Additional Information on your partner's/family member's 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,

You have received this letter because your partner/family member has suffered an ischemic stroke and unfortunately has passed away. First, we would like to offer our sincere condolences for your loss. With this letter we wish to provide additional information about your partner's/family member's participation in medical scientific research. By now you will have been informed about this by the treating physician. Because it was in your partner's/family member's 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 your partner/family member has already undergone the study treatment or the standard treatment. This was decided by randomization.
Unfortunately, your partner's/family member's medical condition deteriorated and he/she passed away before we were able to ask for consent to participate in the study. Your partner's/family member's medical information may be of great importance for future patients who experience a stroke. We will therefore add your partner's/family member's data to our analyses for the entire group of patients treated in this study. This letter of information explains what the study entails and what type of treatment and tests your partner/family member received.
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 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 the condition of your partner/family member. With participation of your partner/family member we are trying to find out if this treatment is also beneficial between 6-24 hours after the start of symptoms.

4. What does participation involve?

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, your partner/family member was 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 your partner/family member was allocated to receive endovascular treatment then he/she 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 your partner/family member was 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):

Your partner/family member was 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 your partner's/family member's stay in hospital, he/she underwent all or part of the following tests:

- 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 of endovascular treatment.
- A CT-scan with and without contrast or MRI-scan of the head of your partner/family member, 24 hours after hospital admission.
- If your partner or family member underwent a CT-scan at 24 hours, a CT-scan without contrast of the head of your partner/family member, 5-7 days after treatment or before discharge from the hospital (if this occurs earlier than 5-7 days).

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.

5. 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 symptoms. 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. The radiation used for the tests in this study could have led to deterioration of your partner's/family member's health. However, this risk is very small.

6. Possible advantages and disadvantages

Potential disadvantages of participation are:

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

7. End of the study

The whole study is completed when all participants have completed the follow-up, or if the MUMC+, government or the judging medical ethical committee decides to stop the study.

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 enrollment of your partner/family member.

8. Use and storage of data

For this study we need to collect and use your partner's/family member's medical and personal data, and samples. Every participating patient receives a code that is linked to the data. His/her name and other personal details are omitted.

Your partner's/family member's data

All his/her 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 his/her code. 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 his/her medical and personal data. These people monitor whether the study is being performed well and is reliable.

People who are permitted access to his/her data are: the research team, the safety monitoring board, independent monitors and the inspection for healthcare. Also, his/her 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. Companies that make medical

devices or drugs can also 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.

Request for data from the ambulance service
We will request the data collected by ambulance personnel about your partner/family member 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.

Samples
The blood samples taken from you partner/family member, 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.

Later use of your data
We want to store your partner's/family member's data and samples for at least 15 years. We might perform further research with his/her data.

9. 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.

10. Informing your partner's/family member's general practitioner
The treating physician will send the general practitioner a letter about the passing of your partner/family member. The general practitioner will also be informed about the participation in this study.

11. No financial compensation for participation
Participation in the study will not cost anything. There will be no payment for participation.

12. 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 partner's/family member's own hospital.
All contact details can be found in appendix A: "contact details".

Appendices

A. Contact Details
B. Information about the insurance

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

Appendix A: contact details

For questions during office hours:

St. Antonius ziekenhuis:

Dr. W Schonewille, neurologist 088 320 30 00
Dr. JA Vos, 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

Or

Complaint committee St. Antonius ziekenhuis
Attn. Complaint manager
Antwoordnummer 2400
3430 VB Nieuwegein
Tel: 088 320 88 31

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 partner’s/family member’s health that would also have manifested had he/she not participated in the study;
- Damages sustained by not (completely) following instructions or recommendations;
- Damages sustained by your partner’s/family member’s offspring, as cause of a negative effect of the study on your partner/family member or his/her offspring;
- Damages by an existing treatment method in a study researching existing treatment methods.