Subject information for participation in medical research

Controlled infection with the gut bacterium *Clostridioides difficile*

'Establishing a controlled infection model for Clostridioides difficile in healthy study subjects'

Introduction

Dear reader,

With this information letter, we would like to ask if you want to participate in medical-scientific research. Participation is voluntary.
Here you will read what kind of research this is, what it means for you, and what the benefits and risks are. The entire study takes about 5 weeks, with a final check-up after 3 months. It is a lot of information. Would you like to read through it and decide if you want to participate? You will have at least 48 hours, starting from the receipt of this information letter, to decide about participation. If you want to participate, you can fill out the form found in **Appendix E**.

Ask your questions

You can make your decision based on the information provided in this letter. In addition, we recommend that you do the following:

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

1. General information

The Leiden University Medical Center (LUMC) has set up this study. This study is conducted by investigator in the LUMC in Leiden. The function of investigator can be fulfilled by physicians, nurses, doctor's assistants and student assistants, among others. Study subjects in medical-scientific studies are often called study subjects. Both patients and healthy people can be study subjects, however only healthy participants can take part in this study. For this study, we are recruiting a total of up to 60 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 in healthy study subjects the safety and tolerability of a controlled infection with *Clostridioides difficile* in , a gut bacterium that can cause diarrhoea. We also examine which dosing regimen (with or without antibiotic pretreatment) is required to induce

mild diarrhoea in the majority of study subjects and which factors influence this. The antibiotic pretreatment may be given to make you more susceptible to an infection with *Clostridioides difficile*.

3. What is the background of this study?

Infection with the gut bacterium *Clostridioides difficile* is the most common cause of diarrhoea in hospitals. With current (antibiotic) treatments, the bacterium often recurs. New treatments are therefore needed.

The *Clostridioides* bacterium is present in the intestines of healthy people without causing any symptoms (colonization). In some individuals, it can cause diarrhoea. It is unclear why some people experience symptoms while others do not. However, previous studies have shown that other bacteria in the gut (the gut microbiota) play a role in protecting against the *Clostridioides* bacterium. What specific components of the gut microbiota and immune system protect people against *Clostridioides* is not yet known. Gaining more knowledge in this area offers opportunities for developing new treatments for *Clostridioides* disease. This research could also be used in the future to test the effectiveness of new treatments against *Clostridioides* disease.

In this study, we investigate the symptoms study subjects experience from exposure to the *Clostridioides* bacterium, which dosing regimen (with or without antibiotic pretreatment) is necessary to induce mild symptoms (such as diarrhoea) in the majority of the study subjects, and the differences in gut microbiota and immune system between study subjects who do and do not experience *Clostridioides* symptoms. To investigate this, we will ask you to ingest capsules (pills) containing the *Clostridioides* bacterium. This will be the first time study subjects are experimentally exposed to this *Clostridioides* bacterium. From data of natural *C. difficile* infections in the healthy population, we expect healthy study subjects to experience mild gastro-intestinal symptoms like diarrhoea, abdominal pain and nausea, which are mostly self-limiting.

4. How will the study be carried out?

How long will the study take?

In case you participate in the study it will take 6 weeks with a final follow-up after 3 months.

Step 1: Are you eligible to participate?

We first want to determine if you are suitable to participate. To be eligible to participate you need to be in good health and between the age of 18 and 45 years old. During a screening visit the investigator will ask questions about your health and conducts several tests:

- Physical examination. The investigator will amongst others listen to your heart and lungs, and measure your weight, height, blood pressure, and heart rate.
- Blood tests. The investigator will take a blood sample from you. We will test the blood for hiv, hepatitis B and C, and also measure kidney function, liver function,

inflammation markers, platelet count, and red and white blood cells. We will inform you of the results.
- Urine test. Your urine will be tested for drug use (cocaine, amphetamines, and GHB). You cannot participate in the study if this test is positive.
- Stool test. We will test whether you already carry the *Clostridioides* bacterium or other harmful gut bacteria. If this is the case you cannot participate in the study
- The investigator will collect demographic data (e.g. age) and also ask about your medical history and the medical history of your family or close contacts. Additionally, we will ask if you have recently used antibiotics (or other substances that affect the gut microbiota, such as probiotics), or acid-reducing medications, if you are otherwise in good health, and we will inquire about your living conditions. You cannot participate if you live, work or have close contact with vulnerable individuals, such as those with weakened immune systems, hospital or nursing home patients, pregnant women, children under the age of 2, and elderly individuals over the age of 70. You also cannot participate if you have a job in healthcare or food processing or have close contact with someone who works in healthcare or food processing.
- The investigator will take a photo of you for identification during the study

