RESEARCH PROTOCOL Dutch ICH Surgery Trial (DIST)

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

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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
ССМО	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
СТ	Computed Tomography
СТА	Computed Tomography Angiography
СТР	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	EuroQoI 5-dimensions 5-level
EuroQol	European Quality of Life
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1C

hs-CRP	High-sensitivity C-Reactive Protein
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, EuroQoI-5D-5L, SS-QOL, iMCQ, iPCQ and iVICQ 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 \geq 70%, and \geq 80%, and with remaining clot volume \leq 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 (\pm 12 hours) and 6 days (\pm 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 care⁷ 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; I² 46%; 20 studies) and minimally invasive surgery (RR 1.47, 95% CI 1.26-1.72; I² 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, interguartile 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; I² 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 <u>Appendix</u> <u>3</u>). 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 <u>Appendix 5</u>.

Figure 1. Flow chart of study procedures



CTA: Computed tomography angiogram; CTP: CT Perfusion; 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 RCT. 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 (<u>Appendix 1</u>). 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 \geq 2 (<u>Table 2</u>);
- 3. Supratentorial 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:

- Considerable pre-stroke dependency in activities of daily living, defined as a pre-stroke mRS ≥3 (<u>Table 1</u>);
- 2. ICH-GS score \geq 11 (<u>Table 3</u>);
- 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;
- The neurosurgeon should adhere to the surgical protocol (See <u>Appendix 6</u>; 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[™] 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 (<u>Appendix 8</u>).

The ArtemisTM 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 ArtemisTM Neuro Evacuation Device is guided to the target location using intraprocedural image-guidance. Inside the ArtemisTM 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 ArtemisTM 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 <u>Appendix 6</u>; 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

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; l^2 46%; 20 studies) and minimally invasive surgery (RR 1.47, 95% CI 1.26-1.72; I² 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; I² 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. Fortysix 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 \geq 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. 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 (\pm 14 days) (see <u>paragraph 8.3.4</u>).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 (<u>Table 1</u>). 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 (<u>Table 2</u>) 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 (<u>Table 5</u>) at 90 days (± 14 days), 180 days (± 14 days) and 365 days (± 14 days);
- Quality of life assessed with the EuroQol 5D-5L (<u>Table 4</u>) and Stroke-Specific Quality of Life scale (<u>Table 6</u>) at 90 days (± 14 days), 180 days (± 14 days) and 365 days (± 14 days);
- Resource use measured with 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 \geq 70%;
- Percentage of participants with hematoma volume reduction $\geq 80\%$;
- 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 and heart rate;
- Neurological examination: NIHSS (see <u>paragraph 8.3.3.</u> and <u>Table 2</u>), Glasgow Coma Scale;
- Pre-stroke functionality: pre-stroke mRS (Table 1);
- Comorbidities/medical history: comorbidity influencing mRS, known hypertension, known hyperlipidemia, peripheral artery disease, diabetes mellitus, atrial fibrillation or flutter, previous ischemic or hemorrhagic stroke, TIA, thromboembolism, 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, mechanical heart valve replacement;

- Medication: use of antiplatelet agents, vitamin K antagonists, dabigatran, 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, and perihematomal perfusion and permeability measurements (see <u>paragraph 8.3.6</u>);
- 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 (<u>Table 3</u>).

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 used, irrigation solution used, conversion to craniotomy, active bleeding during surgery, 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, volume of residual hematoma expected, 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 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).
- Imaging results: ICH volume and perihematomal edema volume at 24 hours (± 6 hours) and 6 days (±1 day) (see paragraph 8.3.6).
- DIST-INFLAME: blood pressure at 3 days and laboratory examinations at 3 (± 12 hours) and 6 days (±1 day) (see <u>paragraph 8.3.5</u>)

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 imaging will be evaluated by assessors blinded for the treatment from the results of baseline imaging. Information on follow-up assessments will be kept separate from the main study database. The steering committee will be kept unaware of the results of interim analyses of efficacy and safety. The independent trial 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).

