Subject information for participation in medical research

Version 1
2022-05-04
Target group: possible participants SAFE-study

A study on safely shortening antibiotic treatment in bloodstream infections with Staphylococcal bacteria: the SAFE study.

Official title: Safe shortening of antibiotic treatment duration for complicated Staphylococcus aureus bacteremia

Introduction
Dear sir/madam,

With this letter, we would like to ask you to take part in a medical study. Participation is voluntary. Your written permission is required to participate. You have received this letter because you have a bloodstream infection with Staphylococcal bacteria, for which you are currently receiving antibiotics.

Before you decide whether you want to participate in this study, you will receive an explanation of what the study entails. Read this information carefully and ask the researcher for an explanation if you have any questions. You can also ask the independent expert, named at the end of this letter, for additional information. You can also talk about it with your partner, friends or family.

General information about participating in a medical study can be found on the website of the Rijksoverheid: www.rijksoverheid.nl/mensenonderzoek. You have at least 24 hours to decide whether you want to participate in the study.

1. General information
This research was set up by the VU Medical Center and is being carried out by doctors in various Dutch hospitals. A total of 396 subjects are needed for this study.

The VUmc medical ethics review committee has approved this study. General information about the assessment of research can be found on the website of the Rijksoverheid: www.rijksoverheid.nl/mensenonderzoek.

2. What is the purpose of the study?
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The aim of this study is to investigate whether treatment with 4 weeks of antibiotics is as good as treatment with 6 weeks of antibiotics for bloodstream infections with Staphylococcal bacteria. The results of this research will be published in a scientific article.

3. What is the background of the study?
It is important to prevent unnecessary use of antibiotics, as this can lead to adverse effects such as kidney or liver damage, prolonged hospitalization and increase of resistant bacteria. Long-term use of antibiotics can also disrupt the intestinal flora, because antibiotics kill bacteria in the gut that contribute to good health. For bloodstream infections with Staphylococcal bacteria, we currently do not know how long to treat with antibiotics. The Dutch treatment guideline recommends treating these types of infections with 4 to 6 weeks of antibiotics. In practice, most patients in the Netherlands are treated for 6 weeks. However, there are also foreign guidelines, for example in Belgium and the United Kingdom, which advise that these type of infections should always be treated for a shorter period of time, i.e. with 4 weeks of antibiotics. The two treatment times, 4 or 6 weeks of antibiotics, have never been compared in a large, well-designed scientific study.

4. What happens during the study?
If you participate, it will take about 6 months in total.

Eligibility
Pregnant women cannot participate in this study. Therefore, female patients of childbearing age (15-49 years) are asked whether they use contraception. If not, a urine pregnancy test will be taken. If you are pregnant, we will tell you. If you do not want to know this, you cannot participate in this study.

Therapy
Half of the subjects will receive 4 weeks of antibiotic treatment, the other half will receive 6 weeks of antibiotic treatment. Whether you receive 4 weeks or 6 weeks of treatment is determined by drawing lots. You and your treating doctor will be told which group you are in.

Visits and measurements
In participants treated for 4 weeks, blood samples will be drawn once a week for 2 weeks. These participants have to come to the hospital for this. If this is not possible for you, blood will be drawn at home or in the institution where you are staying.

During the examination, we want to keep a close eye on how you are doing and whether you have any physical complaints. As long as you are admitted to hospital, we can retrieve this information from your patient file. The researchers will contact you weekly by telephone when you go home. You do not have to come to the hospital for this. It concerns the following moments:

- 4 weeks after starting the antibiotics.
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- 5 weeks after starting the antibiotics.
- 6 weeks after starting the antibiotics.
- 8 weeks after starting the antibiotics.
- 3 months after the start of the study.
- 6 months after the start of the study.

If we are unable to reach you by phone 3 times during these periods, we will contact your GP to ask how you are doing.

