

Protocol for the MR CLEAN-Registry (MR CLEAN-R)

A multicenter registry of intra-arterial treatment for acute ischemic stroke

Authors:

Ivo Jansen¹, Olvert Berkhemer¹, Maxim Mulder³,
Puck Fransen², Debbie Beumer³, Lucie van den Berg¹,
Charles Majoie¹, Yvo Roos¹,
Robert van Oostenbrugge³, Wim van Zwam³,
Aad van der Lugt², Diederik Dippel²

¹Academic Medical Center Amsterdam, departments of neurology and radiology

²Erasmus MC University Medical Center Rotterdam, departments of neurology and radiology

³Maastricht University Medical Center, departments of neurology and radiology

CONTENTS

Acknowledgments 3

Summary 4

1. Introduction and rationale 6

2. Objectives 7

3. Study Design 7

4. Study Population 7

5. Treatment of subjects..... 8

6. Methods 10

7. Safety Reporting 11

8. Statistical analyses 12

9. Ethical considerations, access to appropriate treatment..... 11

10. Administrative aspects and publication 13

11. References 14

12. Tables..... 17

13. Appendices 18

ACKNOWLEDGMENTS

The study is designed, and will be conducted, analyzed and interpreted by the investigators independently of all sponsors.

SUMMARY

RATIONALE AND AIM

After the last inclusion in the MR CLEAN trial there is a momentum in intra-arterial treatment for acute anterior circulation ischemic stroke in the Netherlands. The international guidelines and recommendations allowed intra-arterial treatment as a rescue treatment, but since early 2015, proof of a beneficial effect of intra-arterial treatment on functional outcome is available.

The purpose of the MR CLEAN-R: A post-trial Registry of the Multicenter Randomized Clinical trial of Intra-arterial treatment for acute ischemic stroke in the Netherlands is to monitor implementation and safety of the new intra-arterial treatment in a well-defined set of patients according to explicit criteria, comparable to the MR CLEAN trial population.

MR CLEAN-R is a multicenter registry. In the period following the last inclusion of the MR CLEAN trial this study will register all patients with acute ischemic stroke caused by proximal intracranial occlusion who undergo intra-arterial treatment.

STUDY POPULATION

All patients undergoing intra-arterial treatment for acute ischemic stroke will be registered. The core study population, however, will consist of patients with a clinical diagnosis of acute ischemic stroke, MRI or CT ruling out intracerebral hemorrhage, a score on the National Institutes of Health Stroke Scale (NIHSS) of 2 points or more, a relevant intracranial arterial occlusion, demonstrated by neuro-imaging and the possibility to start intra-arterial treatment within 6 hours after stroke onset. These patients constitute the core study population. Exclusion criteria that pertain to the inclusion in the core study population are similar to the MR CLEAN exclusion criteria. However, all patients undergoing intra-arterial treatment for acute ischemic stroke will be registered.

INTERVENTION

Intra-arterial treatment may consist of intra-arterial thrombolysis with urokinase or alteplase, mechanical treatment or both. Mechanical treatment refers to retraction or aspiration of the thrombus with a catheter guided device, including use of a retrievable stent. The exact choice of intra-arterial treatment modality for each patient is left to the discretion of the local investigator and treating physicians. The steering committee will provide recommendations and guidelines for treatment and selection of patients in the registry. These recommendations may be adjusted to new insights from published observational and controlled studies. Medical management will be delivered according to national standards and guidelines. It may include treatment with intravenous alteplase before inclusion in the registry.

MAIN STUDY OUTCOMES

The primary outcome is the score on the modified Rankin Scale (mRS) 90 days after inclusion in the study. Secondary outcomes are the National Institutes of Health Stroke Scale (NIHSS) score at 24-48 hours,

recanalization (TICI-score), infarct size at 2 days and the occurrence of major bleeding in the first 48 hours after inclusion.

BURDEN AND RISKS ASSOCIATED WITH PARTICIPATION.

All patients participating in the registry will undergo a second CT scan after 2 days, if clinically indicated. All patients will have an interview at three months. Patients undergoing intra-arterial treatment may need sedation or anesthesia and intubation during the procedure. Finally, intra-arterial treatment is associated with increased risk of intra-cerebral hemorrhage. The decision for intra-arterial treatment in a patient will be made by the treating physician on the basis of a professional estimate of the risk and benefits involved.

DISCUSSION

MR CLEAN-R is a post-trial registry of the MR CLEAN trial. Enrollment will start soon after the last inclusion in the MR CLEAN trial (March 17 2014) at least until the eventual start of the next randomized controlled trials. Estimated enrollment period will be April 2014 to at least April 2016. The expected number of registered patients is at least 500.

Key words: alteplase, intra-arterial treatment, acute ischemic stroke, post-trial cohort registry

1. INTRODUCTION AND RATIONALE

1.1 GENERAL INTRODUCTION

In Western Europe and the US, the annual incidence of ischemic stroke is 1-2 per 1000.^{1,2} Half of all patients with stroke die or remain severely disabled. Stroke is one of the major causes of death and the first cause of dependency in the western world. Treatment with intravenous (IV) alteplase, aiming at early reperfusion has been proven effective for these patients, when they are treated within 4.5 hours, and when there are no contra-indications.³⁻⁵ The absolute reduction in the chance of poor outcome in patients treated with IV alteplase within 3 hours from onset amounts to 10%; the number needed to treat is 10.⁶ For the patients treated within 3 to 4.5 hours, this effect is reduced to 7%, for a number needed to treat of 14.⁴

