Subject information for participation in medical research

Colonisation with the non-toxic gut bacterium *Clostridioides difficile*

'Establishing colonisation with non-toxigenic Clostridioides difficile in healthy volunteers'

Introduction

Dear reader,

With this letter, we would like to ask you to take part in a medical study. Participation is voluntary. 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. Please read the information and decide if you want to take part. If you want to take part of the study, you can fill in 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:

- Ask your questions to the investigator who gave you this information.
- Talk to your partner, family or friends about this study.
- Ask questions to the independent expert, see **Appendix A** for contact details.
- Read the information on www.rijksoverheid.nl/mensenonderzoek.

You can only participate 4 times a year maximum in (medicinal) research, and you can only participate in one study at a time.

1. General information

The Leiden University Medical Center (LUMC) has set up this study. This study is conducted by researchers in the LUMC in Leiden. The function of researcher can be fulfilled by physicians, nurses, doctor's assistants and student assistants, among others. Participants in medical-scientific studies are often called study subjects. Both patients and healthy people can be study subjects. For this study, we are recruiting a total of 50 up to a maximum of 70 healthy study subjects. The Medical Ethics Review Committee Leiden Den Haag Delf (in Dutch: METC) approved this study.

2. What is the purpose of this study?

In this study we investigate the safety and tolerability of colonisation with non-toxigenic *Clostridioides difficile* (a gut bacterium which cannot produce toxins) in healthy volunteers. We also investigate which dose of the *Clostridioides* bacterium is needed to establish successful colonisation and what factors influence successful colonisation. Colonisation means that you carry *Clostridioides difficile* in your gut without experiencing complaints. If and what complaints you experience when you carry a *Clostridioides* bacterium is something we do not know exactly.

3. What is the background of this study?

Infection with the gut bacterium *Clostridioides difficile* is the most common cause of diarrhoea in hospital. With the current (antibiotic) treatment the bacterium often comes back. So new treatments are needed.

The *Clostridioides* bacterium does not cause diarrhoea in everyone: healthy people also carry the bacterium in their gut without experiencing any symptoms (colonisation). The reason for this is still not clear, though from previous research we do know that this is partially caused by the differences in bacteria people normally carry in their gut (the gut flora). However what factors in the gut flora raise protection and what factors make people susceptible for the *Clostridioides* bacterium is still not known. More knowledge on this topic offers possibilities for the development of new treatments for *Clostridioides* disease.

In this study we investigate the possible side effects of colonisation with the *Clostridioides* bacterium, which dose of the *Clostridioides* bacterium is needed to establish successful colonisation and the differences in gut flora between study subjects who do and do not get colonised. To investigate this, we ask you to ingest capsules (pills) consisting of *Clostridioides* bacterium. These capsules contain a *Clostridioides* bacterium which cannot produce toxins: the non-toxigenic *Clostridioides difficile* (NTCD). This bacterium is unable to cause severe diarrhoea. Previous research with NTCD with healthy volunteers showed minimal side effects.

4. How will the study be carried out?

How long will the study take?

In case you participate in the study it will take 4 weeks with a final follow-up after 3 months.

Step 1: Are you eligible to participate?

First, we would like to know if you are eligible to take part. That is the reason why investigator will do some checks:

- Physical examination. For example, the investigator can listen to your heart and lungs, and will measure your blood pressure and heart rate.

- Blood test. The investigator will take some blood from you. We will test your blood for HIV and also test your kidney function, liver value, inflammation value, thrombocytes, and red and white blood cells. We will tell you the results of the blood test.
- Urine test. For females we will do a pregnancy test.
- Stool test.
- Discussing your medical history and that of your close family members. Also we will ask you if you have recently used antibiotics (or other microbiota influencing products like probiotics) or antacids and we ask about your living conditions. You cannot participate in this study if you have children under the age of 2 years or if you have household members older than 70 years of with a immunosuppressed status.

