ARISE II

Analysis of Revascularization in Ischemic Stroke with EmboTrap®

Clinical Investigation Plan

Control number

CIP002 rev 05
VERSION DATE 28th June 2016

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Study Sponsor:

Neuravi® Inc.,
51 JFK Parkway, First Floor West
Short Hills, New Jersey, 07078

Revision History

CIP002 Revision 01	Initial draft submitted to FDA	10th March 2015
CIP002 Revision 02	Revised to correct and address FDA considerations: 1. Clarify implications of rescue therapy prior to 3 passes for the adjudication of results. 2. Ensure patients who are treated with IV-tPA fall within the treatment window approved by FDA for IV-tPA.	19th May 2015
CIP002 Revision 03	Revised to correct and address FDA considerations on enrollment.	19th June 2015
CIP 002 Revision 04	Update to remove reference to "target" in definition of rescue therapy and to amend the inclusion 10. To use imaging for all timepoints and amend exclusion criteria to exclude pt.s with severe hypertension.	10th March 2016
CIP002 Revision 05	Update to include a new size of EmboTrap device. Now includes sizes (5×21 mm and 5×33 mm). Increase the maximum patient enrolment allowed in the study from 210 to 228 throughout the protocol. This accounts for the potential increase in number of "roll-in" patients in the study based on the number of US study sites. The evaluable cohort required, 176, remains the same.	28th June 2016

SIGNATURE PAGE

To be signed and returned to *Sponsor, prior to study initiation.*

Trial Title:	**ARISE II (Analysis of Revascularization in Ischemic Stroke with EmboTrap®) Study**
Investigational Device:	**EmboTrap® Revascularization Device**
CIP Revision:	**CIP002 Revision 05**
Trial Sponsor:	**Neuravi Inc.**

I,_____,
(name of principalinvestigator)

_____,
(Specialty, e.g. anesthesiology, neurosurgery or other discipline)

at the_____,
(name of hospital)

the undersigned, attest that I have read and understood this Protocol specified above and agree on its content and to abide by the above mentioned version and any subsequent amendments during my participation in the evaluation. I agree to perform and conduct the study as described in the protocol and in accordance with the relevant parts of the ICH Guidelines for GCP, the ISO 14155:2011, 21 CFR 812, 21 CFR Part 820, 21 CFR Part 50, 21 CFR Part 11, 21 CFR Part 54, 21 CFR Part 56, the Declaration of Helsinki, and the pertinent individual country laws/regulations.

_____ _____

Principal Investigator Signature Date

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the design and specific provisions of this IRB/ ethics committee approved protocol, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP), ISO14155:2011, ISO 13485:2003, 21 CFR 812, 21 CFR Part 820, 21 CFR Part 50, 21 CFR Part 11, 21 CFR Part 54, 21 CFR Part 56, 93/42/EEC MDD and the applicable local regulatory/country law requirement(s). The Principal Investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the sponsor and documented approval from the IRB/ethics committee, except where necessary to eliminate an immediate hazard(s) to the trial participants. The Principal Investigator will promptly report to the IRB/ethics committee and the sponsor of any changes in research activity and all unanticipated problems involving risk to human subjects, or others.

ARISE II Sponsor Approval

ARISE II Clinical Investigation Plan CIP002 Revision 05 is approved by the sponsor

Neuravi Inc.,
51 JFK Parkway,
First Floor West,
Short Hills,
New Jersey,
07078

Mairsíl Claffey
V.P. Clinical, Quality, and Regulatory Affairs

13th Sept 2016
Date

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LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
ASPECTS	Alberta Stroke program early CT score
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
CRO	Contract Research Organization
CT	Computed Tomography
DSMB	Data Safety Monitoring Board
eCRF	Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IA-tPA	Intra-arterial tissue plasminogen activator
ICF	Informed Consent Form
ICH	Intracranial Hemorrhage
IFU	Instructions for Use
ITT	Intention-to-treat
IV	Intravenous
IV-tPA	Intravenous tissue plasminogen activator
mITT	Modified intention-to-treat
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Score
mTICI	modified Thrombolysis in Cerebrovascular Infarction
NIH	National Institutes of Health
NIHSS	National Institutes of Health Stroke Score
pc- ASPECTS	Posterior circulation ASPECTS
PI	Principal Investigator
PP	Per Protocol
PRSAE	Procedure Related Serious Adverse Event
PTAE	Pretreatment Adverse Event
SAE	Serious Adverse Event/Experience
SADE	Serious Adverse Device Effect
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
TFSO	Time From Stroke Onset
TICI	Thrombolysis in Cerebrovascular Infarction
TIMI	Thrombolysis in Myocardial Infarction
UADE	Unanticipated adverse device effect

PROTOCOL SUMMARY

Title	ARISE II: Analysis of Revascularization in Ischemic Stroke with EmboTrap®
Sponsor	Neuravi Inc., 51 JFK Parkway, First Floor West, Short Hills, New Jersey, 07078
Principal Investigator US **Co-Principal Investigator EU**	Dr. Osama Zaidat, MD, MS, FAHA, FAAN Stroke, Neurocritical Care, and Neurointervention Medical Director, Neuroscience and Stroke Programs St Vincent Mercy Medical Center 2222 Cherry Street, Suite M200 Toledo, Oh 43608 Dr. Tommy Andersson, Departments of Neuroradiology and Clinical Neuroscience, Karolinska University Hospital and Karolinska Institutet, Karolinska vägen 1, SE-17176, Stockholm, Sweden. Department of Radiology, AZ Groeninge, President Kennedylaan 4, BE-8500 Kortrijk, Belgium.
Executive Steering committee	Prof. Jeffery L. Saver Geffen School of Medicine at UCLA Director, UCLA Comprehensive Stroke Center 710 Westwood Plaza Los Angeles, CA 90095, USA. Prof. Heinrich Mattle, MD Senior Consultant Dept. of Neurology, Inselspital University of Bern 3010 Bern, Switzerland
Investigational Device	Neuravi® EmboTrap® Revascularization Device
Study Design	This is an open label, single arm, multi center, prospective clinical study of the safety and efficacy of the EmboTrap device in treating acute ischemic stroke patients who have a large artery occlusion in their neurovasculature. The study will include all consecutive patients treated with the EmboTrap device who meet the inclusion and exclusion criteria.
Study Objective	The study objective is to examine the recanalization efficacy of the EmboTrap device and its associated performance characteristics and to record associated clinical outcomes in a manner that facilitates relevant comparison of outputs with that of devices approved in the U.S. for clearing Large Vessel Occlusions.
Enrolment	176 subjects minimum (up to 228 may be enrolled)

Number of Sites	Up to 30 sites.
Device Description and Intended Use	The EmboTrap device is a mechanical recanalization device. It is intended to clear large vessel occlusions in acute stroke patients via mechanical thrombectomy. It is designed for use in the anterior and posterior neurovasculature. Patients enrolled will be treated as described in the EmboTrap device Instructions for Use.
Inclusion Criteria	1. The patient or the patient's legally authorized representative has signed and dated an Informed Consent Form. 2. Aged between 18 years and 85 years (inclusive). 3. A new focal disabling neurologic deficit consistent with acute cerebral ischemia. 4. NIHSS score ≥8 and ≤25. 5. Pre-ictal mRS score of 0 or 1. 6. The interventionalist estimates that at least one deployment of the EmboTrap device can be completed within 8 hours from the onset of symptoms. 7. Patients for whom IV-tPA is indicated and who are available for treatment, are treated with IV-tPA. 8. IV-tPA, if used, was initiated within 3 hrs of stroke onset (onset time is defined as the last time when the patient was witnessed to be at baseline), with investigator verification that the subject has received/is receiving the correct IV t-PA dose for the estimated weight. 9. Angiographic confirmation of an occlusion of an ICA (including T or L occlusions), M1 or M2 MCA, VA, or BA with mTICI flow of 0 – 1. 10. For strokes in the anterior circulation, the following imaging criteria should also be met: a. MRI criterion: volume of diffusion restriction visually assessed ≤50 mL. OR b. CT criterion: ASPECTS 6 to 10 on baseline CT or CTA-source images, or, volume of significantly lowered CBV ≤50 mL. 11. The patient is indicated for neurothrombectomy treatment by the interventionalist and it is confirmed by diagnostic angiography that the device will be able to reach the target lesion proximally.
Exclusion Criteria	1. Life expectancy likely less than 6 months. 2. Females who are pregnant or breastfeeding. 3. History of severe allergy to contrast medium. 4. Known nickel allergy at time of treatment. 5. Known current use of cocaine at time of treatment.

	6. Patient has suffered a stroke in the past 3 months. 7. The patient presents with an NIHSS score <8 or >25 or is physician assessed as being in a clinically relevant uninterrupted coma. 8. Subject participating in another study involving an investigational device or drug. 9. Use of warfarin anticoagulation or any Novel Anticoagulant with International Normalized Ratio (INR) >3.0. 10. Platelet count <50,000/µL. 11. Glucose <50 mg/dL. 12. Any known hemorrhagic or coagulation deficiency. 13. Unstable renal failure with serum creatinine >3.0 or Glomerular Filtration Rate (GFR) <30. 14. Patients who have received a direct thrombin inhibitor within the last 48 hours; must have a partial thromboplastin time (PTT) less than 1.5 times the normal to be eligible. 15. All patients with severe hypertension on presentation (SBP > 220 mmHg and/or DBP > 120 mm Hg). All patients, in whom intravenous therapy with blood pressure medications is indicated, with hypertension that remains severe and sustained despite intravenous antihypertensive therapy (SBP >185 mmHg and/ or DBP >110 mmHg). 16. Known cerebral vasculitis. 17. Rapidly improving neurological status. 18. Clinical symptoms suggestive of bilateral stroke or stroke in multiple territories. 19. Ongoing seizure due to stroke. 20. Evidence of active systemic infection. 21. Known cancer with metastases. 22. Computed tomography (CT) or Magnetic Resonance Imaging (MRI) evidence of recent/ fresh hemorrhage on presentation. 23. Baseline computed tomography (CT) or MRI showing mass effect or intracranial tumor (except small meningioma). 24. Suspicion of aortic dissection, presumed septic embolus, or suspicion of bacterial endocarditis. 25. Stenosis, or any occlusion, in a proximal vessel that requires treatment or prevents access to the site of occlusion. 26. Evidence of dissection in the extra or intracranial cerebral arteries. 27. Occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or anterior/posterior circulation).
Duration of Study	The total duration of the study is expected to be eighteen months for subject recruitment and 3 months for final subject follow-up.

Duration of Subject Participation	Subjects will be on study for up to 90 (±14) days. **Neurological assessment: 168 hours (± 12 hours) /**7 days or discharge (whichever occurs first) **Last Follow-up:** 90 (±14) days
Primary Efficacy Endpoint	The primary efficacy endpoint of the study is revascularization measured using modified Thrombolysis in Cerebrovascular Infarction (mTICI inclusive of the 2c rating). Successful achievement of the endpoint is defined as achieving an mTICI score of 2b or greater in the target vessel following 3 or less passes of the EmboTrap device.
Primary Safety endpoint	The primary safety endpoint will be measured as the occurrence of Symptomatic Intracerebral hemorrhage (sICH) within 24 hours (-8/+12 hrs) post-procedure, together with any other Serious Adverse Device Effects (excluding those already counted in sICH).
Secondary Endpoints	• Good clinical outcome – judged to be an mRS score of ≤2 at 90(+/-14) days. • Time to treat – defined as the time from groin puncture to visualization of the final angiographic result. • All procedure-related mortality at day 7 post-procedure and all-cause mortality at 90(+/-7) days post-procedure. • Serious Adverse Device Effect (SADE). • Procedure Related Serious Adverse Events (PRSAE). • Symptomatic ICH (sICH). • Neurological deterioration – defined by an increase of 4 points or more on the NIHSS score, at the 24-hour time point. • Evidence of Infarction of a previously uninvolved vascular territory, as evaluated from 24-hour imaging (CT/MRI).
Statistics	The primary efficacy endpoint of the study will be tested using a non-inferiority hypothesis for successful revascularization with the EmboTrap against a composite Performance Goal derived from a Bayesian meta-analysis of adjudicated trial data for similar devices. All mTICI outcomes and their proportions will be reported. The primary safety endpoint and the secondary endpoints will not be tested but will be examined using confidence intervals to calculate the relevant population parameter. The primary safety endpoint will be the rate of sICH together with SADEs (excluding those already counted in sICH).

	Secondary endpoints that will be reported using descriptive statistics include: • Clinical outcome at 90 days • Time to treat • Mortality post-procedure – All procedure-related mortality • Serious Adverse Device Effect (SADE) • Procedure Related Serious Adverse Events (PRSAE) • Symptomatic ICH (sICH) • Neurological deterioration • Evidence of Infarction in a previously uninvolved territory The study will also perform subgroup analyses on the cohort based on: • Specific vascular location of the occlusion (i.e. intracranial ICA, carotid T/L, proximal M1/ distal M1 /M2, VA, BA etc.) • Technique of treatment as described below: – Use of a balloon guide vs. no balloon guide – Use of an intermediate catheter vs. no intermediate catheter.