In general, the number of patients eligible for treatment with IV alteplase is limited because of the restricted time window and contra-indications for systemic administration of alteplase. In about 25% of the patients with acute ischemic stroke, symptoms are caused by a proximal occlusion of one of the major intracranial arteries, i.e. the distal intracranial internal carotid artery, the proximal segments of the middle cerebral artery and the anterior cerebral artery.⁷ The likelihood of a proximal intracranial occlusion increases with severity of the neurological deficit at presentation.⁸⁻¹⁰ The effect of IV alteplase in these patients with a symptomatic intracranial arterial occlusion is limited as treatment with IV alteplase leads to recanalization in up to 33% of treated patients only.¹¹ In those without recanalization, outcome is generally poor.^{12, 13}

1.2 EFFECTIVENESS AND SAFETY OF INTRA-ARTERIAL TREATMENT IN RECENT TRIALS

After the last inclusion in the MR CLEAN trial and the start of this Registry there was a momentum in intra-arterial treatment for acute anterior circulation ischemic stroke in the Netherlands. The international guidelines and recommendations allowed intra-arterial treatment as a rescue treatment. During inclusion of patients in this Registry, since early 2015, proof of a beneficial effect of intra-arterial treatment on functional outcome has become available.¹⁴⁻¹⁸ Since then guidelines worldwide have been updated, recommending intra-arterial treatment with stent retrievers as standard therapy in patients with neuro-imaging –confirmed intracranial large vessel occlusion confirmed.^{19, 20}

1.4 RATIONALE: NEED FOR A REGISTRY OF INTRA-ARTERIAL TREATMENT

The purpose of the MR CLEAN-R: A post-trial registry of the Multicenter Randomized Clinical trial of Intra-arterial treatment for acute ischemic stroke in the Netherlands is to monitor intra-arterial interventions for acute ischemic stroke, in order to assess the safety and outcome in clinical practice, in a well-defined set of patients, comparable to the MR CLEAN trial population.

2. OBJECTIVES

To study safety and functional outcome after intra-arterial treatment for acute ischemic stroke caused by thrombo-embolic intracranial occlusion in everyday practice. To identify associations of baseline clinical and neuro-imaging parameters with outcome and adverse events.

3. STUDY DESIGN

This a prospective multicenter registry. At least 17 large hospitals will register patients over a period of at least two years, starting in April 2014. Data of prospectively registered patients after this date, and of patients who died will be entered retrospectively into the database. Actual prospective enrollment will start in January 2015.

4. STUDY POPULATION

4.1 PATIENTS

All patients with acute ischemic stroke of the anterior or posterior circulation who are treated intra-arterial treatment will be registered and followed. Patients who have been included in Randomized Clinical trials will be registered but not data on intervention, clinical and long term follow-up will be entered into the database, in order to maintain the blind.

Patients meeting the inclusion and exclusion criteria as set out below will be entered in the core dataset.

4.2 REGISTRY INCLUSION & EXCLUSION CRITERIA

All patients who underwent IAT for acute ischemic stroke will be registered. We will create a core dataset of patients who conform to specific in- and exclusion criteria, similar to the MR CLEAN trial criteria.

INCLUSION CRITERIA FOR CORE DATA SET

- A clinical diagnosis of acute stroke, with a deficit on the NIH stroke scale of 2 points or more.
- CT or MRI scan ruling out intracranial hemorrhage.
- Intracranial proximal arterial occlusion of a cerebral artery, demonstrated with CTA, MRA or DSA.
- Treatment was started within 6 hours from onset.
- The patient was treated in a MR CLEAN center (list in appendix).
- Age 18 or over.

GENERAL EXCLUSION CRITERIA

- Arterial blood pressure > 185/110 mmHg.
- Blood glucose < 2.7 or > 22.2 mmol/L.
- IV treatment with thrombolytic therapy in a dose exceeding 0.9 mg/kg alteplase or 90 mg.
- IV treatment with thrombolytic therapy despite contra-indications, i.e. major surgery, gastrointestinal bleeding or urinary tract bleeding within the previous 2 weeks, or arterial puncture at a non-compressible site within the previous 7 days.

- Cerebral infarction in the distribution of the relevant occluded artery in the previous 6 weeks.

SPECIFIC EXCLUSION CRITERIA FOR INTENDED MECHANICAL THROMBECTOMY

- Laboratory evidence of coagulation abnormalities, i.e. platelet count $<40 \times 10^9/L$, APTT >50 sec or INR >3.0 .

SPECIFIC EXCLUSION CRITERIA FOR INTENDED INTRA-ARTERIAL THROMBOLYSIS

- History of intracerebral hemorrhage.
- Severe head injury (contusion) in the previous 4 weeks.
- Clinical or laboratory evidence of coagulation abnormalities, i.e. platelet count $<90 \times 10^9/L$, APTT >50 sec or INR >1.7 .
- Current treatment with oral thrombin antagonists, such as argatroban and dabigatran or treatment with oral selective Factor Xa inhibitors, such as rivaroxaban.

EXCLUSION FROM CORE DATA SET

- Violation of one of the preceding in- and exclusion criteria
- Treatment with device without approval of registry steering committee
- Insufficient experience (<5 procedures) with particular type of device
- Treatment in a non-MR CLEAN center.

4.3 PARTICIPATING CENTERS AND CENTER ELIGIBILITY

All centers that have participated in the MR CLEAN trial now participate in the MR CLEAN registry.

As the purpose of the registry is to include all patients had intra-arterial treatment since closure of the MR CLEAN trial, we will also register patients treated in other centers (appendix). These patients will be entered into the extended registry, while we are awaiting a formal procedure for recognition and certification of stroke-intervention centers.

4.4 SAMPLE SIZE

A size of 500 patients allows us to analyze association between outcome such as mRS, neurological deficits (NIHSS) and recanalization and clinical characteristics and imaging at baseline, as well as aspects of the intervention, in multivariable regression models with at most 10 covariates, with sufficient precision.