8.3 Study procedures

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

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 and heart rate will be assessed at baseline upon admission to the neurosurgical center. Additionally, blood pressure will be collected at 1, 6, 12, and 24 hours after admission and at day 6 (\pm 1 day, or discharge if earlier). For DIST-INFLAME, the blood pressure will also be collected at day 3 (\pm 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 (<u>Table 2</u>) 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 (<u>Table 1</u>). The mRS will be assessed at 90 days (\pm 14 days), 180 days (\pm 14 days) and 365 days (\pm 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-1 β , 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 (<u>Table 5</u>). The Barthel index will be assessed during the telephone interviews at 90 days (\pm 14 days), 180 days (\pm 14 days) and 365 days (\pm 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 during the telephone interviews at 90 days (\pm 14 days), 180 days (\pm 14 days) and 365 days (\pm 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 (<u>Table</u> <u>6</u>).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 (\pm 14 days), 180 days (\pm 14 days) and 365 days (\pm 14 days).

8.3.10 Resource use

Resource use will be measured with 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 iMCQ and iPCQ 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 (\pm 14 days), 180 days (\pm 14 days) and 365 days (\pm 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 (\pm 14 days), 180 days (\pm 14 days) and 365 days (\pm 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 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.

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, new 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 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 (<u>Appendix 2</u>). 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, 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 costeffectiveness 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.⁶⁶ 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 <u>Appendix 5b</u>. 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. All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

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 will be registered with ClinicalTrials.gov.

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. Written proposals will be assessed by DIST investigators for appropriateness of use, and 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 <u>Chapter 9.5</u> and de DSMB charter.

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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	No significant disability despite symptoms; able to
	disability	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	Moderately severe disability; unable to walk and
	disability	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	0 = Alert ; keenly responsive.
must choose a response if a full evaluation is prevented	1 = Not alert ; but arousable by minor
by such obstacles as an endotracheal tube, language	stimulation to obey, answer, or respond.
barrier, orotracheal trauma/bandages. A 3 is scored only	2 = Not alert ; required repeated
if the patient makes no movement (other than reflexive	stimulation to attend, or is obtunded and
posturing) in response to noxious stimulation.	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	0 = Answers both questions correctly.
and his/her age. The answer must be correct – there is	1 = Answers one question correctly.
not partial credit for being close. Aphasic and stuporous	2 = Answers neither question correctly.
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.	
1c. LOC Commands. The patient is asked to open and	0 = Performs both tasks correctly.
close the eyes and then to grip and release the non-	1 = Performs one task correctly.
paretic hand. Substitute another one step command if	2 = Performs neither task correctly.
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,	

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	0 = Norma l.
tested. Voluntary or reflexive (oculocephalic) eye	1 = Partial gaze palsy ; gaze is
movements will be scored, but caloric testing is not	abnormal in one or both eyes, but forced
done. If the patient has a conjugate deviation of the eyes	deviation or total gaze paresis is not
that can be overcome by voluntary or reflexive activity,	present.
the score will be a 1. If a patient has an isolated	2 = Forced deviation; or total gaze
peripheral nerve paresis (CN III, IV or VI), score a 1.	paresis not overcome by the
Gaze is testable in all aphasic patients. Patients with	oculocephalic maneuver.
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.	
3. Visual. Visual fields (upper and lower quadrants) are	0 = No visual loss.
3. Visual. Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual	0 = No visual loss. 1 = Partial hemianopia.
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	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia.
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,	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind
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	 0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness)
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	 0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness)
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,	 0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness)
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	 0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness)
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	 0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness)
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	 0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness)
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	 0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness)
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)
 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. 4. Facial Palsy. Ask – or use pantomime to encourage 	 0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia (blind including cortical blindness) 0 = Normal symmetrical movements.
 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. 4. Facial Palsy. Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close 	 0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia (blind including cortical blindness) 0 = Normal symmetrical movements. 1 = Minor paralysis (flattened
 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. 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 	 0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia (blind including cortical blindness) 0 = Normal symmetrical movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling)
 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. 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- 	 0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia (blind including cortical blindness) 0 = Normal symmetrical movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling) 2 = Partial paralysis (total or near-total
 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. 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, 	 0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia (blind including cortical blindness) 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. 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. 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 	 0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia (blind including cortical blindness) 3 = Bilateral hemianopia (blind including cortical blindness) 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
 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. 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 	 0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia (blind including cortical blindness) 3 = Bilateral hemianopia (blind including cortical blindness) 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

