Information letter about a study evaluating very early administration of tranexamic acid after a subarachnoid hemorrhage

Ultra-early tranexamic acid after subarachnoid hemorrhage

The ULTRA-study

Dear Madam/Sir,

You are asked to participate in the study mentioned above. To make the consent easier to understand you receive this information. You can quietly read and discuss it with your partner, friends or family if necessary. If you have any remaining questions, you can ask them to your doctor or researchers. Contact information of these persons are written at the end of this letter. You will also find contact details of a person who does not carry out the research itself, but knows everything about this study.

What is the goal of the study?

You have had a hemorrhagic stroke. This bleeding is called a subarachnoid hemorrhage, abbreviated to SAH. A weak spot at an artery in your brain has ruptured. This weak spot is called an aneurysm. The aneurysm will be treated to ensure that it does not bleed again. If a new bleeding occurs, it may cause (more) damage to your brain. So, it is better to reduce the risk for a new bleed as much as possible. This is possible with a drug that slows the breakdown of the blood clot (tranexamic acid, or Cyklokapron®). Several studies, performed 10 to 20 years ago, have already shown that this drug reduces the risk for a new bleed. This study investigates whether people after 6 months also have a more favorable recovery if they are treated with this drug as soon as possible when compared with standard treatment without the drug. If your bleeding is diagnosed by a CT-scan and you are not being treated for thrombosis, are not pregnant, do not have a history of clotting disorder, have no hepatic or renal impairment, you can participate in the study.

How is the study coordinated?

The study is coordinated by the Neurosurgical Center Amsterdam (Academic Medical Center and VU University Medical Center, Amsterdam, the Netherlands) in close collaboration with the University Medical Center Utrecht, the Netherlands. The hospitals referring patients with SAH to these centers also participate in the study. A total of approximately 950 patients will participate in the study and it is expected that this number is reached in the mid of 2019.

Randomization

After the SAH is diagnosed, you will be drawn as soon as possible for a treatment with or without the drug. You have a 50% chance to be treated with the drug and a 50% chance to be treated without the drug.

Drug administration

If you are selected for the group with drug treatment, it is administered as soon as possible via the already present infusion. The drug is continued in a lower dose until a maximum of 24 hours after the start, or to start of treatment of the aneurysm. The remaining treatment is exactly the same in both groups.

Giving permission
You have not been informed about the study prior to the draw and possible administration of the drug. This has been done because the emergency procedure is applicable in this study, approved by the Medical Ethics Committee of the Academic Medical Center Amsterdam. The emergency procedure allows that the participating individuals are informed about the content and purpose of the study and asked for permission for the use of the data, after the drug has been given (if applicable). The reason for using the emergency procedure is that the time to explain the study and reflection for participation in the study is expected to take too long, owing to the severity of the situation. As required by the emergency procedure, we will inform you as soon as possible at a later time point about the content and purpose of the study and we ask for your approval for the use of your data. You can now think about the decision to give permission as long as necessary. If you do not consent, your data will be destroyed.

Telephone interview and questionnaires
The main outcome of the study is how you are functioning 6 months after the bleeding. We are also very interested in the costs that are caused by the bleeding. At about 3 and 6 months after your bleeding, you will receive a short questionnaire with questions that deal with medical expenses caused by the bleeding and quality of life at that time. You can return the questionnaire free of charge by using the return envelope. Six months after the bleeding you will be called by a nurse who does not know whether you received the drug or not. This nurse should not be told whether you have used the drug or not to make a reliable assessment about your clinical situation. The nurse will take a brief telephone interview about your functioning at that time.

What are the possible benefits and disadvantages of participation in this study?
Benefit
It is unknown whether you benefit from participation in this study. The researchers do not know whether the very early administration of the drug indeed leads to a more favorable recovery. It has been proven that the administration of this drug reduces the number of new bleedings.

