

MR CLEAN-LATE

Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in The Netherlands for Late arrivals: MR CLEAN-LATE

RESEARCH PROTOCOL

Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in The Netherlands for Late arrivals: MR CLEAN-LATE

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PROTOCOL SIGNATURE SHEET



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TABLE OF CONTENTS

| | |
|---|----|
| ■ LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS | 11 |
| ■ SUMMARY | 13 |
| ■ 1. INTRODUCTION AND RATIONALE | 15 |
| ■ 2. STUDY DESIGN | 18 |
| ■ 3. STUDY POPULATION | 19 |
| 3.1 Population (base)..... | 19 |
| 3.2 Participating centers and center eligibility | 19 |
| 3.3 Inclusion criteria..... | 19 |
| 3.4 Exclusion criteria..... | 20 |
| ■ 4. TREATMENT OF SUBJECTS..... | 23 |
| 4.1 Interventional product/treatment..... | 23 |
| 4.2 Use of co-intervention (if applicable)..... | 23 |
| 4.3 Escape medication (if applicable)..... | 23 |
| ■ 5. INVESTIGATIONAL PRODUCT..... | 24 |
| 5.1 Name and description of investigational product(s)..... | 24 |
| 5.2 Summary of findings from non-clinical studies | 24 |
| 5.3 Summary of findings from clinical studies | 24 |
| 5.4 Summary of known and potential risks and benefits..... | 26 |
| 5.5 Description and justification of route of administration and dosage | 26 |
| 5.6 Dosages, dosage modifications and method of administration..... | 26 |
| 5.7 Preparation and labelling of Investigational Medicinal Product..... | 26 |
| 5.8 Drug accountability | 26 |
| ■ 6. NON-INVESTIGATIONAL PRODUCT..... | 27 |
| 6.1 Name and description of non-investigational product(s)..... | 27 |
| 6.2 Summary of findings from non-clinical studies | 27 |
| 6.3 Summary of findings from clinical studies | 27 |

| | | |
|----------|---|-----------|
| 6.4 | Summary of known and potential risks and benefits..... | 27 |
| 6.5 | Description and justification of route of administration and dosage | 27 |
| 6.6 | Dosages, dosage modifications and method of administration..... | 27 |
| 6.7 | Preparation and labelling of Non Investigational Medicinal Product | 27 |
| 6.8 | Drug accountability | 27 |
| ■ | 7. METHODS | 28 |
| 7.1 | Study outcomes | 28 |
| ■ | Primary outcome | 28 |
| ■ | Secondary outcomes | 28 |
| ■ | Safety endpoints | 28 |
| ■ | Other study parameters (if applicable) | 29 |
| 7.2 | Randomization, blinding and treatment allocation | 30 |
| 7.3 | Study procedures..... | 31 |
| 7.4 | Withdrawal of individual subjects | 32 |
| 7.5 | Specific criteria for withdrawal (if applicable)..... | 32 |
| 7.6 | Replacement of individual subjects after withdrawal | 32 |
| 7.7 | Follow-up of subjects withdrawn from treatment | 33 |
| ■ | 8. SAFETY REPORTING | 34 |
| 8.1 | Temporary halt for reasons of subject safety | 34 |
| 8.2 | AEs, SAEs and SUSARs | 34 |
| ■ | Adverse events (AEs) | 34 |
| ■ | Serious adverse events (SAEs) | 34 |
| ■ | Suspected unexpected serious adverse reactions (SUSARs) | 35 |
| 8.3 | Annual safety report..... | 35 |
| 8.4 | Follow-up of adverse events | 35 |
| 8.5 | Data Safety Monitoring Board (DSMB)..... | 35 |
| ■ | 9. STATISTICAL ANALYSIS | 37 |
| | Interim analysis (if applicable)..... | 38 |

| | |
|--|----|
| ■ 10. ETHICAL CONSIDERATIONS | 39 |
| 10.1 Regulation statement..... | 39 |
| 10.2 Recruitment and consent | 39 |
| 10.3 Objection by minors or incapacitated subjects (if applicable) | 41 |
| 10.4 Benefits and risks assessment, group relatedness | 41 |
| 10.5 Compensation for injury | 41 |
| 10.6 Incentives (if applicable) | 41 |
| ■ 11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION..... | 42 |
| 11.1 Handling and storage of data and documents..... | 42 |
| 11.2 Monitoring and Quality Assurance | 42 |
| 11.3 Amendments..... | 42 |
| 11.4 Annual progress report | 43 |
| 11.5 Temporary halt and (prematurely) end of study report | 43 |
| 11.6 Public disclosure and publication policy | 43 |
| ■ 12. STRUCTURED RISK ANALYSIS | 45 |
| 12.1 Potential issues of concern | 45 |
| 12.2 Synthesis | 46 |
| ■ 13. REFERENCES..... | 47 |
| ■ 14. TABLES | 49 |
| Table 1 Modified Rankin Scale | 49 |
| Table 2 Extended Treatment in Cerebral Ischemia (eTICI) scale..... | 50 |
| Table 3 NIH Stroke Scale..... | 51 |
| Table 4 Barthel Index..... | 58 |
| Table 5 EuroQoL 5D-5L..... | 60 |
| Table 6 Clot burden score for CTA and MRA..... | 62 |
| Table 7 ASPECTS | 63 |
| Table 8 Collateral score | 64 |
| Table 9 Medical Consumption and Productivity Cost Questionnaire | 65 |

Table 10 Medical Consumption and Productivity Cost Questionnaire: extended follow-up 75

| | |
|--|-----|
| ■ 15. FIGURES | 89 |
| Figure 1 MR CLEAN-LATE trial logo | 89 |
| Figure 2 Patient flow in the trial | 90 |
| ■ 16. APPENDICES | 91 |
| 16.1 Appendix 1 List of collaborating investigators..... | 91 |
| ■ Coordinating investigators | 91 |
| ■ Principal investigators | 91 |
| ■ Local investigators:..... | 91 |
| 16.2 Appendix 2 Study committees..... | 93 |
| ■ Data safety monitoring board | 93 |
| ■ Executive and writing committee | 93 |
| ■ Imaging assessment committee | 93 |
| ■ Outcome assessment committee | 94 |
| ■ Adverse event adjudication committee | 94 |
| ■ Trial statistician and methodologist..... | 94 |
| 16.3 Appendix 3 CONTRAST: collaboration for new treatments of acute stroke | 95 |
| ■ 16.3.1. CONTRAST Logo..... | 95 |
| ■ 16.3.2. Research leaders CONTRAST | 95 |
| ■ 16.3.3. Overall scientific summary CONTRAST | 95 |
| ■ 16.3.4 Patient flow and selection into the contrast trials | 96 |
| ■ 16.3.5 Common core data set MR CLEAN II trials..... | 98 |
| 16.4 Appendix 4 Schedule of study activities of the MR CLEAN II trials..... | 104 |
| 16.5 Appendix 5 Imaging requirements..... | 105 |
| ■ 16.5.1 Minimum baseline imaging requirements..... | 105 |
| ■ 16.5.2 Intervention-related angiographic imaging | 106 |
| ■ 16.5.3 Minimum follow-up imaging requirements..... | 108 |
| 16.6 Appendix 6 Trial organisation..... | 110 |

16.7 Appendix 7 Deferred consent in acute stroke trials112

■ 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 |
| CA | Competent Authority |
| CCMO | Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek |
| CV | Curriculum Vitae |
| DSMB | Data Safety Monitoring Board |
| EU | European Union |
| EudraCT | European drug regulatory affairs Clinical Trials |
| EVT | Endovascular thrombectomy |
| GCP | Good Clinical Practice |
| IAT | Intra-arterial Treatment |
| IB | Investigator's Brochure |
| IC | Informed Consent |
| ICH | Intracerebral Hemorrhage |
| IMP | Investigational Medicinal Product |
| IMPD | Investigational Medicinal Product Dossier |
| LATE-IAT | Intra-arterial Treatment in the LATE window (6-24h after last seen well or symptom onset). |

| | |
|---------|---|
| METC | Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC) |
| (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 organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation 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 subsidising party. |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| WBP | Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgegevens) |
| WMO | Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen) |

SUMMARY

Rationale: Endovascular thrombectomy (EVT) by means of retrievable stents in patients with acute ischemic stroke (AIS) in the anterior circulation with confirmed proximal intracranial occlusion, in whom the procedure can be started within 6 hours from onset, has been proven safe and effective.

Many patients present beyond the 6 hour time window. In the Netherlands up to 25% of AIS patients arrive in the hospital between 6 and 24 hours after symptom onset. Until recently no proven effective recanalization therapy was available for these patients.

This has changed recently as the DAWN and DEFUSE 3 trials published in 2017 and 2018, showed with convincing evidence that selected patients can benefit from EVT up to 24 hours, if they meet well-defined clinical and/or imaging criteria.

The Dawn trial included patients with an intracranial internal carotid artery occlusion/ M1 occlusion who presented with severe neurological deficit (NIHSS>10) in combination with a small infarct core on perfusion (CTP) or diffusion (MRI DWI) imaging. The DEFUSE 3 trial used similar inclusion criteria: NIHSS \geq 6 in combination with an infarct core of <70ml, but with additional minimal core-penumbra mismatch criteria on CTP or MRI. The clinical profile of patients who were actually included revealed even smaller infarct cores than maximally required and larger mismatch on CTP or MRI. Only a few patients who present in the late time window are expected to have this clinical and imaging profile. [Ref: Jadhav AP, Desai SM, Kenmuir CL, Rocha M, Starr MT, Molyneaux BJ, et al. Eligibility for endovascular trial enrollment in the 6- to 24-hour time window: Analysis of a single comprehensive stroke center. *Stroke*. 2018;49:1015-1017; DOI: 10.1161/STROKEAHA.117.020273] These patients need treatment urgently.

Because the effects in DAWN and DEFUSE were large, it is conceivable that patients with a somewhat less favorable profile may still benefit, but this remains to be proven. We hypothesize that presence of collateral flow into the ischemic area on CTA may be an adequate criterion for patient selection in the late time window.

In order to expand the indication for EVT beyond the 6 hour time interval using a widely available imaging modality, we aim to assess the effect of EVT compared to no EVT against a background of best medical treatment in patients with AIS caused by an intracranial large vessel occlusion of the anterior circulation, who have at least some collateral flow on CTA and who can be treated between 6 and 24 hours after symptom onset, or last seen well less than 24 hours before admission to the hospital (which also includes wake up strokes).

Objective: To assess the effect of EVT compared with best medical treatment in patients with AIS caused by an intracranial large vessel occlusion of the anterior circulation, who have at least some collateral flow on CTA and who can be treated between 6 and 24 hours after symptom onset or last seen well less than 24 hours before admission to the hospital (which also includes wake up strokes).

1. INTRODUCTION AND RATIONALE

In the Netherlands, as in many other countries, stroke is a major cause of death and a disabling disease. In the Netherlands (17 million inhabitants), each year more than 25,000 individuals are admitted to hospital because of stroke, and 8500 patients die because of stroke.¹ Currently, more than 200,000 persons are alive after a stroke and half of these are seriously disabled. For the European Union, with more than 500 million inhabitants, this translates into approximately 1 million new stroke cases per year.²

Early 2015, the outlook for treatment of acute stroke has changed dramatically. We now know that patients with AIS caused by proximal intracranial anterior circulation occlusion benefit from IAT. Early EVT 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 and later confirmed in 6 other trials.^{3,4-8} A recent pooled analysis of individual patient data of these 5 trials showed that EVT leads to an additional 20% of patients being functional independent 90 days after treatment.⁹

Since the publication of these results, EVT has become a novel acute treatment option for AIS. One of the major drawbacks is the limited time window in which the treatment has to be started: within 6 hours from symptom onset. As such, only a limited number of patients are currently eligible for IAT. Although the majority of the patients in the trials were treated within 6 hours from symptom onset, two of these trials included patients beyond the 6 hour window.^{4,5} In REVASCAT, patients could be treated up to 8 hours from symptom onset.⁴ The number of patients treated in the 6 – 8 hour time-window was too small to analyze effect of treatment in this specific time window. However, in a pre-specified subgroup analysis the effect was identical for those treated < 4.5 hours compared to those treated between 4.5 and 8 hours after symptom onset. In ESCAPE, high effectiveness of endovascular treatment was shown in a selected target population.⁵ This target population was selected on basis of imaging parameters as participants needed to have a small core infarct and moderate or good collateral flow in addition to a proven proximal intracranial anterior circulation occlusion. EVT had to be started within 12 hours after symptom onset. Although the majority of the participants were treated within 6 hours after symptom onset a small proportion was treated between 6 and 12 hours from symptom onset. The effect size in the late treated group was the same as in the early treated group. However, this predefined subgroup was too small to draw firm conclusions. The recently published randomized controlled trials DAWN and DEFUSE 3 showed significant benefit of EVT in the late time period (6-24 hours and 6-16 hours respectively since last seen well) when using selection based on clinical and imaging parameters. CT perfusion and diffusion MRI were used to select patients with a small infarct core in

combination with a relatively large penumbra (DEFUSE 3) or severe neurological deficit (DAWN). The imaging profile of patients who were actually included revealed even smaller infarct cores than maximally required and larger mismatch on CTP or MRI, see also paragraph 5.3. Whether late EVT treatment is beneficial for a larger group of patients, is not yet investigated.

Another way to assess possible viable brain tissue is by collateral flow on CTA. Collateral flow to an infarcted area can keep part of this area viable, but this viable area reduces with time due to decreasing collaterals.¹⁰ However, collateral status varies between individuals and it is plausible that patients with a preserved good collateral status even after 6 hours might still have sufficient viable tissue to benefit from IAT.

The MR CLEAN study was done in an unselected target population providing the opportunity to determine whether ASPECTS score and presence of collateral flow interacts with the effect of IAT.³ These analyses of the MR CLEAN trial have recently been published and showed that that collateral status is indeed associated with better outcome and shows a significant interaction with treatment effect. In patients with absent or poor collateral flow no effect of EVT treatment was seen whereas in patients with moderate and good collateral flow a significant effect of EVT was observed.¹¹ Contrary, infarct core size, determined by the ASPECTS score, did not modify the effect of IAT.¹² As such, it seems that the presence of collaterals is the only imaging criterion that indicates patients who will benefit from EVT and therefore can be an adequate tool to select patients with a potential treatment benefit beyond the 6 hour time window.

Earlier we demonstrated that in the Netherlands up to 25% of the patients with AIS arrive in the hospital between 6 and 12 hours after symptom onset.¹³ They constitute a substantial number of patients who might benefit from EVT when this imaging selection criterion is met. We hypothesize that IAT is not only effective for patients treated within 6 hours or beyond 6 hours based on perfusion/diffusion imaging but also for a larger group of patients who can be treated between 6 and 24 hours after symptom onset or last seen well less than 24 hours before admission to the hospital (including wake up strokes). Our proposed strategy is to use imaging defined grade of collateral flow for the selection of patients combined with existing endovascular treatment methods to optimize and personalize acute stroke treatment in the 6 - 24 hour window. We hypothesize that EVT combined with best medical treatment compared with best medical treatment alone in patients with AIS, caused by an intracranial large vessel occlusion of anterior circulation who have poor to good collaterals and who can be treated between 6 and 24 hours after symptom onset or last seen well less than 24 hours before admission (including wake up strokes) may lead to 10% absolute increase in good outcome.

