Subject information for participation in medical scientific research

Ulipristal versus Surgery in treatment of symptomatic uterine fibroids

Official title: Ulipristal versus standaard chirurgische behandeling bij symptomatische uteriene myomen

General information

Dear Madam,

You are asked to take part in a medical-scientific study. Participation is voluntary. Participation requires your written consent. Before you decide whether you want to participate in this study, you will be given an explanation about what the study involves. Please read this information carefully and ask the investigator for an explanation if you have any questions. You can also ask the independent expert, who is mentioned at the end of this document, for additional information. You may also discuss it with your partner, friends or family. Please take all the time you need to consider if you want to participate in this study.
This study has been designed by the Amsterdam UMC, location VUmc and is being carried out by doctors and investigators in various hospitals in the Netherlands. The Medical Research Ethics Committee VUmc (METc VUmc) has approved this study. General information about the assessment of research can be found in the general leaflet on medical research. You can find this leaflet on: https://www.government.nl/documents/leaflets/2016/03/31/medical-research

Introduction

You are visiting a gynaecologist because you have one or multiple fibroids (or myomas) in your uterus. These fibroids are benign, but can cause complaints like heavy menstrual bleeding or menstrual pain. Other mentioned complaints are lower abdominal or back pain, micturition problems or pain during intercourse. Sometimes fibroids don't require treatment. The choice of treatment is dependent of the extent of complaints you experience, in combination with the characteristics of fibroid(s), such as the number of fibroids, size and location in the uterus (see also figure 1). At first, conservative treatment is tried, such as oral contraceptives, an hormonal IUD (intra uterine device) or pain medication. If these medical treatments are insufficient of undesired, women sometimes choose for surgical treatment.

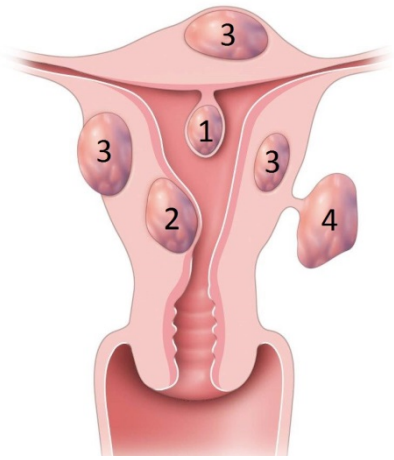

Figure 1: Location of the fibroids

1: Intra uterine fibroid;
2: Fibroid located below endometrium;
3: Fibroid in uterine wall;
4: fibroid on the outside of the uterus

Although surgery has a good effect on women's complaints, it is invasive and a recovery period is needed. Since 2012 there is a new medicine

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available for women with uterine fibroids, which could make surgery avoidable. This medicine is called *ulipristal*, also known under its brand name *Esmya*. The purpose of this study is to investigate the efficacy and safety of long-term (15 to 18 months) treatment with ulipristal acetate (also known as 'Esmya') compared to the efficacy and safety of surgical procedures. Also, we want to compare patient preferences and satisfaction with both treatment options. In order to do so, we will investigate and compare two patient groups. In this study the chance to allocate for ulipristal is twice as big as the change to allocate for surgery, two times as many women will be treated with ulipristal, compared to surgery. If you decide to participate in this study, the computer will allocate your treatment group:

1. The first group will be treated with the medicine ulipristal
2. The second group will be treated surgically (either hysterectomy, myomectomy or embolization).

Neither you, nor your gynecologist can influence the allocation. This will ensure that there will be two groups to compare both treatments. Eventually 179 women will be studied, 119 in the ulipristal group and 60 patients in the surgery group.

Treatment with ulipristal

Ulipristal is prescribed in courses of three months (one tablet a day). In between courses you stop with ulipristal for two months and have your menstruation twice, before you start with a new course. Your menstruation is usually a lot less then it was before the start with ulipristal. Depending on your satisfaction with the medicine, you will stop with ulipristal after three or four treatment courses and we evaluate your complaints. The size-decreasing effect of ulipristal sustains, as well as its effect on your complaints.