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1 Introduction

The large vessels of the brain include the Internal Carotid Artery (ICA), Middle Cerebral Artery (MCA), Vertebral Artery (VA), and the Basilar Artery (BA). Occlusion of these large arteries in ischemic stroke is associated with significant disability and mortality. Revascularization of intracranial artery occlusions is the therapeutic goal in stroke therapy.

Endovascular mechanical revascularization (thrombectomy) is an increasingly used method for intracranial large vessel recanalization in acute stroke. Currently, a number of mechanical recanalization devices are in clinical use. First generation devices included the Merci Retriever device. Newer devices based on stent-like technology, referred to as "stentrievers" or "stent-retrievers", are currently displacing these first generation thrombectomy devices for recanalization in acute ischemic stroke.

The EmboTrap® Revascularization Device (hereafter referred to as the EmboTrap device) has been developed and CE approved for this indication in Europe. The EmboTrap device is approved for use in the US strictly within the confines of the ARISE II IDE Study. It is indicated for use in the anterior and posterior neurovasculature in vessels such as the internal carotid artery, the M1 and M2 segments of the middle cerebral artery, the vertebral artery, and the basilar artery.

1.1 Background

1.1.1 Intra-arterial thrombolytics

Currently, IV lytics are used in Europe and the United States for patients presenting up to 4.5 hours after symptom onset. Although in the US they are only FDA approved for use in patients presenting up to 3 hours after symptom onset, US national clinical practice guidelines [1] recommend administering IV lytics in the 3-4.5h window to those patients who meet the ECASS 3 trial inclusion/exclusion criteria [2].

In addition to time constraints, IV thrombolytic therapy has been demonstrated to be less effective in recanalizing proximal occlusions of large vessels, such as the ICA and MCA. Since a large percentage of strokes presenting at hospitals are large vessel occlusions, this is an important clinical challenge to address. Additionally, not all patients may be treated with thrombolytic therapy, and so mechanical thrombectomy is a valuable alternative in patients contraindicated to t-PA or where t-PA treatment was not effective.

1.1.2 Bridging therapy

Acute stroke treatment protocols vary by hospital center. Often, CT is used to exclude hemorrhagic stroke, and CTA (CT Angiography) is used to confirm Large-Vessel Occlusion. Additional imaging assessment, such as use of MRI and/or CT Perfusion, varies by center. Since the recent presentations of clinical results from the MR. CLEAN, ESCAPE, SWIFT PRIME and Extend-IA studies, centers have adopted a bridging approach to treatment – immediately starting an IV dose of lytics, then transferring the patient to the angiography suite of a comprehensive

stroke center as quickly as possible to speed the time to intra-arterial intervention, if needed. Bridging therapy should occur as determined appropriate by the physician and local practice guidance.

1.1.3 Ethical considerations - Europe

The EmboTrap device is a CE-marked, approved device. It will only be used at the physician's discretion and for its indicated use in line with the instructions for use. The collection and analysis of the data requires ethical approval; however, the use of the EmboTrap device under this trial protocol in Europe does not introduce any new ethical concerns beyond those present when treating any acute stroke patient with an approved mechanical thrombectomy device.

1.1.4 Ethical considerations – United States

The EmboTrap device is not FDA cleared in the US. It is an investigational device that may be used in the U.S. within the confines of the ARISE II IDE Study. The purpose of this study is to gather information on device performance to support an application for clearance to FDA.

1.1.5 Ethical considerations - all territories

The intent of the ARISE II Study is to collect data on subjects in a prospective manner; all patients who meet all Inclusion/Exclusion criteria will be included in the analysis. Coded patient data in the form of angiographic and CT and/or MRI images, and completed case report forms are required in order to assess the study endpoints. Informed consent will be sought from the subject or their legal representative for participation and to give permission for the sponsor and subcontractors (CRO, CEC, DSMB, and Adjudicating core lab) to have access to these data.

Physicians should follow local practice guidance's, their own routine best practice, and the EmboTrap device instructions for use when participating in the study.

2 Investigational device description

The EmboTrap range intends to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke within 8 hours of symptom onset. The product descriptions "EmboTrap Revascularization Device" and the "EmboTrap II Revascularization Device" are both referred to as "EmboTrap" throughout this protocol for readability. The product description "EmboTrap II" was introduced to mark the addition of proximal markers to the EmboTrap and the availability of a choice of two working lengths of the EmboTrap device.

The device is designed for use in the anterior and posterior neurovasculature in vessels such as the internal carotid artery, the M1 and M2 segments of the middle cerebral artery, the vertebral artery, and the basilar arteries. It is intended for use by physicians trained in neuro-interventional catheterization and the treatment of ischemic stroke, and is delivered endovascularly under fluoroscopic guidance in a similar manner to that of other neurovascular clot-retrieval systems. Once across the site of vessel occlusion, the stent-like element of the device is deployed to entrap the clot and allow it to be retrieved, hence restoring blood flow.

The device is available in two lengths, 5×21 mm and 5×33 mm. Both sizes have the same outside diameter, size differences relate to the length of the stent-like portion. The device comprises a three-dimensional Nitinol retrievable stent-like assembly mounted on the distal end of a tapered (guidewire-like), PTFE-coated Nitinol shaft, as shown in Figure 1.

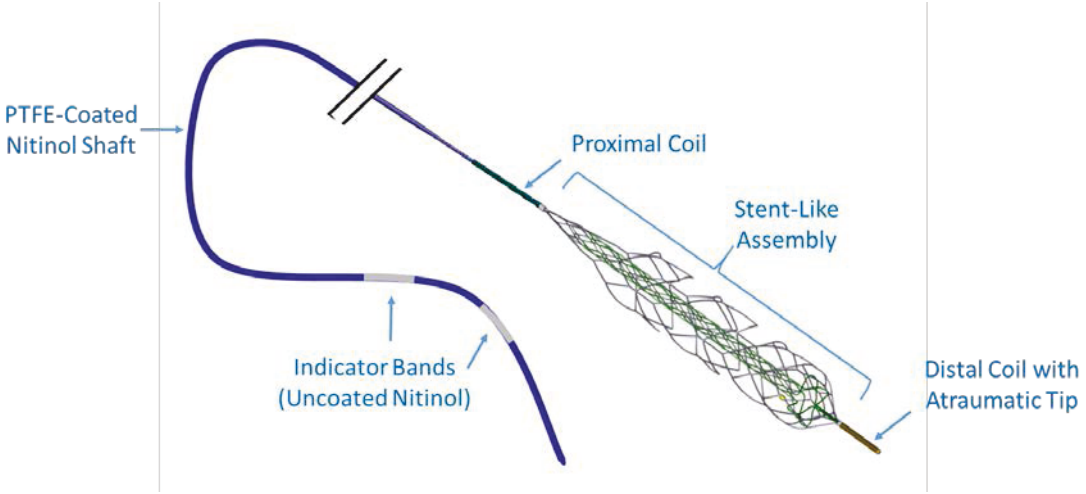


Figure 1: The EmboTrap device

The EmboTrap device is supplied preloaded within an insertion tool – a transparent, PTFE tube incorporating a spiral band of blue color (Figure 2). In use, the physician inserts the insertion tool into the hub of a pre-positioned microcatheter and advances the EmboTrap device forward out of the insertion tool and into the microcatheter. The spiral blue band of color makes the tool easy to find if needed to re-load the device for an additional pass.

Figure 2: An illustration of the Insertion Tool used for loading the EmboTrap device.

Two silver-colored indicator bands (Figure 1) on the proximal portion of the device shaft (i.e. two sections of the Nitinol shaft which are not coated with PTFE), represent an important feature of the device design as they provide a visual and tactile reference point to the physician that the stent-like portion of the device is nearing the end of the microcatheter, thereby helping to avoid unintentional advancement of the device from the end of the microcatheter during delivery. For example, using a standard microcatheter (total length of 155cm and a 7cm Rotating Hemostasis Valve (RHV)), the EmboTrap device tip will be approximately 8cm from the distal end of the microcatheter when the first silver band on the EmboTrap shaft approaches the RHV. When the second silver band on the EmboTrap shaft approaches the RHV, the device tip will be nearing the distal end of the microcatheter. A further benefit of this feature is that it allows the physician to minimize the exposure of the patient to X-rays, as he/she can avoid using fluoroscopic guidance until the indicator bands demonstrate the device's proximity to the end of the microcatheter.

3 Study objective

The study objective is to examine the recanalization efficacy of the EmboTrap device and its associated performance characteristics and to record associated clinical outcomes in a manner that facilitates relevant comparison of outputs with that of devices approved in the U.S. for clearing Large Vessel Occlusions.

3.1 Primary endpoint

The primary efficacy endpoint of the study is revascularization measured using modified Thrombolysis in Cerebrovascular Infarction (mTICI inclusive of the 2c rating). Successful achievement of the endpoint is defined as achieving a mTICI score of 2b or greater in the target vessel, following 3 or less passes of the EmboTrap device.

The primary safety endpoint will be measured as the occurrence of Symptomatic Intracerebral hemorrhage (sICH) within 24 hours (-8/+12 hrs) post-procedure, together with any other Serious Adverse Device Effects (excluding those already counted in sICH).

3.2 Secondary Endpoints

Clinical outcome at 90 days – A good clinical outcome will be judged to be an mRS score of ≤2 at 90(+/-14) days.

Procedure Time is defined as the time from groin puncture to achievement of ≥mTICI II b, or if not achieved, final angiogram.

Time to treat is defined as the time from angiographic visualization of large vessel occlusion to achievement of ≥mTICI II b or if not achieved, final angiogram. The number of passes to get to mTICI 2b or greater flow will also be recorded.

Mortality post-procedure – All procedure-related mortality (i.e. directly traceable to a procedure-related SAE) at Day 7 post-procedure and all-cause mortality at 90(+/-7) days post-procedure.

Serious Adverse Device Effect (SADE) is where the EmboTrap device caused, or cannot be ruled out as having caused, an effect that has resulted in any of the consequences characteristic of a serious adverse event.

Procedure Related Serious Adverse Events (PRSAE) is where the interventional procedure caused, or can not be ruled out as having caused, an effect that has resulted in any of the consequences characteristic of a serious adverse event.

Symptomatic ICH (sICH) is any extravascular blood in the brain or within the cranium associated with clinical deterioration, as defined by an increase of 4 points or more in the score on the NIHSS, or that leads to death and is identified as the predominant cause of the neurologic deterioration [3]. For the purpose of data analysis, subjects with sICH identified through all post–treatment scans up to the 24 hour timepoint (including those performed due to clinical deterioration), will be counted.

Neurological deterioration – defined by an increase of 4 points or more on the NIHSS score, at the 24-hour time point.

Evidence of Infarction – Infarction of a previously uninvolved vascular territory, as evaluated from 24-hour imaging (Computed Tomography (CT)/Magnetic Resonance Imaging (MRI)) by the Angiography Core Lab.

3.3 Rescue Therapy

After the primary endpoint angiogram is taken, if revascularization is inadequate (i.e. less than mTICI 2b), rescue therapy is permitted.

Use of rescue therapy, prior to taking the primary endpoint angiogram, is a protocol violation and the resultant angiogram outcomes will be considered failures to achieve the primary endpoint irrespective of mTICI score.

Use of any of the following, to treat the patient, is considered rescue therapy:

- Use of another mechanical thrombectomy device.
- Use of mechanical pump aspiration (e.g. Penumbra Pump) during the procedure.
- Initiation of IA-tPA.
- Use of intra cranial stenting during the procedure.

Secondary endpoints measured after use of rescue therapy at any time will be censored from the data and where appropriate multiple imputation will be used to ensure sufficient data (i.e. equivalent to that which would be obtained from a sample size of 176 are available for calculation of the secondary endpoints). Further details are contained in section 8.

4 Study justification and rationale

The purpose of this study is to assess whether the EmboTrap device, used under routine clinical conditions within 8 hours of onset of acute ischemic stroke, is at least as effective as similar devices, and for this purpose specifically evaluate the success of vessel.

Research in cases of acute stroke is challenging as the potential study cohort is very restricted. Hence efficient study design is very import.

The study will use core laboratory adjudication to examine the recanalization efficacy of the EmboTrap device in a manner that facilitates relevant comparison of efficacy with a meta-analysis derived composite Performance Goal endpoint based on devices cleared by FDA in the U.S. for unblocking Large Vessel Occlusions. The availability of published core laboratory adjudicated data for a similar population provides an appropriate historical basis to test the hypothesis. Hence, using a single arm study makes efficient use of the available cohort size.

Additionally, descriptive statistical reporting of the secondary outcomes will allow side-by-side comparison of the secondary endpoints with that of comparable stent-retrievers from the SWIFT and TREVO II studies. Hence, the safety and efficacy of the EmboTrap device relative to other devices on the US market may be characterized.

4.1 Measurement scales

The following measurement scales will be used in the ARISE II clinical study:

mTICI – modified thrombolysis in cerebral infarction (TICI) score. The primary study outcome, revascularization, will be measured by an independent adjudicating core laboratory and reported using the mTICI (inclusive of the 2C rating) scale.