The primary objective of this trial is to assess the effect of LATE-IAT with best medical treatment compared with best medical treatment alone on functional outcome in patients with AIS, caused by an intracranial large vessel occlusion of the anterior circulation and poor to good collaterals which are both confirmed by neuro-imaging.

The secondary objective is to assess the effect of LATE-IAT on neurological recovery (NIHSS), infarct size and occurrence of intracerebral hemorrhage.

The tertiary objectives are:

- 1) to collect waste biomaterials (thrombo-emboli, aspirate blood) and to analyze biochemical and biomechanical properties and 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.
- 3) to study the efficiency of national EVT implementation, given the availability of EVT 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 EVT organizational model.
- 4) to perform a treatment-interaction and threshold analysis with data obtained from cerebral CT-perfusion. We will assess if perfusion thresholds and collateral grades (scored on CT-angiography imaging) are associated with safety and clinical outcome in patients who underwent EVT 6-24h after last seen well or symptom onset (LATE-IAT). Thus, we aim to improve the selection of patients who are most likely to benefit from LATE-IAT.
- 5) to perform a cost-effectiveness and cost-utility analysis of the treatment under study. This will be complemented by a budget-impact analysis in order to estimate the financial consequences of the implementation of LATE-IAT.

■ 2. STUDY DESIGN

This is a multicenter phase III clinical trial with randomized treatment allocation, open label treatment and blinded endpoint evaluation (PROBE design). The intervention contrast is EVT versus no EVT. The treatment is provided in addition to best medical management. The study will run for 4 years in Stroke intervention centers in The Netherlands, and will be carried out by members of CONTRAST (Consortium 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 consortium (Flow Chart, appendix of the protocol, page 66). An overview of the Study and the main procedures that subjects will undergo is provided in Figure 2.

■ 3. STUDY POPULATION

3.1 Population (base)

In the Netherlands, the incidence of hospital-admitted AIS is 1.2 per 1000, for a total in excess of 20,000 annually.¹ The study population will be drawn from patients with AIS who enter the ER of the intervention center and their referring regional centers.

Intervention and referring centers admit 300 to 600 acute ischemic stroke patients annually. The intervention centers perform 50-150 IATs annually. The number of intra-arterial interventions for acute ischemic stroke in the Netherlands is rapidly increasing, from 200 in 2014 to more than 800 in 2015, and more than 1000 patients in 2016.

3.2 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

- o the center should have experience in conducting acute stroke trials,
- o 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,
- o the stroke team (which includes neurologists and interventionists) should have sufficient experience with intra-arterial treatment,
- o the intervention team should make use of one or more of the devices that have been approved by the trial steering committee. Other devices are not allowed into the trial,
- o 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.

3.3 Inclusion criteria

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

- o clinical diagnosis of Acute Ischemic Stroke,

- caused by proximal intracranial anterior circulation occlusion (distal intracranial carotid artery or middle (M1/M2)) cerebral artery confirmed by neuro-imaging (CTA or MRA),
- and presence of poor*, moderate or good collateral flow as shown by neuro-imaging (CTA)
- CT or MRI ruling out intracranial hemorrhage,
- Start of IA treatment (groin puncture) possible between 6 and 24 hours after symptom onset or last seen well < 24 hours including wake-up strokes,
- a score of at least 2 on the NIH Stroke Scale
- age of 18 years or older
- written informed consent (deferred).

* Inclusion and randomization will be restricted to patients with moderate or good collaterals when 100 patients with poor collaterals have been included in the study.

3.4 Exclusion criteria

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

- Distal intracranial carotid artery occlusion/M1 occlusion, NIHSS ≥ 10 , infarct core ≤ 25 ml and a mismatch ratio total ischemic volume/ infarct core ≥ 2 (patient is eligible for direct EVT treatment, based on DAWN/DEFUSE 3 patient profile)*
- Pre-stroke disability which interferes with the assessment of functional outcome at 90 days, i.e. mRS > 2 cerebral infarction in the previous 6 weeks with residual neurological deficit or signs of large recent infarction on neuroimaging in the territory of the middle cerebral artery
- Clinical evidence of hemorrhagic diathesis, confirmed by an INR > 3 and/or a platelet count $< 40 \times 10^9/L$ and/or an APTT > 50 sec. In case there is no clinical indication to test for hemorrhagic diathesis, it may be assumed that the INR, APTT and platelet count are within these limits.**
- Clearly demarcated hypodensity in $> 1/3$ of the middle cerebral artery territory, consistent with current symptoms
- participation in medical or surgical intervention trials other than current (or MR ASAP and ARTEMIS)

* Calculation of volumes are automatically generated by locally available Software (e.g. Siemens or Philips) . We recommend to use the standard settings for volume analysis.

*** The clinical indications for assessment of INR, platelet count and APTT for patients included in the trial do not differ from those used in routine clinical practice.*

Inclusion in other medical or surgical 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/>) 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. Sample size calculation We estimated that a sample size of 500 patients would provide a power of 85% with two sided alpha 0.05, using simulation with 5000 runs per assumed sample in R. ³

For the power calculations we assume the distribution over the 7-point modified Rankin Scale (mRS) in the control group which is similar to the distribution of mRS in the control group of the MR CLEAN trial:³ mRS 0: 0%; mRS 1: 6%; mRS 2 13%; mRS 3 16%; mRS 4: 30%; mRS 5: 12%; mRS 6: 22%. We assume a favorable effect of treatment with a common odds ratio of 1.52, which would lead to an 7% absolute increase in the proportion of patients with mRS 0-2. The aim is to include 500 patients. In the analysis covariate adjustment will be used, which reduces the required sample size by approximately 25%.^{14,15} In a simulation with 5000 runs we computed the proportion of positive trials, for a given sample size.¹ The corresponding effective sample size was 670, providing 84% power to detect a true treatment effect (two-sided $\alpha=0.05$).

Our sample size is sufficient to assess the effect of the intervention on secondary endpoints. Analysis of a meaningful reduction on NIH stroke scale at one week of 3-4 points (Cohen's $d=0.33$) would require a sample of 400 patients, assuming that at 24-48 hours mean NIH would be 12, with a standard deviation of 10. A doubling of the recanalization rate from 30% to 60% would require 126 patients to achieve a power of 0.90.

¹ <https://www.r-bloggers.com/simulation-based-power-analysis-using-proportional-odds-logistic-regression/>

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The sample size is realistic and feasible. In The Netherlands, 25% of ischemic stroke patients arrive after 6 hours in an hospital. Based on the experiences in MR CLEAN we expect that one in 5 will have a proximal intracranial occlusion and more than half of these have poor-good collaterals. This means that in the 16 participating centers yearly 1000 patients will be eligible for this study. In case 1:4 of them fulfills the imaging selection criteria (which seems a reasonable assumption based on the ESCAPE trial) and half of these will give inform consent to participate in the study we will reach 500 patients in 4 years.

■ 4. TREATMENT OF SUBJECTS

4.1 Interventional product/treatment

All medical devices for thrombectomy, which are CE marked or FDA approved for this purpose, and have been approved for the use in the study by the steering committee are allowed in the trial.

4.2 Use of co-intervention (if applicable)

4.3 Escape medication (if applicable)

If deemed indicated by the interventionist, local application of maximum dosages of alteplase (30mg), urokinase (1,200,000IU) or abciximab (20mg) is allowed in the intervention group.

5. INVESTIGATIONAL PRODUCT

5.1 Name and description of investigational product(s)

The devices allowed in the trial are retrievable stents and other mechanical devices.

| Device name | Manufacturer | Description |
|-----------------------------|----------------------|----------------------------|
| Solitaire | Medtronic / Covidien | Retrievable stent |
| Trevo | Stryker | Retrievable stent |
| Revive | Codman/DePuy-Synthes | Retrievable stent |
| Catch | Balt | Retrievable stent |
| Embotrap | Neuravi | Retrievable stent |
| Eric | Microvention | Retrievable stent |
| PreSet | Phenox | Retrievable stent |
| 3D Separator | Penumbra | Retrievable stent |
| Penumbra system | Penumbra | Aspiration catheter system |
| Sofia | Microvention | Aspiration catheter |
| Catalyst | Stryker | Aspiration catheter |
| NeVa stent retriever | Vesalio | Retrievable stent |

5.2 Summary of findings from non-clinical studies

This is not relevant, as all medical devices are CE marked and or FDA approved for clinical use as intended.

5.3 Summary of findings from clinical studies

Eight randomized clinical trials using predominantly stent-retrievers have been carried out and published in 2015 and 2016.^{3-8, 24} 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. The treatment is already established as standard of

care. However, few patients were treated outside the 6-hour time window (11% of patients in the pooled analysis of five published trials). In ESCAPE, 15.5% (49/315) of the study population was treated within the 6 – 12 hour time-window. The effect size in the late treated group was the same as in the early treated group (< 6 hours). No interaction was found with the overall highly positive treatment effect, but the effect is not certain and the estimate not precise.

REVASCAT showed comparable effect of EVT in patients treated early (4.5 hours) versus late (> 4.5 hours). No interaction was found between effect of treatment and time of treatment. However, the numbers of patients treated in the 4.5 to 8 hour time-window was small (35/206 = 17%).

DAWN and DEFUSE 3 were the first randomized controlled trials for EVT treatment in the late time period. DAWN was a randomized, open label trial of EVT versus no intervention in 206 patients with occlusion of the intracranial internal carotid artery or proximal middle cerebral artery who had last been known to be well 6 to 24 hours earlier and who had a mismatch between the severity of the clinical deficit and the infarct core volume, with mismatch criteria defined according to age (<80 years or ≥80 years). In total, 52 of 107 patients (49%) allocated intervention were independent (mRS 0 to 2) versus 13 of 99 (13%) in the control group, with an absolute risk difference of 36 (95% CI 24-47%).

Similar to DAWN, DEFUSE 3 was a randomized open label trial of EVT versus no EVT in patients 6 to 16 hours after they were last known to be well and who had remaining ischemic brain tissue that was not yet infarcted. Patients with proximal middle-cerebral-artery or internal-carotid-artery occlusion were included when they had an initial infarct size of less than 70 ml, and a ratio of the volume of ischemic tissue on perfusion imaging to infarct core volume of 1.8 or more.

However, in DAWN the median core size at baseline was 8 cc, and 75% of patients had a core infarct size of 18 cc or less. In DEFUSE 3 comparable small infarct volumes were noticed at baseline; median core size was 10cc, and 75% of patients had a core infarct size of 25 or less, with a relatively large penumbra of 80cc or more. Furthermore, in both trials the median NIHSS at baseline was relatively high (16/17), and in DEFUSE 3 75% of the enrolled patients had a NIHSS of 10 and higher.

Because the effects in DAWN and DEFUSE 3 were large, it is conceivable that patients with a somewhat less favorable profile may still benefit, but this remains to be proven, Sample size of both trials was not sufficient to estimate effects in subgroups with sufficient precision. This is the reason why we based the exclusion criteria that lead to

direct treatment instead of inclusion in the trial on the actual clinical and imaging profile of the patients in DAWN and DEFUSE 3 (see exclusion criteria, paragraph 3.4).

5.4 Summary of known and potential risks and benefits

The potential benefits of the intervention are described in 10.4. The potential risks consist of intracranial and extracranial hemorrhage and hemorrhagic infarction, procedure related risks such as dissection, perforation and infarctions in other vascular territories, and postprocedural events such as infections. In the 5 previous trials, the risks of hemorrhage and hemorrhagic infarction were equal for both the intervention and the control group. Postprocedural events such as pneumonia and other infections occurred in similar frequencies in both groups, and procedure-related events were infrequent.

5.5 Description and justification of route of administration and dosage

Not applicable.

5.6 Dosages, dosage modifications and method of administration

Not applicable.

5.7 Preparation and labelling of Investigational Medicinal Product

Not applicable.

5.8 Drug accountability

Not applicable.

6. NON-INVESTIGATIONAL PRODUCT

6.1 Name and description of non-investigational product(s)

Not applicable.

6.2 Summary of findings from non-clinical studies

Not applicable.

6.3 Summary of findings from clinical studies

Not applicable.

6.4 Summary of known and potential risks and benefits

Not applicable.

6.5 Description and justification of route of administration and dosage

Not applicable.

6.6 Dosages, dosage modifications and method of administration

Not applicable.

6.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable.

6.8 Drug accountability

Not applicable.

7. METHODS

7.1 Study outcomes

Primary outcome

The primary outcome is the score on the modified Rankin Scale (table) at 90 days (\pm 14 days).

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 primary outcome is the score on the modified Rankin Scale (table 1).¹⁶

Secondary outcomes

- Extended Treatment In Cerebral Ischaemia (eTICI) score (Table 2) on final angiography of IAT
- Recanalization rate at 24 hours after randomization, assessed with NCCT/CTA or MRI
- Score on the NIHSS (table 3) at 24 hours and 5-7 days after randomization, or at discharge
- Final infarct volume on NCCT at 5-7 days or 24-48h MRI. Final infarct volume will be assessed with the use of an automated, validated algorithm.¹⁷ 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 (\pm 14 days)
- Dichotomized mRS of 0-2 vs. 3-6 at 90 days (\pm 14 days)
- Dichotomized mRS of 0-3 vs. 4-6 at 90 days (\pm 14 days)
- Death at 90 days (\pm 14 days)
- Score on the Barthel index (table 4) and EQ5D-5L (table 5) at 90 days (\pm 14 days)^{18 19}

Safety endpoints

- Hemorrhages according to the ECASS radiological classification

- sICH scored according to the Heidelberg criteria
- Embolization in new territory on angiography during IAT
- Occurrence of aneurysma spurium
- Occurrence of groin hematoma
- Infarction in new territory at 1 week
- All-cause mortality at 90 days

■ Other study parameters (if applicable)

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 diagnose (referrer); urgency code ambulance (A1/ A2/B; time of arrival ambulance on site; time of departure ambulance towards hospital; 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, imaging results on admission including data from CT-perfusion imaging and Clot Burden Score for CTA and MRA(table 6); and the use of intravenous thrombolysis. In a subset of patients Near-Infrared spectroscopy will be performed before, during or after the IAT.

Additionally, we will record time from onset to ER, CT, 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 (if any) and sedation will be noted.

Last, during the 90 day study period, information regarding the direct treatment costs will be collected. At 90 days (\pm 14 days), patients will be requested to fill out a questionnaire which will further explore direct and indirect costs after hospital discharge (table 9).^{20 21}

In order to study long-term clinical effectiveness and cost-effectiveness, patients will be requested to participate in an extended follow-up cohort with a time horizon of 2 years. In this cohort, data will be collected at 1 and at 2 years post stroke. Data collection will consist of (1) a telephone interview, during which the mRS, Barthel Index and EQ-5D-5L will be scored and information on major vascular events will be collected, and (2) a written questionnaire, which will explore direct and indirect costs (table 10).^{20 21}

7.2 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 and degree of collaterals has been established by CTA. Randomization will be stratified for center and for inclusion in the active treatment arm of MR ASAP. Inclusion and randomization of patients with poor collaterals will be restricted. After 100 patients with poor collaterals have been included and randomized, we will only allow inclusion of patients with moderate to good collaterals.