Sometimes at screening we find an abnormality that needs further research. We will always inform you about this. Further research will take place at the general practitioner or specialist. The costs will be are covered by your own insurance. Please note: it is possible that you are not eligible for this study, even if you are healthy. The investigator will tell you more about this.

Step 2: study design
The study will consist of two or, if necessary, three consecutive phases, which exists of a total of 50 up to a maximum of 70 study subjects. You will only participate in the third phase of the study, 23 study subjects will participate in this phase, who will be divided over three groups (G, H and I). Depending on the results of the second phase the dosing schedule of the third phase will be determined. There are three options for dosing schedules: with high or low dose NTCD and with one or five days pre-treatment with the antibiotic vancomycin, please see the schedule below. There will also be study subjects who receive a placebo (fake remedy). Before the start of the third phase of the study we will know which of the three dosing schedule options will be chosen and you will be informed about this. Subsequently, a draw decides which group you are assigned to. Both you and the investigator will not know in which of the two groups you are participating. If it is important for your health, the blinding will be undone to find out in which group you are participating.
The ingestion of the capsules will be in the LUMC and takes around 15 minutes, you will also have to visit the LUMC on the first day of antibiotic ingestion, this will take around 10 minutes.

The three groups of **phase 3** with the three options for dosing schedules:
Option 1:
Pre-treatment with 1 day 4 tablets of the antibiotic vancomycin, 7 days in advance.
Group G: 3 days daily ingestion of 1 capsule with low dose NTCD.
Group H: 1 day ingestion of 1 capsule with low dose NTCD and 2 days ingestion of daily 1 capsule placebo.
Group I: 3 days daily ingestion of 1 capsule placebo.

Option 2:
Pre-treatment with 1 day 4 tablets of the antibiotic vancomycin, 7 days in advance.
Group G: 3 days daily ingestion of 1 capsule with high dose NTCD.
Group H: 1 day ingestion of 1 capsule with high dose NTCD and 2 days daily ingestion of 1 capsule placebo.
Group I: 3 days daily ingestion of 1 capsule placebo.

Option 3:
Pre-treatment with 5 days 4 tablets daily of the antibiotic vancomycin, 11 days in advance.
Group G: 5 days daily ingestion of 1 capsule with low dose NTCD.
Group H: 5 days daily ingestion of 1 capsule with high dose NTCD.
Group I: 5 days of daily ingestion of 1 capsule placebo.

Step 3: measurements
On the day of capsule ingestion you will come to the LUMC. On these days you will be asked to deliver a stool sample before capsule ingestion. You will also visit the LUMC at the first day of vancomycin treatment (day -7 or day -11, see above schedules), to receive the vancomycin tablets (which you can ingest at home) and deliver a stool sample. In the week between taking the antibiotics and taking the capsule (pill), you are required to submit stool samples twice.
During the second, third and fourth week of the study you will bring a stool sample three times a week, including a more extensive visit once a week to check symptoms. After two and four weeks there will be a safety blood test. After three months you will come to the LUMC for a final visit to check symptoms, blood and stool sample. For a schedule of the study proceedings please refer to **Appendix C**.

Step 4: follow-up
If after 3 months you are still colonised with the *Clostridioides* bacterium, we will continue to check you every one to two months until you no longer carry the bacterium (up to a maximum of one year after the start of the study). This would mean that you would have to visit the hospital several extra times to deliver your stool. No treatment is needed, because most people who carry the bacterium clear it themselves within a few months. Also, the non-toxicogenic *Clostridioides* bacterium is a non-harmful bacterium, that is widespread and does not cause (serious) symptoms. If you do experience symptoms of the *Clostridioides* bacterium, treatment is available.

5. What agreements do we make with you?

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

- You contact the study team if you have symptoms (7 days a week, 24 hours reachable);
- You visit every appointment;

- You will not take part in other medical research during this study;
- You will not take part in other medical research during this study;
- You follow hygienic measures and always use a flush toilet;
- You clean your toilet regularly with soap;
- You will not use probiotics during this study;
- You should contact the investigator in the following situations:

- You want to start taking other medication. Also if these are homoeopathic remedies, natural remedies, vitamins or over-the-counter medicines.
- You are hospitalized or get treatment in a hospital.
- You suddenly have problems with your health.
- You no longer want to take part in the study.
- Your telephone number, address or email address changes.