Sometimes, during the screening, we may find something that requires further medical investigation. We will always inform you of this. Any further investigations will be carried out by your own general practitioner or specialist. The costs for this will be covered by your own insurance.
It is also possible that you are healthy but still not suitable for participation. The investigator will explain this to you in more detail.

Step 2: study design

The study consists of at least one group (cohort A), with the option to expand, if necessary, into a second group (cohort B) or a third group (cohort C). In total, up to 60 study subjects can take part. You are participating only in the second group, cohort B. In cohort B, first five study subjects will be exposed to a five-day antibiotic treatment with vancomycin (group B1). You will take 1 antibiotic tablet 4 times a day. Afterward, you will be exposed to the *Clostridioides* bacteria capsules for 12 days. You will take 1 *Clostridioides* capsule once a day. If the majority of the participants experience *Clostridioides* related diarrhea, 15 additional participants will be included in cohort B (group B2). If only a few participants develop diarrhea, cohort C will be initiated. The first intake of the antibiotic tablet and *Clostridioides* capsule will take place at LUMC and will take approximately 15 minutes, while the remaining antibiotic tablets and *Clostridioides* capsules will be taken at home daily.

Cohort B

Group B1 (5 study subjects): pretreatment with 5 days of taking 1 vancomycin tablet 4 times a day, followed by 12 days of taking 1 *Clostridioides* bacteria capsule once a day.

Optional extension: Group B2 (15 study subjects): pretreatment with 5 days of taking 1 vancomycin tablet 4 times a day, followed by 12 days of taking 1 *Clostridioides* bacteria capsule once a day.

Step 3: visits and measurements
The day before starting the antibiotic treatment, you will come to the LUMC for the final measurements to definitively decide if you can participate in the study (day -6). If you are definitely eligible for the study, you will come to the LUMC the following day to take the first vancomycin antibiotic tablet (day -5). On this day, you must also submit a stool sample before taking the tablet. You will then take the remaining vancomycin antibiotic tablets at home daily (four times a day), and you must come to the LUMC two more times to submit stool samples (on days -3 and -1).
The day after the five days of antibiotic intake, you will start taking the *Clostridioides* capsule (day 0). On this day, you will also come to the LUMC and submit a stool sample before taking the capsule. The remaining 11 *Clostridioides* capsules can be taken daily (once per day) at home. From the first day of taking the *Clostridioides* capsule until 35 days after the first capsule intake, you will be asked to visit the LUMC daily for stool submission, checking for any symptoms, and measuring your temperature (with possible additional physical examinations if deemed medically necessary). Blood samples will also be taken every four days, the investigator will do this by collecting 1 to 10 vials of blood each time. The total amount of blood taken will not exceed a total maximum of 500ml over a 3month time period. This amount does not cause problems in adults. For comparison: if you give blood at the blood bank, you give 500 ml at a time. If you develop symptoms related to the *Clostridioides* bacteria during these days, you will be asked to come to the LUMC the same day for a physical examination, blood and stool samples, and if necessary, treatment with antibiotics against the *Clostridioides* bacteria will be started.
After three months (day 84), you will return for a final check-up of stool, blood, and symptoms at the LUMC. During the study, you will also be asked to complete two questionnaires: one the day before taking the first antibiotic tablet (day -6), and another 35 days after the first *Clostridioides* capsule intake (day 35). These questionnaires will ask about how you experience your health before and after the study.
For an overview of all study procedures and measurements for each visit, see **Appendix C.**

Step 4: follow-up
If you still carry the *Clostridioides* bacterium after three months, we will continue to monitor you every three months until you no longer carry the bacterium (up to a maximum of one year from the start of the study). This would mean additional visits to the hospital to submit a stool sample. Generally, no treatment is necessary, as the bacterium usually clears on its own within a few months in most people who carry it. If you develop symptoms from the *Clostridioides* bacterium, we can provide treatment. Should you wish to have treatment at

another time, the research physician will discuss the advantages and disadvantages of treatment with you and make a decision together with you.

