

Information for clinical trial subjects concerning the participation in medical scientific research

A study on the effect of intravenous thrombolysis before intra-arterial treatment for an acute ischemic stroke

Official English title: 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.

Introduction

Dear sir/madam,

We ask you to participate in medical scientific research. Participation is voluntary. To participate, we need your written consent. You receive this letter because you suffered an ischemic stroke. By now you will have been informed by your treating physician and are recovering from this illness. Because it was in your interest to be treated as quickly as possible the medical ethical committee was asked to defer your consent until after the treatment. As the risks of this study are small, the medical ethical committee gave permission to do so. This means that you have already undergone the study treatment or the standard treatment. This was decided by randomization. When you were admitted to hospital, your medical condition rendered you legally incapacitated to give consent for participation in medical research. We therefore asked your partner, family member or other representative (from here on: *your representative*) for consent to participate in this study. Your representative gave their consent after an explanation of the nature of this study. Now that your medical condition has improved, we can inform you ourselves what the study entails and ask you personally for your consent to participate. Before you decide, this letter of information will explain what the study involves. Take the time to read this information thoroughly and ask any questions to the researcher. You can also consult the independent expert, who is named at the end of this letter, for additional information. Lastly, you can discuss the information with your partner, friends or family.

1. General Information

This study was initiated by the Amsterdam UMC, location AMC (hereafter: AMC) in Amsterdam, The Netherlands, and is performed by doctors in several medical centers in Europe. The medical ethical committee of the Erasmus University Medical Center (EMC) in Rotterdam, the Netherlands approved this study. General information about obtaining approval for medical research can be found in the brochure "Medical scientific research" (appendix F).

2. Aim of this study

The aim of this study is to determine whether it is still necessary to administer a powerful blood clot dissolvent (intravenous thrombolysis, IVT) in addition to the intra-arterial treatment with a catheter for acute ischemic stroke.

3. Study background

You have been admitted to the hospital because you suffered an ischemic stroke. An ischemic stroke is caused by the blocking of an artery in the brain by a blood clot. Therefore, part of the brain did not receive blood and was damaged. The following symptoms can be caused by an ischemic stroke: paralysis, tingling sensation, problems with speaking and understanding speech and/or partial blindness. To improve the chance of recovery, patients are treated with a catheter treatment via the groin (intra-arterial treatment) if possible. With this intra-arterial treatment, the blood clot is removed from the artery. This treatment is only possible if it can be started within 6 hours from the start of symptoms.

Approximately 1 in every 3 treated patients regains functional independence after a recovery period of 3 months. Even if the clot is removed from the artery successfully, not all patients recover well after intra-arterial treatment. Sometimes this may be caused by the development of a hemorrhage, worsening the symptoms. We think that the current standard treatment of IVT, administered before the intra-arterial treatment, may cause these hemorrhages. Not administering IVT could therefore lead to better outcomes. However, not giving IVT could possibly lead to impaired dissolving of small clots that stay behind after intra-arterial treatment. Thus, with this study we wish to determine whether it is better to omit IVT.

4. What does participation involve?

Duration

The total study duration, from treatment to last (telephone) interview approximately 3 months.

Treatment

As the treatment had to be initiated as soon as possible, you already have been allocated to one of the following two groups:

Group 1: was directly treated with the intra-arterial treatment

Group 2: was treated with IVT before intra-arterial treatment (control group, standard treatment).

Treatment allocation and undergoing the treatment before asking consent has been approved by the medical ethical committee because we do not expect increased risk from withholding the standard treatment. Moreover, we expect less hemorrhages if we withhold the standard treatment.

Additionally, it's important to inform you elaborately about this study. As ischemic strokes demand immediate treatment to save as much brain tissue as possible, providing this elaborate information before treatment is not possible nor is it ethical.

To keep the distribution of patients over the two treatment groups as even as possible, we used randomization to decide to which group you were allocated. More information about randomization can be found in the brochure “Medical scientific research” (appendix F).

In total during the whole study, blood will be drawn an extra three times. Further, we want to ask permission to use any remaining material for eventual use in further research. The blood clots taken from the artery will be stored in a biobank. They will be analyzed and studied under a microscope to determine whether certain characteristics of the clots are related to the cause of the infarct and to the eventual effect of the treatment.

If you were randomized into group 1, you underwent the intra-arterial treatment without IVT administered beforehand. This means that you were moved to the intervention room almost immediately after undergoing the scan of your brain. In the intervention room a catheter was inserted in the artery in your groin, under local anesthesia, sedation or general anesthesia. While using X-ray imaging, this catheter was moved to the occluded artery in the head. There, the physician attempted to remove the clot occluding the artery using mechanical thrombectomy (using stents with or without suction). The intervention took approximately 1 hour.