5. TREATMENT OF SUBJECTS

5.1 INTRA-ARTERIAL TREATMENT

Intra-arterial treatment will consist of arterial catheterization with a microcatheter to the level of occlusion and delivery of a thrombolytic agent and/ or mechanical thrombectomy. Both alteplase and

urokinase for intra-arterial thrombolysis are allowed into the trial, a dose of 1 mg alteplase is considered to be equivalent to 10.000-15.000 U urokinase.²¹ Mechanical treatment may consist of mechanical thrombectomy or thrombus aspiration.

6. METHODS

6.1 STUDY OUTCOMES

PRIMARY OUTCOME

The primary outcome is the score on the modified Rankin Scale at 90 days (Appendix 1).

SECONDARY OUTCOMES

IMAGING PARAMETERS

- Infarct size assessed by CT at 2 days, when available. This includes manual tracing of the infarct perimeter and semi-automated pixel thresholding.^{22, 23}
- Pre-treatment and post-treatment TICl-score assessed on DSA acquired intervention.

CLINICAL PARAMETERS

- NIHSS at 24-48 hours days or at discharge.

FUNCTIONAL OUTCOME

Functional outcome will be assessed by means of the modified Rankin Scale at 90 days, this is done routinely in our centers, as standard of care.

SAFETY PARAMETERS

Safety is an issue of concern, as the experience with the intervention, overall, and within the participating centers, is limited. Safety parameters include hemorrhagic complications, and short-term outcome (mortality, NIHSS at 24-48 hours). As we will make use of web-based data-entry, these data will be available on short notice.

The primary safety parameter will be neurologic deterioration within 24 hours from inclusion in the registry. Neurological deterioration is defined as any decline in NIHSS of 4 points or more. In these patients, urgent brain CT is mandatory. This serious adverse event will be further classified as due to intracranial hemorrhage, ischemia or other (undetermined) cause. A full list of serious adverse events is provided in Appendix 5.

6.2 BLINDING

Blinding refers to the assessment of outcome data without knowledge of baseline characteristics or treatment details. Results of neuroimaging will be assessed in a blinded manner, except for symptomatic side. Information on outcome at three months will be assessed as part of routine care.

6.3 STUDY PROCEDURES

BASELINE DATA OBTAINED AT ADMISSION

Clinical data, neuro-imaging data, data that might be related to treatment effect or to adverse events caused by the intervention, as well as several stroke risk factors, will be recorded in order to illustrate the representativeness of the study population (Table 1.1).

INCLUSION AND REGISTRATION

The registry office will be notified when a new patient is entered into the web-based database. Personal data will be sent to the registry office separately, through scrambled email.

FOLLOW-UP DATA

NIHSS scores at baseline and after 24-48 hours will be scored constructed from clinical data when missing. All patients will undergo CT or MR imaging at 2 days, if clinically indicated. Raw data will be forwarded to the trial office for blind evaluation. When there was no three month follow-up to determine mRS at three months, mRS score will be derived of discharge data or data from closed follow-up at another moment.²⁴

WITHDRAWAL

Patients can stop compliance with the registry at any time for any reason if they wish to do so without any consequences. **Every attempt will be made to complete follow-up in these patients. All patient data will be stored without identifying parameters.**

7. SAFETY REPORTING

7.1 SERIOUS ADVERSE EVENTS

A serious adverse event is any untoward medical occurrence or effect that can cause mortality, is life-threatening, requires prolonged hospitalization, or results in persistent significant disability.

Expected serious adverse events are neurologic deterioration, symptomatic intracranial hemorrhage, extracranial hemorrhage, technical complications or vascular damage at the target lesion such as perforation or dissection and mortality in the first week of stroke, aspiration pneumonia, and death from any cause until assessment of the 90-day follow-up.

A cumulative log will be kept of all serious adverse events. The executive committee will publish summary reports every 6 months.

8. STATISTICAL ANALYSES

Baseline characteristics and outcomes will be summarized by means of simple descriptive statistics. The main analysis of this study concerns the primary outcome at 90 days. Associations between baseline demographic and clinical characteristics and intervention details with the primary and secondary outcome will be analyzed. Associations are defined as the relative risk for improvement on the mRs and estimated as an odds ratio with ordinal logistic regression taking the whole range of the modified Rankin Scale (mRS) into account.²⁵ Similar associations of demographic and clinical characteristics and intervention details with secondary outcomes will be analyzed with standard statistical tests and multiple regression models to adjust for other prognostic factors.

9. ETHICAL CONSIDERATIONS, ACCESS TO APPROPRIATE TREATMENT

All patients will receive best medical treatment according to national and local guidelines and current insights. The decision to carry out the intervention will be made the local stroke team and investigators. The steering committee will issue recommendations with regard to treatment and medical management of the patients in the registry.

9.1 REGULATION STATEMENT

The registry will be conducted in accordance with the principles of the Declaration of Helsinki, as amended by the World Medical Association General Assembly in October 2008, and with the guidelines for Good Clinical Practice.

9.2 RECRUITMENT AND CONSENT

All patients will be provided with a written explanation of the study. The patients or their representatives will be given the opportunity to refuse participation. In that case all data will be deleted from the database and clinical material will be destroyed.

This registry makes use of “waste material” only, such as blood aspirated during intervention and retrieved thrombi. No additional blood will be drawn. However, substudies may require additional activities, for which separate written informed consent will have to be obtained.

Data of patients who died before they were asked for consent and data of patients who were recruited retrospectively since April 2014 will be entered anonymously in the study base. Patient material and data will be stored anonymously.

