Subject information for participation in medical research

Control Crohn Safe trial (CoCroS)

Veilige controle van de ziekte van Crohn

Introduction

Dear Sir/Madam,

With this letter, we would like to ask you to take part in a medical study. Participation is voluntary. You have received this letter because the doctor recently has found you have Crohn's disease, or because you have a flare of Crohn's disease and you have not had maintenance treatment before.
You can read about the medical study in this information sheet, what it means for you, and what the pros and cons are. It is a lot of information. Can you please read the information and decide if you want to take part? If you want to take part, complete the form in Appendix D.

Ask your questions

You can take your decision based on the information in this information sheet. We also suggest that you do this:
- Put your questions to the investigator who gave you this information.
- Talk to your partner, family or friends about this study.
- Ask questions to members of the study team, or the independent expert
- Read the information on www.rijksoverheid.nl/mensenonderzoek.

1. General information

Maastricht University has set up this study. Hereafter, we call Maastricht University the 'sponsor'. Investigators, these can be doctors or specialised nurses, conduct the study in different hospitals.
This study needs 158 subjects in the Netherlands. The Medical Ethics Review Committee azM/UM has approved this study.

2. What is the purpose of the study?

We compare the efficacy and safety of adalimumab monotherapy as first line treatment with the efficacy and safety of step-up care starting with corticosteroids. The medicinal products used in this study are already used in clinical practice for the treatment of Crohn's disease.

Subject Information

3. What is the background of the study?

Crohn's disease is a chronic inflammatory bowel disease characterized by a relapsing and remitting course. There is a high variety in severity, disease course and treatment response between patients. Inflammation of the bowels can cause complications, such as intestinal narrowing and the need to operate. Drug therapy is focused on controlling the inflammation, followed by preventing flare-ups. Treatment according to current guidelines follows a step-up approach with subsequent introduction of more potent medication if the previous category fails. This step-up approach prevents patients with a mild disease course from having to take unnecessary medication. About 30% of patients do not need long-term (maintenance) treatment after the treatment of the first flare.

According to current guidelines, the first step is treatment with corticosteroids. Corticosteroids are frequently associated with side effects. One of the treatment goals for Crohn's disease is to prevent a flare for as long as possible without the use of corticosteroids. Another goal is to make the inflammation seen during a colonoscopy disappear. Patients without inflammation during colonoscopy have a lower risk of hospitalization and surgery. This treatment goal is often not reached with the current guidelines. Research shows that patients who start with a more potent drug sooner, reach these treatment goals more often.

Adalimumab is one of the stronger drugs that is used for Crohn's dsease. This drug is an antibody. Antibodies are normally made by your own immune system to remove pathogens from your body. Adalimumab binds to a protein that causes inflammation in Crohn's disease, namely tumor necrosis factor alpha. Since 2007, adalimumab is used for patients with moderate to severe Crohn's disease. However, we cannot adequately predict at diagnosis who is going to have a severe disease course. Hence, we do not know who needs a stronger drug from the start.

According to current guidelines, starting adalimumab is a step later on in the treatment of Crohn's disease. In this study, we compare treatment according to current guidelines to a treatment strategy where we immediately start with adalimumab. With this, we want to investigate what the best treatment approach is for Crohn's disease. We will examine the efficacy of the different strategies, but also patient's experiences. With the study results, we hope to improve treatment for Cohn's disease, by decreasing the amount of side effects and complications.

4. What happens during the study?

Treatment groups

For this study, we will have two groups:

- Group 1. The people in this group will get subcutaneous adalimumab injections; 4 injections at week 0, 2 injections at week 2, and 1 injection every 2 weeks during 22 weeks.
- Group 2. The people in this group will get step-by-step treatment according to current guidelines, starting with oral corticosteroids during 9 weeks. If this has insufficient

Janssen L, *et al. BMJ Open* 2021; 11:e042885. doi: 10.1136/bmjopen-2020-042885

effect, treatment with corticosteroids will be prolonged and an extra drug will be added (as maintenance treatment).

After 24 weeks, a colonoscopy will be performed to evaluate intestinal inflammation. If no inflammation is seen during the colonoscopy, the adalimumab will be stopped in group 1. If the inflammation is still present, treatment will be adjusted to another dose or switched to another drug.
All participants will be strictly monitored during two years to detect and treat flares as soon as possible. If a flare occurs in between these monitoring moments, the treatment will also be adjusted accordingly.
A draw will decide which treatment you are given. You have one in two chance (50%) to receive adalimumab. This study is 'open label'. This means that you and your doctor know which treatment you are given.

Are you eligible to take part?
First, we want to know if you are eligible to take part. That is the reason that the investigator will check your medical history. Patients in group 1 will be tested for hepatitis B/C, HIV and tuberculosis before starting adalimumab by a blood test and chest x-ray. We will tell you if you have any of these diseases.