Standard surgery

Women who are inadequately helped by hormonal medicines like the oral contraceptive pill or pain medication (NSAIDs), can choose between three treatment options, who are well investigated and usually considered to treat fibroid complaints.

Hysterectomy

Hysterectomy is surgery to remove the uterus. The treatment is performed in the hospital. Hysterectomy can be done vaginally, abdominally or by laparoscopic surgery (by a laparoscope and only a few small incisions in your abdomen). The choice for either of these methods is dependent on the size of the uterus. Surgery will be done in the operation theatre under general or spinal anaesthesia. In the first period after the surgery you will have to recover and you may experience abdominal pain and bloody discharge.
Take into account that you will be sick from work for around 4-6 weeks. Removing your uterus means that you will not have any menstruations anymore and can no longer become pregnant. The fibroids will not come back.

Myomectomy (fibroid excision)

Myomectomy is the surgical removal of fibroids, a procedure considered standard of-care for removing fibroids and preserving the uterus. It therefore may be recommended for women who wish to become

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pregnant. Myomectomy is most often performed through a laparoscopic or abdominal surgery, depending on the size and location of the fibroids (see figure 1). Surgery will be done in the operation theatre under general or anaesthesia. In the first period after the surgery you will have to recover and you may experience abdominal pain and bloody discharge. Take into account that you will be sick from work for around 4-6 weeks. The chance that new fibroids will develop, that may cause new complaints is about 25%. You will keep your uterus and menstruation.

Embolization

Uterine artery embolization is a treatment that blocks the blood supply to fibroids. The treatment is performed in the hospital. A radiologist will insert a small tube into a large blood vessel in the inner thigh. The tube is threaded up to the uterine blood vessels. The doctor injects tiny particles into the blood vessel, which stops blood flow to the fibroid. This causes the fibroid to shrink till almost half the size. You will keep your uterus, but pregnancy is not usually recommended after uterine artery embolization. Recovery after this surgery lasts about 2-4 weeks. You can feel feverishly or have abdominal pain for the first two weeks. Some women may experience vaginal discharge. 25% Of the women who had embolization, eventually choose for an additional treatment in the first 5 years after embolization (mostly hysterectomy).

What participation involves

Your participation will last about 24 months.

1. If you are allocated in the medicine group, you will be treated for three to four courses of 3 months with ulipristal. For three months you will take 1 tablet of ulipristal each day, followed by a two months medicine free period. This cycle will be repeated up to three times. Depending on your amount of treatment courses, your complete treatment will be about 18 months (in case of 4 courses):

2. If you are allocated in the surgery group, you will be treated according to standard care. You and your gynaecologist will decide which treatment you prefer.

Both groups will receive a questionnaire at six moments. At the start of the study, after 3, 6, 12, 18 and 24 months. The questionnaires are available both digital (per email) or printed (per mail), depending on your preference. This questionnaire consist of questions about your general health, well-being, experienced side effects, absenteeism, satisfaction, preference for your treatment, a menstruation calendar, menstrual pain and your sexual experiences. In the menstruation calendar, we will ask you to register your menstruation during one month (in case you still have your menstruations).

In the schedule of figure 2, you can see which appointments are standard care and which ones are extra in this study.