TIMI - 'TIMI Grade Flow' is a scoring system from 0-3 referring to levels of blood flow (For comparison of information the core laboratory will also provide adjudication on each image using the TIMI scales)

NIHSS Score - The National Institutes of Health Stroke Scale, or NIH Stroke Scale (NIHSS) is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0.

mRS – The modified Rankin Scale (mRS) is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability.

4.2 Risk / Benefit analysis

While mechanical thrombectomy may speed time to reperfusion, like all therapies it carries risks. Through the EmboTrap device risk assessment process, a multi-functional team identified risks associated with the design, processing and use of the device, and identified the characteristics related to its safety.

All clinical risks were considered, including those identified through the Risk Management Report, and through the clinical literature search process. The risks listed below represent those identified as most clinically relevant through the literature review process.

- Abrupt vessel closure.
- Access complications.
- Access site pain, hematoma or hemorrhage.
- Allergic reaction to anticoagulants or antiplatelet therapy, contrast medium, or device material.
- Aneurysm or pseudo aneurysm.

- Arrhythmias, including VF and VT.
- Clot fragmentation during retrieval.
- Death.
- Delayed Recanalization.
- Device detachment.
- Emboli, distal (air, tissue or thrombotic emboli).
- Embolization of a previously unaffected vessel.
- Hemorrhagic Transformation.
- Hypotension/hypertension.
- Infection, local and/or systemic.
- Peripheral ischemia/peripheral nerve injury.
- Pulmonary edema.
- Renal failure.
- Respiratory failure.
- SAH - Subarachnoid Hemorrhage.
- Sedation complications.
- Shock.
- New Stroke/cerebrovascular accident/transient ischemic attack (TIA).
- Thrombus formation in the vessel (proximal, at the site of and distal).
- Total occlusion of cerebral vessel.
- Vasospasm.
- Vessel trauma, dissection, perforation, rupture or injury.

All efforts will be made to minimize the risks in this study by selecting investigators experienced and skilled in this interventional procedure and who have been trained in the ARISE II Study investigational protocol.

5 Subject selections

5.1 Enrolment

All consecutive patients who meet the inclusion and exclusion criteria will be enrolled.

5.2 Informed consent

Prior to admission to the study, a patient informed consent document will be given to each prospective subject or their Legally Authorized Representative (as defined by the local IRB or ethics committee), including an explanation of the study, duration, explanation of medical record access and patient anonymity, and how their coded data may be transferred, used for publications or in submissions for reimbursement support. The informed consent form will contain language that is non-technical and understandable to the patient or his/her legal representative.

The treatment occurs in an acute emergency situation, so locally required informed consent procedures may apply and will be complied with.

Each potential subject will be provided with written and verbal information regarding the nature of the study in an understandable manner. Adequate time will be allowed for the subject to consider participation in the clinical trial. Signed, written consent will be obtained from each subject prior to data collection and entry into the study. Any coercion or undue influence of potential subjects to participate must be avoided, and the subject's legal rights should not be waived. The investigator or an appropriately designated member of the study staff shall co-sign the consent form, indicating they believe the subject has understood the nature and risks of the study and, in their estimation, the subject clearly understands the scope of the consent. The investigator must inform subjects that they are in a controlled clinical trial, apprise them of their rights as set forth in the informed consent document, and make written documentation that such a discussion took place.

If the subject is not able to sign the informed consent, but has given his/her oral consent to participate, a third party can sign the informed consent for the subject. The procedure will be documented in the medical record. If the subject is not able to give his/her informed consent to participate in the study, a legally authorized relative or independent physician can sign the informed consent for the subject if this is approved by the local Institutional Review Board (IRB) or Ethics Committee (EC).

Short form informed consent may be utilized if approved by the IRB/EC. Each institution must follow their institutional IRB/EC policy for obtaining informed consent. If the short form informed consent is used, the summary must include all the basic elements of informed consent (21 CFR 50.25; ICH E6 4.8.10).

The procedure around how the informed consent is collected will be recorded in each subjects' medical record. The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor on request.

Each site will maintain a log of all screened patients detailing the reasons for any subsequent patient exclusions or non-participation in the study. This could occur if angiographic inclusion and exclusion criteria are not met or if informed consent was withdrawn.

5.3 Subject withdrawals

Participation in this investigation is voluntary, and the subject may withdraw at any time. All enrolled subjects will be included in data analysis, unless they withdraw permission for their data to be used. The Sponsor will retain and continue to use any data collected prior to the withdrawal of consent, unless specified by the Subject or their Legally Authorized Representative.

In the event the subject chooses to withdraw, he/she will be instructed to contact the Investigator immediately. Withdrawal from the investigation will not affect the subject's follow-up care. The subject will be informed of any significant information regarding new findings that may develop

during the course of the research study that may relate to his or her willingness to continue participation as a study subject.

Subjects will participate in their routine follow-up and allow this data to be gathered or their participation in the study will be prematurely terminated. If their participation is terminated, any of their data which has been already gathered will continue to be included. The completion of a subject's participation in the study or early departure from the study must be fully documented in the subject's study progress notes.

Subjects will be considered discontinued from the study if any of the following occur:

- Death or intercurrent illness: If, during the conduct of the study, a subject dies or experiences an intercurrent illness, all available information should be obtained and an appointed Neuravi representative/ study monitor should be notified no more than 24 hours from study staff becoming aware of the event.
- If a subject's death occurs while in the hospital, submit a copy of the physician's death summary report. If an autopsy is performed, submit a copy of the autopsy report, as well. If a subject's death occurs outside of the study site, obtain all information related to the death and submit the investigator's summary of the events associated with the death.
- Subject voluntarily withdraws from the study: A subject may withdraw consent from study participation at any time.
- Subject withdrawn from the study by the investigator: An investigator may withdraw an enrolled subject from the study for the following reason:

Protocol violation: Should a subject be enrolled but later determined ineligible based on previously unavailable source documentation or due to a violation in following the protocol at the study site, this subject will be considered a protocol violation. This subject's data will not be pooled for statistical analysis with those subjects confirmed to be eligible by the investigator and the appointed study monitor for Neuravi. All protocol violations should be documented by the study monitor appointed by Neuravi.

5.4 Subjects lost to follow-up

If a subject fails to return for the follow-up visit, a letter will be sent to their most current mailing address, reminding them of their study obligations. Additionally, the subject will be contacted at their last known home telephone number. When all reasonable attempts to locate the subject have been exhausted, including contacting the subject's general practitioner, the subject will be considered lost to follow-up. Documentation is required for all attempts to locate the subject.

6 Study Design

The study aims to include 176 evaluable patients; however, enrolment of up to 228 patients will be allowed in the event the data is needed to compensate for “roll in" patients, missing or censored outcome data, patient withdrawal, or too small a mITT population to test the primary endpoint for the hypothesis as designed.

There are three FDA cleared stent retrievers indicated for neuro-thrombectomy: Merci, Trevo and Solitaire. The Trevo and Solitaire devices conducted randomized trials using the Merci device as a control in support of premarket clearance. The results, of these trials provide a valid scientific basis for the establishment of a composite performance goal derived using a Bayesian meta-analysis. At 176 evaluable patients and 64% successful endpoint achievement the ARISE II study is expected to allow the EmboTrap device, with 90% power, to claim non-inferiority based on a one-sided test at the 0.025 significance level to U.S. approved predicate devices.

The success rate in ARISE II for the population of interest will be assessed using an Intention To Treat basis and also a modified Intention To Treat analysis.

Vessel recanalization and revascularization based on the final post-EmboTrap device use angiogram is a clearly measurable efficacy endpoint and less susceptible to influencing factors based on the patient population and care than other patient related outcomes.

6.1 Site Selection

The sponsor or a representative of the sponsor will assess each potential site to ensure the principal investigator and their staff has the facilities and expertise required for the study. Sites will be selected based upon a site assessment considering appropriate facilities, and the qualifications of the investigator(s). Individual investigators will be evaluated by the Sponsor based on experience with the intended procedure(s), and ability to conduct the study according to the study protocol.

Principal investigators and sites will be selected based upon the following factors:

- Previous experience with clinical research and mechanical thrombectomy procedures.
- Experience in conducting controlled, clinical studies.
- Willingness to observe confidentiality at all times.
- Currently treating subjects who meet the inclusion/exclusion criteria.
- Ability to enroll an adequate number of subjects.
- Ability to perform required clinical testing, including: angiography, CT, and/or MRI.
- Ability and willingness to provide the sponsor’s representatives, FDA and local regulatory authorities access to the hospital records, study files, and subject files as they pertain to the study.
- Willingness to participate, including compliance with all aspects of the study.

- Adequate staffing to conduct the study. This includes:
    - Principal Investigator (PI): Responsible for overall clinical management of subjects enrolled at his/her institution. Assumes overall responsibility and accountability for the clinical team and for data obtained from each subject participating in the study. Ensures compliance with the protocol, applicable laws, and applicable regulations; ensures informed consents are signed, and reviews and signs eCRFs indicating documents are accurate and complete.
    - Sub/Co-Investigator(s) (Sub-I/Co-I): Responsible for study activities in coordination with PI and in accordance to the investigational plan. Assume the responsibility of the PI should the PI resign from the study. A site is not required to have a co-investigator.
    - Study Coordinator: Assists PI with study activities as delegated by the PI, including tracking subjects involved in the study, scheduling testing and follow-up visits, maintaining study records, completing eCRFs to the sponsor in a timely manner.

6.2 Inclusion criteria

Study subjects must meet all of the inclusion criteria listed below:

1. The patient or the patient's legally authorized representative has signed and dated an Informed Consent Form.
2. Aged between 18 years and 85 years (inclusive).
3. A new focal disabling neurologic deficit consistent with acute cerebral ischemia.
4. NIHSS score ≥8 and ≤25.
5. Pre-ictal mRS score of 0 or 1.
6. The interventionalist estimates that at least one deployment of the EmboTrap device can be completed within 8 hours from the onset of symptoms.
7. Patients for whom IV-tPA is indicated and who are available for treatment, are treated with IV-tPA.
8. IV t-PA, if used, was initiated within 3 hrs of stroke onset (onset time is defined as the last time when the patient was witnessed to be at baseline), with investigator verification that the subject has received/is receiving the correct IV t-PA dose for the estimated weight.
9. Angiographic confirmation of an occlusion of an ICA (including T or L occlusions), M1 or M2 MCA, VA, or BA with mTICI flow of 0 – 1.
10. For strokes in the anterior circulation, the following imaging criteria should also be met:
    a. MRI criterion: volume of diffusion restriction visually assessed ≤50 mL.
    OR
    b. CT criterion: ASPECTS 6 to 10 on baseline CT or CTA-source images, or, volume of significantly lowered CBV ≤50 mL.
11. The patient is indicated for neurothrombectomy treatment by the Interventionalist and it is confirmed by diagnostic angiography that the device will be able to reach the target lesion proximally.

6.3 Exclusion criteria

Subjects must NOT meet ANY of the exclusion criteria listed below:

1. Life expectancy likely less than 6 months.
2. Females who are pregnant or breastfeeding.
3. History of severe allergy to contrast medium.
4. Known nickel allergy at time of treatment.
5. Known current use of cocaine at time of treatment.
6. Patient has suffered a stroke in the past 3 months.
7. The patient presents with an NIHSS score <8 or >25 or is physician assessed as being in a clinically relevant uninterrupted coma.
8. Subject participating in another study involving an investigational device or drug.
9. Use of warfarin anticoagulation or any Novel Anticoagulant with International Normalized Ratio (INR) >3.0.
10. Platelet count <50,000/µL.
11. Glucose <50 mg/dL.
12. Any known hemorrhagic or coagulation deficiency.
13. Unstable renal failure with serum creatinine >3.0 or Glomerular Filtration Rate (GFR) <30.
14. Patients who have received a direct thrombin inhibitor within the last 48 hours; must have a partial thromboplastin time (PTT) less than 1.5 times the normal to be eligible.
15. All patients with severe hypertension on presentation (SBP > 220 mmHg and/or DBP > 120 mm Hg). All patients, in whom intravenous therapy with blood pressure medications is indicated, with hypertension that remains severe and sustained despite intravenous antihypertensive therapy (SBP >185 mmHg and/ or DBP >110 mmHg).
16. Known cerebral vasculitis.
17. Rapidly improving neurological status.
18. Clinical symptoms suggestive of bilateral stroke or stroke in multiple territories.
19. Ongoing seizure due to stroke.
20. Evidence of active systemic infection.
21. Known cancer with metastases.
22. Computed tomography (CT) or Magnetic Resonance Imaging (MRI) evidence of recent/ fresh hemorrhage on presentation.
23. Baseline computed tomography (CT) or MRI showing mass effect or intracranial tumor (except small meningioma).
24. Suspicion of aortic dissection, presumed septic embolus, or suspicion of bacterial endocarditis.
25. Stenosis, or any occlusion, in a proximal vessel that requires treatment or prevents access to the site of occlusion.
26. Evidence of dissection in the extra or intracranial cerebral arteries.
27. Occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or anterior/posterior circulation).

6.4 Roll-in phase

Physicians will be trained in the use of the EmboTrap device before any patient procedures. To further assure protocol compliance, participating sites will be required to conduct some "roll-in" patients prior to the enrolling patients into the study. The number of roll-ins to be conducted is region-specific and takes into account an investigation sites previous experience using the EmboTrap device.