Study and measurements
Are you taking part in the study? Participation in this study will take about two years. During this time, you will be strictly monitored by frequent questionnaires, fecal tests and blood tests. At preset moments you will visit the outpatient department. These examinations and visits are also planned if you do not participate in this study. The examinations described below will be performed. Extra examinations or outpatient visits can be scheduled if your health needs further examination, or if a flare is suspected. Appendix C shows an overview of the investigations we carry out during the study.

Questionnaires via myIBDcoach:
The first three months, you fill out monthly questionnaires via myIBDcoach. Hereafter, you fill out questionnaires three monthly. You can login to the secured webpage of myIBDcoach using a computer, tablet or smartphone. The questionnaires contain questions regarding disease activity and side effects, among others. Filling in these questionnaires takes about 15 minutes. You, your treating doctor and the investigator can check the answers to the questions. Furthermore, you can use myIBDcoach to communicate with your treating physician or IBD-nurse. MyIBDcoach is already part of standard care for patients with Crohn's disease.

Fecal test (calprotectin home test)
The fecal home test is a test you use at home to measure calprotectin in your stool. Calprotectin is a protein that is used as a measure for inflammation of your bowels. If your bowels are inflamed, more calprotectin will be in your stool.

You perform this fecal home test after the first 8 weeks, and three monthly thereafter. The test consists of an extraction kit with a dosing tip and a lateral flow device. You collect your stool using a paper stool-catcher. The test tube is opened and the dosing tip of the stick is dipped three to five times into the stool, after which the dosing tip is transferred back to the test tube with prefilled fluid. The test tube is shaken to mix the stool with the fluid, and a few drops are applied to the sample window of the lateral flow device and left for 15 minutes incubation. Finally, a picture of the lateral flow device is made with a smartphone, after which a test result is calculated. The result is sent to the hospital and displayed in the results window of your smartphone.

Outpatient visits and blood sampling:
During this study, you need to visit the hospital at least 5 times at preset moments. These visits are also necessary if you do not participate in this study. Blood sampling will be done beforehand, so the results are known at your visit. Additional blood sampling can be necessary if another drug is started.

Colonoscopy:
After 24 weeks, all participants will undergo a colonoscopy to evaluate the effect of the initiated treatment, as recommended in the European guidelines for the treatment of Crohn's disease. During this investigation, a long flexible tube is inserted into the rectum. A tiny video camera at the tip of the tube allows the doctor to view the inside of the entire colon. To make the colonoscopy possible, you have to empty your bowels of stool with the use of laxatives prior to the procedure. Prior to the colonoscopy, you will receive painkilling and sedating drugs, so you will experience less pain and discomfort during the investigation.

MRI-scan:
At the end of this study, an extra MRI of the bowels is scheduled to evaluate disease related complications. A MRI-scan (Magnetic Resonance Imaging) uses a strong magnetic field, radiofrequency waves and a computer to make images of various parts of the body. MRI is a painless procedure, and no adverse effects tot the body are known. However, the strong magnetic field can dysregulate pacemakers, so patients with a pacemaker cannot enter the MRI room without precautions. Additionally, certain metallic prosthetics can be unsafe in the magnetic field. To image the small intestine properly, you have to drink contrast fluids right before the scan. Furthermore, during the scan you will get intravenous contrast agent.

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 take the medicine in the way the investigator explained to you.
- You fill out monthly questionnaires in mylBDcoach for the first three months, and three-monthly thereafter
- You do a fecal home test after the first 8 weeks, and thereafter every three months
- You go to every appointment

- You should contact the investigator in these situations:
  - You want to start taking other medication. Also if these are homoeopathic remedies, natural remedies, vitamins or over-the-counter medicines.
  - You suddenly have problems with your health.
  - You no longer want to take part in the study.

Is it OK for you or your partner to get pregnant during the study?
Women who are pregnant or breastfeeding cannot take part in this study. Women should also not get pregnant during the study. Are you male, do you have a female partner and do you have a pregnancy wish? Then you need to consult with the investigator whether the initiated treatment is potentially harmful.

6. What side effects, adverse effects or discomforts could you experience?

All drugs for Crohn's disease have potential side effects, partly because of the suppression of the immune system. Side effects occur in approximately 5-10% of patients using adalimumab. Most side effects are mild to moderate. Some side effects can be serious and require treatment. Side effects can occur up to 5 months after the last administration of adalimumab. Possible side effects are:

- Injection place reaction (redness and swelling); occurs in 5% of patients
- Increased risk of infections
- Skin rash resembling psoriasis
- Severe rash, or other signs or allergic reaction
- Swelling of face, hands or feet
- Trouble breathing or swallowing
- Feeling tired or weak
- Coughing
- Headache, dizziness, or double vision
- Numbness or tingling feelings in hands and feet
- Impaired strength in arms or legs
- Possible increased risk of lymphoma. The absolute chance of getting this malignant disease is still very small (<1:1000).

