Rijnstate

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

A study on the effect of endovascular treatment for an acute ischemic stroke with late arrival in the emergency department

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

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 about this disease. Because it was in your interest to be treated as quickly as possible, the medical ethical committee was asked to defer the consent procedure 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. At this moment, your medical condition is good enough to ask you yourself to give consent. Before you decide whether to participate further in this study you will get information about the study through this letter. Take the time to read it 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 Maastricht University Medical Center (MUMC+), The Netherlands, and is performed by doctors in several medical centers in the Netherlands. 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 E).

2. Aim of this study

The aim of this study is to determine the safety and efficacy of endovascular treatment between 6 and 24 hours after symptom onset in acute ischemic stroke.

3. Background of the study

An ischemic stroke is caused by the blocking of an artery in the brain by a blood clot. Therefore, part of the brain does not receive blood and gets damaged. The following symptoms can be caused by an ischemic stroke: paralysis, tingling sensation, problems with speaking and understanding speech and/or partial blindness.
The goal of endovascular treatment is to restore the blood flow to the brain as soon as possible. This means that the radiologist inserts a catheter via the groin to remove the blood clot from the artery. Additional blood thinners can be administered close to the clot in order to dissolve it.
Endovascular treatment is beneficial for the health of patients who have symptoms less than six hours. This treatment has not been proven effective in your condition. With your participation in this study we

are trying to find out if this treatment is also beneficial between 6-24 hours after the start of symptoms. In that case, you medical data will be coded. Every participating patient receives a code that is linked to the data, and will be securely saved. Your name and other personal details are omitted. The coded data will later be used for scientific research.

4. What does participation involve?

Duration

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

Treatment

The study will compare the medical condition of patients that received endovascular treatment to the medical condition of patients that did not receive endovascular 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 treated with the endovascular treatment
Group 2: was not treated with endovascular treatment, but received standard treatment

Endovascular treatment (group 1):

If you were allocated to endovascular treatment then you received this treatment in the radiology department. The groin artery was punctured to start treatment and local anesthesia was used. Sometimes it is necessary to administer sleep medication or perform general anesthesia. Your treating physician can inform you which of the options was performed. After intra-arterial treatment you were admitted to the neurology ward/medium care. The blood clots that were removed during the treatment are stored in the biobank. They will be analyzed under a microscope to determine if specific characteristics of the clot are related to the cause of the stroke and the treatment effect on recovery.

No endovascular treatment (group 2):

You were admitted from the emergency department and received standard treatment. This standard treatment involved admittance to the stroke unit. Additional analysis will take place to determine the cause of the stroke and treatment (e.g medication) is primarily directed to lowering the risk of another stroke. This information will be provided by your treating physician.

Visits and tests

During the rest of the stay at the hospital, the following tests will possibly take place:

- 3 blood drawings: within 1 hour before, and within 1 hour after the endovascular treatment or within 1 hour before and within 1 hour after randomization in case no endovascular treatment was performed, and after 24 hours. At every blood drawing, a maximum of 20 ml of blood is 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 endovascular treatment.
- A CT-scan with and without contrast or MRI-scan of the head, 24 hours after hospital admission.
- If you received a CT-scan at 24 hours, a CT-scan without contrast, 5-7 days after treatment or before discharge from the hospital (if this occurs earlier than 5-7 days).

Three months after treatment:

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, who has been blinded to the study treatment you received. 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 policlinic, 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

- In case of standard treatment, no intra-arterial treatment is performed if the symptoms already exists 6-24 hours.
- 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 3 blood drawings and the storage of the extracted clot.
- A telephone appointment after three months to determine your current health.

5. What is expected of you?

To ensure the study goes according to plan, it is important he/she adheres 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
- If your contact information changes

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

Based on previous research we expect that the chance of negative effects is small. Complications related to the treatment are: a brain bleed and a bleed from the groin. It could be that the risk of an important brain bleed is increased by 1%. This was found in earlier research of intra-arterial treatment within 6 hours after start of symptom. Despite the possibly higher chance of an important brain bleed, the functional outcome after three months was better in the intra-arterial treatment group.

