma growth on baseline NCCT,[58] small vessel disease burden,[59,60] perihematomal edema volume, (causative) vascular lesions, and perihematomal perfusion and permeability measurements (see paragraph 8.3.6);
- Treatment limitations;
- Logistic parameters: time from symptom onset to arrival at the emergency room in first hospital, time from symptom onset to CT (in neurosurgical center, and referring hospital if applicable), time from symptom onset to arrival at neurosurgical center, time from symptom onset to randomization;
- ICH-GS score (Table 3).

Surgery related parameters:

- Logistic parameters: time from symptom onset to arrival in operating room (OR), time from symptom onset to start anesthesia, time from symptom onset to incision time; time from symptom onset to closure;
- Surgical procedure parameters: duration of surgical procedure (incision to closure), type of device, neuro-navigation and endoscope used, irrigation solution used, conversion to craniotomy, endoscopic clot appearance, active bleeding during surgery and treatment, estimated percentage ICH volume reduction, external ventricular drain placement, rebleeding or new intracranial bleeding during surgery, surgery performed on hybrid OR, highest and lowest blood pressure during surgery, administration of dexamethasone during surgery and dosage, administration of intracranial pressure (ICP) lowering medication (mannitol, hypertonic saline) during surgery, administration of anticoagulant/coagulopathy reversal agents during surgery, procedure related complications, re-operation after intra-operative or direct post-operative NCCT;

- Imaging results: ICH volume remaining directly after evacuation;
- DIST-INFLAME: hematoma aspirate analysis (see paragraph 8.3.13).

Parameters assessed during the first 7 days, or until discharge (if earlier):

- Blood pressure and heart rate at 1, 6, 12, and 24 hours after admission and at 6 days (±1 day);
- Stroke treatment: blood pressure reduction with intravenous antihypertensive medication, administration of anticoagulant/coagulopathy reversal agents, administration of dexamethasone and dosage, administration of ICP lowering medication, external ventricular drain placement, surgery for intracerebral hemorrhage (craniotomy with hematoma evacuation or decompressive hemicraniectomy);
- Neurological examination: NIHSS 6 days (±1 day) (see paragraph 8.3.3. and Table 2);
- Treatment limitations at 24 hours (± 6 hours), 6 days (±1 day) and discharge;
- Imaging results: ICH volume and perihematomal edema volume at 24 hours (± 6 hours) and 6 days (±1 day) (see paragraph 8.3.6).
- Interventions and diagnoses during hospital stay;
- Medication used during hospital stay: antihypertensives, platelet inhibitors, DOACs, vitamin K antagonists and heparin.
- Total numbers of days admitted in the ICU, medium care, stroke unit or general ward;
- Discharge destination
- DIST-INFLAME: blood pressure at 3 days and laboratory examinations at 3 (± 12 hours) and 6 days (±1 day) (see paragraph 8.3.5)

8.2 Randomization, blinding and treatment allocation

Patients will be randomly allocated to minimally invasive, endoscopy-guided surgery, started within 8 hours of symptom onset in addition to standard medical management, or to standard medical management alone. The randomization procedure will be computer- and web-based, using permuted blocks. Back-up by telephone will be provided. Randomization is allowed when the presence of a spontaneous supratentorial ICH has been established by NCCT and an underlying vascular abnormality is ruled out by CTA, and further in- and exclusion criteria are met. Randomization will be stratified for the neurosurgical center.

It will not be possible to view the treatment allocation before the patient is registered in the study database, nor will it be possible to remove the patient from the study base after the treatment assignment has become known. Both patient and treating physician will be aware of the treatment assignment. Information on the outcome at 90, 180 and 365 days will be assessed through standardized, algorithm-based telephone interviews, by trained

investigators unaware of treatment allocation. Assessment of outcome on the mRS will be based on this information, by assessors who are blinded to the treatment allocation. Imaging at baseline will be evaluated by assessors blinded for the baseline characteristics, treatment allocation and outcome measures. Imaging during follow-up will be evaluated by assessors blinded for the baseline characteristics, outcome measures, and for the results of baseline imaging. The steering committee will be kept unaware of the results of interim analyses of efficacy and safety. An independent unblinded statistician will combine data on treatment allocation with the clinical data in order to report to the data safety monitoring board (DSMB; see also chapter 9). Information on follow-up assessments in the main study database will only be visible by the outcome assessors and the independent unblinded statistician.

8.3 Study procedures

An overview of the main study procedures that participants will undergo and the time of assessment, is provided in Appendix 5.

8.3.1 Baseline characteristics

See paragraph 8.1.3. Baseline characteristics will be assessed by the treating physician upon presentation to the emergency department.

8.3.2 Vital signs

Blood pressure, heart rate and temperature will be assessed at baseline upon admission to the neurosurgical center. Additionally, blood pressure and heart rate will be collected at 1, 6, 12, and 24 hours after admission and at day 6 (±1 day, or discharge if earlier). For DIST-INFLAME, the blood pressure and heart rate will also be collected at day 3 (± 12 hours). The assessment of vital signs will be discontinued at hospital discharge.

8.3.3 National Institutes of Health Stroke Scale (NIHSS)

The NIHSS is an ordinal hierarchical scale to evaluate the severity of stroke by assessing a patient's performance.[61] Scores range from 0 to 42, with higher scores indicating a more severe deficit. All participants will undergo an assessment of the NIHSS (Table 2) at baseline and day 6 (±1 day, or discharge if earlier); these are routine clinical procedures. Assessment will be carried out by certified assessors.

8.3.4 Modified Rankin Scale (mRS)

The modified Rankin Scale is an ordinal hierarchical scale ranging from 0 to 5, with higher scores indicating more severe disability.[55] A score of 6 has been added to signify death (Table 1). The mRS will be assessed at 90 days (± 14 days), 180 days (± 14 days) and 365 days (± 14 days).

8.3.5 Laboratory tests

Blood samples (serum, plasma EDTA, whole blood EDTA, citrate and PAXgene tubes; total 40mL) will be drawn in all participants at baseline for storage in our CONTRAST biobank.

If obtained at baseline as part of routine clinical practice, results from the following laboratory tests will be collected: INR at admission (with date and time), INR after correction of vitamin K antagonist (with date and time), serum creatinine, estimated glomerular filtration rate (eGFR), serum glucose, C-reactive protein (CRP), hemoglobin, total white blood cell and neutrophil count, aPTT, PTT, thrombocyte count, bilirubin, AST, ALT and ALP.

For DIST-INFLAME, blood samples will be drawn at two additional time points (at day 3 ± 12 hours and day 6 ± 1 day). Whenever possible, venipuncture will be combined with blood sample collection for clinical care, to minimize patient burden. If a drip is in place, this will be used. At each time point, serum, plasma EDTA, whole blood EDTA, citrate and PAXgene tubes (total volume of 40 mL) will be collected. Laboratory parameters that will be collected will include CRP, serum creatinine, eGFR, INR, neutrophil and total white blood cell count, prothrombin time, activated partial thromboplastin time, levels of IL-1β, IL-6 and IL-10. The whole blood samples will be used for metabolomic profiling.

8.3.6 Neuroimaging

Participants will undergo a brain NCCT and CTA at baseline as part of routine clinical care in each patient with an ICH. The hematoma volume will be calculated using the ABC/2 formula upon presentation at the emergency department, to assess eligibility for the study.[62] An additional CTP (in some sites routine care) with an adapted acquisition protocol will be performed at baseline in the participants in DIST-INFLAME. Neuroimaging at baseline will be assessed centrally by assessors blinded for the baseline characteristics, treatment allocation and outcome measures. NCCT will be performed immediately after surgery to assess the achieved reduction in ICH volume; this is standard care after neurosurgery (Appendix 6). In addition, all participants will undergo a NCCT after 24 hours (± 6 hours) and after 6 days (±1 day, or discharge if earlier), and this imaging will also be centrally assessed for ICH volume and perihematomal edema by assessors blinded for baseline imaging and outcome measures.

8.3.7 Barthel index (BI)

The Barthel index is an ordinal scale used to measure performance in 10 activities of daily living (ADL).[63] Test scores range from 0 to 100, with higher scores indicating better performance in these activities (Table 5). The Barthel index will be assessed during the telephone interviews at 90 days (± 14 days), 180 days (± 14 days) and 365 days (± 14 days).

8.3.8 EuroQol (EQ-5D-5L)

The EuroQol 5-dimensions 5-level questionnaire is a standardized instrument to describe and value health (Table 4), consisting out of a descriptive system and a visual analog scale (VAS).[64] The questionnaire is primarily designed for self-completion by participants, but if the participant will not be able to complete the questionnaire because of aphasia or cognitive impairment, the participant's representative will do this instead of the participant. The EQ-5D-5L will be assessed at day 6 ± 1 day and during the telephone interviews at 90 days (± 14 days), 180 days (± 14 days) and 365 days (± 14 days).

8.3.9 Stroke-Specific Quality of Life scale (SS-QOL)

The Stroke-Specific Quality of Life Scale is a patient-centered outcome measure intended to provide an assessment of health-related quality of life specific to patients with stroke (Table 6).[65] The SS-QOL is a self-report scale, containing 49 items spread over twelve domains. Participants must respond to each question of the SS-QOL with reference to the past week. Scores range from 49 to 245, with higher scores indicating better functioning. The SS-QOL will be assessed during the telephone interviews at 90 days (± 14 days), 180 days (± 14 days) and 365 days (± 14 days).

8.3.10 Resource use

Resource use will be measured with a questionnaire based on the iMTA Medical Consumption Questionnaire (iMCQ) and iMTA Productivity Cost Questionnaire (iPCQ). The iMCQ is a generic instrument for measuring medical costs, whereas the iPCQ is a generic measurement instrument for measuring and valuing productivity losses. The questionnaire will be sent to the participants to be completed and returned prior to the telephone interviews. The questionnaires will then be reviewed at the time of the telephone interviews at 90 days (± 14 days), 180 days (± 14 days) and 365 days (± 14 days) and supplemented if necessary.

8.3.11 Burden for the caregiver

The burden for the caregiver will be measured with the iMTA Valuation of Informal Care Questionnaire (iVICQ). The aim of the iVICQ is to facilitate and promote an accurate description of providing informal care, its effects on informal caregivers, and how such effects are included in economic evaluations of health care interventions. The iVICQ will be sent to the participants to be completed by the primary caregiver and returned prior to the telephone interviews. The questionnaire will then be reviewed at the time of the telephone interviews at 90 days (± 14 days), 180 days (± 14 days) and 365 days (± 14 days) and supplemented if necessary.

8.3.12 Participant location

The location of the participant at noon of the relevant day during the follow-up phase will be recorded and classified as: hospital; rehabilitation service; chronic nursing facility; home (own or relative's). 'Home time' is defined as the number of nights that are spent in the participant's own home or a relative's home since the stroke onset until the follow-up moment. The location of the participant and home time will be assessed during the telephone interviews at 90 days (± 14 days), 180 days (± 14 days) and 365 days (± 14 days). Home time will be extrapolated or interpolated to the specific follow-up moments (90, 180 and 365 days), if follow-up occurs earlier respectively later.

8.3.13 Hematoma aspirate

For DIST-INFLAME, the hematoma aspirate of the participants undergoing minimally invasive endoscopy-guided surgery will be collected and stored in the CONTRAST biobank.

8.4 Withdrawal of individual subjects

Participants can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a participant from the study for urgent medical reasons. Data from participants who have withdrawn will be anonymized and used in the baseline analysis and in the analysis of the outcomes that have been collected up to the time of withdrawal. Data and biomaterial from non-consenting patients will not be used when there is a written objection from the patient or representative. In an effort to describe the non-consenting population, we will ask the patient or his/her representative to allow the use of routinely collected data and materials in a coded manner. If no consent for the use of these data is obtained, only the following will be noted: study number, treatment allocation and refusal. Missing data will be imputed for the main analysis, by multiple imputation.

8.5 Replacement of individual subjects after withdrawal

For each participant who withdraws before the six months outcome assessment, we will include an additional participant.

8.6 Follow-up of subjects withdrawn from treatment

All participants in the study will be followed until final assessment at twelve months. Only participants who do not give or have withdrawn consent will be assessed immediately and their records will be closed.