7. What are the pros and cons if you take part in the study?

If you participate in this research, you might suffer less from your disease, but that is not certain. However, if you take part you will help in the search for a better treatment for Crohn's disease.

Possible benefits for patients in the adalimumab group are:

- Lower chance of Crohn's disease related complications
- Less use of corticosteroids and the possible corresponding side effects
- Less visits to the outpatient department
- Lower chance of hospitalization and surgeries

Participants in both group will be strictly monitored by myIBDcoach and fecal home tests, so treatment can be adjusted promptly if necessary. This might lead to better control of the inflammation.

Taking part in the study can have these cons:

- You may experience the side effects or adverse effects of adalimumab, as described in Section 6.
- You may experience mild abdominal complaints by drinking the contrast agent for the MRI; additionally, there is a small chance of getting an allergic reaction to the intravenous contrast agent.
- Taking part in the study will cost you extra time.
- You have to comply with the study agreements.
- You have to fill out questionnaires and have to perform fecal home test

It is possible that an accidental discovery is made during the extra MRI scan that is not directly related to the research, but does concern your health. If this happens, your own doctor or specialist will discuss with you what needs to happen next.

You do not wish to participate in the study?
It is up to you to decide if you wish to participate in the study. You do not wish to participate? Then you will receive the standard treatment for Crohn's disease. Your doctor can tell you more about the standard treatment, and about the pros and cons.

8. When does the study end?

The investigator will let you know if there is any new information about the study that is important to you. The investigator will then ask you if you want to continue to take part.

In these situations, the study will stop for you:

- All checks according to the schedule are finished.
- You want to stop participating in the study yourself. You can stop at any time. Report this to the investigator immediately. You do not have to explain why you want to stop. Your doctor will discuss with you what the best treatment is. The investigator will still invite you for a follow-up check.
- The investigator thinks it is better for you to stop. The investigator will still invite you for a follow-up check.
- One of the following authorities decides that the study should stop:
    - Maastricht University,
    - the government, or
    - the Medical Ethics Review Committee assessing the study

What happens if you stop participating in the study?
The investigators use the data that have been collected up to the moment that you decide to stop participating in the study.

The entire study ends when all the participants have finished all the checks according to the schedule.

9. What happens after the study has ended?

Can you continue taking the medicinal products?

You can continue to use the medicinal products you were taking during the study after the study has finished. Your treating doctor will discuss with you what other medical care you will get.

Will you get the results of the study?

When the entire study has ended, the investigator will inform you about the most important results of the study.

10. What will be done with your data?

Are you taking part in the study? Then you also give your consent to collect, use and store your data.

What data do we store?

We store these data:

- your name
- your gender
- your address
- your date of birth
- information about your health
- (medical) information that we collect during the study

Why do we collect, use and store your data?

We collect, use and store your data to answer the questions of this study. And to be able to publish the results.

How do we protect your privacy?

To protect your privacy, we give a code to your data. We only put this code on your data. We keep the key to the code in a safe place in the hospital. When we process your data, we always use only that code. Even in reports and publications about the study, nobody will be able to see that it was about you.

Who can see your data?

Some people can see your name and other personal information without a code. These are people checking whether the investigators are carrying out the study properly and reliably. These persons can access your data:

- Members of the research team.
- An auditor who is hired by the sponsor.
- National supervisory authorities: the Healthcare and Youth Inspectorate.

These people will keep your information confidential. We ask you to give permission for this access.

For how long do we store your data and body material?
We store your data in the hospital for 15 years. And for 15 years with the sponsor. Your blood and fecal samples will be destroyed immediately after use.

Can we use your data for other research?
Your data may also be important after this study for other medical research on Crohn's disease. For this purpose, your data will be stored in the research centre for 15 years. Please indicate in the consent form whether you agree with this. Do you not want to give your consent? Then you can still take part in this study. You will get the same healthcare.

What happens if there are accidental discoveries?
It is possible that during the study we discover something that is important to your health. In that case, the investigator will contact your doctor. You will then discuss what needs to be done with your doctor or specialist. With the form, you give consent to inform your doctor or specialist.

Can you take back your consent for the use of your data?
You can take back your consent for the use of your data at any time. This applies both to the use in this study and to the use in other medical research. But please note: if you take back your consent, and the investigators have already collected data for research, they are still allowed to use this information.

Do you want to know more about your privacy?