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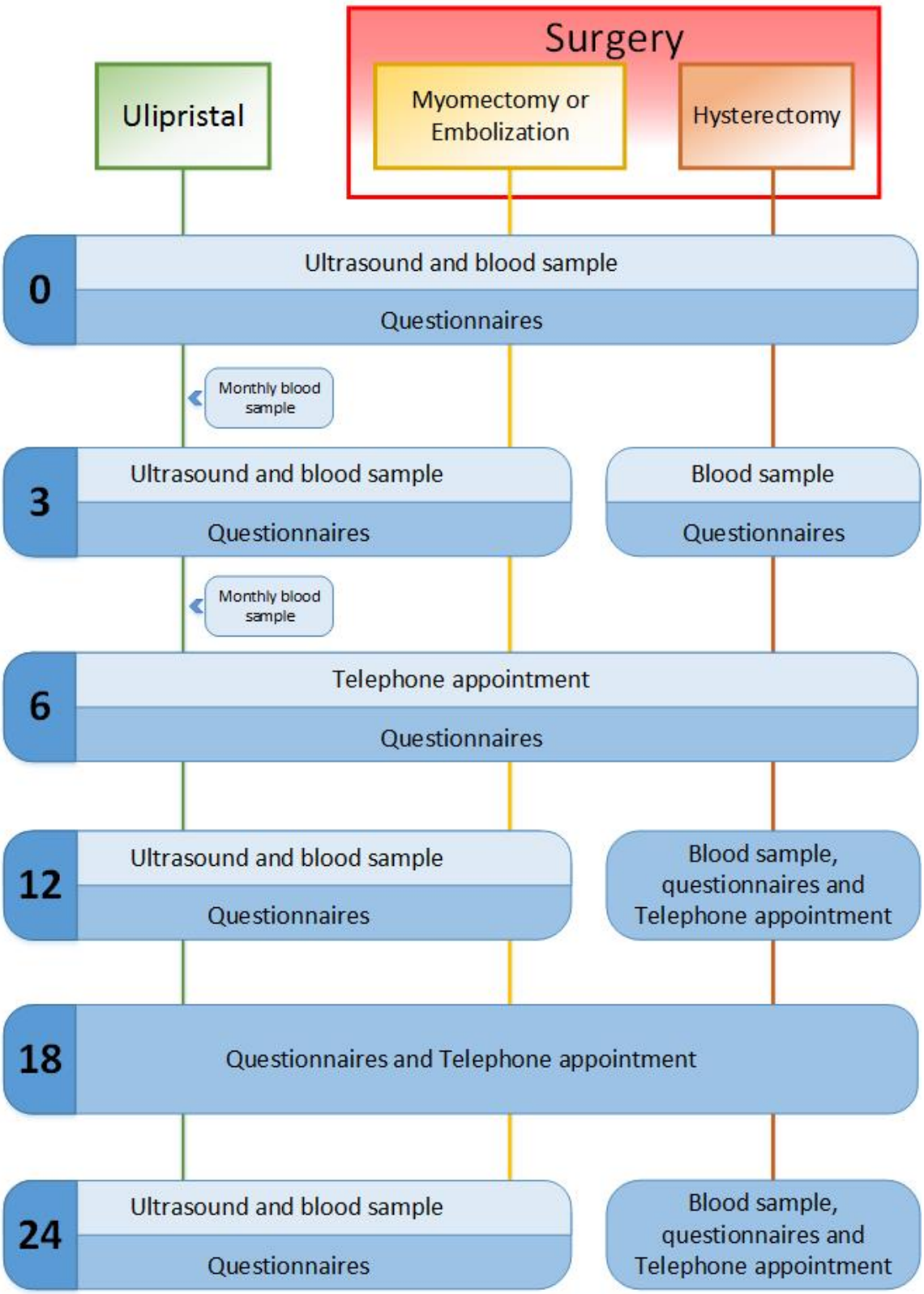

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What is expected of you

In order to carry out the study properly, it is important that you follow the study instructions.
The study instructions require that you:

- do not participate in another medical study, unless this is agreed with the investigator.
- keep appointments for visits.

It is important that you contact the investigator:

- before you start using other medicines. Even if they are homeopathic or natural remedies, vitamins and/or over-the-counter medicines.
- if you are admitted to hospital or are going for treatment there.
- if you suddenly develop any health problems.
- if you no longer want to participate in the study.
- if your contact details change.

Pregnancy

It is recommended not to conceive during the ulipristal treatment. Chances on a pregnancy are small (due to its hormonal effect), but it is advised to use additional (non-hormonal) contraceptives. Pregnancy after embolization is discouraged, due to insufficient experience. After a myomectomy it is sometimes advised to deliver by a caesarean, because the risks during pregnancy or delivery can be higher when you had uterine surgery. After hysterectomy it is not possible to become pregnant anymore.