During the study, we ask all subjects to fill in questionnaires at 4 moments. However, it is also possible to participate in the study without completing the questionnaires. It concerns the following 4 moments:

1) 2 questionnaires at the start of the study. These questionnaires are about your state of health and your quality of life. Completing these 2 questionnaires takes approximately 20 minutes in total.
2) 1 questionnaire upon discharge from hospital. This questionnaire is about the possible consequences of health problems on your work. It takes approximately 20 minutes to complete this questionnaire.
3) 2 questionnaires 6 weeks after starting antibiotics. These questionnaires are about your state of health and your quality of life. Completing these 2 questionnaires takes approximately 20 minutes in total.
4) 4 questionnaires 6 months after the start of the study. These questionnaires are about your state of health, your quality of life, your use of healthcare and the possible consequences of health problems for any work you do. Completing these 4 questionnaires takes approximately 80 minutes in total.

When you are no longer in hospital at these times, you will receive the questionnaires by email or on paper.

Appendix C lists the measurements that will take place during the study.

Different from standard care

The following matters are different in this study from usual care:
- The questionnaires that are administered at 4 moments.
- Telephone contact with the researchers.

5. What agreements do we make with you?

We want the study to go well. That is why we want to make the following agreements with you.

- You do not take part in any other medical research during this study.
- You go to every appointments for blood sampling and telephone contact with the researchers.
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- You carry the participant card of the study with you. In your wallet, for example. It states that you are taking part in this study. And who should be warned in an emergency. Show this card when you visit a doctor.
- You should contact the investigator in these situations:
  - You are hospitalised or get treatment in a hospital.
  - You no longer want to take part in the study.
  - Your telephone number, address or email address changes.

Pregnancy of you or your partner
Women who are pregnant or breastfeeding cannot take part in this study. Women should also not get pregnant during the study when treated with antibiotics. Inform your partner about this.

This study can have consequences for an unborn child. The consequences are not known. It is important to discuss this with your partner. The investigator will tell you how best to prevent pregnancy.

If you do become pregnant during the study, inform the investigator immediately. It could mean that the pregnancy needs to be monitored more closely and information about the course and outcome of the pregnancy can be requested from other healthcare providers. But only if you/your pregnant partner give separate permission for this.

6. What side effects, adverse effects or discomforts could you experience?
The antibiotics you receive may cause side effects. These possible side effects are the same for the treatment you will receive if you do not participate in the study.

You should contact your treating doctor if you experience:
- More than 3 loose stools per day.
- Nausea and/or vomiting after taking or administering the antibiotics.
- Confusion, sensory disorders or seizures.
- Newly developed skin lesions.
- Shortness of breath
- Swelling of lip and/or tongue.
- Pain, redness and/or swelling around the infusion over which you will receive antibiotics.

If you participate in the study, you will receive the package leaflet for the antibiotic, which lists all possible side effects.

7. What are the pros and cons if you take part in the study?
It is important to weigh the pros and cons, before deciding to take part in the study.
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If you participate in the study, you will be drawn in the 4 or 6 week of antibiotic therapy group. In both cases, your participation in this study can contribute to more knowledge about the best treatment of bloodstream infections with Staphylococcal bacteria. If the draw determines that you will be treated with antibiotics for 4 weeks, a possible benefit is that you are less likely to experience side effects from the antibiotics such as kidney and liver damage and less risk of adverse effects from long-term hospitalization, such as contracting infections in the hospital and developing thrombosis. Disadvantages of participating in the study may be that 4 weeks of antibiotic treatment is less effective than 6 weeks of treatment for bloodstream infections with Staphylococcal bacteria. In this case, you may be at an increased risk of the consequences of an insufficiently treated infection. We think this risk is small. We will keep a close eye on you during the investigation to avoid this risk. If you do not participate in the study, you will receive the standard treatment of 6 weeks. A possible advantage is that more experience has been gained with this treatment in the past. A possible disadvantage of this treatment is longer hospital stay and possibly more side effects of the antibiotics.

