Title of Research Study: *A Randomized Placebo-Controlled Clinical Trial of Fecal Microbiota Transplantation in Patients with Acute Myeloid Leukemia and Allogeneic Hematopoietic Cell Transplantation Recipients*
ARM A – Patients With AML

Investigator Team Contact Information: *Armin Rashidi MD, PhD*
For questions about research appointments, the research study, research results, or other concerns, call the study team at:

Investigator Name: Armin Rashidi MD, PhD **Investigator Departmental Affiliation:** Division of Hematology, Oncology and Transplantation **Phone Number:** 612-625-9604 **Email Address:** arashidi@umn.edu	**If you need emergency care:** • Call 911 or go to your nearest emergency room right away. **If you do NOT need emergency care:** • Call or go to your regular doctor. It is important that you tell your regular doctor that you are participating in a research study. If possible, take a copy of this consent form with you when you go.

If your doctor is also the person responsible for this research study, please note that he is interested in both your clinical care and the conduct of this research study. You have the right to discuss this study with another person who is not part of the research team before deciding whether to participate in the research.

Supported By: This research is supported by The National Institute of Health and the Chainbreaker Grant.

Key Information About This Research Study

The following is a short summary to help you decide whether or not to be a part of this research study. More detailed information is listed later on in this form.

What is research?

Doctors and investigators are committed to your care and safety. There are important differences between research and treatment plans:

- The goal of research is to learn new things in order to help groups of people in the future. Investigators learn things by following the same plan with a number of participants, so they do not usually make changes to the plan for individual research participants. You, as an individual, may or may not be helped by volunteering for a research study.
- The goal of clinical care is to help you get better or to improve your quality of life. Doctors can make changes to your clinical care plan as needed.

Research and clinical care are often combined. One purpose of this informed consent document

is to provide you clear information about the specific research activities of this study.

Why am I being asked to take part in this research study?

This protocol is for two different groups of patients – a group with AML (Arm A), and a group receiving stem cell transplants (Arm B). We are asking you to take part in Arm A of this research study because you are planning to undergo chemotherapy for acute myeloid leukemia and will be receiving antibiotics during and after chemotherapy.

What should I know about a research study?

- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

Why is this research being done?

The antibiotics that patients receive during chemotherapy can destroy the helpful bacteria that live in the gut. This change in the gut microbes can increase the risk of infections because harmful bacteria tend to increase as beneficial bacteria disappear. Doctors are researching ways to prevent this destruction, or replace the beneficial bacteria.

This research trial is studying a way to restore the bacteria in your gut with bacteria from a healthy donor. The donor bacteria will be contained in capsules, which will be given to you after your blood counts recover from your chemotherapy. This is called “Fecal Microbiota Transplant,” or “FMT.” The main purpose of this study is to learn how effective FMT is. We will do this by giving patients a capsule to swallow that will contain either the study product (FMT) or a placebo (an identical capsule without any fecal microbiota), and comparing their results. Neither you, nor the study doctors will know which patients are getting FMT and which are getting a placebo.

The FMT capsules contain a small portion of a healthy donor’s feces (stool), mixed with saline and then “freeze dried.”

The study involves an investigational product, the FMT capsule. Investigational means that the drug or device is not approved by the Food and Drug Administration (FDA); however this study is being conducted with the FDA’s permission under an Investigational New Drug (IND) application.

How long will the research last?

We expect that you will be in this research study for up to 10 months. You may receive the FMT treatment or a placebo up to three times within a 3 month period. Depending on how many times you receive the treatment, you may have up to six assessments in the clinic or in the inpatient unit. These assessments will generally take about an hour.

What will I need to do to participate?

You will be asked to take the study drug/placebo up to three times after your chemotherapy and exposure to antibiotics, come to the clinic, or be assessed in the inpatient unit, for up to six study visits, provide blood samples (about 1 tablespoon) 4 times, and provide a stool sample up to 11 times.

More detailed information about the study procedures can be found under ***"What happens if I say yes, I want to be in this research?"***

Is there any way that being in this study could be bad for me?

Although there have been no side effects observed when the FMT capsules were given in previous studies, it is possible that you could feel sick to your stomach or vomit after taking them. This has been uncommon with the previous experience with these capsules. Because your disease treatment suppresses your immune system, there is also a potential risk that you could contract an infection which may cause a fever. This side effect has been very rare.

More detailed information about the risks of this study can be found under ***"What are the risks of this study? Is there any way being in this study could be bad for me? (Detailed Risks)"***

Will being in this study help me in any way?

Being in this study may or may not help you. Our goal is to decrease the risk of infections after chemotherapy. We cannot promise any benefits to others from your taking part in this research. However, possible benefits to others include that we may learn new ways of helping patients recover from chemotherapy.

What happens if I do not want to be in this research?