5. What agreements do we make with you?

We want the study to proceed smoothly. Therefore, we ask you to agree to the following:

- You contact the research team if you experience any symptoms (available 24/7);
- You do not participate in any other medical-scientific research during this study;
- You ingest the remaining antibiotic tablets (vancomycin) and *Clostridioides* pills, as agreed, at home;
- You attend all scheduled hospital appointments for check-ups;
- You practice good hygiene (which amongst others means properly wash your hands with water and soap) when using the toilet and always use a toilet that can be flushed with tap water;
- You clean your toilet regularly with cleaning agents or wipes;
- You do not use probiotics during the study;
- You carry the study subject card with you, for example, in your wallet. This card indicates that you are participating in this study and whom to contact in an emergency. Show this card if you visit another doctor.
- Additionally, please contact the investigator in the following situations:
    - You wish to start using other medications, (in particular antibiotics, antacids, corticosteroids or other immune modifying drugs and strong P-glycoprotein inhibitors like ciclosporin, ketoconazole, erythromycin, clarithromycin, verapamil or amiodaron), including homeopathic remedies, natural supplements, vitamins, or over-the-counter medicines;
    - You are admitted to or treated in a hospital;
    - You suddenly experience health issues;
    - You wish to withdraw from the study;
    - Your phone number, address, or email address changes.

Are you allowed to become pregnant during the study?

Women who are pregnant or breastfeeding cannot participate in this study. Women are also not allowed to become pregnant during the study, as it is unknown what effects the study may have on an unborn child. The investigator will inform you about the best ways to prevent pregnancy; for more information, see **Appendix D**. Discuss this with your partner.

Pregnant after all?

If you do become pregnant during the study, please inform the investigator immediately. You will then need to stop participating in the study as soon as possible in consultation with the investigator. See section 8 for what happens if you stop participating in the study.

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

Clostridioides capsule

The capsule containing the *Clostridioides* bacterium may lead to *Clostridioides* infection, which can cause gastrointestinal symptoms.

The main symptoms of *Clostridioides* infection are:

- Diarrhoea
- Abdominal pain/cramps
- Fever
- Nausea
- Reduced appetite

The following symptoms are rare but can be serious:

- Severe inflammation of the large intestine
- Severely distended large intestine
- Severely constipated bowel
- Low blood pressure

Due to the above symptoms a hospital admission may be necessary.

Large studies on the above-mentioned serious *Clostridioides*-related symptoms are lacking in the healthy population. As a result, we cannot provide an exact percentage for the occurrence of these symptoms in young, healthy participants. However, based on other studies and population data, we estimate that the likelihood of the above-mentioned serious symptoms is very small.

Contact the investigator on the same day if you experience:

- Diarrhoea;
- Abdominal pain;
- Fever.

This allows us to treat you promptly with antibiotics to prevent symptoms from becoming severe.

Vancomycin (antibiotic) tablets

The most important side effects of vancomycin are:

- Overgrowth by bacteria or fungi (1-10%)
- Gastrointestinal complaints such as nausea, abdominal pain, or diarrhoea (0.1-1%)
- In rare cases, an allergic reaction (including skin changes) (0.01-0.1%), hypotension (0.1-1%), fever (0.1-1%), hearing loss (0.1-1%), or kidney function decline (0.01-0.1%) may occur.

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

- Blood draws: blood draws may be painful or cause bruising.
- Stool collection: for most visits to the LUMC, you will need to bring a stool sample that you collect at home. You will be provided with materials to make stool collection easier.
- Visits to the study center: you will need to come to the LUMC a total of 22 to 23 times. This includes the screening, the inclusion visit, the first ingestion and receipt of the vancomycin tablets and *Clostridioides* capsules, and follow-up visits for stool submission and, if necessary, blood tests. The screening lasts 1.5 hours, the follow-up visits will take approximately 10-15 minutes and if you only need to hand in a fecal sample this will take about 5 minutes.

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

Participating in the study may have both benefits and drawbacks. Below we outline these. Please think carefully about them and discuss them with others.

Benefits of participating in the study:

- You will not benefit directly from participating in this study. However, by taking part, you will help investigator gain more insight into *Clostridioides* infection and the development of new treatments for *Clostridioides* disease.