Is it OK for you 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. It is not known what the effects of this study are for an unborn child. The investigator will tell you how best to prevent pregnancy, options for adequate anticonception include the hormone pill, a copper or hormonal intrauterine device and condom use. Talk to your partner about this.

Pregnant after all?
If you do become pregnant during the study, inform the investigator immediately. In this case, you should stop participating in the study as soon as possible in consultation with the investigator.

6. Which side effects, adverse effects or inconveniences may you encounter?

The study medications could cause the following side effects:

- Side effects NTCD: complaints of flatulence, bowel cramps, diarrhoea and nausea can occur after taking NTCD. In a previous study all these symptoms were mild and disappeared within a few days. We do not know whether and to what extent you will experience complaints during this study. NTCD could also cause side effects which we do not know yet.
- Side effects placebo; the placebo is expected to cause minimal to no side effects.
- Side effects vancomycin: gastro-intestinal complaints like abdominal cramps, nausea or diarrhoea can occur. In rare cases an allergic reaction can develop. As you only get a short treatment of this antibiotic the expectation is that the side effects will be short and self-limiting.

What are the possible inconveniences of the measurements during the study?

- Blood sampling: blood sampling can hurt or give a bruise.
- Urine delivery: done once for females for a pregnancy test.
- Collection of stool samples: at every visit to the LUMC you will have to deliver stool which you collect at home. You will get materials to help collect your stool.
- Visits to the LUMC: you will have to visit the LUMC between 19 and 20 times. This is for the ingestion of capsules (NTCD/placebo), check-up visits (which includes three times of blood sampling), first ingestion of vancomycin and to deliver your stool. The ingestion of the capsules and the check-up visits will take about 15 minutes, the delivery of your stool will be at a flexible time and will take shorter than 5 minutes.

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

Taking part in the study can have pros and cons. We will list them below. Think about this carefully and talk to other people about it.

Advantages of participating in this study:

- You do not benefit from taking part in this study yourself. But if you take part you will help the investigators to get more insight into colonisation with *Clostridioides difficile* and in developing new treatments against *Clostridioides* disease.

Disadvantages of participating in this study:

- Possible side effects of NTCD (as described in Section 6);
- Possible side effects of treatment with vancomycin (as described in Section 6)
- There may be some discomfort from the measurements during the study. For example: taking a blood sample can be a little painful, or you could get a bruise.
- Taking part in the study will cost you extra time.
- You have to comply with the study agreements.

8. When will 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 have become pregnant;
- 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. The investigator could arrange a check-up visit for your safety;
- The investigator thinks it is better for you to stop. The investigator will still invite you for a last follow-up.

- One of the following authorities decides that the study should stop:
  - The LUMC;
  - The government;
  - The Medical Ethics Review Committee assessing the study.

What happens if you stop participating in the study?
If you want to stop you can receive a treatment for the *Clostridioides* bacterium. This is only needed if you experience a lot of complaints related to the *Clostridioides* bacterium. If you are treated, you have to come back to the LUMC for a follow-up.
The investigators use the data and body materials (blood) that have been collected up to the moment that you decide to stop participating in the study.

9. What happens after the study has ended?

Will you get the results of the study?
The whole study is finished when all the study subjects are done, the investigator will inform you about the most important results of the study. The investigator may also tell you what group you were in. Do you prefer not to know? Please tell the investigator. He/she will not tell you in that case.

10. What will be done with your data and body material?

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

What data do we store?
We store these data:
- your name;
- your sex;
- your address;
- your date of birth;
- your bank details (for payment at the end of the trial);
- details about your health;
- (medical) information that we collect during the study.

What body material do we store?
We will store blood and feces.

