Official Title: CSP 2004, Microbiota or Placebo After Antimicrobial Therapy for Recurrent C. Difficile at Home (MATCH)

NCT Number: NCT03005379

Document Type: Informed Consent Form

Document Date: 05/23/2022

Department of Veterans Affairs **VA RESEARCH CONSENT FORM**

IRB #: 4713-B

Date: ☐☐ / ☐☐ / ☐☐☐☐ (mm/dd/yyyy) **Participant ID:** ☐☐☐☐☐

Title of Study: MATCH: Microbiota or placebo after Antimicrobial Therapy for recurrent *C. difficile* at Home

Principal Investigator: Andrew Reinink MD **VAMC:** Minneapolis - 618

Principal Investigators for Multisite Study: Aasma Shaukat, MD MPH, and Dimitri Drekonja, MD MS

IN-PERSON CONSENT FORM

INTRODUCTION

It is important that you read and understand the following explanation of the proposed research study before you agree to participate. This consent form describes:

- The purpose,
- The description of the study,
- The benefits,
- The risks and/or discomforts,
- Steps taken to decrease or eliminate the risks, discomforts, or possible pain,
- Any other treatments that may be available, and
- Confidentiality and use of research results.

This consent form may contain words you do not understand. Please ask the study doctor or the study staff to explain any words or information that are not clear to you.

PURPOSE OF THE STUDY

You are being asked to voluntarily participate in a research study because you have justcompleted treatment for an episode of *Clostridioides difficile* infection that recurred after at least one previous episode. This study is being done to find out whether fecal microbiota transplantation (also known as a "stool transplant" or "fecal transplant"), is an effective treatment to prevent future episodes of *Clostridioides difficile* infection, when it is given after a course of antibiotics as the initial treatment. In this study, you will be randomized (like the flip of a coin) to receive fecal transplant or placebo after having a favorable response to a standard course of antibiotic treatment. Placebo treatment will appear identical to fecal transplant, but contains no fecal material or other medicine.

Patients are thought to be at risk for *Clostridioides difficile* infection when the normal communities of microbes (the microbiota) that live in the colon (large intestine) are disrupted, which is usually due to antibiotic use. A normal or healthy microbiota is made up of hundreds of different types of bacteria, containing trillions of individual bacteria. This healthy microbiota is believed to be a barrier for disease-causing bacteria like *Clostridioides difficile* to enter the colon and cause disease. An unhealthy, or disrupted, microbiota is one where the diversity and number of bacteria is decreased, making it easier for *Clostridium difficile* to enter and cause disease. Patients who have just completed treatment for an episode of *Clostridioides difficile* infection have a very disrupted

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microbiota, and are at high risk of recurrent infection. Restoring the microbiota by use of a fecal transplant is thought to provide protection against recurrent infection by repopulating the colon with a healthy microbiota. This healthy microbiota is recovered from the feces of a screened donor, and then separated, measured, characterized, and stored frozen in a special solution.

Studies show that about 35% of patients who have had at least one prior episode of *Clostridioides difficile* infection will experience another episode of infection (also called recurrence) within 8 weeks of completing standard antimicrobial treatment. Although generally treatable with repeated antibiotic treatment, *Clostridioides difficile* infection can cause serious problems. These include malnutrition, incontinence, repeated clinic visits and hospital stays, need for surgical removal of the colon, and even death. In previous studies of patients diagnosed with *Clostridioides difficile* infection, death occurred in 5-7% of patients. This study is being done to see if fecal transplant can prevent recurrent infections.

You have an equal chance of being assigned to either treatment and you will not get to choose which treatment you receive. For this study, both fecal transplant and placebo will be given as oral capsules that you will swallow in one session.

Your participation will last for 6 months, and approximately 318 people will be enrolled into the study throughout the entire Veterans Affairs (VA) system.

DESCRIPTION OF STUDY

The following information describes what will happen if you participate in the study, which is funded by the VA Cooperative Studies Program, and led by study doctors at the Minneapolis VA Healthcare System. Participation begins after a discussion of the risks and benefits of the study with a study coordinator. You should make sure that all of your questions have been answered, and that you understand what participating in this study will involve.

Study visit

After learning about the study and signing the informed consent, you will receive a randomly assigned treatment from the study coordinator. Neither you nor the study team will know which of the treatments you have received. You will be asked to provide a stool sample at the time of the visit using a stool collection kit. Providing the stool sample is optional and refusing does not disqualify you from participating in the study. The stool collection can be completed independently by you. The study coordinator can provide some assistance in collecting the

sample at your request. If you choose to provide a stool sample, after completing the stool sample, the study coordinator will provide you with the study capsules. Study treatment consists of 5 capsules, which contain either fecal transplant or placebo.

