

MR CLEAN

Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands. The effect of periprocedural MEDication: heparin, antiplatelet agents, both or neither.

Multicentrum gerandomiseerde klinische studie naar de endovasculaire behandeling van het acute herseninfarct in Nederland. Het effect van periprocedurele medicatie: heparine, plaatjesaggregatieremmers, beide of geen van beide.

RESEARCH PROTOCOL

PROTOCOL TITLE

MR CLEAN-MED: 'Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands. The effect of periprocedural MEDication: heparin, antiplatelet agents, both or neither.'

Protocol ID	ISRCTN76741621
Short title	MR CLEAN-MED
EudraCT number	2017-001466-21
Version	1.4
Date	April, 2018
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
AIS	Acute ischemic stroke
AR	Adverse Reaction
ASA	Acetylsalicylic acid
AR	Adverse Reaction
BI	Barthel index
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CT	Computed tomography
CTA	Computed tomography angiography

CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
IB	Investigator's Brochure
IAT	Intra-arterial treatment
IC	Informed Consent
ICH	Intracerebral hemorrhage
IU	International standard unit
IV	Intravenous
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)

MRI	Magnetic resonance imaging
MRA	Magnetic resonance angiography
mRS	modified Rankin Scale
NET	Neutrophil extracellular traps
NIHSS	National Institute of Health Stroke Scale
PROBE	Prospective randomized open blinded end-point
(S)AE	(Serious) Adverse Event
SICH	Symptomatic intracerebral hemorrhage
SPC	Summary of Product Characteristics (in Dutch: officiële productinformatie IB1-tekst)
Sponsor	The sponsor is the party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidizing party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
tPA	Tissue plasminogen activator

WMO

Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)

SUMMARY

Rationale: Intra-arterial treatment (IAT) by means of retrievable stents, in patients with acute ischemic stroke (AIS) with confirmed intracranial large vessel occlusion of the anterior circulation in whom the procedure can be started within 6 hours from onset, has been proven safe and effective. Still, a considerable proportion of patients do not recover despite recanalization. This is for a major part attributable to incomplete microvascular reperfusion (IMR). Antiplatelet agents and heparin may reduce IMR. Yet, it is unknown whether peri-procedural antiplatelet agents and anticoagulant medication in patients with acute ischemic stroke treated with IAT can improve clinical outcome.

Objective: To assess the effect of acetylsalicylic acid (ASA) and unfractionated heparin, alone, or in combination, in patients with AIS, who undergo IAT for a confirmed intracranial large vessel occlusion of the anterior circulation.

Study design: This is a multicenter phase III randomized clinical trial with open-label treatment and a 2x3 factorial design, comparing IV ASA and two dosages of unfractionated heparin as co-medication in IAT. It has blind assessment of primary outcomes and of neuro-imaging at baseline and follow-up.

Study population: We will enroll 1,500 patients with a clinical diagnosis of AIS, intracranial hemorrhage ruled out with non-contrast CT, who will undergo IAT with or without prior intravenous thrombolysis according to standard care. Intracranial large vessel occlusion of the anterior circulation should be confirmed by CTA or MRA. It should be possible to start intervention within 6 hours from onset. Age should be 18 or over and NIHSS should be 2 or more.

Interventions: Treatment with moderate dose unfractionated heparin (loading dose of 5000 IU followed by 1,250 IU/hour x 6 hours). Treatment with unfractionated heparin in a low dose (loading dose of 5000 IU followed by 500 IU/hour x 6 hours). Treatment with IV acetylsalicylic acid (300 mg). At 24 hours after start of IAT, all patients will receive antiplatelet therapy or anticoagulation according to local protocol, at the discretion of the treating physician.

Primary and secondary outcomes: The primary outcome is the score on the modified Rankin Scale (mRS) 90 days after inclusion in the study. The primary effect parameter is defined as the relative risk for improvement on the mRS estimated as a common odds ratio with ordinal logistic regression. Multivariable regression analysis will be used to adjust for chance imbalances in main prognostic variables. Secondary outcomes include mortality at 90 days, stroke severity measured with the National Institutes of Health Stroke Scale (NIHSS) at 24 hours and 5-7 days, recanalization on post-procedural DSA (measured with the extended treatment in cerebral ischemia (eTICI)) and on CTA at

24 +/- 12 hours or MRA at 24-48 hours and infarct size at 5-7 days, or 24-48 hours when MRI performed, and dichotomized mRS, death, score on the EQ-5D-5L and Barthel index at 90 days. In a subset of 600 patients we will assess reperfusion and infarct size with MRI. Safety endpoints include (symptomatic) intracerebral hemorrhage.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

Clinical equipoise and considerable practice variation exist with respect to the peri-procedural antiplatelet and anticoagulant treatment. There is a potential benefit, and a low risk which includes the risk of intracranial hemorrhage. However, every hour delay in reperfusion leads to 6-7% absolute risk reduction in good outcome. We therefore make use of deferred written informed consent (by proxy). At three months, all patients will be interviewed to assess functional outcome.

Trial registration: <https://doi.org/10.1186/ISRCTN76741621>

1. INTRODUCTION AND RATIONALE

In the Netherlands, as in many other countries, ischemic stroke is a major cause of death and a disabling disease. Each year more than 20,000 ischemic stroke patients (of 16.7 million inhabitants) are admitted to a Dutch hospital and 8500 patients die because of stroke.¹ Currently, more than 200,000 persons have suffered an ischemic stroke and half of these are seriously disabled. For the European Union, with a more than 500 million inhabitants, this translates into approximately 1 million new stroke cases per year.^{2,3}

Early 2015, the outlook for treatment of acute ischemic stroke (AIS) has improved dramatically. We now know that patients with AIS caused by intracranial large vessel occlusion of the anterior circulation benefit from intra-arterial treatment (IAT). Early IAT or thrombectomy leads to functional recovery in about 15% to 25% of patients treated within 6 hours. This was first reported in the MR CLEAN trial – a landmark trial performed by members of our collaboration – and later confirmed in 6 other trials.⁴⁻¹⁰ In MR CLEAN, still 67% of the patients in the endovascular treatment arm were dead or dependent at three months. The high risk of a poor outcome, even after these acute revascularization strategies, may to a large extent be explained by incomplete microvascular reperfusion (IMR).

IMR has been linked to distal microvascular damage or dysfunction as a result of tissue necrosis and cell death, intervention simply being late, but also to distal microvascular occlusion. This may be due to occlusion of distal vessels by pericyte contraction, distal embolization of microthrombi from the original occluding the proximal artery, in situ formation of microthrombi and cellular plugs caused by platelet activation and increased hemostasis, activated by formation of neutrophil extracellular traps (NETs).¹¹ NETs and vessel wall-derived pro-thrombotic factors are known to be abundantly present in patients with thrombo-embolic occlusions. In coronary models and in observational studies the presence of NETs has been associated with IMR.¹² NETs can capture platelets and increase fibrin deposition, but cannot be resolved by tissue-type plasminogen activator (tPA, alteplase). Pericyte contraction causes capillary constriction and obstructs erythrocyte flow in the mouse brain. The use of mechanical devices for thrombectomy is known to cause extensive damage to the vascular endothelium, and beyond. This is a source for acute platelet adhesion and aggregation resulting in distal microvascular occlusion.^{13,14}

It is therefore important to target treatment on the reduction of IMR. Yet, it is likely that in patients with AIS treated with IAT, periprocedural antiplatelet or anticoagulant treatment improves distal reperfusion but whether it improves clinical outcome is unknown.

The use of antiplatelet agents in AIS in general has a small beneficial effect,¹⁵ but its use in patients treated with IV alteplase is associated with increased risk of intracranial hemorrhage.^{16,17} However, there are no trial data on acute treatment with antiplatelet agents in patients treated with IAT.¹⁸ Previous trials on the effect of unfractionated heparin in AIS have failed to demonstrate a beneficial effect.¹⁵ However, the use of unfractionated heparin in IAT has not been tested in randomized controlled trials. The risk of hemorrhage due to treatment with low or moderate dosages of heparin are low in patients with moderate or severe ischemic stroke.¹⁵

Histological studies of thrombus composition have revealed the presence of neutrophil extracellular traps (NETs) which add to the structure of the thrombus but cannot be resolved by alteplase, similar to fibrin. NETs are known for their pro-coagulant effects in various subacute conditions. Unfractionated heparin, especially its non-coagulant fraction, is effective in dissolving NETs in vitro. Potentially, unfractionated heparin may be of great value in counteracting the effect of NETs and improving microvascular reperfusion. A recent review confirms that there are no data on periprocedural antithrombotic treatment, and consequently, there is large practice variation.¹⁸

In conclusion, what we need is an answer to the question whether treatment with antithrombotic or antiplatelet agents directly before the start mechanical thrombectomy is beneficial and leads to better outcomes than the current strategy, which is to postpone this treatment to 24 hours after intervention, similar to what was recommended after IV alteplase treatment.¹⁷

2. OBJECTIVES

The primary objective of this trial to assess the effect of unfractionated heparin and acetylsalicylic acid, alone, or in combination on functional outcome at 3 months in patients with AIS caused by a confirmed intracranial large vessel occlusion of the anterior circulation, who undergo intra-arterial treatment with or without prior intravenous thrombolysis according to standard care.

The secondary objective is to assess the safety and effect of unfractionated heparin and acetylsalicylic acid, alone, or in combination, on neurological outcome, revascularization and infarct size in patients who undergo intra-arterial treatment for AIS caused by a confirmed intracranial large vessel occlusion of the anterior circulation.

The tertiary objectives are 1) to collect (waste) biomaterials (including thrombo-emboli, aspirate blood) and to analyze biofactors in blood samples with respect to their potential for treatment effect modification, 2) to collect and analyze data regarding the deferred consent procedure and its association with patient recall and satisfaction at three months from randomization, and 3) to study the efficiency of national IAT implementation, given the availability of IAT hospitals and capacity, and travel times of ambulance services. To this end, we aim to collect data (time delays and diagnostics) from each step in the acute stroke pathway as input parameters for a simulation model. This way we can study the regional set-up of the IAT organizational model.

3. STUDY DESIGN

This is a multicenter phase III randomized clinical trial with open-label treatment and blinded outcome assessment (PROBE), with a 2x3 factorial design. The study will run for 4 years in stroke intervention centers in the Netherlands. An overview of the study and the main procedures that subjects will undergo is provided in Figure 2.

4. STUDY POPULATION

4.1 POPULATION (BASE)

In the Netherlands, the incidence of hospital-admitted AIS is 1.2 per 1000, for a total of 20,000 annually.¹ The study population will be drawn from patients with AIS who enter the emergency department of the intervention center. Intervention centers admit 300 to 600 AIS patients annually, and perform 50-150 intra-arterial interventions annually. The number of intra-arterial interventions for acute ischemic stroke in the Netherlands is rapidly increasing, from 200 in 2014 to more than 1000 in 2016. The estimate for 2017 is 1200-1500 treated patients. The trial will be carried out by members of CONTRAST (Collaboration for New TReatments of Acute Stroke). Although the study draws from the pool of patients with acute ischemic stroke, there is no competition between trials in the collaboration (Appendix 4.3).

4.2 PARTICIPATING CENTERS AND CENTER ELIGIBILITY

To be fully eligible for participation in the trial and to include patients in the trial, centers should meet the following minimum criteria:

- The center should have experience in conducting acute stroke trials.
- The intervention team should have ample experience with endovascular interventions for cerebrovascular disease (carotid stenting or aneurysm coiling), peripheral artery disease, or coronary artery disease.
- The stroke team (which includes neurologists and interventionists) should have sufficient experience with intra-arterial treatment.
- The intervention team should make use of one or more of the devices that have been approved by the trial steering committee. The use of other devices is not allowed in the trial.
- At least one member of the intervention team should have sufficient experience with the particular device.

Note that patients may only be included in the trial when the intervention team that will actually treat the patient includes at least one interventionist with sufficient experience.

4.3 INCLUSION CRITERIA

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

- a clinical diagnosis of acute ischemic stroke;
- caused by intracranial large vessel occlusion of the anterior circulation (distal intracranial carotid artery or middle (M1/proximal M2) cerebral artery) confirmed by neuro-imaging (CTA or MRA);
- CT or MRI ruling out intracranial hemorrhage;
- treatment possible (groin puncture) within 6 hours from symptom onset or last seen well;
- a score of at least 2 on the NIH Stroke Scale;
- age of 18 years or older;
- written informed consent (deferred).

Note that pretreatment with IV alteplase is not a prerequisite.

4.4 EXCLUSION CRITERIA

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

- Pre-stroke disability which interferes with the assessment of functional outcome at 90 days, i.e. mRS >2
- Treatment with IV alteplase despite the following contra-indications for IV alteplase:
 - o cerebral infarction in the previous 6 weeks with residual neurological deficit or signs of recent infarction on neuroimaging,
 - o previous intracerebral hemorrhage within the previous 3 months,
 - o INR exceeding 1.7,
 - o prior use of direct oral anticoagulant (DOAC),
- IV alteplase infusion >4.5 hours after symptom onset.
- Contra-indications for ASA/unfractionated heparin, for instance: allergy, recent surgery, heparin induced thrombocytopenia.
- Therapeutic heparin use
- INR exceeding 3.0
- Thrombocyte count <100⁹/L

- Participation in medical or surgical intervention trials other than current (or MR ASAP / ARTEMIS).