Disadvantages of participating in the study:

- Possible symptoms from the *Clostridioides* bacterium (as described in Section 6);
- Possible inconveniences from the measurements in the study (as described in Section 6);
- Possible side effects of vancomycin tablets (as described in Section 6);
- Participating in the study will take up extra time;
- You will need to follow the study-related agreements.

8. When will the study end?

The investigator will inform you if new information about the study becomes available that is important for you. The investigator will then ask if you wish to continue participating.

The study will stop for you in the following situations:

- All scheduled study visits have been completed.
- You become pregnant.
- You wish to stop participating in the study. You may stop at any time. Please inform the investigator immediately. You do not need to provide a reason for stopping. The investigator may schedule one or more follow-up visits for your safety.

- The investigator believes it is better for you to stop. The investigator will still invite you for a follow-up visit.
- One of the following authorities decides that the study must stop:
    - LUMC;
    - The government; or
    - The medical-ethical committee that reviews the study.

What happens if you stop participating in the study?
If you wish to stop, and you are colonized with the *C. difficile* bacterium, you can receive treatment for it.. The study doctor will discuss the advantages and disadvantages of this treatment with you. If you are treated, you will need to return to the LUMC several times for follow-up visits.
The investigator will continue to use the data and biological materials collected up until the point you stop participating. If you wish, the collected biological materials can be destroyed. Please inform the investigator of your decision.

9. What happens after the study?

Will you get the results of the study?

The study will be completed once all study subjects have finished. After processing all the data, the investigator will inform you of the key findings of the study. This will happen either at your final visit or shortly afterward.

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

If you participate in the study, you also give consent for your data and biological materials to be collected, used, and stored.

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 biological material do we store?
We will store blood and feces.

Why do we collect, use, and store your data and biological materials?

We collect, use, and store your data and biological materials in order to answer the questions of this study and to publish the results. The data and/or biological materials may be used by the sponsor and companies that assist the sponsor with measurements on the biological materials and/or the analysis of research data.

How do we protect your privacy?

To protect your privacy, we assign a code to your data and biological materials. Only this code is used on your data and biological materials. The data can only be traced back to you with the key to the code. The key to the code is stored in a secure location at the LUMC. When we process your data and biological materials, we always use only this code. Even in reports and publications about the study, it will not be possible to trace back that the information refers to you.

Who can see your data?

Some individuals may be able to view your name and other personal information without the code. This may include data specifically collected for this study, as well as data from your medical record.
These are people who monitor whether the investigator are conducting the study properly and reliably. These individuals may have access to your data:

- Members of the committee overseeing the safety of the study;
- A monitor working for the LUMC;
- National and international regulatory authorities.

These individuals are required to keep your data confidential. We ask for your consent to allow these individuals to access your data. The Health and Youth Care Inspectorate can access your data without your consent.

How long do we store your data and biological materials?

We store your data for 25 years at the research center. Your biological materials are also stored there. They are kept for 15 years to allow for any future analyses related to this study. Once this is no longer necessary, we will destroy your biological materials.

What happens in the case of unexpected findings?

During the study, we may accidentally discover something that is not directly related to the study but could be important for your health. If this is significant for your health, the investigator will inform you. You can then discuss with your general practitioner or specialist what steps should be taken. The costs for this will be covered by your own health insurance. You give consent for your general practitioner or specialist to be informed by signing the form.

Can you withdraw your consent for the use of your data?

You can withdraw your consent for the use of your data at any time. Simply inform the investigator. However, please note: if you withdraw your consent and the investigator have already collected data for the study, they may still use this data. For your biological materials, the investigators will destroy them after you withdraw your consent. However, if measurements have already been taken using your biological material, the investigator may continue to use the results.

Consent for collaboration with commercial companies
For some studies, it is important to collaborate with a company, for example, when the company has specialized knowledge or equipment, or because the company is developing a new treatment or test for a disease. It is possible that the LUMC (Leiden University Medical Center) may receive a contribution. A researcher from the LUMC will always remain involved, and the material will only be used for research purposes. The results from such collaborations may belong to the company. You cannot become the owner of these results, and you are not entitled to any profits the company makes from these results.
The research team for this study includes researchers from Sanofi and GSK. You specifically give consent to share your coded data with these researchers if necessary for the study.