If you were randomized to group 2, the control group, you also were administered IVT before the intra-arterial treatment. This means that, after the scan of your brain was completed, we administered a very powerful blood clot dissolving drug. Afterwards, you were also brought to the intervention room, where you underwent intra-arterial treatment.

Visits and tests

During your stay in hospital so far, you possibly already underwent part or all of the following tests:

- Physical examination on the ER before the intra-arterial treatment and directly after the intra-arterial treatment on the stroke unit by the treating physician.
- CT-scan or MRI-scan with and without contrast administration on the ER.
- 3 blood drawings: within 1 hour before, and within 1 hour after the intra-arterial treatment, and after 24 hours. At every blood drawing, a maximum of 20 ml of blood was drawn to analyze biomarkers (including DNA and coagulation). These blood drawings are meant to assess at a later date the relation between coagulation and the severity, extent and origin of the infarct, and the relation with the effect of not giving the powerful clot dissolution.
- Intra-arterial treatment with or without administration of IVT beforehand.
- Storage of the clot that has been removed during the intra-arterial treatment.
- A CT-scan with and without contrast or MRI-scan of your head, 24 hours after treatment.
- At approximately 5-7 days after treatment or before discharge from the hospital (if this occurs earlier than 5-7 days).
 - o A physical examination;
 - o If you underwent a CT-scan at 24-hours, a CT-scan without contrast of your head.

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After discharge from the hospital you will be called once by a member of the study team from the AMC, EMC, Maastricht University Medical Center or University Medical Center Utrecht. This telephone interview will take place approximately 3 months after treatment. You will be questioned about your health. This telephone interview will take 15-30 minutes and will be planned with a member of the study team. If you have a routine check in the polyclinic, we will draw 20 ml of blood one additional time. It is possible that you will be asked to fill in a questionnaire about the informed consent procedure.

Differences from standard care

Some tests are part of standard care. Additional tests specifically for this study are the CT-scan with and without contrast or MRI-scan after 24 hours and the CT-scan without contrast after 5-7 days or before discharge from the hospital, the 4 blood drawings and the storage of the extracted clot.

In appendix C you will find a schematic overview of all these tests.

5. What is expected of you

To ensure the study goes according to plan, it is important you adhere to the following rules:

- 1) You do not participate in another medical study with the exception of the MR ASAP trial.
- 2) You contact the researcher
 - If you are admitted to or treated in a hospital.
 - If you have sudden problems with your health.
 - If you no longer want to participate in the study
 - If your contact information changes

6. Possible side-effects/complications or other unfavourable effects

It is known that IVT increases the risk of hemorrhages in patients with an ischemic stroke. Not giving IVT would therefore lower the risk of hemorrhage.

Tests

Blood drawings can be painful or cause a hematoma. In total, a maximum of 100 ml is drawn (spread out over 4 drawings). This amount does not cause problems in adults. To compare: 500 ml of blood is drawn at time for a blood donation.

Radiation

For the CT-scan we make use of x-rays. The total dose of irradiation in this study is 5,6 mSv for the CT scan with contrast administration and 1,2 mSv for the CT scan with and without contrast administration. The background radiation for a resident in the Netherlands accumulates to yearly

dose of ~2,5 mSv. The radiation used for the tests in this study could lead to deterioration of your health. However, this risk is very small.

7. Possible advantages and disadvantages

It is important that you weigh the advantages and disadvantages of participation before you enroll in this study. Not administering IVT could positively affect your recovery after the ischemic stroke, but it is not certain that it will. No study has been performed yet that provides solid evidence on this matter. However, in previous studies, patients who weren't treated with IVT before intra-arterial treatment demonstrated similar treatment effect from intra-arterial treatment to patients who did get IVT. Additionally, we think that in the group of patients who do not get IVT there will be less hemorrhagic complications, improving the outcome.

Potential disadvantages of participation are:

- Any adverse effects/discomforts of tests in the study
- A potential moderately higher risk of new infarction for patients in group 1
- A potential moderately smaller chance to dissolve the blood clot after an unsuccessful intra-arterial treatment for patients in group 1.

8. If you do not wish to participate or wish to stop participating in the study

You decide for yourself if you want to continue to participate in the study. Participation is on a voluntary basis.

If you do not wish to participate anymore, the rest of your treatment will comprise of standard care. Data and samples that were collected until that moment will only be used in a coded form, not directly traceable to your person, if you do not object. If you do object, the data and samples are destroyed. You can specify your choice on the form "Use of clinical data in case of no consent". The treating physician can tell you more about the treatment possibilities and their advantages or disadvantages.