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 database 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. Assessors who are blinded to the treatment allocation will base assessment of outcome on the modified Rankin scale on this information. 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 trial statistician will combine data on treatment allocation with the clinical data in order to report to the data monitoring committee (DSMB).

Registry of patients treated with EVT outside of the trial based on DAWN/DEFUSE 3 patient profile

To investigate if the results from the MR CLEAN LATE are of additional value in daily clinical practice, we will compare our data with data from patients already treated according to standard care in the late time-window. We will also use this data to evaluate if there was any selection bias of patients included in the trial. We ask all participating centers to register the patients that were excluded from our trial and received 'direct

treatment.' These patients will be informed by the use of an opt-out procedure about the usage and storage of pseudonymized data from their patient records, imaging, and waste biomaterials (such as thrombi) for research. Subject records are coded by a unique study number, different from the MR CLEAN LATE studynumbers. In case of consent, we will amongst others register the variables: age, gender, pre-mRS, cardiovascular history/comorbidity, medication use, time of last seen well, time of symptom onset, time of arrival in primary and intervention center, time of groin puncture, NIHSS at baseline and discharge, all imaging (including core and penumbra volume) and mRS +SAE at 90 days (resulting from follow-up in the context of standard care). Imaging will amongst others be assessed on core and penumbra volumes. Thrombi will be used for visualization of e.g. contact-activation factors and endothelial damage with the use of different coloring techniques. Patient information will be removed from imaging data and will be linked to the Study number. In case no permission is obtained from the patient or their legal representative, data will not be registered/ used for research.

7.3 Study procedures

All patients will undergo assessment of the NIHSS at baseline (immediately before randomization), 24 hours and 5-7 days after randomization, which is a routine clinical procedure. It will be carried out by certified assessors. Patients will undergo NCCT and CTA at baseline, which also belongs to usual care. CTP at baseline will mostly be carried out by intervention centers in order to select patients for direct EVT treatment before randomization. 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 hours +/- 12 hours, NCCT (or preferably dual energy CT [DECT], if available) and CTA are repeated to assess intracranial hemorrhage and to determine recanalization. At 5-7 days or discharge, patients will undergo NCCT 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. At 90 days +/- 14 days all participants will undergo a telephone interview to assess clinical outcome.

In participating centers in the Netherlands, (1) within 1 hour before the IAT, (2) within 1 hour after the IAT or 1 hour after hospital admission in case the patient is part of the control group and (3) at 24 hours after the IAT or admission 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.

7.4 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, for example deterioration from NIHSS <10 to NIHSS \geq 10 in patients with a small core who would then qualify for direct treatment outside the trial protocol. 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 baseline data will be imputed for the analysis by means of multiple regression imputation.

7.5 Specific criteria for withdrawal (if applicable)

Not applicable.

7.6 Replacement of individual subjects after withdrawal

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

7.7 Follow-up of subjects withdrawn from treatment

All patients in the study will be followed until final assessment at 90 days. Only patients who have withdrawn consent will be assessed immediately and their records will be closed.

Due to the deferred consent procedure, study allocation and possible intervention will have taken place prior to obtaining informed consent. The procedure requires that all information on patients who did not provide consent after EVT is discarded and deleted. This may be against the interest of patients who did provide consent, and against the interest of the general public, as patients with sICH and other serious adverse events might be more likely to refuse consent for participation. Not considering these records might very well result in an underestimation of the true risk and validity of the data, and it might lead to undetected safety concerns for all consenting patients in the trial. To overcome this concern, we will register the following variables in a strictly anonymized safety registry for all patients, irrespective of whether a patient has provided written informed consent: patient's study number, study treatment, in-hospital sICH occurrence (yes/no), and in-hospital survival status (yes/no). All other information will be completely erased from the patient's study record in case no consent is provided. The link to the study database will be erased from the patient's medical record.

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.

8. SAFETY REPORTING

8.1 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.

8.2 AEs, SAEs and SUSARs

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 experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

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;

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, based upon appropriate medical judgment, will also be considered an SAE. An elective hospital admission will not be considered a serious adverse event.

Serious adverse events that occur before the 90 day follow-up and meet the aforementioned criteria will immediately after coming to notice of the (local) investigator, be reported to the trial coordinator, who is available 24/7.

The (local) investigator will report the following SAEs occurring in the study period (from inclusion up until the 90 day follow-up) to the sponsor without undue delay of obtaining knowledge of the events: Death from any cause; symptomatic intracranial

hemorrhage, extracranial hemorrhage, aspiration pneumonia, allergic contrast reactions, new ischemic stroke in 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 or new ischemic stroke, but are considered as consistent with the natural course of the ischemic stroke and its treatment, should be reported before the patient's 90 day follow-up.

The sponsor will report all 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.

■ Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

8.3 Annual safety report

Not applicable.

8.4 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 from randomization up until the 90 day follow-up interview.

8.5 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 100 patients (whichever comes first), and assess the occurrence of unwanted effects by center and by procedure. During the period of intake to the study,

interim analyses of mortality and of any other information that is available 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 Board may request. In the light of these analyses, 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 sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed. No futility criterion will be applied.

9. STATISTICAL ANALYSIS

The primary effect parameter will be the common odds ratio, estimated with ordinal logistic regression, which represents the shift on the full distribution of modified Rankin scale at 3 months. The estimate will be adjusted for the prognostic variables age, pre-stroke mRS, time from onset to randomization, stroke severity (NIHSS), collaterals, and unwitnessed stroke. Adjusted and unadjusted estimates with corresponding 95% confidence intervals will be reported.

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

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

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

Pre-defined 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 (m/f)
- 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 (y/n)
- Atrial fibrillation (y/n)
- Extracranial carotid obstruction (y/n)
- Occlusion location (ICA, ICA-T, M1, M2/3)
- ASPECTS (0-4, 5-7, 8-10; table 7)
- Collaterals (none, poor, moderate, good; table 8)
- Wake-up stroke (y/n)

- Inclusion in active treatment arm of MR ASAP

Interim analysis (if applicable)

For interim analyses we refer to the chapter on safety reporting (Data Safety Monitoring Board).

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (October 2013)²², according to ICH-GCP principles and in accordance with the Medical Research Involving Human Subjects Act (WMO).

10.2 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, or after randomization for patients in the control arm. We consider deferred consent warranted because immediate application of endovascular treatment will lead to additional benefit; for every hour delay, the absolute benefit of treatment (probability of recovery to independent living) decreases by 6%.²³ We know that proper informed consent procedures take 1 to 3 hours and this time is not available in the acute treatment phase. Half of all patients with severe ischemic cortical stroke, such as in the MR CLEAN trial, have language impairment, anosognosia or other acute cognitive symptoms. 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, after the intervention, or after randomization for patients in the control arm. We will strive to obtain consent as soon as possible but deemed reasonable and appropriate by the investigator, preferably within 24 hours. When the patient is not competent, the investigator will search for a legal representative available. If there is no legal representative available, study procedures will be continued until a proxy is present. Subjects or their representatives will be provided with a patient information form 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 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, their representatives will be informed about the 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 representatives by the medical center where the patient last resided.

Rationale for deferred consent

This study evaluates the effect of an acute treatment in an emergency situation concerning a life-threatening disorder. For every hour delay, the absolute benefit of treatment (probability or recovery to independent living) decreases by 6%.²³ Treatment should therefore be started as soon as possible.

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.^{24 25} 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 1476 of 1497 patients we documented symptoms indicating a lack of decision making capacity; 5 patients (0.3%) had recanalized after DSA and in 16 (1.1%) insufficient documentation was available to assess 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. Even after intervention, in the first 24 hours, the emotional stress can still be such that informed consent cannot be accurately and carefully obtained.

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. Furthermore, the executive committee feels that in some cases 24 hours might not be enough time to defer consent in case of severe emotional stress. Although the goal is to obtain consent as soon as possible after the study procedure a timeframe of 72 hours might be warranted in certain cases.

10.3 Objection by minors or incapacitated subjects (if applicable)

In the situation that a legally incompetent patient shows behavior suggesting objection to participation in the trial, the patient will not be included in the study, or the study treatment will be stopped. 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'.

10.4 Benefits and risks assessment, group relatedness

The expected benefit from intra-arterial treatment on top of best medical treatment compared to best medical treatment alone may amount to 10% absolute increase in independent living at 3 months. Patients who have been allocated to the control group will be given usual treatment according to international, national and local guidelines. *The Executive Committee of MR CLEAN-LATE expects that the potential benefit of intra-arterial therapy outweighs the limited risk of harm of these study treatment. We refer to the chapters 5.3 and 12.2 for more details on these potential benefits and harms.*"

10.5 Compensation for injury

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

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

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study. The insurance policy is attached to this document.

10.6 Incentives (if applicable)

Patients will not receive any incentives.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 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.

11.2 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 MRCLEAN.³ The likelihood that severe damage was caused by the treatment was very low, and this was the case for all 8 thrombectomy trials published to date.^{3-8, 26} According to 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, sex, time of onset, time of randomization, NIHSS at baseline, performance of baseline and follow up imaging. 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 (dates, times, clinical scores) by the study coordinators.

11.3 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.

11.4 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.

11.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last 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 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.

11.6 Public disclosure and publication policy

The trial will be registered with The Netherlands National Trial Register (NTR). 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,

NL58246.078.17/ MR CLEAN LATE

including individual patient meta-analyses, and with commercial parties for regulatory purposes. Patient consent will be asked specifically for these purposes.

12. STRUCTURED RISK ANALYSIS

12.1 Potential issues of concern

a. Level of knowledge about mechanism of action

The intervention concerns a group of devices, all aiming at mechanical removal of the thrombus. The mechanism of action is well known, and tested in phase III RCTs as well as a large number of case series.

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

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

Yes, mechanical thrombectomy has been tested in various animal models.

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

Recanalization (mTICI 2b-3) occurs in 60-90% of the treated patients. Recovery is a function of time since onset and likely extent of collateral circulation. This will be further explored in MR CLEAN-LATE.

j. Can effects be managed?

Not applicable

12.2 Synthesis

For the in this trial selected patient population benefit of thrombectomy outside the 6 hour time window might be in the same range as shown for this treatment within the 6 hour time-window. The risks are acceptable: There is a slight increase in new infarctions, but is this offset by a large increase in good functional outcome. The current trial is aiming to find out whether risks of treatment will be smaller and benefits larger, by introducing IAT. The burden is low. All patients in the intervention group will be transferred to the angio suite immediately. The procedure involves catheterization by puncture of the common femoral artery, with a small risk of groin hematoma and dissection. At three months, all patients will be interviewed to assess functional outcome.

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14. TABLES

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. 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 |

Table 2 Extended Treatment in Cerebral Ischemia (eTICI) scale.

| 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 |

MCA: middle cerebral artery; eTICI; Extended Treatment in Cerebral Ischemia Scale
 Ref: M Goyal *J Neurointerv Surg.* 2014 March ; 6(2): 83–86.

Table 3 NIH Stroke Scale

The NIHSS is an ordinal hierarchical scale to evaluate the severity of stroke by assessing a patient’s performance. 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.</p> <p>1 = Not alert; but arousable by minor stimulation to obey, answer, or respond.</p> <p>2 = Not alert; required repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped).</p> <p>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</p> | <p>0 = Answers both questions correctly.</p> <p>1 = Answers one question correctly.</p> <p>2 = Answers neither question correctly.</p> |

unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not “help” the patient with verbal or non-verbal clues.

1c. LOC Commands: The patient is asked to open and 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

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.

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.

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.

- 0 = **No visual loss.**
- 1 = **Partial hemianopia.**
- 2 = **Complete hemianopia.**
- 3 = **Bilateral hemianopia** (blind including cortical blindness)

4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly response or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or

- 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

| | |
|---|---|
| <p>other physical barriers obscure the face, these should be removed to the extent possible.</p> | <p>(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 as untestable (UN), and clearly write the explanation for this choice.</p> | <p>0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds.</p> <p>1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support.</p> <p>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.</p> <p>3 = No effort against gravity; limb falls.</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> |

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 extended arm position.

0 = **Absent.**
 1 = **Present in one limb.**
 2 = **Present in two limbs.**
 UN = **Amputation** or joint fusion, explain:

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

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.

quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.

9. Best language: A great deal of information about 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 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.

0 = **No aphasia**; normal
 1 = **Mild-to-moderate aphasia**; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes 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 exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response.
 3 = **Mute, global aphasia**: no usable speech or auditory comprehension.

10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if patient is intubated or has other physical barriers to producing speech, the

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

| | |
|--|--|
| <p>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>out of proportion to any dysphasia, or is mute/anarthric.</p> <p>UN = Intubated or other physical barrier.</p> <p>Explain:</p> |
| <p>11. Extinction and Inattention (formerly Neglect):</p> <p>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.</p> <p>1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities.</p> <p>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> |

Table 4 Barthel Index

The Barthel index (BI) is an ordinal scale used to measure performance in 10 activities of daily living (ADL).^{56, 61, 62} 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) | <p>0 = unable, no sitting balance</p> <p>5 = major help (one or two people, physical), can sit</p> <p>10 = minor help (verbal or physical)</p> <p>15 = independent</p> |
| MOBILITY (ON LEVEL SURFACES) | <p>0 = immobile or < 50 yards</p> <p>5 = wheelchair independent, including corners, > 50 yards</p> <p>10 = walks with help of one person (verbal or physical) > 50 yards</p> <p>15 = independent (but may use any aid; for example, stick) > 50 yards</p> |
| STAIRS | <p>0 = unable</p> <p>5 = needs help (verbal, physical, carrying aid)</p> <p>10 = independent</p> |

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.

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.^{17, 21, 63}

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

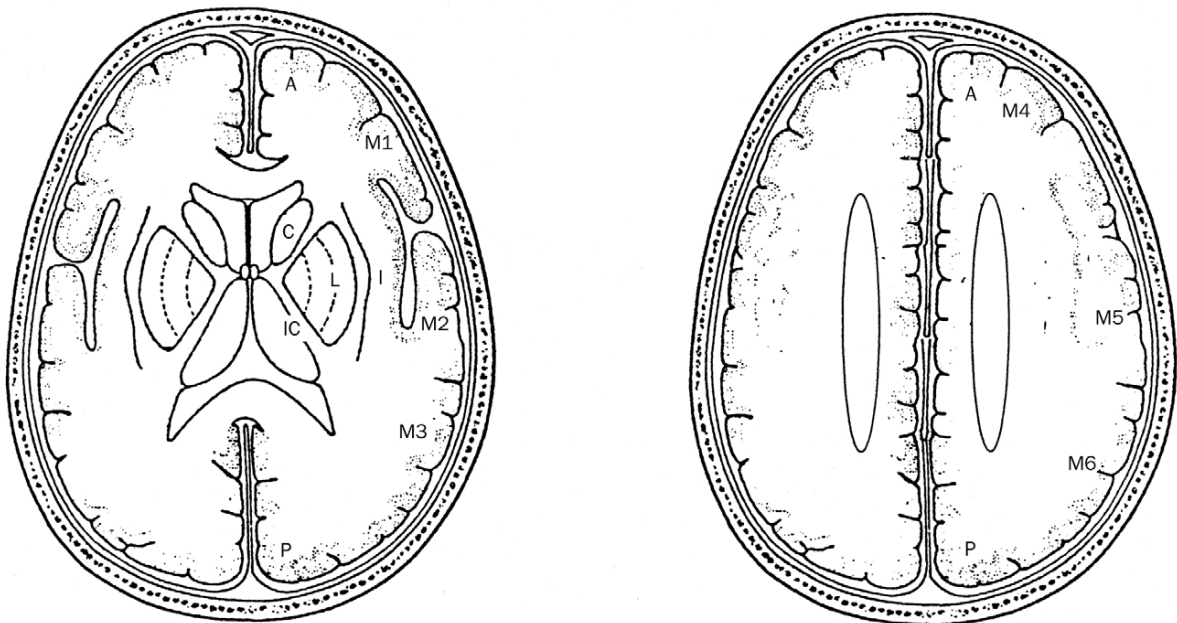
Table 6 Clot burden score for CTA and MRA

| 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 | |

Reference Puetz et PMID: 18811738

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 MCA (Yoo AJ, Lancet Neurology).