Due to the deferred consent procedure, study allocation and possible intervention will have taken place prior to obtaining informed consent. The procedure requires that all information on

patients who did not provide consent after the surgical procedure or allocation to the control group, is discarded and deleted. This may be against the interest of patients who did not provide consent, and against the interest of the general public, as patients with serious adverse events might be more likely to refuse consent for participation. Eliminating these records could result in an overestimation of the true safety and validity of the data, and might lead to undetected safety concerns for all consenting patients in the trial in case patients with a poor outcome will selectively withdraw from study participation. To overcome this safety concern, we will at least register in a very strictly anonymized safety registry for all patients – irrespective of whether a patient has provided written informed consent – only the variables: patient's study number, study treatment, in-hospital rebleeding occurrence (yes/no), and in-hospital survival status (yes/no). All other information will be completely erased from the patient's study record in case no consent is provided. The link to the study database will be erased from the patient's study record. The link to the study database will be erased from the medical record.

8.7 Premature termination of the study

The study will only be terminated prematurely if the Data Safety Monitoring Board recommends stopping. In case of premature termination of the study, the database will be closed after 365 days assessment of the last enrolled participant and results will be reported.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize the subject's health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

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

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life-threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention, but could have been based upon appropriate judgment by the investigator.

An elective hospital admission will not be considered a serious adverse event.

Serious adverse events that meet the aforementioned criteria should be reported to the sponsor, within 24 hours after coming to notice of the (local) investigator, by making use of the appropriate forms in the eCRF.

The investigator of each participating center will report the following SAEs occurring in the study period to the sponsor without undue delay after obtaining knowledge of the events: Death

from any cause, new symptomatic intracerebral hemorrhage, subdural/epidural hematoma, ischemic stroke, major cardiac event, pulmonary embolism.

Technical complications during surgery that do not lead to clinically detectable SAEs and neurological deterioration, will be recorded but not reported immediately.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life-threatening followed by a period of a maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

9.3 Annual safety report

Not applicable

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till the end of study within the Netherlands, as defined in the protocol.

9.5 Data Safety Monitoring Board (DSMB)

To increase the safety of the intervention, the study will be monitored by an independent data safety monitoring board (DSMB). The DSMB includes a neurosurgeon, a neurologist and an independent methodologist/statistician (Appendix 2). The DSMB will meet (in person, or by teleconference) at least annually, and assess the occurrence of SAEs by center and procedure, as laid out in the DSMB charter (supplement K5. Data Safety Monitoring Board (DSMB) DIST).
During the inclusion period of the study, interim analyses on safety and efficacy will be performed after the inclusion and 30-day follow-up of the first 50 and next 100, 250 and 400 participants. Results of interim analyses on major endpoints (including serious adverse events believed to be due to treatment) will be supplied by an independent unblinded statistician, in strict confidence, to the chair of the DSMB, along with any other analyses that the DSMB may

request. In the light of these analyses, the DSMB will advise the chair of the Steering Committee if, in their view, the randomized comparisons in the trial have provided both (i) "proof beyond reasonable doubt" that for all, or some specific types of patients, one particular treatment is clearly indicated or contraindicated in terms of a net difference in outcome, and (ii) evidence that might reasonably be expected to influence materially patient management. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least 3 standard deviations in an interim analysis of a major endpoint may be needed to justify halting or modifying, the study prematurely. This criterion has the practical advantage that the number of interim analyses is of little importance.

The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

10. STATISTICAL ANALYSIS

The analysis and reporting of the trial will be in accordance with the CONSORT guidelines. Baseline data by treatment allocation will be reported with standard statistical procedures. Missing values for baseline characteristics will be reported. Missing baseline characteristics will be imputed using regression imputation. All analyses will be performed according to the intention-to-treat principle.

10.1 Primary study parameter(s)

The primary effect parameter will be the common odds ratio, estimated with ordinal logistic regression, which represents the shift on the 7-category modified Rankin scale, measured at 180 days from randomization. The treatment effect estimate will be adjusted for known prognostic variables: age, pre-stroke mRS, time from onset of symptoms to randomization, systolic blood pressure on admission, stroke severity (NIHSS), ICH volume, presence of IVH, CTA spot sign, known history of antiplatelet or oral anticoagulant use immediately before stroke onset. Adjusted and unadjusted estimates with corresponding 95% confidence intervals will be reported.

10.2 Secondary study parameter(s)

Secondary effect parameters will be determined using linear, logistic, or ordinal regression analyses as appropriate, with the same adjustment variables as the primary outcome.

For the cost-effectiveness analysis we will measure costs and quality-adjusted life years (QALYs) in both groups over the 12-month follow-up period. QALYs will be calculated for the participant, based on the EQ-5D-5L questionnaire using the Dutch tariff, and for the caregiver, based on the CarerQol, which is part of the iVICQ. Hospital resource use will be recorded using case record forms, and other resource use will be estimated by iMCQ, iPCQ and iVICQ. Costs will be calculated according to the Dutch guideline for costing research, by multiplying resource use with the corresponding unit costs. If minimally invasive endoscopy-guided surgery is more effective and more costly, we will calculate incremental cost-effectiveness ratios (ICERs) by dividing estimated differences in costs over a 1-year horizon by differences in QALYs. Second, we will perform a model-based economic evaluation to explore the lifetime cost-effectiveness of minimally invasive endoscopy-guided surgery. For this purpose, we will use our pre-trial modelling study. We have already built an early health economic model,[66] which will be updated using the most recent literature as well as the results of the clinical trial.

Budget impact analysis (BIA) will be performed according to The Professional Society for Health Economics and Outcomes Research (ISPOR) and ZonMw guidelines, adopting at least

a hospital and societal perspective. For this purpose, we will use the results of the cost-effectiveness analysis, combined with data that reflect the size and characteristics of the patient population and changes in treatment mix. The ZonMw BIA tool will be used to calculate the BIA.

10.3 Other study parameters

Pre-specified subgroup analyses will be performed by testing for interaction between the specific baseline characteristic and treatment.

The effect of the intervention on the modified Rankin scale will be analyzed in subgroups determined by the following variables:

- Tertiles of age
- Sex
- Location of ICH (deep versus lobar)
- Tertiles of (systolic) blood pressure at baseline
- Tertiles of NIHSS at baseline
- Tertiles of ICH volume
- Tertiles of time from onset of symptoms to randomization, surgery start (first cut), and surgery closure (last stitch)
- Presence of CTA spot sign
- Type of neuro-evacuation device used (if applicable)
- Prior use of antiplatelet agents or oral anticoagulants

10.4 Interim analysis

See paragraph 9.5

10.5 Sensitivity analysis

To determine the robustness of the results of the included data from participants who deviate from the protocol (i.e. crossovers), we will perform a per-protocol and an as-treated analysis for the primary effect parameter as sensitivity analyses.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (October 2013), ICH-GCP principles, and in accordance with the Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

In this study, we will defer written consent until after the treatment, or after randomization for patients in the control arm. Recently, a flow chart in emergency interventional research has been proposed to select the most appropriate informed consent procedures based on several study particulars.[67] The eight-hour therapeutic window after symptom onset allows time for an informed consent procedure in most cases. However, it is not feasible to obtain valid patient or proxy informed consent before intervention within the time window. Proper informed consent procedures take 1 to 3 hours and this time is not available in the therapeutic window, partly due to the time-consuming logistics involved in arranging the intervention. Another valid reason is that the vast majority of patients will not be able to provide valid consent due to a lack of decision-making capacity (e.g. due to impaired consciousness, aphasia, or other cognitive disorder). In addition, the patient's proxy is often not directly on the scene and will also lack the capacity for informed consent, due to the emergency situation, the necessity for fast treatment, and the emotional stress of the situation.[68] Conversely, participation in the trial may be of direct benefit to the patient.

The executive committee feels that the emergency situation, the vulnerable patient group, and the importance of early treatment provide ethically and legally valid reasons for an emergency procedure where obtaining consent after the study procedure takes place (deferred consent). The trial cannot practically and ethically be carried out without deferred consent, nor can the trial be investigated in any other patient group than the one mentioned above. In the DIST pilot study, we recently showed that the surgical treatment performed within eight hours of symptom onset is safe and feasible. In the context of participatory research, we conducted interviews with patients who participated in the DIST pilot study and their relatives, in which they expressed to prefer the deferred consent procedure. Experiences of other CONTRAST trial participants support that deferred consent is considered acceptable.[68] According to common clinical practice for any procedure, we will ask the patient or proxy (onsite or by telephone if not present) for consent for the surgical treatment (e.g. a patient may have previously indicated that they do not want any surgical treatment). If the patient is unable to provide consent for the

surgical treatment due to its medical condition and there is no proxy available to provide consent instead, the patient will not be included in the study.

An overview of the deferred consent procedure is included in Appendix 5b. Written informed consent will be obtained from the patient or a representative by one of the investigators, after the intervention, or after randomization for patients in the control arm. We will strive to obtain consent as soon as possible but when deemed reasonable and appropriate, preferably within 24 hours. Although the goal is to obtain consent as soon as possible after the study procedure, a timeframe of 72 hours might be warranted in certain cases. When the patient is not competent, the investigator will search for a legal representative available. If there is no legal representative available, study procedures will be continued until a proxy is present. Subjects or their representatives will be provided with a patient information form (PIF) and a verbal explanation of the purpose of the study. They will be informed about the inclusion in the trial, data, and biomaterials that have been collected, and treatment they may have received. They will be asked for consent in follow-up and data usage. Written informed consent will be obtained from the patient or the legal representative. Patients and their representatives will be provided as much time as necessary to decide whether they want to continue participation in the study. When consent by proxy has been obtained and the patient regains competency during the study period, the patient will be asked to sign informed consent at that time. The patient or representative may, at any given time, withdraw informed consent. An explanation is not needed. If a patient has died before deferred consent has been obtained, their representatives will be informed about the treatment the patient has received, trial procedures, and use of the collected data and biomaterials. A separate information form will be sent to the representative of the patient.

11.3 Objection by minors or incapacitated subjects

Minors (patients under 18 years old) will not be included in the trial. About 50% of the patients in the trial will have a language impairment due to the ICH or impaired consciousness. In these cases, we will inform both the patient and legal representative, and request written consent from the latter. If a patient regains competence during the study period, the patient will be asked to sign informed consent at that time.

11.4 Benefits and risks assessment, group relatedness

The expected benefit from endoscopy-guided surgery compared to standard care may amount to 11% relative risk reduction for death or dependence.[43,69] Patients from the control group will be given the usual treatment according to international, national and local guidelines, including

treatment of high blood pressure in the acute phase and monitoring for hyperglycemia and treatment thereof.
Because outcome after ICH is generally poor, with 40% of patients dead at one month, and because a large proportion of patients with ICH present with dysphasia or impaired consciousness that may incapacitate them, it is essential to also include the incapacitated patients in this trial, and not restrict the trial to capacitated patients only. The Executive Committee of DIST expects that the potential benefit of minimally invasive endoscopy-guided surgery performed within eight hours after symptom onset outweighs the risk of harm of this study treatment. We refer to paragraphs 6.4 and 13.2.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance that is in accordance with article 7 of the WMO.
The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives

Participants will not receive any incentives or compensation.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

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

12.2 Monitoring and Quality Assurance

The Dutch ICH Surgery Trial will be monitored by an independent monitor according to ICH-GCP guidelines and relevant national regulations. Monitoring of the trial will be done in accordance with the criteria laid down in the monitoring plan and Data Safety Monitoring Board charter. On-site data monitoring includes the verification of data with source documents, considering critical aspects of the trial, such as informed consent, inclusion and exclusion criteria, and (serious) AEs. A monitoring report will be drawn up at the end of each monitoring visit. The last monitoring visit will also be the close-out visit. In addition, continuous remote monitoring with telephone and web-based monitoring will be performed to assure the resolution of all queries.

12.3 Amendments

Amendments are changes made to the research after a favorable opinion from the accredited METC. All amendments will be notified to the METC that gave a favorable opinion.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, the number of subjects included and the number of subjects that have completed the trial, serious adverse events/reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last follow-up of the final participant.
The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the

accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

The trial is registered on ClinicalTrials.gov with identifier: NCT05460793.

The study database will be closed within one month of the last scheduled follow-up date of the last included participant. A manuscript, which at least describes the study and the answer to the primary research question, will be submitted to a major clinical journal within six months of the database closure. The manuscript will be shared with the funding parties one month before submission, but the funding parties will have no influence on its contents.

De-identified data may be shared with other parties to maximize the usefulness of the collected research data. Data can be requested from the principal investigators with a detailed description of the objectives and methods of the study for which the data is intended. Data will be made available for this purpose at least 18 months after the publication of the main report. Data may also be shared with non-commercial parties for scientific purposes, including individual patient meta-analyses, and with the commercial parties involved in this study as manufacturers of minimally invasive neuronavigation integrated endoscopy-guided devices For these purposes, specific consent will be asked from the participants. In addition, specific consent will be asked for sharing of de-identified data outside of the European Union. The CONTRAST data access and writing committee will review all data requests for approval, and for external parties a data sharing agreement in accordance with Dutch regulations will be put in place before data is shared.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

The minimally invasive, endoscopy-guided devices will all be CE-marked or FDA-approved for clinical use. Information of non-clinical studies is otherwise not applicable. Therefore, this chapter will be skipped for the minimally invasive, endoscopy-guided devices of ICH removal.