The study physician will inform the patient orally and in writing. In case the patient is legally incompetent, for example because of aphasia or anosognosia, the information will be given to a legal representative. Because the study physicians are also involved in the clinical care of patients with acute ischemic stroke, it appears inevitable that in some occasions the study physician and treating physician will be the same person.

9.3 BURDENS TO THE PATIENT

All patients will undergo an additional CT scan after 2 days to assess infarct size, if clinically indicated. Radiation exposure for this CT scan is 2.1-2.3 mSV (milliSievert).²⁶

Patients may be asked to participate in substudies (see section 10.2). Also, during the intervention aspirated blood may be kept and stored, as well as the thrombo-embolic material which is retrieved from the retraction devices (THRAPS substudy).

10. ADMINISTRATIVE ASPECTS AND PUBLICATION

10.1 PRIVACY

All included patients will be assigned a unique number. Name and address will be stored separately from the study data. The study physician will inform the patient orally and in writing. The information describes the purpose of the study, interventions, potential hazards and benefits and the procedures for recording of clinical information and three month follow up.

10.2 SUBSTUDIES

Within the framework of the MR CLEAN-R, several observational substudies are carried out. They were also active within the framework of the MR CLEAN trial itself. They will be summarized below. For each substudy the patients' written consent will be asked. For a full description of the study procedures see the appendices with study protocols.

THRAPS

THRAPS is an observational study of the thrombo-emboli and aspirate blood (waste material) that is retrieved during the intervention. We will relate histopathologic parameters with the effect of the procedure (recanalization, no reflow and functional recovery).

CLOT-MR CLEAN

The CLOT-MR CLEAN is a study on long term follow-up and cost-effectiveness of endovascular treatment for acute ischemic stroke. During a two-year period data on costs as well as clinical outcome will be assessed. The primary outcome parameters are the costs per patient without poor outcome on the modified Rankin Scale (mRS) and the costs per quality-adjusted life year (QALY). For the long-term clinical effect of endovascular treatment the mRs will be used as well as occurrence of recurrent strokes and mortality.

10.3 PUBLICATION POLICY

The writing committee for the main publication consists of members of the executive committee. Publication of the main study results, substudies described in this protocol and of future substudies will

be on behalf of the MR CLEAN-R investigators. All investigators will have the opportunity to read and comment on a manuscript before it will be submitted for publication.

11. REFERENCES

1. 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;13:581-598
2. Vaartjes I VDS, Peters RGJ, Bots ML. Hart en vaatziekten in nederland naar geslacht. In: Vaartjes i, van dis sj, peters rjg, bots ml, editors. Hart- en vaatziekten in nederland 2008. Cijfers over ziekte en sterfte nederlandse hartstichting. . *Den Haag: Nederlandse Hartstichting; 2008.* .
3. Tissue plasminogen activator for acute ischemic stroke. The national institute of neurological disorders and stroke rt-pa stroke study group. *N Engl J Med.* 1995;333:1581-1587
4. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med.* 2008;359:1317-1329
5. Wardlaw JM, Murray V, Berge E, Del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev.* 2009:CD000213

6. Wardlaw JM, Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev.* 2003;CD000213
7. Weimar C, Goertler M, Harms L, Diener HC. Distribution and outcome of symptomatic stenoses and occlusions in patients with acute cerebral ischemia. *Arch Neurol.* 2006;63:1287-1291
8. Derex L, Nighoghossian N, Hermier M, Adeleine P, Froment JC, Trouillas P. Early detection of cerebral arterial occlusion on magnetic resonance angiography: Predictive value of the baseline nihss score and impact on neurological outcome. *Cerebrovasc Dis.* 2002;13:225-229
9. Fischer U, Arnold M, Nedeltchev K, Brekenfeld C, Ballinari P, Remonda L, et al. Nihss score and arteriographic findings in acute ischemic stroke. *Stroke.* 2005;36:2121-2125
10. Maas MB, Furie KL, Lev MH, Ay H, Singhal AB, Greer DM, et al. National institutes of health stroke scale score is poorly predictive of proximal occlusion in acute cerebral ischemia. *Stroke.* 2009;40:2988-2993
11. Alexandrov AV. Ultrasound enhanced thrombolysis for stroke. *Int J Stroke.* 2006;1:26-29
12. Christou I, Burgin WS, Alexandrov AV, Grotta JC. Arterial status after intravenous tpa therapy for ischaemic stroke. A need for further interventions. *Int Angiol.* 2001;20:208-213
13. Janjua N, Brisman JL. Endovascular treatment of acute ischaemic stroke. *Lancet Neurol.* 2007;6:1086-1093
14. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-pa vs. T-pa alone in stroke. *N Engl J Med.* 2015;372:2285-2295
15. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med.* 2015;372:2296-2306
16. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med.* 2015;372:1019-1030
17. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med.* 2015;372:1009-1018
18. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med.* 2015;372:11-20
19. Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, 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;46:3020-3035
20. Casaubon LK, Boulanger JM, Blacquièrè D, Boucher S, Brown K, Goddard T, et al. Canadian stroke best practice recommendations: Hyperacute stroke care guidelines, update 2015. *Int J Stroke.* 2015;10:924-940
21. Arnold M, Schroth G, Nedeltchev K, Loher T, Remonda L, Stepper F, et al. Intra-arterial thrombolysis in 100 patients with acute stroke due to middle cerebral artery occlusion. *Stroke.* 2002;33:1828-1833

