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INFORMED CONSENT

Fred Hutchinson Cancer Center

Consent to take part in a research study: Randomized phase

Fecal microbiota transplantation to prevent acute graft-versus-host disease after allogeneic hematopoietic cell transplantation

Principal Investigator: Armin Rashidi, MD, PhD; 206-667-2506

Emergency number (24 hours): Hematology/Oncology fellow 206-598-6190

Important things to know about this study.

You are invited to participate in a research study. The purpose of this research is to determine whether fecal microbiota transplantation (FMT) combined with the current standard regimens will further reduce the risk of developing acute graft-vs-host disease (GVHD). FMT involves transferring intestinal microbes from a healthy unrelated donor (stool donor) to the patient through oral capsules. You are being considered by your clinical team for an allogeneic hematopoietic cell transplantation for the treatment of your blood cancer. This procedure also involves a donor (stem cell donor) who is different from you. The stool donor and stem cell donor are different individuals. Acute GVHD is a common complication of allogeneic transplantation.

People who agree to join the study will be asked to take 3 study capsules daily for 7 days, starting at approximately 2-6 weeks after transplant. In addition, the study involves collecting 3 stool samples between the time you consent and 3 months after transplantation. An optional online diet survey after the first and third stool samples is also included. Finally, the study involves a screening visit before transplantation, and 4 brief phone calls after starting the study drug.

We do not know if FMT would help prevent acute GVHD, and it could even make your condition/disease worse. FMT could cause side effects such as nausea, vomiting, abdominal discomfort, or diarrhea, as described below in this form.

You do not have to join this study. You can choose to receive standard methods to prevent acute GVHD instead of participating in this study. We will give you details about the purposes, procedures, risks, and possible benefits related to this study. We will explain other choices that you have. We will also

give you any other information that you need to make an informed decision about joining this study.

Following is a more complete description of this study. Please read this description carefully. You can ask any questions you want to help you decide whether to join the study. If you join this study, we will give you a signed copy of this form to keep for future reference.

We invite you to join this research study.

We invite you to join this research study because you are a candidate for allogeneic transplant, and therefore you will be at risk for a complication of transplant called acute graft-versus-host disease (GVHD). We intend to enroll 138 patients at our center for this study.

Research is not the same as treatment or medical care. The purpose of a research study is to answer scientific questions.

You do not have to be in the study. You are free to say “yes” or “no”, or to drop out after joining. If you say “no,” you would have no penalty or loss of benefits. Whatever you decide, your regular medical care would not change.

Why are we doing this study?

We are doing this study to determine whether adding FMT to the existing medication regimen for preventing acute GVHD will reduce the risk of developing acute GVHD after transplant. Acute GVHD is a disease caused by an immune reaction of donor cells against patient tissues. The skin, stomach, intestines, and liver are the most affected organs. If acute GVHD becomes severe, it can be disabling or lead to death. Medication must be given for prevention of acute GVHD.

We host many microbes in our intestinal tract. These microbes interact closely with us and regulate our immune system and keep it in balance. During transplant, these microbes change, partly due to inevitable antibiotic exposures after transplant. Our own research and those by other groups have linked some of these changes with the risk of subsequent acute GVHD. Inspired by these discoveries, we recently attempted to replace the patients’ damaged microbial communities with healthy donor’s intestinal microbes. The idea was to improve the patient’s microbes and prevent acute GVHD. We did this by transferring intestinal microbes, encapsulated for oral administration, from healthy donors to transplant recipients. Forty-nine patients received this treatment. We found signals for less acute GVHD in patients who gained more microbes from their stool donor. The stool donors were unrelated to the stem cell donors. The process of transferring whole microbial communities is called “fecal microbiota transplantation (FMT)”.

Two FMT products have been approved for the treatment of a severe form of infectious diarrhea called C. difficile diarrhea. Our specific FMT product does not have an FDA-approved indication at this time and is considered experimental. We will use our product in this study to try to prevent acute GVHD. Specifically, the study includes 2 phases:

The first phase is called the “run-in” phase. This phase has now been completed so you are not considered for this phase. During phase 1, we identified the best stool donor for phase 2.