13.2 Synthesis

We refer to Chapter 6.4.

The main potential risk of the minimally invasive neuronavigation-guided aspiration of the ICH is rebleeding, as it may be related to poor outcome.[70,71] In light of the poor outcome after ICH without surgical treatment, the reported safety of the applied surgical technique, and the potential benefit of surgery, the risk of the minimally invasive, endoscopy-guided hematoma removal is acceptable. In order to monitor the safety of the intervention, the trial will be monitored by an independent DSMB, as is described in Chapter 9.5 and de DSMB charter.

14. REFERENCES

1. Feigin VL, Stark BA, Johnson CO, et al. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet Neurology*. 2021;20(10):795-820. doi:10.1016/s1474-4422(21)00252-0

2. Krishnamurthi RV, Ikeda T, Feigin VL. Global, Regional and Country-Specific Burden of Ischaemic Stroke, Intracerebral Haemorrhage and Subarachnoid Haemorrhage: A Systematic Analysis of the Global Burden of Disease Study 2017. *Neuroepidemiology*. 2020;54(2):171-179. doi:10.1159/000506396

3. van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurol*. Feb 2010;9(2):167-76. doi:10.1016/s1474-4422(09)70340-0

4. Samarasekera N, Fonville A, Lerpiniere C, et al. Influence of intracerebral hemorrhage location on incidence, characteristics, and outcome: population-based study. *Stroke*. Feb 2015;46(2):361-8. doi:10.1161/STROKEAHA.114.007953

5. Gross BA, Jankowitz BT, Friedlander RM. Cerebral Intraparenchymal Hemorrhage: A Review. *JAMA*. Apr 2 2019;321(13):1295-1303. doi:10.1001/jama.2019.2413

6. Poon MT, Fonville AF, Al-Shahi Salman R. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. Jun 2014;85(6):660-7. doi:10.1136/jnnp-2013-306476

7. Langhorne P, Fearon P, Ronning OM, et al. Stroke unit care benefits patients with intracerebral hemorrhage: systematic review and meta-analysis. *Stroke*. Nov 2013;44(11):3044-9. doi:10.1161/STROKEAHA.113.001564

8. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med*. Jun 20 2013;368(25):2355-65. doi:10.1056/NEJMoa1214609

9. Qureshi AI, Palesch YY, Barsan WG, et al. Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage. *N Engl J Med*. Sep 15 2016;375(11):1033-43. doi:10.1056/NEJMoa1603460

10. Schreuder FH, Sato S, Klijn CJ, Anderson CS. Medical management of intracerebral haemorrhage. *J Neurol Neurosurg Psychiatry*. Jan 2017;88(1):76-84. doi:10.1136/jnnp-2016-314386

11. Cordonnier C, Demchuk A, Ziai W, Anderson CS. Intracerebral haemorrhage: current approaches to acute management. *Lancet*. Oct 6 2018;392(10154):1257-1268. doi:10.1016/S0140-6736(18)31878-6

12. Parry-Jones AR, Sammut-Powell C, Paroutoglou K, et al. An intracerebral hemorrhage care bundle is associated with lower case-fatality. *Ann Neurol*. Jul 10 2019;doi:10.1002/ana.25546

13. Hemphill JC, 3rd, Greenberg SM, Anderson CS, et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. Jul 2015;46(7):2032-60. doi:10.1161/STR.0000000000000069

14. Steiner T, Al-Shahi Salman R, Beer R, et al. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. *Int J Stroke*. Oct 2014;9(7):840-55. doi:10.1111/ijs.12309

15. Sondag L, Jacobs FA, Schreuder FH, et al. Variation in medical management and neurosurgical treatment of patients with supratentorial spontaneous intracerebral haemorrhage. *Eur Stroke J*. Jun 2021;6(2):134-142. doi:10.1177/23969873211005915

16. Mendelow AD, Gregson BA, Fernandes HM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. *Lancet*. Jan 29-Feb 4 2005;365(9457):387-97. doi:10.1016/S0140-6736(05)17826-X

17. Mendelow AD, Gregson BA, Rowan EN, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. *Lancet*. Aug 3 2013;382(9890):397-408. doi:10.1016/S0140-6736(13)60986-1

18. Gregson BA, Broderick JP, Auer LM, et al. Individual patient data subgroup meta-analysis of surgery for spontaneous supratentorial intracerebral hemorrhage. *Stroke*. Jun 2012;43(6):1496-504. doi:10.1161/STROKEAHA.111.640284

19. Hanley DF, Thompson RE, Rosenblum M, et al. Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial. *Lancet*. Mar 9 2019;393(10175):1021-1032. doi:10.1016/S0140-6736(19)30195-3

20. Sondag L, Schreuder F, Boogaarts HD, et al. Neurosurgical Intervention for Supratentorial Intracerebral Hemorrhage. *Ann Neurol*. Aug 2020;88(2):239-250. doi:10.1002/ana.25732

21. Hanley DF, Thompson RE, Muschelli J, et al. Safety and efficacy of minimally invasive surgery plus alteplase in intracerebral haemorrhage evacuation (MISTIE): a randomised, controlled, open-label, phase 2 trial. *The Lancet Neurology*. 2016;15(12):1228-1237. doi:http://dx.doi.org/10.1016/S1474-4422%2816%2930234-4

22. Kellner CP, Song R, Pan J, et al. Long-term functional outcome following minimally invasive endoscopic intracerebral hemorrhage evacuation. *J Neurointerv Surg*. May 2020;12(5):489-494. doi:10.1136/neurintsurg-2019-015528

23. Kellner CP, Song R, Ali M, et al. Time to Evacuation and Functional Outcome After Minimally Invasive Endoscopic Intracerebral Hemorrhage Evacuation. *Stroke*. Aug 2021;52(9):e536-e539. doi:10.1161/STROKEAHA.121.034392

24. Al-Shahi Salman R, Frantzias J, Lee RJ, et al. Absolute risk and predictors of the growth of acute spontaneous intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. *Lancet Neurol*. Oct 2018;17(10):885-894. doi:10.1016/S1474-4422(18)30253-9

25. Urday S, Kimberly WT, Beslow LA, et al. Targeting secondary injury in intracerebral haemorrhage--perihaematomal oedema. *Nat Rev Neurol*. Feb 2015;11(2):111-22. doi:10.1038/nrneurol.2014.264

26. Askenase MH, Sansing LH. Stages of the Inflammatory Response in Pathology and Tissue Repair after Intracerebral Hemorrhage. *Semin Neurol*. Jun 2016;36(3):288-97. doi:10.1055/s-0036-1582132

27. Inaji M, Tomita H, Tone O, Tamaki M, Suzuki R, Ohno K. Chronological changes of perihematomal edema of human intracerebral hematoma. *Acta Neurochir Suppl*. 2003;86:445-8. doi:10.1007/978-3-7091-0651-8_91

28. Venkatasubramanian C, Mlynash M, Finley-Caulfield A, et al. Natural history of perihematomal edema after intracerebral hemorrhage measured by serial magnetic resonance imaging. *Stroke*. Jan 2011;42(1):73-80. doi:10.1161/STROKEAHA.110.590646

29. Rodriguez-Luna D, Coscojuela P, Rubiera M, et al. Ultraearly hematoma growth in active intracerebral hemorrhage. *Neurology*. Jul 26 2016;87(4):357-64. doi:10.1212/WNL.0000000000002897

30. Davis SM, Broderick J, Hennerici M, et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. Randomized Controlled Trial. *Neurology*. Apr 25 2006;66(8):1175-81.

31. Morgenstern LB, Demchuk AM, Kim DH, Frankowski RF, Grotta JC. Rebleeding leads to poor outcome in ultra-early craniotomy for intracerebral hemorrhage. *Neurology*. May 22 2001;56(10):1294-9.

32. Li Y, Wang J, Li Z, et al. Computed Tomography Angiography Spot Sign as an Indicator for Ultra-Early Stereotactic Aspiration of Intracerebral Hemorrhage. *World Neurosurg*. Jan 2018;109:e136-e143. doi:10.1016/j.wneu.2017.09.121

33. Jansen TC, Kompanje EJ, Bakker J. Deferred proxy consent in emergency critical care research: ethically valid and practically feasible. *Crit Care Med*. Jan 2009;37(1 Suppl):S65-8. doi:10.1097/CCM.0b013e3181920851

34. Kuhrij LS, Wouters MW, van den Berg-Vos RM, de Leeuw FE, Nederkoorn PJ. The Dutch Acute Stroke Audit: Benchmarking acute stroke care in the Netherlands. *Eur Stroke J*. Dec 2018;3(4):361-368. doi:10.1177/2396987318787695

35. Hernandez AV, Steyerberg EW, Butcher I, et al. Adjustment for strong predictors of outcome in traumatic brain injury trials: 25% reduction in sample size requirements in the IMPACT study. *J Neurotrauma*. Sep 2006;23(9):1295-303. doi:10.1089/neu.2006.23.1295

36. Lingsma H, Roozenbeek B, Steyerberg E, investigators I. Covariate adjustment increases statistical power in randomized controlled trials. *J Clin Epidemiol*. Dec 2010;63(12):1391; author reply 1392-3. doi:10.1016/j.jclinepi.2010.05.003

37. Fu C, Wang N, Chen B, et al. Surgical Management of Moderate Basal Ganglia Intracerebral Hemorrhage: Comparison of Safety and Efficacy of Endoscopic Surgery, Minimally Invasive Puncture and Drainage, and Craniotomy. *World Neurosurg*. Feb 2019;122:e995-e1001. doi:10.1016/j.wneu.2018.10.192

38. Wang WZ, Jiang B, Liu HM, et al. Minimally invasive craniopuncture therapy vs. conservative treatment for spontaneous intracerebral hemorrhage: results from a randomized clinical trial in China. *Int J Stroke*. Feb 2009;4(1):11-6. doi:10.1111/j.1747-4949.2009.00239.x

39. Mould WA, Carhuapoma JR, Muschelli J, et al. Minimally invasive surgery plus recombinant tissue-type plasminogen activator for intracerebral hemorrhage evacuation decreases perihematomal edema. *Stroke*. Mar 2013;44(3):627-34. doi:10.1161/STROKEAHA.111.000411

40. Morgan T, Zuccarello M, Narayan R, Keyl P, Lane K, Hanley D. Preliminary findings of the minimally-invasive surgery plus rtPA for intracerebral hemorrhage evacuation (MISTIE) clinical trial. *Acta Neurochir Suppl*. 2008;105:147-51.

