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Department of Medicine

Division of Gastroenterology

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Information Sheet and Consent Form

Study Name: Serial fecal microbiota transplant (FMT) plus fidaxomicin in the treatment of severe or fulminant *Clostridium difficile* infection, with detailed characterization in microbiota, metabolomics and host immune response

Study Doctors: Dr. Dina Kao, Dr. Lindsey Russell, Dr. Karen Wong, Dr.Haili Wang, Dr. Lynora Saxinger

Study Coordinator: 780 248 1342

In the case of third party consent, 'you' always refers to the research participant. The pronouns 'you' and 'your' should be read as referring to the participant rather than the parent/guardian/next of kin who is signing the consent for the participant.

Purpose of study

You are being asked to voluntarily participate in this study because you have a severe *Clostridium difficile* infection.

Before you make a decision one of the researchers will go over this form with you. You are encouraged to ask questions if you feel anything needs to be made clearer. You will be given a copy of this form for your records.

Clostridium difficile (C diff) is an infection that results when the healthy bacterial population of the colon is substantially altered by antibiotic treatment. The decrease in the normal, or good, bacteria allows for the overgrowth of the *C. difficile* bacteria. C diff makes a toxin that can make a person sick with diarrhea and abdominal pain. Treatment for mild infections can be done with antibiotics called vancomycin or metronidazole. A small portion of patients can become very ill, where they do not respond to antibiotic treatment and ultimately will need surgery to remove the large intestine. Despite surgery, 5% of affected patients can still die, and many patients are not fit for surgery. Therefore, better treatments are needed to help these sicker patients.

Fecal microbiota transplantation (FMT), also known as stool transplant, is when stool from a healthy person is transplanted into the bowel of sick patients to help restore the balance of normal bacteria in the colon. FMT has been very effective in treating patients when mild C diff infection keeps coming back. However, it is unclear if FMT will help patients with a more severe C diff infection. A previous study used both FMT with an antibiotic called vancomycin to treat a small number of patients with severe C diff infection and found that they were able to cure these patients with a success rate of 91% with several cycles of FMT puls vancomycin. In our own experience, we've learned that FMT alone is not sufficient to treat severe C diff infection in the initial stage, and that an antibiotic against C diff would be necessary to suppress C diff. In addition, multiple cycles of FMT treatments plus an antibiotic to kill C diff are usually needed to manage this problem. However, the use of antibiotic to kill C diff can also kill good bacteria that we implant with FMT.

There is another new antibiotic approved by Health Canada for C diff called fidaxomicin, which is very specific for C diff and has been shown to be effective in treating mild to moderate C diff infection. We believe it is a better option than vancomycin and metronidazole in this situation because vancomycin and metronidazole not only kill C diff but will also kill good bacteria in the gut. Fidaxomicin has not been studied yet to be used for treating severe C diff infection. That is why we are doing this study to see if using FMT with fidaxomicin can potentially reduce the number of treatment cycles we need to manage this

problem. The only other option is surgery. This is a pilot study, meaning the data collected will be used to plan future studies.

For this study, we have assembled a team of specialists from different fields: gastroenterology, infectious diseases, general surgery, intensive care unit, and scientists. We plan to use a combination of FMT and fidaxomicin and then monitor the clinical response very closely. FMT will be given by enema, which is a solution that will be given through a tube inserted into the rectum. We will also collect blood, and stool, samples, which will be analyzed to understand how FMT works. This will allow us to ultimately design a better treatment protocol and develop more targeted options for patients with this severe infection.

Currently Health Canada only allows FMT to be provided in a liquid form. This means that we cannot provide FMT in a pill form unless patients are in a research study. In this study, we are using enema because sometimes patients get very sick and cannot take anything by mouth.

We will need to have your permission or consent to begin the study. In the event that you are not able to make your own medical decision, a substitute decision maker can make such a decision for you.

Description of the study, procedures to be used, and how long it will last
Approximately 30 participants are expected to participate in this trial, which will take place in Edmonton, Calgary and Victoria. Each participant will be treated with multiple FMTs and fidaxomicin. After a bowel prep, which is a medication or 2 L of a laxative to clean out your bowel of stoolyou will be given FMT by enema for 3 days in a row. You will also receive fidaxomicin at the same time for 7-10 days depending on how you respond to the treatment. This completes cycle 1. The study doctors will perform daily physical exams and blood work to thoroughly track your response to treatment. If you do not respond or if your condition worsens during this time, we would recommend that you undergo surgery. However, if you do have a good response but the diarrhea has not cleared up, you will be given a second cycle (multiple FMT enemas + fidaxomicin) and your response will be monitored. If at the end of cycle 2 your diarrhea still has not cleared up, you will be given a 3rd cycle. When your diarrhea clears up, you will receive a final FMT enema. If by the fourth cycle you have not cleared up, then we will consider surgery to help you. For this study we think that you may need at least 2 cycles of treatment.