ASPECTS (Barber et al.)

Glossary: A=Anterior circulation; P=posterior circulation; MCA=middle cerebral artery

10 defined segments: C=caudate; L=lentiform; IC=internal capsule; I=insular ribbon; M1="anterior MCA cortex," corresponding to frontal operculum; M2= MCA cortex lateral to insular ribbon, corresponding to anterior temporal lobe; M3=posterior MCA cortex, corresponding to posterior temporal lobe; M4=anterior MCA territory immediately superior to M1; M5=lateral MCA territory immediately superior to M2; M6=posterior MCA territory immediately superior to M3

Table 8 Collateral score

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

Reference Demchuck. PMID19147716, DOI:[10.3174/ajnr.A1408](https://doi.org/10.3174/ajnr.A1408)

Table 9 Medical Consumption and Productivity Cost Questionnaire

[voor start vragenlijst: algemene informatie en instructie vragenlijst. Er is een separate proxy versie met inhoudelijk dezelfde vragen.]

Vragen over uw zorggebruik

U was 3 maanden geleden in een ziekenhuis opgenomen vanwege een herseninfarct (beroerte). U bent hierna met ontslag uit het ziekenhuis gegaan. **Alle vragen gaan over de periode ná uw ontslag.** Dus niet over de opname in het ziekenhuis of de periode daarvoor.

Wij willen graag weten met welke dokters u in de afgelopen 3 maanden een afspraak had. Het gaat om afspraken voor uzelf. Ook andere zorgverleners tellen mee. Bijvoorbeeld de fysiotherapeut.

Welke afspraken tellen mee?

- Controles
- Afspraken omdat u een lichamelijke of psychische klacht had
- Afspraken waarbij de dokter bij u thuis kwam
- Telefonische afspraken
- Telefoontjes met de receptenlijn

Wat telt niet mee?

- Afspraken die u heeft gehad tijdens uw opname of dagbehandeling in een revalidatiecentrum
- Afspraken voor een ander, bijvoorbeeld voor uw partner
- Telefoontjes om een afspraak te maken

Weet u niet precies hoeveel afspraken het waren? Schrijf dan op hoeveel het er ongeveer waren.

Vraag 1. Had u in de afgelopen 3 maanden een afspraak met één van deze zorgverleners? Zo ja, hoe vaak?

| | | | |
|-------------------------------|------------------------------|------------------------------|-------------|
| Huisarts | <input type="checkbox"/> Nee | <input type="checkbox"/> Ja, | _ _ _ keer |
| Praktijkondersteuner huisarts | <input type="checkbox"/> Nee | <input type="checkbox"/> Ja, | _ _ _ keer |
| Neuroloog | <input type="checkbox"/> Nee | <input type="checkbox"/> Ja, | _ _ _ keer |
| Fysiotherapeut | <input type="checkbox"/> Nee | <input type="checkbox"/> Ja, | _ _ _ keer |
| Ergotherapeut | <input type="checkbox"/> Nee | <input type="checkbox"/> Ja, | _ _ _ keer |
| Logopedist | <input type="checkbox"/> Nee | <input type="checkbox"/> Ja, | _ _ _ keer |
| Diëtist | <input type="checkbox"/> Nee | <input type="checkbox"/> Ja, | _ _ _ keer |
| Psycholoog / psychiater | <input type="checkbox"/> Nee | <input type="checkbox"/> Ja, | _ _ _ keer |

| | | | |
|------------------------|------------------------------|------------------------------|-------------|
| Bedrijfsarts | <input type="checkbox"/> Nee | <input type="checkbox"/> Ja, | _ _ _ keer |
| Revalidatiearts | <input type="checkbox"/> Nee | <input type="checkbox"/> Ja, | _ _ _ keer |
| Maatschappelijk werker | <input type="checkbox"/> Nee | <input type="checkbox"/> Ja, | _ _ _ keer |

Een andere zorgverlener, namelijk:

..... |_|_|_| keer

..... |_|_|_| keer

Vraag 2. Hoe vaak bent u op de spoedeisende eerste hulp van een ziekenhuis geweest? Een andere naam voor spoedeisende eerste hulp is EHBO.

- Geen enkele keer
- keer

Vraag 3. Hoe vaak bent u met een ambulance naar het ziekenhuis gebracht? Een andere naam voor ambulance is ziekenauto.

- Geen enkele keer
- keer

Vraag 4a. Heeft u in het ziekenhuis opgenomen gelegen? U moest dus blijven slapen. Bijvoorbeeld omdat u geopereerd was en niet meteen naar huis kon.

- Nee
- Ja

Heeft u "Ja" aangekruist? Beantwoord dan vraag 4b.
Ga anders verder met vraag 5.

Vraag 4b. Hoe lang heeft u toen in het ziekenhuis gelegen? Heeft u meer dan 1 keer in het ziekenhuis gelegen? Tel dan alle dagen bij elkaar op.

|_|_|_| dagen op de gewone afdeling
|_|_|_| dagen op de intensive care

Vraag 5a. Bent u in de afgelopen 3 maanden overdag in het ziekenhuis geweest voor een behandeling? U bleef dus niet slapen. U kwam bijvoorbeeld voor een bloedtransfusie, nierdialyse of chemokuur.

Nee

Ja

Heeft u "Ja" aangekruist? Beantwoord dan vraag 5b en 5c.

Ga anders verder met vraag 6.

Vraag 5b. Voor welke soort behandeling was dit? Was dit voor meer dan 1 soort behandeling? Vul dan alle soorten behandelingen in.

Behandeling 1:

.....

Behandeling 2:

.....

Behandeling 3:

.....

Vraag 5c. Hoeveel keer moest u in de afgelopen 3 maanden voor deze behandelingen naar het ziekenhuis?

..... keer voor behandeling 1

..... keer voor behandeling 2

..... keer voor behandeling 3

Vraag 6a. Bent u in de afgelopen 3 maanden ergens anders geweest voor een behandeling overdag? U bleef dus niet slapen. U ging bijvoorbeeld naar de dagopvang van een woon-/zorgcentrum of een psychiatrische instelling. Of naar de dagbehandeling van een revalidatiecentrum.

- Nee
- Ja

Heeft u “Ja” aangekruist? Beantwoord dan vraag 6b en 6c.
Ga anders verder met vraag 7.

Vraag 6b. Wat voor instelling was dit? Kruis het goede antwoord aan. U kunt meer dan 1 hokje aankruisen.

- Woon-/zorgcentrum
- Revalidatiecentrum
- Psychiatrische instelling
- Een andere instelling, namelijk

.....

Vraag 6c. Hoe vaak moest u hier in de afgelopen 3 maanden naartoe? Heeft u bij vraag 6b meer dan 1 hokje aangekruist? Vul dan hieronder voor iedere instelling in hoe vaak u er bent geweest.

Naar het woon-/zorgcentrum: keer in de afgelopen 3 maanden

Naar het revalidatiecentrum: keer in de afgelopen 3 maanden

Naar de psychiatrische instelling: keer in de afgelopen 3 maanden

Naar de andere instelling: keer in de afgelopen 3 maanden

Vraag 7a. Moest u in de afgelopen 3 maanden ergens anders blijven slapen voor uw gezondheid? Bijvoorbeeld in een woon-/zorgcentrum, psychiatrische instelling of revalidatiecentrum.

- Nee
- Ja

Heeft u "Ja" aangekruist? Beantwoord dan vraag 7b en 7c.
Ga anders verder met vraag 8.

Vraag 7b. Wat voor instelling was dit? U kunt meer dan 1 hokje aankruisen.

- Woon-/zorgcentrum
- Revalidatiecentrum
- Psychiatrische instelling
- Een andere instelling, namelijk

.....

Vraag 7c. Hoe lang bent u in deze instelling geweest? Heeft u bij vraag 7b meer dan 1 hokje aangekruist? Vul dan hieronder voor iedere instelling in hoe lang u er bent geweest. Bent u ergens meer dan 1 keer geweest in de afgelopen 3 maanden? Tel dan alle dagen bij elkaar op.

In het woon-/zorgcentrum: dagen in de afgelopen 3 maanden

In het revalidatiecentrum: dagen in de afgelopen 3 maanden

In de psychiatrische instelling: dagen in de afgelopen 3 maanden

In de andere instelling: dagen in de afgelopen 3 maanden

Vraag 8a. Heeft u in de afgelopen 3 maanden hulp van de thuiszorg gehad?

- Nee
 Ja

Heeft u "Ja" aangekruist? Beantwoord dan vraag 8b tot en met 8d.
Ga anders verder met vraag 9.

Vraag 8b. Wat voor hulp van de thuiszorg heeft u gehad in de afgelopen 3 maanden? U kunt meer dan 1 hokje aankruisen.

Huishoudelijke hulp
voorbeeld: stofzuigen, bed opmaken, boodschappen doen

Verzorging van uzelf
voorbeeld: hulp bij douchen of aankleden

Verpleging
voorbeeld: verband omdoen, medicijnen geven, bloeddruk meten

Vraag 8c. Hoeveel weken heeft u deze thuiszorg gehad? Tel alle weken in de afgelopen 3 maanden bij elkaar op. Let op: een periode van 3 maanden telt 13 weken.

Huishoudelijke hulp: weken in de afgelopen 3 maanden

Verzorging van uzelf: weken in de afgelopen 3 maanden

Verpleging: weken in de afgelopen 3 maanden

Vraag 8d. Hoeveel uur thuiszorg kreeg u in deze weken gemiddeld?

Huishoudelijke hulp: gemiddeld uur in de week

Verzorging van uzelf: gemiddeld uur in de week

Verpleging: gemiddeld uur in de week

Vraag 9a. Heeft u in de afgelopen 3 maanden hulp gekregen van een familielid of een bekende vanwege uw lichamelijke of psychische problemen?

- Nee
 Ja

Heeft u “Ja” aangekruist? Beantwoord dan vraag 9b tot en met 9d.

Ga anders verder met vraag 10.

Vraag 9b. Wat voor hulp van familieleden of bekenden heeft u gehad in de afgelopen 3 maanden? U kunt meer dan 1 hokje aankruisen.

- Huishoudelijke hulp

voorbeeld: stofzuigen, bed opmaken, boodschappen doen, klaarmaken van eten en drinken, verzorgen van kinderen

- Verzorging van uzelf

voorbeeld: hulp bij douchen of aankleden, hulp bij het eten en drinken of het geven van medicijnen

- Praktische hulp

voorbeeld: ondersteuning bij wandelen, het maken van uitstapjes of bezoeken aan bekenden, bezoeken aan de huisarts of het ziekenhuis, het regelen van hulp of het regelen van financiële zaken

Vraag 9c. Hoeveel weken heeft u deze hulp gehad? Tel alle weken in de afgelopen 3 maanden bij elkaar op. *Let op: een periode van 3 maanden telt 13 weken.*

Huishoudelijke hulp: ... weken in de afgelopen 3 maanden

Verzorging van uzelf: ... weken in de afgelopen 3 maanden

Praktische hulp: ... weken in de afgelopen 3 maanden

Vraag 9d. Hoeveel uur hulp kreeg u in deze weken gemiddeld?

Huishoudelijke hulp: gemiddeld ... uur in de week

Verzorging van uzelf: gemiddeld ... uur in de week

Praktische hulp: gemiddeld ... uur in de week

Vraag 10. Heeft u na uw herseninfarct extra kosten voor vervoer moeten maken?

Bijvoorbeeld omdat u met de auto of het openbaar vervoer naar het ziekenhuis of een revalidatie instelling moest.

- Nee
- Ja, namelijk euro per maand

Vraag 11. Heeft u in de afgelopen 3 maanden aanpassingen in huis moeten maken? U

kunt meerdere antwoorden aankruisen.

- Ja, een douchezitje
- Ja, een bedpapegaai
- Ja, wandbeugels
- Ja, een traplift
- Nee, dit is niet van toepassing
- Anders, namelijk

.....

Vraag 12. Heeft u in de afgelopen 3 maanden hulpmiddelen moeten kopen of huren? U

kunt meerdere antwoorden aankruisen.

- Een rollator
- Een scootmobiel
- Een rolstoel
- Nee, dit is niet van toepassing
- Anders, namelijk

.....

Vragen over uw zorggebruik

De volgende vragen gaan over uw baan. Dus over werk waarvoor u betaald wordt. De vragen gaan over uw werk in de afgelopen 3 maanden.

Vraag 1. Heeft u een betaalde baan? Als u in de ziektewet zit, telt dit ook als betaald werk.

- Nee
- Ja

Heeft u “Ja” aangekruist? Ga dan verder met de volgende vraag.
Ga anders naar het einde van de vragenlijst.

Vraag 2. Hoeveel uur per week werkt u? Tel alleen de uren waarvoor u betaald wordt.

..... uren

Vraag 3. Op hoeveel dagen in de week werkt u?

Op dagen

Vraag 4. Bent u in de afgelopen 3 maanden afwezig geweest van uw werk omdat u ziek was?

- Nee
- Ja, ik ben deze hele periode afwezig geweest
- Ja, ik ben dagen afwezig geweest

(Tel alleen de werkdagen in de afgelopen 3 maanden)

Vraag 5. Waren er in de afgelopen 3 maanden dagen waarop u wel gewerkt heeft, maar tijdens uw werk last had van lichamelijke of psychische problemen?

Nee

Ja

Heeft u “Ja” aangekruist? Beantwoord dan vraag 6 en 7.

Ga anders naar het einde van de vragenlijst.

Vraag 6. Op hoeveel werkdagen had u tijdens uw werk last van uw lichamelijke of psychische problemen? Tel alleen de werkdagen in de afgelopen 3 maanden.

..... werkdagen

Vraag 7. Op de dagen dat u last had, kon u misschien niet zoveel werk doen als normaal. Hoeveel werk kon u op deze dagen gemiddeld doen? Kijk naar de cijfers hieronder. Een 10 betekent dat u op deze dagen net zoveel kon doen als normaal. Een 0 betekent dat u op deze dagen niets kon doen. Zet een cirkel om het goede cijfer.

*Ik kon op deze
dagen niets doen*

*Ik kon onge-
veer de helft
doen*

*Ik kon net
zoveel doen als
normaal*

0 1 2 3 4 5 6 7 8 9 10

Dit was de laatste vraag.

Table 10 Medical Consumption and Productivity Cost Questionnaire: extended follow-up

[voor start vragenlijst: algemene informatie en instructie vragenlijst. Er is een separate proxy versie met inhoudelijk dezelfde vragen.]

