Participant information for participation in medical scientific research

Contrast-enhanced ultrasound of the uterus

Dear participant,

With this information letter, we would like to ask you if you would like to participate in medical-scientific research. Participation is voluntary. You are receiving this letter because you have complaints such as painful and/or heavy menstrual bleeding, and/or because your doctor suspects that you have a disorder of your uterus. Or you receive this letter because you are asked to participate as a healthy volunteer.
You will read about what kind of examination is involved, what it means for you, and what the advantages and disadvantages are. It is a lot of information. Please read the information carefully and decide if you want to participate. If you want to participate, you can fill in the form found in **Appendix C**.

Ask your questions
You can make your decision with the information you find in this information letter. In addition, we encourage you to:
- Ask questions to the researcher giving you this information;
- Talk to your partner, family or friends about this study;
- Ask questions to the independent expert. For contact details, see **Appendix A**;
- Read the information at www.government.nl/documents/leaflets/2020/06/03/medical-research-information-for-human-subjects

1. General information

Amsterdam UMC, location VUmc, set up this study. Therefore, we call Amsterdam UMC the 'contractor'. Researchers, who may also be doctors or research nurses, are carrying out the research in multiple hospitals. Participants in a medical-scientific study are often referred to as *test subjects*. Both patients and healthy people can be test subjects. For this study, 253 subjects from multiple countries are required. In the Netherlands, about 220 subjects are expected to participate. Amsterdam UMC's medical ethics review committee has approved this research. This study is funded by the Dutch Research Council (NWO) and co-funded by Samsung Medison.

2. What is the purpose of the study?

To establish contrast-enhanced ultrasound as a new ultrasound technique in the Gynaecology department, so that we can detect uterine disorders better and faster in the future.

3. What is the background to the study

You have been asked to participate in a study in which we want to make a so-called 'contrast-enhanced ultrasound' of your uterus. Just like a normal ultrasound, we will make an ultrasound image of your uterus using sound waves, but this time we will administer a contrast agent through an intravenous drip

on your hand or arm. This contrast agent makes the smallest blood vessels visible. The smallest blood vessels in our body contain a lot of information about the tissue they are in and about various conditions. With everyday ultrasound techniques, it is unfortunately not possible to visualise these tiny blood vessels. Contrast-enhanced ultrasound has long been used in cardiology and to diagnose for example abnormalities in the liver and kidneys, but in gynaecology it is still a little-used technique. Research has shown differences between the network of the smallest blood vessels between uteri with various disorders and uteri without disorders. Therefore, contrast-enhanced ultrasound could theoretically improve the diagnostics of uterine disorders. But, we first need to research this. Through this study, we want to set up contrast-enhanced ultrasound at the Gynaecology department at the Amsterdam UMC. We hope that this will help us to detect various uterine disorders better and faster in the future.

4. How does the examination proceed?

How long will the examination last?

Are you participating in the research? Then we will make one additional appointment with you for the contrast-enhanced ultrasound in the Amsterdam UMC, location AMC.

Step 1: are you suited to participate?

We first want to know whether you are suited to participate. Therefore, we will call you to ask you some questions about your medical history. We will also ask about your ethnic background, as uterine fibroids are more common in people with an African background. You cannot participate if you are pregnant, or have a hormonal or copper intra-uterine device.

Step 2: examinations and measurements

The examination requires one additional visit to the hospital. This visit takes about one hour. During this visit, we will do a regular and a contrast-enhanced ultrasound exam.

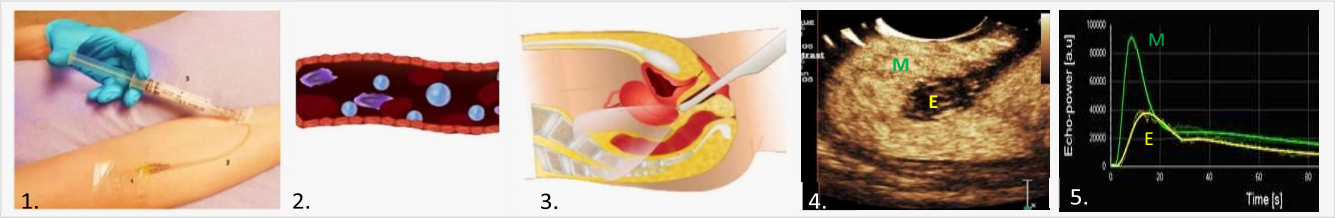
Step 3: collecting patient file data

At 3, 6, 12, 18 and 24 months after your visit, we will email you to ask you via a survey whether you had an MRI or surgery of your uterus after your visit. If so, we will collect these results for the research. Filling in the survey takes 1 to 2 minutes. The surveys are online in a secure and protected environment. Therefore, we ask for your permission to use your email address to send you the link, so that you can fill in the survey online.