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

of blindness, test by having the patient touch nose from		
extended arm position.		
8. Sensory. Sensation or grimace to pinprick when	0 = Normal; no sensory loss.	
tested, or withdrawal from noxious stimulus in the	1 = Mild-to-moderate sensory loss;	
obtunded or aphasic patient. Only sensory loss	patient feels pinprick is less sharp or is	
attributed to stroke is scored as abnormal and the	dull on the affected side; or there is a	
examiner should test as many body areas (arms [not	loss of superficial pain with pinprick, but	
hands], legs, trunk, face) as needed to accurately check	patient is aware of being touched.	
for hemisensory loss. A score of 2, 'severe or total	2 = Severe to total sensory loss;	
sensory loss', should only be given when a severe or	patient is not aware of being touched in	
total loss of sensation can be clearly demonstrated.	the face, arm and leg.	
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.		
9. Best language. A great deal of information about	0 = No aphasia ; normal	
comprehension will be obtained during the preceding	1 = Mild-to-moderate aphasia; some	
sections of the examination. For this scale item, the	obvious loss of fluency or facility of	
patient is asked to describe what is happening in the	comprehension, without significant	
attached picture, to name the items on the attached	limitation on ideas expressed or form of	
naming sheet and to read from the attached list of	expression. Reduction of speech and/or	
sentences. Comprehension is judged from responses	comprehension, however, makes	
here, as well as to all the commands in the preceding	conservation about provided materials	
general neurological exam. If visual loss interferes with	difficult or impossible. For example, in	
the tests, ask the patient to identify objects placed in the	conversation about provided materials,	
hand, repeat, and produce speech. The intubated	examiner can identify picture or naming	
patient should be asked to write. The patient in a coma	card content from patient's response.	
(item 1a=3) will automatically score 3 on this item. The	2 = Severe aphasia; all communication	
examiner must choose a score for the patient with	is through fragmentary expression; great	
stupor or limited cooperation, but a score of 3 should be	need for inference, questioning, and	
used only if the patient is mute and follows no one-step	guessing by the listener. Range of	
commands.	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	0 = Normal.
adequate sample of speech must be obtained by asking	1 = Mild-to-moderate dysarthria;
patient to read or repeat words from the attached list. If	patient slurs at least some words and, at
the patient has severe aphasia, the clarity of articulation	worst, can be understood by some
of spontaneous speech can be rated. Only if patient is	difficulty.
intubated or has other physical barriers to producing	2 = Severe dysarthria: patient's speech
speech, the examiner should record the score as	is so slurred as to be unintelligible in the
untestable (UN), and clearly write an explanation for this	absence of or out of proportion to any
choice. Do not tell the patient why he or she is being	dysphasia, or is mute/anarthric.
tested.	UN = Intubated or other physical
	barrier. Explain:
11. Extinction and Inattention (formerly Neglect).	0 = No abnormality.
Sufficient information to identify neglect may be obtained	1 = Visual, tactile, auditory, spatial, or
during the prior testing. If the patient has a severe visual	personal inattention or extinction to
loss preventing visual double simultaneous stimulation,	hilatanal almostera anno athrophathan in an a
	bilateral simultaneous stimulation in one
and the cutaneous stimuli are normal, the score is	of the sensory modalities.
and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to	of the sensory modalities. 2 = Profound hemi-inattention or
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 the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality;
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	of the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients
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	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	<40 mL	1
supratentorial	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 EuroQoI-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.	1	I have no problems doing my usual activities
(house)work, study,	2	I have slight problems doing my usual activities
family or leisure	3	I have moderate problems doing my usual activities
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



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	0	Unable, no sitting balance	
back)	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		Sco	ring					
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	
Per	sonality						
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.	l 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		
Up	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		
Sco	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.