Algemene vraag

Vraag 1. Wat is de hoogste opleiding die u heeft afgemaakt? Zoek uw hoogste opleiding en kruis het hokje daarvoor aan.

- Ik heb geen school of opleiding afgemaakt
- Lagere school of basisschool
- Huishoudschool, vbo, lbo, lts, leao of lhno

- Mavo, mulo, ivo of vmbo
- MBO, mts, meao, mhno, inas of intas
- Havo, vwo, hbs, mms, atheneum of gymnasium

- Hbo, hts, heao of hhno
- Universiteit
- Ik heb een andere opleiding afgemaakt, namelijk

.....

Vragen over uw zorggebruik

Wij willen graag weten met welke dokters u in de afgelopen **3 maanden** een afspraak had. Het gaat om afspraken voor uzelf. Ook andere zorgverleners tellen mee. Bijvoorbeeld de fysiotherapeut.

Welke afspraken tellen mee?

- Controles
- Afspraken omdat u een lichamelijke of psychische klacht had
- Afspraken waarbij de dokter bij u thuis kwam
- Telefonische afspraken
- Telefoontjes met de receptenlijn

Wat telt niet mee?

- Afspraken die u heeft gehad tijdens uw opname of dagbehandeling in een revalidatiecentrum
- Afspraken voor een ander, bijvoorbeeld voor uw partner
- Telefoontjes om een afspraak te maken

Weet u niet precies hoeveel afspraken het waren? Schrijf dan op hoeveel het er ongeveer waren.

Vraag 1. Had u in de afgelopen 3 maanden een afspraak met één van deze zorgverleners? Zo ja, hoe vaak?

| | | | |
|-------------------------------|------------------------------|------------------------------|-------------|
| Huisarts | <input type="checkbox"/> Nee | <input type="checkbox"/> Ja, | _ _ _ keer |
| Praktijkondersteuner huisarts | <input type="checkbox"/> Nee | <input type="checkbox"/> Ja, | _ _ _ keer |
| Neuroloog | <input type="checkbox"/> Nee | <input type="checkbox"/> Ja, | _ _ _ keer |
| Fysiotherapeut | <input type="checkbox"/> Nee | <input type="checkbox"/> Ja, | _ _ _ keer |
| Ergotherapeut | <input type="checkbox"/> Nee | <input type="checkbox"/> Ja, | _ _ _ keer |
| Logopedist | <input type="checkbox"/> Nee | <input type="checkbox"/> Ja, | _ _ _ keer |
| Diëtist | <input type="checkbox"/> Nee | <input type="checkbox"/> Ja, | _ _ _ keer |
| Psycholoog / psychiater | <input type="checkbox"/> Nee | <input type="checkbox"/> Ja, | _ _ _ keer |
| Bedrijfsarts | <input type="checkbox"/> Nee | <input type="checkbox"/> Ja, | _ _ _ keer |
| Revalidatiearts | <input type="checkbox"/> Nee | <input type="checkbox"/> Ja, | _ _ _ keer |
| Maatschappelijk werker | <input type="checkbox"/> Nee | <input type="checkbox"/> Ja, | _ _ _ keer |

Een andere zorgverlener, namelijk:

.....

|_|_|_| keer

.....

|_|_| keer

Vraag 2. Hoe vaak bent u op de spoedeisende eerste hulp van een ziekenhuis geweest? Een andere naam voor spoedeisende eerste hulp is EHBO.

- Geen enkele keer
- keer

Vraag 3. Hoe vaak bent u met een ambulance naar het ziekenhuis gebracht? Een andere naam voor ambulance is ziekenauto.

- Geen enkele keer
- keer

Vraag 4a. Heeft u in het ziekenhuis opgenomen gelegen? U moest dus blijven slapen. Bijvoorbeeld omdat u geopereerd was en niet meteen naar huis kon.

- Nee
- Ja

Heeft u "Ja" aangekruist? Beantwoord dan vraag 4b.

Ga anders verder met vraag 5.

Vraag 4b. Hoe lang heeft u toen in het ziekenhuis gelegen? Heeft u meer dan 1 keer in het ziekenhuis gelegen? Tel dan alle dagen bij elkaar op.

|_|_| dagen op de gewone afdeling

|_|_| dagen op de intensive care

Vraag 5a. Bent u in de afgelopen 3 maanden overdag in het ziekenhuis geweest voor een behandeling? U bleef dus niet slapen. U kwam bijvoorbeeld voor een bloedtransfusie, nierdialyse of chemokuur.

- Nee
- Ja

Heeft u “Ja” aangekruist? Beantwoord dan vraag 5b en 5c.
Ga anders verder met vraag 6.

Vraag 5b. Voor welke soort behandeling was dit? Was dit voor meer dan 1 soort
behandeling? Vul dan alle soorten behandelingen in.

Behandeling 1:

.....

Behandeling 2:

.....

Behandeling 3:

.....

**Vraag 5c. Hoeveel keer moest u in de afgelopen 3 maanden voor deze behandelingen
naar het ziekenhuis?**

..... keer voor behandeling 1

..... keer voor behandeling 2

..... keer voor behandeling 3

**Vraag 6a. Bent u in de afgelopen 3 maanden ergens anders geweest voor een
behandeling overdag? U bleef dus niet slapen.** U ging bijvoorbeeld naar de dagopvang van
een woon-/zorgcentrum of een psychiatrische instelling. Of naar de dagbehandeling van een
revalidatiecentrum.

Nee

Ja

Heeft u “Ja” aangekruist? Beantwoord dan vraag 6b en 6c.

Ga anders verder met vraag 7.

Vraag 6b. Wat voor instelling was dit? Kruis het goede antwoord aan. U kunt meer dan 1 hokje aankruisen.

- Woon-/zorgcentrum
- Revalidatiecentrum
- Psychiatrische instelling
- Een andere instelling, namelijk

.....

Vraag 6c. Hoe vaak moest u hier in de afgelopen 3 maanden naartoe? Heeft u bij vraag 6b meer dan 1 hokje aangekruist? Vul dan hieronder voor iedere instelling in hoe vaak u er bent geweest.

Naar het woon-/zorgcentrum: keer in de afgelopen 3 maanden

Naar het revalidatiecentrum: keer in de afgelopen 3 maanden

Naar de psychiatrische instelling: keer in de afgelopen 3 maanden

Naar de andere instelling: keer in de afgelopen 3 maanden

Vraag 7a. Moest u in de afgelopen 3 maanden ergens anders blijven slapen voor uw gezondheid? Bijvoorbeeld in een woon-/zorgcentrum, psychiatrische instelling of revalidatiecentrum.

- Nee
- Ja

Heeft u “Ja” aangekruist? Beantwoord dan vraag 7b en 7c.

Ga anders verder met vraag 8.

Vraag 7b. Wat voor instelling was dit? U kunt meer dan 1 hokje aankruisen.

- Woon-/zorgcentrum
- Revalidatiecentrum
- Psychiatrische instelling
- Een andere instelling, namelijk

.....

Vraag 7c. Hoe lang bent u in deze instelling geweest? Heeft u bij vraag 7b meer dan 1 hokje aangekruist? Vul dan hieronder voor iedere instelling in hoe lang u er bent geweest. Bent u ergens meer dan 1 keer geweest in de afgelopen 3 maanden? Tel dan alle dagen bij elkaar op.

In het woon-/zorgcentrum: dagen in de afgelopen 3 maanden

In het revalidatiecentrum: dagen in de afgelopen 3 maanden

In de psychiatrische instelling: dagen in de afgelopen 3 maanden

In de andere instelling: dagen in de afgelopen 3 maanden

Vraag 8a. Heeft u in de afgelopen 3 maanden hulp van de thuiszorg gehad?

- Nee
- Ja

Heeft u “Ja” aangekruist? Beantwoord dan vraag 8b tot en met 8d.

Ga anders verder met vraag 9.

Vraag 8b. Wat voor hulp van de thuiszorg heeft u gehad in de afgelopen 3 maanden? U kunt meer dan 1 hokje aankruisen.

Huishoudelijke hulp

voorbeeld: stofzuigen, bed opmaken, boodschappen doen

Verzorging van uzelf

voorbeeld: hulp bij douchen of aankleden

Verpleging

voorbeeld: verband omdoen, medicijnen geven, bloeddruk meten

Vraag 8c. Hoeveel weken heeft u deze thuiszorg gehad? Tel alle weken in de afgelopen 3 maanden bij elkaar op. Let op: een periode van 3 maanden telt 13 weken.

Huishoudelijke hulp: weken in de afgelopen 3 maanden

Verzorging van uzelf: weken in de afgelopen 3 maanden

Verpleging: weken in de afgelopen 3 maanden

Vraag 8d. Hoeveel uur thuiszorg kreeg u in deze weken gemiddeld?

Huishoudelijke hulp: gemiddeld uur in de week

Verzorging van uzelf: gemiddeld uur in de week

Verpleging: gemiddeld uur in de week

Vraag 9a. Heeft u in de afgelopen 3 maanden hulp gekregen van een familielid of een bekende vanwege uw lichamelijke of psychische problemen?

- Nee
 Ja

Heeft u “Ja” aangekruist? Beantwoord dan vraag 9b tot en met 9d.
Ga anders verder met vraag 10.

Vraag 9b. Wat voor hulp van familieleden of bekenden heeft u gehad in de afgelopen 3 maanden? U kunt meer dan 1 hokje aankruisen.

Huishoudelijke hulp
voorbeeld: stofzuigen, bed opmaken, boodschappen doen, klaarmaken van eten en drinken, verzorgen van kinderen

Verzorging van uzelf
voorbeeld: hulp bij douchen of aankleden, hulp bij het eten en drinken of het geven van medicijnen

Praktische hulp
voorbeeld: ondersteuning bij wandelen, het maken van uitstapjes of bezoeken aan bekenden, bezoeken aan de huisarts of het ziekenhuis, het regelen van hulp of het regelen van financiële zaken

Vraag 9c. Hoeveel weken heeft u deze hulp gehad? Tel alle weken in de afgelopen 3 maanden bij elkaar op. *Let op: een periode van 3 maanden telt 13 weken.*

Huishoudelijke hulp: ... weken in de afgelopen 3 maanden

Verzorging van uzelf: ... weken in de afgelopen 3 maanden

Praktische hulp: ... weken in de afgelopen 3 maanden

Vraag 9d. Hoeveel uur hulp kreeg u in deze weken gemiddeld?

Huishoudelijke hulp: gemiddeld ... uur in de week

Verzorging van uzelf: gemiddeld ... uur in de week

Praktische hulp: gemiddeld ... uur in de week

Vraag 10. Heeft u na uw herseninfarct extra kosten voor vervoer moeten maken?

Bijvoorbeeld omdat u met de auto of het openbaar vervoer naar het ziekenhuis of een revalidatie instelling moest.

- Nee
- Ja, namelijk euro per maand

Vraag 11. Heeft u in de afgelopen 3 maanden aanpassingen in huis moeten maken? U

kunt meerdere antwoorden aankruisen.

- Ja, een douchezitje
- Ja, een bedpapegaai
- Ja, wandbeugels
- Ja, een traplift
- Nee, dit is niet van toepassing
- Anders, namelijk

.....

Vraag 12. Heeft u in de afgelopen 3 maanden hulpmiddelen moeten kopen of huren? U

kunt meerdere antwoorden aankruisen.

- Een rollator
- Een scootmobiel
- Een rolstoel
- Nee, dit is niet van toepassing
- Anders, namelijk

.....

Vragen over uw werk

Vraag 1 Wat deed u vóór uw herseninfarct in het dagelijks leven? Kruis aan wat u de meeste tijd deed.

- Ik zat op school, ik studeerde
- Ik werkte in loondienst
- Ik was zelfstandig ondernemer
- Ik was huisvrouw, huisman

- Ik was werkloos
- Ik was arbeidsongeschikt, voor %

- Ik was met pensioen of prepensioen
- Ik deed iets anders, namelijk
-

De volgende vragen gaan over uw baan. Dus over werk waarvoor u betaald wordt. De vragen gaan over uw werk in de afgelopen 3 maanden.

Vraag 2. Heeft u een betaalde baan? Als u in de ziektewet zit, telt dit ook als betaald werk. Als u zelfstandig ondernemer was vóór het herseninfarct, mag u hier ook 'ja' aankruisen.

Nee

Ja

Heeft u "Ja" aangekruist? Ga dan verder met de volgende vraag.

Ga anders verder met vraag 13. *Lees eerst de toelichting boven vraag 13.*

Vraag 3. Hoeveel uur per week werkte u vóór het herseninfarct? Tel alleen de uren waarvoor u betaald werd.

..... uren

Vraag 4. Op hoeveel dagen in de week werkte u vóór het herseninfarct?

..... dagen

Vraag 5. Bent u na het herseninfarct weer (gedeeltelijk) begonnen met werken?

- Nee
- Ja, en ik heb dezelfde baan als vóór het herseninfarct.
- Ja, en ik heb een andere baan, namelijk

.....

Heeft u “Ja” aangekruist? Ga dan verder met de volgende vraag.

Ga anders verder met vraag 13. Lees eerst de toelichting boven vraag 13.

Vraag 6. Wanneer bent u weer (gedeeltelijk) begonnen met werken?

dag maand jaar

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| □ | □ | □ | □ | □ | □ | □ | □ | □ | □ |
|---|---|---|---|---|---|---|---|---|---|

Vraag 7. Hoeveel uur per week werkt u sindsdien gemiddeld? Tel alleen de uren waarvoor u betaald wordt.

..... uren

Vraag 8. Op hoeveel dagen per week werkt u sindsdien gemiddeld?

..... dagen

Vraag 9. Heeft u zich in de afgelopen 3 maanden moeten ziekmelden? Bijvoorbeeld omdat u de griep had. Of omdat u onverwacht in het ziekenhuis werd opgenomen.

Nee

Ja, ik ben dagen afwezig geweest.

(Let op: tel alleen de werkdagen)

Vraag 10. Waren er dagen waarop u wel gewerkt heeft, maar tijdens uw werk last had van lichamelijke of psychische problemen?

Nee

Ja

Heeft u "Ja" aangekruist? Beantwoord dan vraag 11 en 12.

Ga anders verder met vraag 13. *Lees eerst de toelichting boven vraag 13.*

Vraag 11. Op hoeveel werkdagen had u tijdens uw werk last van uw lichamelijke of psychische problemen? Tel alleen de werkdagen.

..... werkdagen

Vraag 12. Op de dagen dat u last had, kon u misschien niet zoveel werk doen als normaal. Hoeveel werk kon u op deze dagen gemiddeld doen? Kijk naar de cijfers hieronder. Een 10 betekent dat u op deze dagen net zoveel kon doen als normaal. Een 0 betekent dat u op deze dagen niets kon doen. Zet een cirkel om het goede cijfer.

*Ik kon op
deze dagen
niets doen*

*Ik kon ongeveer
de helft doen*

*Ik kon net
zoveel doen
als normaal*

0 1 2 3 4 5 6 7 8 9 10

Toelichting

Ook bij onbetaald werk kunt u last hebben van uw lichamelijke of psychische problemen. Soms kunt u daardoor minder doen. U kunt bijvoorbeeld niet goed voor de kinderen zorgen of vrijwilligerswerk doen. Of geen boodschappen doen of in de tuin werken. Daarover gaan de volgende vragen.