What is different from regular care?

In addition to the regular ultrasound examination of your uterus, we want to do a contrast-enhanced ultrasound of your uterus. The figure below schematically shows how a contrast-enhanced ultrasound works. 1) You are given an IV drip through which the contrast agent is administered. 2) The contrast agent spreads through all the blood vessels. 3) An internal ultrasound of the uterus is performed.

4) This produces a contrast-enhanced ultrasound image, showing in the centre the inner lining of the uterus; the endometrium (E) and around it the uterine wall; the myometrium (M). 5) We will analyse this contrast-enhanced ultrasound image at a later time. The used contrast agent is SonoVue, which is injected through an IV drip. We inject this twice so that we can make a contrast-enhanced ultrasound twice. About 10-15 minutes after the ultrasound exam, the contrast medium will have disappeared from your blood.



5. What agreements will we make with you?

We want the examination to go as planned. That is why we make the following agreements with you:

- You will not take part in any other medical-scientific study unless this has been discussed with and authorised by the investigator of this study;
- You will come to your scheduled appointment at the gynaecology outpatient clinic for the contrast-enhanced ultrasound.

It is important that you contact the researcher:

- If you no longer wish to participate in the study;
- If your phone number, address or email address changes.

Can you become pregnant during the study?

People who are pregnant cannot participate in this study. This is because it has not yet been investigated whether this examination could affect an unborn child.

Nevertheless pregnant?

If you have indicated that you wish to participate in the study and it turns out that you are pregnant during the planned contrast-enhanced ultrasound, please inform the investigator immediately. The appointment for the contrast-enhanced ultrasound will then be cancelled.

Repeat examination

You may be asked to repeat the ultrasound scan on another day. The researchers will ask this if it can help them in assessing the scan. You decide whether you want to participate in this repeat examination.

6. What discomforts can you experience?

The risks of participating in this study are minimal. The contrast agent (SonoVue®) that is used, is widely used and is a safe agent. Side effects are rare and may include: temporary change in taste, headache and pain around the injection site. There is a very small chance of having an allergic reaction to the contrast agent.

7. What are the advantages and disadvantages of taking part in the study?

Taking part in the study can have advantages and disadvantages. We list them below. Think about them carefully and talk about them with others.

No advantages for participants

You will not personally benefit from this research. However, your participation will help the researchers to diagnose uterine disorders better and faster in the future.

Taking part in the study may have these disadvantages:

- You may experience the previously-mentioned discomforts;
- You need to come to the Amsterdam UMC, location AMC, for making the ultrasound;
- Participation will cost you extra time;
- You have to keep the agreements of the research;
- It is possible that, during the examination, something may be accidentally discovered that is not directly relevant to the examination, but is important for your health or that of your family members. You will then discuss what to do with your GP or specialist. This may lead to additional investigations. See also section 10 on unexpected discoveries.

Do you not want to participate?

You decide whether you want to take part in the study. Do you not want to participate? Then this will not affect your treatment. If you are not currently being treated, this will not change.

8. When does the study stop?

The researcher will inform you if there is new information about the research that is important to you. In that case, the researcher will ask you whether you still want to participate.

In these situations, the study stops for you:

- You became pregnant before the contrast-enhanced ultrasound was made;
- You want to stop participating in the research. You can decide this at any time. If so, report this to the investigator immediately. You do not have to say why you want to stop.
- The investigator thinks it is better for you to stop;
- One of the following bodies decides that the research should stop:
    - Amsterdam UMC,
    - the government, or
    - the medical ethics committee reviewing the research.

What happens if you stop the research?

The researchers use the data collected up to the time of stopping.
The entire study ends when the required data of all participants has been collected.

9. What happens after the study?

Will you receive the results of the study?

About two years after the study is completed, the researcher will let you know the main results of the study.

10. What do we do with your data?

Are you participating in the study? Then you also give us permission to collect, use and store your data.

What information will we store?

- Your name
- Your address
- Your date of birth
- Your email address
- Your ethnicity
- Information about your medical history and health
- (Medical) information we collect during the study

Why do we collect, use and store your information?