Participation in the study also means:
- Taking part in the study will cost you extra time.
- You have to comply with the study agreements.

All these matters have been described above under points 4, 5 and 6

8. If you stop participating in the study

It is up to you to decide if you wish to participate in the study. Participation is voluntary. If you wish not to participate, then you will receive the standard treatment for a bloodstream infection with Staphylococcal bacteria, which is 4 to 6 weeks. The researcher or treating doctor can tell you more about the available options for treatment and about the pros and cons.

If you do participate, you can always change your mind and stop anyway, even during the study. You will then receive standard of care. You don't have to say why you're stopping. You do must report this to the researcher immediately.
The data collected up to that point will be used for the research. If you wish, collected body material can be destroyed.

If there is new information about the study that is important to you, the researcher will let you know. You will then be asked if you want to continue participating

9. End of the study

Your participation in the study will end if
- all visits as described under point 4 and in Appendix C have been completed
- you choose to stop yourself
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- you become pregnant during the antibiotic treatment
- the researcher and/or your treating doctor think it's better for you to stop
- The VUmc, the government or the assessing medical-ethical review committee, decides to stop the research.

The entire study ends when all participants have completed follow-up. After processing all the data, the researcher will inform you about the most important results of the research.

10. Use and storage of your data and body material

For this study, your personal data and blood are collected, used and stored. This concerns data such as your name, address, date of birth and data about your health. A blood sample is required for this study. The collection, use and storage of your data and your blood are necessary to answer the questions posed in this study and to publish the results.

We ask for your permission for the use of your data and blood by means of the consent form.

Confidentiality of your data and body material

To protect your privacy, your data and your body material are given a code. Your name and other information that can directly identify you are omitted. Data can only be traced back to you with the password of the code. The password to the code remains securely stored in the local research facility. The data sent to the client only contains the code, but not your name or other data with which you can be identified. Also in reports and publications about this research, the data cannot be traced back to you.

Access your data for control

Some individuals may have access to all of your data at the study site. Also to the data without code. This is necessary to be able to check whether the research has been carried out properly and reliably. Persons who have access to your data for inspection are: an inspector who works for the VUmc and national and international supervisory authorities, for example de inspectie Gezondheidszorg en Jeugd. They keep your data secret. We ask you to give permission for this inspection.

Retention period data and body material

We store your data in the hospital where you are being treated for 15 years. Your body material is not destroyed immediately after use. It will be kept in order to be able to perform additional tests related to this research in the course of this investigation.

Retention and use of data for other research

After this research, your data may also be important for other scientific research in the field of infections caused by Staphylococcal bacteria. For this purpose, your data and blood will be stored for 15 years. You can indicate on the consent form whether or not you agree to this. If you do not agree to this, you are still able to participate in this study.
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Information about unexpected findings
During this research, something may accidentally be found that is not important for the research, but is important for you. If this is important for your health, you will be informed by your treating doctor from the hospital. You can then discuss with your treating doctor what should be done. We also ask for your permission for this by means of the consent form.

Withdraw permission
You can always withdraw your consent for the use of your personal data. This applies to this study as well as to storage and use for future research. The research data collected up to the moment you withdraw your consent will still be used in the research. Your body material will be destroyed after withdrawal of your consent. If assessment have already been taken with that bodily material, those data will still be used.

More information about your rights when processing data
For general information about your rights when processing your personal data, you can visit the website of the Dutch Data Protection Authority.

If you have any questions about your rights, please contact the person responsible for processing your personal data. For this study, that is:

drs. DTP Buis, researcher VUmc. See Appendix A for contact details.
Drs. S. Douiyeb, researcher VUmc. See Appendix A for contact details

If you have any questions about complaints about the processing of your personal data, we recommend that you first contact the research location. You can also contact the Data Protection Officer of the VUmc, see Appendix A of the Dutch Data Protection Authority.