22. van der Worp HB, Claus SP, Bar PR, Ramos LM, Algra A, van Gijn J, et al. Reproducibility of measurements of cerebral infarct volume on ct scans. *Stroke*. 2001;32:424-430
23. Gavin CM, Smith CJ, Emsley HC, Hughes DG, Turnbull IW, Vail A, et al. Reliability of a semi-automated technique of cerebral infarct volume measurement with ct. *Cerebrovasc Dis*. 2004;18:220-226
24. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19:604-607
25. Murray GD, Barer D, Choi S, Fernandes H, Gregson B, Lees KR, et al. Design and analysis of phase iii trials with ordered outcome scales: The concept of the sliding dichotomy. *J Neurotrauma*. 2005;22:511-517
26. Mettler FA, Jr., Huda W, Yoshizumi TT, Mahesh M. Effective doses in radiology and diagnostic nuclear medicine: A catalog. *Radiology*. 2008;248:254-263

12. TABLES

1.1 Baseline characteristics	
Demographics	Age, gender
Clinical	NIHSS, NIHSS supplemental motor score, pre-stroke mRs, blood pressure, GCS, weight, height, body temperature.
Medical history	Previous stroke, previous MI, PAD, diabetes mellitus
Medication	Antiplatelet agents, coumarines, heparin(oids), oral thrombin antagonists and

	oral factor Xa inhibitors., statines
Vascular risk factors	Hypertension, atrial fibrillation, diabetes mellitus, smoking, hypercholesterolemia
Laboratory parameters	INR, kreatinine, GFR (Cockcroft-Gault), serum glucose, CRP.
Neuroimaging	Thin slice and standard unenhanced: location, ASPECTS score, hemorrhagic transformation (NINDS/ECASS classification), hyperdense artery sign.
Treatment	Intended mode of endovascular treatment

1. STUDY PARAMETERS

1.2 Follow-up	
Treatment	Pre- and post intervention TICI-score, duration of procedure, actual mode of treatment
Clinical assessment at 24-48 hours	Clinical status, NIH Stroke Scale, NIHS supplemental motor scale
Neuro-imaging at 2 days (if clinically indicated)	Plain CT: location, ASPECTS score, hemorrhagic transformation (NINDS/ECASS classification), hyperdense artery sign.
Clinical assessment at 90 days	Modified Rankin Scale
Serious adverse events	See appendix 5

13. APPENDICES

1. MODIFIED RANKIN SCALE (MRS)

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	Dead	Death

2. STUDY PERSONNEL

Principal investigators:

Diederik WJ Dippel, neurologist Erasmus MC

University Medical Center Rotterdam,

PO Box 2040; 3000 CA Rotterdam, The Netherlands

Tel: +31 10 7043979

d.dippel@erasmusmc.nl.

Charles BLM Majoie, neuroradiologist AMC

Academic Medical Center Amsterdam

PO box 22660; 1100 DD Amsterdam, The Netherlands

Tel: +31 20 5669111

C.B.Majoie@amc.uva.nl

Coordinating investigators:

Ivo Jansen, MD, AMC Amsterdam

Maxim Mulder, MD, Erasmus MC Rotterdam

Executive committee:

Yvo Roos, neurologist, AMC Amsterdam

Aad van der Lugt, radiologist, Erasmus MC Rotterdam

Robert van Oostenbrugge, neurologist, Maastricht UMC

Wim van Zwam, interventional radiologist, Maastricht UMC

3. PARTICIPATING MR CLEAN INTERVENTION CENTERS

1. Erasmus MC Rotterdam

2. Amsterdam Medical Center
3. Maastricht Medical Center
4. UMC Utrecht
5. LUMC Leiden
6. UMC Nijmegen
7. Haaglanden Ziekenhuis Den Haag
8. Haga Ziekenhuis Den Haag
9. UMC Groningen
10. St. Elisabeth Ziekenhuis Tilburg
11. Isala klinieken Zwolle
12. Catharina Ziekenhuis Eindhoven
13. St. Antonius Nieuwegein
14. Rijnstate Ziekenhuis Arnhem
15. Medisch Spectrum Twente
16. Atrium Heerlen (close collaboration with Maastricht Medical Center)
17. Reinier de Graaf Groep Delft (close collaboration with Haga Ziekenhuis Den Haag)

OTHER PARTICIPATING CENTERS

1. Albert Schweitzer Ziekenhuis, Dordrecht
2. Amphia Ziekenhuis, Breda
3. Canisius-Wilhelmina Ziekenhuis, Nijmegen

4. PARTICIPATING NON-INTERVENTION CENTERS

1. VU Medisch Centrum Amsterdam
2. St. Lucas Andreas Ziekenhuis Amsterdam

5. ADVERSE EVENTS

1. Neurological deterioration
2. Symptomatic intracranial hemorrhage
3. Extracranial hemorrhage requiring surgery or blood transfusion

4. Technical complications at the target lesion such as perforation or dissection
5. Aspiration pneumonia and other infections, deep venous thrombosis and pulmonary embolism
6. Allergic reaction towards contrast fluid
7. Death from any cause within the registry period

An adverse event is considered serious when it causes mortality, is life-threatening, requires prolonged hospitalization, or results in persistent significant disability.

AMENDMENTS

AMENDMENT NO 1

February 15, 2016

Whole protocol: Barthel index and EQ5D are deleted from this protocol and not done in the Registry. Therefore every mention of this scores was deleted.

Page 1 the subtitle: "A multicenter registry of intra-arterial treatment for acute anterior circulation ischemic stroke" was changed into:

"A multicenter registry of intra-arterial treatment for circulation ischemic stroke"

At 'Authors' Maxim Mulder was added.