We collect, use and store your personal and medical information to answer the questions in this study. And to publish the results. Information may be used by the Amsterdam UMC and companies that help the Amsterdam UMC analyse the research data.

How do we protect your privacy?

To protect your privacy, we give your information a code. On all your information, we put only this code. We keep the key to the code in a secure place in the research centre. When we process your information, we always use only this code. Also in reports and publications about the research, no one can trace the data back to you. Your coded ultrasound images will be sent to researchers at Eindhoven University of Technology, Angiogenesis Analytics and Samsung Medison, who are all part of the research group. They will analyse only coded ultrasound images.

Who can see your personal and medical information?

Some people will be able to see your name and other personal information without a code. This could be data collected specifically for this study, as well as information from your medical record. These are people who check that the researchers are conducting the study properly and reliably. These people can access your information:

- A controller working for the Amsterdam UMC;
- National and international supervisory authorities;

These individuals will keep your information confidential. For inspection by these persons, we ask you to give permission. The Health Care and Youth Inspectorate can view your information without your permission.

How long do we store your data?
It is determined by law that your information will be stored for 15 years at the Amsterdam UMC.

May we use your information for other research?
Your collected information may also be relevant for other scientific research in the field of ultrasound and uterine disorders after this study is completed. For this reason, your information will be stored for 15 years in the research centre. On the consent form, please indicate whether you agree to this. Do you not consent to this specific use of your information? Then you can still take part in this study.

What happens if unexpected discoveries are made?
During this study, we may by chance find something that is not directly relevant to the study, but is important for your health. The investigator will then contact your GP or specialist. You will discuss what to do with your GP or specialist. You give permission on the form for your GP or specialist to be informed.

Can you withdraw your consent to the use of your information?
You can withdraw your consent to the use of your information at any time. Please tell the researcher. This applies to use in this study and to use in other studies. Please note: if you withdraw your consent when the researchers have already collected the information for the research, then they may still use this information.

We will send your coded information to countries outside the European Union
In this study, we will send your coded ultrasound images to Samsung Medison in South Korea. European Union privacy rules do not apply in this country, but your privacy will be protected at an equivalent level.

Want to know more about your privacy?
- If you want to know more about your rights on processing your personal information, then please visit http://www.autoriteitpersoonsgegevens.nl/en.
- Do you have any questions about your rights? Or do you have a complaint about the processing of your personal information? Please contact the person responsible for processing your personal information, which is the Amsterdam UMC. See **Appendix A** for contact details and website.
- If you have complaints about the processing of your personal information, we recommend that you first discuss this with the research team. You can also go to the Amsterdam UMC's Data Protection Officer. Or you can file a complaint with the Personal Data Authority.

Where can you find more information about the study?
You can find more information about the study on the following website: www.clinicaltrials.gov. After the study, the website may show a summary of the results of this study. U can find this study by searching for ‘UteroVue’.

Consent follow-up study
When we have successfully set up contrast-enhanced ultrasound in the future, we would like to use this technique to diagnose uterine disorders better and faster. We ask for your consent to contact you in writing or by telephone for this follow-up research.

11. Will you be reimbursed if you take part in the study?

There are no additional costs for participating in this study. You will receive a gift card of 25 euros, and a reimbursement for any additional travel costs.

12. Are you insured during the study?

Insurance has been arranged for everyone participating in this study. The insurance covers any damage caused by the study. Not all damages are covered. **Appendix B** provides more information about the insurance and the conditions. It also says who you can report damage to.

13. Do you have any questions?

Please direct any questions about the study to research team. Would you like advice from someone who has no interest in this research? Then go to the independent expert, for contact details see **Appendix A**. She knows a lot about the study, but is not collaborating in this study.

Do you have a complaint? Please discuss it with the researcher or the doctor treating you. Would you rather not? Then go to the complaints officer of the research centre. **Appendix A** shows where you can find them.

14. How do you consent to the study?

First take your time to think about this research. Then tell the researcher if you understand the information and whether or not you want to participate. Do you want to participate? Then fill in the consent form that you will find enclosed with this information letter. You and the researcher will both receive a signed version of this consent form.

Thank you for your time.