Vraag 13. Waren er dagen waarop u minder onbetaald werk kon doen door uw lichamelijke of psychische problemen? Het gaat om dagen in de afgelopen 3 maanden.

Nee

Ja

Heeft u "Ja" aangekruist? Beantwoord dan vraag 14 en 15.

Ga anders naar het einde van de vragenlijst.

Vraag 14. Op hoeveel dagen was dit zo? Tel de dagen in de afgelopen 3 maanden.

..... dagen

Vraag 15. Stel dat iemand, bijvoorbeeld uw partner, familielid of een bekende, u op deze dagen had geholpen. En al het onbetaalde werk wat u niet kon doen, voor u had gedaan. Hoeveel uur was die persoon hier op deze dagen dan gemiddeld mee bezig geweest?

Gemiddeld uur per dag

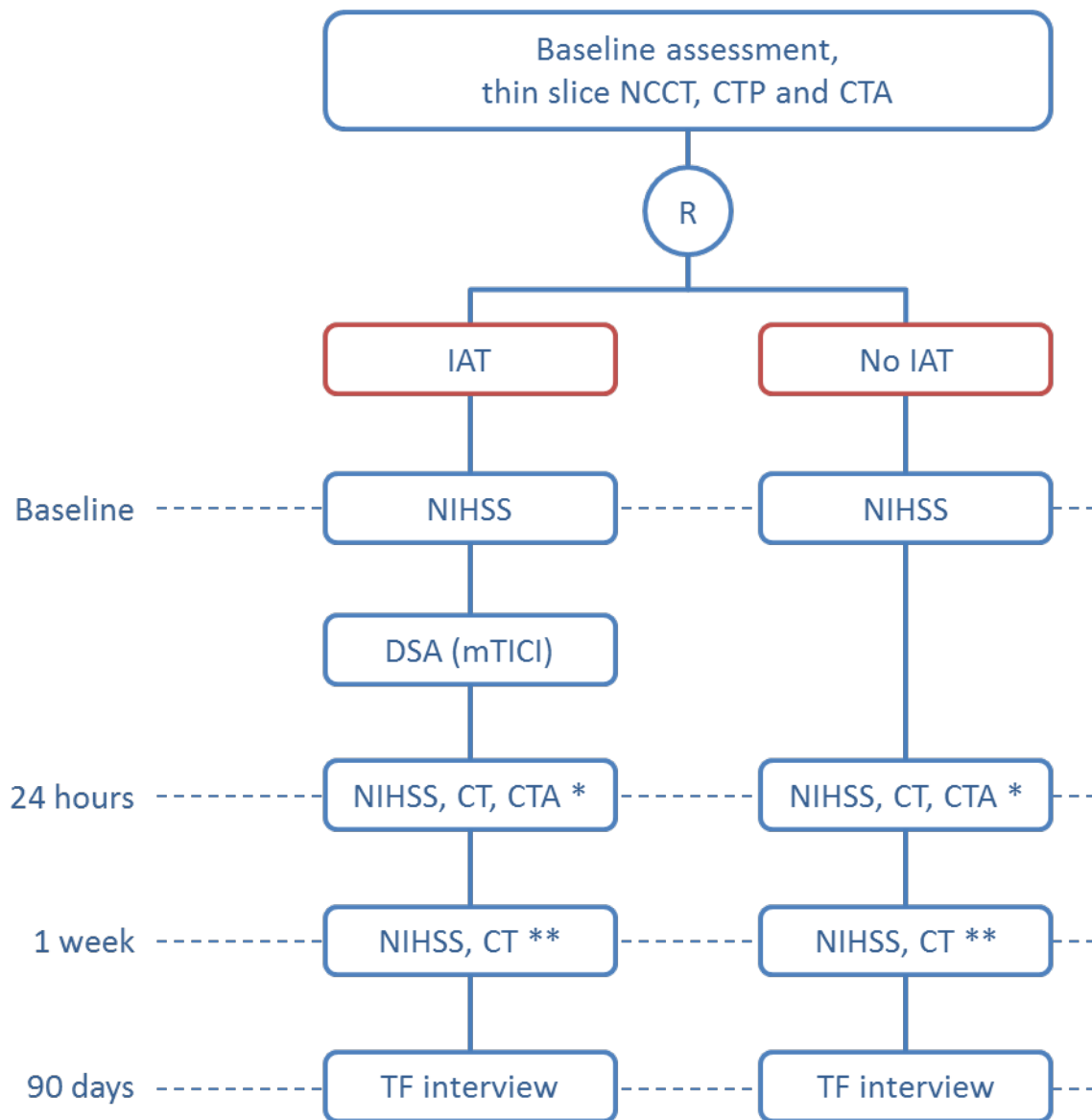
Dit was de laatste vraag.

15. FIGURES

Figure 1 MR CLEAN-LATE trial logo



Figure 2 Patient flow in the trial.



* NCCT/CTA at 24 hours (+/- 12h) or MRA at 24-48 hours after randomization

** CT follows only when CTA at 24 hours after randomization was made

16. APPENDICES

16.1 Appendix 1 List of collaborating investigators

Coordinating investigators

Drs. R.B. Goldhoorn, Dept of Neurology, Maastricht University Medical Center

Drs. F.A.V. Pirson, Dept of Neurology, Maastricht University Medical Center

Drs. S.G.H. Olthuis, Dept of Neurology, Maastricht University Medical Center

Principal investigators

Prof. dr. Robert J. Oostenbrugge, neurologist, Maastricht University Medical Center

Prof. dr. Wim H. van Zwam, radiologist, Maastricht University Medical Center

Local investigators:

- Maastricht University Medical Center:
 - Dr. J.E.A. Staals, neurologist
 - Prof. dr. W.H van Zwam, neuroradiologist
- Academic Medical Center:
 - dr. J. Coutinho, neurologist
 - Prof. dr. C.B.L.M. Majoie, neuroradiologist
- University Medical Center Utrecht
 - Dr. H.B. van der Worp, neurologist
 - Dr. T.H. Lo, radiologist
- Erasmus MC Rotterdam
 - Prof. dr. D.W.J. Dippel, neurologist
 - Prof. dr. A. van der Lugt, neuroradiologist
- Haaglanden Medical Center:
 - Dr. I.R. van den Wijngaard, neurologist
 - Dr. G. Lycklama à Nijeholt, neuroradiologist
- Radboud University Medical center:
 - Dr. E.J. van Dijk, neurologist
 - Dr. J. Boogaards, neuroradiologist
- Leidsch University Medical Center:

NL58246.078.17/ MR CLEAN LATE

- Dr. M. Wermer, neurologist
 - Dr. M. van Walderveen, neuroradiologist
- University Medical Center Groningen:
 - Dr. M. Uyttenboogaart, neurologist
 - Dr. R.P.H Bokkers, neuroradiologist
- Sint Antonius Hospital Nieuwegein:
 - Dr. W.J. Schonewille, neurologist
 - Dr. J.A. Vos, neuroradiologist
- Catharina Hospital:
 - Dr. R.A.R. Gons, neurologist
 - Dr. L. Yo, neuroradiologist
- Medical Spectrum Twente:
 - Dr. P.J.A.M. Brouwers, neurologist
 - Drs. T. Bulut, neuroradiologist
- Elisabeth-TweeSteden Hospital:
 - Dr. J.H. van Tuijl, neurologist
 - Drs. H.G.J. Kortman, neuroradiologist
- Isala Clinics:
 - Dr. H. den Hertog, neurologist
 - Dr. B.A.A.M van Hasselt, neuroradiologist
- Rijnstate Hospital:
 - Dr. J. Hofmeijer, neurologist
 - Dr. J.M. Martens, neuroradiologist
- Haga Hospital:
 - Dr. K.F. de Laat, neurologist
 - Dr. L.C. van Dijk, neuroradiologist
- Albert Schweitzer Hospital:
 - Dr. A.D. Rozeman, neurologist
 - Dr. O.E.H. Elgersma, neuroradiologist
- Amphia Hospital:
 - Dr. J.M. Remmers, neurologist
 - Dr. T.E.A.M de Jong, neuroradiologist
- Noordwest Ziekenhuisgroep:
 - Drs. B. van der Veen, neurologist
 - Drs. D. Sudiono, neuroradiologist

16.2 Appendix 2 Study committees

■ Data safety monitoring board

Chair: Professor Heinrich Mattle

Member: Doctor Jens Fischer

Independent Statistician: Sander van de Kuijk

■ Executive and writing committee

Prof. dr. Robert van Oostenbrugge, neurologist MUMC

Dr. Wim van Zwam, intervention radiologist, MUMC

Dr. Marianne van Walderveen, neuroradiologist, LUMC

Dr. Geert Lycklama a Nijeholt, neuroradiologist, MCH, The Hague

Dr. Wouter Schonewille, neurologist, St. Antonius Hospital, Nieuwegein

Dr. Maarten Uyttenbogaart, neurologist, UMCG Groningen

Prof. dr. Charles Majoie, neuroradiologist, AMC Amsterdam

Junior researchers at Maastricht University Medical Center.

■ Imaging assessment committee

CONTRAST Work Package: Imaging data management and analysis

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

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

WP collaborators (imaging assessments)

Dr. Wim van Zwam, Dr. Linda Jacobi (MUMC, Maastricht); Dr. Hugo de Jong, Dr. Irene van der Schaaf, Dr. Jan Willem Dankbaar (UMCU, Utrecht); Dr. Jasper Martens (Rijnstate Arnhem); Dr. René van den Berg, Dr. Stefan Roosendaal, Dr. Marieke Sprengers, Dr. Ludo F. Beenen, Dr. Bart Emmer (AMC, Amsterdam); Dr. Joost C. Bot (VUmc, Amsterdam); dr. Ad van Es, drs. Pieter-Jan Doormaal, Drs. W. Dinkelaar (Erasmus MC); Dr. Geert Lycklama and Dr. Bas van der Kallen (MCH, Den Haag); Sjoerd Jenniskens

(UMCN, Nijmegen); Marianne A. van Walderveen, Ido van den Wijngaard (LUMC, Leiden); Dr. Jo Peluso (Elisabeth Hospital, Tilburg); Dr. Albert J. Yoo (Texas Stroke Institute, Plano, Texas, United States of America)

■ Outcome assessment committee

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

Members:

Sanne Manschot, MD, PhD; Ido van den Wijngaard, MD, PhD; Jelis Boiten, MD, PhD (Haaglanden Medical Center, the Hague); Diederik Dippel, MD, PhD; Peter Koudstaal, MD, PhD (Erasmus MC, Rotterdam); Henk Kerkhof, MD, PhD, (Albert Schweitzer Hospital, Dordrecht); Jonathan Coutinho, MD, PhD (AMC, Amsterdam); Koos Keizer, MD, PhD (Catharina hospital, Eindhoven)

■ Adverse event adjudication committee

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

Members:

Bart Emmer, MD, PhD; Jonathan Coutinho, MD, PhD (AMC, Amsterdam); Ben Jansen, MD, PhD (Elisabeth-TweeSteden Hospital, Tilburg); Martine Truijman, MD, PhD; Julie Staals, MD, PhD (MUMC, Maastricht).

■ Statistical advisor and trial methodologist

Hester Lingsma, methodologist, Erasmus MC Rotterdam

■ Independent trial statistician

Daan Nieboer, Erasmus MC Rotterdam

16.3 Appendix 3 CONTRAST: collaboration for new treatments of acute stroke

16.3.1. CONTRAST Logo



16.3.2. 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

16.3.3. Overall scientific summary CONTRAST

The MR CLEAN-LATE 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 EVT and the expansion of its indication.

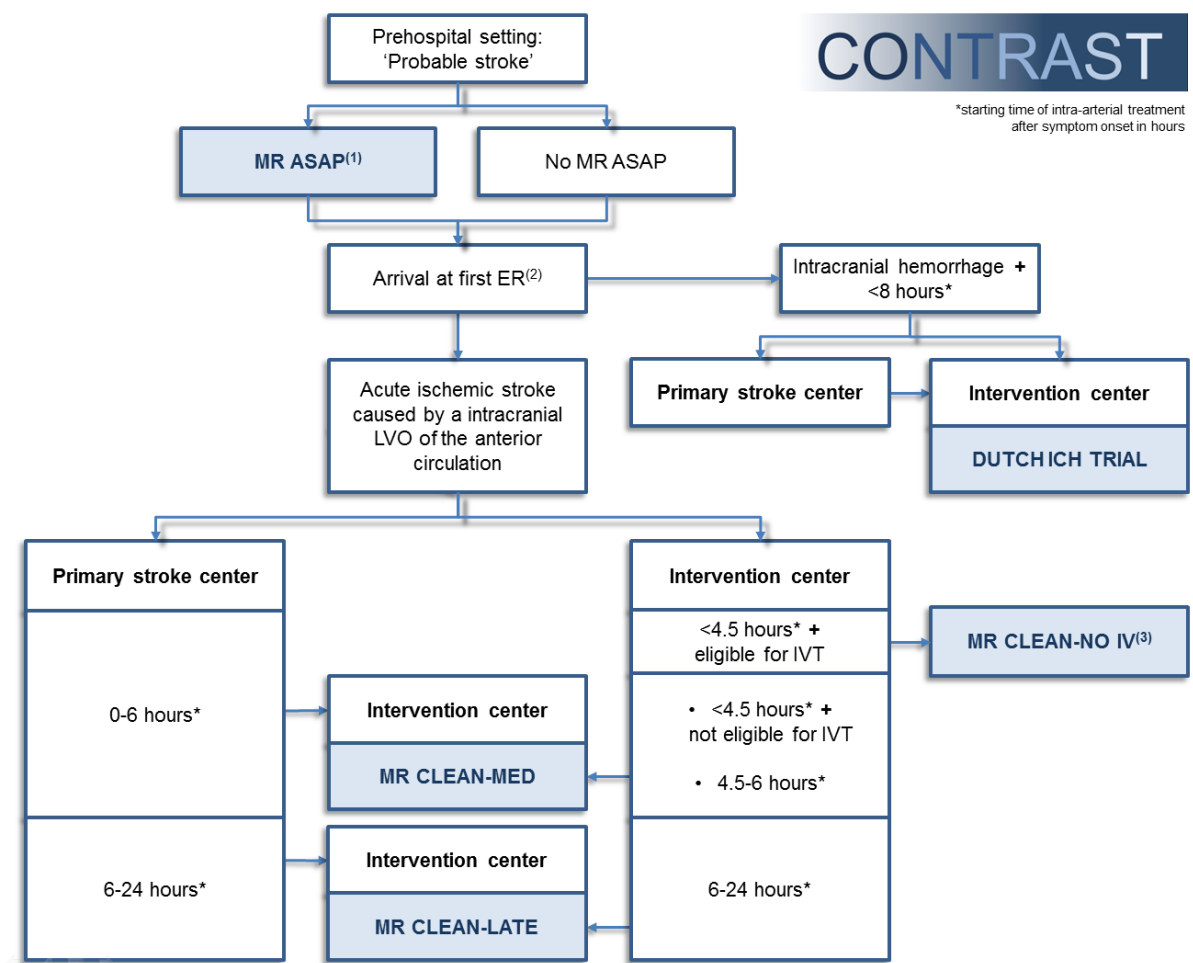
1. Multicentre Randomised trial of Acute Stroke treatment in the Ambulance with a nitroglycerin Patch (MR ASAP): pre-hospital augmentation of collateral blood flow and blood pressure reduction;
2. Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands. 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 EVT without preceding thrombolysis;
4. Multicenter Randomized Clinical Trial of Endovascular Stroke treatment in The Netherlands for Late arrivals: MR CLEAN-Late (MR CLEAN-LATE): EVT 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.