There are no known alternatives, other than deciding not to participate in this research study.

Detailed Information About This Research Study

The following is more detailed information about this study in addition to the information listed above.

How many people will be studied?

We expect about 144 people here will be in this research study.

What happens if I say "*Yes, I want to be in this research*"?

If you consent to enrolling on this study, then you will be randomly assigned (like the flip of a coin or drawing lots) to one of two groups: the FMT group or the placebo control group. You will have a 2 in 3 chance of being assigned to the FMT group. Both groups will have the same number of assessments and study visits.

<u>Study Product</u>

You will receive your first dose of FMT/placebo treatment in the clinic or the inpatient unit after your blood counts have recovered from your chemotherapy and you have been off antibiotics for 2-4 days. The FMT/placebo will be given as 4-6 capsules. You will only be able to eat or drink clear liquids and take any medications, for 2 hours before and 2 hours after taking the FMT/placebo. If necessary, you are permitted to eat crackers or other light snacks to manage nausea, but do not eat a full meal or a large snack. You also need to remain sitting (or standing) upright for 2 hours after taking the FMT/placebo.

Some patients may receive second and third dose of FMT/placebo. These will occur if:

- It has been 3 months or less since your initial randomization
- You are given additional courses of anti-bacterial antibiotics at the University of Minnesota (or at a location near enough to the University of Minnesota to make it convenient to you to return for additional treatment within 2-4 days after finishing the antibiotics)

Study Assessments

Prior to receiving the FMT/placebo and at specific time points after, you will be assessed in the clinic (or in the inpatient unit if you are in the hospital) to see how you are doing. During these visits you will have a clinical evaluation with a physical. At some of these visits, you will have research samples taken (see below). The timing of these visits will be as follows:

- An initial study assessment, prior to the start of your chemotherapy
- A pre-FMT/placebo assessment will take place after you have had your chemotherapy, but before you are given each FMT/placebo
- 4 weeks after the first FMT/Placebo dose.
- 6 months after your last dose of FMT/placebo. At this visit we will perform a final physical evaluation.

Research Samples

You will be asked to provide a stool sample at the time you enroll on this study, within 7 days prior to each FMT/placebo dose and then you will be asked to mail out samples:

- 10 days and 4 weeks after each FMT/Placebo dose. If you begin a second course of FMT/placebo within 4 weeks after your first dose, then the study visit calendar re-sets and samples will be collected 10 days and 4 weeks after the second dose. The number of total samples you have will depend on how many doses of FMT/placebo you take.

We will collect a final stool sample at your 4 month clinic visit. At most, you will need to provide 11 samples.

You will be asked to provide 4 research blood samples (about 1 tablespoon each):

- at the time you enroll on this study,
- within 7 days prior to the first FMT/placebo dose
- 4 weeks after the first FMT/Placebo dose
- 6 months after last FMT/Placebo dose.

Drug Reaction Diary

At discharge from the clinic you will be provided with a "diary" to be completed once a day for the 7 days after each dose of FMT/Placebo. The diary consists of 5 questions and a place to record your temperature each morning.

Telephone Assessments

A member of the study committee will contact you 1 day, 3 days, and 1 week after each FMT/placebo dose and 9 months after the initial randomization to go over your diary and see how you are doing. If you are already in the hospital or visiting the clinic during any of these times, a member of the study team may check in with you in person, instead of calling you.

What are my responsibilities if I take part in this research?

If you take part in this research, you will be responsible for: making sure that you do not eat anything or drink anything except clear liquids for 2 hours before and 2 hours after the FMT/placebo dose, for coming to your scheduled clinic visits, and mailing stool samples to the lab in the provided kits. You will also be responsible for filling out your diary after each dose of FMT/placebo.

What happens if I say "Yes", but I change my mind later?

You can leave the research study at any time and no one will be upset by your decision.

If you decide to leave the research study, contact the investigator so that the investigator can ensure that you are no longer contacted to schedule study visits. We may ask to perform a final study assessment, if it has been more than two weeks after your last visit.

Choosing not to be in this study or to stop being in this study will not result in any penalty to you or loss of benefit to which you are entitled. This means that your choice not to be in this study will not negatively affect your right to any present or future medical care.

If you stop being in the research, information about you that has already been collected may not be removed from the study database. You will be asked whether the investigator can collect information from your routine medical care, such as your medical records. If you agree, this information will be handled the same as the information obtained for the research study.