If you choose to continue participating in the study, you can always decide to stop, even during the study. The rest of the treatment will comprise of standard care. You do not need to give a reason why you wish to stop participating. If you wish to withdraw, you must inform the researcher immediately.

If there is new information about the study that is relevant for you, the researcher will let you know. The researcher will ask if you continue to participate.

9. End of the study

Your participation in this study ends when

- the telephone interview with the trial nurse at 3 months has been completed;

- you choose to withdraw from the study;
- the AMC, the government or the judging medical ethical committee decides to discontinue the study.

The whole study is completed when all participants have completed the follow-up.

After all the data has been analyzed the researcher will inform you about the most important results of the study. This will happen 4 years after your participation at the latest.

10. Use and storage of your data

For this study, we need to collect and use your medical and personal data. Every participating patient receives a code that is linked to the data. Your name and other personal details are omitted.

Your data

All your data remains confidential. Only the researchers from the where you were admitted hospital and the coordinating research team from the AMC know your code. Your contact information will only be used by the research team at the Erasmus MC Rotterdam, AMC, UMC Utrecht, Maastricht UMC for the telephone call at 3 months. The key to the code will remain with the research team. In study reports only the code will be used. We further ask for your permission to retrieve your medical information from other physicians, e.g., in other hospitals or from your general practitioner. This way, we can gather more information about other (new) illnesses you may experience in the months after your stroke. It also allows us, if necessary, to gather extra information on your past medical history.

Some people are permitted access to your medical and personal data. These people monitor whether the study is being performed well and is reliable.

People who are permitted access to your data are: the research team, the safety monitoring board, independent monitors and the inspection for healthcare. Also, with your permission your coded data can be used to investigate other scientific questions, for example by including them in international databases with data from other comparable studies to combine and analyze them. With your permission, companies that make medical devices or drugs can be given access to the coded data. Regulatory bodies such as the Food and Drug Administration (FDA) can also be permitted access the medical data. All aforementioned persons or institutions will keep the data confidential. If you sign the consent form, you permit the collection, storage and access to the medical and personal data. The researcher will store the data for at least 15 years. If you do not consent, you can register your objection for the use of already collected data (in coded form, not directly traceable to your person) on the form "Use of clinical data in case of no consent", attached to this letter (appendix D).

Request for data from the ambulance service

We will request the data collected by ambulance personnel about your case at the ambulance services. These are data, for example, about the severity of your symptoms and the time interval between the start of symptoms and the arrival at the hospital. We would like to use these data to study the work flow process from the moment of symptom onset until treatment, and how this can be further improved in the future. If you give us your consent on the consent form, you also give permission for us to request your data from the ambulance service.

Samples

The blood samples taken from you, and the extracted blood clot will be stored in a coded manner in the Erasmus University Medical Center in Rotterdam. We will analyze the samples in the laboratory

(for example by performing measures and looking at the sample under the microscope). The goals of these tests are to determine whether there is an association between the composition of the sample or blood clot and the effect of the treatment on your recovery.

Later use of your data

We want to store your data for at least 15 years. We might perform further research with your data. You can give us your consent to do so on the consent form. You may always withdraw your consent. Should you withdraw consent, we will no longer use your data for this study. If certain tests have already been performed on your data, these results will only be used consent is acquired to do so.

11. Insurance for study participants

We have acquired an insurance for all participants in this study. This insurance covers damages caused by the study. Not all damages are insured. More information about the insurance policy can be found in appendix B. This appendix also states who to contact if you wish to report damages.

12. Informing your general practitioner

Your general practitioner will receive a letter from us, stating that you are a participant in this study. This is for your own safety. If you do not consent this practice, you cannot participate in this study. Even if you do not consent to participate in the study, we will send a letter to your general practitioner, informing him/her which study treatment you may have had.

13. No financial compensation for participation

Participation in the study will not cost you anything. You will not be paid for participation. You will be compensated for possible (additional) travel costs.

14. Do you have any questions?

If you have any questions, please contact the research team. For objective council about participation in this study you can call the independent expert. He knows a lot about the study but is not involved in its execution.

If you have any complaints, the best thing to do is to contact the complaints department in your own hospital.

All contact details can be found in appendix A: "contact details".

15. Signing the consent form

After having had sufficient time to deliberate, you will be asked to decide whether you wish to continue participation in the study. Should you give your consent, we will ask you to sign the written informed consent form. With your written consent you confirm that you have understood the information you received, and that you consent with both participation in the trial and the use of and access to your data and samples as mentioned above.