Possible complications and other discomforts

Ulipristal

Ulipristal causes side effects such as: absence of menstruation (usually this is a preferred effect), thickening of the endometrium (inner linage of the uterus), this usually normalizes after you stop the treatment. Other side effects can be headache, dizziness, abdominal pain, nausea, acne, pain of the muscle or bones, ovarian benign cysts, sensitive or painful breasts, pelvic pain, hot flushes, tiredness or weight gain. It is good to realise that these side effects occasionally occur. The long term effects, especially regarding the endometrial changes, are not yet known. We also don't know the exact effect of ulipristal on pregnancy. A very rare, but severe complication of ulipristal usage is the occurrence of liver injury. This happened in less than 1 out of 95.000 patients. To track this complication, your liver function will be tested regularly. In case of a severe increase of the liver values, treatment with ulipristal will be stopped. More information about ulipristal is found in the package leaflet.

Surgeries

Most of the *hysterectomies* are performed without severe complications. The chance on short term complications is approximately 1:100. These Complications are infection, haemorrhage or urinary tract or bowel injury. These complications may extend your hospital stay, require blood transfusion or medication, or an rehospitalisation. Other complications are e.g. thrombosis, adhesions in the abdominal cavity or an

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increased risk on urine incontinence later in life. You will not menstruate anymore and a pregnancy is impossible. Sexuality is usually experienced as improved, compared to before the surgery. Women usually become menopausal 1-2 years earlier than average.

Most of the *myomectomies* are performed without severe complications. Complications that can occur during or shortly after surgery are similar to those of hysterectomy, such as infection, haemorrhage or urinary tract or bowel injury. You will keep your menstruations and a pregnancy is still possible, but is sometimes accompanied with more risks due to uterine 'scarring'. Chances of recurrence of the fibroids is approximately 25%.

Most *embolizations* are performed without severe complications. Complications that can occur during or shortly after the procedure are infection, flulike complaints, vaginal discharge or pain. Also for these complications it is sometimes necessary to extend your hospital stay or a need for prolonged use of pain medication. You will keep your menstruations. A small part of the women >45 years, will not menstruate anymore due to less functioning ovaries. The chances are that the ovaries were already working less before the procedure. The chances that you will need a secondary procedure or surgery approximately 25% after 5 years.

Possible advantages and disadvantages

It is important that you properly weigh up the possible benefits and disadvantages before you decide to join. You will not personally benefit from participation in this study. Your participation may contribute to increased knowledge and a better treatment of fibroids. A possible advantage of treatment with ulipristal could be that you won't need a radical surgery with the corresponding short and long term complications (as described above). A possible disadvantage could be that you have to take daily medication and can experience adverse effects. A possible advantage of surgery could be that you won't have any periods (in case of hysterectomy) or doesn't need to take daily medication. A possible disadvantage of surgery could be that you will experience a complication or can't conceive anymore.

If you do not want to participate or you want to stop participating in the study

You will have at least a week, but as much time that you require to decide if you whether or not to participate in this study. Participation is voluntary. If you do not want to participate (anymore), you will be treated as usual. If you do participate in the study and are allocated to the ulipristal group, you can always change your mind and decide to stop, at any time during the study, in which case we will discuss different treatment options. You do not have to say why you are stopping, but you do need to tell the investigator immediately. The data collected until that time will still be used for the study.
If there is any new information about the study that is important for you, the investigator will let you know. You will then be asked whether you still want to continue your participation.

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End of the study

Your participation in the study stops when:

- you have completed all the visits
- you choose to stop
- the end of the entire study has been
- the investigator considers it best for you to stop
- The government or Medical Research Ethics Committee, decides to stop the study.

The study is concluded once all the participants have completed the study. After processing the data, the investigator will inform you about the most important results of the study. This will happen about 1-2 years after your participation.

Usage and storage of your data

Your personal will be collected, used and stored for this study. This concerns data such as your name, address, date of birth and data about your health. The collection, use and storage of your data is required to answer the questions asked in this study and to publish the results. We ask your permission for the use of your data.

Confidentiality of your data

To protect your privacy, your data will be given a code. Your name and other information that can directly identify you, will be omitted. Data can only be traced back to you with the encryption key. The encryption key remains safely stored in the local research institute. The data that is sent to the (main)investigator of the Amterdam UMC, location VUmc will only contain the code, not your name or other data with which you can be identified. The data cannot be traced back to you in reports and publications about the study.