Roll-in patients will be analyzed separately from the patients enrolled in the pivotal study, but the information will be recorded and included with the clinical data reported from the study.

6.4.1 US Sites

Participating sites will be required to conduct two roll-in patients with the EmboTrap device prior to commencing patient enrolment into the pivotal phase of the study.

6.4.2 OUS Sites

As the device is CE marked and currently on the market in Europe, sites who did not participate in the earlier ARISE study will be required to conduct one roll-in patient with the EmboTrap device to confirm the sites' ability to upload information to the eCRF appropriately. Sites which have already enrolled subjects in the ARISE Study and have successfully uploaded information into the eCRF system will automatically move into the pivotal phase of ARISE II without roll-in patients.

All sites both in the US and OUS will be subject to a monitoring visit with 100% source data verification (SDV) as soon as possible after the enrolment of the first patient. Monitoring will focus on correct adherence to the protocol and the complete and appropriate data entry. Continued participation in the study depends on satisfactory study compliance.

6.5 Study Procedures

6.5.1 Study Flow

Subjects presenting with acute ischemic stroke will be evaluated by the physician, in accordance with their institutional practice, to establish an appropriate treatment plan based on the Subject's medical condition and available diagnostic screening procedures prior to recruitment in the ARISE II Study. A representative overview of the study flow is shown in Figure 3.

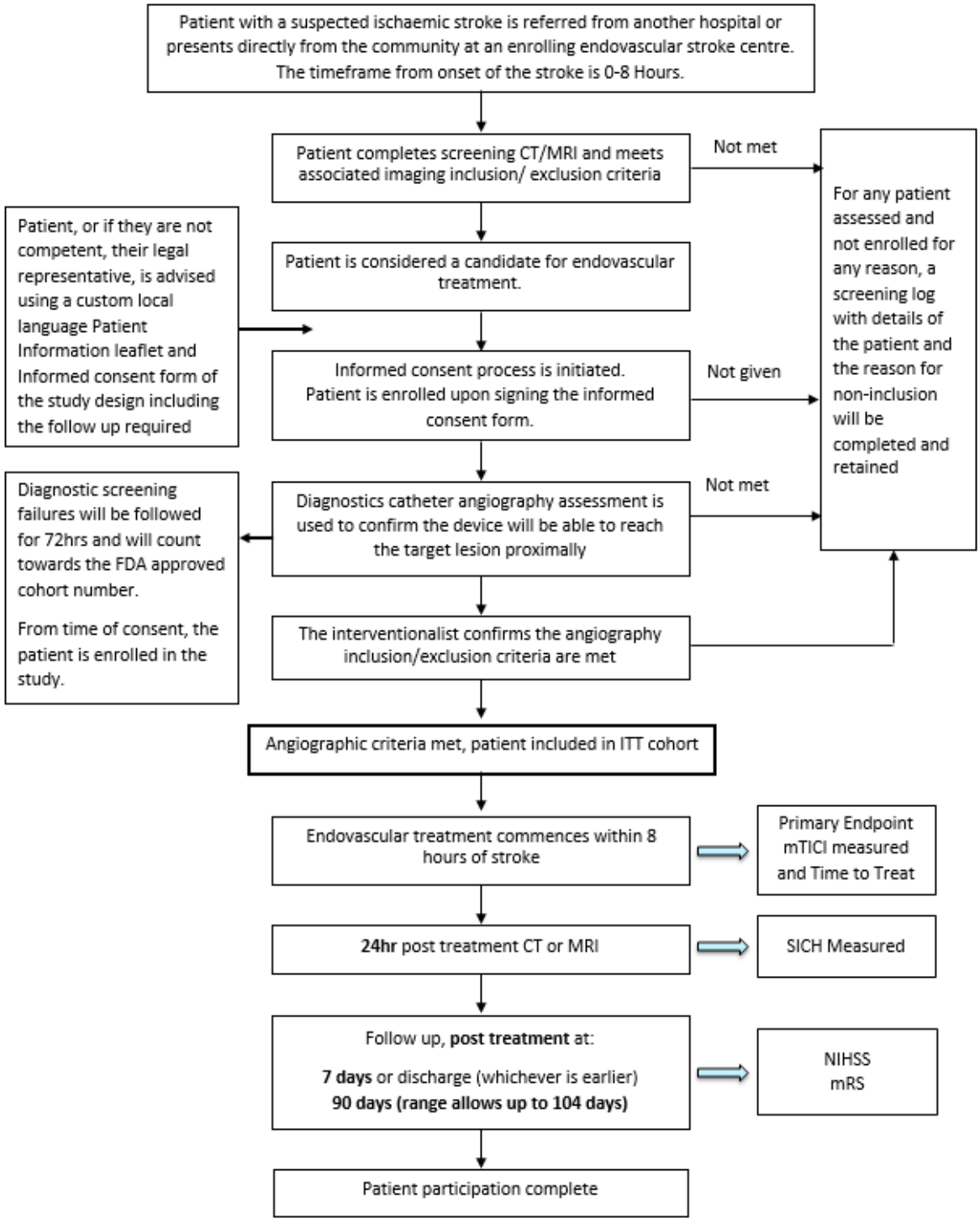


Figure 3: Study Flow: Patient is in study from time informed consent is obtained

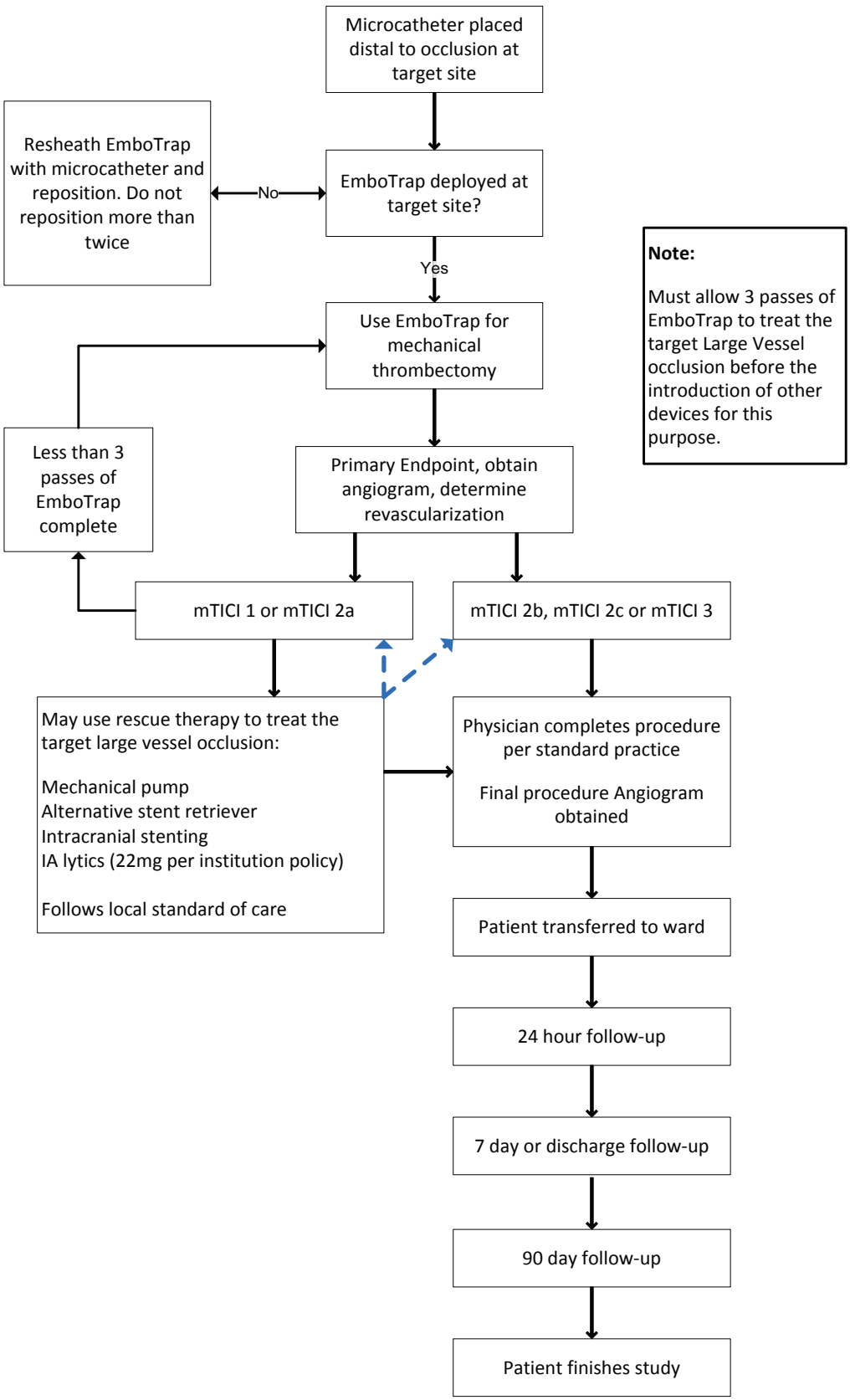


Figure 4: Procedure flow diagram for revascularization with EmboTrap device

6.5.1.1 Screening

Subjects will be screened against the study inclusion/exclusion criteria to determine their initial eligibility. A member of the research team (hospital/institution personnel assigned to the ARISE II Study) should review their eligibility. All subjects screened will be documented on the Screening/Enrolment log, including the reason for non-participation for subjects who do not enroll.

6.5.1.1.1 General Medical Evaluation

- A physical examination and medical history.
- Blood pressure and pulse prior to treatment with the EmboTrap device.
- Concomitant medication at baseline

6.5.1.1.2 Laboratory Evaluation

Blood and/or urine specimens for the following laboratory studies:

1. Pregnancy test (for female patients with childbearing potential)
2. Hemoglobin, and platelet count.
3. Coagulation parameters: activated partial thromboplastin time (aPPT) and international normalized ratio.
4. Kidney function: creatinine or GFR
5. Serum glucose.

6.5.1.1.3 Neurologic Evaluation

Screening NIHSS should be recorded as performed. At screening, an historical mRS will be obtained from the subject or the subject's caretaker.

6.5.1.1.4 Computed tomography or magnetic resonance imaging

Computed tomography (CT) or magnetic resonance imaging (MRI) obtained prior to study enrolment will be used for baseline assessment.

6.5.1.1.5 Procedural angiography

Angiography obtained during the procedure will consist of a baseline angiogram, post-device use angiograms (if applicable), a post-final EmboTrap device use angiogram, and if rescue therapy is used, a final post-procedure angiogram.

Baseline angiogram will be obtained prior to device deployment to assess inclusion exclusion criteria as well as to assess clot location. Post-device use angiograms will be obtained immediately after completion of each EmboTrap device and/or rescue therapy pass. The primary endpoint assessment angiogram will be considered any angiogram achieving a rating of mTICI 2b or greater reperfusion, after 3 or less passes of the EmboTrap device, or in the case this is not achieved, the third post EmboTrap device use angiogram. The final post-procedure angiogram will be obtained after all treatments, including any rescue therapies, have been completed. The final post procedure angiogram should comprise a full A-P lateral image.

CT or MRI will also be obtained at 24 hours (16–36 hours) post-procedure to assess any presence

of hemorrhage. It is preferred, but not required, that whether CT or MRI is taken at baseline, to make direct comparison easier, the same imaging modality is obtained at follow-up.

6.5.1.2 Adverse Events

Record any adverse events which occur during the procedure.

The procedure description follows.

6.5.2 Preparation & Delivery

- Using standard interventional techniques access the arterial system and using angiography, determine the location of the occluded vessel.
- Advance an appropriate Guide Catheter, Sheath or Balloon Guide Catheter as close to the occlusion as possible. Connect a rotating hemostasis valve (RHV) to the proximal end of this catheter and connect to a continuous flush system.
- Select an appropriate Microcatheter. Connect an RHV to the proximal end of the Microcatheter and connect to a continuous flush system.
- With the aid of a suitable guidewire, and using standard catheterization techniques and fluoroscopic guidance, advance the Microcatheter up to and across the occlusion so that the distal end of the Microcatheter is positioned distal of the occlusion.
- Remove the guidewire from the Microcatheter and, if desired, gently infuse contrast media through the Microcatheter to visualize the distal end of the occlusion.
- Remove the Insertion Tool with the preloaded Device from the packaging hoop, taking care not to accidentally retract or advance the Device from the Insertion Tool while doing so.
- Insert the distal end of the Insertion Tool through the RHV of the Microcatheter and wait until fluid is seen exiting the proximal end of the Insertion Tool, confirming that the Device is flushed. Advance the Insertion Tool until it contacts the hub of the Microcatheter. Fully tighten the RHV to hold the Insertion Tool securely in position.
- Confirm that the Insertion Tool is fully seated in the hub of the RHV before proceeding to advance the Device. Advance the Device until at least half of the shaft length has been inserted into the Microcatheter, at which point the Insertion Tool may be removed.

6.5.3 Positioning and Deployment

- Continue to advance the Device until the distal radiopaque tip of the Device aligns with the distal tip of the Microcatheter.