Inclusion in other intervention trials during the study period is not allowed. Note that preceding inclusion in the Multicenter Randomized trial of Acute Stroke Treatment with a nitroglycerine patch (MR ASAP) is not an exclusion criterion for participating centers in the Netherlands. This study will include patients in the ambulance and assess the effect of a nitroglycerine patch on functional outcome. Inclusion in the ARTEMIS trial (NCT02808806, <https://www.lumc.nl/org/neurologie/research/artemis/de-trial/>) is also not an exclusion criterion for participating centers in the Netherlands. The purpose of the ARTEMIS trial is to investigate if real-time feedback to caregivers reduces the time between patient's first medical contact and start of intravenous thrombolysis and/or intraarterial thrombectomy in patients with acute ischemic stroke.

4.5 SAMPLE SIZE CALCULATION

For the control arm in the study, we assume the a similar distribution over the 7-point modified Rankin Scale (mRS) as in the intervention arm of the MR CLEAN trial: mRS 0: 3%; mRS 1: 9%; mRS 2: 21%; mRS 3: 18%; mRS 4: 22%; mRS 5: 6%; mRS 6: 21%. For aspirin, we assume a favorable effect with a common odds ratio (cOR) of 1.27, which corresponds to an absolute risk difference of having a score on the mRS of 0-2 of approximately 5%.

The aim is to include 1500 patients. In the analysis covariate adjustment will be used, which reduces the required sample size by approximately 25%.^{19,20} Thus the effective sample size with 1500 patients is 2000, which will provide 84% power to detect a true treatment effect (two-sided $\alpha=0.05$).

Assuming the same treatment effect, the power to detect a difference between the three heparin dose groups is 78%. Power was estimated by simulation in a Monte Carlo model.²¹

5. TREATMENT OF SUBJECTS

5.1 INVESTIGATIONAL PRODUCT

The investigational treatments are unfractionated heparin and acetylsalicylic acid, which both are being used for similar indications since several decades. The study has an open label design; no placebo will be used.

6. INVESTIGATIONAL PRODUCT

6.1 NAME AND DESCRIPTION OF INVESTIGATIONAL PRODUCTS

6.1.1 HEPARIN

Heparin is a sulfated polysaccharide with a molecular weight range of 3,000 to 30,000 Da (mean, 15,000 Da). It produces its major anticoagulant effect by inactivating thrombin and activated factor X (factor Xa) through an antithrombin (AT)-dependent mechanism. Heparin binds to AT through a high-affinity penta-saccharide, which is present on about a third of heparin molecules. For inhibition of thrombin, heparin must bind to both the coagulation enzyme and AT, whereas binding to the enzyme is not required for inhibition of factor Xa. Molecules of heparin with fewer than 18 saccharides lack the chain length to bridge between thrombin and AT and therefore are unable to inhibit thrombin. In contrast, very small heparin fragments containing the penta-saccharide sequence inhibit factor Xa via AT. By inactivating thrombin, heparin not only prevents fibrin formation but also inhibits thrombin-induced activation of platelets and of factors V and VIII.²² An additional property of heparin is that it acts against NETs, and thus makes thrombi with a large proportion of NETs more easily dissolvable. Adverse effects of heparin treatment stem directly from its anticoagulant action. It may increase the risk of periprocedural hemorrhage and by inhibition of fibrin formation it may adversely affect the binding of thrombus to the struts of a retrievable stent. On the other hand, by counteracting NETs, thrombin and fibrin formation, it may decrease the risk of distal microvascular obstruction, and therefore improve tissue perfusion after recanalization has been reached.

6.1.2 ACETYLSALICYLIC ACID

Acetylsalicylic acid or aspirin exerts its effect primarily by interfering with the biosynthesis of cyclic prostanoids, i.e. thromboxane A₂ (TXA₂), prostacyclin, and other prostaglandins. These prostanoids are generated by the enzymatically catalyzed oxidation of arachidonic acid, which is itself derived from membrane phospholipids. Arachidonic acid is metabolized by the enzyme prostaglandin (PG) H-synthase, which, through its cyclooxygenase (COX) and peroxidase activities, results in the production of PGG₂ and PGH₂, respectively. PGH₂ is then modified by specific synthases, thus producing prostaglandins D₂, E₂, F₂α, I₂ (prostacyclin), and TXA₂, all of which mediate specific cellular functions.²³

Aspirin imparts its primary antithrombotic effects through the inhibition of PGH-synthase/COX by the irreversible acetylation of a specific serine moiety (serine 530 of COX-1 and serine 516 of COX-2) and

is ≈170-fold more potent in inhibiting COX-1 than COX-2. In the presence of aspirin, COX-1 is completely inactivated, whereas COX-2 converts arachidonic acid not to PGH₂, but to 15-R-hydroxyeicosatetraenoic acid (15-R-HETE). The end result is that neither affected isoform is capable of converting arachidonic acid to PGH₂, a necessary step in the production of prostanoids. The resultant decreased production of prostaglandins and TXA₂ likely accounts for the therapeutic effects, as well as the toxicities, of aspirin. From a cardiovascular standpoint, it is principally the antithrombotic effect of aspirin that results in its clinical utility. Platelet production of TXA₂ in response to a variety of stimuli (including collagen, thrombin, and ADP) results in the amplification of the platelet aggregation response and in vasoconstriction. Conversely, vascular endothelial cell production of prostacyclin results in inhibition of platelet aggregation and induces vasodilation. Aspirin-induced inhibition of TXA₂ and PGI₂ has opposing effects on hemostasis; however, the available data suggest that the potentially prothrombotic effects of PGI₂ inhibition are not clinically relevant and that the antithrombotic effects of TXA₂ inhibition predominate. This may, in part, be a result of the ability of vascular endothelial cells to regenerate new COX and thus recover normal function, whereas COX inhibition in platelets is irreversible owing to the limited mRNA pool and protein synthesis in these anuclear cells.²²

For the purpose of this study, we use 300 mg intravenous aspirin (lysine acetylsalicylate, Aspégic, Sanofi-Aventis, Netherlands) to be administered directly after groin puncture when no pretreatment with IV alteplase is given or (directly) after IV alteplase infusion. Intravenous, instead of regular oral administration, was chosen to prevent exclusion of patients with dysphagia and to guarantee faster uptake.

6.2 SUMMARY OF FINDINGS FROM NON-CLINICAL STUDIES

This is not relevant for the current study, as both investigational drugs are used for similar indications for several decades.

6.3 SUMMARY OF FINDINGS FROM CLINICAL STUDIES

Intra-arterial treatment: Seven randomized clinical trials that investigated intra-arterial treatment for AIS, which used predominantly stent thrombectomy have been published. All trials showed a beneficial effect of intervention compared to usual care, which most often included treatment with IV alteplase. The effect size ranged from 13% to approximately 25% increase in proportion of non-disabled patients at 3 months after randomization.⁴⁻¹⁰ The treatment is already established as standard of care.²⁴⁻²⁷

Aspirin, acute ischemic stroke and intra-arterial treatment: The use of antiplatelet medication in AIS in general has a small beneficial effect.¹⁵ The results of the ENCHANTED study suggest that in patients on prior antiplatelets lower dose of IV alteplase (0.6mg/kg) is preferred.¹⁶ So far, standard care for this subgroup has not been changed. In the ARTIS study, patients were randomized for early administration of intravenous aspirin (300 mg IV within 24 hours after IV alteplase). Acute aspirin treatment was associated with increased risk of intracranial hemorrhage but did not alter functional outcome.¹⁷ The study was terminated prematurely. However, the 4.3% risk of symptomatic intracranial hemorrhage in the intervention group is considered to be very low, since in the Cochrane analysis the MR CLEAN study symptomatic intracranial hemorrhage occurred in 7.7% of the intervention group and 6.4% of the control group.

There are no data on acute treatment with aspirin in AIS patients treated with IAT.¹⁸ A post-hoc analysis of the MR CLEAN showed that 144 of all 500 randomized patients (29%) were on antiplatelet treatment prior to randomization. Of the patients on prior antiplatelet treatment, 21/144 (15%) had a symptomatic intracerebral hemorrhage (sICH), whereas only 14/356 (4%) who were not on antiplatelets had an sICH. However, no interaction with intra-arterial treatment on functional outcome or occurrence of sICH was noted. Furthermore, prior use of antiplatelet agents doubled the effect of successful revascularization on functional outcome in the intervention arm of the trial. These data suggest that in patients with revascularization due to IAT, peri-procedural antiplatelet agents may be beneficial. The improved functional outcome in the antiplatelet agents group may be explained by improved microvascular perfusion, since there were no differences in recanalization achieved with IAT.

Heparin, acute ischemic stroke and intra-arterial treatment: The International Stroke Trial (IST) showed no net effect of heparin treatment in AIS patients.¹⁵ In the IST, patients allocated to heparin had significantly fewer recurrent ischemic strokes within 14 days (2.9% vs 3.8%) but this was offset by a similar-sized increase in hemorrhagic strokes (1.2% vs 0.4%), so the difference in death or non-fatal recurrent stroke (11.7% vs 12.0%) was not significant. Heparin was associated with a significant excess of 9 (SD 1) transfused or fatal extracranial bleeds per 1000. Compared with 5000 IU bd heparin, 12500 IU bd heparin was associated with significantly more transfused or fatal extracranial bleeds, more hemorrhagic strokes, and more deaths or non-fatal strokes within 14 days (12.6% vs 10.8%).¹⁵ There are no data whether acute heparin treatment improves functional outcome in AIS treated with IV alteplase.²⁸ In RCTs treating patients with intra-arterial pro-urokinase, PROACT-I and – II, all patients received heparin. In the control patients of these studies, who received heparin only, sICH occurred in 7.1% and 2.0% respectively. Patient in the intervention group receiving IA recombinant pro-urokinase in combination with heparin, sICH occurred in 15.4% and 10%

respectively.^{29,30} However this local thrombolytic treatment is not comparable with the current approach of mechanical thrombectomy. There are no data on acute treatment with heparin in AIS patients treated with IAT with the currently used devices.¹⁸ In MR CLEAN, only 17 of 500 patients (3.4%) were on heparin(oids). We observed no increased risk of hemorrhage, nor was there interaction with treatment with regard to functional outcome or hemorrhage risk (unpublished data).

6.4 SUMMARY OF KNOWN AND POTENTIAL RISKS AND BENEFITS

The potential benefits of the intervention have been described in section 1. The potential risks consist of intracranial and extracranial hemorrhage and hemorrhagic infarction (described in paragraph 6.3).

6.5 DESCRIPTION AND JUSTIFICATION OF ROUTE OF ADMINISTRATION AND DOSAGE

Both drugs will be administered intravenously. Intravenous, instead of regular oral administration, was chosen to prevent exclusion of patients with dysphagia and to guarantee faster uptake. Standard dosing will be used for acetyl-salicylic acid (300 mg). The experience from IST suggests that low and moderate doses of heparin (up to 10000 IU within a 24-hour time period) are associated with acceptable risks.

6.6 DOSAGES, DOSAGE MODIFICATIONS AND METHOD OF ADMINISTRATION

Acetylsalicylic acid will be administered intravenously, in a loading dose of 300 mg. Unfractionated heparin will be administered intravenously in a moderate dose (loading dose of 5,000 IU followed by 1,250 IU/hour x 6 hours) or low dose (loading dose of 5,000 IU followed by 500 IU/hour x 6 hours).

After 24 hours, all patients will continue on antithrombotic medication according to local guidelines (either clopidogrel or acetylsalicylic acid, with appropriate loading dose). A switch to oral anticoagulants when indicated is recommended after 1 week.

Both the IV acetylsalicylic acid and heparin treatment should be started directly after groin puncture when no IVT is administered or directly after/when the IV alteplase has been stopped, in order to prevent a treatment delay. When the occlusion seen on CTA is not present on DSA and the patient has been randomized for unfractionated heparin the continuous infusion will be stopped. In case an untoward event will occur (e.g. perforation) and the administration or continuation of the study

medication is unfeasible the decision to stop the study medication is left to the discretion of the treating physician.

6.7 PREPARATION AND LABELLING OF INVESTIGATIONAL MEDICINAL PRODUCT

Commercially available preparations of the investigational medicinal products will be used. The hospital pharmacy of Erasmus MC will label and store the investigational medicinal products according to the Good Manufacturing Practice Guideline (2003/94/EG).

6.8 DRUG ACCOUNTABILITY

The investigational medicinal products (IMPs) will be labelled and distributed by the central pharmacy at Erasmus MC. Each participating hospital will store the IMPs under prespecified, secured conditions. In each patient randomized to aspirin and/or heparin, the batch number, subject identification number, and the time of administration of the IMP will be recorded by the investigator's team at the local participating hospital. The local pharmacies of the participating hospitals will maintain patient-level drug accountability records for all locally enrolled patients. The central pharmacy of Erasmus MC will maintain patient-level drug accountability records for patients enrolled at Erasmus MC and a center-level drug accountability record for the full trial.