Page 4: we replaced of 'Rational and aim' the first paragraph "After the last inclusion in the MR CLEAN trial there is a momentum in intra-arterial treatment for acute anterior circulation ischemic stroke in the Netherlands. The international guidelines and recommendations allow intra-arterial treatment as a rescue treatment, but proof of a beneficial effect of intra-arterial treatment on functional outcome is not available. New approaches to treatment that make use of stent-retrievers however, show promising results. Until the results of trials that make use of these stent-retrievers are known, clinicians will be inclined to use these devices on selected patients, especially on those that do not respond to or have contraindications for treatment with intravenous thrombolytics." with:

"After the last inclusion in the MR CLEAN trial there is a momentum in intra-arterial treatment for acute anterior circulation ischemic stroke in the Netherlands. The international guidelines and recommendations allowed intra-arterial treatment as a rescue treatment, but since early 2015, proof of a beneficial effect of intra-arterial treatment on functional outcome is available.¹⁴⁻¹⁸"

Furthermore on this page in the section 'study population' we changed "anterior circulation stroke" in "acute ischemic stroke" in both the first and last sentence.

Furthermore on this page under section 'intervention' we changed the second sentence of this paragraph by deleting "or stenting" and adding: ",including use of a retrievable stent"

Page 5: in the 'burden and risks associated with participation' we deleted "telephone" in the second sentence.

Furthermore in the ‘discussion section’ we changed the paragraph:

“MR CLEAN-R is a post-trial registry of the MR CLEAN trial. Enrollment will start soon after the last inclusion in the MR CLEAN trial (March 17 2014) until the eventual start of the next randomized controlled trial. Estimated enrollment period will be April 2014 to April 2016. The expected number of registered patients is at least 500.” into:

““MR CLEAN-R is a post-trial registry of the MR CLEAN trial. Enrollment will start soon after the last inclusion in the MR CLEAN trial (March 17 2014) at least until the eventual start of the next randomized controlled trials. Estimated enrollment period will be April 2014 to at least April 2016. The expected number of registered patients is at least 500.””

Page 6: the second paragraph of section ‘1.1 general introduction’ the seconde sentence “anterior circulation” was deleted.

the text of section ‘1.2 Effectiveness and safety of intra-arterial treatment trials’ was completely replaced by:

“After the last inclusion in the MR CLEAN trial and the start of this Registry there was a momentum in intra-arterial treatment for acute anterior circulation ischemic stroke in the Netherlands. The international guidelines and recommendations allowed intra-arterial treatment as a rescue treatment. During inclusion of patients in this Registry, since early 2015, proof of a beneficial effect of intra-arterial treatment on functional outcome has become available.¹⁴⁻¹⁸ Since then guidelines worldwide have been updated, recommending intra-arterial treatment with stent retrievers as standard therapy in patients with neuro-imaging –confirmed intracranial large vessel occlusion confirmed.^{19, 20”}

Page 6: in the section ‘1.3 Rationale: need for a registry of intra-arterial treatment’ the first paragraph was deleted. In the second paragraph “anterior circulation” was deleted.

Page 7, section ‘2.objectives’ we chanced the last sentence: “To identify associations of baseline clinical parameters with outcome and adverse events.” Into:

“To identify associations of baseline clinical and neuro-imaging parameters with outcome and adverse events.”

Furthermore we replaced the text of section 3 “This a prospective collected multicenter registry. At least 10 large hospitals will register patients over a period of at most two years, starting in April 2014. For the period of April 2014 through December 2014, data of prospectively registered patients in this period, and of patients who died before consent could be given will be entered retrospectively into the database. Actual prospective enrollment will start in January 2015.” with:

“This a prospective multicenter registry. At least 17 large hospitals will register patients over a period of at least two years, starting in April 2014. Data of prospectively registered patients after this date, and of patients who died will be entered retrospectively into the database. Actual prospective enrollment will start in January 2015.”

Section ‘4.1 patients’ we changed the first paragraph: “All patients with acute ischemic stroke of the anterior circulation who are treated intra-arterial treatment will be registered and followed.” Into:

“All patients with acute ischemic stroke of the anterior or posterior circulation who are treated intra-arterial treatment will be registered and followed. Patients who have been included in Randomized Clinical trials will be registered but not data on intervention, clinical and long term follow-up will be entered into the database, in order to maintain the blind.”

Page 8: in section ‘4.2 Registry inclusion and exclusion criteria’ we added the following sentence as begin: “All patients who underwent IAT for acute ischemic stroke will be registered. We will create a core dataset of patients who conform to specific in- and exclusion criteria, similar to the MR CLEAN trial criteria.”

We added the following to the inclusion criterion under section 4.2

- The patient was treated in a MR CLEAN center (list in appendix).

We added the following under exclusion from core data set, under section 4.2:

- Treatment in a non-MR CLEAN center.

Section ‘4.3 participating centers and center eligibility’ the total text was deleted and replaced by:

“All centers that have participated in the MR CLEAN trial now participate in the MR CLEAN registry.

As the purpose of the registry is to include all patients had intra-arterial treatment since closure of the MR CLEAN trial, we will also register patients treated in other centers (appendix). These patients will be entered into the extended registry, while we are awaiting a formal procedure for recognition and certification of stroke-intervention centers.”

Page 10: the section ‘Functional outcome’ was deleted and replaced by:

“Functional outcome will be assessed by means of the modified Rankin Scale at 90 days, this is done routinely in our centers, as standard of care.”

At section ‘6.2 Blinding’ the following changes were made:

Second sentence was deleted and the following sentence was added at the end:

“Information on outcome at three months will be assessed as part of routine care.”

Page 11: section ‘Follow-up data’ the next changes were made to the first paragraph:

Following sentence was added at the beginning: “NIHSS scores at baseline and after 24-48 hours will be scored constructed from clinical data when missing.”

And the last sentence was deleted and replaced by:

“When there was no three month follow-up to determine mRS at three months, mRS score will be derived of discharge data or data from closed follow-up at another moment.”

