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

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 had 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.
With this letter we wish to provide you with the opportunity to formally object to the use of your partner's/ family member's data and samples that have been collected up until this moment for this study. Before you decide if you want to object, this letter of information will explain what the study involves and what type of treatment and tests your partner/family member underwent.
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 friends or family.

1. General Information

This study was initiated by the Academic Medical Center (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 D).

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. Background of the study

Your partner/family member has been admitted to the hospital because he/she 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?

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 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 as we do not expect increased risk from withholding the standard treatment. Moreover, we expect less hemorrhages when 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 your partner/family member was allocated. More information about randomization can be found in the brochure "Medical Research" (Appendix D).

In total during the whole study, extra blood was drawn an extra three times at maximum. Further, we want to ask permission to use any remaining samples 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 your partner/family member was randomized into group 1, he/she underwent the intra-arterial treatment without IVT administered beforehand. This means that he/she was moved to the intervention room almost immediately after undergoing the scan of his/her brain. In the intervention room a catheter was inserted in the artery in his/her 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 your partner/family member was randomized to group 2, the control group, he/she also received IVT before the intra-arterial treatment. This means that, after the scan of his/her brain was completed, we administered a very powerful blood clot dissolving drug. Afterwards, he/she was also brought to the intervention room, where he/she underwent intra-arterial treatment.

Visits and tests

During your partner's/family member's stay in hospital, he/she underwent all or part 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 dissolvent.
- 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 the head of your partner/family member, 24 hours after treatment.

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, the 3 blood drawings and the storage of the extracted clot.

5. What would we wish to receive from you?

We would wish to receive from you a signed copy of the 'Opt-out form after death of a partner/family member' within 1 month from receiving this information letter. With this form, you can partially or completely object to the use of your partner's/family member's data and samples that have been collected up until the moment of his/her passing. This form is attached at the end of this letter.

6. Possible side-effects/complications or other unfavorable 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 40 ml was drawn (spread out over 3 drawings). This amount does not cause problems in adults. To compare: 500 ml of blood is drawn at time for a blood donation.

7. Possible advantages and disadvantages

Not administering IVT may positively affect recovery after an ischemic stroke, but this is not certain. 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 a 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 object to the use of your partner's/family member's data for this study

Your partner/family member underwent study procedures and passed away before we were able to ask his/her consent to participate. You may decide to object to the use of his/her data for this study.
You do not have to provide an explanation for your partial or complete objection. We do, however, ask you to notify the researchers of this objection within one month of receiving this letter.
The data and samples that have been collected for the study will be destroyed.

9. End of the study

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

After all data has been analyzed, the researcher will inform you about the most important results of the study. This will happen, at the latest, 4 years after enrollment of your partner/family member.

10. Use and storage of data

For this study, we need to collect your partner's/family member's medical and personal data. 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 the AMC know his/her code. The personal data of your partner/family member 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 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, with your permission 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. 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 the medical data. All aforementioned persons or institutions will keep the data confidential.
If you do not object, you permit the collection, storage and access to the medical and personal data. The researcher will store the data for at least 15 years.

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

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. If you give us your consent on the consent form, you also give permission for us to request your partner's/family member's data from the ambulance service. If you do not object, you give permission to collect these data.

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 the data and samples for at least 15 years. We might perform further research with this data. If you do not object you consent this practice. If you do object, we will no longer use his/her data for this study and the samples will be destroyed.

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 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 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 the participation in this study.

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

14. Do you have any questions?
If you have any questions, please contact the research team. For objective council 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".

15. How to object.

We request that you notify us of your objection for use of your partner's/family member's data and samples within 1 month after receiving this letter.
If you wish to object or partially object, please fill in and sign the attached 'Opt-out form after death of a partner/family member' and send it to us. Your written objection states that you do not consent to the use of your partner's/family member's data or sample for the above mentioned purposes.

The signature form will be stored by your partner's/family member's treating physician. You will receive a copy of the form for your own administration.

If you do **not** object, you don't have to do anything. If we do not receive your objection within one month after receiving this letter, we will assume your full consent for use of your partner's/family member's data for the abovementioned purposes.

16. Appendices

A. Contact Details
B. Information about the insurance
C. Opt-out form after death of a partner/family member
D. Brochure 'Medical Research – General Information for Subjects' (version March 2016)

Appendix A: contact details for the Amsterdam University Medical Center, location AMC

Researchers:

Prof. Dr. Y.B.W.E.M. Roos, neurologist,
Prof. Dr. C.B.L.M. Majoie, radiologist,
Dr. J.M. Coutinho, neurologist
Drs. N.E. LeCouffe, physician-researcher department of neurology
K.M. Treurniet, physician-researcher radiology
All can be reached via 020-5663547 of 020-5662432

Independent physician:
Prof. dr. H.Q. Hintzen
Can be reached via: 010- 7033780

Complaints:
Complaints committee AMC
Can be reached via 020-56 63355

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, 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:	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 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.

Appendix C: Opt-out form after death of a partner/family member

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I have been asked to notify the research team within one month after receiving this letter, if I object to the use of the data and samples of the following person for medical scientific research:

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

I hereby object to:

□ **The use of this person's data for the study's purposes as mentioned above.**

□ **The storage of this person's data for 15 years after the study. This data may be used for new research, as mentioned in this letter.**

□ **The storage of this person's samples for 15 years after the study. This data may be used for new research, as mentioned in this letter.**

□ **Sharing this person's data with companies or regulatory bodies,** in coded form, not directly traceable to his/her person, in the Netherlands, Europe and/or the United States of America.

Name of subject's representative
Relation to subject:
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 objection of the representative, I will inform the representative 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.