7. NON-INVESTIGATIONAL PRODUCT

This is not applicable for this study.

8. METHODS

8.1 STUDY PARAMETERS/OUTCOMES

8.1.1 MAIN STUDY PARAMETER/OUTCOME

The primary outcome is the score on the modified Rankin Scale (mRS) at 90 days (± 14 days).³¹ The mRS is the preferred disability parameter of clinical trials in stroke. The mRS is an ordinal hierarchical scale incorporating six categories from 0 up to and including 5, and describes the range of disability encountered post stroke. 'Death' is assigned a score of 6 (Table 1). Assessment of outcome on the mRS will be performed by independent assessors, blinded to the allocated and actually received treatment. Their assessment will be based on standardized reports of a telephone interview by trained research personnel who are not aware of treatment allocation. The blinded assessors are members of the outcome assessment committee.

8.1.2 SECONDARY STUDY PARAMETERS/OUTCOMES

Secondary outcomes are the following:

- Extended treatment in cerebral ischaemia (eTICI) score on final angiography of IAT (Table 2)³²
- Recanalization rate at 24 +/- 12 hours, assessed with CTA, or at 24-48 hours assessed with MRI 3D TOF³³
- Score on the NIHSS at 24 hours and 5-7 days, or at discharge (Table 3)³⁴
- Final infarct volume at 5-7 days, assessed with NCCT or 24-48 hours MRI in a subset of 600 patients. Final infarct volume will be assessed with the use of an automated, validated algorithm.³⁵ Infarct size at day 5-7 will be compared with plain CT and perfusion CT or MRI results (if available) at baseline.
- Dichotomized mRS of 0-1 vs. 2-6 at 90 days (± 14 days)
- Dichotomized mRS of 0-2 vs. 3-6 at 90 days (± 14 days)
- Dichotomized mRS of 0-3 vs. 4-6 at 90 days (± 14 days)
- Score on the EQ-5D-5L and Barthel index at 90 days (± 14 days) (Table 4 and 5)^{36,37}

Safety endpoints are the following:

- Intracerebral hemorrhage according to the Heidelberg Bleeding Classification³⁸
- Symptomatic intracerebral hemorrhage (sICH) scored according to the Heidelberg Bleeding Classification, with the addition of sICH that led to death and that was identified as the predominant cause of the neurologic deterioration³⁸
- Extracranial hemorrhages requiring transfusion or resulting in death
- Embolization in new territory on angiography during IAT

- Infarction in new territory within 5-7 days NCCT or 24-48h MRI
- Death from all causes within 90 days (+14 days)

8.1.3 OTHER STUDY PARAMETERS

Prehospital data that will be recorded include witnessed stroke onset; time of symptom onset/symptoms noticed/last seen well; time of call for help; time of 112 call; referrer of stroke; suspected diagnosis (referrer); urgency code ambulance (A1/ A2/B); time of arrival ambulance on site; time of departure of ambulance from site; name and postal code ambulance destination; time of arrival ER. When transfer from a primary stroke center to a comprehensive stroke center takes place, we will also collect departure time of the primary stroke center and arrival time at the ER of the comprehensive stroke center.

Baseline parameters that will be recorded include age; sex; pre-stroke mRS; previous stroke; conditions such as hypertension, diabetes mellitus, atrial fibrillation, myocardial infarction; smoking status; medication including antihypertensive treatment, antiplatelet agents and anticoagulants; vital parameters such as blood pressure, body temperature; weight and height, neurological examination including NIHSS; laboratory examination including INR, APTT, C-reactive protein, glucose, creatinine; and imaging results on admission including the Clot Burden Score for CTA and MRA (Table 6).

We will record the received dose, type and timing of IVT medication and if applicable of unfractionated heparin and/or ASA.

Additionally, we will record time from symptom onset to: ER, Imaging (CT/MRI), randomization, start of IAT, first reperfusion and end of procedure. The devices and the order in which they are used will be recorded, and the type of anesthesia and sedation (if any) will be noted.

Last, during the 90-day study period, information regarding the direct treatment costs will be collected.

8.2 RANDOMIZATION, BLINDING AND TREATMENT ALLOCATION

The randomization procedure will be computer- and web-based, using permuted blocks. Back-up by telephone will be provided. Randomization is allowed when the occlusion has been established by CTA or MRA. Randomization will be stratified for center and, for participating centers in The Netherlands, by inclusion in the active treatment arm of MR ASAP.

It will not be possible to view the treatment allocation before the patient is registered in the study database, nor will it be possible to remove the patient from the study base after treatment assignment

has become known. Both patient and treating physician will be aware of the treatment assignment. Information on outcome at three months will be assessed through standardized forms and procedures, by a trained investigator blinded for treatment allocation. Interviews will be recorded. Assessment of outcome on the modified Rankin scale will be based on this information, by assessors who are blinded to the treatment allocation. Results of neuroimaging will also be assessed in a blinded manner. Information on treatment allocation will be kept separate from the main study database. The steering committee will be kept unaware of the results of interim analyses of efficacy and safety. The independent trial statistician will combine data on treatment allocation with the clinical data in order to report to the data safety monitoring board (DSMB).

8.3 STUDY PROCEDURES

All patients will undergo assessment of the NIHSS at baseline, 24 hours and 5-7 days, which is routine in clinical procedure. It will be carried out by certified assessors. Patients will undergo NCCT and CTA at baseline, which also belongs to usual care. For baseline imaging MRI and CEMRA is also permitted. Follow-up imaging can be performed with either CT or MRI, and the choice of modality is left to the individual participating centers. However, participating centers should adhere to the chosen modality during the trial to prevent bias by indication. For CT imaging, after 24 +/- 12 hours NCCT and CTA is repeated to determine recanalization. This is not part of usual care in every hospital. At 5-7 days or discharge, patients will undergo NCCT or MRI to assess infarct size. If follow-up imaging is performed with MRI, at 24-48h DWI, FLAIR, T2* and intracranial 3DTOF sequences should be performed. If follow-up at 24-48h is performed with MRI, no additional imaging at 5-7days or discharge is required. If MRI is chosen as the modality for follow-up imaging, only in the event of contra-indications for MRI (e.g. pacemakers) CT-imaging may be performed instead. The condition of the patient should not drive the decision to deviate from the chosen imaging protocol. Follow-up imaging is not part of usual care in every hospital.

(1) Within 1 hour before the IAT, (2) within 1 hour after the IAT and (3) at 24 hours after the IAT a blood sample will be taken, if possible, during routine blood drawings. We will also take a blood sample if the patient has a regular (none trial-related) outpatient clinic appointment (2-6 months after treatment). One tube EDTA (+/- 5 mL), one tube without anticoagulant (+/- 7 mL) and two tubes citrated blood (2.7 mL) will be drawn, which is no more than 20 mL. Substudies may require extra blood tubes, never more than 20 mL per blood draw. When a drip is in place, which will be the case in blood drawing at moment 1,2 and 3, this will be used. Samples will be stored at -80 degrees Celsius for later analysis of procoagulant and genetic factors that may interact with treatment effect. In addition, this trial also makes use of "waste material": blood aspirated during intervention with

retrieved thrombi during intervention. All biomaterials will be stored in our CONTRAST biobank for 15 years.

8.4 WITHDRAWAL OF INDIVIDUAL SUBJECTS

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Data and biomaterials from non-consenting subjects will not be used when there is a written objection from the subject or representative. In an effort to describe the non-consenting population we will ask the subject or his/her representative to allow the use of routinely collected data and materials in a coded manner. If no consent for the use of these data is obtained, only the following will be noted: study number, treatment allocation and refusal. Missing data, including final mRS, will be imputed for the main analysis, by multiple imputation.

8.5 REPLACEMENT OF INDIVIDUAL SUBJECTS AFTER WITHDRAWAL

For each patient that withdraws before the final outcome assessment, an additional patient will be included.

8.6 FOLLOW-UP OF SUBJECTS WITHDRAWN FROM TREATMENT

All patients in the study will be followed until final assessment at 90 days. Only patients who do not give or have withdrawn consent will be assessed immediately and their records will be closed.

8.7 PREMATURE TERMINATION OF THE STUDY

The study will only be terminated prematurely if the Data Safety Monitoring Board recommends stopping. In case of premature termination of the study the database will be closed after 90 days assessment of the last enrolled patient and results will be reported

9. SAFETY REPORTING

9.1 TEMPORARY HALT FOR REASONS OF SUBJECT SAFETY

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will notify the accredited METC with undue delay of a temporary halt including the reason for such an action. The study will be suspended pending further review by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AES, SAES AND SUSARS

9.2.1 ADVERSE EVENTS (AES)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 SERIOUS ADVERSE EVENTS (SAES)

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

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

Any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate medical judgment. An elective hospital admission will not be considered as a serious adverse event.

Serious adverse events will be immediately after coming to notice of the investigator reported to the trial coordinator, who is 24/7 available.

The investigator will report the following SAEs occurring in the study period to the sponsor without undue delay of obtaining knowledge of the events: Death from any cause; symptomatic intracranial hemorrhage, extracranial hemorrhage, cardiac ischemia, pneumonia, allergic reactions, new ischemic stroke in a different vascular territory.

Technical complications or vascular damage at the target lesion such as perforation or dissection that do not lead to clinically detectable SAE and neurological deterioration not caused by intracranial hemorrhage, new ischemic stroke, but are considered as consistent with the natural course of the ischemic stroke, will not be reported immediately.

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

9.2.3 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARS)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

- 1) the event must be serious (see chapter 9.2.2);
- 2) there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
- 3) the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
 - Summary of Product Characteristics (SPC) for an authorised medicinal product;

All SUSARS occurring between randomisation and the end of follow-up at day 90 (\pm 14 days) have to be reported by the local Investigator to the study Sponsor within 24 hours of Investigator's first awareness about the event. The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The expedited reporting of SUSARs through the web portal Eudravigilance or *ToetsingOnline* is sufficient as notification to the competent authority.

In the event this becomes applicable, the sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

9.3 ANNUAL SAFETY REPORT

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 FOLLOW-UP OF ADVERSE EVENTS

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

SAEs need to be reported until end of study within the Netherlands, as defined in the protocol.

9.5 DATA SAFETY MONITORING BOARD (DSMB)

In order to increase the safety of the intervention, the trial will be monitored by an independent data safety monitoring board (DSMB). The DSMB will be chaired by a neurologist, and include a neuro-interventionist and an independent methodologist/statistician. The DSMB will meet frequently, at least annually or after inclusion of the next 300 patients (whichever comes first) and assess the occurrence of unwanted effects by center and by procedure. During the period of intake to the study, safety assessment are required after every 5 symptomatic intracranial hemorrhages and after every 10 deaths. The boundary to allow the trial to be stopped, if one of the study medications was found to be harmful in terms of increased mortality or symptomatic intracranial hemorrhage, will be discussed by the DSMB in consultation with the steering committee. For deaths, a direct comparison of the survival curves will be made with a log-rank test. For symptomatic intracranial hemorrhage, the rate among patients treated with aspirin and/or heparin was compared with the rate of 10 percent. Results of safety assesment on major endpoints (including serious adverse events believed to be due to treatment) will be supplied, in strict confidence, to the chairman of the DSMB, along with any other analyses that the DSMB may request. In the light of these analyses, the DSMB will advise the chairman of the Steering committee if, in their view, the randomized comparisons in the trial have provided both (i) "proof beyond reasonable doubt" that for all, or for some specific types of patients, one particular treatment is clearly indicated or clearly contraindicated in terms of a net difference in outcome, and (ii) evidence that might reasonably be expected to influence materially patient management. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least 3 standard deviations in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the study prematurely. This criterion has the practical advantage that the number of interim analyses is of little importance.

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

10. STATISTICAL ANALYSIS

The analysis and reporting of the trial will be in accordance with the CONSORT guidelines.

Baseline data by treatment allocation will be reported with standard statistical procedures. Missing

values for baseline characteristics will be reported. Missing baseline characteristics will be imputed using regression imputation. All analyses will be performed according to the intention-to-treat principle.

10.1 PRIMARY STUDY PARAMETER

The primary effect parameter will be the common odds ratio, estimated with ordinal logistic regression, which represents the shift on the 7-category modified Rankin scale, measured at 3 months from randomization. The treatment effect estimates for both acetylsalicylic acid versus no acetylsalicylic acid and heparin versus no heparin will be adjusted for known prognostic variables: age, pre-stroke mRS, time from onset of symptoms to randomization, stroke severity (NIHSS) and collateral score. Adjusted and unadjusted estimates with corresponding 95% confidence intervals will be reported.

10.2 SECONDARY STUDY PARAMETERS

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

Last, a cost utility analysis will be performed to assess the cost-effectiveness of the intervention under study. The outcome parameters of the cost-effectiveness analysis will be the cost per patient with good functional outcome and the cost per QALY.