Registration of the study
Information about this study is also included in an overview of medical scientific studies https://www.trialregister.nl. It does not contain any data that can be traced back to you. After the study, the website may display a summary of the results of this survey. You can find this study under SAFE-trial, Trial NL8347.

11. Insurance for study participants
Insurance has been taken out for everyone who takes part in this study. The insurance pays for damage caused by the study. But not for all damage. You can find more information about this insurance and any exceptions in Appendix B. It also says who you can report damage to.

12. Informing your general practitioner and treating specialist will
The investigator will send your general practitioner and treating specialist a letter to let them know that you are taking part in the study. This is for your own safety. If you do not agree with
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this, you cannot participate in this study. We may contact your general practitioner, treating
specialist or pharmacy to request information, for example about your medical history or
about medication use. You must give permission for this via the permission form.

13. No compensation for participating
The extra tests and treatment for the study will not cost you anything. You will not be
paid for participating in this study. You will, however, be reimbursed for your (extra)
travel and parking costs. The own risk of the health insurance is not reimbursed,
because you also have to pay this yourself if you do not participate in the study.

14. Do you have any questions?
If you have any questions, please contact the researcher. For independent advice
about participating in this study, you can contact the independent doctor. She knows
a lot about the study and your condition, but has nothing to do with this study.
If you have any complaints about the study, you can discuss this with the researcher
or your attending physician. If you prefer not to do this, you can contact the
complaints officer of your hospital. All details can be found in Appendix A: Contact
details.

15. Signing consent form
When you have had sufficient reflection time, you will be asked to decide whether to
participate in this study. If you give permission, we will ask you to confirm this in
writing on the accompanying informed consent form. By your written consent, you
indicate that you have understood the information and agree to participate in the
study.
Both you and the researcher will receive a signed version of this consent form.

Thank you for your attention.
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16. Appendices to this information

- Contact details participating center
- Information about the insurance
- Overview of measurements
- Consent form study participant
Appendix A: contact details for VUmc

Principal researcher VUmc:
Dr. K.C.E. Sigaloff, internist
Departement interne geneeskunde, VUmc
De Boelelaan 1117, 1118, 1081 HV Amsterdam
Email: k.sigaloff@amsterdamumc.nl

Executive researcher
Drs. D.T.P. Buis, researcher
Departement interne geneeskunde, VUmc
Email: d.t.p.buis@amsterdamumc.nl

Independent doctor:
Dr. M. Bomers, internist-infectioloog
Afdeling interne geneeskunde, VUmc
Email: m.bomers@amsterdamumc.nl

Complaints:
Complaints officer VUmc
Email: zorgsupport@vumc.nl

For more information about your rights

Data protection officer:

Email: privacy@vumc.nl
Appendix B: information about the insurance

The sponsor has taken out insurance for everyone who takes part in the study. The insurance pays for the damage you have suffered because you participated in the study. This concerns damage you suffer during the study or within 4 years after the study has ended. You must report damage to the insurer within 4 years.

The insurance does not cover all damage. At the bottom of this text is a brief description of which damage is not covered.

These conditions are set out in the ‘Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015’. This decision can be found in the government's Wettenbank (https://wetten.overheid.nl).

In the event of damage, you can contact the insurer directly via the contact details below.

<table>
<thead>
<tr>
<th>The insurer of the study is:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name: Centramed</td>
</tr>
<tr>
<td>Address: Onderlinge Waarborgmaatschappij B.A., Postbus 7374, 2701 AJ Zoetermeer</td>
</tr>
<tr>
<td>Telephone number: 070 3017070</td>
</tr>
<tr>
<td>Email: <a href="mailto:schade@centramed.nl">schade@centramed.nl</a> (Policy number: ...)</td>
</tr>
<tr>
<td>Polis number: 624.529.204</td>
</tr>
</tbody>
</table>

The insurance offers cover of €650,000 as a maximum per claim per participant, with a maximum of €5,000,000 for the entire study and €7,500,000 per year for all studies by the same client.