Phase 2 is the randomized phase. **You are being considered for this phase.** We will randomly assign patients in phase 2 to two groups. One group will receive FMT while the other group will receive placebo. A computer program will be used to decide which treatment you receive. You will not be allowed to choose the treatment. You will have a 1-in-2 chance of receiving FMT. Neither you nor your doctors will know which group you have been assigned to. Placebo capsules are similar in appearance to FMT capsules except they contain no active compound. FMT and placebo capsules have no taste or smell. The goal of this phase is to determine whether the FMT group will have less acute GVHD than the placebo group.

All patients in both phases will receive standard GVHD preventative medications. The study treatment will be an “add on”, as a supportive care to further decrease the risk of acute GVHD.

What research tests, procedures, and treatments are done in this study?

Before your transplantation, you will need to complete a screening visit. If you complete the screening visit and enroll in the study, you will have a study visit shortly before the first dose of the study drug. Further details are provided below.

If you decide to join this study, we will do these tests and procedures:

- **Study visit –** We plan to perform most study visits in the form of brief phone calls. You would receive phone calls from the study staff to assess for any potential side effects. Each call would take a few minutes and we would ask questions about symptoms such as fever, nausea, vomiting, abdominal discomfort, diarrhea, and new antibiotics. Phone calls would occur 3 times during your 7 days of taking the study drug, then 7 days after the last dose of the study drug. If you happen to be in the clinic or hospital at the time of these phone calls, we may do some of these visits in the private room where you are at. We may collect additional information as related to the study from your clinical chart.

- **Study Drug (FMT or placebo) –** The study drug consists of 3 capsules per day, taken at once with at least one glass of water or any

clear liquid, for 7 days in a row. We ask that you take the capsules first thing in the morning and avoid meals for 2 hours after the capsules, but you may drink clear liquids or have crackers if needed. We also ask you to avoid lying down for 1 hour after the capsules. We give you a 7-day supply once we have determined that you are ready to start. You would take your capsules on your own.

- **Research stool samples** – By taking part in this study, you would have additional stool samples obtained that are not part of standard of care. With these stool samples, we will determine how the study treatment influences your intestinal microbes. These are self-collected samples, meaning we will show you how to collect them using a simple kit, you will then collect a small sample from the toilet paper using our swab and provide us with the sample. We will collect 3 samples for research before you are discharged from the BMT clinic.

- **Optional diet survey** – We invite you to complete a secure online diet survey, once with your first stool sample and once with your third stool sample. Completing the survey takes about 25 minutes each time. The survey shows you a visual list of food items and portions. It asks you to provide an estimate of how many times you have taken each item in the last month. Information about your diet helps us better understand how the study treatment works.

- **Pregnancy test –** If you are a woman of childbearing potential, we will do a blood test to check for pregnancy before you begin taking the study drug.

How long would you stay in this study?

If you join this study, you will stay in this study for 6 months after transplant.

Doctors could decide that you should stop taking the study drug (or not even start it) but continue with study follow up assessments. Some situations where this would happen include:

- Your doctors think it is in your best interest not to continue in the study.
- You have unacceptable toxicity from the treatment.
- You are not able or willing to follow study procedures.
- You develop severe acute GVHD before starting or during the period of study treatment.
- Your readiness to start study treatment according to study criteria is delayed.

Under certain circumstances, doctors could decide that you should stop taking the study drug and discontinue participation from all follow up procedures. This would happen if:

- You decide to withdraw from the study.
- The whole study is stopped.

If you decide to withdraw from the study, there will be no penalty or loss of benefits in your routine medical care or any other benefit(s) that you would otherwise be entitled to receive.

If you withdraw from the study for any reason, previously collected information will remain in the study records and would be included in the analysis of results. This information will not be removed from the study records.

What are the side effects (risks)?

In this part of the consent form, we describe the side effects we expect from the tests and treatments in this study. If you join this study, we will tell you if we discover new side effects that could affect you.