What are the risks of being in this study? Is there any way being in this study could be bad for me? (Detailed Risks)

Many treatments can cause unwanted side effects. Although large amount of clinical experience suggests these are very rare, the number of careful controlled studies remains small. We consider the gut microbes to be an integral part of the human body and in addition to the infection risk, we cannot know whether the new microbes will necessarily work well with your individual body physiology:

Risks of the FMT/Placebo

- The FMT/placebo capsules may make you feel sick to your stomach or make you vomit
- You may contract an infection that causes a fever
- Disease could be transmitted from the donor to the person getting the transplant.
- Transmission of microbes that can cause an infection or carry antibiotic resistance genes that can be passed to other microbes and make it difficult to treat infections.
- 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.It is possible that getting a transplant could trigger a gastrointestinal problem.
- It is possible that getting a transplant could trigger a problem with your immune system. Rare side effects include constipation, stomach pain, diarrhea, or belching

Although rare, there is the possibility of long-term side effects (appearing months after you stop taking the medicine) due to a condition called metabolic syndrome that could be transmitted from the donor to the person getting the transplant. Metabolic syndrome increases the risks of developing diseases such as heart disease, obesity, diabetes, pre-diabetes, hypertension, or autoimmune diseases

In addition to these risks, this research may hurt you in ways that are unknown. These might be minor or be severe as to cause death.

To minimize the risks of receiving a transplant, all donors in this study will be thoroughly screened by the study doctor 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 research blood draws:
Taking blood may cause some pain, bleeding or bruising at the spot where the needle enters your body. Rarely, taking blood may cause fainting or infection.

Risk of stool sample collection:
Any stool sample may contain germs that spread disease. It is important to carefully wash your hands and use careful handling techniques to avoid spreading infection.

Some people may feel uncomfortable or embarrassed using the stool collection kit. There should be no pain while collecting the stool sample. However, if you are constipated, straining to pass stool may be painful.

Risks of Randomization:
There are no risks from randomization per se. The risks are all attributable to the risks of the

various treatment assignments. If you are in the group that receives the placebo, you risk not receiving what may be an effective treatment.

Risks associated with breach of confidentiality:
As with any study involving collection of data, there is the possibility of breach of confidentiality of data. Every precaution will be taken to secure participants' personal information to ensure confidentiality.

At the time of participation, each participant will be assigned a study identification number. This number will be used on data collection forms, blood samples, and stool samples. A separate list will be maintained that will links each participant's name to the study identification number for future reference and communication.

What do I need to know about reproductive health and/or sexual activity if I am in this study?

The research may also hurt a pregnancy or fetus in ways that are unknown. These may be a minor inconvenience or may be so severe as to cause death.

You should not be or become pregnant or father a baby and/or breastfeed and/or donate eggs/sperm while on this research study.

If you are sexually active, both men and women should use at least one effective means of birth control while participating in this research study. According to the World Health Organization and the United States Center for Disease Control and Prevention, the most effective forms of birth control include complete abstinence, surgical sterilization (both male and female), intrauterine devices (IUDs), and the contraceptive implant. The next most effective forms of birth control include injectables, oral contraceptive pills, the contraceptive ring, or the contraceptive patch. Acceptable, but least effective, methods of birth control include male condoms (with or without spermicide) and female condoms.

If you or your partner become pregnant while participating in this research study, it is important that you tell the study doctor or other research team member immediately. You might be required to stop participation in this study; however, other clinical care options will be discussed with you at that time if necessary.

If you or your partner [are/is] considered to be postmenopausal, you are not required to use contraception while participating in this research study. Postmenopausal women rarely become pregnant. If you or your partner become pregnant while participating in this research, it is important that you tell the study doctor or other research team member immediately. You may be required to stop participation in this study; however, other clinical care options will be discussed with you at that time if necessary.

Will it cost me anything to participate in this research study?

The FMT/placebo will be provided by the study and all research samples and research study visits will be paid for by study funds.

You and your insurance company will be charged for the health care services that you would ordinarily be responsible to pay. In some cases, insurance will not pay for services ordinarily covered because these services are performed in a research study. You should check with your insurance to see what services will be covered by your insurance and what you will be responsible to pay.

What happens to the information collected for the research?

Efforts will be made to limit the use and disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete confidentiality. Organizations that may inspect and copy your information include the Institutional Review Board (IRB), the committee that provides ethical and regulatory oversight of research, and other representatives of this institution, including those that have responsibilities for monitoring or ensuring compliance.

- The University of Minnesota, and the study team, research staff and medical staff.
- Any person who provides services or oversight responsibilities in connection with this study.
- Every member of the University of Minnesota workforce who provides services in connection with this study.
- Any laboratories, individuals, and organizations that use your health information in connection with this study.
- Any federal, state, or local governmental agency that regulates the study (such as the U.S. Food and Drug Administration (FDA), the U.S. Department of Health & Human Services (DHHS), and the Office for Human Research Protections (OHRP)).
- Other government agencies in this or other countries.
- The designated Protocol Review and Monitoring Committees, Institutional Review Boards such as the University of Minnesota IRB, Privacy Boards, Data and Safety Monitoring Board and their related staff that have oversight responsibilities for this study.
- The Masonic Cancer Center at the University of Minnesota and/or their designee

If you decide to participate in this study, some private health information about you will be stored in a computer database at the University of Minnesota Masonic Cancer Center. This information will include your name and medical record number, date of birth, diagnosis, race/ethnicity, and information about your participation in this study. The purpose of storing this information is to assist the Cancer Center in creating reports about research and in making sure that research studies are being done correctly. Your information will not be used for any other purpose. There are no plans to erase information from the database. It will be stored indefinitely at the Masonic Cancer Center.