Note: There are two silver bands positioned on the proximal portion of the Device shaft to assist in minimizing the amount of fluoroscopic exposure required during Device insertion. If using a standard Microcatheter (total length of 155cm and a 7cm RHV), then when the first silver band on the shaft approaches the RHV, the Device tip will be approximately 8cm from the distal end of the Microcatheter. When the second silver band on the Device shaft approaches the RHV the Device tip will be nearing the distal end of the Microcatheter.

- Advance the Device in the Microcatheter and position the EmboTrap within the clot as described in the Instructions for Use.
- While stabilizing the Device shaft, retract the microcatheter to deploy the Stent-like assembly within the clot. The EmboTrap will be fully deployed once the distal tip of the microcatheter has been retracted to a position over the proximal radiopaque coil of the Device.
- The EmboTrap should be left to embed within the clot for 3-5 minutes prior to withdrawal.

6.5.4 Retrieval

Note: The use of a Mechanical Pump for aspiration is not allowed per protocol.

- Optimum control of the Device and microcatheter relative positions during retrieval may be achieved by advancing a torque device over the Device shaft and tightening it against the microcatheter RHV.
- If using a Balloon Guide Catheter inflate the balloon to occlude the vessel as per the Balloon Guide Catheter IFU.
- Withdraw the Device and Microcatheter slowly and carefully as a unit to the Guide Catheter tip while aspirating through the Guide Catheter with a syringe.
- As the device reaches the Guide Catheter, apply vigorous aspiration (by syringe), withdraw the Device and microcatheter into the Guide Catheter and continue to aspirate until the Device reaches the proximal RHV.

Note: If withdrawal into the Guide Catheter is difficult (as may be the case with a large clot burden) then deflate the balloon (if applicable) and withdraw the guide, Microcatheter and Device together through the Introducer Sheath.

- Disconnect the RHV from the Guide Catheter and remove the Device, Microcatheter and RHV together from the Guide Catheter.
- Use the syringe to further aspirate the Guide Catheter to ensure it is clear of any thrombus material.

6.5.5 Cleaning and Re-use

- Each EmboTrap Revascularization Device may be used for up to three (3) retrieval attempts.
- If an additional pass is to be made with the Device then carefully remove any captured thrombus from the Device and clean the Device in heparinized saline, rubbing gently from proximal to distal to remove any residual thrombus material. Inspect the Device carefully and if any damage or deformity is observed do not use the Device – instead use a new EmboTrap Revascularization Device for any subsequent passes. If using the same Device, replace the Insertion Tool onto the proximal shaft and retract the Device into the Insertion Tool until it is fully resheathed.

  Do not attempt more than three (3) retrieval attempts in the same vessel.

6.5.6 24 Hour (-8/+12 hrs) Follow-up

The 24(-8/+12) hour follow-up visit includes:

- An NIHSS examination
- CT or MRI imaging.
- Record any adverse events which occur after the procedure and up to the time of the 24 hour examination.

6.5.7 72Hour (±12 hrs) Follow-up of angiographic screening failures

For patients who were consented but not included due to failure to meet angiographic inclusion or exclusion criteria; record any adverse events which occur up to the time of the 72 (±12) hour examination.

6.5.8 7 Day/ 168 Hour (±12 hrs) Follow-up

The 7 Day/ 168 Hour (±12 hrs) follow-up visit includes:

- An NIHSS examination
- Physical Examination
- Concomitant medications
- Record any adverse events which occur after the 72 hour time point and up to the time of the 168 hour examination.

6.5.9 90 Day (±14 Days) Follow-up

The 90 Day (±14 Days) follow-up visit includes:

- An NIHSS examination and an mRS
- Record any adverse events which occur after the 168 hour time point and up to the time of the 90 day examination.

Subjects who successfully complete the 90 day visit will be discharged from the study.

Table 1: Study visits and assessments

Study Requirement	Screening	Procedure	Post Procedure			
	Within 8 hrs. of onset of stroke	Time Ø	24 Hours (-8/+12 hrs)	72 Hours (± 12 hrs)	7 Day 168 Hours (± 12 hrs) or at Discharge	90 Days (± 14 days)
Informed consent	X(1)					
Pregnancy test	X(2)					
NIHSS Score	X(5)		X		X(3)	X
Modified Rankin Scale (mRS)	X					X
Medical history	X					
Physical examination	X				X(3)	
Blood Pressure and Pulse	X					
Assess/confirm study eligibility	X					
CT or MRI	X		X			
Angiography	X(6)	X(7)				
Hemoglobin and Platelet Count	X					
Serum Glucose	X					
Serum Creatinine or GFR	X					
International normalized ratio (INR), activated partial thromboplastin time (APTT)	X					
Mechanical thrombectomy procedure (EmboTrap as well as any rescue devices)		X				
Concomitant medications	X				X(3)	
Record adverse events	X(4)	X	X	X(8)	X(3)	X

(1) Patient or Legally Authorized Representative must sign informed consent prior to screening specific tests which are beyond the local standard of care.
(2) For females of childbearing potential, subjects must have a documented negative pregnancy test prior to device insertion except in the case of local regulations and ethic committee approvals requiring consent post the emergency situation.
(3) To be performed at 168 Hours (+/- 12 hrs) or at discharge (whichever occurs first).
(4) Record all adverse events from the time of signature of the ICF.
(5) Perform prior to angiography.
(6) Perform just prior to mechanical thrombectomy in order to verify the angiographic inclusion/exclusion criteria are met.
(7) Perform angiography after every EmboTrap device pass, at the final EmboTrap device use, after each rescue therapy device pass. Obtain a final angiogram at the end of the interventional procedure.
(8) Follow up at 72 hours is exclusively for adverse events in the consented but not included patients where they were not enrolled because they did not meet the angiographic inclusion or exclusion criteria.

6.5.10 Imaging Core Laboratory

The objective of the Imaging Core Lab is to provide an unbiased assessment of the rate of revascularization defined by mTICI scores based on angiographic imaging from the study sites. The Core Lab will review all angiograms obtained. Data provided by the Core Lab will serve as the 'gold standard' and will be used for data analysis and determination of device efficacy. Each angiogram will be read independently by two experienced Core Lab neurointerventionalists. Any discrepancies in mTICI scoring will be resolved by a third, independent reader.

The Core Lab will also have the responsibility to evaluate CT/MRI examinations to detect and assess hemorrhages. Hemorrhages will be radiologically classified as described in section 7.1.

6.6 Subjects

WHO estimates that of the 15M annual strokes world-wide, one-third of patients die and one-third are disabled. Two of the primary factors associated with mortality in these patients are the occlusion location and the time to treatment. Per Smith et al [12], large-vessel occlusions, present in 46% of unselected acute stroke patients presenting in academic medical centers, are associated with higher stroke severity. These more proximal vessels feed a large volume of brain tissue, ergo clinicians use the presenting NIHSS score as an indicator of large-vessel occlusion.

6.6.1 Use of OUS data

The clinical practice for treatment of acute ischemic stroke is very similar in Europe to that in the U.S., endovascular device handling and use is identical and these are the factors that most affect revascularization outcome.

6.6.2 Clinical Practice

The use of MRI for screening is more common in the US than in Europe. Either method is appropriate. Actual endovascular treatment in both the US and Europe occurs in a catheterization laboratory. Between the continents cath lab practices and procedures do not differ in a manner that could affect revascularization outcome measured angiographically at a centralized core laboratory.

In both the US and Europe, patients experiencing an acute ischemic stroke receive lytic IV-tPA (if they are suitable candidates); if this is not effective then they are treated endovascularly with a stentriever. In the US, and in some European sites, the interventionalist waits sixty minutes to see if the lytics achieve revascularization before using the stent retriever. Although there is a potential here for a difference in the duration of exposure to lytic therapy before stentriever treatment, it is expected that very few ARISE II patients will be treated within an hour of receiving lytic therapy.

While in both the United States and Europe lytic therapy is recommended for patients meeting the ECASS inclusion/exclusion criteria between the 3-4.5 hour TFSO, lytics are not FDA approved for use in this time window. Local practice follows the guidances.

There are no other population or location specific treatment differences present between the

patients treatment in the US and that in Europe which could reasonably be suggested to influence revascularization results.

7 Assessment of safety

The following assessment criteria will be used to evaluate the safety endpoint of the study.

7.1 Cerebral CT or MR Imaging

This study will collect imaging data in line with routine practice as follows:

- Pre-procedure CT/ MR imaging
- Pre-treatment angiogram, post-device placement angiogram (if this was performed) & post-procedure angiogram
- 24(-8/+12) hour CT/ MR imaging

All imaging should be in line with standard of care. No extra imaging should be performed for the purpose of the study. No patient should be exposed to extra radiation as a result of participation.

Any other imaging performed (for example as a result of clinical deterioration) will also be provided.

In the event of abrupt neurologic deterioration or when deemed necessary by the investigator, an emergency CT or an MR imaging evaluation should be performed. An immediate evaluation of the presence/absence of hemorrhage, edema, and/or infarction as contributors to the clinical deterioration will be made. Any imaging taken prior to the routine 24hr imaging (which may be taken in a time window of 16-36 hours without becoming a protocol deviation) for this reason will be included in the analysis.

Cerebral hemorrhage is categorized as hemorrhagic infarct or parenchymal hematoma by the following definitions:

- *Hemorrhagic infarct* is any area of petechial or small, confluent hemorrhages within larger regions of hypodense, ischemic injury without mass effect.
- A *parenchymal hematoma* is a more homogenous area of hemorrhage, with or without intraventricular extension, usually with mass effect.

Hemorrhages will be classified clinically and radiologically according to the following categories [4]:

Clinical categories:

- C1: Clinical deterioration where hemorrhage is the primary cause< 4 NIHSS points
- C2: Clinical deterioration where hemorrhage is the primary cause ≥ 4 NIHSS points

Radiological categories:

- HI 1: small petechiae within the ischemic field without mass effect
- HI 2: confluent petechiae within the ischemic field without mass effect
- PH 1: Hematoma within ischemic field with mild space occupying effect but involving ≤30% of the infarcted area
- PH 2: Hematoma within ischemic field with space occupying effect involving >30% of the infarcted area
- RIH: Any intraparenchymal hemorrhage remote from the ischemic field
- IVH: Intraventricular hemorrhage
- SAH: Subarachnoid hemorrhage
- SDH: Sub Dural Hematoma
- EDH: Extra Dural Hematoma

7.2 Neurologic Evaluations

Repeat NIHSS determinations are performed in line with standard of care at 24 hours (-8/+12 hrs) and at 7 days (or discharge whichever is sooner) time points post-procedure. An additional NIHSS score should be obtained when any signs of neurologic deterioration occur or in the event of an ICH to assess the degree of deterioration. A certified examiner should perform all neurologic evaluations. The 90-day evaluation will record the mRS score.

8 Statistical analysis

8.1 Study Design

The objective of this prospective, multi-center open label study using core laboratory adjudication of results is to investigate the performance of the EmboTrap device against a performance goal for efficacy ($PG_{efficacy}$). In order to claim non-inferiority against an efficacy driven performance goal, the lower bound of a (95%) confidence interval must be shown to be greater than a non-inferiority limit (N_L) which is the predetermined $PG_{efficacy}$.

The $PG_{efficacy}$ has been derived from a meta-analysis of revascularization efficacy rates from approved predicate devices' adjudicated performances as reported in the literature.

The Performance Goal (PG) is calculated using a Bayesian Hierarchical Random Effects Meta-Analysis which incorporates a down-weighting of the Merci data by treating patients from the Trevo and Solitaire trials only as exchangeable.

The test for non-inferiority for performance will be based on a one-sided test (at the 0.025 significance level) for a binomial proportion with hypotheses:

$$H_0: PG_{efficacy} \leq N_L \text{ versus } H_1: PG_{efficacy} > N_L$$

An equivalent testing procedure is available by using the sample data to calculate a confidence interval for the population proportion. Demonstrating non-inferiority for efficacy necessitates rejecting the null hypothesis in favor of the alternative hypothesis, in this case based on the upper

limit of a 95% confidence interval for a population proportion.

Estimates of each population parameter of interest for all other endpoints will be provided using appropriate confidence intervals.

8.2 Sample Size Considerations

An evaluable sample size of 176 revascularization results is needed in order to have 90% power to demonstrate non-inferiority against a non-inferiority limit (N_L) with an efficacy level of 0.56, based on a one-sided exact test for a binomial proportion [5] [6] at the 0.025 significance level and assuming that the proportion of adjudicated successes with the EmboTrap device is 0.68.

The estimate of device success rate used above is based on early clinical *in vivo* experience with the EmboTrap device in an open case series of the CE-marked product across five European centers. The TICI 2b or greater rating achieved was reported by interventionalists at over 74%. It is expected that adjudication may reduce this somewhat as was the case in both the Trevo II and SWIFT studies. Using 68% will ensure the statistical comparison is valid in the event the adjudicated success rate of the EmboTrap device is lower than that self-reported by 6%.

The evaluable sample of 176 in the ARISE II trial will be representative of the population of interest and the revascularization results are independent of each other.

8.2.1 Missing and Censored Data

An extra 30% to the required evaluable patient cohort number of 176 is included to allow for roll in patients (up to 36 roll ins in US sites, and up to 12 in the EU) and missing data, bringing the total cohort to 228. Missing data will be examined, and the reasons will be investigated and reported. Multiple imputation methods will be used, where needed, to address any missing endpoint data in both the ITT and mITT analysis.