Neurosurgical hospitals

Site 1: Amsterdam University Medical Center, Amsterdam Prof. Dr. W.P. Vandertop, neurosurgeon Dr. J.M. Coutinho, neurologist

Site 2: Erasmus Medical Center, Rotterdam 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 <u>Prof. Dr. M.J.H. Wermer, neurologist</u> 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 Dr. I.R. de Ridder, neurologist Dr. R. 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

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.

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

Prof. Dr. M.M. Rovers, Department for Health Evidence, Radboud University Medical Center, Nijmegen
16.3 Appendix 3. CONTRAST: Collaboration for new treatments of acute stroke



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, <u>d.dippel@erasmusmc.nl</u>
- Charlos Majoie, MD PhD, department of Radiology, C1-426, AMC, PO Box 22660,
 1100 DD Amsterdam, Tel. +31295669111, <u>c.b.majoie@amc.uva.nl</u>

Overall scientific summary CONTRAST

The DIST RCT 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 the coming years, including and beyond the trial described in this protocol.

16.4 Appendix 4. Common Core Data Set

Background	information
Dackyrounu	mormation

Inclusion center

Time and date of inclusion

Study ID number

Inclusion check list

Age ≥18 years

NIH Stroke Scale score ≥ 2

Supratentorial 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

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, NIHSS, Glasgow Coma Scale, pre-stroke mRS
Medical history	Comorbidity influencing mRS, known hypertension, known
	hyperlipidemia, peripheral artery disease, diabetes mellitus,
	atrial fibrillation or flutter, previous ischemic or hemorrhagic
	stroke, TIA, thromboembolism, 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, mechanical heart valve
	replacement
Medication	Antiplatelet agents, vitamin K antagonists, dabigatran,
	heparin, antihypertensives, statins, NSAIDs,
	immunosuppressant and immunomodulatory drugs
Intoxications	Use of alcohol, smoking status, use of drugs
Laboratory parameters (if	INR at admission (with date and time), INR after correction of
obtained as part of	vitamin K antagonist (date and time), serum creatinine,
routine clinical practice)	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, 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, 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	1
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, cross-over to surgical treatment (type, date,
	time after randomization)
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.							
	Name 1 st and 2 nd neurosurgeon, neuronavigation used,							
	endoscope used, device used for ICH removal, irrigation							
	solution used, conversion to craniotomy, active bleeding							
	during surgery, 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, volume of							
	residual hematoma expected, re-operation after intra-							
	operative or direct post-operative NCCT, analysis of							
	hematoma aspirate (DIST-INFLAME)							
Timing	Time of:							
	Onset of symptoms							
	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 of symptom							
	onset; if no: time of last seen well and time of symptoms							
	noticed. Time of arrival of ambulance on site.							
In-hospital	Referrer of stroke yes/no.							
	If yes: time of hospital admission transfer hospital, departure							
	time transfer hospital, transferring hospital name/postal code,							
	time of arrival (door) intervention hospital, intervention							
	hospital name/postal code							
	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	Blood pressure
hours; and at day 3 (±12 hours) (DIST-	
INFLAME)	
Serum inflammatory markers at day 3	CRP, serum creatinine, eGFR, INR,
(±12 hours) and day 6 (±1 day) (DIST-	neutrophil and total white blood cell count,
INFLAME)	prothrombin time, activated partial
	thromboplastin time, levels of IL-1 β , IL-6
	and IL-10, and others
Neuroimaging postoperative	Date and time, ICH volume
Neuroimaging at 24 hours (±6 hours) and	ICH volume, subdural extension,
at day 6 (±1 day)	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	Blood pressure, NIHSS
discharge if earlier)	
Discharge	Neuroimaging during clinical follow-up,
	interventions and diagnosis during hospital
	stay (including use of medication),
	admission days, destination of discharge
Clinical assessment at 90, 180 and 365	mRS, Barthel index, EQ-5D-5L, SS-QoL,
days (±14 days) via telephone interview	iMCQ, iPCQ, iVICQ, home time, patient
	location
Serious adverse events (at any given	1. Intracerebral hemorrhage progression
time)	2. Intracerebral hemorrhage (other location,
An adverse event is considered serious	symptomatic)
when it causes mortality, is life-	3. Ischemic stroke
threatening, requires prolonged	4. Subdural/epidural hematoma
hospitalization, or results in persistent	5. Extracranial hemorrhage (e.g. gastro-
significant disability	intestinal)
	6. Cardiac ischemia