10.2.1 SUBGROUP ANALYSES

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

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

- Tertiles of age
- Sex
- Tertiles of (systolic) blood pressure at baseline
- Tertiles of NIHSS at baseline
- Tertiles of time from onset of symptoms to randomization, groin puncture and revascularization
- Diabetes mellitus
- Atrial fibrillation
- Extracranial carotid obstruction
- Occlusion location

- ASPECTS (Table 7)
- Collateral score (Table 8)
- Type of device
- IVT versus no IVT
- Prior use of antiplatelet agents or vitamin K antagonists
- Antagonist usage
- Inclusion in active treatment arm of MR ASAP

10.3 INTERIM ANALYSIS

See Paragraph 9.5.

11. ETHICAL CONSIDERATIONS

11.1 REGULATION STATEMENT

The study will be conducted according to the principles of the Declaration of Helsinki (October 2013)³⁷, ICH-GCP principles, and in accordance with the Medical Research Involving Human Subjects Act (WMO).

11.2 RECRUITMENT AND CONSENT

Because of the short time (minutes) between diagnosis and start of treatment we will defer written informed consent until after the treatment. We consider deferred consent warranted because it endovascular treatment has been proven safe and effective, but where immediate application of the treatment will lead to additional benefit; for every hour delay, the absolute benefit of treatment (probability of recovery to independent living) decreases by 6%.³⁹ We know that proper informed consent procedures take 1 to 3 hours and this time is not available in the acute treatment phase. Approximately 99% of all patients with severe cortical ischemic stroke eligible for IAT have neurological deficits interfering with their decision-making capacity. Representatives are often not directly on the scene.

Written informed consent will be obtained from the patient or from a representative by one of the investigators, as soon as possible after the procedure (within 72 hours), because after that new study procedures will follow. Subjects or their representatives will be provided with a patient information form and verbal explanation of the purpose of the study. They will be informed about the inclusion in the trial, data and biomaterials that have been collected, and treatment they may have received. They will be asked for consent in follow-up and data usage. Participation in this trial is voluntary. Patients or their legal representatives will have ample time (several hours) to decide whether they want to continue participation in the study. When the patient is not competent and no representative is available or present, we will stop the study procedures until we can inform the representative and ask for consent. When consent by proxy has been obtained and the patient recovers, we will again ask for written consent from the patient (Figure 3). The patient or representative may, at any given time, withdraw informed consent. An explanation is not needed. If a patient has died before deferred consent has been obtained, his/her representative will be informed about the study treatment the patient may have received, trial procedures and use of the collected data and biomaterials. A separate information form will be sent to the representative by the medical center where the patient last resided. Representatives will have one month to object to the (full or partial) use of the collected data and

biomaterials with an opt-out option. If no objection is made, all data will be used as if full consent was obtained.

This study evaluates the influence of an acute treatment in an emergency situation concerning a life-threatening disorder. For every hour delay, the absolute benefit of treatment (probability of recovery to independent living) decreases by 6%.⁴⁰ Treatment should therefore be started as soon as possible. When there is no apparent emergency situation and there is sufficient time to inform patients or their representatives about their treatment, this is the appropriate route in deriving informed consent. However, as set-out above, all patients suffering from an acute ischemic stroke caused by a large vessel occlusion are involved in an emergency situation. Therefore, all patients or representatives will be approached for deferred consent.

Furthermore, a vital criterion for valid consent by the patient for inclusion in a clinical trial is the patient's decision-making capacity. The criteria for assessing decision-making capacity vary, but generally include four interrelated capacities: to understand relevant information, to appreciate the current situation and consequences of decisions, to use sufficient reasoning to make decisions, and to communicate a choice.^{41,42} Patients with an LVO of the anterior circulation, by definition, are severely incapacitated (e.g. due to a reduced level of consciousness, aphasia, or another cognitive disorder). Their brain is seriously damaged. In this situation, they will therefore always have a diminished capacity to provide informed consent. Analysis of the MR CLEAN registry data confirms this: In 1469 of 1526 patients we documented symptoms indicating a lack of decision making capacity.

The patient's proxy will also lack capacity for informed consent, for similar reasons as mentioned above, namely that they are in an emergency situation, the necessity for fast treatment and the emotional stress of the situation. Conversely, participation in the trial may be of direct benefit to the patient.

The executive committee feels that the emergency situation, the vulnerable patient group and the importance of early treatment provide ethically and legally valid reasons for an emergency procedure where obtaining consent after the study procedure takes place (deferred consent). The trial cannot practically and ethically be carried out without deferred consent, nor can the trial be investigated in any other patient group than the one mentioned above.

If the subject is considered mentally competent to provide consent, the subject will be informed and asked for consent. However, if the subject lacks decision-making capacity, the investigator will search for a legal representative available. If there is no legal representative available, study procedures will

be continued until a proxy is present. Consent will be asked in writing within 72 hours, but as early as deemed appropriate and reasonable (by stroke team).

11.3 OBJECTION BY MINORS OR INCAPACITATED SUBJECTS

Minors (patients of 18 years old and less) will not be included in the trial. About 99% of the patients eligible for the trial have acquired neurological deficits due to the stroke interfering with their decision-making capacity. We will follow the procedure as described in 11.2. In the situation that a legally incompetent patient shows behavior suggesting objection to participate in the trial, the patient will be not be included in the study. The investigators will adhere to the following code of conduct: 'Verzet bij wilsonbekwame (psycho) geriatrische patiënten in het kader van de Wet Medisch-Wetenschappelijk Onderzoek met Mensen' (<http://wetten.overheid.nl/BWBR0009408/2017-03-01>).

11.4 BENEFITS AND RISKS ASSESSMENT, GROUP RELATEDNESS

All patients included in the trial will receive usual care, including indicated interventions. Participation in the trial will lead to a slightly increased risk of hemorrhage, at an expected excess rate of 1%. However, participants may also experience improved outcome, with an estimated likelihood of 5%, all depending on the treatment allocation. The Executive Committee of MR CLEAN-MED expects that the potential benefits of heparin and aspirin outweigh the limited risks of harm of these study treatments. We refer to the chapters 6.3 and 13.1 for more details on these potential benefits and harms.

11.5 COMPENSATION FOR INJURY

Each participating center has a liability insurance, which is in accordance with article 7 of the WMO.

The sponsor has an insurance, which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 HANDLING AND STORAGE OF DATA AND DOCUMENTS

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

12.2 MONITORING AND QUALITY ASSURANCE

Monitoring schedules will be kept as proposed in the NFU position paper “Kwaliteitsborging mensgebonden onderzoek 2.0”. We propose that the trial will be placed in the category “kleine kans-ernstige schade” (“low likelihood, severe damage”), i.e. moderate risk, as the risk of serious adverse events, including symptomatic intracranial hemorrhage, was similar for the intervention and control group in MR CLEAN.⁴ The likelihood that severe damage was caused by the treatment was very low, and this was the case for all 5 thrombectomy trials published to date.⁴⁻¹⁰ Following the NFU guidelines, an independent monitor will perform 2-3 monitoring visits per center per year (depending on the inclusion speed and the previously found deviations). The first 3 included patients in each center will be verified concerning their in- and exclusion criteria followed by 25% of all subjects. Informed consent and source data verification will also take place for 25% of all subjects. The monitored data will comprise: age, time of onset, time of randomization, NIHSS at baseline and performance of baseline and follow up imaging. The patient-level drug accountability records will be reviewed. A screen for occurrence of study-related SAE, and 3-month assessment of primary outcome will also take place, as well as a verification of the presence of a study log and documentation. All other data will be monitored for completeness and consistency by the study coordinators.

12.3 AMENDMENTS

Amendments are changes made to the research protocol after a favorable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favorable opinion.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 ANNUAL PROGRESS REPORT

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

12.5 TEMPORARY HALT AND (PREMATURELY) END OF STUDY REPORT

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

12.6 PUBLIC DISCLOSURE AND PUBLICATION POLICY

The trial is registered as ISRCTN76741621 (<https://doi.org/10.1186/ISRCTN76741621>).

The study database will be closed within one month after the last scheduled follow-up date of the last included patient. A manuscript which at least describes the study and the answer to the primary research question will be submitted to a major clinical journal within 3 months from closure of the database. The manuscript will be shared with the financial sponsor(s) one month before submission, but the financial sponsor(s) will have no influence on its contents.

Anonymous data can be requested from the PI with a detailed description containing the aims and methods of the study for which the data are intended to be used. Data will be made available for this purpose at least 18 months after publication of the main report. Data may also be shared with non-commercial parties for scientific purposes, including individual patient meta-analyses, and with commercial parties for FDA approval. Consent will be asked specifically for these purposes.

13. STRUCTURED RISK ANALYSIS

13.1 POTENTIAL ISSUES OF CONCERN

a. Level of knowledge about mechanism of action

The intervention concerns periprocedural medication during thrombectomy for acute ischemic stroke. There is ample evidence for the safety of heparin and acetylsalicylic acid for patients with acute ischemic stroke. The risk of hemorrhage is slightly increased in patients already on antiplatelet treatment, but there is no interaction with intra-arterial treatment. What remains is that we need to know the effect on good outcome. If during the trial period standard care changes, for example regarding IVT, antithrombotic or anticoagulant medication, this trial will follow the corresponding standard care/will proceed according to standard care. The exact side effects of one dose of IV aspirin and/or IV heparin, as applied in this trial, are unknown but their frequency is expected to be low. In general, hypersensitivity (hives, rash, itching) to aspirin or heparin occurs in less than 1% of all patients. Treatment benefit is expected to outweigh the occurrence and severity of this potential side effect.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism.

The two substances have been extensively tested and used in clinical practice for similar indications. In fact, in many centers, heparin is used directly during intervention and acetylsalicylic acid is started immediately after admission.

c. Can the primary or secondary mechanism be induced in animals and/or in ex-vivo human cell material?

Not applicable.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Not applicable.

e. Analysis of potential effect

Not applicable.

f. Pharmacokinetic considerations

Not applicable

g. Study population

The study population exists of patients with acute ischemic stroke.

h. Interaction with other products

Not applicable.

i. Predictability of effect

Not applicable.

j. Can effects be managed?

Not applicable.

14. REFERENCES

1. Vaartjes I, O'Flaherty M, Capewell S, Kappelle J, Bots M. Remarkable Decline in Ischemic Stroke Mortality is Not Matched by Changes in Incidence. *Stroke*. 2013;44(3):591-+.
2. Heuschmann PU, Di Carlo A, Bejot Y, et al. Incidence of Stroke in Europe at the Beginning of the 21st Century The European Registers of Stroke (EROS) Investigators. *Stroke*. 2009;40(5):1557-1563.
3. Truelsen T, Piechowski-Jozwiak B, Bonita R, Mathers C, Bogousslavsky J, Boysen G. Stroke incidence and prevalence in Europe: a review of available data. *Eur J Neurol*. 2006;13(6):581-598.
4. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372(1):11-20.
5. Bracard S, Ducrocq X, Mas JL, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet Neurology*. 2016;15(11):1138-1147.
6. Campbell BCV, Donnan GA, Lees KR, et al. Endovascular stent thrombectomy: the new standard of care for large vessel ischaemic stroke. *Lancet Neurol*. 2015;14(8):846-854.
7. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372(11):1019-1030.
8. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke. *New Engl J Med*. 2015;372(24):2296-2306.
9. Muir KW, Ford GA, Messow CM, et al. Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. *J Neurol Neurosurg Ps*. 2017;88(1):38-44.
10. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. 2015;372(24):2285-2295.
11. Yemisci M, Gursoy-Ozdemir Y, Vural A, Can A, Topalkara K, Dalkara T. Pericyte contraction induced by oxidative-nitrative stress impairs capillary reflow despite successful opening of an occluded cerebral artery. *Nat Med*. 2009;15(9):1031-U1082.
12. Geddings JE, Mackman N. New players in haemostasis and thrombosis. *Thromb Haemostasis*. 2014;111(4):570-574.
13. Gory B, Bresson D, Rouchaud A, Yardin C, Mounayer C. A Novel Swine Model to Evaluate Arterial Vessel Injury after Mechanical Endovascular Thrombectomy. *Interv Neuroradiol*. 2013;19(2):147-152.
14. Park S, Hwang SM, Song JS, Suh DC, Lee DH. Evaluation of the Solitaire System in a Canine Arterial Thromboembolic Occlusion Model: Is It Safe for the Endothelium? *Interv Neuroradiol*. 2013;19(4):417-424.
15. Sandercock P, Collins R, Counsell C, et al. The International Stroke Trial (IST): A randomised trial of aspirin, subcutaneous heparin, both, or neither among 19 435 patients with acute ischaemic stroke. *Lancet*. 1997;349(9065):1569-1581.
16. Anderson CS, Robinson T, Lindley RI, et al. Low-Dose versus Standard-Dose Intravenous Alteplase in Acute Ischemic Stroke. *New Engl J Med*. 2016;374(24):2313-2323.
17. Zinkstok SM, Roos YB, Investigators A. Early administration of aspirin in patients treated with alteplase for acute ischaemic stroke: a randomised controlled trial. *Lancet*. 2012;380(9843):731-737.
18. Widimsky P, Kocka V, Rohac F, Osmancik P. Periprocedural antithrombotic therapy during various types of percutaneous cardiovascular interventions. *Eur Heart J-Cardiova*. 2016;2(2):131-140.