Consent for sharing with countries outside the European Union
In Europe, your privacy is protected by a law that applies in all European Union countries. Everyone is required to comply with this law.
In countries outside the European Union, this law does not apply. These countries have their own privacy laws. When we share your material and data with countries outside the European Union, we will do everything we can to protect your privacy as best as possible.
The University of Oxford is part of the research team for this study. If you participate in this study, we will share your coded data with Oxford. You specifically give consent for this.

Would you like to know more about your privacy?
Would you like to learn more about your rights regarding the processing of personal data? Visit www.autoriteitpersoonsgegevens.nl.
If you have questions about your rights or a complaint about the processing of your personal data, please contact the person responsible for processing your data. For your study, this is:

- The Data Protection Officer at the LUMC (see **Appendix A** for contact details and website).
- If you have complaints about the processing of your personal data, we recommend that you first discuss them with the research team. For more information on privacy, please refer to the LUMC privacy statement on the LUMC website (see **Appendix A**). You can also contact the Data Protection Officer at the LUMC, or file a complaint with the Dutch Data Protection Authority (Autoriteit Persoonsgegevens).

Where can you find more information about the study?

Information about this study is also included in an overview of medical and scientific studies on the website www.ClinicalTrials.gov. After the study, the website may display a summary of the results of this study. You can find the study by searching for the number: NCT06702345.

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, this compensation includes any travel expenses. Additionally, you will receive a bonus of €100 at the end of the study if you complete all visits. This means that for cohort B, you will receive €1,200-1,250 (depending on whether you need to visit the LUMC again due to issues related to the *Clostridioides* bacterium). If it is necessary to continue following up after the three-month time point because you are still carrying the *Clostridioides* bacterium, you will receive €50 for each additional visit. If you decide to stop early, you will receive a reduced compensation; you will receive compensation for the number of visits you have completed up to that point. The reimbursement for participation in this study may need to be reported to the tax authorities (“Belastingdienst” in Dutch) as 'income from other work.' If necessary, check this with the tax authorities.

12. Are you insured during the study?

Insurance has been arranged for everyone participating in this study. The insurance covers damages caused by the study, but not all types of damage. **Appendix B** contains more information about the insurance and the exceptions. It also explains to whom you can report any damages.

13. We will inform your general practitioner

The investigator will send a letter to your general practitioner to inform them that you are participating in the study. This is for your own safety. If you do not agree with this, you cannot participate in the study. You cannot participate in the study if you do not have a general practitioner.

14. Do you have any questions?

If you have any questions about the study, you can contact the research team. If you would like advice from someone who has no interest in the study, you can contact the independent expert. Contact details can be found in **Appendix A.** This expert knows a lot about the study but is not involved in conducting it.
Do you have a complaint? Discuss it with the investigator. If you would prefer not to do this, you can contact the complaints committee at the LUMC. The location and contact details are provided in **Appendix A.**

15. How can I provide consent for the study?

You can first take some time to think carefully about this study. Afterward, you can tell the investigator whether you understand the information and whether or not you would like to participate. If you wish to participate, you will fill out the consent form that accompanies this information letter during the screening visit. Both you and the investigator will receive a signed copy of the consent form.

Thank you for your time.

16. Appendices accompanying this information

A. Contact details
B. Information about the insurance
C. Overview of visits and measurements
D. Adequate contraceptive methods
E. Consent form

Appendix A: Contact details

In case of any (substantive) questions about the study, you can call:

Principal investigator
Prof. M. Roestenberg, internist-infectioloog
Drs. A.D.O. Hensen. arts-onderzoeker
Leiden University Center for Infectious Diseases
Tel: 06-20942061
Email: vaccinonderzoek@lumc.nl

Independent expert
Andrea van der Meulen- de Jong, Gastroenterologist
Department of Gastroenterology
Tel: 071-5262915 / 071-5299134
Email: ae.meulen@lumc.nl

Complaints

If you have any complaints about the study, you can contact the LUMC Complaints Team via email at: patiëntenservicebureau@lumc.nl. You can also contact the Patient Service Bureau by phone (071-5262989; during office hours). They will handle the complaint according to the applicable procedures.