Your time in the study will be approximately 20 weeks.

If you choose to participate, the following tests and/or procedures will be done as part of this study:

At the beginning of the study you will have a medical and medication history taken. You will answer questions about your overall health. A physical exam will be performed. Blood (15 mL or about 3 teaspoons) and stool samples will be collected from you. The blood sample is to look at your blood count, liver and kidney function, HIV and hepatitis B and C status. Of note, any positive finding will be reported to the provincial health authority as required by Alberta law. All the samples collected will be analyzed immediately. There will not be any genetic testing performed with the blood sample. Only the study doctors have access to the samples.

You will likely already be taking either vancomycin and metronidazole prior to the beginning of the study for the severe C diff infection. You will continue to take those antibiotics, until the time of the first FMT. You will also need to take 2 liters of a laxative the night before the FMT to clean out your intestine. Once the FMT cycle starts, then you start taking the fidaxomicin as well.

What will happen for enema delivery FMT:
The procedure will take place in the hospital at the bedside. FMT liquid will be injected into your large intestine through a tube that is inserted in the rectum (day 1). You will be asked to stay in bed for an hour and keep the liquid inside for as long as possible. After the first large volume enema of 720cc, it will be followed by two days of smaller volume enemas of 360cc and 180cc to complete the first FMT cycle.

In the event that you need to have a colonoscopy to make sure that there is not another condition causing your diarrhea during this study, then FMT can be delivered at the time of colonoscopy.

While you are participating in this study:
The research team will track your bowel movements and ask questions about how you are feeling. You will be monitored by the study team closely to make sure there are no concerns and to follow up on how you are feeling after each intervention. If at any point your condition gets worse during the trial, then we will adjust your treatment plan accordingly to provide the best clinical care, which may include surgery.

We will also be collecting blood and stool samples at various points during the study, especially before and after a FMT. We expect to collect a total of about 8 batches of bloodstool samples from each participant. This will help us create a complete analysis of what is going on in your body while using this method to treat severe CDI. All samples will be promptly used for analysis. Only the study doctors have access to the samples.

Once you have the final FMT treatment, we will continue to monitor you to see how you are doing and to take blood, and stool samples and assess you in the clinic at 1, 2, 4 and 8 weeks afterwards. Telephone follow up will take place at 3, 5, 6 and 7 weeks afterwards.

Termination
You can decide to withdraw from this study at any time for any of the following reasons:

- You develop side effects that are considered dangerous
- You do not follow the study instructions given to you by the study doctors
- Your treating physician decides that it is not in your best interest to continue in the study
- You no longer want to be in the study

Your care will not be affected by withdrawing from the study.

What will I be asked to do during this study
If you choose to be a part of this study, your main role will be to allow us to take the blood and stool samples as needed and to check on your clinical status through history and physical exams throughout the study at various times. If you want to be in this study you will agree to the proposed treatments that involve multiple FMTs and courses of the fidaxomicin antibiotic as given by the study investigators.

If you choose to stop your participation in the study for any reason, tell your study doctor immediately so that the final clinical evaluations and laboratory tests as described above can be performed and an alternative plan can be made for your care.

Risks
Risks of blood Tests. There may be some discomfort, swelling, or bruising around the vein from which blood is drawn. Some persons may become lightheaded or faint when blood is being drawn. Rarely, infections can occur at the blood drawing site. If a specific condition is identified during this process, we will make sure appropriate referral is made to further deal with the problem.

Risks Associated with Fidaxomicin. In previous trials many participants did not have much trouble taking fidaxomicin for C diff infections. Side effects could include minor nausea occurring in 10% of participants, vomiting(6%), headache (7%), dizziness (4%), and rash (3%). However, no participant stopped taking the medication.

Risks Associated with FMT. The FMT will be made using the stool of a healthy donor who has been fully screened to ensure there is no HIV, syphilis, viral hepatitis and other viruses which can cause a chronic infection. Also, the donor's stool has been examined to rule out underlying parasites and bacterial infection. These volunteer donors go through the same rigorous screening process as they would if they are blood or organ donors. However, we can never guarantee 0% chance of a rare infection, just as with blood transfusion or with organ transplantation. If a blood borne infection happens, people can have fever, chills and possibly

low blood pressure. In 2019, 2 patients in the USA developed a multi drug resistant infection, commonly known as as a 'super bug,' that was transmitted through FMT. Once of these patients died of the infection. As a result, stool donors are now screened for these types of bacteria. People who may be more likely to carry these types of bacteria are not allowed to become donors. Recent studies have shown the presence of the SARS-CoV-2 virus (which causes COVID-19 disease) in the stool of infected individuals even if they do not have symptoms. This means that SARS-CoV-2 may be transmitted by FMT however the likelihood of this occurring is not known. According to the Center for Disease Control, the risk is expected to be low based on information from past outbreaks such as SARS.