19. Hernandez AV, Steyerberg EW, Butcher I, et al. Adjustment for strong predictors of outcome in traumatic brain injury trials: 25% reduction in sample size requirements in the IMPACT study. *J Neurotrauma*. 2006;23(9):1295-1303.
20. Lingsma H, Roozenbeek B, Steyerberg E, investigators I. Covariate adjustment increases statistical power in randomized controlled trials. *J Clin Epidemiol*. 2010;63(12):1391; author reply 1392-1393.
21. BioStatMatt. Simulation-based power analysis using proportional odds logistic regression. 2015; <https://www.r-bloggers.com/simulation-based-power-analysis-using-proportional-odds-logistic-regression/>, 2017.
22. Hirsh J, Anand SS, Halperin JL, Fuster V. Mechanism of action and pharmacology of unfractionated heparin. *Arterioscler Thromb Vasc Biol*. 2001;21(7):1094-1096.
23. Awtry EH, Loscalzo J. Aspirin. *Circulation*. 2000;101(10):1206-1218.
24. Casaubon LK, Boulanger JM, Blacquiére D, et al. Canadian Stroke Best Practice Recommendations: Hyperacute Stroke Care Guidelines, Update 2015. *Int J Stroke*. 2015;10(6):924-940.
25. NICE. Mechanical clot retrieval for treating acute ischaemic stroke: NICE interventional procedure guidance. February 2016.
26. Powers WJ, Derdeyn CP, Biller J, et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2015;46(10):3020-3035.
27. Ringleb AP VR. Akuttherapie des ischämischen Schlaganfalls - Ergänzung 2015 - Rekanalisierende Therapie. 2015.
28. Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2014(7):CD000213.
29. del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT Investigators. *Prolyse in Acute Cerebral Thromboembolism*. *Stroke*. 1998;29(1):4-11.
30. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. *Prolyse in Acute Cerebral Thromboembolism*. *JAMA*. 1999;282(21):2003-2011.
31. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19(5):604-607.
32. Goyal M, Fargen KM, Turk AS, et al. 2C or not 2C: defining an improved revascularization grading scale and the need for standardization of angiography outcomes in stroke trials. *J Neurointerv Surg*. 2014;6(2):83-86.
33. Zaidat OO, Yoo AJ, Khatri P, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke*. 2013;44(9):2650-2663.
34. Brott T, Adams HP, Jr., Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*. 1989;20(7):864-870.
35. Boers AM, Marquering HA, Jochem JJ, et al. Automated cerebral infarct volume measurement in follow-up noncontrast CT scans of patients with acute ischemic stroke. *AJNR Am J Neuroradiol*. 2013;34(8):1522-1527.
36. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208.
37. Mahoney FI, Barthel DW. Functional Evaluation: The Barthel Index. *Md State Med J*. 1965;14:61-65.

- 38.von Kummer R, Broderick JP, Campbell BC, et al. The Heidelberg Bleeding Classification: Classification of Bleeding Events After Ischemic Stroke and Reperfusion Therapy. *Stroke*. 2015;46(10):2981-2986.
- 39.World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194.
- 40.Fransen PS, Berkhemer OA, Lingsma HF, et al. Time to Reperfusion and Treatment Effect for Acute Ischemic Stroke: A Randomized Clinical Trial. *JAMA Neurol*. 2016;73(2):190-196.
- 41.Appelbaum PS, Grisso T. Assessing patients' capacities to consent to treatment. *N Engl J Med*. 1988;319(25):1635-1638.
- 42.Sessums LL, Zembrzuska H, Jackson JL. Does This Patient Have Medical Decision-Making Capacity? *Jama-J Am Med Assoc*. 2011;306(4):420-427.
- 43.Puetz V, Dzialowski I, Hill MD, et al. Intracranial thrombus extent predicts clinical outcome, final infarct size and hemorrhagic transformation in ischemic stroke: the clot burden score. *Int J Stroke*. 2008;3(4):230-236.
- 44.Yoo AJ, Berkhemer OA, Fransen PSS, et al. Effect of baseline Alberta Stroke Program Early CT Score on safety and efficacy of intra-arterial treatment: a subgroup analysis of a randomised phase 3 trial (MR CLEAN). *Lancet Neurol*. 2016;15(7):685-694.
- 45.Tan IY, Demchuk AM, Hopyan J, et al. CT angiography clot burden score and collateral score: correlation with clinical and radiologic outcomes in acute middle cerebral artery infarct. *AJNR Am J Neuroradiol*. 2009;30(3):525-531.
- 46.Jansen TC, Kompanje EJ, Bakker J. Deferred proxy consent in emergency critical care research: ethically valid and practically feasible. *Crit Care Med*. 2009;37(1 Suppl):S65-68.

15. TABLES

15.1 TABLE 1: MODIFIED RANKIN SCALE

The modified Rankin Scale (mRS) is an ordinal hierarchical scale ranging from 0 to 5, with higher scores indicating more severe disability.³⁰ A score of 6 has been added to signify death.

Category	Short description	Long description
0	No symptoms	No symptoms
1	Symptoms, no disability	Minor symptoms that do not interfere with lifestyle
2	Slight disability	Slight disability, symptoms that lead to some restriction in lifestyle, but do not interfere with the patient's capacity to look after himself.
3	Moderate disability	Moderate disability, symptoms that significantly restrict lifestyle and prevent totally independent existence
4	Moderately severe disability	Moderately severe disability, symptoms that clearly prevent independent existence though not needing constant attention
5	Severe disability	Severe disability, totally dependent patient requiring constant attention day and night.
6	Death	Death

15.2 TABLE 2: EXTENDED TREATMENT IN CEREBRAL ISCHEMIA (ETICI) SCALE.³²

eTICI Grades	Short description	Long description
0	No perfusion	No antegrade flow beyond the point of occlusion
1	Limited reperfusion	Antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion
2a	<50% reperfusion	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	≥50% and <90% reperfusion	Antegrade reperfusion of more than half of the previously occluded target artery ischemic territory (eg, in 2 major divisions of the MCA and its territories)
2c	≥90% reperfusion	Near complete antegrade reperfusion of the previously occluded target artery ischemic territory, except for slow flow or distal emboli in a few distal cortical vessels
3	100% reperfusion	Complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches

eTICI, Extended Treatment in Cerebral Ischemia Scale; MCA: middle cerebral artery

15.3 TABLE 3: NIH STROKE SCALE

The NIHSS is an ordinal hierarchical scale to evaluate the severity of stroke by assessing a patient’s performance.³⁴ Scores range from 0 to 42, with higher scores indicating a more severe deficit. Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e. repeated requests to patient to make a special effort).

Instructions	Scale definition
<p>1a. Level of consciousness. The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.</p>	<p>0 = Alert; keenly responsive. 1 = Not alert; but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert; required repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid and areflexic.</p>
<p>1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct – there is not partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the</p>	<p>0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.</p>

examiner not “help” the patient with verbal or non-verbal clues.

1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e. follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.

0 = **Performs** both tasks correctly.
 1 = **Performs** one task correctly.
 2 = **Performs** neither task correctly.

2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be a 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.

0 = **Normal**.
 1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present.
 2 = **Forced deviation;** or total gaze paresis not overcome by the oculocephalic maneuver.

<p>3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving finger appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patients receives a 1, and the results are used to respond to item 11.</p>	<p>0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness)</p>
<p>4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly response or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.</p>	<p>0 = Normal symmetrical movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling) 2 = Partial paralysis (total or near-total paralysis of lower face) 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).</p>
<p>5. Motor arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score</p>	<p>0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls.</p>

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

extended arm position.

8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, 'severe or total sensory loss', should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.

0 = **Normal**; no sensory loss.
 1 = **Mild-to-moderate sensory loss**; patients feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched.
 2 = **Severe to total sensory loss**; patient is not aware of being touched in the face, arm and leg.

9. Best language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item

0 = **No aphasia**; normal
 1 = **Mild-to-moderate aphasia**; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response.
 2 = **Severe aphasia**; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be

<p>1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.</p>	<p>exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia: no usable speech or auditory comprehension.</p>
<p>10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.</p>	<p>0 = Normal. 1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood by some difficulty. 2 = Severe dysarthria: patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = Intubated or other physical barrier. Explain:</p>
<p>11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.</p>	<p>0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.</p>

15.4 TABLE 4: BARTHEL INDEX

The Barthel index (BI) is an ordinal scale used to measure performance in 10 activities of daily living (ADL).³⁷ Test scores range from 0 to 100, with higher scores indicating better performance in these activities.

Category	Scale definition
FEEDING	0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent
BATHING	0 = dependent 5 = independent (or in shower)
GROOMING	0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)
DRESSING	0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)
BOWELS	0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent
BLADDER	0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent
TOILET USE	0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)
TRANSFERS (BED TO CHAIR AND BACK)	0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit

	10 = minor help (verbal or physical) 15 = independent
MOBILITY (ON LEVEL SURFACES)	0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards
STAIRS	0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent

Guidelines

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

15.5 TABLE 5: EUROQOL-5D-5L

The EuroQoL 5-dimensions 5-level (EQ-5D-5L) questionnaire is a standardised measure of health outcome that has been used extensively in patients with stroke.³⁶

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

SELF-CARE

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

PAIN / DISCOMFORT

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

ANXIETY / DEPRESSION

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

15.6 TABLE 6: CLOT BURDEN SCORE FOR CTA AND MRA⁴³

Absence of contrast opafication at	Score	
Supraclinoid internal carotid artery	2	
Proximal M1	2	
Distal M1	2	
Infraclinoid internal carotid artery	1	
A1 branch	1	
M2 brances	1	
Total score: 10 – Sum	Sum	

15.7 TABLE 7: ASPECTS

Alberta Stroke Program Early CT Score (ASPECTS) is a 10-point systematic quantitative topographic CT-scan scoring system, to assess early ischemic changes on pretreatment NCCT in patients with acute ischemic stroke in the territory of the middle cerebral artery. Segmental assessment of the MCA vascular territory is made, and for every defined region of ischemic change, such as focal swelling or parenchymal hypoattenuation, one point is subtracted from the initial score of 10. A score of 10 indicates a normal scan and a score of 0 diffuse ischemia throughout the territory of the MCA⁴⁴

15.8 TABLE 8: COLLATERAL SCORE⁴⁵

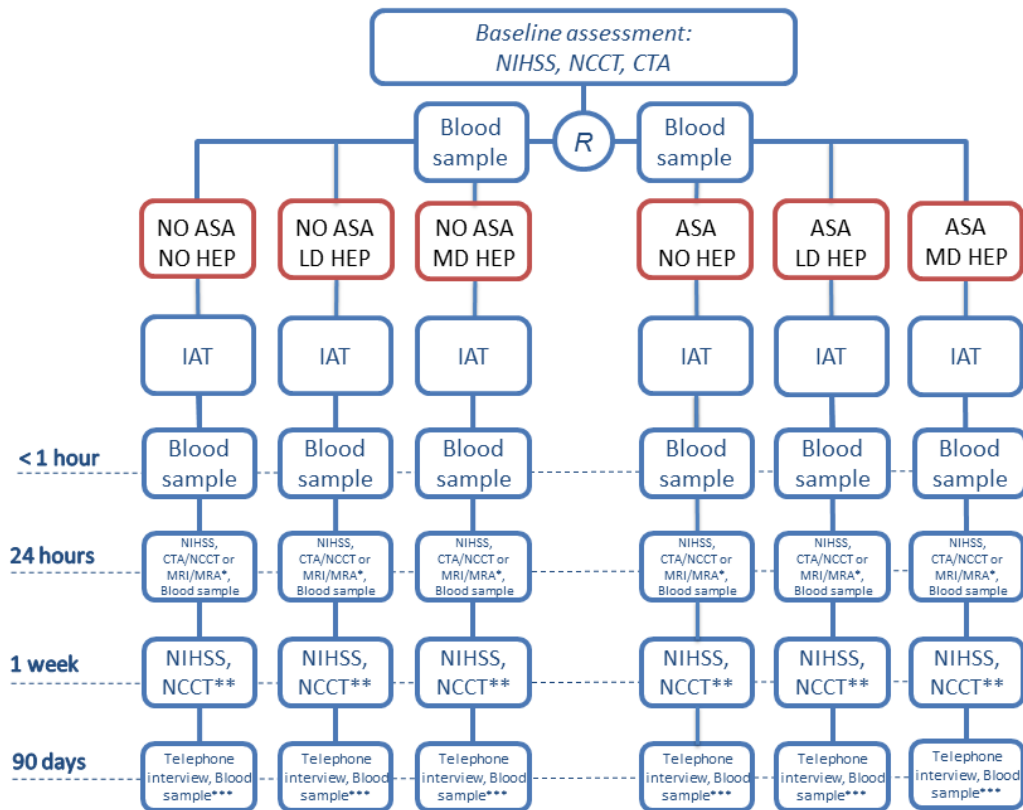
Category	Score	Description
None	0	Absent collaterals
Poor	1	Collaterals filling $\leq 50\%$ of the occluded territory
Intermediate	2	Collaterals filing $>50\%$, but $<100\%$ of the occluded territory
Good	3	Collaterals filling 100% of the occluded territory