41. Auer LM, Deinsberger W, Niederkorn K, et al. Endoscopic surgery versus medical treatment for spontaneous intracerebral hematoma: a randomized study. *J Neurosurg*. Apr 1989;70(4):530-5. doi:10.3171/jns.1989.70.4.0530

42. Cho DY, Chen CC, Chang CS, Lee WY, Tso M. Endoscopic surgery for spontaneous basal ganglia hemorrhage: comparing endoscopic surgery, stereotactic aspiration, and craniotomy in noncomatose patients. *Surg Neurol*. Jun 2006;65(6):547-55; discussion 555-6. doi:10.1016/j.surneu.2005.09.032

43. Akhigbe T, Okafor U, Sattar T, Rawluk D, Fahey T. Stereotactic-Guided Evacuation of Spontaneous Supratentorial Intracerebral Hemorrhage: Systematic Review and Meta-Analysis. *World Neurosurg*. Aug 2015;84(2):451-60. doi:10.1016/j.wneu.2015.03.051

44. Jianhua X, Zhenying H, Bingbing L, et al. Comparison of Surgical Outcomes and Recovery of Neurologic and Linguistic Functions in the Dominant Hemisphere After Basal Ganglia Hematoma Evacuation by Craniotomy versus Endoscopy. *World Neurosurg*. Sep 2019;129:e494-e501. doi:10.1016/j.wneu.2019.05.193

45. Goyal N, Tsivgoulis G, Malhotra K, et al. Minimally invasive endoscopic hematoma evacuation vs best medical management for spontaneous basal-ganglia intracerebral hemorrhage. *J Neurointerv Surg*. Jun 2019;11(6):579-583. doi:10.1136/neurintsurg-2018-014447

46. Griessenauer C, Medin C, Goren O, Schirmer CM. Image-guided, Minimally Invasive Evacuation of Intracerebral Hematoma: A Matched Cohort Study Comparing the Endoscopic and Tubular Exoscopic Systems. *Cureus*. Nov 10 2018;10(11):e3569. doi:10.7759/cureus.3569

47. Fiorella D, Gutman F, Woo H, Arthur A, Aranguren R, Davis R. Minimally invasive evacuation of parenchymal and ventricular hemorrhage using the Apollo system with simultaneous neuronavigation, neuroendoscopy and active monitoring with cone beam CT. *J Neurointerv Surg*. Oct 2015;7(10):752-7. doi:10.1136/neurintsurg-2014-011358

48. Spiotta AM, Fiorella D, Vargas J, et al. Initial multicenter technical experience with the Apollo device for minimally invasive intracerebral hematoma evacuation. *Neurosurgery*. Jun 2015;11 Suppl 2:243-51; discussion 251. doi:10.1227/NEU.0000000000000698

49. Kellner CP, Chartrain AG, Nistal DA, et al. The Stereotactic Intracerebral Hemorrhage Underwater Blood Aspiration (SCUBA) technique for minimally invasive endoscopic intracerebral hemorrhage evacuation. *J Neurointerv Surg*. Aug 2018;10(8):771-776. doi:10.1136/neurintsurg-2017-013719

50. Kellner CP, Song R, Pan J, et al. Long-term functional outcome following minimally invasive endoscopic intracerebral hemorrhage evacuation. *J Neurointerv Surg*. Jan 8 2020;doi:10.1136/neurintsurg-2019-015528

51. Dong J, Jiang Z, Chen J, Huang N, Chen J, Liu G. Evacuation assisted by endoscopy has better efficacy for supratentorial intracerebral hematoma than CT-guided minimally invasive aspiration: a retrospective observational cohort study. *Br J Neurosurg*. Jun 2019;33(3):348-351. doi:10.1080/02688697.2018.1559273

52. Ye Y, Wang Q, Ou W, He J, Zhao Z. Endoscopic Surgery Without Decompressive Craniectomy in Large Putaminal Intracerebral Hemorrhage: Assessment of Efficacy and Safety. *Neurocrit Care*. Dec 16 2019;doi:10.1007/s12028-019-00880-8

53. Uchida D, Nakatogawa H, Yamazoe T, Inenaga C, Tanaka T. Neuroendoscopic Surgery with a Combination of Image Detectable Sheath, Intraoperative Computed Tomography Scan, and Navigation System Improves Accuracy and Safety in Minimally Invasive Evacuation of Intracerebral Hematoma: Technical Note. *World Neurosurg*. Jan 2020;133:1-7. doi:10.1016/j.wneu.2019.09.058

54.Vespa P, Hanley D, Betz J, et al. ICES (Intraoperative Stereotactic Computed Tomography-Guided Endoscopic Surgery) for Brain Hemorrhage: A Multicenter Randomized Controlled Trial. *Stroke*. Nov 2016;47(11):2749-2755. doi:10.1161/STROKEAHA.116.013837

55. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. May 1988;19(5):604-7.

56. Charidimou A, Schmitt A, Wilson D, et al. The Cerebral Haemorrhage Anatomical RaTing inStrument (CHARTS): Development and assessment of reliability. *J Neurol Sci*. Jan 15 2017;372:178-183. doi:10.1016/j.jns.2016.11.021

57. Morgan TC, Dawson J, Spengler D, et al. The Modified Graeb Score: an enhanced tool for intraventricular hemorrhage measurement and prediction of functional outcome. *Stroke*. Mar 2013;44(3):635-41. doi:10.1161/STROKEAHA.112.670653

58. Morotti A, Arba F, Boulouis G, Charidimou A. Noncontrast CT markers of intracerebral hemorrhage expansion and poor outcome: A meta-analysis. *Neurology*. Oct 6 2020;95(14):632-643. doi:10.1212/WNL.0000000000010660

59. Arba F, Inzitari D, Ali M, et al. Small vessel disease and clinical outcomes after IV rt-PA treatment. *Acta Neurol Scand*. Jul 2017;136(1):72-77. doi:10.1111/ane.12745

60. van Swieten JC, Hijdra A, Koudstaal PJ, van Gijn J. Grading white matter lesions on CT and MRI: a simple scale. *J Neurol Neurosurg Psychiatry*. 1990;53:1080-1083.

61. Brott T, Adams HP, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale *Stroke*. 1989;20:864-70.

62. Kothari RU, Brott T, Broderick JP, et al. The ABCs of Measuring Intracerebral Hemorrhage Volumes. *Stroke*. 1996;27(8):1304-1305. doi:10.1161/01.STR.27.8.1304

63. Mahoney FI, Barthel DW. FUNCTIONAL EVALUATION: THE BARTHEL INDEX. *Md State Med J*. Feb 1965;14:61-5.

64. EuroQol. EQ-5D instruments. Accessed 2021/09/29, https://euroqol.org/eq-5d-instruments/

65. Williams LS, Weinberger M, Harris LE, Clark DO, Biller J. Development of a Stroke-Specific Quality of Life Scale. *Stroke*. 1999;30(7):1362-69. doi:https://doi.org/10.1161/01.STR.30.7.1362

66. Schreuder FHBM, Scholte M, Ulehake MJ, et al. Identifying the Conditions for Cost-Effective Minimally Invasive Neurosurgery in Spontaneous Supratentorial Intracerebral Hemorrhage. *Front Neurol*. 2022;13:830614. doi:10.3389/fneur.2022.830614

67. Kompanje EJO, van Dijck JTJM, Chalos V, et al. Informed consent procedures for emergency interventional research in patients with traumatic brain injury and ischaemic stroke. *The Lancet Neurology*. 2020;19(12):1033-1042. doi:10.1016/s1474-4422(20)30276-3

68. van den Bos N, van den Berg SA, Caupain CMM, et al. Patient and proxies' attitudes towards deferred consent in randomised trials of acute treatment for stroke: A qualitative survey. *European Stroke Journal*. 2021;6(4):395-402. doi:10.1177/23969873211057421

69. Zhou X, Chen J, Li Q, et al. Minimally invasive surgery for spontaneous supratentorial intracerebral hemorrhage: a meta-analysis of randomized controlled trials. *Stroke*. Nov 2012;43(11):2923-30. doi:10.1161/STROKEAHA.112.667535

70. Brouwers HB, Chang Y, Falcone GJ, et al. Predicting hematoma expansion after primary intracerebral hemorrhage. *JAMA Neurol*. Feb 2014;71(2):158-64. doi:10.1001/jamaneurol.2013.5433

71. Morgenstern LB, Frankowski RF, Shedden P, Pasteur W, Grotta JC. Surgical treatment for intracerebral hemorrhage (STICH): a single-center, randomized clinical trial. *Neurology*. Nov 1998;51(5):1359-63.

72. Ruiz-Sandoval JL, Chiquete E, Romero-Vargas S, Padilla-Martinez JJ, Gonzalez-Cornejo S. Grading scale for prediction of outcome in primary intracerebral hemorrhages. *Stroke*. May 2007;38(5):1641-4. doi:10.1161/STROKEAHA.106.478222

73. Rothrock RJ, Chartrain AG, Scaggiante J, et al. Advanced Techniques for Endoscopic Intracerebral Hemorrhage Evacuation: A Technical Report With Case Examples. *Oper Neurosurg (Hagerstown)*. Dec 15 2020;20(1):119-129. doi:10.1093/ons/opaa089

74. Dankbaar JW, Hom J, Schneider T, et al. Dynamic perfusion CT assessment of the blood-brain barrier permeability: first pass versus delayed acquisition. *AJNR Am J Neuroradiol*. Oct 2008;29(9):1671-6. doi:10.3174/ajnr.A1203

75. Hom J, Dankbaar JW, Schneider T, Cheng SC, Bredno J, Wintermark M. Optimal duration of acquisition for dynamic perfusion CT assessment of blood-brain barrier permeability using the Patlak model. *AJNR Am J Neuroradiol*. Aug 2009;30(7):1366-70. doi:10.3174/ajnr.A1592

76. Bennink E, Riordan AJ, Horsch AD, Dankbaar JW, Velthuis BK, de Jong HW. A fast nonlinear regression method for estimating permeability in CT perfusion imaging. *J Cereb Blood Flow Metab*. Nov 2013;33(11):1743-51. doi:10.1038/jcbfm.2013.122

15. TABLES

15.1 Table 1. Modified Rankin Scale

The modified Rankin Scale (mRS) is an ordinal hierarchical scale ranging from 0 to 5, with higher scores indicating more severe disability.[55] A score of 6 has been added to signify death.

Category	Short description	Long description
0	No symptoms	No symptoms at all
1	Symptoms, no disability	No significant disability despite symptoms; able to carry out all usual duties and activities.
2	Slight disability	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance.
3	Moderate disability	Moderate disability; requiring some help, but able to walk without assistance.
4	Moderately severe disability	Moderately severe disability; unable to walk and attend to bodily needs without assistance.
5	Severe disability	Severe disability; bedridden, incontinent and requiring constant nursing care and attention.
6	Death	Death

15.2 Table 2. NIH Stroke Scale (NIHSS)

The NIHSS is an ordinal hierarchical scale to evaluate the severity of stroke by assessing a patient's performance.[61] Scores range from 0 to 42, with higher scores indicating a more severe deficit.

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e. repeated requests to patient to make a special effort).

Instructions	Scale definition
1a. Level of consciousness (LOC). The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert**; keenly responsive. 1 = **Not alert**; but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert**; required repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid and areflexic.
1b. LOC Questions. The patient is asked the month and his/her age. The answer must be correct – there is not partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal clues.	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.
1c. LOC Commands. The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command,	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.

the task should be demonstrated to him or her (pantomime), and the result scored (i.e. follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	
2. Best Gaze. Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be a 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = **Norma**l. 1 = **Partial gaze palsy**; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation**; or total gaze paresis not overcome by the oculocephalic maneuver.
3. Visual. Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving finger appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patients receive a 1, and the results are used to respond to item 11.	0 = **No visual loss**. 1 = **Partial hemianopia**. 2 = **Complete hemianopia**. 3 = **Bilateral hemianopia** (blind including cortical blindness)
4. Facial Palsy. Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly response or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling) 2 = **Partial paralysis** (total or near-total paralysis of lower face) 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).

5. Motor arm. The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift**; limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift**; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity**; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity**; limb falls. 4 = **No movement**. UN = Amputation or joint fusion: explain: 5a = Left Arm. 5b = Right arm.
6. Motor leg. The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift**; leg holds 30-degree position for full 5 seconds. 1 = **Drift**; leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity**; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity**; leg falls to bed immediately. 4 = **No movement**. UN = Amputation or joint fusion, explain: 6a. Left Leg 6b. Right Leg.
7. Limb ataxia. This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case	0 = **Absent**. 1 = **Present in one limb**. 2 = **Present in two limbs**. UN = Amputation or joint fusion, explain:

of blindness, test by having the patient touch nose from extended arm position.	
8. Sensory. Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, 'severe or total sensory loss', should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal**; no sensory loss. 1 = **Mild-to-moderate sensory loss**; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss**; patient is not aware of being touched in the face, arm and leg.
9. Best language. A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia**; normal 1 = **Mild-to-moderate aphasia**; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conservation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia**; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia**: no usable speech or auditory comprehension.

10. Dysarthria. If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal**. 1 = **Mild-to-moderate dysarthria**; patient slurs at least some words and, at worst, can be understood by some difficulty. 2 = **Severe dysarthria**: patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated or other physical barrier**. Explain:
11. Extinction and Inattention (formerly Neglect). Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosognosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality**. 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality**; does not recognize own hand or orients to only one side of space.

15.3 Table 3. Intracerebral Hemorrhage Grading Scale (ICH-GS)

The ICH-GS Score (Table 3a) is a simple clinical grading scale that allows risk stratification (Table 3b) on presentation with ICH.[72] Test scores range from 5 to 13, with higher scores indicating a higher probability of death within 30 days and lower probability of good functional outcome.

Table 3a ICH-GS Score

Feature	Finding	Points
Age	<45	**1**
	45-64	**2**
	≥65	**3**
Glasgow Coma Score	13-15	**1**
	9-12	**2**
	3-8	**3**
Location	Supratentorial	**1**
	Infratentorial	**2**
ICH Volume supratentorial	<40 mL	**1**
	40-70 mL	**2**
	>70 mL	**3**
Intraventricular blood	No	**1**
	Yes	**2**
ICH-GS score		**5 - 13**

Table 3b Risk stratification with ICG-GS score

ICH-GS Score	30-Day Mortality	Good functional outcome*
5	17%	83%
6	8%	76%
7	20%	60%
8	43%	27%
9	71%	16%
10	87%	4%
11	100%	0%
12	100%	0%
13	100%	0%

*Defined as Glasgow outcome scale IV (no need for assistance in everyday life, employment is possible but may require special equipment) and V (light damage with minor neurological and psychological deficits).