The second paragraph was deleted.

Page 12: The first paragraph on “recruitment and consent” (9.2) which reads as follows:

“Written informed consent will be obtained from all patients who have been prospectively recruited and a copy will be retained by the including centre and forwarded to the central trial office. All patients will be provided with a written explanation of the study. Because the treatment decision will be a clinical one informed consent for study participation and follow-up will be asked within 48 hours, before any study activity is undertaken. Any material (blood) and information that is taken from a patient who does not give consent for participation will be destroyed. This procedure has the advantage that no avoidable delays occur prior to the intervention.”

Was replaced with:

“All patients will be provided with a written explanation of the study. The patients or their representatives will be given the opportunity to refuse participation. In that case all data will be deleted from the database and clinical material will be destroyed.

This registry makes use of “waste material” only, such as blood aspirated during intervention and retrieved thrombi. No additional blood will be drawn. However, substudies may require additional activities, for which separate written informed consent will have to be obtained.”

We replaced the following sentence “Data of patients who died before they were asked for consent and data of patients who were recruited in the period April to December 2014 will be entered anonymously in the study base. “ with:

“Data of patients who died before they could be provided with information about the study and data of patients who were recruited retrospectively since April 2014 will be entered anonymously in the study base. Patient material and data will be stored anonymously.”

The first sentence of the last paragraph of section 9.2 is not applicable anymore and therefore the following text was deleted:

“After approval by the patient or his/her legal representative, the patient’s treating physician will inform a study physician of the presence of a patient with acute ischemic stroke who is potentially eligible for the present study.”

The following part of the last paragraph of 9.2 which reads:

“The study physician will inform the patient orally and in writing and will obtain his/her written informed consent. In case the patient is legally incompetent, for example because of aphasia or anosognosia, written informed consent will be obtained from a legal representative. Because the study physicians are also involved in the clinical care of patients with acute ischemic stroke, it appears inevitable that in some occasions the study physician and treating physician will be the same person.”,

was replaced by:

“The study physician will inform the patient orally and in writing. In case the patient is legally incompetent, for example because of aphasia or anosognosia, the information will be given to a legal representative. Because the study physicians are also involved in the clinical care of patients with acute

ischemic stroke, it appears inevitable that in some occasions the study physician and treating physician will be the same person.”

Page 13: the second sentence in “privacy” (9.2) which reads as follows:

“Consent with participation in the study will be asked from all patients after presenting them with standard written forms.”

Was replaced with:

“The study physician will inform the patient orally and in writing.”

Page 13: the first sentence of the second paragraph in “substudies” (10.2) with subheading “THRAPS” which reads as follows:

“THRAPS is an observational study of the thrombo-emboli and aspirate blood that is retrieved during the intervention.”

Was replaced by:

“THRAPS is an observational study of the thrombo-emboli and aspirate blood (waste material) that is retrieved during the intervention.”

Page 16: section coordinating investigators: “Maxim Mulder, MD, Erasmus MC Rotterdam” was added.

Page 17 section title of appendix 3. “participating intervention centres” was changed into:

“participating MR CLEAN intervention centres”

Furthermore the following was added to this section:

“other participating centers

1. Albert Schweitzer Ziekenhuis, Dordrecht
2. Amphia Ziekenhuis, Breda
3. Canisius-Wilhelmina Ziekenhuis, Nijmegen”

AMENDMENT NO 2

Februari 15, 2016

According to the changes in study protocol, we changed our “Patiëntinformatieformulier”.

The footer of every page which reads: “Patiëntinformatie – en toestemmingsformulier MR CLEAN-R, versie 2.2, 27-08-2014 PIF_REGISTRY_v2.2_trk.doc” was changed into

“Patiëntinformatie formulier MR CLEAN-R, versie 2.3, 5 januari 2015 PIF_REGISTRY_v2.3.doc”

Page 2 under “4. Wat wordt er van u verwacht?” we changed the sentence under subheading “1-2 dagen na de behandeling”, which reads as follows: “Tijdens de intra-arteriële behandeling zal het bij u verwijderde stolsel, mits mogelijk, bewaard worden. Dit zal vervolgens verder worden onderzocht.”

Into: " Na 1 of 2 dagen is het mogelijk dat er een extra CT-scan van het hoofd gemaakt wordt."

Page 2 under "4. Wat wordt er van u verwacht?" we changed the part under subheading "3 maanden na behandeling". which reads as follows: 'Na 3 maanden zal telefonisch contact met u opgenomen worden, waarbij een kort interview over uw gezondheidstoestand op dat moment zal worden afgenomen.

Als uzelf niet goed in staat ben om het interview te ondergaan zullen we contact opnemen met uw contactpersoon, en zo nodig ook met de artsen en andere zorgmedewerkers die bij u betrokken zijn.

Het is daarnaast mogelijk dat we u in de toekomst willen benaderen voor vervolginterviews. Op het toestemmingsformulier kunt u aangeven of u dat goed vindt.

We vragen u alleen om toe te staan dat we uw gegevens gebruiken voor wetenschappelijk onderzoek. Dit gebeurt uiteraard anoniem. We willen graag uw toestemming om het stolsel dat is verwijderd uit uw slagader op te slaan voor onderzoek. Ook vragen we u dan of we nog een keer interview mogen afnemen, maar dat is niet verplicht."

Into: " Na 3 maanden zal zoals altijd door uw behandelend artsen contact met worden u opgenomen om uw gezondheidstoestand te beoordelen en de behandeling af te ronden. We vragen u alleen om toe te staan dat we uw gegevens gebruiken voor wetenschappelijk onderzoek. Dit gebeurt uiteraard anoniem. "

We changed page 2 "6. WAT ZIJN DE MOGELIJKE VOOR EN NADELEN VAN DEELNAME AAN HET ONDERZOEK?" into: "6.WAT ZIJN DE MOGELIJKE VOOR- EN NADELEN VAN DEELNAME AAN DIT ONDERZOEK?" for typographical reasons.