Radiation

For the CT-scan we make use of x-rays and contrast agent. The total dose of irradiation in this study is ~15 mSv for the scans. The background radiation for a resident in the Netherlands accumulates to yearly dose of ~2,5 mSv. If you often participate in research with radiation, discuss with the researcher if participation in this trial is advisable. The radiation used for the tests in this study could lead to deterioration of your health. However, this risk is very small. We do advise you not to participate in other research with radiation the next few months. Scans or treatment with radiation for medical reasons is no problem.

7. Possible advantages and disadvantages

It is important that you weigh the advantages and disadvantages of participation before you give consent to enroll your partner/family member in this study.

Potential disadvantages of participation are:

- Any adverse effects/discomforts of tests in the study (see chapter 6)

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

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

If you do not wish to participate, 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.
The study investigators are responsible for the safety of the patients in relation to the study treatment. In case you experience any untoward medical event, we are obliged to register this as an adverse event to ensure the safety of all patients in relation to the endovascular treatment. The adverse events are defined in our study protocol. All other personal data will be destroyed.

If you choose to enroll 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 MUMC+, 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 his/her 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, and samples. 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 hospital of your partner/family member and the coordinating research team from AUMC, Erasmus MC, UMC Utrecht, and MUMC+ know your code. We also ask your permission to retrieve medical information from other treating physicians or other hospitals, in case necessary for the study. Your personal data will only be used 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.

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 the 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 his/her coded

data. Regulatory bodies such as the Food and Drug Administration (FDA) can also be permitted access to 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 his/her 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 workflow 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 and samples 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 and the samples will be destroyed. 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.

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 enroll 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 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. Consent form
D. Use of clinical data in case of no consent

Brochure 'Medical Research – General Information for Subjects' (version March 2016)

Appendix A: contact details

For questions during office hours:

Rijnstate ziekenhuis:

Dr. J. Hofmeijer, neurologist, Tel: 088-005 8888
Dr. J.M.M. Martens, radiologist

Maastricht University Medical Center:

Coordinative researchers:

Drs. S.G.H. Olthuis, researcher neurology MUMC+, 043-3875616
Drs. F.A.V. Pirson, researcher neurology MUMC+, 043-3877207

For pressing questions outside office hours: 06-51447776

Independent physician:
Prof. dr. B.C. Jacobs, neurologist, immunologist
Can be reached via: 010- 7033780

Complaints:
Prof. Dr. R.J. van Oostenbrugge, neurologist MUMC+, 043-3877058
Prof. Dr. W. van Zwam, radiologist MUMC+, 043-3874904

Complaints:
Complaint manager Rijnstate
Postbus 9555
6800 TA Arnhem
Tel: 088-0057539

Appendix B: Information on insurance

The MUMC+ 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, thee 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 copany that insures this study is:	
Name:	CNA insurance company Ltd.
Address:	Strawinskylaan 703, 1077 XX, Amsterdam
Tel. Nr.:	020-5737272
Policy number:	10174880

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 you 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 your offspring;
- Damages by an existing treatment method in a study researching existing treatment methods.

Appendix C: Consent form participant

A study on the effect of endovascular treatment for an acute ischemic stroke with late arrival in the emergency department

I have been asked to give consent for enrollment in medical scientific research of the following person:

Subject's name: Subject's date of birth: __ / __ / __

- 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 this study.
- I know that participation in this 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 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 permission to use my data for research purpose in international databases.
- I give permission to retrieve medical information from other treating physicians, if deemed necessary for this study.
- I □ **give**
  □ **do not give** permission store the 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 person 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 subject's representative is provided with a complete information letter, with a copy of the signed consent form.

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

A study on the effect of endovascular treatment for an acute ischemic stroke with late arrival in the emergency department

I have been asked to consent enrollment in scientific medical research of the following person:

Subject's name: Subject's date of birth: __ / __ / __

- I have read the information letter. I was able to ask questions. My questions have been sufficiently answered to decide if I wish to participate in this 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 data already collected 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 coded form, not directly traceable to the person, in the Netherlands, Europe and/or the United States of America.

Name of participant:
signature: Date : __ / __ / __

I hereby declare that I completely informed this person 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 subject's representative is provided with a complete information letter, with a copy of the signed consent form.