15.4 Table 4. EuroQol 5-dimensions 5-level (EQ-5D-5L)

The EuroQol-5D is a family of instruments that has been developed to describe and value health, that is widely used around the world in clinical trials, population studies and real-world clinical setting across a wide range of disease areas.[64] The EQ-5D-5L consists of two parts: a descriptive system and a visual analogue scale (VAS).

The EQ descriptive system comprises five dimensions, with five response levels within each dimension. The respondent is asked to indicate his/her health state by checking the box next to the most appropriate response level for each of the five dimensions. Responses are coded as single-digit numbers expressing the severity level selected in each dimension. The digits for the five dimensions can be combined in a 5-digit code.

The EQ VAS records the respondent's overall current health on a vertical visual analogue scale. The EQ VAS provides a quantitative measure of the patient's perception of their overall health.

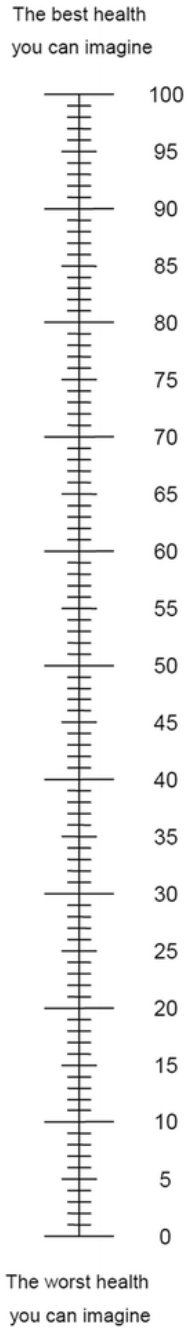
EQ-5D-5L health states can be summarized using the EQ descriptive system as a health profile, EQ VAS as a measure of overall self-rated health status, or represented by the EQ-5D-5L index value which reflects how good or bad a health state is according to the preferences of the general population of a country/region.

Dimension		Answer categories
Mobility	1	I have no problems in walking about
	2	I have slight problems in walking about
	3	I have moderate problems in walking about
	4	I have severe problems in walking about
	5	I am unable to walk about
Self-care	1	I have no problems washing or dressing myself
	2	I have slight problems washing or dressing myself
	3	I have moderate problems washing or dressing myself
	4	I have severe problems washing or dressing myself
	5	I am unable to wash and dress myself
Usual activities (e.g. (house)work, study, family or leisure activities	1	I have no problems doing my usual activities
	2	I have slight problems doing my usual activities
	3	I have moderate problems doing my usual activities
	4	I have severe problems doing my usual activities
	5	I am unable to do my usual activities
Pain/discomfort	1	I have no pain or discomfort
	2	I have slight pain or discomfort
	3	I have moderate pain or discomfort
	4	I have severe pain or discomfort

	5	I have extreme pain or discomfort
Anxiety/depression	1	I am not anxious or depressed
	2	I am slightly anxious or depressed
	3	I am moderately anxious or depressed
	4	I am severely anxious or depressed
	5	I am extremely anxious or depressed

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



15.5 Table 5. Barthel Index (BI)

The Barthel index is an ordinal scale used to measure performance in 10 activities of daily living (ADL).[63] Test scores range from 0 to 100, with higher scores indicating better performance in these activities.

Dimension	Score	Answer categories
Feeding	0	Unable
	5	Needs help cutting, spreading butter etc. or requires modified diet
	10	Independent
Bathing	0	Dependent
	5	Independent (or in shower)
Grooming	0	Needs help with personal care
	5	Independent face/hair/teeth/shaving (implements provided)
Dressing	0	Dependent
	5	Needs help but can do about half unaided
	10	Independent (including buttons, zips, laces etc.)
Bowels	0	Incontinent (or needs to be given enemas)
	5	Occasional accident
	10	Continent
Bladder	0	Incontinent, or catheterized and unable to manage alone
	5	Occasional accident (maximum 1 per day)
	10	Continent (or catheterized by patient self alone)
Toilet use	0	Dependent
	5	Needs some help, but can do something alone
	10	Independent (on and off, dressing, wiping)
Transfers (bed to chair and back)	0	Unable, no sitting balance
	5	Major help (one or two people, physical), can sit
	10	Minor help (verbal of physical)
	15	Independent
Mobility (on level surfaces)	0	Immobile or <50 yards
	5	Wheelchair independent, including corners, >50 yards
	10	Walks with help of one person (verbal or physical) >50 yards
	15	Independent (but may use any aid; for example stick) >50 yards
Stairs	0	Unable
	5	Needs help (verbal, physical, carrying aid)
	10	Independent (up and down)
Total score	**0-100**	

Guidelines

1. The index should be used as a record of what a patient does, not as a record of what a patient could do.
2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
3. The need for supervision renders the patient not independent.
4. A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives and nurses are the usual sources, but direct observation and common sense are also important. However direct testing is not needed.
5. Usually the patient's performance over the preceding 24-48 hours is important, but occasionally longer periods will be relevant.
6. Middle categories imply that the patient supplies over 50 per cent of the effort.
7. Use of aids to be independent is allowed.

15.6 Table 6. Stroke-Specific Quality of Life scale (SS-QOL)

The Stroke-Specific Quality of Life Scale (SS-QOL) is a patient-centered outcome measure intended to provide an assessment of health-related quality of life specific to patients with stroke.[65] The SS-QOL is a self-report scale, containing 49 items spread over twelve domains. Patients must respond to each question of the SS-QOL with reference to the past week. Scores range from 49 to 245, with higher scores indicating better functioning. Items are rated on a 5-point Likert scale. Each item is answered using one of three different response sets. The SS-QOL provides both domain specific scores and an overall SS-QOL summary score. The domain scores are composed of unweighted averages of the associated items, while the summary score is composed of an unweighted average of the twelve domain average scores.

Response sets: each item shall be scored with the following key			
1	Total help	Couldn't do it at all	Strongly agree
2	A lot of help	A lot of trouble	Moderately agree
3	Some help	Some trouble	Neither agree nor disagree
4	A little help	A little trouble	Moderately disagree
5	No help needed	No trouble at all	Strongly disagree

Domains		Scoring				
Energy						
1.	I felt tired most of the time	1	2	3	4	5
2.	I had to stop and rest during the day	1	2	3	4	5
3.	I was too tired to do what I wanted to do	1	2	3	4	5
Family Roles						
1.	I didn't join in activities just for fun with my family	1	2	3	4	5
2.	I felt I was a burden to my family	1	2	3	4	5
3.	My physical condition interfered with my personal life	1	2	3	4	5
Language						
1.	Did you have trouble speaking? For example, get stuck, stutter, stammer, or slur your words?	1	2	3	4	5
2.	Did you have trouble speaking clearly enough to use the telephone?	1	2	3	4	5
3.	Did other people have trouble in understanding what your said?	1	2	3	4	5

4.	Did you have trouble finding the word you wanted to say?	1	2	3	4	5
5.	Did you have to repeat yourself so others could understand you?	1	2	3	4	5
Mobility						
1.	Did you have trouble walking? (If patient can't walk, go to question 4 and score questions 2-3 as 1).	1	2	3	4	5
2.	Did you lose your balance when bending over to reaching for something?	1	2	3	4	5
3.	Did you have trouble climbing stairs?	1	2	3	4	5
4.	Did you have to stop and rest more than you would like when walking or using a wheelchair?	1	2	3	4	5
5.	Did you have trouble with standing?	1	2	3	4	5
6.	Did you have trouble getting out of a chair?	1	2	3	4	5
Mood						
1.	I was discouraged about my future	1	2	3	4	5
2.	I wasn't interested in other people or activities	1	2	3	4	5
3.	I felt withdrawn from other people	1	2	3	4	5
4.	I had little confidence in myself	1	2	3	4	5
5.	I was not interested in food	1	2	3	4	5
Personality						
1.	I was irritable	1	2	3	4	5
2.	I was inpatient with others	1	2	3	4	5
3.	My personality has changed	1	2	3	4	5
Self-Care						
1.	Did you need help preparing food?	1	2	3	4	5
2.	Did you need help eating? For example, cutting food or preparing food?	1	2	3	4	5
3.	Did you need help getting dressed? For example, putting on socks or shoes, buttoning buttons, or zipping?	1	2	3	4	5
4.	Did you need help taking a bath or a shower?	1	2	3	4	5
5.	Did you need help to use the toilet?	1	2	3	4	5
Social Roles						

1.	I didn't go out as often as I would like	1	2	3	4	5
2.	I did my hobbies and recreation for shorter periods of time than I would like	1	2	3	4	5
3.	I didn't see as many of my friends as I would like	1	2	3	4	5
4.	I had sex less often than I would like	1	2	3	4	5
5.	My physical condition interfered with my social life	1	2	3	4	5
Thinking						
1.	It was hard for me to concentrate	1	2	3	4	5
2.	I had trouble remembering things	1	2	3	4	5
3.	I had to write things down to remember them	1	2	3	4	5
Upper Extremity Function						
1.	Did you have trouble writing or typing?	1	2	3	4	5
2.	Did you have trouble putting on socks?	1	2	3	4	5
3.	Did you have trouble buttoning buttons?	1	2	3	4	5
4.	Did you have trouble zipping a zipper?	1	2	3	4	5
5.	Did you have trouble opening a jar?	1	2	3	4	5
Vision						
1.	Did you have trouble seeing the television well enough to enjoy a show?	1	2	3	4	5
2.	Did you have trouble reaching things because of poor eyesight?	1	2	3	4	5
3.	Did you have trouble seeing things off to one side?	1	2	3	4	5
Work/productivity						
1.	Did you have trouble doing daily work around the house?	1	2	3	4	5
2.	Did you have trouble finishing jobs that you started?	1	2	3	4	5
3.	Did you have trouble doing the work you used to do?	1	2	3	4	5
Scores						
Total SS-QOL score		49-245				

16. APPENDICES

16.1 Appendix 1. List of collaborating investigators

Coordinating investigators:

Prof. Dr. C.J.M. Klijn, neurologist, Radboud University Medical Center, Nijmegen

Dr. R. Dammers, neurosurgeon, Erasmus MC, Rotterdam

Local investigators:

The names of the local principal investigator of each center are underlined.

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Dr. R. Dammers, neurosurgeon

Drs. P.M. Janssen, neurologist

Prof. Dr. D.W.J. Dippel, neurologist

Site 3: Elisabeth Tweesteden Ziekenhuis, Tilburg

Dr. H.B. Brouwers, neurosurgeon

Dr. B.P.W. Jansen, neurologist

Site 4: Haaglanden Medical Center, Den Haag

Dr. J. Boiten, neurologist

Dr. W.A. Moojen, neurosurgeon

Site 5: Isala, Zwolle

Dr. W.M.T. Jolink, neurologist

Dr. D. Nanda, neurosurgeon

Site 6: Leiden University Medical Center, Leiden

Prof. Dr. M.J.H. Wermer, neurologist

Dr. W.A. Moojen, neurosurgeon

Site 7: Medisch Spectrum Twente, Enschede
Dr. R.M. Arntz, neurologist
Dr. K.H. Kho, neurosurgeon

Site 8: Maastricht University Medical Center, Maastricht
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Dr. R.H.L. Haeren, neurosurgeon

Site 9: Radboud University Medical Center, Nijmegen
Prof. Dr. C.J.M. Klijn, neurologist
Dr. H.D. Boogaarts, neurosurgeon

Site 10: University Medical Center Groningen, Groningen
Dr. M. Uyttenboogaart, neurologist
Prof. Dr. J.M.C. van Dijk, neurosurgeon

Site 11: University Medical Center Utrecht, Utrecht
Prof. Dr. A. van der Zwan, neurosurgeon
Prof. Dr. L.J. Kappelle, neurologist

16.2 Appendix 2. Study committees

Data Safety Monitoring Board

Chair:

Craig Anderson, MD PhD FRACP, Professor of Neurology and Epidemiology, UNSW Sydney, Australia

Members:

Hiren Patel, MD FRCS PhD, Consultant Neurosurgeon, University of Manchester, United Kingdom

Laurent Billot, MSc MRes AStat, Director of Biostatistics and Data Science, UNSW Sydney, Australia

Independent unblinded statistician:

Jan Willem van Dalen, MD PhD, Amsterdam University Medical Center, the Netherlands.