Please note that the insurance does not cover the following damage:

- Damage due to a risk about which we have given you information in this sheet. But this does not apply if the risk turned out to be greater than we previously thought. Or if the risk was very unlikely.
- Damage to your health that would also have happened if you had not taken part in the study.
- Damage that happens because you did not follow directions or instructions or did not follow them properly.
- Damage to the health of your children or grandchildren.
- Damage caused by a treatment method that already exists. Or by research into a treatment method that already exists.
Appendix C – Overview of measurements

Time 1: 3rd week after starting antibiotics
- Determining whether you are eligible to participate in the study.
- The lottery. This will determine whether you will receive antibiotics for 4 weeks or 6 weeks.
- 2 questionnaires: about your state of health and quality of life.

Time 2: 4th week after starting antibiotics
- If you are no longer in hospital, telephone contact with researchers about physical complaints and possible side effects.

Time 3: on discharge from hospital (time varies)
- 1 questionnaire about possible consequences of health problems for your work.

Time 4: 5th week after starting antibiotics
- A blood sample to determine whether the antibiotic treatment is working and whether there are any side effects.
- If you are no longer in hospital, telephone contact with researchers about physical complaints and possible side effects.

Time 5: 6th week after starting antibiotics
- A blood sample to determine whether the antibiotic treatment is working and whether there are any side effects.
- 2 questionnaires: about your state of health and quality of life.
- If you are no longer in hospital, telephone contact with researchers about physical complaints and possible side effects.

Time 6: 8th week after starting antibiotics
- Telephone contact with researchers about physical complaints and possible side effects.

Time 7: 3 months after the start of the study
- Telephone contact with researchers about physical complaints

Time 8: 6 months after the start of the study
- 4 questionnaires: about your state of health, quality of life, possible consequences of health problems for your work and your use of healthcare.
- Telephone contact with researchers about physical complaints
Subject information SAFE study

Appendix D - Informed consent form – subject
Versie 1
2022-05-04

A study on safely shortening antibiotic treatment in bloodstream infections with Staphylococcal bacteria: the SAFE study.

- I have read the information sheet. I was able to ask questions. My questions have been answered well enough. I had enough time to decide if I wanted to take part.
- I know that taking part is voluntary. I also know that at any time I can decide not to take part in the study. Or to stop taking part. I do not have to explain why.
- I give the investigator consent to inform my general practitioner, treating specialist and pharmacy that I am taking part in this study.
- I give consent to request information from my general practitioner, treating specialist and pharmacy about my medical history and medicine use.
- I give consent to collect and use my data and body material. The investigators only do this to answer the question of this study.
- I give permission for the storage of my data for 15 years.
- I know that some people will be able to see all of my data to review the study. These people are mentioned in this information sheet. I give consent to let them see my data for this review.
- I give permission for my general practitioner and/or treating specialist to be informed of unexpected findings that are (or may be) important for my health.
- I know that if necessary I must undergo a pregnancy test, prior to participation I cannot become pregnant as long as I am being treated with antibiotics.
- The investigator discussed with me how I can best prevent becoming pregnant.

I give □ Yes  ☐ No

consent to request information from my general practitioner if I am not available by phone 3 times

I give □ Yes  ☐ No

consent to store my personal data longer and use it for future research into my condition.

I want to take part in this study.

My name is (subject): ………………………………..
Signature: ………………………………………. Date : __/__/__

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Subject information SAFE study

I declare that I have fully informed this subject about the study mentioned.

If any information becomes known during the study that could influence the subject’s consent, I will let this subject know in good time.

Investigator name (or their representative): ......................
Signature:.......................... Date: __/__/__

Additional information was given by:
Name:..............................
Job title:............................
Signature:.......................... Date: __/__/__

The study subject will receive a complete information sheet, together with a signed version of the consent form.