Tests to detect the virus in the stool are not widely available and it is not known how reliable these tests are at this time.We do however carefully screen our donors with COVID-19 questionnaire, which includes symptoms, travel history and history of contact with anyone suspected of having/known to have COVID-19.

Some of the potential side effects may include nausea, transient loose stools, constipation, abdominal discomfort and bloating. There is also the possible risk of developing disease which may be related to donor gut bacteria (obesity/metabolic syndrome, autoimmune conditions, allergic/atopic disorders, neurologic disorders, and malignancy, however, there have not been good data demonstrating this risk. There is a very small risk of bowel perforation (tear) at a chance of 1 in 10,000 with enemas.

You should report anything that is causing you concern.

COVID-19 Risk

In March 2020, COVID-19/ the Severe Acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was recognized as a global pandemic, and the impacts have been widespread globally, including Alberta. We have changed out procedure in this study because of the need to keep participants and researchers safe during the pandemic.

Risk associated with this includes risk associated with travel, time within a healthcare facility and increased exposure to other patients, participants or people.

It is also important to be aware that elderly patients, immunocompromised individuals, and/or individuals with underlying or pre-existing conditions, are at increased risk for more severe complications related to COVID-19.

Additional measures have been undertaken to reduce the risk including pre-screening patients for COVID-19 prior to study appointment, using personal protective equipment while attending appointments such as masks and gloves, the use of hand sanitizer when entering and leaving study appointments, and using physical distancing measures.

Benefits

There may be no health benefit to you from being in this study. What we learn from these studies may benefit society by finding a treatment other than surgery for severe *C. difficile*.

Voluntary Participation

Being in this study is your choice. If you decide to be in the study, you can change your mind and stop being in the study at any time and it will in no way affect the care or treatment you are entitled to.

Alternatives

You do not have to participate in the study to receive treatment for your condition. Alternative therapies include surgery which is the way we normally treat severe CDI not responding to treatment. Your doctor will discuss which option is best for you if you do not want to participate in the study.

Payment for Participation

Participants will not be paid to participate in this study.

Costs to You

During the study, you will be provided with the stool transplant and fidaxomicin at no charge. No commitment is made to provide the study treatment or to pay the expenses for the study treatment following the termination of the study.

Research related injury

If you become ill or injured as a result of being in this study, you will receive necessary medical treatment, at no additional cost to you. By signing this consent form you are not releasing the investigator(s), and institution(s) from their legal and professional responsibilities.

New findings

You will be told in a timely manner of any significant new findings that develop during the course of your participation in this study and that may relate to your willingness to continue to participate.

Confidentiality

During the study we will be collecting health data about you. We will do everything we can to make sure that this data is kept private. No data relating to this study that includes your name will be released outside of the study doctor's office or published by the researchers. Sometimes, by law, we may have to release your information with your name so we cannot guarantee absolute privacy. However, we will make every legal effort to make sure that your health information is kept private.

The study doctor/study staff may need to look at your personal health records held at the study doctor's office, and/or kept by other health care providers that you may have seen in the past (i.e. your family doctor). Any personal health information that we get from these records will be only what is needed for the study. During research studies, it is important that the data we get is accurate. For this reason, your health data, including your name, may be looked at by people from the University of Alberta auditors and members of the Research Ethics Board, and/or Health Canada.

By signing this consent form you are giving permission for the study doctor/staff to collect, use and disclose information about you from your personal health records as described above.

After the study is done, we will still need to securely store your health data that was collected as part of the study. In Canada, the law says we have to keep the data stored for 25 years after the end of the study. If you leave the study, we will not collect new health information about you, but we will need to keep the data that we have already collected.

Contact information

If you have any questions about your participation in this research study or if you feel that you have experienced a research-related injury or reaction to the study treatment, contact:

Dr. Dina Kao at 780-492-8307 or please contact the hospital switchboard at 780 407 8822 and ask for the gastroenterologist on call.

If you have any questions regarding your rights as a research participant, you may contact the Health Research Ethics Board at 780-492-2615. This office is independent of the investigators.

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	Yes	No
Do you understand that you have been asked to be in a research study?	☐	☐
Have you read the attached Information Sheet? You will receive a signed copy.	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Do you understand that you are free to withdraw from the study at any time, without having to give a reason and without affecting your future medical care?	☐	☐
Has the issue of confidentiality been explained to you?	☐	☐
Do you understand who will have access to your records, including personally identifiable health information?	☐	☐
Do you want the investigator(s) to inform your family doctor that you are participating in this research study?	☐	☐

If so, your doctor's name is: _____

Who explained this study to you? _____

I agree to take part in this study:

Participant name	Participant signature	Date: (dd/month/yy)
Witness name	Witness signature	Date: (dd/month/yy)

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of the person who obtained consent	Date: (dd/month/yy)

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A SIGNED COPY GIVEN TO THE RESEARCH PARTICIPANT