Why do we collect, use and store your data and samples?
We collect, use and store your data and your body material to answer the questions of the 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 and your body material. We only put this code on your data and body material. We keep the key to the code in a safe place in the LUMC. When we process your data and body material, 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. The following persons can access your data:

- Members of the committee that keeps an eye on the safety of the study;
- An auditor who works for the LUMC;
- National and international supervisory authorities.

These people will keep your information confidential. We ask you to give permission for this access. The Healthcare and Youth Inspectorate (in Dutch: *Inspectie Gezondheidszorg en Jeugd)* can see this information without your permission.

For how long will we store your data and bodily matter?

We store your data in the LUMC for 25 years. We will also store body materials in the LUMC. They will be stored for 25 years in order to be able to make new assessments related to this study. If no longer needed, we will destroy your body material.

Collaborating partners

We cooperate with the University of Cologne and the Paul-Ehrlich-Institut in Germany. Stool samples can be sent to them for analysis. The samples will be labeled with a code, in this way your personal information will not be shared with these collaborating partners.

What will happen 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 general practitioner. 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.
The investigators will destroy your body material after you take back your consent. But if assessments with your body material have been carried out, the investigator can continue to use the results.

Do you want to know more about your privacy?
Do you want to know more about your rights when processing personal data? Visit https://www.autoriteitpersoonsgegevens.nl/en.
Do you have questions about your rights? Or do you have a complaint about the processing of your personal data is processed? Please contact the person who is responsible for processing your personal data. For the present, this is:

- The LUMC, see **Appendix A** for contact details and website.
- If you have complaints about how your personal data is processed, we advise you to first discuss the matter with the research team. For further privacy-related information, refer to the privacy statement of the LUMC on the LUMC website: see **Appendix A**. You can also contact the Data Protection Officer at the LUMC. Alternatively, you can submit a complaint to the Dutch Data Protection Authority.

Where can you find more information about the study?
More information about the study can be found on the following website: www.ClinicalTrials.gov. After the study, the website may display a summary of the study results. You can find this study by searching for 'NCT05693077'.

11. Will you be reimbursed for taking part in the study?

For participating in this study you will receive a reimbursement of €50,- per visit and €25,- for delivery of stool. Next you will get a bonus of €100,- at the end of the study if you have been at all visits. This means for phase 3 you will get €825,- if dosing schedule option 1 or 2 is chosen and €900,- if dosing schedule option 3 is chosen. If it is necessary to check your stool after the three months timepoint because you still carry the *Clostridioides* bacterium in your gut, you will receive €50,- per extra visit. If you quit the study before it is completed, you will receive less compensation. The compensation for taking part in this study should possible be declared to the Tax and Customs Administration as 'income from other work'. When needed, ask the National Tax Administration (in Dutch: *de Belastingdienst*) for more information.

12. Are you insured during the study?

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.

13. We will inform your general practitioner

The investigator will send your general practitioner a letter to let them know that you are taking part in the study. This is for your own safety. You cannot participate in this study if you do not have a general practitioner.

14. Do you have any questions?

You can ask questions about the study to the research team. Would you like to get advice from a neutral party? Ask advice of the independent specialist, for contact details see **Appendix A**. This specialist knows a lot about the study but is not involved in it.
Do you have a complaint? Discuss it with the investigator. Would you prefer not to? Then please contact the complaints committee at the LUMC. **Appendix A** explains how you can do this.

15. How can I provide 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 during the screenings visit. You and the investigator will both get a signed version of this consent form.

Thank you for your time.

16. Appendices accompanying this information

A. Contact details

B. Information about the insurance

C. Overview of measurements

D. Consent form

Appendix A: Contact details

Principal investigator
Prof. M. Roestenberg
Drs. A.D.O. Hensen
Department of Parasitology
Tel: 06-20942061
Email: vaccinonderzoek@lumc.nl

Independent expert
H. Jolink
Department of Infectious Diseases
Tel: 071-526 2613
Email: h.jolink@lumc.nl

Complaints
If you have a complaint about the study, you can contact Team Klachten of the LUMC via e-mail: patientenservicebureau@lumc.nl. You can also contact the Patiëntenservicebureau by phone: 071-5262989, during office hours. They will process your complaint according to the applicable regulations.