The sponsor, monitors, auditors, the IRB, the University of Minnesota Research Compliance Office and other University compliance units, the US Office of Research Integrity (ORI), the US Office for the Protection of Human Research Protections (OHRP), the US Food and Drug Administration (FDA) may be granted direct access to your medical records to conduct and oversee the research. By signing this document you are authorizing this access. We may publish

the results of this research. However, we will keep your name and other identifying information confidential.

A description of this clinical trial will be available at 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.

Data or Specimens Collected
Leftover samples will be stored in labs at the University of Minnesota for future analysis. These stored specimens will be labelled only with a bar code and not contain any information that would make it possible to identify you. These samples may be stored for up to ten years.

If identifiers are removed from your identifiable private information or identifiable samples that are collected during this research, that information or those samples could be used for future research studies or distributed to another investigator for future research studies without your additional informed consent.

Your information and samples (both identifiable and de-identified) may be used to create products or to deliver services, including some that may be sold and/or make money for others. If this happens, there are no plans to tell you, or to pay you, or to give any compensation to you or your family.

Genetic Information
A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Will I receive research test results?
Most tests done on samples in research studies are only for research and have no clear meaning for health care. The investigator(s) will not contact you or share your individual test results.

Whom do I contact if I have questions, concerns or feedback about my experience?
This research has been reviewed and approved by an IRB within the Human Research Protections

Program (HRPP). To share feedback privately with the HRPP about your research experience, call the Research Participants' Advocate Line at 612-625-1650 or go to https://research.umn.edu/units/hrpp/research-participants/questions-concerns. You are encouraged to contact the HRPP if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

Will I have a chance to provide feedback after the study is over?

The HRPP may ask you to complete a survey that asks about your experience as a research participant. You do not have to complete the survey if you do not want to. If you do choose to complete the survey, your responses will be anonymous.

If you are not asked to complete a survey, but you would like to share feedback, please contact the study team or the HRPP. See the "Investigator Contact Information" of this form for study team contact information and "Whom do I contact if I have questions, concerns or feedback about my experience?" of this form for HRPP contact information.

Can I be removed from the research?

The person in charge of the research study or the sponsor can remove you from the research study without your approval. Possible reasons for removal include

- If the study doctor believes, for any reason, that it is in your best interest.
- If you develop side effects that the study doctor considers unacceptable.
- If you refuse to take the study drug or return for follow-up as recommended by your study doctor, or do not follow the study doctor's instructions.
- If you refuse to have tests that are needed to determine whether the study drug is safe and effective.
- If other causes prevent you from continuing in this study.

We will tell you about any new information that may affect your health, welfare, or choice to stay in the research.

What happens if I am injured while participating in this research?

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to you or your insurance company. If you think that you have suffered a research related injury let the study physicians know right away.

Use of Identifiable Health Information

We are committed to respect your privacy and to keep your personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal

health information that includes health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number or social security number. Those persons who get your health information may not be required by Federal privacy laws (such as the 1099 Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission. Please read the HIPAA Authorization form that we have provided and discussed.

The results of this study may also be used for teaching, publications, or for presentation at scientific meetings.

Optional Elements:

The following research activities are optional, meaning that you do not have to agree to them in order to participate in the research study. Please indicate your willingness to participate in these optional activities by placing your initials next to each activity.

Yes, I agree	**No, I disagree**	
_____	_____	The investigator may retain any leftover blood or tissue samples taken during the study. These samples may be used for other research not related to this study. These samples will be retained in non-identifiable form, meaning that there will be no information associated with the blood or samples that will allow anyone to readily ascertain my identity.

Your written or electronic signature documents your permission to take part in this research. You will be provided a copy of this signed document.

_____ _____
Signature of Participant Date

_____
Printed Name of Participant

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Person Obtaining Consent

Signature Block for Witness:

WITNESS STATEMENT:
The participant was unable to read or sign this consent form because of the following reason:

☐ The participant is illiterate

☐ The participant is visually impaired

☐ The participant is physically unable to sign the consent form. Please describe:

_____

☐ Other *(please specify)*:

_____

My signature below documents that the information in the consent document and any other written and information was accurately explained to, and apparently understood by, the participant, and that consent was freely given by the participant.

_____ _____
Signature of Witness to Consent Process Date

_____
Printed Name of Person Witnessing Consent Process