- Do you want to know more about your rights when processing personal data? Visit www.autoriteitpersoonsgegevens.nl.
- Do you have questions about your rights? Or do you have a complaint about the processing of your personal data? Please contact the person who is responsible for processing your personal data. For the present, this is:
    - Maastricht University; See Appendix A for contact details, and website.
- If you have any complaints about the processing of your personal data, we recommend that you first discuss them with the research team. You can also contact the Data Protection Officer of Maastricht University. Or you can submit a complaint to the Dutch Data Protection 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. You can find the study by searching for ' NCT03917303'.

11. Will you receive compensation if you participate in the study?

You will not get any compensation if you take part in this study. But you will be paid for your (extra) travel expenses. The hospital will receive compensation to cover the costs of extra administrative proceedings, and to cover the MRI at the end of the study.

12. Are you insured during the study?

Maastricht University will pay for the damage caused by the study. But not all damage. You can find more information about damage and any exceptions in Appendix B. It also says who you can report damage to.

13. We will inform your doctor.

The investigator will send your doctor a letter to let them know that you are taking part in the study. We may contact your doctor, for example, about your medical history. This is for your own safety. If you do not want to give your consent for this, you cannot participate in this study.

14. Do you have any questions?

You can ask questions about the study to the investigator or research team. Would you like to get advice from someone who is independent from the study? Then contact the independent expert. He knows a lot about the study, but is not a part of this study.
Do you have a complaint? Discuss it with the investigator or the doctor who is treating you. If you prefer not to do so, please visit complaints officer/complaints committee of your hospital. Appendix A tells you where to find this.

15. How do you give consent for the study?

You can first think carefully about this study. Then you tell the investigator if you understand the information and if you want to take part or not. If you want to take part, fill in the consent form that you can find with this information sheet. You and the investigator will both get a signed version of this consent form.

Thank you for your attention.

16. Appendices to this information

A. Contact details
B. Information about the insurance
C. Schedule of study interventions
D. Informed Consent Form
E. Brochure ‘Medical Research’

Subject Information

Appendix A: contact details for [name of participating centre]

For questions concerning your health, you can contact the principal investigator of your hospital, or the independent expert:

City	Hospital	Principal investigator
xxx	xxx	Name xxx Contact details xxx
Independent expert		Name xxx Contact details xxx

For questions regarding the study itself, you can contact the coordinating investigator of this study: name xxx + contact details xxxx

Complaints:

Data Protection Officer of the institution:

For more information about your rights:

Janssen L, *et al. BMJ Open* 2021; 11:e042885. doi: 10.1136/bmjopen-2020-042885

Subject Information

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.

Have you suffered damage as a result of the study? Please report this to this insurer:

The insurer of the study is:
Name: …
Address: …
Telephone number: …
Email: …
(Policy number: …)
(Contact person: …)

The claims representative of the study is:
Name: …
Address: …
Email:
Telephone number: …

The insurance pays a maximum of *at least €650,000* per person and *at least €5,000,000* for the entire study (and *at least € 7,500,000* per year for all studies by the same sponsor).

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.

These provisions can be found in the 'Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015' ('Medical Research (Human Subjects) Compulsory Insurance Decree 2015'). This decision can be found in the Government Law Gazette (https://wetten.overheid.nl).

Appendix C: Overview of study investigations

The schedule below shows an overview of all investigations and their time points during the study. If at screening some of the investigations have not been done yet, for example an MRI, these will yet be scheduled. At week 72 blood sampling takes places without a scheduled outpatient visit. The IBD team will check the results of this sampling together with the results of the myIBDcoach questionnaires, and handle accordingly.

Overview of all investigations in both study groups											
Week	Screening/ diagnosis	4	8	12	24	36	48	60	72	84	96
myIBDcoach questionnaires	+	+	+	+	+	+	+	+	+	+	+
Fecal home test (calprotectin)	+		+	+	+	+	+	+	+	+	+
Blood sampling	+			+	+		+		+		+
Outpatient department visit	+			+	+		+				+
Colonoscopy	+				+						
MRI scan	+										+

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Appendix D: Informed consent form – subject

Belonging to Control Crohn safe trial (CoCroS)

- 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 doctor/specialist (s) who treats me/pharmacist that I am taking part in this study.
- I give consent to request relevant medical information from my doctor/specialist (s) treating me/pharmacist.
- I give consent to give my doctor or specialist information about accidental discoveries made during the study that are important for my health.
- I give consent to collect and use my data. The investigators only do this to answer the question of this study.
- 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.
- Please tick yes or no in the table below.

I give consent to store my data to use for other research, as stated in the information sheet.	Yes ☐	No☐
I give consent to ask me after this study if I want to participate in a follow-up study.	Yes ☐	No☐
I give consent to inform me about the results of this study by sending a letter.	Yes ☐	No☐

- I want to take part in this study.

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

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: __/__/__

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