Executive and writing committee

Prof. Dr. C.J.M. Klijn, neurologist Radboud University Medical Center; Dr. R. Dammers, neurosurgeon Erasmus Medical Center; Dr. F.H.B.M. Schreuder, neurologist Radboud University Medical Center; Dr. H.D. Boogaarts, neurosurgeon Radboud University Medical Center; Prof. Dr. W.P. Vandertop, neurosurgeon Amsterdam University Medical Center; Prof. Dr. M.J.H. Wermer, Leiden University Medical Center; Prof. Dr. D.W.J. Dippel, neurologist Erasmus Medical Center; Dr. H.B. Brouwers, neurosurgeon Elisabeth Tweesteden Ziekenhuis; Dr. W.M.T. Jolink, neurologist Isala; Drs. F.N.H. Wilting, PhD student Radboud University Medical Center; Drs. A. Wolsink, PhD student Radboud University Medical Center; Drs. N.H.C. Colmer, PhD student Erasmus Medical Center.

Imaging assessment committee

To be announced

WP leaders

To be announced

WP members

To be announced

WP-collaborators (imaging assessments)

To be announced

Outcome assessment committee

To be announced

Adverse event adjudication committee

To be announced

Trial statistician and methodologist

Dr. G. Hannink, Department of Radiology and Nuclear Medicine, Radboud University Medical Center, Nijmegen

16.3 Appendix 3. CONTRAST: Collaboration for new treatments of acute stroke

Research leaders CONTRAST

- Diederik Dippel, MD PhD, department of Neurology, Ee2240, Erasmus MC, PO Box 2040, 3000 CA Rotterdam, Tel.+31107043979, d.dippel@erasmusmc.nl
- Charlos Majoie, MD PhD, department of Radiology, C1-426, AMC, PO Box 22660, 1100 DD Amsterdam, Tel. +31295669111, c.b.majoie@amc.uva.nl

Overall scientific summary CONTRAST

The DIST will be carried out by members of Collaboration for New TReatments of Acute Stroke (CONTRAST). The overarching aim of CONTRAST is to improve outcome of patients with stroke by a consortium that blends mechanistic, basic scientific projects with pragmatic randomized clinical trials with a firm view of the future of Dutch Stroke Research for the coming years, including and beyond the trial described in this protocol.

16.4 Appendix 4. Common Core Data Set

Background information
Inclusion center
Time and date of inclusion
Study ID number

Inclusion criteria check list
Age ≥18 years
NIH Stroke Scale score ≥ 2
Supratentorial non-traumatic ICH confirmed by NCCT, without a CTA confirmed causative vascular lesion (e.g. aneurysm, AVM, DAVF, CVST) or other known underlying lesion (e.g. tumor, cavernoma)
Minimal ICH volume of 10 mL
Intervention can be started within 8 hours of symptom onset
Written informed consent (deferred)

Exclusion criteria check list
Pre-stroke mRS ≥3
ICH-GS score ≥11
Hemorrhage due to hemorrhagic transformation of an infarct
Untreated coagulation abnormalities, including INR > 1.3 (point of care measurement allowed) and treatment with thrombin or oral factor Xa antagonists.
Moribund (e.g. coning, bilateral dilated unresponsive pupils), or progressively deteriorating clinical course with imminent death
Pregnancy
DIST-INFLAME: patients that use immunosuppressive or immune-modulating medication

Baseline characteristics	
Demographics	Age, sex, ethnicity
Clinical	Weight, height, systolic and diastolic blood pressure, heart rate, temperature, NIHSS, Glasgow Coma Scale, pre-stroke mRS
Medical history	Comorbidity influencing mRS, premorbid cognitive complaints, falls in the past year, known hypertension, known hyperlipidemia, peripheral artery disease, diabetes

	mellitus, atrial fibrillation or flutter, previous ischemic or hemorrhagic stroke, TIA, myocardial infarction, chronic heart failure, deep venous thrombosis, pulmonary embolism, known renal disease (serum creatinine >200micromol/L, dialysis or renal transplant), known liver disease (bilirubin > 2x upper normal limit (UNL) with AST/ALT/ALP >3x UNL, or cirrhosis), history of major bleeding, predisposition to bleeding, mechanical heart valve replacement
Medication	Antiplatelet agents, vitamin K antagonists, DOACs, therapeutic heparin, antihypertensives, statins, NSAIDs, immunosuppressant and immunomodulatory drugs
Intoxications	Use of alcohol, smoking status, use of drugs
Laboratory parameters (if obtained as part of routine clinical practice)	INR at admission (with date and time), INR after correction of vitamin K antagonist (date and time), serum creatinine, eGFR, serum glucose, CRP, hemoglobin, total white blood cell and neutrophil count, aPTT, PTT, thrombocyte count, bilirubin, AST, ALT and ALP
Neuroimaging*	Date and time of admission CT and CTA, ICH location, ICH volume, IVH extension, subarachnoid extension, subdural extension, hydrocephalus, CTA spot sign, other predictors of hematoma growth on baseline NCCT, small vessel disease burden, perihematomal edema volume, (causative) vascular lesions, and perihematomal perfusion and permeability measurements
ICH-GS score	See table 3a

* Neuro imaging parameters will be assessed by a central subcommittee.

Treatment and intervention	
Standard treatment	Date and time of informed consent, administration of anticoagulant/coagulopathy reversal agents, administration of dexamethasone (e.g. vitamin k, prothrombin complex concentrate, platelets), administration of ICP lowering medication (mannitol, hypertonic saline), administration of intravenous antihypertensive medication, external ventricular drain placement, treatment limitations at admission, cross-over to surgical treatment (type, date, time after randomization and reason)

Surgical	Date and time of informed consent, administration of anticoagulant/coagulopathy reversal agents (e.g. vitamin k, prothrombin complex concentrate, platelets), administration of dexamethasone, administration of ICP lowering medication (mannitol, hypertonic saline), administration of intravenous antihypertensive medication, treatment limitations at admission, cross-over to standard medical treatment (and reason). Name 1st and 2nd neurosurgeon, neuronavigation used, endoscope used, device used for ICH removal, irrigation solution used, conversion to craniotomy, endoscopic clot appearance, active bleeding during surgery and treatment, estimated percentage ICH volume reduction, external ventricular drain placement, rebleeding or new intracranial bleeding during surgery, surgery performed on hybrid OR, highest and lowest blood pressure during surgery, ventricular drain placement, procedure related complications, re-operation after intra-operative or direct post-operative NCCT, analysis of hematoma aspirate (DIST-INFLAME)
Timing	Time and date of: Onset of symptoms / last seen well Arrival in emergency room Arrival in operating room Start anesthesia Start of operative procedure (skin incision) End of procedure (end of skin closure)
Complications	Procedure related complications
Neuroimaging*	ICH volume remaining directly after evacuation

Workflow (logistics)	
Pre-hospital	Witnessed stroke onset yes/no. If yes: time and date of symptom onset; if no: time and date of last seen well and time of symptoms noticed.
In-hospital	Transfer from primary stroke center yes/no. If yes: time and date of arrival other (first) hospital, name other (first) hospital.

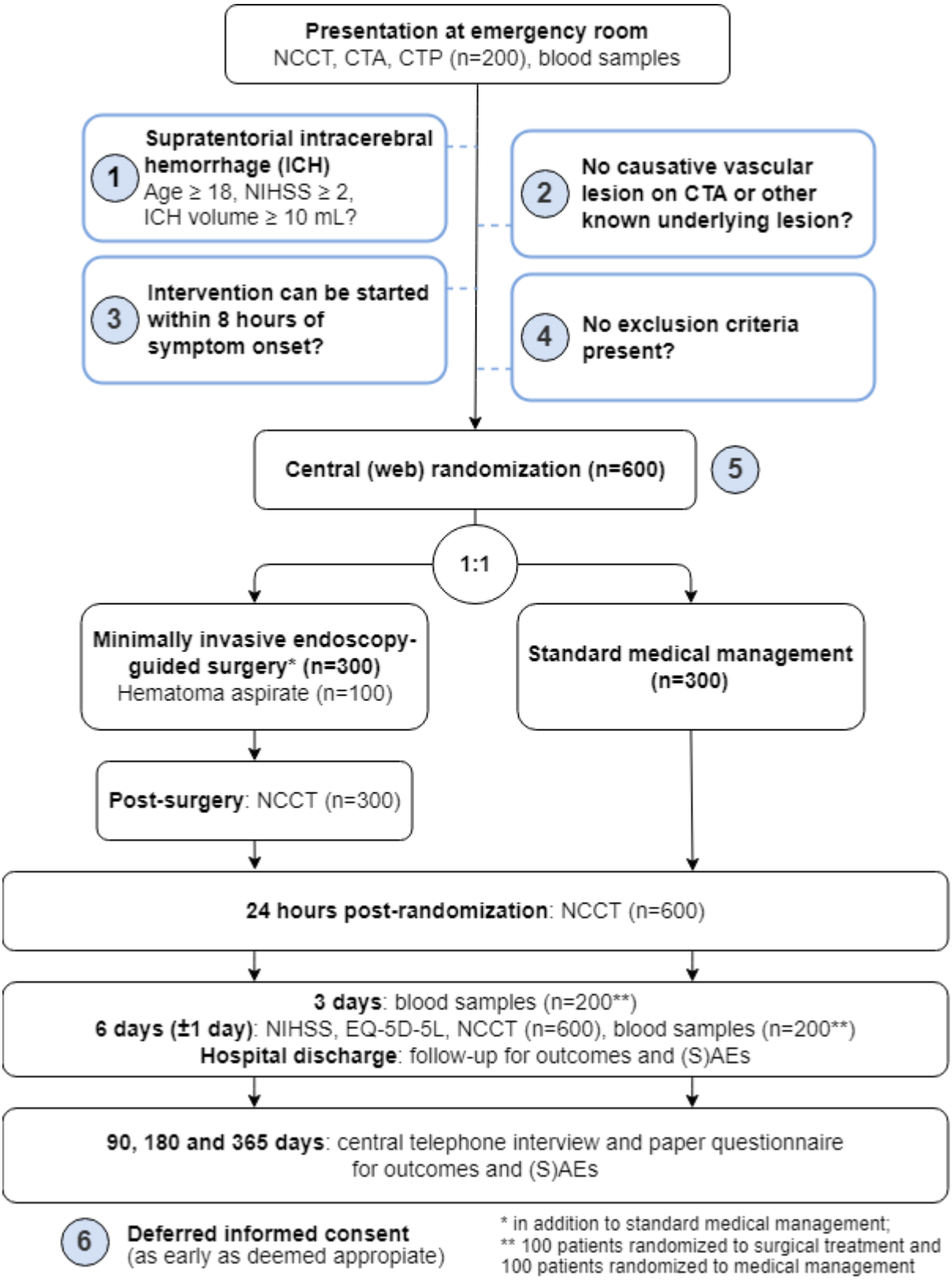
	Time and date of arrival neurosurgical hospital, neurosurgical hospital name If no: time of arrival (door) intervention hospital, intervention hospital name/postal code
Timing	Time of: NCCT, CT angiography, perfusion CT, post-operative CT, neuronavigation CT, 24 hours ±6 hours CT, 6 ±1 day CT

Follow-up	
Clinical assessment at 1, 6, and 12 hours; and at day 3 (±12 hours) (DIST-INFLAME)	Blood pressure and heart rate; treatment limitations
Serum inflammatory markers at day 3 (±12 hours) and day 6 (±1 day) (DIST-INFLAME)	CRP, serum creatinine, eGFR, INR, neutrophil and total white blood cell count, prothrombin time, activated partial thromboplastin time, levels of IL-1β, IL-6 and IL-10, and others
Neuroimaging postoperative	Date and time, ICH volume
Neuroimaging at 24 hours (±6 hours) and at day 6 (±1 day)	ICH volume, subdural extension, subarachnoid extension, ventricular extension, IVH volume, perihematomal edema
Additional NCCT in case of deterioration	Date and time ICH volume, subdural extension, subarachnoid extension, ventricular extension, IVH volume, perihematomal edema
Clinical assessment at 6 days (±1 day, or discharge if earlier)	Blood pressure, NIHSS, EQ-5D-5L, treatment limitations
Discharge	Neuroimaging during clinical follow-up, interventions and diagnosis during hospital stay (including use of medication), admission days, destination of discharge, treatment limitations
Clinical assessment at 90, 180 and 365 days (±14 days) via telephone interview	mRS, Barthel index, EQ-5D-5L, SS-QoL, health economic evaluations (medical

	consumption, productivity loss and burden for the caregiver), home time, patient location; parameters related to blinded outcome assessment
Serious adverse events (at any given time) **An adverse event is considered serious when it causes mortality, is life-threatening, requires prolonged hospitalization, or results in persistent significant disability**	1. Intracerebral hemorrhage progression 2. Intracerebral hemorrhage (other location, symptomatic) 3. Ischemic stroke 4. Subdural/epidural hematoma 5. Hydrocephalus 6. Extracranial hemorrhage (e.g. gastro-intestinal) 7. Cardiac ischemia 8. Allergic reaction 9. Pneumonia 10. Intracranial infection 11. Postoperative site infection 12. Other infection (specify) 13. Deep venous thrombosis or pulmonary embolism 14. Seizure(s) 15. Other (specify)