Your doctors will decide on your standard medications to prevent acute GVHD. The study will not influence that decision. We do not expect any interactions between the study treatment and any other medications. The study intervention is the transfer of intestinal microbes from a healthy donor to you in the form of oral capsules. With any medication, there may be complications or other side effects that we do not know about. Some side effects may require that hold the study drug. Your doctor (attending physician) may suggest that you take certain medications to reduce some of the side effects.

In our own experience with these study capsules in transplant patients like you, we have not seen serious side effects. Most side effects were limited to mild and transient nausea, abdominal discomfort, and soft bowel movements. We had no infections that were attributed to the transferred microbes.

Rare or unknown side effects include the following:

<u>Potential Infectious Risk - Rare (less than 1%)</u>
Gut microbiota are generally non-pathogenic since their well-being depends on the well-being of the host. Some pathogens known to cause chronic infections, e.g., hepatitis viruses, can be shed in the fecal material. However, the donors supplying fecal material for transplantation are screened for the presence of these organisms and cannot donate material unless they test negative for the pathogens of concern. If any suspected or confirmed pathogens are transmitted from the FMT capsules to any participant within the study, the Investigator will impose a study-wide halt to all subjects until medical safety monitoring has been completed.

<u>Multi-Drug Resistant Organisms (MDRO) - Rare (less than 1%)</u>
The transmission of microbes can cause an infection or carry antibiotic resistance genes that can be passed to other microbes and make it difficult to

treat infections. The donors supplying fecal material for transplantation are screened for multiple MDROs per FDA requirements and cannot donate material unless they test negative for these MDROs. If suspected or confirmed MDROs are transmitted from the FMT capsules to any participant within the study, the Investigator will impose a study-wide halt to all subjects until medical safety monitoring has been completed.

Metabolic Risk - Rare (less than 1%)
All donors in the program are lean (BMI ≤ 30.0 kg/m^2). Any single feature of metabolic syndrome (BMI, hypertension, abnormal lipid panel, abnormal fasting glucose, abnormal liver function tests) excludes donor candidates from participation. However, clinical donor indicators may not be perfectly predictive of metabolic potential of their microbiota, and it is possible that an opposite from desired effect could result from the intervention.

Risk of Autoimmunity – Unknown Risk
The role of the gut microbiota in the function of a mature immune system is unknown. There is a risk that some form of immune disorder can be triggered by a new composition of gut microbiota in a recipient. This includes allergic disorders, serological evidence of autoimmunity, or autoimmune disorders.

Risk of Colorectal Cancer - Rare (less than 1%)
Gut microbiota may cause colon cancer, although the link between microbiota and colon cancer development has not been proven. This risk is mitigated by eliminating potential donors of fecal microbiota considered at increased risk for colon cancer, e.g., significant family history or positive screening test.

Risk of COVID-19 – Unknown Risk
It is possible that SARS-CoV-2, the coronavirus that causes COVID-19, can spread through FMT. To decrease this risk, the manufacturer tests their donors for COVID-19 using a nasopharyngeal (back of the nose) swab test for the SARS-CoV-2 virus before using their stools in the FMT capsules. However, it is still possible for SARS-CoV-2 virus to be passed on through the stool of an infected donor who may not have symptoms of COVID-19 and may have a negative nasopharyngeal swab for SARS-CoV-2 virus.

To minimize the risks of receiving a transplant, all donors in this study will be thoroughly screened before they are accepted as donors. After they are accepted, they will continue to be screened on an ongoing basis. Importantly, fecal microbiota is very complex biological material. We acknowledge that our tests are not perfect and can miss important information about individual or groups of microbes present in the preparation.

Risk of Monkeypox - Rare (less than 1%)
It is not known whether monkeypox can be transmitted via fecal microbiota transplant. While the disease is transmitted through contact with someone who has monkeypox, it is possible for monkeypox to be passed on through the stool of an infected donor who may not have symptoms.