On the day of your treatment, have only clear liquids 4 hours before study treatment. You can drink clear liquids to help swallow the capsules. After swallowing the capsules, you should not eat anything for two hours but you may continue to drink clear liquids. After that, you can go back to your normal diet. The study coordinator will provide you with a stool diary and some stool sample collection kits for study follow-up.

Follow-up

During this part of the study, you will be monitored for any recurrence of *Clostridioides difficile* infection, which typically begins with diarrhea. You will be asked to keep a daily record of your bowel movements up to day 56 of the study, and share it with the study team during scheduled calls. To help collect information in a similar manner from all participants, a chart of different stool consistencies is included with the stool diary. You will also receive kits to collect and mail a stool sample to the study team in case of diarrhea. Additionally, you will also be asked to provide a stool sample on days 14 and 56 of the study if you volunteered to provide one at the time of enrollment.

The follow-up part of the study also involves scheduled phone calls. You will be contacted by the study team or an automated voice response system. These calls are scheduled for day 2, and weeks 2, 4, 6, and 8 after the study visit. After the week 8 call, phone calls will occur once a month until 6 months after the study visit. In addition to the scheduled calls, you should call the study coordinator if you have diarrhea or other symptoms of *Clostridioides difficile* infection. Study personnel will also review your medical records for any symptoms of recurrent *Clostridioides difficile* infection, and may contact you to follow-up on these symptoms.

It is important for you to understand that study personnel are not replacing your current medical provider or providing ongoing treatment for your *Clostridioides difficile* infection. If you develop diarrhea, abdominal pain, or other concerning symptoms, you should seek care with your medical provider as you would normally. You will be provided with an information card that lists details about this study and provides instruction on how to contact study personnel. You are encouraged to let your treating medical care provider know that you are participating in this study.

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RISKS AND/OR DISCOMFORTS

Risks and discomforts of swallowing capsules:

The capsules used for this study of fecal transplant are fairly large, about the size of a large multivitamin. You will swallow 5 capsules. The picture below shows a capsule similar in size and shape to the study medication.

There is a rare risk of choking on capsules, or aspirating them (having them enter the breathing tube, instead of the esophagus, which leads to the stomach). This could cause an infection in your lungs. The study coordinator will watch you swallow one capsule at a time to make sure you are not at high risk for choking or aspirating.

Taking many pills at once may make some people nauseous, or even vomit. The capsules are designed to dissolve after they have passed through your stomach and are in your intestines. However, if you have a condition that makes your stomach empty slowly, there is a chance that the capsules could dissolve in your stomach. If you experience vomiting after swallowing the capsules you may be at an increased risk of pneumonia caused by inhaling the vomited substance.

None of these risks have been observed in previous studies of fecal transplant delivered by capsule, and are estimated to occur in less than 1 in 1,000 people.

Risks and discomforts of fecal transplant:

Although fecal transplant has been used in over 500 cases that have been reported in medical journals, it is considered to be an investigational treatment. We do not know if it is effective for preventing C. difficile and there may be risks that we are not aware of.
The most common side effects of oral fecal transplant are gastrointestinal problems like cramping, constipation, and bloating. These symptoms are usually mild and last no more than

three days. Because human stool contains a large amount of microorganisms (including bacteria,viruses, and fungi), having another person's stool transferred to your intestines could transmit certain types of infection. The stool used comes from a group of healthy donors who are screened for any risk factors that would increase the chance of having an infection, like having recently traveled out of the country or illegal drug use. The donor center also tests the stool and the person donating for specific types of infection, including hepatitis viruses, human immunodeficiency virus (HIV, the virus that causes AIDS), *Salmonella*, dangerous types of *E. coli*, antibiotic resistant bacteria and many other microorganisms. To minimize the chance that something could be missed, these tests are done twice before stool is used.

There have been rare cases of infections, including stomach viruses, antibiotic resistant infections and possibly other infections caused by fecal transplants. There have also been possible adverse effects other than infections, including nerve damage that required hospitalization. Based on what we currently know, these problems are uncommon and it is not clear if they were caused by fecal transplant.

In June 2019, the US Food and Drug Administration (FDA) issued an alert to researchers conducting oral fecal transplant studies. Two patients who received FMT in a different study later developed clinical infections with drug-resistant bacteria, one person died from the infection. This bacteria was an extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli (E. coli.). E. coli* is found in most human stool but those that produce ESBLs are rare. We have tested the stool donors and the capsules made from their donations in the MATCH study and none of the donated stool contain the ESBL-producing E. coli. This means that the capsules you will receive do not carry this bacteria.