Prof. dr. Judith Huirne,
Gynaecologist, project leader

Appendices to this information letter:

A. Contact details
B. Insurance information
C. Consent form

APPENDIX A: Contact details for Amsterdam UMC, location AMC

Coordinating researcher
Drs. Eva J.E. de Bock
Department of Obstetrics & Gynaecology
Tel: 020 - 566 1601 (Gynaecology outpatient clinic)
E-mail: ceus@amsterdamumc.nl

Project leader
Prof. Dr. Judith A.F. Huirne (gynaecologist)
Department of Obstetrics & Gynaecology
Tel: 020 - 566 1601 (Gynaecology outpatient clinic)

Independent doctor
Dr. Marjon A. de Boer (gynaecologist)
Department of Obstetrics & Gynaecology
Tel: 020 - 566 1601 (Gynaecology outpatient clinic)

Complaints
The Patient Information and Complaints Department is located on the ground floor of the outpatient clinic (A0). The department is opened on weekdays from 9.00 – 12:30 and 13:00 – 15:30. During these hours, the department can also be reached by telephone (020 566 3355). If the department is closed, you can leave a voicemail message or send an email. The department's email address is klachten@ammsterdamumc.nl.

Data Protection Officer of the Amsterdam UMC: privacy@amsterdamumc.nl

For more information on your rights:
Prof. dr. J.A.F. Huirne
Tel: 020 - 566 3754 (secretariat Women's Clinic)

APPENDIX B: Insurance information

Insurance has been taken out for everyone participating in this study. The insurance covers damage resulting from participation in the study. This applies to damage that comes to light during the study, or within four years of finishing participation in the study. You must also have reported the damage to the insurer within these four years.

Do you have damage from the investigation? If so, report it to this insurer:

The insurer of this research is:	
Name insurer:	CentraMed B.A.
Address:	Postbus 7374, 2701 AJ Zoetermeer
Telephone number:	070-3017070
E-mail:	info@centramed.nl
Policy number:	620.872.009

The insurance will cover €650,000 per participant with a maximum of €5,000,000 for the entire study and €7,500,000 for damage resulting from medical scientific research that is reported per insurance year.

The insurance does **not** cover the following damages:

- damage due to a risk about which you were informed in the written information. This does not apply if the risk occurs more severely than was foreseen or if the risk was very unlikely;
- damage to health that would have occurred even if you had not participated in the study;
- damage resulting from not (fully) following directions or instructions;
- damage to your offspring, resulting from a negative effect of the research on you or your offspring;
- damage caused by an existing treatment method when researching existing treatment methods.

These regulations are found in the "Decree on Compulsory Insurance in Medical Scientific Research with Human Subjects 2015. This decree can be found in the Government Law Database (https://wetten.overheid.nl).

APPENDIX C: Study participation consent form for *'Contrast-enhanced ultrasound of the uterus'*

- I read the information letter. I was also able to ask questions. My questions were sufficiently answered. I had enough time to decide whether to participate.
- I know that participating is voluntary. I also know that I can decide at any time not to participate in the study after all. Or to stop. I do not have to say why I want to stop.
- I give the researcher permission to request information from my family doctor or treating specialist about my uterus.
- I give permission for my GP and/or specialist to be informed of unexpected findings that may be important to my health.
- I give the researchers permission to collect and use my data. The researchers do this only to answer the research question of this study.
- I know that to monitor the study, some people will be able to see all of my data. Those people are listed in this information letter. I give these people permission to see my data for this audit.
- I give permission to send my coded ultrasound images to researchers of the Eindhoven University of Technology and Angiogenesis Analytics, for image analysis.
- I give permission to send my coded ultrasound images to researchers of Samsung Medison (South Korea), where EU privacy rules do not apply. I know that an equivalent level of protection has been agreed upon for my data.
- I give permission for collecting my ethnicity data.
- I know that I should not be pregnant during the contrast ultrasound.
- I consent to the use of my contact information to contact me about the study and to send the surveys.

Would you please check yes or no in the table below?

I give permission to keep my data to use this for other research, as stated in the information letter.	Yes ☐	No ☐
I give permission to ask me if necessary after this study if I want to participate in a follow-up study.	Yes ☐	No ☐

I want to participate in this study.

My name is (participant): ……

Date of birth: ___ / ___ /_____

Signature:…… **Date:** ___ / ___ /_____

To be completed by the researcher

I declare that I have fully informed this participant about the said study. Will any information become known during the study that may affect the participant's consent? If so, I will let this participant know in time.

Name Researcher (or representative):……

Signature:…… Date: ___ / ___ /_____

A complete information letter will be given to the participant along with a copy of the signed consent form.