The signature form will be stored by your treating physician. You will receive a copy of the consent form for your own administration.

If you do not give your consent, please sign the form 'Use of clinical data in case of no consent'. This form allows you to object to use of your clinical data or samples that have been gathered up until this point (in coded form, not directly traceable to your person).

16. Appendices

- A. Contact Details
- B. Information about the insurance
- C. Schematic representation of all study related tests
- D. Consent form
- E. Use of clinical data in case of no consent
- F. Brochure 'Medical Research – General Information for Subjects' (version March 2016)

Appendix A: contact details for the UMCG

Local principal investigators:

Dr. M. Uyttenboogaart, interventional neurologist

Dr. R.P. Bokkers, interventional radiologist

Phone number: 050 – 361 3500

Independent physician:

Prof. dr. B.C. Jacobs, neurologist Erasmus MC

Phone number: 010 – 7033780

Complaints:

Complaints committee Rijnstate

Phone number: 088 - 0057539

Appendix B: Information on insurance

The AMC has obtained an insurance for everybody who participates in this study. This insurance covers damages sustained during the study and within 4 years after the study ends. Damage has to be reported to the insurance company within those 4 years.

This insurance does not cover all damages. The damages that are not covered are briefly listed below.

These conditions are defined in the “Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen”. This document can be found on www.ccmo.nl, the website of the Central Committee on Research Involving Human Subjects (see ‘Library’, and then ‘Legal Framework’).

In case of damage you can directly contact the insurance company.

The insurance company that insures this study is:

Name:	Centramed
Address:	Postbus 7374, 2701 AJ Zoetermeer
Tel. Nr.:	070 301 7070
E-mail:	
Policy number:	624.528.303
Contact:	

The insurance covers damages up to € 650.000 per participant, € 5.000.000 for the whole study and € 7.500.000 per year for all studies by the same initiator.

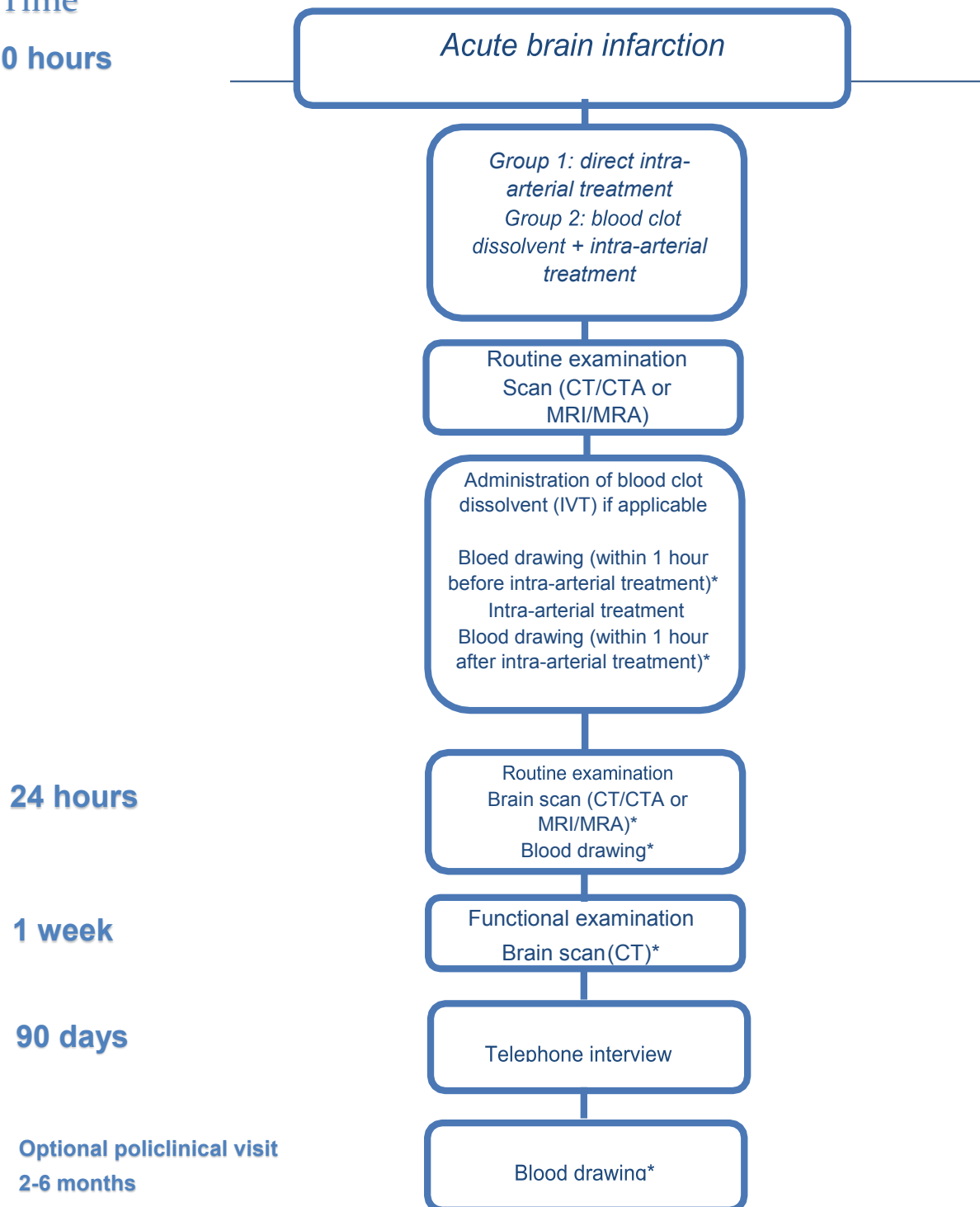
The insurance does **not** cover the following damages:

- Damages caused by a risk for which you were informed in the information letter. This does not apply if the risk manifests more severely than expected or if the risk was very unlikely to occur;
- Damage to your health that would also have manifested had not participated in the study;
- Damages sustained by not (completely) following instructions or recommendations;
- Damages sustained by your offspring, as cause of a negative effect of the study on you or your offspring;
- Damages by an existing treatment method in a study researching existing treatment methods.

Appendix C: Schematic overview of all tests in the study

Time

0 hours



*extra tests compared to usual care

Appendix D: Consent form participant 2nd instance

A study on the effect of intravenous thrombolysis before intra-arterial treatment for an acute ischemic stroke

- I have read the information letter. I was able to ask questions. My questions have sufficiently been answered to decide if I wish to participate in the study.
- I know that participation in the study is voluntary. I also know that I can decide at any moment to withdraw from this study. For this, I do not need to provide an explanation
- I give permission to inform my general practitioner that I participate in this study.
- I permit that certain people have access to my data. These people are specified in this information letter.
- I give permission to retrieve medical information from other physicians, should that be necessary for this study.
- I give permission for the retrieval of data from the ambulance services concerning the transport to the hospital.
- I give permission for the collection and use of my data, for the goals as specified in the information letter.
- I give permission to store my data for at least 15 years on the research site. This data may be used for new research.
- I **give**
 do not give permission store samples taken for 15 years after the end of this study. Possibly these samples can be used for more research, as explained in the information letter.
- I **give**
 do not give permission for the transfer of my data for analysis by companies or regulatory bodies in the Netherlands, Europe and/or the United States of America.
- I **give**
 do not give permission to approach me again after this study for another follow-up study.

Name participant:

signature:

Date : __ / __ / __

Time: :

I hereby declare that I completely informed this participant about the study.

If any information surfaces during the study that could influence the consent of the participant, I will inform the participant in a timely matter.

Name researcher (or his/her representative):

Role:

Treating physician

Researcher

signature:

Date: __ / __ / __

The participant is provided with a complete information letter, with a copy of the signed consent form.

Appendix E: Use of clinical data in case of no consent

A study on the effect of intravenous thrombolysis before intra-arterial treatment for an acute ischemic stroke

- I have read the information letter. I was able to ask questions. My questions have sufficiently been answered to decide if I wish to participate in the study.
- I **do not** consent to participation in the study. No tests can be performed that are not necessary for my treatment.
- I **do**
 - do not** object to the use of my already collected data in this study in coded form, not directly traceable to my person.
- I **do**
 - do not** object to the use of the still to be collected clinical data during the first 3 months after treatment, that become available as a result of usual care, in coded form, not directly traceable to my person.
- I **do**
 - do not** object to the storage of the already collected study data and remaining material for another 15 years after the end of this study. This data could be used for additional studies as stated in the information letter.
- I **do**
 - do not** object to the transfer of data for analysis by companies or regulatory bodies in the Netherlands, Europe and/or the United States of America.

Name participant:

signature: _____

Date : __ / __ / __

I hereby declare that I completely informed this participant about the study.

If any information surfaces during the study that could influence the consent of the participant, I will inform the participant in a timely matter.

Name researcher (or his/her representative):

Role:

Treating physician

Researcher

signature: _____

Date: __ / __ / __

The participant is provided with a complete information letter, with a copy of the signed consent form.