It is important to know that:

- There may be unknown microorganisms not tested for. It's possible these could make you sick.
- A test may be falsely negative (meaning that the test says no microorganisms are present when in reality they are) if the donor was exposed to the microorganisms very recently.
- No test is 100% accurate.

There is a potential for transmission of SARS-CoV-2, the coronavirus that causes COVID-19, via FMT including FMT prepared from stool of infected donors who do not have symptoms of COVID-19. To decrease this risk, we are doing the following:

- All donors are vaccinated against COVID-19.
- The manufacturer will conduct additional screening of their stool donors for symptoms of COVID-19 with nasopharyngeal (back of the nose) swab testing for the SARS-CoV-2 virus before using their stools in the FMT capsules.

However, it is possible that SARS-CoV-2 virus could be transmitted through the stool of an infected stool donor who may not have symptoms of COVID-19 and may have a negative nasopharyngeal swab for SARS-CoV-2 virus.

Some recent research suggests that intestinal germs may affect the metabolism and body weight of laboratory animals, with fecal transplant from obese animals leading to obesity in the recipient of the transplant. Based on these findings, stool donations are only obtained from non-obese donors.

There may be other side effects that could occur that we may be unaware of.

EMPLOYEES AS RESEARCH SUBJECTS

If you are a VA employee you are considered a special class of research subjects who deserve special protections: 1) Your decision to participate in this study should be free from pressure or coercion to participate. 2) The VA research team will work to secure your information according to VA data security and privacy policies, and every effort will be made to keep your information from your supervisor and co-workers. However, accidental disclosure or release of your private information could occur during the conduct of this study.

BENEFITS

There may be no direct benefit to you from participating in the study. The knowledge gained from this study may benefit others in the future.

COMPENSATION

You will be paid a total of $250 for your participation to compensate for your time and effort spent recording and reporting your information. You will receive $100 at the time of enrollment during the study visit, $50 approximately 8 weeks after enrollment, and $100 approximately 6 months after enrollment. Payment will be in the form of a debit card or by an electronic transfer of funds, or according to local medical center procedures. An Internal Revenue Service (IRS) Form 1099, which documents that you are receiving income, will be generated using your Social Security Number. Because participant compensation for involvement in this study is disbursed

through the Bureau of the Fiscal Service, it is possible that your compensation may be reduced (an "offset"), via the Treasury Offset Program (TOP), if the Bureau's Debt Management Services identifies outstanding debt owed to a Federal agency.

PARTICIPATION IS VOLUNTARY

It is up to you to decide whether or not to take part in this study. If you decide to take part, you have the option to withdraw at any time. If you do not wish to be in this study or leave the study early, you will not lose any benefits to which you are otherwise entitled. You must notify the study team in writing to withdraw permission for us to continue reviewing and accessing your medical information. If you do not take part in this study, you can still receive all usual care that is available to you.

ALTERNATIVES (OTHER AVAILABLE TREATMENTS)

You do not have to participate in this study, which is investigating how to prevent recurrent *Clostridioides difficile* infection. The alternative to participating would be to discuss with yourprimary care provider whether any other preventative treatments are currently available for *Clostridioides difficile* infection or to receive standard medical care if an episode of *Clostridioides difficile* infection recurs.

CONFIDENTIALITY AND USE OF RESEARCH RESULTS

Taking part in this study will involve collecting some of your private information, including health information, name, address, telephone number, and social security number. All research data will be stored on password protected computers or in locked file cabinets. Only approved research staff will have access to this data.

The results of this study may be published or presented but your identity and records will not be revealed unless required by Federal Law. A Federal Law allows the U.S. Food and Drug Administration, Office for Human Research Protections, Government Accountability Office and other Federal agencies, the Research and Development Committee and/or the Institutional Review Board (IRB)/Human Studies Subcommittee of the VA Medical Center to review records. By participating in this research, you have also agreed to allow the sponsor of the research project (the VA Cooperative Studies Program) to review your medical records. Because of the need for these inspections, absolute confidentiality cannot be guaranteed.

Per federally mandated government sponsored research requirements, de-identified data sets willbe created upon completion of the study so results can be shared with other investigators and groups. Your identity cannot be determined from these shared data sets.

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If you are a VA patient, you already have a VA medical record. We will put information about your participation in this study into your medical record. This electronic record will be kept in accordance with the VA Records Control schedule and is accessed only by authorized users within the VA Healthcare System. All authorized users in the Veterans Health Administration can have access to your medical record if they have a legitimate need to do so.