Secondary endpoint data will be censored where rescue therapy was used. Where less than 176 evaluable data points are available, data will be imputed using chained equations with 20 imputations per observation [7].

The final analysis of the multiple imputed data will involve two steps: 1) running the analysis on each of the imputed datasets, and 2) aggregating the estimates from each dataset to obtain the final result using Rubin's rules [8] to combine the estimates while adjusting for the variance between imputations and across imputed datasets [9].

8.3 Analysis Methods

8.3.1 Primary Endpoint

The primary endpoint will be examined using the hypothesis described in section 8.1 above, for both the ITT population and for the mITT described below.

8.3.2 Intention to Treat

All subjects confirmed to meet the inclusion and exclusion criteria via angiography in the ARISE II Study will be included in the ITT analysis of safety and effectiveness, as data allows.

8.3.2.1 Modified Intention To Treat

In order to analyze a comparable population to that used in the predicate studies, SWIFT and TREVO II, the primary hypothesis will also be tested on a "Modified Intention to Treat" (mITT) subgroup. The mITT subgroup will reflect the lytic regime used in the TREVO II and SWIFT studies.

- This subgroup will exclude screen failures for inclusion criterion 11.
- This subgroup will have been treated in compliance with the protocol and will meet the lytic regime requirements set out in inclusion criteria 7 and 8.
- And only patients who are contra-indicated for IV-tPA or in whom IV-tPA has failed will be included in the mITT analysis. Failure of IV-tPA is defined as angiographic evidence of persistent target vessel occlusion, one hour or more after the initiation of IV-tPA therapy.

The cut off time point for initiation of lytic therapy will be in line with the FDA approved time indicated which is within 3 hours of stroke onset. All patients who meet the study entry criteria, are enrolled in the trial and were treated per the protocol (introduction of rescue therapy prior to three retrieval attempts with EmboTrap is a protocol violation) will be included in the mITT analysis sample. It is expected this will include most of the ARISE II population and the facility to enroll up to 228 should ensure that an evaluable sample of 176 are available for the mITT analysis.

8.3.3 Analysis of the Secondary endpoints

All other binary endpoints will be treated using the Wilson exact Binomial Proportion test to allow a statement on the corresponding population proportion be made.

Descriptive statistics will be used to summarize the clinical outcome variables collected on all vessels treated in this investigation overall and for each center.

The typical value for each continuous response variables will be estimated using the mean and median while the variability will be estimated using the range, interquartile range and standard deviation. All categorical variables will be reported as counts and percentages.

Box and bean plots will be generated for each continuous response variables while bar charts will be generated for each categorical variable.

At study completion summaries of each clinical outcome variable will include corresponding 95% confidence intervals in order to provide an estimate of the corresponding population means, medians and proportions.

The following primary efficacy endpoint will be examined using the model discussed:

- Revascularization measured using modified Thrombolysis in Cerebrovascular Infarction (mTICI inclusive of the 2c rating). Successful achievement of the endpoint is defined as achieving a mTICI score of 2b or greater in the target vessel, following 3 or less passes of the EmboTrap device.

The primary safety endpoint will be evaluated descriptively:

- The primary safety endpoint will be the rate of sICH together with SADEs (excluding those already counted in sICH).

The secondary endpoints will be examined descriptively to further advance the safety and efficacy profile of the device. Full definitions are provided in section 3.2 of this protocol:

Demographics, baseline characteristics, procedural information, and clinical outcomes (efficacy and safety) will also be summarized.

The study will also perform subgroup analyses of descriptive statistics for the cohort based on

- Specific vascular location of the occlusion (i.e. proximal M1/ distal M1 /M2, etc.)
- Technique of treatment as described below
  - Use of a balloon guide vs. no balloon guide
  - Use of an intermediate catheter vs. no intermediate catheter

A summary of the proportions of subjects receiving each category score on the mTICI scale will be reported.

Note that adverse events will be adjudicated as to the relationship to the EmboTrap device, procedure or the disease state as well to the severity of the event. Subgroup analyses of the points described in the synopsis will be completed.

8.3.4 Analysis of Ability to Pool Data Across Investigational Sites

This is a multi-center clinical study, with standardization of subject enrollment, data entry and adverse event reporting. All investigational sites will follow the requirements of a common protocol, data collection procedures and forms. To present the data from this clinical study in a summary form, a comparison of the primary endpoint across sites will be completed to determine if the generated data can be pooled using a test for homogeneity.

8.3.5 Deviations from the statistical plan

Any departure or deviation from these planned statistical methodologies will be documented and discussed in the Statistical Analysis Plan that will include the statistical rationale for change.

9 Amendment to the CIP

Only Neuravi is allowed to modify this protocol. The change will be in the form of a protocol amendment. Any modification that potentially affects subjects' rights or safety must also be approved by the EC or IRB and other regulatory agencies. In an emergency situation, where action is necessary to protect the life or physical wellbeing of the subject, a departure from the protocol for an individual subject may be allowed, and that departure will be for that subject only. In such circumstances, the investigator must notify the EC or IRB and Neuravi and must describe the conditions necessitating the departure from the protocol and the outcome of the emergency intervention in a written report. Neuravi will determine whether the subject is to continue in the study or be considered a protocol violation.

10 Deviations from the CIP

10.1 Protocol violation

A *protocol violation* is defined as an event that resulted in an increased risk to a subject or others; affected the right, safety or welfare of a subject; or affected the integrity of the study. Protocol violations include, but are not limited to, the following list:

- Failure to obtain informed consent prior to patient enrolment
- Enrolled patient did not meet the inclusion/exclusion criteria
- Source data permanently lost
- Introduction of rescue therapy prior to attempting revascularization with EmboTrap for three passes.

10.2 Protocol deviation

Any other events that do not comply with the requirements of the protocol will be considered *protocol deviations*.

Protocol deviations include, but are not limited to, the following list:

- Incorrect version of the informed consent form used.
- Patient did not attend follow-up visit or follow-up visit was outside the required window.

All protocol violations and deviations from the study protocol must be reported to the appointed Neuravi representative/ study monitor on a protocol violation/deviation form, regardless of whether medically justifiable, pre-approved by Neuravi or taken to protect the subject in an emergency. In addition, the investigator is required to adhere to the ethics committee/IRB procedures for reporting protocol violations and deviations.

Investigators must obtain prior approval from Neuravi before initiating deviations from the investigational protocol, except in situations where necessary to protect the life or physical well-being of a subject in an emergency situation, or situations beyond the investigator's control (such as subjects not attending scheduled follow-up visits, etc.). Approval for deviations shall be documented in writing and maintained in the investigator and clinical study management files. All deviations will be reported to Neuravi, regardless of medical justification, pre-approval by Neuravi, or emergency nature. Subject-specific protocol deviations will be reported using the protocol deviation form eCRF. Non-subject-specific protocol deviations (e.g. unauthorized use of the investigational device in the US outside the study, unauthorized use of the investigational device in the US by a physician who has not signed the investigator agreement, etc.) shall be notified in writing to Neuravi FDA regulations (21 CFR 812.140 (a) (4)) require investigators to maintain accurate, complete and current records, including documentation showing the dates of and reasons for each deviation from the protocol. Per 21 CFR 812.46 (a), failure to comply with the investigational plan may result in termination of the investigator's participation in the study.

11 Device Accountability

11.1 Europe

As the study device for this clinical investigation is legally marketed and approved for use in all participating centers the regulatory requirements for device accountability and traceability are those outlined in ISO13485:2012. Device traceability will be maintained by Neuravi under the documented provisions of their ISO13485:2012 accredited quality system.

11.2 United States

Neuravi is responsible for the traceability of the study device (EmboTrap) for this clinical investigation. Neuravi assumes responsibility for maintaining the following records:

- Quantity of the devices, the dates the devices are delivered to the study suite.
- Lot numbers of all devices to be used for the study.
- Records of the shipment of the study devices and ancillary supplies to the investigational site.

Neuravi will ship devices only to qualified sites participating in the investigation who have the appropriate traceability and stock management controls in place. The appointed Neuravi representative/ study monitor will ensure the study site meets the record-keeping requirements for accountability and reconciliation of the study devices and ancillary supplies as part of the Site Initiation Visit. The investigator is responsible for proper storage of received devices and ancillary supplies at the hospital, and for maintaining a current device-tracking log for the duration of the study. The study monitor will review device storage conditions and the completion of the site's device tracking log. Reconciliation of device disposition will be documented. The names of all persons who received, used, or disposed of any device at the site will be recorded.

Records for the return of all study devices and ancillary supplies to Neuravi will be completed by the study site, verified by the appointed Neuravi representative (study monitor), and final disposition records will be maintained by Neuravi.

12 Safety and adverse events

An **Adverse Event (AE)** is any untoward medical occurrence in a subject that may, or may not, have a causal relationship with the study treatment.

An **Adverse Device Effect (ADE)** is any untoward and unintended response to a medical device. This includes Serious Adverse Device Effects and any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device, and any event resulting from a user error.

A **Serious Adverse Event (SAE)** is an adverse event which

a) Led to death,

b) Led to serious deterioration in the health of the subject, that either resulted in

1) A life-threatening illness or injury, or

2) A permanent impairment of a body structure or a body function, or

3) In-patient or prolonged hospitalization, or

4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

A **Serious Adverse Device Effect (SADE)** is one where the EmboTrap device caused, or cannot be ruled out as having caused, an effect that has resulted in any of the consequences characteristic of a serious adverse event (e.g. Vessel dissections or perforations caused by EmboTrap device).

Procedure Related Serious Adverse Events (PRSAE) is where the interventional procedure caused, or can not be ruled out as having caused, an effect that has resulted in any of the consequences characteristic of a serious adverse event.

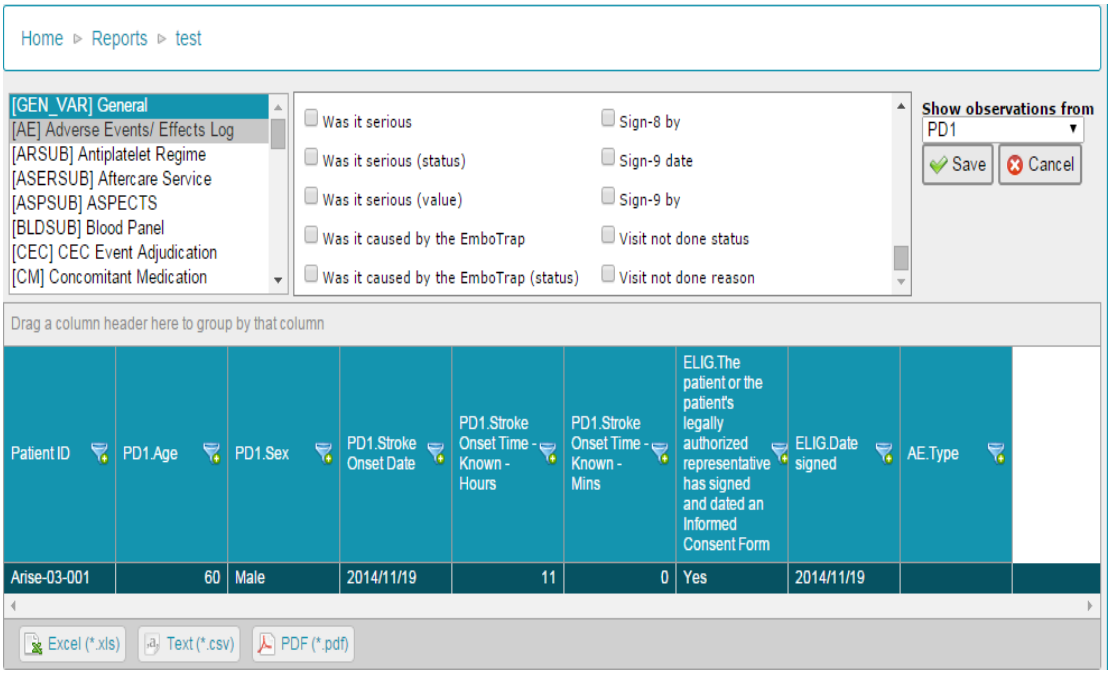
Unanticipated Adverse Device Effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

The sponsor will report the results of an evaluation of any UADE to FDA and all reviewing IRB/ethics committees and investigators within 10 working days from receiving notice of the UADE.

In addition to the events referenced above, the following procedure-related adverse events should be reported to Neuravi regardless whether or not the subject experienced clinical sequelae:

- Vessel perforation
- Intramural arterial dissection
- Asymptomatic intracranial hemorrhage
- Embolization in a previously uninvolved territory

The Electronic Data Capture program "www.e-capture.net" will record all subject information including any specific incident details for all participants in the trial. This includes all AE, ADE, SAE, SADE and UADE events. The program will also capture all subsequent interventions and/or treatments administered to the subject. The information is entered directly into the database by the Principle Investigator or an assigned designate at each study center who has been trained in the use of the program by Neuravi. The screen-shot below provides an illustration of the type of information recorded by the program.