Disadvantage
By giving the drug there is a small risk of adverse side effects such as allergic reactions, nausea, vomiting and hypotension. More serious but less common side effects are deep vein leg or arm thrombosis or pulmonary embolism. Thanks to many previous studies with this drug, the occurrence of an unwanted event is estimated to be very small. If an unwanted event occurs, the investigator should be notified as soon as possible.
This study will provide useful data and according to the outcome it will be decided whether this treatment will be applied to all SAH patients.

What happens if you do not want to participate in the study?
Participation in this study is completely voluntary. If you do not want to participate, you do not need to give any reason for it. Not participating in the study does not mean any difference in your treatment or counseling. If you or a substitue decision maker have given informed consent, you can always withdraw without reason.

What happens when the study has finished?
After completion of the study the results will be published within a year. You will be informed about the results.

What happens to your data?
We treat your data confidentially. All personal information shall be replaced by a code. Only the study's researchers have access to the code. Also when the study results are published, your personal information is kept confidential. Your family doctor will be informed of your participation in this study.
Representatives of the Health Care Inspectorate and the project leader of the research can be given access to the medical file to inspect the integrity of the research. This inspection will take place under the responsibility of the treating physician. The study data are kept for 20 years. Afterwards, the data will be destroyed.

What happens to your contact information?
On the consent form you will be asked for your contact information. The reason for this is so we can contact you for the measurements at three and six months after the bleed. The contact details will be sent to the research nurse at the AMC. They will only use the contact information in order to approach you for the final telephone measurement after six months and to send you the results of the study. Your contact information will be destroyed as soon as the study ends.

Are you insured when you participate in the study?
The AMC Medical Research B.V. is sponsor for this study and has taken out a risk insurance for participants in medical research. More about this can be found in the annex to this letter.

Are you being informed when relevant information about the study is becoming available in the mean time?

The research will be performed according to plan as accurately as possible. However, it may happen that your physical reactions or newly discovered facts force us to change the study. This will be discussed directly with you, to give the opportunity to decide whether you want to continue with the study or not. If your safety or well-being is at risk, the researcher terminates your participation in the survey immediately.

Which Research Ethics Board has approved this study?

The Research Ethics Board (REB) of the Academic Medical Center in Amsterdam, the Netherlands with its referring hospitals have approved this study.

Do you want to know anything more?

There is an independent physician available for asking questions and gaining more information about this study. This physician is not involved in the study itself, but knows a lot about this study.

We thank you for reading this information letter.

Kind regards,

the ULTRA-team

Attachments

1. Information of research team and independent physician
2. Insurance information

Attachment 1: **INFORMATION OF RESEARCH TEAM AND INDEPENDENT PHYSICIAN**

Principal investigators

The Netherlands

D. Verbaan, senior clinical epidemiologist
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Co-investigators

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R. Post, neurosurgical resident in training (AMC)
M.R. Germans, neurosurgeon
B.A. Coert, neurosurgeon
Y.B.W.E.M. Roos, neurologist
R. v.d. Berg, neuroradiologist
Prof. C.B.L.M. Majoie, neuroradiologist
J. Horn, neurointensivist
Prof. G.J.E. Rinkel, neurologist
R.L. Macdonald, neurosurgeon

Information of independent physician

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Attachment 2: **Insurance**

In accordance with the Dutch Medical Research (Human Subjects) Act (*Wet medisch-wetenschappelijk onderzoek met mensen*, WMO), AMC Medical Research B.V. has taken out an insurance cover for claims resulting from the death or bodily injury of human subjects of clinical trials.

* This concerns injuries that become apparent during the clinical trial or the four years immediately following said trial, and that have been reported within four years from the participation in the clinical trial.
* The sum insured under this policy is EUR450,000 per subject, with a maximum of EUR3,500,000 for the clinical trial project and EUR5,000,000 for injuries arising from medical research per insurance year.