Members of the Human Rights Committee (HRC) at the VA Cooperative Studies Program Coordinating Center conduct site visits and interviews during the course of the study to determine if the rights and safety of participants are being properly protected. A member from the Human Rights Committee or a member of the study team may contact you to set up an interview.

COSTS TO YOU FOR PARTICIPATING

There is no cost to you for taking part in this study. All the study costs, including any study medications provided by the sponsor and procedures related directly to the study, will be paid for by the VA. Veterans who must make a co-payment for their usual medications or treatments will continue to be required to make such a co-payment for non-study related drugs. There should be no additional medical costs to you for taking part in this study. However, the study visit may result in possible wages lost due to time missed from work.

MEDICAL CARE IF YOU ARE INJURED

In case you are injured from this research study, treatment will be available, including first aid, emergency treatment and follow-up care, as needed, by the VA Medical Center. In the event you cannot reach a VA facility, the VA will pay for necessary medical care for any injury or illness directly related to your participation in this research study. If you receive this type of medical care, you must contact the Research Investigator for this study. You can find contact information in the next section, “Compensation for Any Injuries”.

COMPENSATION FOR ANY INJURIES

Every reasonable safety measure will be used to protect your well-being. If you are injured as a result of taking part in this study, the VA will provide the necessary medical treatment at no cost to you unless the injury occurred because you were not following the study procedures. Financial compensation is not available for things such as lost wages, disability or discomfort due to an injury. You should immediately report any injuries resulting from your participation in this study to Dr. Andrew Reinink, 612-467-4100 during regular business hours.

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NEW INFORMATION
You will be given any new significant information which is discovered during the course of this study which may influence your willingness to continue participating.

OTHER INFORMATION
A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can review this website at any time.

RIGHT OF INVESTIGATOR TO TERMINATE PARTICIPATION
The investigators reserve the right to terminate your participation if, in the judgment of the investigators, your continued participation represents a potential for harm. One reason for this may be the loss of capacity to consent.

RESEARCH SUBJECT'S RIGHTS: I have read or have had read to me all of the above. A study team member has explained the study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available. **I understand that I do not have to take part in this study and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this study at any time without penalty or loss of VA or other benefits to which I am entitled.**

The results of this study may be published but my identity and records will not be revealed unless required by law.

We will collect optional stool samples from you at the time of the study visit, and at 14 days and 56 days after the visit. This is to determine what effect fecal transplant has on the bacteria in your intestines. We will also ask you to collect a stool sample and send it to a study laboratory for confirming *Clostridium difficile* if you have any symptoms of recurrent *Clostridium difficil*e infection. The samples used to confirm *Clostridium difficile* infection will be discarded after testing. We would like to store the optional samples collected on day 1, day 14 and day 56 to use for future research. You can refuse storage of your samples and still participate in this study. The samples will be stored without identifying information about you (such as your name or Social Security number) but will be labeled with a unique numerical code. Your personal information and the corresponding code will be kept in a secure computer system that will only be available

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to the study investigators. Although use of your stool samples will be under the supervision of the investigators participating in this study, the samples may be used by investigators not associated with this study. No identifiable information will be provided to any investigator requesting access to your stool sample and the sample will not be used to sequence your genome.

The stool samples will be stored indefinitely, but you may request that your stool sample, and all links to the identifying information, be destroyed at any time. You will not be re-contacted after the original study is completed and information about individual research results will not be given to you or placed in your medical record.

Any samples you have donated that are used in research may result in new products, tests, or discoveries. In some instances, these may have potential commercial value and may be developed and owned by the investigators, the VA, and/or others. You will not be financially compensated if this happens. The study doctor does not have any commercial interest from which *he/she* may benefit financially, directly or indirectly.

Please initial one of the following

____ By initialing here, I authorize the use of any stool samples collected during this study to be used for future research studies. I understand that no identifying information will be included with the sample.

____ I do not authorize the use of stool samples collected during this study to be used for future research studies

____ I am not interested in providing the optional stool samples

I have been informed that because this study involves articles regulated by the FDA (Food and Drug Administration), the FDA may choose to evaluate this study, identifying me as a subject of this investigation.

If I have any questions about the rights of a research subject, or would like to:

- obtain information
- discuss problems or concerns, or ask questions about this study
- offer input regarding this research study

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and would like to speak to an individual who is not part of the research team of this study, I may contact the Patient Representative at (612) 725-2106. If I wish to verify the validity of the study and its authorized contacts, I may call the patient representative or contact the Minneapolis IRB office at (612) 629-7387.

My questions have been answered and I voluntarily consent to participate in this study. By signing this form, I have not given away any of my legal rights that I have as a subject of this research study. I will receive a signed copy of this consent form.

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Subject's Signature Date

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