Access to your data for verification

Some people can access all your data at the research location. Including the data without a code. This is necessary to check whether the study is being conducted in a good and reliable manner. Persons who have access to your data for review are: the committee that monitors the safety of the study, a monitor working for the investigator of the study, national supervisory authorities, for example, the Healthcare and Youth Inspectorate. They will keep your data confidential. We ask you to consent to this access.

Retention period of your data

Your data must be kept for 15 years at the research location and 15 years at the Amsterdam UMC, location VUmc.

Storage and use of data for other research

Your data may also be of importance for other scientific research in the field of fibroid treatment. To this end, your data will be stored for 15 years. You can indicate on the consent form whether or not you agree with this, and you can always withdraw this consent. If you do not agree with this, you can still participate in the

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current study. The study data collected until the moment you withdraw your consent will still be used in the study.

Consent follow up research
We would like your consent to approach you in writing or by phone for any follow up research. If you agree now, you can always withdraw this consent later. To approach you in the future we would like save your contact details (name, address, phone number and email). These contact details will be stored on save location at your hospital and will not be used for different purposes.

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

If you have questions about your rights, please contact the person responsible for the processing of your personal data. For this study, that is: *Amsterdam UMC, location AMC.* See Appendix A for contact details and our website.

If you have questions or complaints about the processing of your personal data, we advise you to first contact the research location. You can also contact the Data Protection Officer of the institution (see Appendix A for contact details) or the Dutch Data Protection Authority.

Registration of the study
Information about this study is included in a list of medical-scientific studies namely www.trialregister.nl. It does not contain any information that can be traced to you. After the study, the website may display a summary of the results of this study. You can find this study under MYOMEX-2.

Study subject insurance

Insurance has been taken out for everyone participating in this study. This insurance covers damage caused by the study. The insurance does not cover all damages. Appendix C contains more information about the insurance. It also tells you who to report damage to.

Will my GP be informed if I participate?

We will always send your GP a message to let them know that you are participating in the study. This is for your own safety. If you do not agree to this, you cannot participate in this study

No compensation for participation

There are now extra costs involved in participation of this study, also you will not be paid for your participation in this study. You will be reimbursed for you travel costs. You will be treated over several years (both in the ulipristal as the surgery group), which means that you will have to pay healthcare costs over

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several years up to your policy excess (of your healthcare insurance). This is also the case when you won't participate in this study. In case you allocate to the surgery group and choose for a hysterectomy, you will have two extra blood sample collections (at 12 and 24 months). The costs for these samples will be compensated. You will receive the information regarding declaration of these costs from your gynaecologist.

Any questions?

If you have any questions, please contact or study team. If you would like any independent advice about participation in this study, you may contact our independent expert, dr van Kesteren. He knows about the study but is not involved in it (see the contact details in **Appendix A**).
If you have any complaints, you may contact the complaints' officer at your hospital. All the relevant details can be found in **Appendix A**: Contact details.

Signing the consent form

When you have had sufficient time for reflection, you will be asked to decide on participation in this study. If you give permission, we will ask you to confirm this in writing on the appended consent form. By your written permission you indicate that you have understood the information and consent to participation in the study. The signature sheet is kept by the investigator. You will get a copy or a second copy of this consent form.

Brochure

General information about the assessment of research can be found in the general brochure on medical research. You will get this brochure, together with all the study information. This brochure is also available on the internet: https://www.government.nl/documents/leaflets/2016/03/31/medical-research

Thank you for your attention.