To minimize the risks of receiving a transplant, all donors in this study will be thoroughly screened before they are accepted as donors. The donors are screened for monkeypox symptoms as well as possible contacts with individuals with suspected or confirmed diagnoses of monkeypox. After they are accepted, they will continue to be screened on an ongoing basis. Nevertheless, no screening procedures can definitively exclude the risk of monkeypox transmission.

What about birth control and pregnancy during the study?

Participation in this study may involve unknown risks to a pregnant woman, unborn baby or nursing infant. You must not take part in this study if you are pregnant, plan to become pregnant during the research study period, or are breast-feeding a baby. Female subjects must have a blood test when beginning this study that shows they are not pregnant.

You must be willing to use at least 1 accepted method of contraception until day 180 after transplant and agree to not donate eggs/sperm for 180 days.

Additional Risks

Stool samples are self-collected using a swab from the toilet paper. You can collect these samples in the clinic, in the hospital, or at your residence, whichever you find most convenient. No risk is anticipated.

There is a risk of loss of confidentiality of your information. Results of genetic tests on your intestinal microbes may be released by accident. This risk is very small, because we keep your personal information private. The diet survey is completed online through a secure web portal accessible only to you. As long as your internet-connected device has a good antivirus software and you do not share your log in info with anyone, the risk associated with doing these surveys is considered minimal.

You will read more about the protection of your information later in this form. Please ask the study doctor or study staff if you would like to know more about how your information will be protected while you are in this study.

What are the benefits?

We do not know if this study will help you. We are testing FMT to see its effects on people at risk of developing acute GVHD after stem cell transplant. You might do better if you receive the study drug, but your risk of acute GVHD could stay the same or even get worse. We hope the information from this study will help other people undergoing stem cell transplants in the future.

You have other choices besides this study.

You do not have to join this study. You are free to say “yes” or “no”. Your regular medical care will not change if you decide to say “no”.

You have other choices for treatment. Each of these choices has risks and benefits. You should talk to your doctor or healthcare provider about these choices.

Enrollment in this study may exclude you from other research studies.

Protecting Privacy as an Individual and the Confidentiality of Personal Information

If you join this study, some people or organizations might need to look at your medical records and research records for quality assurance or data analysis. They include:

- Researchers involved with this study.
- University of Minnesota, provider of the study capsules for this study.
- Institutional Review Boards (IRB), including the Fred Hutchinson Cancer Center IRB. An IRB is a group that reviews the study to protect the rights and welfare of research participants.
- Fred Hutchinson Cancer Center.
- Leukemia and Lymphoma Society, a funder of this study.
- Office for Human Research Protections, Food and Drug Administration, and other regulatory agencies as required.

We will do our best to keep personal information confidential. But we cannot guarantee total confidentiality. Personal information may be given out if required by law. For example, workplace safety rules may require health workers to contact you about lab tests. Or a court may order study information to be disclosed. Such cases are rare.

We will not use personal information in any reports about this study, such as journal articles or presentations at scientific meetings.

If you join this study, information about your participation will be made part of your permanent medical record. This information will include a copy of this consent form. If an insurance company or employer or anyone else were authorized to see your medical record, they will see a copy of this consent form.

Would we pay you if you join this study?

There is no payment for being in this study.

Would you have extra costs if you join this study?

If you join this study, the study-specific treatments and assessments, including the study product, will be paid for by the study budget and not billed to you or your insurance provider.

In contrast, as is true if you were not taking part in this study, you or your insurance provider is responsible for the routine aspects of your medical care that are not direct components of this study (medications, tests, clinic and hospital visits as part of your routine care as a transplant recipient).

However, if you needed other medical care because of this study, your insurance company might pay the associated costs, but some insurance policies do not cover these costs.

What if you get sick or hurt after you join this study?

For a life-threatening problem, call 911 right away or seek help immediately. Contact your study doctor when the medical emergency is over or as soon as you can.