7. Allergic reaction
8. Pneumonia
9. Intracranial infection
10. Postoperative site infection
11. Other infection (specify)
12. Deep venous thrombosis or pulmonary
embolism
13. Seizure(s)
14. Other (specify)

16.5 Appendix 5. Overview of study procedures



CTA: Computed tomography angiogram; CTP: CT Perfusion; 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 RCT. Based on the flow chart for use of proxy-deferred consent in emergency critical care research by Jansen et al.³³

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

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

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 <u>"Study Population"</u> and 8 <u>"Methods"</u>.

INVESTIGATIONAL PRODUCT

The devices allowed into the trial are minimally invasive neuronavigation integrated endoscopy-guided devices. At present, this only includes the ArtemisTM Neuro Evacuation Device, manufactured by Penumbra, Inc., which is CE marked (<u>Appendix 8</u>). For more details on the investigational product itself and a review of its use to date be referred to the RESEARCH PROTOCOL <u>Section 6 "Investigational Product"</u>. 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 CTimaging 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 (\pm 6 hours) after randomization, and 6 \pm 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	Pa	rameters	Remarks			
Scan range	be	ow foramen magnum - cranial	obligatory			
	ent	tire sagittal sinus)				
Scan type	spi	ral with gantry/head tilt in orbite	omeatal line	1 st choice		
	spi	ral without gantry/head tilt in o	rbitomeatal line	2 nd choice		
	sec	quential with gantry/head tilt in	orbitomeatal line	3 rd choice		
Collimation	nu	mber of detector rows available	e × ≤ 1.0 mm	preferred		
Rotation time (n.a. for	COO	operative patient	≥ 1.0 second	preferred		
sequential scanning)	un	cooperative (moving) patient	≤ 0.4 seconds	preferred		
Pitch (n.a. for	un	cooperative (moving) patient	0.6-0.85	preferred		
sequential scanning)	mc	ving patient	preferred			
Tube voltage (kVp)	loc	al practice				
Tube amperage (mAs)	loc	al practice				
CTDI _{vol} 16cm indication	30-	-50 mGy (iterative)	1 st choice			
	50-	-70 mGy (filtered back projectio	n)	2 nd choice		
Image reconstruction	Pa	rameters		Remarks		
Field of view	fit t	fit to skull				
Scan direction	cau	caudal-cranial				
Scan plane	axi	obligatory				
Reconstructed slice	1:	range 3-5 mm / 2.0-3.0 mm	obligatory			
thickness/increment	2:	≤ 1.0 mm / ≤ 0.7 mm	obligatory			
Brain kernel	loc	local practice				