Kind Regards,

Dr. W.M. Ankum, gynaecologist
Principal investigator
Amsterdam UMC, location AMC

Dr. W.J.K. Hehenkamp, gynaecologist
Principal Investigator
Amsterdam UMC, location VUmc
De Boelelaan 1117 | 1081 HV Amsterdam
Phone: 020-4444444
Email: w.hehenkamp@vumc.nl

Appendices to this information

A. Contact details
B. Informed Consent Form
C. Insurance information

Appendix A: contact details for Amsterdam UMC, location AMC

Principal Investigator location AMC: Dr. W.M. Ankum
Available by phone: 020-5663400

Research doctor: Drs. M.A. Middelkoop, resident obstetrics and gynaecology Amsterdam UMC, location VUmc.
Available by phone: 020-4441851
Email: m.middelkoop@vumc.nl | myomex2@zorgevaluatienederland.nl

Independent expert: Dr Van Kesteren, gynaecologist in the OLVG-Oost in Amsterdam. He is available by phone: 020-5999111, ask for the secretary of gynaecology.

Complaints: Department of 'Patiëntenvoorlichting & Klachtenopvang'.
Available by phone: 020-5663355
Email: patientenvoorlichting@amc.nl

Data Protection Officer of the institution: fg@amc.nl.

For more information about your rights: fg@amc.nl.

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Appendix B: Subject Consent Form
Ulipristal versus Surgery in treatment of symptomatic uterine fibroids

- I have read the subject information form. I was also able to ask questions. My questions have been answered to my satisfaction. I had enough time to decide whether to participate.
- I know that participation is voluntary. I know that I may decide at any time not to participate after all or to withdraw from the study. I do not need to give a reason for this.
- I give permission for my GP to be informed about my participation in this study.
- I know that some people can access my data. These people are listed in this information sheet.
- I consent to my data being used in the way and for the purpose stated in the information sheet.
- I agree that my data for this study being forwarded to the main investigator of the coordinating hospital, so that I can be contacted by phone, post or email with questionnaires as mentioned in the information sheet.
- I consent to my data being stored at the research location for another 15 years after this study.
- I □ **do**
  □ **do not**
  consent to keeping my personal data longer and to use it for future research in the field of fibroid treatment.
- I □ **do**
  □ **do not**
  consent to being contacted again after this study for a follow-up study.
- I want to participate in this study.

Name of study subject:
Signature: Date: __ / __ / __

I hereby declare that I have fully informed this study subject about this study.

If information comes to light during the course of the study that could affect the study subject's consent, I will inform him/her of this in a timely fashion.

Name of investigator (or his/her representative):
Signature: Date:__ / __ / __

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

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Contact data for future research

In case you consented to be contacted in the future about additional research (about this treatment and/or subject), we kindly ask you to fill in the next form. Your data will be handled with care and stored safely. By filling in this form, you consent to be contacted in the future for further research.

Name: ……
Address: ……
Phone number: ……
Email: ……

Results

☐ I would like to be informed about the result of this study. I consent that my email will be used to inform me about any results about this study.

Appendix C: Insurance Information

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Insurance has been taken out by Amsterdam UMC, location VUmc for everyone participating in this study. The insurance covers damage due to participation in the study. This applies to damage manifesting during the study or within four years of the end of your participation in the study. You must notify the insurance company about the damage within those four years.

The insurance does not cover all damages. The damages that are not covered are listed briefly at the end of this text.
This is set out in the Medical Research (Human Subjects) Compulsory Insurance Decree. This decree is listed on the website of the Central Committee on Research Involving Human Subjects www.ccmo.nl (see "Library" and then "Legislation and regulations").

In the event of damage please contact the insurance company or claims adjustor directly.

The insurance company for the study is:	
Name:	Onderlinge Waarborgmaatschappij Centramed B.A.
Address:	Postbus 7374, 2701 AJ Zoetermeer
Telephone number:	070-3017070

The insurance offers a cover of at least €650,000 per study subject and at least €5,000,000 for the entire study. For all studies from the same sponsor, the maximum amount of coverage is at least €7,500,000 annually.

The insurance policy does **not** cover the following damage:

- damage as a result of a risk that you were informed about in the written information. This does not apply if the risk occurs in a more severe form than envisaged, or if the risk was very unlikely to occur;
- damage to your health that would also have occurred if you had not participated in the study;
- damage resulting from not or not entirely following directions or instructions;
- damage to descendants as a result of a negative effect of the study on you or your descendants;
- damage as a result of an existing treatment method for research into existing methods of treatment.

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