16. FIGURES

16.1 FIGURE 1: MR CLEAN-MED TRIAL LOGO



16.2 FIGURE 2: PATIENT FLOW IN THE TRIAL



Glossary: ASA, IV acetylsalicylic acid; CTA, Computed tomography angiogram; HEP, unfractionated heparin; IAT, intra-arterial treatment; LD, low dose; MD, Moderate dose; MRI, Magnetic Resonance Imaging; MRA, Magnetic Resonance Angiography; NCCT, Non contrast computed tomography; NIHSS, National Institutes of Health Stroke Scale

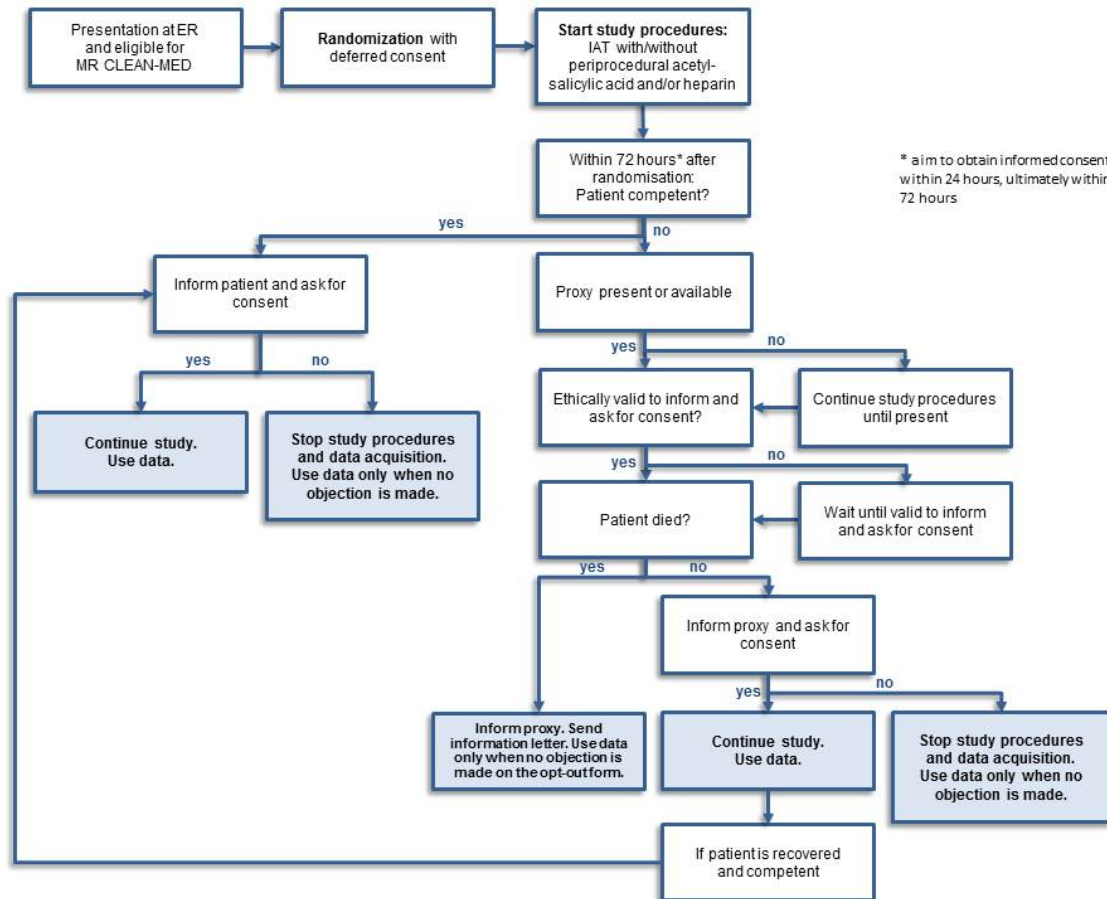
* Time-window for CT/CTA: 24 +/- 12 hours, for MRI/MRA 24-48 hours

** Only to be performed if imaging at 24 hour was acquired with CT

*** Blood sample drawn only in case of regular outpatient clinic appointment within 2-6 months after intervention.

16.3 FIGURE 3: FLOWCHART OF DEFERRED CONSENT PROCEDURE SPECIFICALLY FOR THE MR CLEAN-MED TRIAL

Based on the flowchart proxy-deferred consent in emergency critical care research, by T. Jansen, E. Kompanje, et al.⁴⁶



Glossary: ER: Emergency Room; IAT: intra-arterial treatment; MR CLEAN-MED: Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands. The effect of periprocedural MEDication: heparin, antiplatelet agents, both or neither;

17.APPENDICES

17.1 APPENDIX 1: LIST OF COLLABORATING INVESTIGATORS

17.1.1 COORDINATING INVESTIGATORS

Bob Roozenbeek, MD, PhD; neurologist; Erasmus MC Rotterdam

Rob van de Graaf, MD; PhD-student; Erasmus MC Rotterdam

17.1.2 PRINCIPAL INVESTIGATORS

Diederik Dippel, MD, PhD; neurologist; Erasmus MC Rotterdam

Aad van der Lugt, MD, PhD; neuroradiologist; Erasmus MC Rotterdam

17.1.3 LOCAL INVESTIGATORS

Academic Medical Center:

- Yvo Roos, MD, PhD; neurologist
- Charles Majoie, MD, PhD; neuroradiologist

University Medical Center Utrecht

- Bart van der Worp, MD, PhD; neurologist
- Rob Lo, MD, PhD; radiologist

Maastricht University Medical Center

- Inger de Ridder, MD, PhD; neurologist
- Wim van der Zwam, MD, PhD; neuroradiologist

Catharina Hospital:

- Koos Keizer, MD, PhD; neurologist
- Lonneke Yo, MD, PhD; neuroradiologist

Haaglanden Medical Center:

- Jelis Boiten, MD, PhD; neurologist
- Ido van den Wijngaard, MD, PhD; neurointerventionist

Rijnstate Hospital:

- Jeanette Hofmeijer, MD, PhD; neurologist
- Jasper Martens, MD, PhD; neuroradiologist

Antonius Hospital:

- Wouter Schonewille, MD, PhD; neurologist
- Jan Albert Vos, MD, PhD; neuroradiologist

Radboud UMC:

- Anil Tuladhar, MD, PhD; neurologist
- Sjoerd Jenniskens, MD, PhD; neuroradiologist

Haga Hospital:

- Karlijn de Laat, MD, PhD; neurologist
- Lukas van Dijk, MD, PhD; neuroradiologist

Isala Hospital:

- Heleen den Hertog, MD, PhD; neurologist
- Boudewijn van Hasselt, MD; neuroradiologist

Medisch Spectrum Twente:

- Paul Brouwers, MD, PhD; neurologist
- Emiel Sturm, MD; neuroradiologist

Amphia Hospital:

- Michel Remmers, MD; neurologist
- Thijs de Jong, MD; neuroradiologist

Albert Schweitzer Hospital:

- Anouk Rozeman, MD; neurologist
- Otto Elgersma, MD, PhD; neuroradiologist

UMC Groningen:

- Maarten Uyttenboogaart, MD, PhD; neurologist
- Reinoud Bokkers, MD, PhD; neuroradiologist

17.2 APPENDIX 2: STUDY COMMITTEES

17.2.1 DATA SAFETY MONITORING BOARD

Chair: Peter Rothwell, MD, PhD

Member: Adrew Molyneux, MD, PhD

Independent Statistician: Ziyah Mehta, PhD

17.2.2 EXECUTIVE AND WRITING COMMITTEE

Diederik Dippel, MD, PhD (Erasmus MC Rotterdam); Aad van der Lugt, MD, PhD (Erasmus MC Rotterdam); Adriaan van Es, MD, PhD (Erasmus MC, Rotterdam); Heleen den Hertog, MD, PhD (MST, Enschede); Julie Staals, MD, PhD (MUMC, Maastricht); Lukas van Dijk, MD, PhD (HAGA ziekenhuis, Den Haag); Sjoerd Jenniskens, MD, PhD (Radboud UMC, Nijmegen)

Research coordinators:

Bob Roozenbeek, MD, PhD, Erasmus MC Rotterdam.

Rob van de Graaf, MD, PhD, Erasmus MC Rotterdam.

17.2.3 IMAGING ASSESSMENT COMMITTEE

CONTRAST Work Package: Imaging data management and analysis

WP leaders: Charles Majoie, MD, PhD (AMC, Amsterdam) and Aad van der Lugt, MD, PhD (Erasmus MC, Rotterdam).

WP members: Henk Marquering, MD, PhD (AMC, Amsterdam), Wiro Niessen, MD, PhD (Erasmus MC, Rotterdam), Birgitta Velthuis, MD, PhD (UMCU, Utrecht), Jan Albert Vos, MD, PhD (Antonius Ziekenhuis, Nieuwegein); Yvo Roos, MD, PhD (AMC, Amsterdam); Rick Dijkhuizen, MD, PhD (UMCU, Utrecht).

WP collaborators (imaging assessments)

Wim van Zwam, MD, PhD (MUMC, Maastricht), Linda Jacobi, MD, PhD (MUMC, Maastricht); Hugo de Jong, MD, PhD (UMCU, Utrecht); Irene van der Schaaf, MD, PhD (UMCU, Utrecht); Jan Willem Dankbaar, MD, PhD (UMCU, Utrecht); René van den Berg, MD, PhD (AMC, Amsterdam); Marieke Sprengers, MD, PhD (AMC, Amsterdam); Ludo Beenen, MD (AMC, Amsterdam); Bart Emmer, MD, PhD (AMC, Amsterdam); Joost Bot, MD, PhD (VUmc, Amsterdam); Adriaan van Es, MD, PhD (Erasmus MC, Rotterdam); Pieter-Jan Doormaal, MD (Erasmus MC, Rotterdam); Wouter Dinkelaar,

MD, PhD (Erasmus MC, Rotterdam); Geert Lycklama, MD, PhD (MCH, Den Haag); Sjoerd Jenniskens, MD, PhD (UMCN, Nijmegen); Marianne van Walderveen, MD, PhD (LUMC, Leiden), Ido van den Wijngaard, MD, PhD (LUMC, Leiden); Jo Peluso, MD, PhD (Elisabeth Hospital, Tilburg); Albert J. Yoo, MD, PhD (Texas Stroke Institute, Plano, Texas, United States of America)

17.2.4 OUTCOME ASSESSMENT COMMITTEE

Chair: Yvo Roos, MD, PhD (AMC, Amsterdam)

Members: to be announced

17.2.5 ADVERSE EVENT ADJUDICATION COMMITTEE

Chair: Robert van Oostenbrugge, MD, PhD (MUMC, Maastricht)

Members: to be announced

17.2.6 TRIAL STATISTICIAN AND METHODOLOGIST

Hester Lingsma, PhD (Erasmus MC, Rotterdam)

17.2.7 ADVISORY BOARD

Gregory del Zoppo, MD, PhD (University of Washington, Seattle)

17.3 APPENDIX 3: MR CLEAN-MED RECOMMENDATIONS OF THE STEERING COMMITTEE WITH REGARD TO TYPE OF MECHANICAL THROMBECTOMY AND USE OF THROMBOLYTIC AGENTS DURING ENDOVASCULAR PROCEDURES.

17.3.1 GENERAL

Inclusion in the trial, randomization, and subsequent endovascular treatment with/without aspirin and/or heparin injection should be started as soon as possible after presentation in all eligible patients. The time-path below gives an indication about how soon the following steps need to take place in the most optimal situation.

The optimal time-path for treatment and inclusion in MR CLEAN-MED of patients with acute ischemic stroke and relevant intracranial large vessel occlusion of the anterior circulation is listed below:

Procedure	Transfer	No transfer
Arrival at ER	0	0
Start neuroimaging and start IV alteplase (if eligible)	20 min	20 min
Transfer	30 min	-
Randomization	90 min	30 min
Start endovascular treatment With IV aspirin and/or IV heparin injection directly after groin puncture	110 min	50 min

17.3.2 NEUROIMAGING

Neuroimaging studies to assess vessel patency should be done before or simultaneously with treatment with intravenous (IV) alteplase, in order not to lose time and brain. We aim to not cause any delay prior to intra-arterial treatment, by infusion of IV alteplase.

17.3.3 ADDITIONAL THROMBOLYTIC AGENTS, DOSE AND TYPE

If deemed indicated by the interventionist, local application (intra-arterial) of urokinase, alteplase or other antithrombo(ly)tic agents is allowed in any of the patients included in the MR CLEAN-MED.

Patients who have been pre-treated with IV alteplase should not receive more than 30 mg alteplase during intra-arterial treatment, or an equivalent dose of 400,000 U urokinase. The steering committee recommends that the thrombolytic agent is delivered in shots of 5 mg alteplase or 50.000 – 100.000 U urokinase, in 5-10 minutes time intervals. Vessel patency should be checked after each shot.