n.a. = not applicable

CT-angiography head-neck acquisition protocol requirements

CTA head-neck - Version 1.0 February 1st 2022

Data acquisition	Parame	eters				Remarks
Scan range	cranial	cranial vertex (includes entire sagittal sinus) – just				
	below a	below aortic arch				
Scan direction	cranial	- caudal				preferred
Scan type	spiral					preferred
Collimation	number	r of detector row	vs avail	lable	× ≤ 1.0 mm	preferred
Rotation time	coopera	ative patient			≥ 0.5 seconds	preferred
	uncoop	erative (moving) patier	nt	≤ 0.4 seconds	preferred
Pitch	coopera	ative patient			0.8-0.9	preferred
	uncoop	erative (moving) patier	nt	1.2-1.7	preferred
Tube voltage (kVp)	automa	ted tube curren	t select	tion f	or vascular	1 st choice
	exam ty	/pe				
	fixed k\	/p, as close to 1	00 kVp	p as	possible	2 nd choice
Tube amperage (mAs)	local pr	actice				
CTDI _{vol} indication (prior	16 cm	12-26 mGy (ite	erative))		1 st choice
to kV/mA modulation)		16-32 mGy (fil	tered b	back	projection)	2 nd choice
	32 cm	6-13 mGy (iter	ative)			1 st choice
		8-16 mGy (filte	ered ba	ack p	rojection)	2 nd choice
Contrast media	flux (ad	ministered iodin	ie 1	.3-1.	8 *	obligatory
	in gram	is / second)				
	maximu	um amount	9	90 ml	-	obligatory
	injectio	n site	ri	ight c	cubital fossa	preferred
NaCl flush bolus amount	≥ 40 ml	L				obligatory
Scan delay	timed w	ith contrast bolu	us tracl	king		obligatory
Image reconstruction	Parame	eters				Remarks
Directions	axial					obligatory
Brain kernel	local pr	actice				
Reconstruction	Slice w	idth/increment	Field	of vi	ew	Remarks
1. Extracranial arteries	\leq 1.0 mm / \leq 0.6 mm small to fit carotids a		t carotids and	obligatory		
			verte	bral a	arteries	
2. Intracranial arteries	≤ 0.75 r	mm / ≤ 0.4 mm	small	l to fi	t intracranial	obligatory
			arteri	es		

* 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 (\geq 100) scans.

CT-perfusion brain acquisition protocol requirements

CTP brain - Version 1.0 February 1st 2022

Data acquisition	Para	Parameters			
Moment of acquisition	befo	before CTA or >4 min after CTA			
Tube voltage (kVp)	local	practice			
Tube amperage (mAs)	local	practice			
Start of acquisition	dela	y < 6 seconds			obligatory
	direc	t with as little o	delay as j	possible	preferred
Max acquisition time	210	seconds			obligatory
Acquisition sequence	Cano	on Aquilion	20 x 2 s	s + 4 x 5 s + 5 x 30 s	obligatory
	Sierr	nens	20 x 1.5	5 s + 10 x 3 s + 5 x	obligatory
	Som	atom	30 s		
	Phili	Philips Brilliance 30 x 2 s + 5 x 30 s			obligatory
	Phili	os iQON	18 x 3.4	4 s + 5 x 30 s	obligatory
Contrast media	flux (administered i	odine in	1.8 *	obligatory
	gram	ns / second)			
	total	iodine dose		15 g *	obligatory
	injec	tion site		right cubital fossa	preferred
NaCl flush bolus amount	40 m	ηL			obligatory
Image reconstruction	Para	meters			Remarks
Field of view	whol	obligatory			
Brain coverage	≥80	obligatory			
	whol	preferred			
Reconstructed slice	1:	5 mm / ≤ 3.0	mm		obligatory
thickness/increment	2:	≤ 1.5 mm / ≤	1.0 mm		obligatory

* Corresponding contrast volume and injection rate per iodine concentration used				
lodine 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.



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:

Original Approval:

Last Amended on:

Remains valid until:

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)

Signed:

NRAT

252.962 10 November 2015

20 December 2019

09 November 2023



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:

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

Signed:

e Officer, NSAI

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	ш
	AP21	Artemis Neuro Evacuation Device 2.1 mm	
	AP28	Artemis Neuro Evacuation Device 2.8 mm	