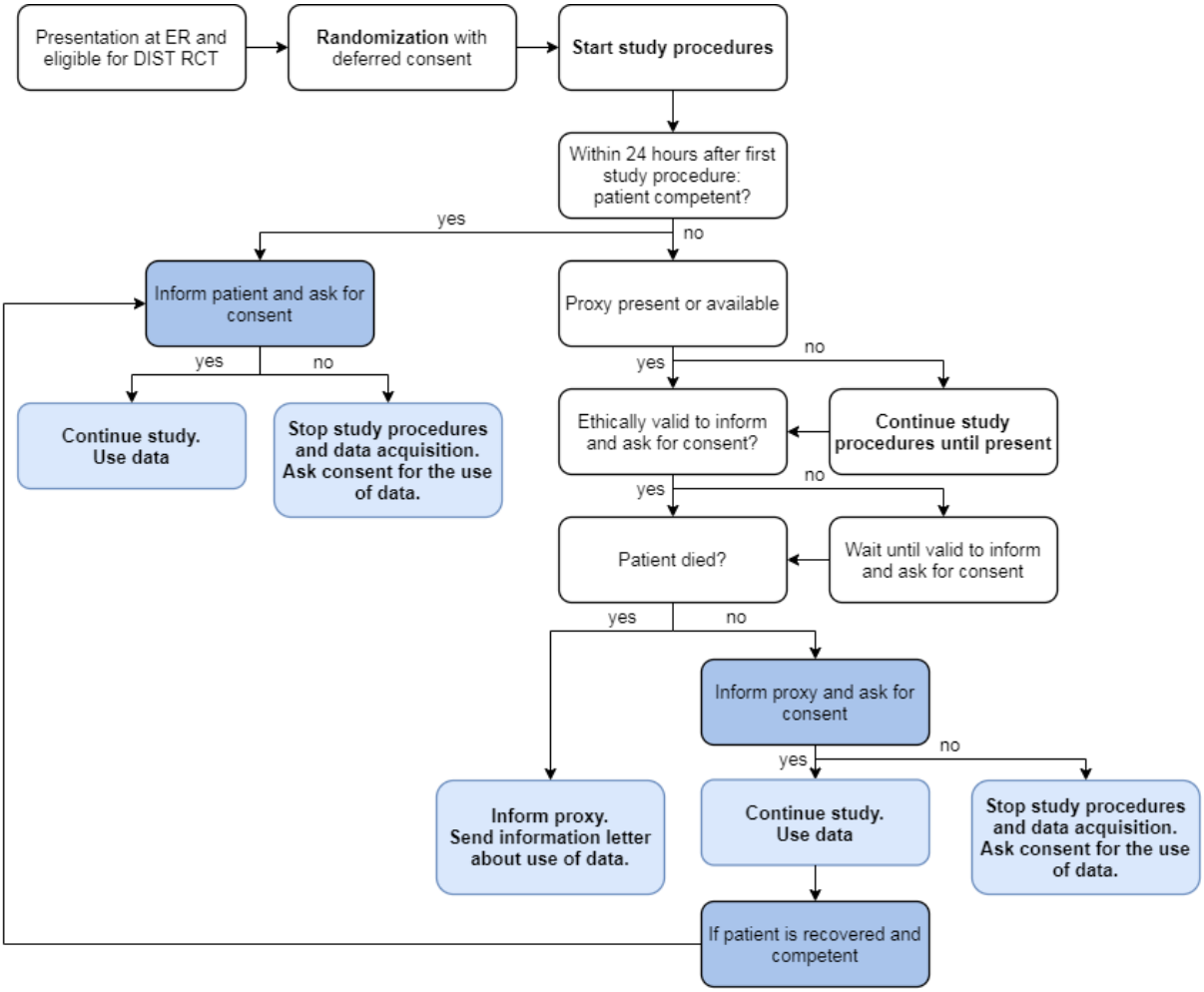
16.5 Appendix 5. Overview of study procedures

16.5.1 Appendix 5a. Flow chart of study procedures



CTA: Computed tomography angiogram; CTP: CT Perfusion; EQ-5D-5L: EuroQol 5-dimensions 5-level; ICH: intracerebral hemorrhage; NCCT: Non-contrast computed tomography; NIHSS: National Institutes of Health Stroke Scale; (S)AEs: (Serious) Adverse Events.

16.5.2 Appendix 5b. Flow chart of deferred consent procedure



Flow chart of deferred consent procedure specific for the DIST. Based on the flow chart for use of proxy-deferred consent in emergency critical care research by Jansen et al.[33]

16.5.3 Appendix 5c. Table of study procedures and time assessment

Study procedure	Time of assessment							
	Clinical phase					*Non-clinical phase*		
	Baseline	Day 0	Day 1	Day 3	Day 6±1	90 days	180 days	365 days
Vital signs	X	X^	X	X*	X			
NIHSS	X				X			
Blood samples	X			X*	X*			
Imaging	X	X°	X		X			
Surgery		X°						
Hematoma aspirate		X°*						
mRS						X	X	X
Barthel index						X	X	X
EQ-5D-5L					X	X	X	X
SS-QoL						X	X	X
Resource use						X	X	X
Burden for the caregiver						X	X	X
Home time						X	X	X
Patient location						X	X	X
^: assessed at 1, 6 and 12 hours. *: only in the DIST-INFLAME sub-study. **°**: only in the surgical arm of the DIST.								

16.6 Appendix 6. Surgical protocol

Surgical protocol accompanying the Dutch ICH Surgery Trial; minimally invasive endoscopy-guided surgery for spontaneous ICH

Version 1.0 February 4th 2022

INTRODUCTION

This surgical protocol is supplemental to the "RESEARCH PROTOCOL the Dutch ICH Surgery Trial (DIST); minimally invasive endoscopy-guided surgery for spontaneous ICH". This study intends to study whether minimally invasive endoscopy-guided surgery for treatment of supratentorial sICH performed within 8 hours of symptom onset, improves functional outcome at 6 months. Moreover, the effect on (perihematomal) edema and the cost-effectiveness and budget-impact of this treatment will be assessed. Lastly, the immune profiles over time in venous blood between surgically treated patients and controls will be compared. To ensure minimal performance bias we outline a surgical protocol to which including centers are obliged to adhere.

For details on the study population, patient eligibility, and study procedures we refer to the RESEARCH PROTOCOL Sections 4 "Study Population" and 8 "Methods".

INVESTIGATIONAL PRODUCT

The devices allowed into the trial are minimally invasive neuronavigation integrated endoscopy-guided devices. At present, this only includes the Artemis™ Neuro Evacuation Device, manufactured by Penumbra, Inc., which is CE marked (Appendix 8). For more details on the investigational product itself and a review of its use to date be referred to the RESEARCH PROTOCOL Section 6 "Investigational Product". The choice of a particular device is left to the discretion of the neurosurgeon. When other devices will become available, they may be used when they are deemed admissible by the steering committee.

SURGICAL PROTOCOL

All participants undergoing minimally invasive endoscopy-guided surgery will be treated according to this surgical protocol and the local institutional guidelines.

Training

Surgeons will undergo a detailed instructional training on the stereotactic-guided endoscopic procedure, including direct mentoring of the detailed step-by-step surgical protocol by the surgical principal investigator and hands-on training in a dry-lab setting. The latter will be provided by Penumbra, Inc., manufacturer of the Artemis™ Neuro Evacuation Device at the IRCAD training facility in Strasbourg, France, or a similar set-up at another location.

Pre-operative neuroimaging and planning for frameless image-guided endoscopic surgery

Depending on the institution and neuronavigation systems used, appropriately protocolled CT-imaging studies will be uploaded into the neuronavigation software for procedural planning and guidance. The use of surface merging or fiducial markers will be at the discretion of the surgeon. If an additional neuronavigation (non-contrast CT) scan is necessary, it will be performed as soon as possible after randomization in the surgical arm. A trajectory will be selected that is both technically feasible and allows access to the longest possible axis of the hematoma. For this, we adhere to the protocol as described in the ICES study.[54] The ideal trajectory, which is parallel to the longitudinal axis of the hematoma, is selected determining a candidate entry and target point. One of three approaches will be selected: (A) anterior frontal lobe approach, (B) posterior parietal lobe approach, or (C) surface cortical approach; each of which will be designed to be parallel and in the middle of the longitudinal axis of the hematoma while avoiding the internal capsule, vasculature, eloquent white matter tracts, and ventricles.

Surgical procedure

The patient is placed upon the procedural table according to the approach used. The procedure is performed under general anesthesia, and prophylactic antibiotics are administered according to local protocol. An external localization array or other neuronavigation localization is placed for registration according to the neuronavigation system in use. Once the appropriate entry point is identified, this area is prepared and sterile draped according to institutional guidelines. The image guidance probe is positioned over the candidate entry point. The virtual extension of the probe tip can be employed to interrogate the candidate entry points to assess whether the endoscope sheath will transgress any critical functional areas. If need be, the entry point can be adapted intra-operatively.

Hereafter, a 1.5-2.0 cm burr hole or minicraniotomy (maximum diameter 3-5 cm) of a size large enough to accommodate the selected endoscopy sheath is created. The dura is opened and the cortical surface coagulated and incised. A localization array (e.g., Instrument Adapter Clamp with Instrument Adapter Array, Brainlab AG) is attached to the selected neuroendoscopic sheath and registered to the navigation system. Using neuronavigation, the sheath is then advanced into the targeted landing zone until the distal aspect is located 2/3 of the longitudinal axis of the hematoma (point # 1), after which the inner obturator is removed. The sheath is then stabilized (e.g., manually stabilized, mechanically stabilized, or peeled away and stapled down) into position.

The neuroendoscope is then inserted into the sheath, and under direct visualization the Artemis™ Neuro Evacuation Device is placed through the working channel of the trocar. The

sheath is irrigated at the discretion of the surgeon using the irrigation port of the endoscope. Preferably, Lactated Ringer's Irrigation or Sterofundin® is used as an irrigant (instead of Sodium Chloride Irrigation Solution). The irrigant is intermittently aspirated with the Artemis™ system until a clear working view is created within the sheath that allows visualization of the surgical field at the sheath tip. The Artemis™ wand is advanced under direct visualization to, or just beyond the tip of the sheath and actuated to evacuate the blood products. If the working view becomes obscured by blood products within the sheath, additional irrigation and aspiration is performed intermittently to clear the field. This is repeated until no further clot can be evacuated at this location. The endoscope sheath is then irrigated to be sure that there is no evidence of active bleeding. If active bleeding is detected, irrigation is continued until the bleeding stops. If the bleeding does not stop adequately, the endoscope is introduced into the sheath, fixed in place, after which the bleeding point identified endoscopically and coagulated. Once hemostasis is obtained, the endoscope sheath is retracted to approximately 1/3 of the longitudinal axis of the hematoma cavity (point # 2). The suctioning and irrigation process is then repeated at point # 2. Suctioning is continued until at least 75% of the hematoma volume is thought to be removed, though maximal hematoma evacuation is desirable. Lastly, the endoscope is reintroduced to ensure there is no sign of active bleeding that may require additional irrigation or bipolar coagulation. However, no rotational steering of the sheath or lateral exploration of the hematoma cavity is permitted. Subsequently, the endoscope and sheath are removed. These endoscopic techniques are elaborately described elsewhere as well.[49,73] The cortical surface is carefully inspected to ensure that there is no bleeding from the corticotomy. Finally, the dura and skin are closed routinely.

A control NCCT is performed immediately after surgery, or intra-operatively if possible (hybrid room with intra-operative CT) to confirm adequate hematoma evacuation and to assess for any complications (e.g., rebleeding, hydrocephalus, increased mass effect). The surgical goal is to reduce the hematoma volume by at least 75%. It is at the surgeon's discretion to opt for an immediate return to the operating room (OR) to evacuate any residual hematoma.

Postoperative care protocol

Patients are either admitted to the (neuro-)intensive care unit (ICU) or a dedicated stroke unit for postoperative care. Neurological evaluation is performed according to institutional guidelines. Hypertension is treated according to National Guidelines as part of standard medical management, as is the case with patients in the non-surgical arm of the study. The aim is to achieve a target systolic blood pressure of 140 mmHg, if necessary, using intravenous hypertensive agents in the acute phase.