17.3.4 TYPE OF MECHANICAL THROMBECTOMY DEVICE(S)

All stent retriever and aspiration -devices for IAT, which are CE marked approved for this purpose, and have been approved for use in the study by the steering committee are allowed in the trial as a first line of defense and are listed below:

Device name	Manufacturer	Description
Solitaire	Medtronic / Covidien	Retrievable stent
Trevo stent	Stryker	Retrievable stent
Embotrap	Codman	Retrievable stent
Revive stent	Codman/DePuy-Synthes	Retrievable stent
Catch	Balt	Retrievable stent
3D Separator	Penumbra	Retrievable stent

Eric	Microvention	Retrievable stent
PreSet	Phenox	Retrievable stent
ACE	Penumbra	Aspiration device

A second device is allowed as a second option, when the first device has failed according to the interventionist. The further choice of the particular device for a certain patient is left to the discretion of the interventionist.

17.4 APPENDIX 4 CONTRAST: COLLABORATION FOR NEW TREATMENTS OF ACUTE STROKE

17.4.1 CONTRAST LOGO

The logo for CONTRAST features the word "CONTRAST" in a large, bold, blue sans-serif font. The letters are set against a dark blue rectangular background that has a subtle gradient from left to right.

Collaboration for New Treatments of Acute Stroke

17.4.2 RESEARCH LEADERS CONTRAST

- Diederik Dippel, MD, PhD, Dept. Neurology, Ee2240, Erasmus MC, PO Box 2040, 3000 CA Rotterdam, Tel. +31107043979, d.dippel@erasmusmc.nl
- Charles Majoie, MD, PhD, Dept. Radiology, C1-426, AMC, PO Box 22660, 1100 DD Amsterdam, Tel. +31205669111, c.b.majoie@amc.uva.nl

17.4.3 OVERALL SCIENTIFIC SUMMARY CONTRAST

The MR CLEAN-MED will be carried out by members of Collaboration for New Treatments of Acute Stroke (CONTRAST). The overarching aim of CONTRAST is to improve outcome of patients with stroke by creating a consortium that blends mechanistic, basic scientific projects with pragmatic randomized clinical trials with a firm view of the future of Dutch Stroke Research beyond the coming five years.

The CONTRAST consortium will perform five large randomized clinical trials in acute stroke patients in the Netherlands, to test novel treatment strategies, aimed at preservation of ischemic tissue and to improve outcome after intra-arterial treatment by focusing on the optimization of IAT and the expansion of its indication.

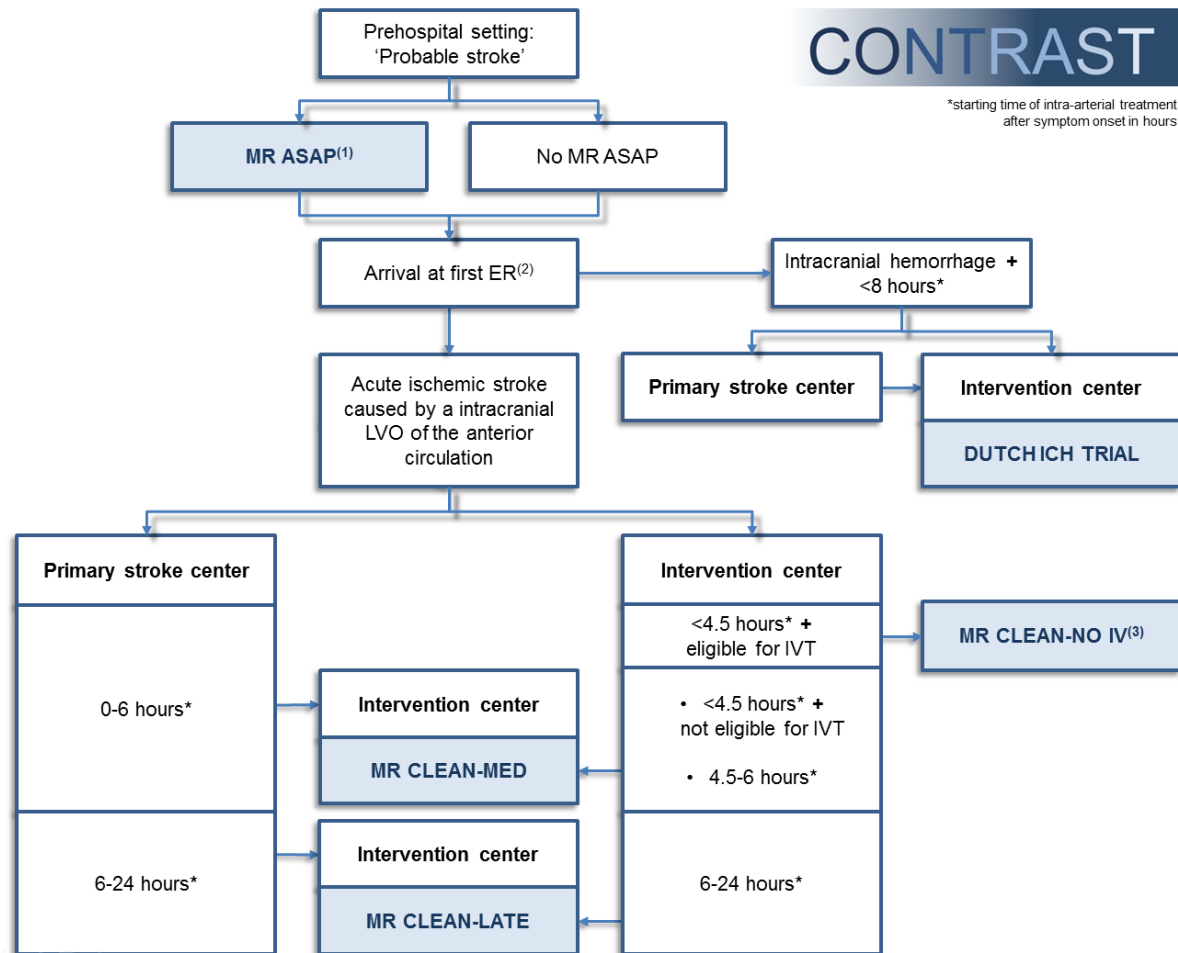
1. Multicentre Randomised trial of Acute Stroke treatment in the Ambulance with a nitroglycerin Patch (MR ASAP): pre-hospital augmentation of collateral blood flow and blood pressure reduction;

2. Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands. The effect of periprocedural MEDication: heparin, antiplatelet agents, both or neither (MR CLEAN-MED): antithrombotics to prevent microvascular occlusion after IAT;
3. Intravenous treatment followed by intra-arterial treatment versus direct intra-arterial treatment for acute ischemic stroke caused by a proximal intracranial occlusion (MR CLEAN-NO IV): immediate IAT without preceding thrombolysis;
4. Multicenter Randomized Clinical Trial of Endovascular Stroke treatment in The Netherlands for Late arrivals: MR CLEAN-Late (MR CLEAN-LATE): IAT in the 6 to 24 hour time window;
5. A prospective, multicenter, randomized open, blinded end-point clinical trial of minimally-invasive surgery, steroids or both in patients with spontaneous, non-traumatic supratentorial ICH in the Netherlands (DUTCH ICH Trial): microsurgical hematoma evacuation and dexamethasone in patients with ICH.

17.4.4 PATIENT FLOW AND SELECTION INTO THE CONTRAST TRIALS

Participating centers may largely be similar for all five RCT's.

Therefore, patient selection into the proper trial is represented in the following flow chart.



Glossary: MR ASAP: Multicentre Randomised trial of Acute Stroke treatment in the Ambulance with a nitroglycerin Patch; ER: Emergency Room; DUTCH ICH TRIAL: A prospective, multicenter, randomized open, blinded end-point clinical trial of minimally-invasive surgery, steroids or both in patients with spontaneous, non-traumatic supratentorial ICH in the Netherlands; MR CLEAN-MED: Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands. The effect of periprocedural MEDication: heparin, antiplatelet agents, both or neither; MR CLEAN-NO IV: Intravenous treatment followed by intra-arterial treatment versus direct intra-arterial treatment for acute ischemic stroke caused by a proximal intracranial occlusion; IVT: intravenous thrombolysis with alteplase; MR CLEAN-LATE: Multicenter Randomized Clinical Trial of Endovascular Stroke treatment in The Netherlands for Late arrivals

Considerations

- (1) The CONTRAST studies are independent RCT's. Patients who have been included in MR ASAP may also be included in one of the intervention trials for ischemic or for hemorrhagic stroke. Being eligible for two trials at the same time raises questions whether the trials influence each other's results. Therefore, we will perform pre-specified subgroup analyses to test for interaction between the different performed treatments. Further, part of the potential treatment effect in MR ASAP will be represented in the baseline characteristics measured at inclusion in the second trial, such as collaterals, blood pressure and NIHSS, which we will adjust for in all analyses.
- (2) At the first ER (either a primary stroke center or a participating intervention center), all patients with a probable diagnosis of acute stroke will undergo non-contrast CT to differentiate between acute cerebral infarction or acute intracranial hemorrhage. When the first ER is a primary stroke center and the patient could be eligible for the DUTCH ICH TRIAL, MR CLEAN-MED or MR CLEAN-LATE study, the patient should be transferred to a participating intervention center (where inclusion in one of these studies, randomization and treatment takes place).
- (3) Patients arriving first at a primary stroke center first, will never be eligible for the MR CLEAN-NO IV, since intravenous thrombolysis with alteplase (IVT) cannot be withheld until after patient transfer to the participating intervention center, unless the perceived contraindications for alteplase are not present anymore upon arrival at the intervention center. Then inclusion in MR CLEAN-NO IV will have priority over inclusion in other trials.
Patients who are eligible for inclusion in MR CLEAN-NO IV (primary presentation at intervention center, <4.5 hours + eligible for IVT) will not be included in MR CLEAN-MED. Patients presenting at the primary stroke center within 6 hours (both eligible or not eligible for IVT), could be eligible for the MR CLEAN-MED. Importantly by this scheme, competition between the intervention trials will not occur.

17.4.5 COMMON CORE DATA SET MR CLEAN II TRIALS

The MR CLEAN II trials include: MR CLEAN-MED, MR CLEAN-NO IV, MR CLEAN-LATE.

Inclusion check list
A clinical diagnosis of acute ischemic stroke
Caused by a intracranial large vessel occlusion of the anterior circulation: distal intracranial carotid artery or middle (M1/proximal M2) cerebral artery, confirmed by neuro-imaging (CTA or MRA)
CT or MRI ruling out intracranial hemorrhage
Intra-arterial treatment (groin puncture) possible within the ** hours from symptom onset or last seen well ** MR CLEAN-NO IV: 0-4.5 hours; MR CLEAN-MED: 0-6 hours; MR CLEAN-LATE: 6-24 hours
A score of at least 2 on the NIH Stroke Scale
Age of 18 years or older
Written informed consent (deferred)

Baseline characteristics	
Demographics	Age, sex
Clinical	NIHSS, pre-stroke mRS, systolic and diastolic blood pressure, Glasgow coma scale, weight, height, body temperature, heart rate
Medical history and intoxications	Previous stroke, myocardial infarction, hypertension, hypercholesterolemia, peripheral arterial disease, diabetes mellitus, atrial fibrillation, chronic heart failure, intra-cranial

	hemorrhage, smoking (current or stopped within 6 months), mechanical aortic and/or mitral valve replacement
Medication	Antiplatelet agents (and if yes, subtypes: acetylsalicylic acid, clopidogrel, dipyridamole, ticagrelor, other), coumarines, direct oral anticoagulants (DOAC), therapeutic heparin(oids), statins, benzodiazepines, NSAIDs
Laboratory parameters	INR, serum creatinine, GFR (Cockcroft-Gault), serum glucose, C-Reactive Protein, when available APTT. Biobank laboratory directly after randomization and +/-1 hour after IAT.
Neuro imaging¹	CT brain: severity of ischemia with ASPECTS CT Angiography, Clot Burden Score, collateral score, occlusion site, status extracranial carotid artery
Inclusion in other trial	Inclusion in the MR ASAP yes/no, study number MR ASAP, treatment allocation MR ASAP (for stratification during randomization)

Intra-arterial treatment	
General information	Date of IAT, name first and second interventionalist,
Time registration	Time of: patient arrival in angiosuite; start of endovascular procedure (needle in groin); device attempts;

¹ Neuro-imaging parameters will be assessed by a central subcommittee.