Privacy & Rights

If you have questions about the protection of your privacy, you can contact one of the data protection officers (DPO) at LUMC via privacy@lumc.nl.
For more information about your rights, you can contact 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

	Time duration	Urine test	Physical examination	Vanco-mycin ingestion[1]	Capsule ingestion[2]	Stool sample	Side effects check	Blood sample	Questio nnaire
Screening	1.5 hour	X	X			X		X	
Day -6	15 min		X[3]					X[4]	X
Day -5	15 min			X[1]		X			
Day -3	5 min			X[1]		X			
Day -1	5 min			X[1]		X			
Day 0	15 min		X[3]		X[2]	X	X	X	
Day 2	15 min		X[3]		X[2]	X	X	X	
Day 4	15 min		X[3]		X[2]	X	X	X	
Day 6	10 min		X[3]		X[2]	X	X		
Day 8	15 min		X[3]		X[2]	X	X	X	
Day 10	10 min		X[3]		X[2]	X	X		
Day 12	15 min		X[3]			X	X	X	
Day 14	10 min		X[3]			X	X		
Day 16	15 min		X[3]			X	X	X	
Day 18	10 min		X[3]			X	X		
Day 20	15 min		X[3]			X	X	X	
Day 22	15 min		X[3]			X	X		
Day 24	15 min		X[3]			X	X	X	
Day 26	10 min		X[3]			X	X		
Day 28	15 min		X[3]			X	X	X	
Day 30	10 min		X[3]			X	X		
Day 32	15 min		X[3]			X	X	X	
Day 35	15 min		X[3]			X	X	X	X
Day 0-35[5]	15 min		X			X	X	X	
Day 84	15 min					X	X	X	

[1] Vancomycin (antibiotic) intake daily for 5 days (D-5 to D-1), with tablet intake and distribution at LUMC on D-5, and subsequent tablet intake at home on the following days.
[2] Daily pill intake for 12 days (D0-D11), with pill intake and distribution at LUMC on D0, and subsequent pill intake at home on the following days.
[3] During these visits, standard temperature measurements will be taken, and only more extensive measurements and physical exams will be conducted if medically indicated.
[4] Only for women who can become pregnant, blood will be taken for a pregnancy test.
[5] Optional extra visit to the LUMC only needed if you

Appendix D: Highly effective contraception methods according to EMA Clinical Trials Coordination Group:

- Combined hormonal contraception (estrogens and progestogens) that suppresses ovulation:
    - The Pill (excluding the so-called "minipill," which only contains progesterone)
    - Administration via the skin or vagina
- Contraception that only contains progesterone but still suppresses ovulation
- IUD (both hormonal IUD and copper IUD)
- Vasectomy in the partner
- Bilateral tubal ligation
- No (heterosexual) sexual contact

Appendix E: consent form study subjects

Related to the study: *"Controlled infection with the gut bacterium Clostridioides difficile"*

- I have read the information letter. I was also able to ask questions, and my questions were answered adequately. I had enough time to decide whether or not to participate.
- I know that participation is voluntary. I also know that I can decide at any time not to participate in the study or to stop my participation. I do not have to explain why I want to stop.
- I give the investigator permission to inform my general practitioner that I am participating in this study.
- I give the investigator permission to provide my general practitioner or specialist with information about any unexpected findings from the study that are relevant to my health.
- I give the investigator permission to collect and use my data and/or bodily material. The investigator will only use this to answer the research question of this study.
- I give the investigator permission to take a photo of me during the screening for identification purposes during the study.
- I give permission for my coded data and biological material to be used in research in collaboration with commercial companies, such as Sanofi and GSK.
- I give permission for my coded data and biological material to be sent to countries outside the European Union, such as Oxford in the UK. All measures will be taken to protect my privacy.
- I know that, for the monitoring of the study, some people may access all my data. These individuals are listed in this information letter. I give these people permission to view my data for this purpose.
- For women with childbearing potential: I understand that I must not become pregnant during the study.
- For women with childbearing potential: The investigator has discussed with me how to best avoid pregnancy during the study.

- Would you like to check 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 want to participate in this study

My name is (study subject):

Signature:

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

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

If any information comes to light during the study that could affect the study subject's consent, I will ensure that I inform the study subject in a timely manner.

Name investigator (or their representative):

Signature:

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

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