Ideally, patients should emerge rapidly from anesthesia to permit immediate assessment of surgery results and to provide a baseline for continued postoperative neurologic follow-up.

Nevertheless, there are some categories of patients in whom early awakening will not be deemed appropriate by the attending neurosurgeon (e.g. preoperative impaired consciousness or inadequate airway control, high postoperative risk of brain edema, elevated ICP, or deranged intracerebral hemostasis). This will remain at the discretion of the surgeon.

Prophylactic use of low-molecular-weight heparin (LMWH) in immobile patients is allowed at least 48 hours after the onset of the intracerebral hemorrhage. Intermittent pneumatic compression and elastic stockings can be applied in the first 72 hours. Restarting anticoagulant or antiplatelet medication in patients with a clear indication will be allowed as of three days after surgery. There are no trials to determine the optimal timing of restarting anticoagulants after ICH. The decision on whether and when to restart this medication is left to the local team and will depend on the indication for the antithrombotic treatment and a careful risk/benefit assessment.

16.7 Appendix 7. CT acquisition protocol and imaging requirements

CLINICAL IMAGING IN PATIENTS WITH ICH

Non-contrast CT and CT angiography

Patients suspected of an acute stroke and no significant renal insufficiency or contrast allergy routinely undergo a stroke CT study on presentation at the emergency department, which consists of a non-contrast CT (NCCT) of the brain and a CT-angiogram (CTA) of the (cervical) and intracranial arteries.

Before randomization, a NCCT and CTA should be performed to assess eligibility for the study. In addition, 24 hours (± 6 hours) after randomization, and 6 ± 1 day after randomization or at discharge (if earlier) a NCCT should be performed to assess the hematoma volume and perihematomal edema. Patients in the surgical arm will undergo an additional NCCT for the purpose of neuronavigation if deemed necessary by the operating neurosurgeon, and a NCCT immediately after surgery to assess the achieved reduction in ICH volume.

CT perfusion

In some sites, a CT perfusion (CTP) is already performed in patients with an intracerebral hemorrhage, as a standard part of the stroke CT study in addition to the NCCT and CTA upon presentation to the emergency department. The standard CTP acquisition protocol of these sites consists of one phase with a short acquisition time, which is used to calculate the perfusion parameters. However, for permeability measurements, which are relevant for assessment of blood-brain barrier (BBB) breakdown, a delayed acquisition is necessary.[74-76] In context of the DIST-INFLAME sub-study, a CTP with an adapted acquisition protocol will be performed prior to randomization.

IMAGING ACQUISITION PROTOCOLS DIST

The specific imaging protocols for acquisition of the NCCT, neuronavigation NCCT, CTA and CTP varies by center. To allow for a structured systematic analysis of all image data and an automated imaging biomarkers extraction, standardized image acquisition protocols are important. Therefore, we describe the minimum requirements for image acquisition protocols to be used in the medical centers that participate in the DIST.

Non-contrast CT brain acquisition protocol requirements

Non-contrast CT brain - *Version 1.0 February 1st 2022*

Data acquisition	Parameters		Remarks
Scan range	below foramen magnum - cranial vertex (includes entire sagittal sinus)		**obligatory**
Scan type	spiral **with** gantry/head tilt in orbitomeatal line		1st choice
	spiral **without** gantry/head tilt in orbitomeatal line		2nd choice
	sequential **with** gantry/head tilt in orbitomeatal line		3rd choice
Collimation	number of detector rows available × ≤ 1.0 mm		**preferred**
Rotation time (n.a. for sequential scanning)	cooperative patient	≥ 1.0 second	**preferred**
	uncooperative (moving) patient	≤ 0.4 seconds	**preferred**
Pitch (n.a. for sequential scanning)	uncooperative (moving) patient	0.6-0.85	**preferred**
	moving patient	1.2-1.7	**preferred**
Tube voltage (kVp)	local practice		
Tube amperage (mAs)	local practice		
$CTDI_{vol}$ 16cm indication	30-50 mGy (iterative)		1st choice
	50-70 mGy (filtered back projection)		2nd choice
Image reconstruction	Parameters		Remarks
Field of view	fit to skull		**obligatory**
Scan direction	caudal-cranial		**preferred**
Scan plane	axial		**obligatory**
Reconstructed slice thickness/increment	1:	range 3-5 mm / 2.0-3.0 mm	**obligatory**
	2:	≤ 1.0 mm / ≤ 0.7 mm	**obligatory**
Brain kernel	local practice		

n.a. = not applicable

CT-angiography head(-neck) acquisition protocol requirements

CTA head(-neck) - Version 1.1 December 22nd 2022

Data acquisition	Parameters			Remarks
Scan range	cranial vertex (includes entire sagittal sinus) - below foramen magnum			**obligatory**
	in case of CTA neck: just below aortic arch			**preferred**
Scan direction	cranial - caudal			**preferred**
Scan type	spiral			**preferred**
Collimation	number of detector rows available × ≤ 1.0 mm			**preferred**
Rotation time	cooperative patient		≥ 0.5 seconds	**preferred**
	uncooperative (moving) patient		≤ 0.4 seconds	**preferred**
Pitch	cooperative patient		0.8-0.9	**preferred**
	uncooperative (moving) patient		1.2-1.7	**preferred**
Tube voltage (kVp)	automated tube current selection for vascular exam type			1st choice
	fixed kVp, as close to 100 kVp as possible			2nd choice
Tube amperage (mAs)	local practice			
$CTDI_{vol}$ indication (prior to kV/mA modulation)	16 cm	12-26 mGy (iterative)		1st choice
		16-32 mGy (filtered back projection)		2nd choice
	32 cm	6-13 mGy (iterative)		1st choice
		8-16 mGy (filtered back projection)		2nd choice
Contrast media	flux (administered iodine in grams / second)		1.3-1.8 *	**obligatory**
	maximum amount		90 mL	**obligatory**
	injection site		right cubital fossa	**preferred**
NaCl flush bolus amount	≥ 40 mL			**obligatory**
Scan delay	timed with contrast bolus tracking			**obligatory**
Image reconstruction	**Parameters**			**Remarks**
Directions	axial			**obligatory**
Brain kernel	local practice			
Reconstruction	**Slice width/increment**		**Field of view**	**Remarks**
1. Extracranial arteries (in case of CTA neck)	≤ 1.0 mm / ≤ 0.6 mm		small to fit carotids and vertebral arteries	**obligatory**
2. Intracranial arteries	≤ 0.75 mm / ≤ 0.4 mm		small to fit intracranial arteries	**obligatory**

*** Example contrast injection:**
Contrast media Visipaque: 320mg iodine / mL = 0,320 g iodine / mL.
Example calculation flowrate at flux 1,3 is: 1,3 / 0,320 = 4,0 mL / second.

Considerations:
A higher iodine flux is preferred over a lower iodine flux, but it should be feasible over i.v. canula in the individual patient.
With faster scans/scanners injection protocol tends to shift to lower volumes due to shorter scan time, but a resulting drop in peak Hu needs to be compensated with higher flux.
Low kVp (< 100) can tolerate lower iodine flux compared to high kVp (≥ 100) scans.

CT-perfusion brain acquisition protocol requirements

CTP brain - Version 1.0 February 1st 2022

Data acquisition	Parameters		Remarks
Moment of acquisition	before CTA or >4 min after CTA		**obligatory**
Tube voltage (kVp)	local practice		
Tube amperage (mAs)	local practice		
Start of acquisition	delay < 6 seconds		**obligatory**
	direct with as little delay as possible		**preferred**
Max acquisition time	210 seconds		**obligatory**
Acquisition sequence	Canon Aquilion	20 x 2 s + 4 x 5 s + 5 x 30 s	**obligatory**
	Siemens Somatom	20 x 1.5 s + 10 x 3 s + 5 x 30 s	**obligatory**
	Philips Brilliance	30 x 2 s + 5 x 30 s	**obligatory**
	Philips iQON	18 x 3.4 s + 5 x 30 s	**obligatory**
Contrast media	flux (administered iodine in grams / second)	1.8 *	**obligatory**
	total iodine dose	15 g *	**obligatory**
	injection site	right cubital fossa	**preferred**
NaCl flush bolus amount	40 mL		**obligatory**
Image reconstruction	Parameters		Remarks
Field of view	whole brain		**obligatory**
Brain coverage	≥80 mm		**obligatory**
	whole brain		**preferred**
Reconstructed slice thickness/increment	1:	5 mm / ≤ 3.0 mm	**obligatory**
	2:	≤ 1.5 mm / ≤ 1.0 mm	**obligatory**

*** Corresponding contrast volume and injection rate per iodine concentration used**		
Iodine concentration	Contrast volume	Injection rate
270 mg/ml	55.6 ml	6.7 ml/s
300 mg/ml	50 ml	6 ml/s
320 mg/ml	46.9 ml	5.6 ml/s
350 mg/ml	42.9 ml	5.1 ml/s
400 mg/ml	37.5 ml	4.5 ml/s

16.8 Appendix 8. CE-mark for investigational device Artemis™, Neuro Evacuation Device, Penumbra, Inc.

NSAI

Quality System Approval Certificate
Medical Devices Directive 93/42/EEC

The National Standards Authority of Ireland as a duly designated Notified Body, (identification number 0050), for the purposes of the European Communities (Medical Devices) Regulations (S.I. No. 252 of 1994)

APPROVES THE QUALITY SYSTEM APPLIED BY

Penumbra, Inc.

One Penumbra Place
Alameda
CA 94502
USA

to the Product Family

Surgical irrigation/aspiration handpiece, single-use (Artemis™ Neuro Evacuation Device)

GMDN Code: 60793

on the basis of examination under the requirements of Directive 93/42/EEC on Medical Devices, Annex II, excluding (4)
The use of the NSAI Notified Body identification number 0050 in conjunction with CE Marking of Conformance for this product family is hereby authorised.

Registration Number:	**252.962**
Original Approval:	**10 November 2015**
Last Amended on:	**20 December 2019**
Remains valid until:	**09 November 2023**

Signed:

Approved by:
Geraldine Larkin
Chief Executive Officer, NSAI

Approved by:
Elaine Darcy
European Medical Device Operations Manager

This certificate remains valid on condition that the Approved Quality System is maintained in an adequate and efficacious manner.
Details of the operational locations included within the scope of this approval can be obtained from NSAI

In the case of a Class III device, this certificate must be supported by a valid design examination certificate

National Standards Authority of Ireland, 1 Swift Square, Northwood, Santry, Dublin 9, Ireland.

Cert-114: EC Annex II-NL-A4 (9)

EC Design Examination Certificate
Medical Devices Directive 93/42/EEC

*The National Standards Authority of Ireland as a duly designated Notified Body, (identification number **0050**), for the purposes of the European Communities (Medical Devices) Regulations (S.I. No. 252 of 1994)*

HAS EXAMINED THE DESIGN DOSSIER
Submitted by

Penumbra, Inc.

One Penumbra Place
Alameda
CA 94502
USA

For Product Family

Surgical irrigation/aspiration handpiece, single-use (Artemis™ Neuro Evacuation Device)

GMDN Code: 60793

CONCLUSION of EXAMINATION:

NSAI have performed an examination of the design dossier relating to the above named product family and conclude that the design complies with the requirements of Directive 93/42/EEC on Medical Devices, Annex II (4)

Registration Number:	**252.962**
Original Approval:	**10 November 2015**
Last Amended on:	**20 December 2019**
Remains valid until:	**09 November 2023**

Signed:

Approved by:
Geraldine Larkin
Chief Executive Officer, NSAI

Approved by:
Elaine Darcy
European Medical Device Operations Manager

CONDITIONS OF VALIDITY:

This certificate remains valid on condition that the Approved Quality System is maintained in an adequate and efficacious manner.
Approved model numbers are included in the associated attachment
Note: Not valid without a valid Annex II Section 3 Certificate.
Changes which could affect conformity with the essential requirements of Directive 93/42/EEC or with the conditions prescribed for use of the product must receive further approval from NSAI.
National Standards Authority of Ireland, 1 Swift Square, Northwood, Santry, Dublin 9, Ireland.

Cert-116: ECDEC-NL-A4 (8)

Attachment to Certificate 252.962

dated 10 November 2015

This Certificate covers 3 model(s)

Sub-Family	Catalogue Number	Description	Class
Artemis Neuro Evacuation Device	AP15	Artemis Neuro Evacuation Device 1.5 mm	III
	AP21	Artemis Neuro Evacuation Device 2.1 mm	
	AP28	Artemis Neuro Evacuation Device 2.8 mm	