Privacy & rights
If you have questions about the protection of your privacy, you can contact the data protection officer at the LUMC (FG) via privacy@lumc.nl. For more information about your rights, you can contact the LUMC:

Contact details LUMC
Albinusdreef 2
2333 ZA Leiden
Central telephone number: (071) 526 91 11
For further information about your rights, please visit the website of the LUMC.
https://www.lumc.nl/12367/Deelnemers-wetenschappelijk-onderzoek/

Appendix B: information about the insurance

The LUMC 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 your participation in the study has ended. You must report damage to the insurer within 4 years.

Have you suffered damage due to the study? Please report this to this insurer:

The insurer for this study is:	
Name:	Centramed
Address:	Maria Montessorilaan 9, 2719 DB Zoetermeer
Telephone:	+31 (0)70-3017070
E-mail:	info@centramed.nl
Policy number:	624.530.305

The insurance will pay maximum €650,000 per person and €5,000,000 for the whole 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.

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: Schedule of visits and measurements

Option 1 and 2:

	Time duration	Pill ingestion (NTCD/ Placebo)	Stool sample	Vancomycin (antibiotic) ingestion	Side effects check	Blood sample
Screening	1 hour		X			X
Day -7*	10 min		X	X		
Day -5	5 min		X			
Day -3	5 min		X			
Day 0	15 min	X	X			
Day 1	15 min	X	X			
Day 2	15 min	X	X			
Day 5	5 min		X			
Day 7	15 min		X		X	
Day 9	5 min		X			
Day 12	5 min		X			
Day 14	15 min		X		X	X
Day 16	5 min		X			
Day 19	5 min		X			
Day 21	15 min		X		X	
Day 23	5 min		X			
Day 26	5 min		X			
Day 28	15 min		X			X
Day 84	15 min		X		X	X

* Females will have to undergo a urine pregnancy test on the day of vancomycin ingestion.

Option 3:

	Time duration	Pill ingestion (NTCD/ Placebo)	Stool sample	Vancomycin (antibiotic) ingestion	Side effects check	Blood sample
Screening	1 hour		X			X
Day -11*	10 min		X	X		
Day -10	5 min			X (at home)		
Day -9	5 min			X (at home)		
Day -8	5 min			X (at home)		
Day -7	5 min			X (at home)		
Day -5	5 min		X			
Day -3	5 min		X			
Day 0	15 min	X	X			
Day 1	15 min	X	X			
Day 2	15 min	X	X			
Day 3	15 min	X	X			
Day 4	15 min	X	X			
Day 7	15 min		X		X	
Day 9	5 min		X			
Day 12	5 min		X			
Day 14	15 min		X		X	X
Day 16	5 min		X			
Day 19	5 min		X			
Day 21	15 min		X		X	
Day 23	5 min		X			
Day 26	5 min		X			
Day 28	15 min		X			X
Day 84	15 min		X		X	X

* Females will have to undergo a urine pregnancy test on the first day of vancomycin ingestion.

Appendix D: Consent form study subjects

Belonging to the study: '*Colonisation with non-toxigenic Clostridioides difficile'.*

- 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 or specialist treating me that I am taking part in this study.
- 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 and/or body material (blood). The investigators only do this to answer the question of this study.
- I give consent to make a picture of me during screening for identification during the 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.
- For women: I know that I cannot get pregnant during the study.
- For women: The investigator discussed with me how I can best prevent becoming pregnant.
- Please tick yes or no in the table below.

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 the investigators to let me know after the study in which group I was.	**Yes ☐**	**No ☐**

- I want to take part in this study.

My name is (participant):

Signature:

Date (DD/MMM/YYYY) : ____ / _____ / _____ Time __ : __ (24h notation)

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 (DD/MMM/YYYY) : ____ / _____ / _____ Time __ : __ (24h notation)

The participant will receive the entire patient information form, together with a certified copy of the signed informed consent form.