16.3.4 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 Treatment of Acute Ischemic Stroke 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 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.

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.

16.3.5 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 ischemic stroke, myocardial infarction, hypertension, hypercholesterolemia peripheral artery 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 | Serum creatinine, serum glucose, C-Reactive Protein, when available APTT and INR, - Biobank laboratory directly after randomization and +/- 1 hour after IAT. |

| | |
|----------------------------------|---|
| Neuro imaging² | [By imaging core lab] MR CLEAN LATE: infarctcore volume and penumbra volume according to local software assessment |
| 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; 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 |

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

| | |
|---|---|
| | descriptions; final DSA directions (PA/Lateral); post-eTICI on DSA |
| Complications | <p>Procedure-related complications: distal thrombus, dissection and location, embolization in new/other vascular territory and location, perforation and location, other complication and description;</p> <p>Neurological deterioration of 4 points or more on the NIHSS; Neurological deterioration of 2 points or more on one NIHSS item</p> |
| 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 | <p>Target lesion/occlusion location per attempt;</p> <p>eTICI score after every attempt;</p> <p>Technique: guiding catheter, distal access catheter , stent retriever, intra-arterial thrombolysis;</p> <p>Types and sizes: guiding catheter type and size, microcatheter type, distal access catheter type and size, stent retriever dimensions and type</p> <p>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)</p> |
| Stent/thrombus | <p>Stent sent for pathology yes/no (BIOBANK)</p> <p>Thrombus sent for pathology yes/no (BIOBANK)</p> |
| 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 |

NL58246.078.17/ MR CLEAN LATE

| | |
|-------------|--|
| | 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 (not for MR CLEAN-NO IV): 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, CT perfusion or DWI MRI randomization |

| Follow-up | |
|---|---|
| Clinical assessment at 24 hours | NIH Stroke Scale |
| Laboratory at 24 hours | CONTRASTBiobank blood drawn |
| CT/CTA at 24 hours | CT angiography: Occlusion location, Clot Burden Score, Collateral score |
| MRI/MRA at 24-48 hours | MRI: infarct size and location, hemorrhagic transformation (Heidelberg Bleeding Classification) MRA: Occlusion location, Clot Burden Score, Collateral Score |
| Neuro imaging at 5-7 days (following CT imaging at 24 hours) | 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 |
| 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 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> |
|--|---|

16.4 Appendix 4 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 |
| EQ5D5L | | | | 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 appointment at 3 months.

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

16.5 Appendix 5 Imaging requirements

16.5.1 Minimum baseline imaging requirements

- **When**

1) Before randomization a NCCT, CTP and CTA 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 CTP:
 1. CTP should preferably cover the whole brain. If whole brain coverage is not available, then a minimum 8 cm coverage is required, from skull base to upper border of A2 segment.
3. 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
4. After acquisition
 1. All images (NCCT, CTP and CTA) 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).

■ 16.5.2 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 TICl 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.
- o 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.

16.5.3 Minimum follow-up imaging requirements

▪ When

1) 24 hours after randomization, a CTA or MRI and MRA (24-48h) should be performed.

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 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

○ 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.

○ 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)

NL58246.078.17/ MR CLEAN LATE

- Additional, clinically required imaging
- 6. At the discretion of the treating physician
After acquisition
- 7. All images (NCCT, CTA, MRI, MRA 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).

16.6 Appendix 6 Trial organisation

The MR CLEAN LATE 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.

Deferred consent in acute stroke trials - CONTRAST

- Concept research protocol

Investigators

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■ Background and rationale

The informed consent procedure is considered fundamental for inclusion in a randomised clinical trial. However, the informed consent procedure in acute stroke research is challenging.

Acute stroke patients are often incapacitated and not able to provide their own consent prior to enrolment. Many patients have a decreased decision making capacity due to severe neurological deficits. In a Dutch registry with data of all patients who underwent endovascular treatment for acute ischemic stroke, 88% had neurological symptoms (aphasia, neglect, lowered consciousness level or confusion) interfering with their capacity to decide about participation in a clinical trial (unpublished data).

According to the 'time is brain' principle and time to treatment effects of endovascular treatment and intravenous thrombolysis, treatment should be initiated as soon as possible.(1) Each hour delay to reperfusion is associated with an increase in absolute risk of death or disability of 6-7%.(2)

As an alternative, a legal representative can be asked to give consent for participation in the trial. However, family members are often not available in the acute setting.(4,5) They might be too overwhelmed to understand the provided information to give valid consent, and experience psychological stress.(6) Also, not all patients want their family members to be their surrogate and many proxies do not know what the patient's wishes are for acute medical research.(7,8,9)

A person who gives consent should be able to understand information, balance benefits and risks and comprehend the severity of the illness. The capacity to consent for enrolment in a trial is subjectively estimated by the researcher or clinician. The comprehension of stroke patients and their proxies of the methods of the trial after providing (prospective) consent is diminished, as shown in a few studies.(10–13) Moreover, data is lacking on whether acute stroke patients and their proxies judge themselves capable of consenting to a clinical trial.

Deferred consent

An alternative for prospective (proxy) informed consent is deferred consent. In this procedure, consent is asked after enrolment in the study. In the Netherlands, deferred consent is possible in emergency situations. According to the Medical Research Human Subjects Act (Dutch: WMO), procedures of the clinical trial may be undertaken without consent as long as circumstances prevent the giving of consent and if inclusion in the trial may benefit the person in urgent need of medical treatment. No data on deferred consent in acute stroke research has been published yet.

The COllaboration for New Treatment of Acute Stroke (CONTRAST) investigates novel treatment strategies, aimed at preservation of ischemic tissue and improvement of functional outcome in patients with acute ischemic stroke. The CONTRAST consortium entails three trials on endovascular treatment and one prehospital trial. In these trials we will use a deferred consent procedure (figure 1).

Benefits and drawbacks of deferred consent

– Effect on treatment delays.

The use of the deferred consent procedure might reduce time to study (drug) treatment, with potential beneficial effects, and reduce delay to standard stroke treatments since the CONTRAST trials will study adaptations of endovascular treatment. No disadvantages of deferred consent on treatment delays are expected.

Influence on decision-making competence.

Decision-making competence is based on factual understanding, evidencing a choice (consent or refusal), and reasoning and appreciation of the situation. In the acute phase of an emergency situation, patients and relatives are in emotional distress and can be considered temporarily incompetent in these three points. Hence, patients and their relatives can be regarded temporarily incompetent for valid proxy consent in an emergency situation.(6) Deferment of the conversation might lead to a more ethically valid informed consent and a better informed decision.

Still, there is no consistency in the duration of the acute phase of the emergency situation. The moment patients and proxies regain decision-making competence is not defined. Also, patients and proxies might not regard themselves competent of making a decision in the day(s) after the emergency situation.

In addition, some patients and proxies will feel capable of making a decision and could object to the deferred consent procedure itself because they not understand the reasons for the postponement of asking consent. This could interfere with the decision they will make.

– Patient enrolment and selection bias.

It might increase patient enrolment and reduce selection bias resulting in better generalizable study results. Meanwhile, should many patients and proxies object against enrolment, this could likewise contribute to selection bias.

■ Main objective

The aim of the current study is to increase knowledge about the deferred consent procedure in acute stroke research. We will collect and analyse data on logistics of the procedure and on patient recall, satisfaction, and comprehension at three months from randomization.

Specific objectives

1. To estimate the proportions of patients and proxies that give consent for and object against enrolment in acute stroke trials using deferred consent procedures;
2. To map the workflow and timeline of the deferred consent procedure;
3. To explore the personal feeling of capability of patients and proxies to provide consent for participation in an acute stroke controlled trial;
4. To explore appreciation of patients and proxies of the deferred informed consent procedure;
5. To investigate recall and comprehension by patients and proxies of study methods of the acute stroke trial for which they provided deferred consent;
6. To compare the observations on 1-5 with data from previous acute stroke trials.

■ Methods

Study design

This study will be a descriptive, observational substudy nested in 4 acute stroke trials within the CONTRAST consortium. We will prospectively collect data on logistics of the deferred consent procedure and ask patients and proxies to fill out questionnaires.

Study population

Patients and their proxies participating in one or two of the CONTRAST trials.

Inclusion criteria

- Participation in at least one of the CONTRAST trials.
 - Multicentre Randomised trial of Acute Stroke treatment in the Ambulance with a nitroglycerin Patch (MR ASAP)
 - Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands. The effect of concomitant MEDication: heparin, antiplatelet agents, both or neither (MR CLEAN-MED)
 - 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)
 - Multicenter Randomized Clinical Trial of Endovascular Stroke treatment in The Netherlands for Late arrivals: MR CLEAN-Late (MR CLEAN-LATE)

Exclusion criteria

Proxies of deceased patients will not be interviewed.

Duration of data collection

We aim to collect data on deferred consent of 300 patients during the first year of enrolment in the CONTRAST trials. Data collection will start 3 months after the first inclusion in the study.

Patient recruitment

Patients / proxies who provided consent for participation in the trial

During the 3 month telephone follow-up of the CONTRAST trial, the subject who provided consent will be asked to participate in this substudy. The purpose of the study will be explained and the study procedures will be described. Questionnaire 1 will be sent to their

home address. The feeling of capability for giving consent, appreciation of the informed consent process and recall and comprehension will be explored in this questionnaire.

For participation in this substudy, no additional written informed consent from individual subjects is needed.

Patients / proxies who withheld consent for participation in the trial

The patient or proxy who refused to give deferred consent for participation in the CONTRAST trial will be approached. The purpose of the study will be explained and the study procedures will be described. They will be asked to only fill out Questionnaire 2, which concerns the reasons for not giving consent. It will be emphasized that it is not mandatory to answer. No additional questionnaires or interviews will be carried out within this patient group.

■ Study procedures

Baseline information

The following baseline characteristics, already collected in the CONTRAST trials, will be used: age, sex, baseline NIHSS - including NIHSS subitems, stroke type, study site and treatment arm (intervention vs. control). The 3 month modified Rankin Scale score (mRS) will also be used.

Additionally we will document the educational level of the subject who provided consent.

Patient enrolment

The CONTRAST trials use different deferred informed consent forms (ICFs):

- 1) Patient: the patient is mentally competent to provide consent, as estimated by the researcher/clinician
- 2) Proxy (partner or family member): the patient is not mentally competent to provide consent, as estimated by the researcher/clinician, and the researcher/clinician believes it is ethically valid to inform and ask for consent

In case the patient has deceased before consent could be asked, the proxy will have the ability to object to the anonymous use of the data which has been documented so for study purposes (figure 1).

The following data will be documented regarding patient enrolment:

- the number of patients providing consent vs. not providing consent + reasons for not providing consent
- the number of proxies providing consent vs. not providing consent + reasons for not providing consent
- the number of patients who deceased before consent could be asked
- the number of patients that withdrew their consent within 3 months

Deferred consent workflow and timeline

The study protocols of the CONTRAST trials state that deferred informed consent will be obtained as soon as possible. In the MR ASAP trial, the nitroglycerin patch will be removed after 24 hours. However, when a patient refuses to provide consent, the patch will be removed directly. For the subsequent CONTRAST trials, the first follow-up CT scan will be performed 24 hours after randomisation (Figure 1).

We will document time intervals from symptom onset until consent has been obtained. The timeline will contain the following time measurements, if applicable.

1. MR ASAP: onset – randomisation/treatment – ER – inclusion in subsequent CONTRAST trial – IVT – EVT – start IC conversation – signature patient/proxy
2. MR CLEAN-NO IV: onset – inclusion in MR ASAP – ER – randomisation – IVT – EVT – start IC conversation – signature patient/proxy
3. MRCLEAN-MED: onset – inclusion in MR ASAP – ER – IVT – randomisation – EVT – start IC conversation – signature patient/proxy
4. MRCLEAN-LATE: onset – inclusion in MR ASAP – ER – IVT – randomisation – EVT – start IC conversation –signature patient/proxy

ER: emergency room; IVT: intravenous thrombolysis; IAT: intra-arterial treatment; IC: informed consent

On the ICF we will record date and time of:

- start of informed consent conversation; and
- signature of patient or proxy.

The remaining time measurements will be recorded in the electronic case report form (eCRF).

We will compare of the numbers and time intervals of patient vs. proxy consent in our study with data from the Multicenter Randomized CLinical trial of Endovascular treatment for Acute Ischemic stroke in the Netherlands (MR CLEAN).

1. Capability of patients and proxies of providing consent for participation

After 3 months the primary outcome of the CONTRAST trials will be assessed during a telephone interview by a blinded assessor. During the follow-up interview the patient or proxy will be asked if they would like to continue participating in this substudy.

Questionnaire 1 will be sent to their home address with the questions regarding this objective and objective 4 and 5.

2. Appreciation of patients and proxies of the deferred informed consent procedure

See objective 3.

3. Recall and comprehension of study methods of the trial

See objective 3.

■ **Statistical analysis**

Results will be reported for the trials separately and the CONTRAST trials all together.

This is an observational study. We will describe the distribution of consent process variables, as well as time and logistics parameters. We will relate characteristics of the neurological deficit, as measured with the NIHSS scale with the legal capability status of the patient. Finally, we will compare the consent parameters, including time intervals, with data from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN). Variables will be compared with Chi square test for categorical variables and Mann-Whitney for continuous variables. A p-value below 0.05 will be considered statistically significant.

■ **Ethical considerations**

This study will be performed according to ICH-GCP principles, the Declaration of Helsinki as most recently amended in 2013, and national regulatory requirements, as the European trial Directive and the European privacy regulation. We are awaiting approval by the institutional review board of the Erasmus MC University Medical Center.

■ **Nature and extent of the burden of participation**

The study procedures will require an estimated maximum of 30 minutes of the subject's time at 3 months (Questionnaire 1) and 5 minutes of the subject's time during hospital admission (Questionnaire 2) and. We therefore consider the burden minimal.

■ **Handling of data and documents**

The results of this substudy will be reported during the active enrolment in the CONTRAST trials. The conclusions of this substudy may have consequences for the actual consent study procedures.