12.1 Clinical Events Committee (CEC)

An independent board consisting of stroke neurologists and neurointerventionalists who are not participating in the study will adjudicate serious adverse events in the trial.

The role of the CEC will be to:

- Adjudicate all hemorrhages documented by the Independent Core Laboratory image reviewer as symptomatic or asymptomatic based on the neurological status of the subject.
- Adjudicate all dissections/perforations documented by the Independent Angiographic reviewer as to relationship to the EmboTrap device and/or IA therapy used.
- Adjudicate whether an SAE is deemed attributable to the procedure, to the EmboTrap Device, Adjuvant therapy (IA thrombolysis, thrombectomy), or from the natural course of the initial stroke.
- Continuous evaluation of available external data and/or knowledge, as presented at major congresses and /or published in peer-reviewed journals, which may have an impact on the adjudication and analysis of the reported events.

12.2 Data and Safety Monitoring Board (DSMB)

An independent board consisting of stroke neurologists, neurointerventionalist(s) and a statistician who are not participating in the study will monitor the adverse events and the occurrence rate in the trial.

The role of the DSMB will be to:

- Monitor the SAE rate and establish specific "stopping rules" for the trial.
- Make recommendations for revisions to the protocol to the EmboTrap device regarding safety of the study.
- Periodically review and monitor aggregated and individual subject data related to safety, data integrity, scientific validity and overall conduct of the study, to ensure the rights, safety, and welfare of the study participants;
- Monitor subject accrual and retention;
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or on the ethical conduct of the study;
- Ensure the confidentiality of the trial data and the results of monitoring;

12.3 Event notification

12.3.1 Adverse Events (AE) and Adverse Device Effects (ADE)

All adverse events and adverse device effects shall be recorded on sponsor-provided adverse event electronic case report forms eCRF. The safety assessments will consist of Adverse Events (AE) from the time the ICF is signed through Day 90 for those patients enrolled, and to discharge or 72 hours for those patients identified as screening failures though angiographic criteria. Adverse events and adverse device effects shall be recorded in the form of a diagnosis, rather than providing the various signs and symptoms for a particular health condition. The investigator or investigator-appointed study personnel will complete these eCRFs. Adverse event eCRFs should be provided to an appointed Neuravi representative (study monitor) for review within 30 days of becoming aware of the event, and within 24 hours of knowledge of device related adverse events. Copies of related records and reports shall be provided to Neuravi upon request. If the Investigator is made aware of any SAEs after Day 90, these should also be reported to Neuravi or its designee provided the SAE is considered related to the investigational device. The site would then provide a completed SAE form within 1 business day and the event will be followed until resolution, or until adequate stabilization is met.

An AE that occurs after the ICF has been signed and before the treatment with the EmboTrap has started is identified as a pretreatment AE (PTAE). This will include AEs occurring in those patients identified as screening failures through the angiographic inclusion or exclusion criteria. An AE that occurs after treatment using EmboTrap has started will be considered a treatment emergent AE (TEAE). All AEs must be recorded and reported accordingly, whether they appear causally related to the interventional procedure, or not. Adverse events will be followed until the outcome is known or until the Investigator feels no further medical follow-up is warranted.

All AEs will be reported verbatim as provided by the investigator. The AEs will be categorized using MedDRA Coding of Adverse Events nomenclature Standardized nomenclature that will be ascertained includes lowest level and preferred MedDRA terms, MedDRA System Organ Class. The Adverse Events will be monitored and trended by Neuravi and reported to the clinical events committee and DSMB for review and adjudication on a periodic basis. Adverse Events are subject to adjudication as detailed in section 12.1.

12.3.2 Serious Adverse Events (SAE) and Serious Adverse Device Effects (SADE)

The investigator must notify the appointed Neuravi representative/ study monitor of all serious adverse events and serious adverse device effects immediately after becoming aware of the event (no later than 24 hours from being notified of the event). The investigator may also contact the appointed Neuravi Representative/ study monitor for assistance in determining whether or not the event in question is considered serious. Notification should be provided by completing all available fields of the adverse event eCRF and then faxing or sending the form by e-mail to the appointed Neuravi representative.

Any Serious Adverse Event (SAE) or Serious Adverse Device Effect (SADE) must be reported "in writing" to Neuravi within 5 days of knowledge. Copies of all related correspondence and documentation shall be provided to the appointed Neuravi representative/ study monitor.

Should potential SAEs or SADEs be discovered during the study of which the investigator was not aware, Neuravi or the appointed Neuravi Ltd representative/ study monitor will provide relevant documentation within 10 days from becoming aware of the event for the investigator's review and submission to the ethics committee, if applicable.

12.3.3 Device failure, malfunction, misuse and near incidents

All device failures, malfunctions, misuse and near incidents (as defined below) will be documented on the electronic case report form and reported to Neuravi within 1 working day after the investigator becomes aware of the event, and reported to the IRB as required.

- **Device failure:** A device has failed if it is used according to the labeling, including without limitation, instructions for use, and applicable standards of medical practice but does not perform according to the labeling and negatively impacts the treatment.
- **Device malfunction:** A device malfunction is a change in the function of the device that is not described in the labeling and that may or may not affect device performance.
- **Device misuse:** A misused device, i.e. one that is not used by the investigator in compliance with applicable standards of medical practice, including without limitation, those described in the instructions for use and labeling, will not be considered a malfunction.

13 Site Initiation

Neuravi or a representative of Neuravi will conduct a training session with the study site team as described in 13.1.

Prior to enrolling subjects at a study site, the following documentation must be provided to Neuravi or a representative of Neuravi:

- IRB/EC approval for the Investigational Plan.
- IRB/EC and Neuravi approved Informed Consent Form for the study.
- Investigator(s') curriculum vitae (CV).
- Financial Disclosure(s) for the PI and Sub/Co-I(s).
- Signed Investigator's Agreement.
- Signed Clinical Study Agreement (CSA).
- Training Log documentation to verify the appropriate study staff has been trained on the protocol, device, eCRFs and study conduct.

13.1 Training

Appropriate clinical site personnel at each investigational site, including Principal Investigator, Sub/Co-Investigator(s), and Research Co-ordinator(s), will be trained to the investigational plan. To ensure proper device usage, data collection and protocol compliance, Neuravi will schedule an initiation visit at each site. Investigator/Site Personnel will undergo training prior to performing any study-related procedures. All training must be documented. Training to the investigational plan will include the following topics:

- Study objectives.
- Protocol review and compliance.
- Responsibilities and obligations of the investigator/study site team.
- Delegation of authority for study-related tasks.
- The Instructions for Use of the EmboTrap® Revascularization Device.
- Informed Consent process, including any relevant IRB/EC requirements.
- Techniques for identification of eligible subjects.
- Study documentation required (essential documents).
- Electronic Case Report Forms and completion instructions.
- Documentation of protocol deviations.
- Adverse, Serious Adverse Event Reporting.
- Product malfunction reporting.
- Image submission procedure.
- General guidelines for good clinical practices.
- Follow-up scheduling.
- Regulatory requirements.

Existing study site personnel who have been delegated new tasks and new study site personnel will undergo training to the investigational plan, as appropriate.

14 Study monitoring

The study data will be monitored regularly by a dedicated monitor to make sure that all data are correct. There will be a site initiation visit, the first monitoring visit will occur as soon as possible after enrollment of the first subject followed by a visit after the fourth subject is enrolled during the enrolment phase. A minimum of one monitoring visit (per site) will be performed during the follow-up phase.

When the monitor requests additional data or clarification of data for the eCRF, the request must be answered satisfactorily before the next monitoring visit. The principal investigator must sign all eCRFs. Completed eCRF will be electronically signed off by the study monitor after they have been verified against source data. For SAEs or SADEs discovered during the study of which the investigator was not aware, Neuravi or the appointed Neuravi representative/study monitor will provide relevant documentation within 10 days from becoming aware of the event for the investigator's review and submission to the ethics committee, if applicable.

There will be a site closure visit to ensure all documentation is in place and all outstanding items have been addressed.

15 Data collection

15.1 Data Management Responsibilities

The handling of data, including data quality assurance, will comply with regulatory guidelines (for example, GCP) and the sponsor's SOPs and work instructions. All steps and actions taken regarding data management and quality assurance will be documented in the sponsor's SOPs and data handling guidelines.

Completed eCRFs will be 100% verified against source data and visually checked by the study monitor for completeness, consistency, and legibility.

All adverse event terms recorded on the eCRF will be entered into the sponsor's safety database.

All data on the eCRFs will be entered into a validated database. Edit checks will be implemented to ensure data quality and accuracy. Responses to requests for further clarification of data recorded in the eCRF will be answered, dated, and electronically signed by the investigator. Changes will be implemented in the sponsor's database and the data review and validation procedures will be repeated as needed.

At the end of the study, the database will be locked and the data will be released for reporting and statistical evaluation.

15.2 Confidentiality

The investigator and institution involved in this study will only provide direct access to source data and documents to the sponsor, Neuravi, and to appropriate authorities for the purposes of monitoring, audit, ethics committee review or regulatory inspection. Each subject taking part in the study will have agreed explicitly to such access in writing.

All subject data will always be treated with strict adherence to professional standards of confidentiality. All reports and communications relating to subjects in the study will identify the subjects by their subject ID number only.

15.3 Electronic Case Report Forms

Data collected for each subject will be recorded on an electronic Case Report Form (eCRF) provided by Neuravi Instructions for proper completion will be provided. The investigator is responsible for ensuring that all sections of each eCRF are complete and correct and that those entries can be verified against source data (such as patient hospital files or programmer print-outs).

15.4 Source Documentation

Investigators are required to prepare and maintain adequate and accurate case histories, recording all observations and other data pertinent to the investigation on each subject.

15.5 Data record keeping

All study material shall be stored for at least 10 years and only destroyed after written approval from Neuravi

16 Audits/Inspections

An independent audit by Neuravi or external regulatory agencies from the investigator's own country or from abroad may take place at any time during or after the study. This may include on-site inspections and source data verification at the investigator's hospital. If the authorities announce inspection, the investigator should inform Neuravi immediately.

17 Criteria for Terminating Study

The Sponsor reserves the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons and reasons related to protection of patients. Investigators and associated IRB will be notified in writing in the event of termination.

Possible reasons for study termination include:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- A decision on the part of the sponsor to suspend or discontinue development of the device.

18 Criteria for Terminating a Study Center

The sponsor reserves the right to stop the enrollment of patients at a study center at any time after the study initiation visit if no patients have been enrolled or if the center has multiple or severe protocol violations without justification or fails to follow remedial actions. Possible reasons for terminating a study center include:

- Insufficient enrolment rate i.e. less than 1 patient in a 10 week period.
- Repeated failure to complete CRFs in a timely manner.
- Failure to obtain Informed Consent.
- Failure to report serious adverse events within 24 hours of knowledge.
- Loss of (or unaccounted for) investigational product inventory.

19 Study Finances

A Clinical Investigation Agreement (or equivalent) will be prepared by Neuravi, which will be signed by the participating site. This agreement describes the legal conditions, conditions for financial compensation, and reimbursement details for the co-operation between Neuravi and the investigator in this study.

20 Study Management

The flow chart in Figure 5 outlines the supervisory bodies that will oversee all clinical trial activities including protocol development and protocol amendment during study conduct. Neuravi Inc. as the sponsor will perform monitoring at each site to ensure protection of the rights of subjects, the safety of subjects, and the quality and integrity of the data collected and submitted according to FDA regulations. The Study Principal Investigator will be available at all times to provide consultation to study investigators regarding any technical and procedural issues that may arise during the treatment procedure.