For all other medical problems or illness related to this research, immediately contact Armin Rashidi, MD, PhD; 206-667-2506 (principal investigator) or the Hematology/Oncology fellow on call 206-598-6190. They will treat you or refer you for treatment. You or your health insurance will have to pay for the treatment. There are no funds to pay you for a research-related injury, added medical costs, loss of a job, or other costs to you or your family. State or national law may give you rights to seek payment for some of these expenses. You do not waive any right to seek payment by signing this consent form.

You or your insurer will be billed for treatment of problems or complications that result from your condition or from standard clinical care.

You will not lose any legal right to seek payment for treatment if you sign this form.

What will my information and/or samples be used for?

Your information and samples will be used for the purposes of this study.

Your samples might help researchers develop new products. This research could be done by for-profit companies. There is no plan to share with you any revenue generated from products developed using your tissue samples.

During this study, we do not expect any research test results that would affect your care, so we do not plan to return results to you.

In addition, by agreeing to participate in this study, your information or samples could be used for future research studies or sent to other investigators for future research studies without additional consent from you. These future research studies will be reviewed by the IRB if required by law. The information that identifies you will first be removed from your clinical data or samples.

DNA sequencing of stool samples

By studying the genes in your intestinal microbes, we will identify the microbes. This procedure requires sequencing (reading) the DNA within the microbes. A small amount of your own DNA may also be present in the stool samples, but your own DNA will not be kept or shared for this and future studies. At the end of sequencing, we will exclude your own DNA from the files because we are only interested in microbial DNA in this research. As your own DNA will not be studied, data from this line of research will not identify you or your family.

As part of this study, we will deposit the genetic information obtained from your intestinal microbes into a standard, recommended shared database. The goal is to maximize knowledge dissemination. All your personal information will be removed and only information about your microbes' DNA and your condition will be sent to the database. Genetic information from intestinal microbes do not identify the individual with those microbes. Once we release your intestinal microbes' genetic information to the database, we are no longer in control of it.

Once we have obtained sequencing data from the microbes and confirmed their quality, we will discard any leftover stool samples.

Your rights

- You do not have to join this study. You are free to say "yes" or "no".
- If you get sick or hurt in this study, you do not lose any of your legal rights to seek payment by signing this form.
- During the study, we might learn new information that you need to know. For example, some information may affect your health or well-being. Other information might make you change your mind about being in this study. If we learn these kinds of information, we will tell you.
- If you join this study, you will not have to stay in it. You could stop at any time (even before you start). Your regular medical care would not change. You would have no penalty for stopping, but it would be better not to join the study if you think that you would change your mind later.

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

Your responsibilities

If you join this study, you will have some responsibilities.

- Follow the schedule of study visits and procedures.
- Take study medications as directed.
- Prevent pregnancy.
- Tell us about side effects.

For more information

If you have questions or concerns about this study, you can talk to your doctor anytime. Other people you could talk to are listed below.

If you have questions about:	**Call:**
This study (including complaints and requests for information)	Armin Rashidi, MD, PhD; 206-667-2506 Liliia Senyshyn; 206-667-5154
If you get sick or hurt in this study	Armin Rashidi, MD, PhD; 206-667-2506
Your rights as a research participant	206-667-5900 or email irodirector@fredhutch.org (Director of Institutional Review Office, Fred Hutchinson Cancer Center)
Your bills and health insurance coverage	206-606-6226 or 800-804-8824

Optional diet survey
Do you agree to complete the optional diet survey? Yes ---- No -----

Signatures

Please sign below if you:

- have read this form (or had it read to you);
- had the opportunity to ask any questions you have;
- had the opportunity to discuss the research with the person obtaining consent; and
- agree to participate in this study.

Participant:

Printed Name	Signature	Date

If you served as an interpreter or impartial witness during the consent process, sign below to indicate you attest to the accuracy of the presentation and the participant's apparent understanding of and willingness to participate in the research.

Impartial Witness or Interpreter:

Printed Name	Signature	Date

Researcher's statement

I have discussed the research study, including procedures and risks, with the person signing above. A copy of the signed consent form will be given to the participant.

Person obtaining consent signature:

Printed Name	Signature	Date

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