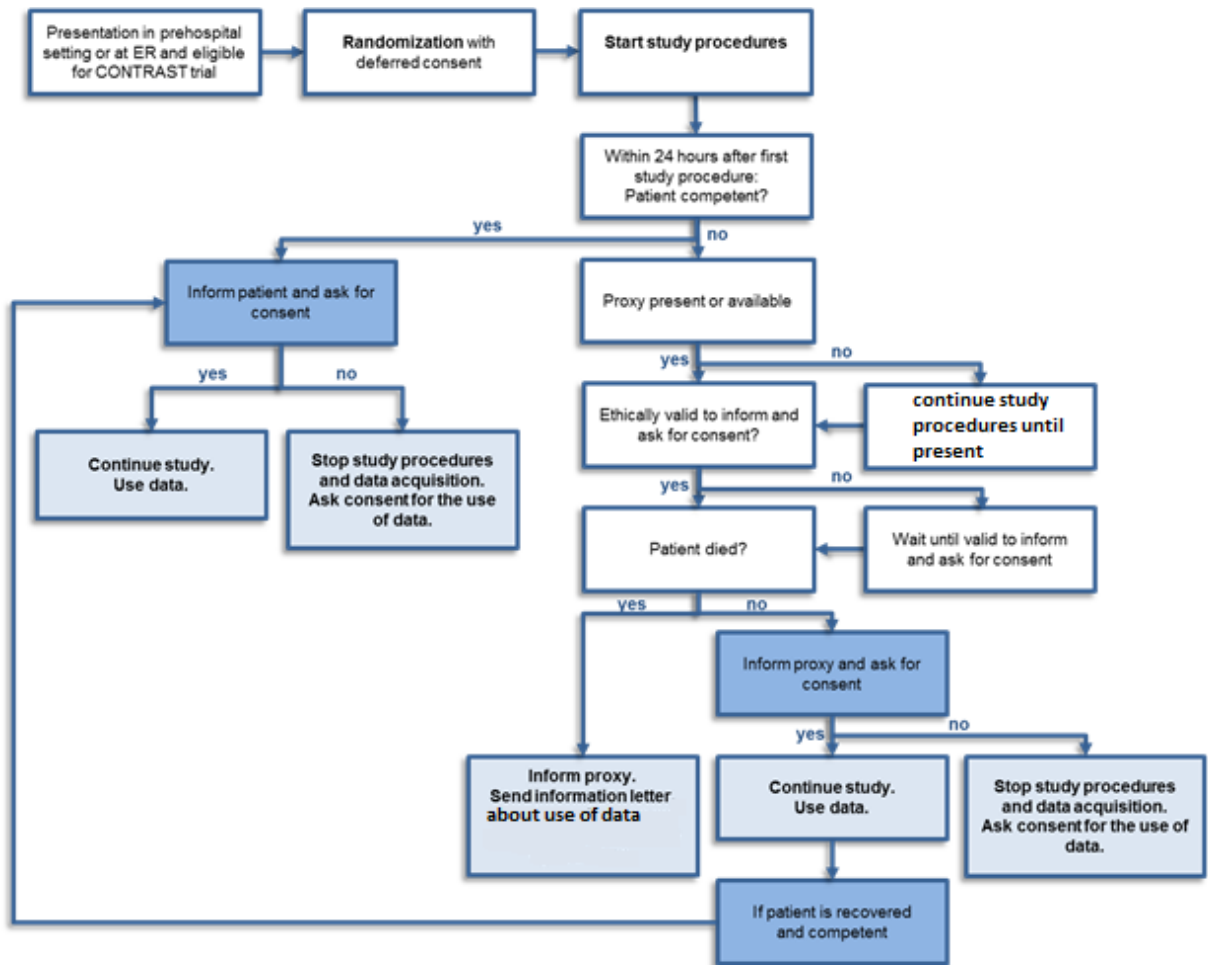
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Figure 1



■ Questionnaire 1 – patient – after 3 months

Enquêtevragen als patiënt toestemming heeft gegeven voor deelname aan het onderzoek.

[voor start vragenlijst: informatie deferred consent en redenen voor dit onderzoek]

Algemeen

Wat is uw hoogst genoten opleiding? (keuze)

- geen
- basisschool
- lager beroepsonderwijs (LBO, VMBO)
- middelbaar algemeen voorbereidend onderwijs (MAVO)
- middelbaar beroepsonderwijs (MBO)
- hoger algemeen voorbereidend, wetenschappelijk onderwijs (HAVO, VWO)
- hoger beroepsonderwijs (HBO)
- kandidaats/propedeuse wetenschappelijk onderwijs (WO)
- (post) wetenschappelijk onderwijs
- weet niet / wil ik niet zeggen

Vragen over uw kennis en begrip over de methode van het onderzoek

1. Vindt u zelf dat u voldoende weet over het onderzoek?

I. Ik vind dat ik voldoende weet over het **doel** van het onderzoek

- Ja
- Nee

II. Ik vind dat ik voldoende weet over de **opzet** van het onderzoek

- Ja
- Nee

2. Heeft u de informatiebrief gelezen?

- Ja
- Nee

3. Heeft u de informatiebrief begrepen?

- Ja
- Nee

4. Welke behandeling werd in dit onderzoek getest? (vrije tekst)

5. Hoe werd besloten welke behandeling u kreeg? (vrije tekst)

6. Welke behandeling heeft u of uw naaste gekregen? (vrije tekst)

7. Waren er risico's en nadelen verbonden aan meedoen aan het onderzoek? (ja/nee + vrije tekst)

8. Waren er voordelen verbonden aan meedoen aan het onderzoek? (ja/nee + vrije tekst)

9. Was deelname aan het onderzoek vrijwillig of verplicht?

- Vrijwillig
- Verplicht

10. Was het mogelijk uw toestemming voor deelname aan het onderzoek in te trekken?

- Ja
- Nee

11. Wie had toegang tot uw persoonlijke gegevens en ziektegeschiedenis? (vrije tekst)

Vragen over uw waardering over de toestemmingsprocedure

12. Voelde u zich destijds in staat om te beslissen over deelname aan dit onderzoek?

- Ja (ga naar vraag 16)
- Nee (ga hieronder verder)

13. Wie had u liever deze beslissing willen laten maken?

- Mijn behandelend arts
- Een familielid, namelijk:
- Toestemming voor dit onderzoek vind ik niet nodig

14. Waarom voelde u zich niet in staat om te beslissen over deelname aan dit onderzoek?
(meerdere antwoorden mogelijk)

- I. Ik vond het te veel informatie
- II. Ik begreep de uitleg niet goed
- III. Ik voelde mij gestresst
- IV. Deze vraag kwam te snel na de beroerte
- V. Ik heb te weinig bedenktijd gehad
- VI. Anders, namelijk:

15. Had u genoeg tijd om een beslissing te maken?

- Ja
- Nee

16. Had u liever gewild dat de vraag voor deelname aan het onderzoek op een ander moment was gekomen?

- Ja (ga naar de volgende vraag)
- Nee (ga naar vraag 19)

17. Zo **ja**, op welk moment had u liever gewild dat deze vraag aan u was gesteld? (één keuze)

- Eerder: nog vóór alle studiehandelingen, inclusief de behandeling
- Eerder na de studiehandelingen: binnen 12 uur in plaats van binnen 24 uur
- Later: binnen 72 uur in plaats van binnen 24 uur

18. Had u het goed vonden als een familielid voor u deze beslissing had gemaakt?

- Ja

Nee

19. Welke beslissing zou uw familielid hebben gemaakt, als uw familielid voor u deze beslissing had gemaakt?

Meedoen met het onderzoek

Niet meedoen met het onderzoek

20. Als de toestemmingsprocedure op een later tijdstip had plaatsgevonden (bijvoorbeeld binnen 72 uur in plaats van binnen 24 uur), zou u ermee akkoord gaan als er dan ook meer studiehandelingen (zoals bloedprikken of een CT-scan van het hoofd) zouden zijn uitgevoerd?

Ja

Nee

21. Hoe ervaart u de uitgestelde toestemmingsprocedure? (onderstaande Likert schaal + vrije tekst)

————— ————— ————— —————

heel negatief redelijk negatief neutraal redelijk positief heel positief

■ Questionnaire 1 – proxy – after 3 months

Enquêtevragen als proxy (familielid of partner) toestemming heeft gegeven voor deelname aan het onderzoek.

[voor start vragenlijst: informatie deferred consent en redenen voor dit onderzoek]

Algemeen

- Geslacht
 - Man
 - Vrouw
- Leeftijd (vrije tekst)

Wat is uw hoogst genoten opleiding? (keuze)

- geen
- basisschool
- lager beroepsonderwijs (LBO, VMBO)
- middelbaar algemeen voorbereidend onderwijs (MAVO)
- middelbaar beroepsonderwijs (MBO)
- hoger algemeen voorbereidend, wetenschappelijk onderwijs (HAVO, VWO)
- hoger beroepsonderwijs (HBO)
- kandidaats/propedeuse wetenschappelijk onderwijs (WO)
- (post) wetenschappelijk onderwijs
- weet niet / wil ik niet zeggen

Vragen over verloop toestemmingsprocedure en methode van het onderzoek

1. Vindt u zelf dat u voldoende weet over het onderzoek?
 - I. Ik vind dat ik voldoende weet over het **doel** van het onderzoek

- Ja
- Nee

II. Ik vind dat ik voldoende weet over de **opzet** van het onderzoek

- Ja
- Nee

2. Heeft u de informatiebrief gelezen?

- Ja
- Nee

3. Heeft u de informatiebrief begrepen?

- Ja
- Nee

4. Welke behandeling werd in dit onderzoek getest? (vrije tekst)

5. Hoe werd besloten welke behandeling u kreeg? (vrije tekst)

6. Welke behandeling heeft u of uw naaste gekregen? (vrije tekst)

7. Waren er risico's en nadelen verbonden aan meedoen aan het onderzoek? (ja/nee + vrije tekst)

8. Waren er voordelen verbonden aan meedoen aan het onderzoek? (ja/nee + vrije tekst)

9. Was deelname aan het onderzoek vrijwillig of verplicht?

- Vrijwillig
- Verplicht

10. Was het mogelijk uw toestemming voor deelname aan het onderzoek in te trekken?

- Ja
- Nee

11. Wie had toegang tot uw persoonlijke gegevens en ziektegeschiedenis? (vrije tekst)

Vragen over uw waardering van de toestemmingsprocedure

12. Voelde u zich destijds in staat om te beslissen over deelname aan dit onderzoek?

- Ja (ga naar vraag 16)
- Nee (ga hieronder verder)

13. Wie had u liever deze beslissing willen laten maken?

- Mijn behandelend arts
- Een familielid, namelijk:
- Toestemming voor dit onderzoek vind ik niet nodig

14. Waarom voelde u zich niet in staat om te beslissen over deelname aan dit onderzoek?
(meerdere antwoorden mogelijk)

- I. Ik vond het te veel informatie
- II. Ik begreep de uitleg niet goed
- III. Ik voelde mij gestresst
- IV. Deze vraag kwam te snel na de beroerte
- V. Ik heb te weinig bedenktijd gehad
- VI. Anders, namelijk:

15. Had u genoeg tijd om een beslissing te maken?

- Ja
- Nee

16. Had u liever gewild dat de vraag voor deelname aan het onderzoek op een ander moment was gekomen?

- Ja (ga naar de volgende vraag)
- Nee (ga naar vraag 19)

17. Zo **ja**, op welk moment had u liever gewild dat deze vraag aan u was gesteld? (één keuze)

- Eerder: nog vóór alle studiehandelingen, inclusief de behandeling
- Eerder na de studiehandelingen: binnen 12 uur in plaats van binnen 24 uur
- Later: binnen 72 uur in plaats van binnen 24 uur

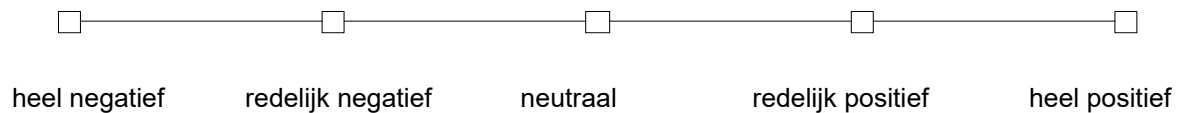
18. U hebt als familielid de beslissing voor uw naaste gemaakt. Welke beslissing zou uw naaste zelf hebben gemaakt?

- Meedoen met het onderzoek
- Niet meedoen met het onderzoek

19. Als de toestemmingsprocedure op een later tijdstip had plaatsgevonden (bijvoorbeeld binnen 72 uur in plaats van binnen 24 uur), zou u ermee akkoord gaan als er dan ook meer studiehandelingen (zoals bloedprikken of een CT-scan van het hoofd) zouden zijn uitgevoerd?

- Ja
- Nee

20. Hoe ervaart u de uitgestelde toestemmingsprocedure? (onderstaande Likert schaal + vrije tekst)



■ Questionnaire 2 – patient

[voor start vragenlijst: informatie deferred consent en redenen voor dit onderzoek]

Enquêtevragen als patiënt om uitgestelde toestemming is gevraagd voor deelname aan de CONTRAST trial en geen toestemming heeft gegeven.

Wat was de reden dat u geen toestemming heeft gegeven? (meerdere opties mogelijk)

- Dit wil ik niet zeggen
- Ik wil niet dat er gegevens verzameld worden van mij
- Ik vond het te veel informatie
- Ik begreep de uitleg niet goed
- Ik voelde mij gestresst
- Deze vraag komt te snel na de beroerte
- Ik heb te weinig bedenktijd gehad
- Ik vind dat iemand anders, namelijk de behandelend arts deze beslissing voor mij moet maken
- Ik vind dat iemand anders, namelijk mijn partner en/of ander familielid deze beslissing voor mij moet maken
- Anders, namelijk:

Wat is uw hoogst genoten opleiding? (keuze)

- geen
- basisschool
- lager beroepsonderwijs (LBO, VMBO)
- middelbaar algemeen voorbereidend onderwijs (MAVO)
- middelbaar beroepsonderwijs (MBO)
- hoger algemeen voorbereidend, wetenschappelijk onderwijs (HAVO, VWO)

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- hoger beroepsonderwijs (HBO)
- kandidaats/propedeuse wetenschappelijk onderwijs (WO)
- (post) wetenschappelijk onderwijs
- weet niet / wil ik niet zeggen

■ Questionnaire 2 – proxy

[voor start vragenlijst: informatie deferred consent en redenen voor dit onderzoek]

Enquêtevragen als proxy (familielid of partner) om uitgestelde toestemming is gevraagd voor deelname aan de CONTRAST trial en geen toestemming heeft gegeven.

Wat was de reden dat u geen toestemming heeft gegeven? (niet verplicht)

- Dit wil ik niet zeggen
 - Ik wil niet dat er gegevens verzameld worden van mijn partner/familielid
 - Ik vond het te veel informatie
 - Ik begreep de uitleg niet goed
 - Ik voelde mij gestresst
 - Deze vraag komt te snel na de beroerte
 - Ik heb te weinig bedenktijd gehad
 - Ik vind dat iemand anders, namelijk de behandeld arts deze beslissing moet maken
 - Ik vind dat iemand anders, namelijk een ander familielid deze beslissing moet maken
 - Anders, namelijk:
-
- Geslacht
 - Man
 - Vrouw
 - Leeftijd (vrije tekst)
 - Wat is uw hoogst genoten opleiding? (keuze)
 - geen
 - basisschool

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- lager beroepsonderwijs (LBO, VMBO)
- middelbaar algemeen voorbereidend onderwijs (MAVO)
- middelbaar beroepsonderwijs (MBO)
- hoger algemeen voorbereidend, wetenschappelijk onderwijs (HAVO, VWO)
- hoger beroepsonderwijs (HBO)
- kandidaats/propedeuse wetenschappelijk onderwijs (WO)
- (post) wetenschappelijk onderwijs
- weet niet / wil ik niet zeggen