	recanalization (TICI \geq 2B) or last contrast bolus; end of procedure/sheath withdrawal
Anesthetic management	Anesthetic team present from the start; first anesthetic management: none, local with bolus short working opiates, moderate sedation (patients reacts purposefully to verbal/tactile stimuli), deep sedation (patient sleeps, no intubation), general anesthesia (intubation); conversion of anesthetic management
Pre-treatment	Final systolic and diastolic blood pressure before groin puncture in angiosuite; entry location and side, sheath length and size, target lesion/occlusion on DSA location and side, pre-eTICI on DSA
Treatment – main data	Performed procedure: catheterization only (no access to target lesion), cerebral DSA only (i.e. spontaneous recanalization or migration), intra-arterial treatment (use of device or IA thrombolysis), other (if procedure ended before thrombectomy attempt despite target occlusion), and descriptions; final DSA directions (PA/Lateral); post-eTICI on DSA
Complications	Procedure-related complications: distal thrombus, dissection and location, embolization in new/other vascular territory and location, perforation and location, other complication and description; Neurological deterioration of 4 points or more on the NIHSS; Neurological deterioration of 2 points or more on one NIHSS item
Non-trial medication during procedure	Non-trial medication given during procedure and specification of name and dose if yes: heparin, abciximab,

	acetylsalicylic acid, nimodipine, other
Stent placement/PTA in ICA	Stent placed yes/no and timing: before or after IAT; time of stent placement, stent type, PTA performed yes/no and timing: before, after or without stent placement; balloon size
10 attempts	Target lesion/occlusion location per attempt; eTICI score after every attempt; Technique: guiding catheter, distal access catheter , stent retriever, intra-arterial thrombolysis; Types and sizes: guiding catheter type and size, microcatheter type, distal access catheter type and size, stent retriever dimensions and type Additional information: balloon used during guiding, aspiration on guiding and pump/manual, aspiration on distal access catheter and pump/manual; stent retriever unfolded ≥5 minutes yes/no; intra-arterial thrombolysis name and dose (alteplase, urokinase, other)
Stent/thrombus	Stent sent for pathology yes/no (BIOBANK) Thrombus sent for pathology yes/no (BIOBANK)

Other treatments	
Intravenous thrombolysis (IVT)	IVT given yes/no, if yes: time of start IVT, if no: contraindication specified

Workflow (logistics)	
Pre-hospital	Witnessed stroke onset yes/no. If yes: time of symptom onset; if no: time of last seen well and time of symptoms

	noticed, time of call for help, time of 112 call, referrer of stroke, suspected diagnose(referrer), urgency code ambulance(A1/A2/B), time of arrival of ambulance on site, time of departure ambulance towards hospital, name and postal code target destination ambulance
In-hospital	Transfer from other hospital: yes/no If yes: time of hospital admission transfer hospital, departure time transfer hospital Time of arrival (door) intervention hospital; intervention hospital name/postal code
Timing	Time of: plain CT, CT angiography, randomization

Follow-up	
Clinical assessment at 24 hours	NIH Stroke Scale
Laboratory at 24 hours	CONTRAST Biobank blood drawn
Neuro-imaging CT/CTA at 24 +/-12 hours² MRI/MRA at 24-48 hours	CT angiography: Occlusion location, Clot Burden Score, Collateral score MRI: infarct size and location, hemorrhagic transformation (Heidelberg Bleeding Classification)

² Neuro-imaging parameters will be assessed by a central subcommittee.

³ Neuro-imaging parameters will be assessed by a central subcommittee.

	MRA: Occlusion location, Clot Burden Score, Collateral Score
Neuro imaging at 5-7 days (following CT imaging at 24 hours)³	Plain CT (or MRI in subset of 600): infarct size and location, hemorrhagic transformation (Heidelberg Bleeding Classification)
Clinical assessment at 5-7 days or discharge	NIH Stroke Scale; Global assessment of improvement or deterioration; Laboratory: biobank
Clinical assessment at 90 days (+/- 14 days) via telephone interview	Modified Rankin Scale score, Barthel index, EQ5D-5L
Laboratory at 90 days (+/- 30) in case of regular outpatient clinic appointment at 90 days	CONTRAST Biobank blood drawn
(Serious) adverse events (at any given time)	<p>Name investigator; date of report; date of (S)AE onset; description of (S)AE;</p> <p>SAE category: an adverse event is considered serious when it: causes mortality, is life-threatening, results in required or prolonged hospitalization, results in risk of persistent or significant disability or incapacity, results in medical or surgical intervention;</p> <p>Most likely cause for (S)AE and other causes:</p> <ol style="list-style-type: none"> 1. Stroke progression 2. New ischemic stroke in a different vascular territory

	<ol style="list-style-type: none"> 3. Intracranial hemorrhage 4. Extracranial hemorrhage 5. Cardiac ischemia 6. Allergic reaction 7. Pneumonia 8. Other infection and description 9. Other cause for (S)AE and description; <p>Relationship with the study treatment: none, unlikely, possible, probable, definite;</p> <p>Actions regarding the study treatment: none, interrupted, discontinued, other and description;</p> <p>Outcome and date: resolved without sequela(e); resolved with sequela(e) and description, death</p>
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17.5 SCHEDULE OF STUDY ACTIVITIES OF THE MR CLEAN II TRIALS

	Inclusion	24 hours	day 5-7	3 months
NIHSS	x	x	x	
Laboratory	x	x		x*
Neuroimaging	x	x	X**	
Barthel index				x
Modified Rankin Scale				x
EQ-5D-5L				x

* Only in case of regular outpatient clinic appointment (none trial-related). All other study activities will be done by a telephone interview, even in case of a regular outpatient clinic appoint at 3 months.

** Only if 24h imaging was performed using CT/CTA

17.6 IMAGING REQUIREMENTS

17.6.1 MINIMUM BASELINE IMAGING REQUIREMENTS

WHEN

1) Before randomization either a NCCT/CTA OR MRI/MRA should be performed to assess eligibility for the study.

HOW

1. Pre-randomization NCCT:
 1. The NCCT study should contain both thick (5mm) and thin slices (maximum of 2.5mm).
 2. The NCCT study should include the whole head.
2. Pre-randomization CTA:
 1. The CTA study should cover the whole area from the aortic arch to the vertex
 2. The CTA study should include thin slices (maximum of 1.0 mm)
 3. The CTA study should include the following reconstructions
 - i. Axial maximum intensity projection (MIP),
 1. MIP slab thickness: 25 mm
 2. Overlap: 5 mm
 - ii. Coronal MIP
 1. MIP slab thickness: 25 mm
 2. Overlap: 5 mm
3. Pre-randomization MRI/MRA:
 1. The study should include the following sequences
 - i. Axial DWI and ADC maps
 - ii. Axial FLAIR
 - iii. Axial T2*
 - iv. Contrast Enhanced MRA (CEMRA)
 2. The MRI study should cover the whole head
 3. The CEMRA study should cover the whole are from the aortic arch to the vertex
4. After acquisition

1. All images (NCCT/CTA or MRI/MRA) should be saved to the DICOM format
2. All available series should be sent to the core lab for assessment, including thin slice series (for thrombus assessment).

17.6.2 INTERVENTION-RELATED ANGIOGRAPHIC IMAGING

WHEN

- 1) Before the intervention complete AP and Lateral angiograms (of whole head and including venous phase) should be performed to evaluate the site of vessel occlusion, extent of thrombus, territories involved, concomitant pathologies and to assess collateral flow. ⁴⁵
- 2) After each passage of a mechanical or aspirational device, a control angiogram should be performed.
- 3) After each bolus of (a rescue) thrombolytic agent a control angiogram should be performed.
- 4) At the end of the procedure complete AP and Lateral angiograms (of whole head and including venous phase) should be repeated. Without these complete runs optimal TICI scoring is not possible

HOW

Pre-intervention and end-of-procedure angiogram:

- a. Angiograms should be performed through the guiding catheter
- b. Baseline and final AP views and lateral views of the intracranial arteries are mandatory. Both are required to assess reperfusion after the procedure.
- c. Baseline and final angiograms should include both the arterial and venous phases of the injection to evaluate the collateral pathways and perfusion of the distal vascular bed.
- d. Baseline and final angiograms should include the internal carotid artery feeding the target vessel as demonstrated on CTA.
- e. Baseline and final angiograms should include the common carotid and internal carotid artery in case of occlusion, dissection or severe stenosis in the carotid feeding the target vessel as demonstrated on CTA.
- f. Angiograms should be performed via the guiding catheter with the same catheter position and same views before and after the procedures to adequately assess the results of therapy.

After each device placement:

- g. A non-contrast radiograph should be obtained
- h. At least one view at the discretion of the interventionalist

After each passage of mechanical or aspirational device or bolus of (rescue) thrombolytic agent :

- i. Angiograms should be performed through the guiding catheter
- j. At least one view, at the discretion of the interventionalist.

After the procedure

- k. Complete series of the angiograms and microcatheter injections (when performed) should be saved according to the DICOM standard.
- l. All series should be forwarded to the imaging assessment committee.

17.6.3 MINIMUM FOLLOW-UP IMAGING REQUIREMENTS

WHEN

1) 24 hours after undergoing endovascular treatment a NCCT and CTA (24 hours +/- 12h) or MRI and MRA (24-48h) should be performed to assess treatment efficacy.

2) In case of CT imaging at 24 hours, a NCCT should be performed 5-7 days after undergoing endovascular treatment, or before discharge to assess final lesion volume and potential hemorrhagic complications.

3) If clinically required (I.e. in cases of clinical deterioration of the patient) additional imaging as needed, at the discretion of the treating physician is acquired.

HOW

24 hours CT/CTA:

1. The NCCT study should contain both thick (5mm) and thin slices (maximum of 2.5mm).
2. The NCCT study should include the whole head.
3. The CTA study should cover the whole area from the aortic arch to the vertex
4. The CTA study should include thin slices (maximum of 1.0 mm)
5. The CTA study should include the following reconstructions
 - i. Axial maximum intensity projection (MIP),
 1. MIP slab thickness: 25 mm
 2. Overlap: 5 mm
 - ii. Coronal MIP
 1. MIP slab thickness: 25 mm
 2. Overlap: 5 mm

24 hours MRI/MRA:

1. The MRI study should cover the intracranial vasculature
2. The MRI study should include thin slices (maximum of 1.0 mm)
3. The MRI study should include the following sequences
 - i. Axial DWI and ADC maps

- ii. Axial FLAIR
- iii. Axial T2*
- iv. Axial and 3D reconstructed MRA (3D TOF)

5-7 days NCCT (or before discharge)

- 4. The NCCT study should contain both thick (5mm) and thin slices (maximum of 2.5mm).
- 5. The NCCT study should include the whole head.

Additional, clinically required imaging

- 6. At the discretion of the treating physician

After acquisition

- 7. All images (NCCT, CTA, and additional imaging) should be saved to the DICOM file format
- 8. All available series should be sent to the core lab for assessment, including thin slice series (for thrombus assessment).

17.7 DRAFT STUDY PROTOCOL “DEFERRED CONSENT IN ACUTE
STROKE TRIALS”

See following pages.

17.8 TRIAL ORGANIZATION

The MR CLEAN-MED trial is embedded in the CONTRAST consortium. It has an independent leadership, which reports progress in form of milestones to the CONTRAST Scientific committee. Funding is provided through the CONTRAST Consortium based on these milestones.

The Steering committee of the trial consists of all local Principal Investigators (PI) of the participating centers. Each participating center has two PIs: a vascular neurologist and a neuro-interventionist. The Steering committee will meet at least annually. Final decisions concerning protocol changes, publication and reporting will be made by the Steering committee. The Steering committee is chaired by the central PIs of the trial. Decisions will be made in consensus, but if unavoidable by majority vote. Day to day conduct of the trial will be managed by the trial coordinators, who will be supervised by the central PIs of the trial.

The Executive committee of the trial consists of the central PIs of the trial and a representation of local PIs. They meet regularly, discuss trial progress and prepare information for the Steering committee.

The Writing committee consists of the Executive committee and local PIs of the five collaborating centers that have contributed the most patients to the trial in the first two years of trial execution. The task of the Writing committee is to prepare the main publication which will be drafted by the study coordinators, supervised by the two central PIs. Typically, the main paper will be authored by the study coordinators (first), the local PIs, the committee members, and the central PIs. Authorship has to comply with the criteria of the International Committee of Medical Journal Editors (ICMJE), <http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html>.

The other trial committees are not trial specific and will be formed in collaboration with the four CONTRAST randomized clinical trials: MR ASAP, MR CLEAN-LATE, MR CLEAN-MED and MR CLEAN-NO IV. These are: the Outcome assessment committee, the Imaging committee, and the Adverse event committee. The committees work for and report to the other three CONTRAST trials.

The Outcome assessment committee consists of at least 3 members, all seasoned neurologists, their task is to evaluate all coded and masked structured reports of outcome assessments at three months of patients in the trials. In this way, the blind assessment is maintained. The chair of this committee will not assess reports, as he is involved as PI in one of the trials.

The Imaging committee is chaired by the CONTRAST WP leaders and consists of neuroradiologists from the collaborating centers. Their task is to assess and evaluate masked baseline and follow-up

imaging, which is made per protocol and stored in a central web-based database. Assessments will be stored in Research forms and entered in the clinical database. And will be accessible to investigators after approval by the Steering committee.

The Adverse event committee consists of at least 3 members, including a neurologist and a neuro-interventionist. Their task is to oversee the review and reporting process of all reported serious adverse events. The chair of this committee will not assess reports, as he is involved as PI in one of the trials. The committee will regularly report to the four Steering committees.