And after "6.WAT ZIJN DE MOGELIJKE VOOR- EN NADELEN VAN DEELNAME AAN DIT ONDERZOEK?" we changed the paragraph which reads as follows: "Er is een tijdsinvestering van enkele minuten omdat u na drie maanden telefonisch wordt geïnterviewd. Het voordeel is dat u bijdraagt aan nieuwe kennis over de behandeling van deze ernstige ziekte."

Into: "Er zijn geen nadelen of voordelen aan deelname verbonden. U krijgt altijd de voor u optimale behandeling."

On page 2 and 3 after " 7. Wat gebeurt er als u niet wenst deel te nemen aan dit onderzoek?" we changed the paragraph which reads as follows: "U beslist zelf of u meedoet aan het onderzoek. Deelname is vrijwillig. Als u besluit niet mee te doen, hoeft u verder niets te doen. U hoeft niets te tekenen. U hoeft ook niet te zeggen waarom u niet wilt meedoen. Als u patiënt bent, krijgt u gewoon de behandeling die u anders ook zou krijgen. Als u wel meedoet, kunt u zich altijd bedenken en toch stoppen. Ook tijdens het onderzoek."

Into: "U beslist zelf of u uw gegevens beschikbaar wilt stellen voor dit onderzoek. Deelname is vrijwillig. Als u dit niet wilt, kunt u dit mondeling bij uw behandelend arts, telefonisch, per email of schriftelijk aan ons mededelen. Zie hiervoor pagina 3 met contactgegevens. U hoeft ook niet te zeggen waarom u niet wilt meedoen. Als u patiënt bent, krijgt u gewoon de behandeling die u anders ook zou krijgen. Als u wel toestemming geeft, kunt u zich altijd bedenken en uw eerdere toestemming intrekken. Ook tijdens het onderzoek."

Page 3 after “ 8. WAT GEBEURT ER MET UW GEGEVENS?” we changed the part which reads as follows:
“Wij willen uw gegevens en lichaamsmateriaal bewaren. Want misschien kunnen we daar later een ander onderzoek mee uitvoeren. Als u dat niet wilt, respecteren wij dat natuurlijk. U kunt uw keuze op het toestemmingsformulier aangeven.

Vindt u het goed als wij uw gegevens/lichaamsmateriaal bewaren? Als het nieuwe onderzoek gaat beginnen, vragen wij u opnieuw om uw toestemming. U kunt dan nog beslissen of wij uw gegevens echt mogen gebruiken.

De gegevens zullen anoniem worden opgeslagen in een database en zullen vertrouwelijk worden behandeld. De tot uw persoon herleidbare gegevens kunnen slechts met uw toestemming door daartoe bevoegde personen worden ingezien. Deze personen zijn medewerkers van het onderzoeksteam, medewerkers van de inspectie voor de gezondheidszorg en leden van de medisch-ethische toetsingscommissie (METC) van het Erasmus MC.

De gegevens worden bewaard gedurende de gebruikelijke periode van 15 jaar. U dient hiervoor wel extra toestemming te geven via het bijbehorende toestemmingsformulier.”

Into: “Wij willen uw gegevens en lichaamsmateriaal bewaren. Want misschien kunnen we daar later een ander onderzoek mee uitvoeren. Als u dat niet wilt, respecteren wij dat natuurlijk.

De gegevens en het restmateriaal zullen anoniem worden opgeslagen in een database en zullen vertrouwelijk worden behandeld. De tot uw persoon herleidbare gegevens kunnen slechts worden ingezien door de onderzoeksleider en medewerkers van het onderzoeksteam, medewerkers van de inspectie voor de gezondheidszorg en leden van de medisch-ethische toetsingscommissie (METC) van het Erasmus MC.”

Page 3 and 4 after “11. WILT U VERDER NOG IETS WETEN?” under subheading “ Coördinatoren” we changed:

“COÖRDINATOREN

I. Jansen, arts-onderzoeker radiologie 010-7044206

Dr. D. Dippel, neuroloog 010-7043979”

Into:” Coördinatoren 06-48212353

I.G.H. Jansen, arts-onderzoeker radiologie

M.J.H.L. Mulder, arts-onderzoeker neurologie

Prof.dr. D.W.J. Dippel, neuroloog “

And: “ Wij danken u vriendelijk voor het lezen van deze informatie.

Hoogachtend,

I. Jansen, arts-onderzoeker radiologie

Dr. D. Dippel, neuroloog”

Into: “Wij danken u vriendelijk voor het lezen van deze informatie.

Hoogachtend,

I.G.H. Jansen, arts-onderzoeker radiologie

M.J.H.L. Mulder, arts-onderzoeker neurologie

Prof.dr. D.W.J. Dippel, neuroloog”

We deleted the final two pages (5 and 6) in total:

“ STUDIE NAAR HET EFFECT VAN INTRA-ARTERIËLE BEHANDELING OP DE GEZONDHEIDSTOESTAND BIJ EEN HERSENINFARCT

TOESTEMMINGSFORMULIER: VERSIE VOOR PATIËNT”

And: “ STUDIE NAAR HET EFFECT VAN INTRA-ARTERIËLE BEHANDELING OP DE GEZONDHEIDSTOESTAND BIJ EEN HERSENINFARCT

TOESTEMMINGSFORMULIER: VERSIE VOOR WETTELIJKE VERTEGENWOORDIGER”