The policy provides cover for:
* injuries resulting from the realization of risks attached to participating in a clinical trial, of which the participant had not been informed in writing;
* injuries resulting from the realization of risks, of which the participant had been informed, but which manifest themselves to a greater degree than expected;
* injuries resulting from the realization of risks of which the participant had been informed, but which were considered to be extremely unlikely.

The policy does not cover:
* claims resulting from a lack of improvement in the subject's health problems, or from a continued deterioration of the subject's health problems, if the subject's participation in this clinical trial is part of the treatment of this health problem;
* claims resulting from an impairment of the subject's health, which would likely also have come to light if the subject had not taken part in the research;
* claims resulting from an impairment of the subject's health in case the subject takes part in a comparative clinical trial and it is likely that the injury results from procedures that are already commonly used in the medical profession;
* claims for injury that manifests itself in the subject's descendant as a result of an adverse effect of the clinical trial on the subject and/or his/her descendant;
* claims for injury that is inevitable or practically inevitable, given the nature of the clinical trial;
* claims for injury resulting from the subject's own failure to follow the instructions, or to follow them completely, insofar as the subject is able to do so.

The policy covers losses of individuals only.

The cover of specific injuries and costs is limited to the amounts stipulated above.

To lay claim to damages, the subject has to report the putative injury as a result of the clinical trial to:

Name of insurer: Centramed B.A.
Address insurer: Appelgaarde 4, 2272 TK Voorburg
policy number: 620.872.806

Authorisation form for the ULTRA study

(Ultra-early tranexamic acid after subarachnoid hemorrhage)

I have read the information letter for the patient (version 5, 24-3-2014). I could ask additional questions. My questions are sufficiently answered. I had plenty of time to decide whether I would participate or not.

I know that participation is completely voluntary. I know I can still decide to withdraw at any time, without any given reason.

I know some people can see my personal information. Those people are listed in the information letter.

I give permission to use my data for the goals that are stated in the information letter.

I give permission to store my data to a maximum of 20 years upon completion of this study.

I give permission to inform my family doctor about participation in the study.

I **do / do not*** consent to approach me for further research in the future.
(*delete as applicable)

I agree with my participation in the above mentioned study.

Name study participant :

Phone number study participant :

Address study participant :

Signature :

Date (day/month/year) : … / … / 20 ...

I hereby declare that I have informed this study participant about the above mentioned study.

If new information is becoming available during the study that could affect the participant, I'll inform him/her in a timely manner.

Name investigator (or his representative) :

Signature :

Date (day/month/year) : … / … / 20 ...

For the legal representative / spouse / partner or partner, or if absent, the parents of the person concerned or, where these are not available, reasonably accessible adult children or, if these also do not exist, the reasonably achievable adult brothers and sisters of the person concerned.

Authorisation form for the ULTRA study

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I am asked to give consent for the below mentioned person, so he/she participates in the aforementioned study:

Name subject:

Date of birth (day / month / year): ... / ... / ...

I have read the information letter for legal representative (version 5, 24-03-2014). I could ask additional questions. My questions are sufficiently answered. I had plenty of time to decide whether my relative/family member could participate or not.

I know that participation is completely voluntary. I know I can still decide to withdraw the consent at any time, without any given reason.

I know some people can see personal information of the subject. Those people are listed in the information letter.

I give permission to use the subject's data for the goals that are stated in the information letter.

I give permission to store the subject's data to a maximum of 20 years upon completion of this study.

I give permission to inform the subject's family doctor about participation in the study.

I **do / do not*** consent to approach the subject for further research in the future.
(*delete as applicable)

I agree with the continued participation in the above mentioned study.

Name Legal representative :

Relationship to the study participant :

Name study participant :

Phone number study participant :

Address study participant :

Signature :

Date (day/month/year) : … / … / 20 ...

I hereby declare that I have informed this person(s) about the above mentioned study.

If new information is becoming available during the study that could affect the participant, I'll inform him/her in a timely manner.

Name investigator (or his representative) :

Signature :

Date (day/month/year) : … / … / 20 ...