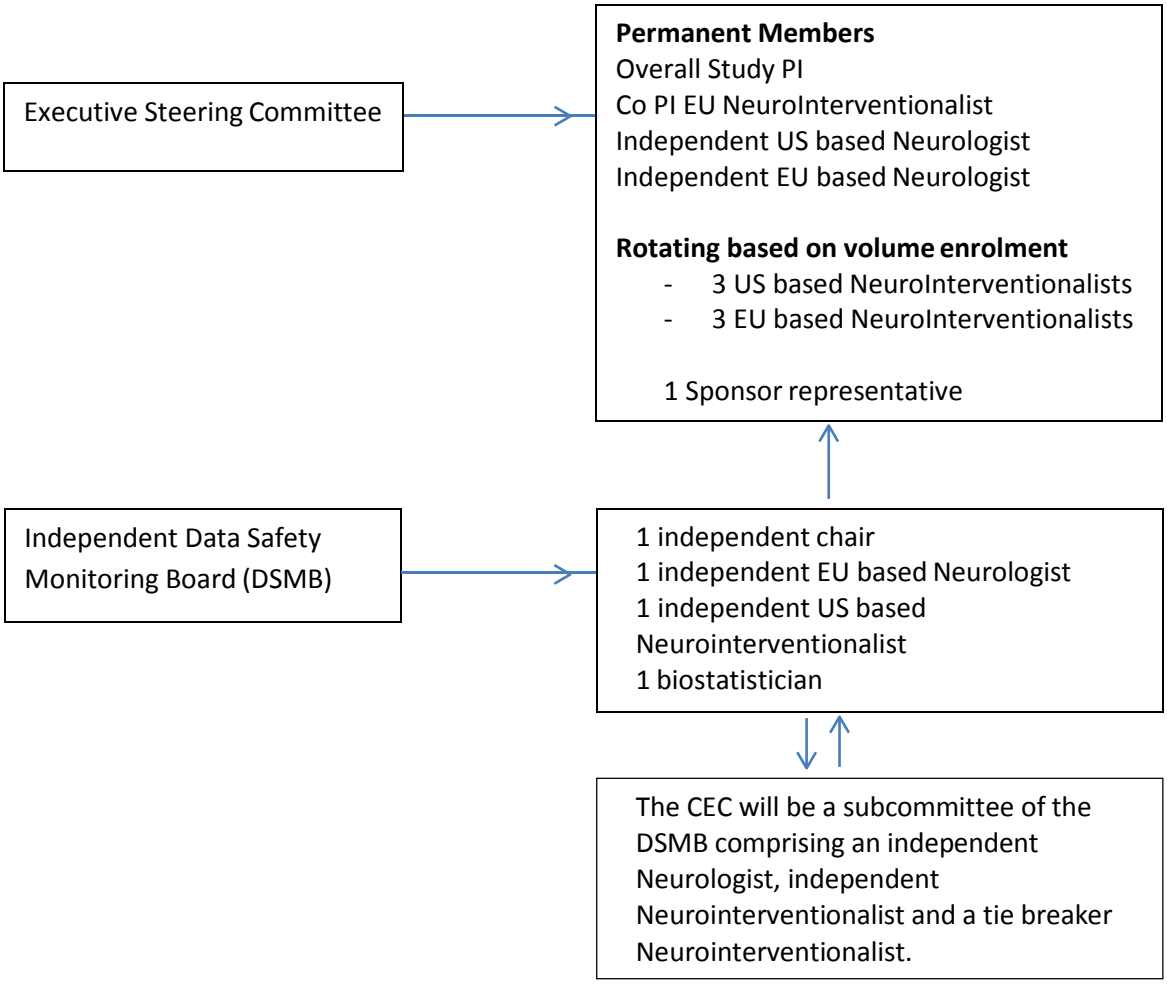


Figure 5: Supervision responsibility for the Clinical Investigation

21 Clinical trial insurance

Product liability insurance is in place for the EmboTrap device use as described under the Instructions for use. Neuravi maintains appropriate product liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. An insurance statement/ certificate will be provided to the Ethics Committee/IRB.

22 Publications Plan

All information concerning the EmboTrap device or Neuravi (e.g. patent applications, manufacturing processes, basic scientific data, and materials information) supplied to the investigator by Neuravi and not previously published is considered confidential and shall remain the sole property of Neuravi. The investigator agrees to use this information only in accomplishing the study and will not use it or the data generated from the study for other purposes without first obtaining the written consent of Neuravi.

It is understood that Neuravi will use the information developed in this clinical study as part of a development program for the EmboTrap device, and therefore may disclose this information as required to other Neuravi clinical investigators or to government regulatory agencies. The investigator understands that she or he has the obligation to provide complete test results and all data developed during this study to Neuravi or its designate.

Every effort will be made to publish the results of this study irrespective of whether the findings are in favor of the EmboTrap device. To this end, and to avoid publication bias, the ARISE II study will be registered, prior to enrolment commencing, on the clinicaltrials.gov database.

A Publications Committee will be formed to review and publish the data from the study. This committee will include the principal investigator, co-principal investigator, and one representative of the sponsor. The committee will create a publication policy describing in detail the organization of authorship. The Publications Committee will write/review all drafts of abstracts and full-length manuscripts, and will choose the appropriate journal (for manuscripts) or meeting (for abstracts) for submission. All members of the Executive Steering Committee will be named on the study report publication in order of volume of enrollment. For clarity, the Principal Investigators will have the final decision making and editorial rights on the paper submitted for publication.

Bibliography

[1] E. C. Jauch, J. L. Saver, H. P. Adams, A. Bruno, J. J. Connors, B. M. Demaerschalk, P. Khatri, P. W. McMullan, A. I. Qureshi, K. Rosenfield, P. A. Scott, D. R. Summers, D. Z. Wang, M. Wintermark, H. Yonas, American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease and Council on Clinical Cardiology, "Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association," *Stroke,* vol. 44, no. 3, pp. 870-947, 2013.

[2] W. Hacke, M. Kaste, C. Fieschi, D. Toni, E. Lesaffre, R. von Kummer, G. Boysen, E. Bluhmki, G. Höxter and M. H. Mahagne, "Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS)," *The Journal of the American Medical Association,* vol. 274, no. 13, pp. 1017-1025, 1995.

[3] V. Larrue, R. von Kummer, A. Müller and E. Bluhmki, "Risk Factors for Severe Hemorrhagic Transformation in Ischemic Stroke Patients Treated with Recombinant Tissue Plasminogen Activator: A Secondary Analysis of the European-Australasian Acute Stroke Study (ECASS II)," *Stroke,* vol. 32, no. 2, pp. 438-441, 2001.

[4] R. Sacco, S. Kasner, J. Broderick, L. Caplan, J. Connors, A. Culebras, M. Elkind, M. George, A. Hamdan, R. Higashida, B. Hoh, L. Janis, C. Kase, D. Kleindorfer, J. Lee, M. Moseley, E. Peterson and T. Turan, "An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association," *Stroke,* vol. 44, no. 7, pp. 2064-2089, 2013.

[5] W. C. Blackwelder, "Equivalence Trials.," *Encyclopedia of Biostatistics,* vol. 2, pp. 1367-1372, 1998.

[6] J. L. Fleiss, B. Levin and M. C. Paik, Statistical Methods for Rates and Proportions, Wiley, 2003.

[7] I. R. White, P. Royston and A. M. Wood, "Multiple imputation using chained equations: Issues and guidance for practice," *Statistics in Medicine,* vol. 30, no. 4, pp. 377-399, 2011.

[8] D. B. Rubin, Multiple Imputation for Nonresponse in Surveys, New York: John Wiley & Sons, 1987.

[9] J. L. Schafer and J. W. Graham, "Missing data: our view of the state of the art," *Psychological Methods,* vol. 7, no. 2, pp. 147-177, 2002.

Appendix A - DECLARATION OF HELSINKI

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, South Africa, October 1996 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification on paragraph 29 added) 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification on Paragraph 30 added) 59th WMA General Assembly, Seoul, Korea, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. The committee may make no change to the protocol without consideration and approval.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the

physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of

research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

Appendix B - Terms and definitions

For the purposes of this protocol the following terms and definitions apply.

1. Adverse device effect (ADE)

Adverse event related to the use of an investigational medical device.

NOTE 1 This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

NOTE 2 This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

2. Adverse event (AE)

Any untoward medical occurrence in a subject that may, or may not, have a causal relationship with the study treatment.

NOTE 1 This definition includes events related to the investigational medical device or the comparator.

NOTE 2 This definition includes events related to the procedures involved.

NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.

3. Audit

Systematic independent examination of activities and documents related to clinical investigation to determine whether these activities were conducted, and the data recorded, analyzed and accurately reported, according to the CIP, standard operating procedures, this International Standard and applicable regulatory requirements.

4. Clinical investigation

Systematic investigation in one or more human subjects, undertaken to assess the safety or performance of a medical device.

NOTE "Clinical trial" or "clinical study" are synonymous with "clinical investigation".

5. Clinical investigation plan (CIP)

Document that state(s) the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation.

6. Clinical investigation report

Document describing the design, execution, statistical analysis and results of a clinical investigation.

7. Clinical performance

Behaviour of a medical device or response of the subject(s) to that medical device in relation to its intended use, when correctly applied to appropriate subject(s).

8. Contract research organization (CRO)

Person or organization contracted by the sponsor to perform one or more of the sponsor's clinical investigation-related duties and functions.

9. Coordinating investigator

Investigator who is appointed by the sponsor to coordinate work in a multicenter clinical investigation.

10. Data Safety and Monitoring Board (DSMB)

Independent committee established by the sponsor to assess, at intervals, the progress of the clinical investigation, the safety data or the critical performance endpoints and to recommend the sponsor whether to continue, suspend, modify, or stop the clinical investigation.

11. Deviation

Instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CIP.

12. Device deficiency

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

NOTE Device deficiencies include malfunctions, use errors, and inadequate labelling.

13. Informed consent process

Process by which an individual is provided information and is asked to voluntarily participate in a clinical investigation.

NOTE Informed consent is documented by means of a written, signed and dated informed consent form.

14. Investigator

Individual member of the investigation site team designated and supervised by the principal investigator at an investigation site to perform critical clinical-investigation-related procedures or to make important clinical investigation-related decisions.

NOTE An individual member of the investigation site team can also be called “sub-investigator” or “co-investigator”.

15. Investigator's brochure (IB)

Compilation of the current clinical and non-clinical information on the investigational medical device(s), relevant to the clinical investigation.

16. IV-tPA failure

Failure of IV-tPA is defined as angiographic evidence of persistent target vessel occlusion 60 minutes or more after initiation of IV-tPA.

17. Legally authorized representative

Individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical investigation.

18. Malfunction

Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP

19. Modified Thrombolysis in Cerebrovascular Infarction (mTICI)

0	No perfusion
1	Perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion
2a	Perfusion of less than half of the vascular distribution of the occluded artery
2b	Perfusion of half or greater of the vascular distribution of the occluded artery
3	Full perfusion with filling of all distal branches

AJNR March 2008 29: 582-587. “*Revascularization Results in the Interventional Management of Stroke II Trial*”. T Tomsick et al.

19b. mTICI inclusive of the 2c rating:

	Consensus clarification*
0	No perfusion
1	Antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion
2	Incomplete antegrade reperfusion wherein the contrast passes the occlusion and opacifies the distal arterial bed but there are residual antegrade perfusion deficits • 2a Antegrade reperfusion of less than half of the occluded target artery previously ischemic territory (eg, in 1 major division of the MCA and its territory) • 2b Antegrade reperfusion of more than half of the previously occluded target artery ischemic territory (eg, in 2 major divisions of the MCA and their territories) • 2c Antegrade reperfusion of >90% but less than TICI 3 or near complete reperfusion
3	Complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches

***Clarification on practical application of this scale based on "Recommendations on Angiographic Revascularization Grading Standards for Acute Ischemic Stroke: A Consensus Statement"** of the Stroke J American Heart Association 2013; 44:2650-2663. Originally published online August 6, 2013 Zaidat et al.

20. Monitoring

Act of overseeing the progress of a clinical investigation and to ensure that it is conducted, recorded, and reported in accordance with the CIP, written procedures, this International Standard, and the applicable regulatory requirements.

21. Point of enrolment

Time at which, following recruitment, a subject signs and dates the informed consent form

22. Principal investigator

Qualified person responsible for conducting the clinical investigation at an investigation site.

NOTE 1 If a clinical investigation is conducted by a team of individuals at an investigation site, the principal investigator is responsible for leading the team.

NOTE 2 Whether this is the responsibility of an individual or an institution can depend on national regulations.

23. Recruitment

Active efforts to identify subjects who may be suitable for enrolment into the clinical investigation.

24. Serious adverse device effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

25. Serious adverse event (SAE)

Adverse event that

a. Led to death,
b. Led to serious deterioration in the health of the subject, that either resulted in
    1. a life-threatening illness or injury, or
    2. a permanent impairment of a body structure or a body function, or
    3. in-patient or prolonged hospitalization, or
    4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

26. Source data

All information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation.

27. Source document

Printed, optical or electronic document containing source data.

EXAMPLES Hospital records, laboratory notes, device accountability records, photographic negatives, radiographs, records kept at the investigation site, at the laboratories and at the medico-technical departments involved in the clinical investigation.

28. Sponsor

Individual or organization taking responsibility and liability for the initiation or implementation of a clinical investigation.

29. Subject

Individual who participates in a clinical investigation.

30. Thrombolysis in Cerebrovascular Infarction (TICI)

0	No perfusion.
1	Perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion.
2a	Perfusion of less than two-thirds of the vascular distribution of the occluded artery.
2b	Perfusion of two-thirds or more of the vascular distribution of the occluded artery.
3	Full perfusion with filling of all distal branches.

Lancet 2012 Oct 6;380(9849):1231-40. "Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial". R.G. Nogueira et al.

31. Thrombolysis in Myocardial Infarction (TIMI)

0	No perfusion
1	Penetration with no perfusion
2	Partial perfusion of the artery
3	Complete perfusion

N Engl J Med. 1985 Apr 4; 312(14):932-6. "The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group." The TIMI Study Group.

The definition of TIMI rating scale used by the adjudicating core laboratory will be identical to that used in the SWIFT study.

32. Procedure Related Serious Adverse Event (PRSAE)

A serious adverse event where the interventional procedure caused, or can not be ruled out as having caused, an effect that has resulted in any of the consequences characteristic of a serious adverse event.

33. Unanticipated serious adverse device effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

NOTE Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

34. Use error

Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

NOTE 1 Use error includes slips, lapses, and mistakes.

NOTE 2 An unexpected physiological response of the subject does not in itself constitute a use error.

[ISO 14971:2007, definition 2.27]

35. Vulnerable subject

Individual whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate.

EXAMPLE Individuals with lack of or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention.