Masonic Cancer Center
University of Minnesota

A Randomized Placebo-Controlled Clinical Trial of Fecal Microbiota Transplantation in Patients with Acute Myeloid Leukemia and Allogeneic Hematopoietic Cell Transplantation Recipients

2017LS170
MT2018-01
IND# 18607

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Version Date:
March 16, 2022

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Revision History

Revision #	Version Date	Summary of Changes	Consent Change
n/a	08/06/2018	Original submission to CPRC	n/a
1	09/17/2018	Removed MMF PKs from study; Increased accrual goal to 72 patients per arm; Updated stopping rules; Updated to note that the study will use a REDCap database; added details on procedures for patients withdrawing from study; added guidance on patients unable to receive additional study drug doses; updated sample procurement and processing; minor edits for clarity	n/a
1A	11/29/2018	Per FDA request: updated exclusion criteria, safety follow-up, and monitoring; added patient drug reaction diary.	Yes
2	2/11/2019	Following study start up meeting: clarified eligibility procedures; expanded window for subsequent treatments; simplified drug administration procedures; removed research blood draws; deleted clinical visits; updated AE reporting procedures, added to ad hoc DSMC reporting procedures Per FDA request: added concomitant medications to patient diary Administrative changes: Updated to use Oncore database alone (removed REDcap) and blood to be stored in the TTL lab; added IND number to cover page; updated co-investigator list	Yes
2A	04/19/2019	Updated event monitoring per FDA request	No
3	04/26/2019	Table 8.1 Removed KPS score as this it is not done standard of care; changed 4 month visit to 4 week visit Table 8.2 Simplified table format, removed specification of tube size for bloods; moved 4 month research blood draw to 6 months, deleted clinic visit at 4 month Section 12 – added details about the make-up and procedures of DSMC Removed Appendix III – Karnofsky scale Throughout – minor edits for clarity and spelling; clarification of Oncore forms used	Yes
4	07/25/2019	Section 5.2, 7.1.2,6.1, 6.3, Appendix I and II – patients will be permitted to co-enroll on other research studies Section 6.2 – Removed reference to biostatistician performing randomization Section 7.2 – Updated study drug administration guidelines to allow for patients consuming medications and light snacks within 2 hours prior to and post FMT/Placebo administration Sections 7.2, 9.1.2, 9.1.3 – Clarified that study product will be prepared and administered by trained study staff Sections 8.1, 8.2, 11.2, 13.2, schema – Clarified that procedures will occur 9 months after randomization Sections 8.2, 10.2 – Removed references that specified method of stool sample collection Section 11.5 – updated reporting to IRB Ethos system Throughout protocol – minor edits for punctuation	Yes

5	09/18/2019	Schema, Section 8.2 – reduced amount of blood collected; combined week 1 & week 2 stool sample collections into a single collection at day 10 Synopsis, Secondary Objectives, Endpoints – revised first secondary objective/endpoint to clarify time frame of engraftment	Yes
6	11/06/2019	Study design, inclusion criteria, eligibility checklist: clarified eligibility on Arm A to include any patients receiving chemotherapy Fixed typo in flow chart	Yes (AML consent only)
7	01/15/2020	Section 4 –clarification that patients will not be enrolled more than once on the same protocol Section 5.2, Section 6.3, Section 6.4, Section 7, Appendix I, Appendix II – minor clarifications to pre-treatment eligibility criteria; added allowance for patients to receive antibiotics for Pneumocystis carinii prophylaxis Section 8.1 – footnote clarification Section 8.2 – Added GVHD evaluation; updated footnote to allow for more frequent patient contact Section 11.1 – removed adverse events related to underlying disease process from definition of reportable events	No
8	07/07/2020	Section 5.1, Section 6, Section 6.1, Section 12.6, and Section 15.3 - Updated consenting procedures to allow for remote consenting.	Yes
8A	7/27/2020	Section 5.1, Section 12.6, and Section 15.3 – Per IRB request, clarified documentation for remote consent.	Yes
9	11/11/2020	Section 8.2 Edited the window around research related sample collection Seciton 11.5, Section 12.3, Section 14.5 Added additional medical monitor to the trial to review stopping rule events.	No
10	05/07/2021	Section 8.2 research blood sample amount reduced to 6 mL	Yes
11	09/22/2021	Section 8.2 and Section 11.2 Simplified follow-up, removing monthly updates regarding the following potential findings: weight gain, or new diagnosis of pre-diabetes, diabetes, hypertension, obesity, or autoimmune conditions	Yes
12	3/16/2022	Change in Primary Principal Investigator/IND Sponsor	Yes

IND Sponsor/Principal Investigator Contact Information:

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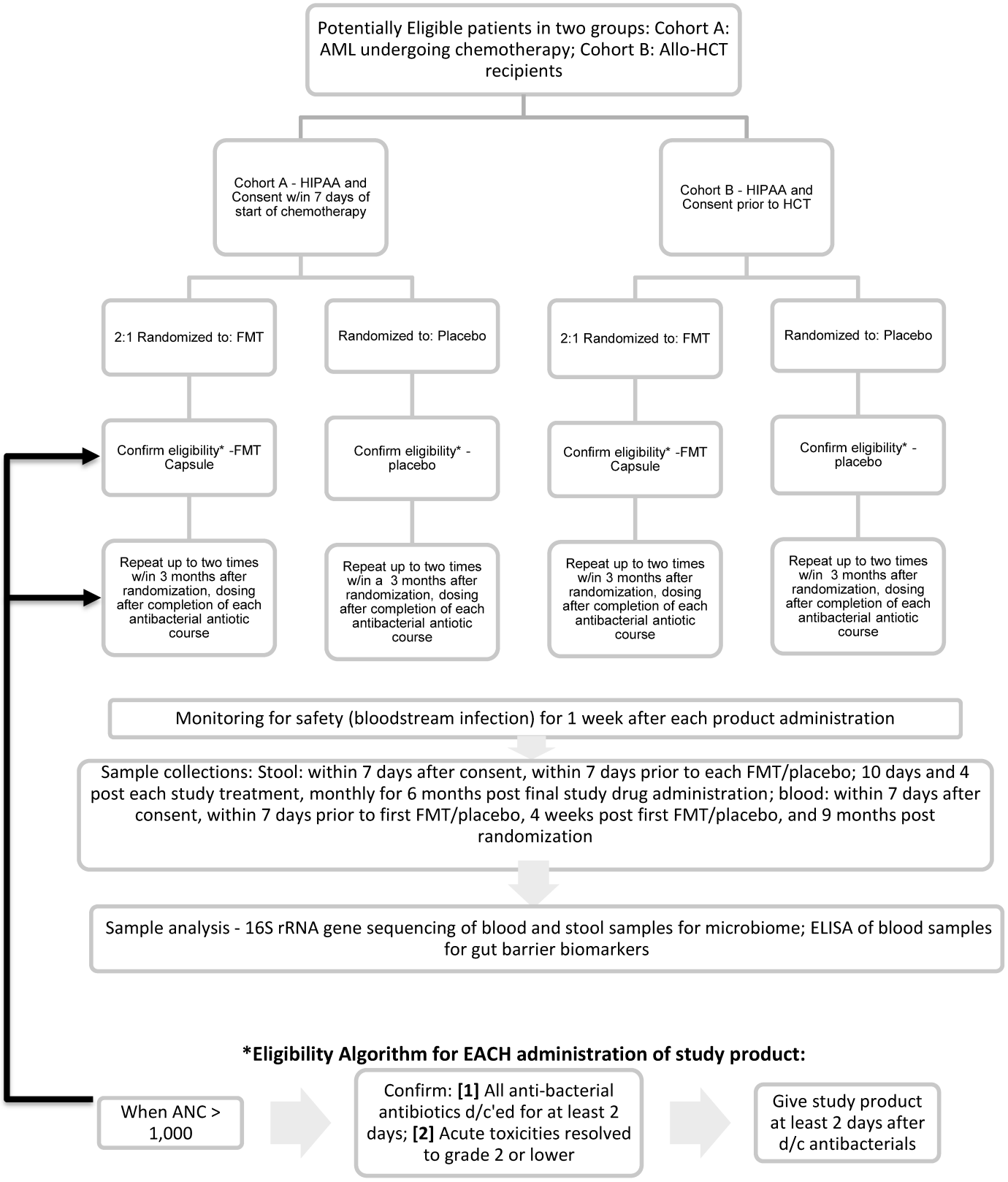
ABBREVIATIONS

AE	Adverse Event
ALL	Acute Lymphoblastic Leukemia
Allo-HCT	Allogeneic Hematopoietic Stem Cell Transplant
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
CBC/diff	Complete Blood Count With Differential
C. Diff	*Clostridium difficile* Infection
CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DMSO	Dimethyl Sulfoxide
DSMP	Data & Safety Monitoring Plan
DNA	Deoxyribonucleic acid
FDA	Food and Drug Administration
FMT	Fecal Microbiota Transplant
GVHD	Graft versus Host Disease
IND	Investigational New Drug
MCT	Molecular and Cellular Therapeutics facility
IRB	Institutional Review Board
PBMC	Peripheral Blood Mononuclear Cells
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TTL	Translational Therapy Lab
UPIRTSO	Unanticipated Problems Involving Risks to Subjects or Others

Protocol Synopsis

Study Design:	This is a randomized, double-blind, placebo-controlled clinical trial of Fecal Microbiota Transplant (FMT) in 2 independent cohorts (72 acute myeloid leukemia patients undergoing chemotherapy and 72 Allo-HCT patients). Participants in each cohort will be randomized in a 2:1 ratio to receive up to 3 treatments of FMT vs. placebo after each exposure to antibacterial antibiotics until 3 months after randomization. The primary endpoint is 4-month all-cause, clinically defined infection rate. Interim safety analysis will be performed.
Primary Objective:	To demonstrate the efficacy of FMT in acute myeloid leukemia patients and stem cell transplant recipients, as measured by the number of all infections within 4 months after the first study drug administration.
Secondary Objectives:	• To determine FMT engraftment rate at 10 days and 4 weeks post-FMT • In the Allo-HCT cohort, determine the cumulative incidence of acute grade II-IV GVHD until day 180 post-HCT • In both cohorts, determine the incidence of bloodstream infection (BSI) until 1 week after each FMT • In both cohorts, determine the number of bacterial, viral, and fungal infections within 4 months after the first study drug administration.
Inclusion Criteria:	• Age≥ 18 years • Acute myeloid leukemia (AML) undergoing chemotherapy, or patients undergoing Allo-HCT • For each study treatment: ANC > 1,000, resolution of all acute toxicities to grade 2 or lower, and at least 2 days post discontinuation of all antibacterial antibiotics
Exclusion Criteria:	• Planned continuation of antibacterial antibiotics after the first neutrophil recovery (ANC > 1,000) • Subjects with severe food allergies • Subjects with a history of chronic aspiration
Accrual Goal	72 subjects in each cohort over 2 years

Protocol Schema



Objectives

1.1 Primary Objective

To demonstrate the efficacy of FMT in AML patients and allo-HCT recipients, as measured by the number of all infections within 4 months after the first study drug administration.

1.2 Secondary Objectives

- To determine FMT engraftment rate at 10 days and 4 weeks post-FMT
- In the Allo-HCT cohort, determine the incidence of acute grade II-IV GVHD until day 180 post-HCT
- In both cohorts, determine the incidence of BSI until 1 week after each FMT
- In both cohorts, determine the number of bacterial, viral, and fungal infections within 4 months after the first study drug administration.

1.3 Correlative Objectives

- To determine the effect of FMT on biomarkers of gut barrier integrity

2 Background

Perturbations in gut microbiota ecology and homeostasis play an important role in pathogenesis of various disease states [1] [2]. This includes stem cell transplant complications such as acute GVHD [3] [4] [5] and bloodstream infections in patients receiving intensive chemotherapy [6] [7]. Disruptions of the gut barrier as a result of cytotoxic chemotherapy and/or radiation in the setting of anti-leukemic treatment or transplant preparative regimen exposes the host to the gut microbiota in a dysregulated fashion. In addition, routine use of prophylactic and therapeutic antibiotics in these patients leads to microbiota injury manifested as a reduction in beneficial bacteria (e.g., Clostridia) and dominance of a few pathogenic bacteria (e.g., Enterococci) [8]. Collectively, these changes result in pathologic cytokine release, deregulation of local and systemic immune responses (i.e., the underlying event in acute GVHD), and bloodstream infection.

Microbiota restoration is an active field of research with the overarching goal of preventing disease states associated with dysbiosis. One promising such approach is fecal microbiota transplantation (FMT) from healthy donors. The safety of this approach is becoming apparent even in immunosuppressed patients. The best example is FMT in allo-HCT patients to treat steroid-refractory acute GVHD and correct dysbiosis after engraftment, now reported from 2 independent groups [9] [10]. Stem cell transplant patients, particularly those with acute GVHD, represent one of the most severely immunocompromised patients and the demonstrated safety of FMT in these patients has made this approach a popular therapeutic strategy in less immunosuppressed patient populations.

Our primary goal in the present study is to demonstrate the efficacy of our FMT product in allo-HCT and AML patients upon count recovery. These patients are at risk of dysbiosis-related complications such as BSI and GVHD. The freeze-fried encapsulated preparation of fecal microbiota was originally developed as a treatment option for patients suffering with the recurrent *C. diff.* infection who have failed multiple attempts to cure the infection with antibiotics alone [11]. Overall, 43/49 (88%) of patients achieved a clinical success, defined as no recurrence of CDI over 2 months. Analysis of the fecal microbiome demonstrated near normalization of the fecal microbial community by 1 month following FMT treatment.

3 Summary and Rationale

The adverse effect of dysbiosis in various disease states has been well established. Dysbiosis is very common and particularly problematic in the setting of curative treatments for hematologic malignancies, partly due to the routine use of antibiotics. Dysbiosis increases complications of cancer treatment such as BSI, GVHD, and *C. difficile* infection. FMT is a promising approach to restore the normal composition and diversity of microbiome, and may improve outcomes of chemotherapy in patients at high risk for complications.

4 Study Design

This is a randomized, double-blind, placebo-controlled clinical trial of Fecal Microbiota Transplant (FMT) procedure in 2 independent cohorts (72 Acute Myeloid Leukemia (AML) patients undergoing chemotherapy and 72 Allo-HCT patients). Participants in each cohort will be randomized in a 2:1 ratio to receive up to 3 treatments of FMT vs. placebo after each exposure to antibacterial antibiotics until 3 months after randomization. Patients will not be enrolled more than once on this protocol. The primary endpoint is the number of all infections within 4 months after the first study drug administration. Interim safety analysis will be performed.

5 Patient Selection

Study entry is open to adult patients regardless of gender or ethnic background. While there will be every effort to seek out and include women and minority patients, the patient population is expected to be no different than that of other leukemia and HCT studies at the University of Minnesota.

5.1 Inclusion Criteria

- Age≥ 18 years
- Cohort A: Patients undergoing chemotherapy for acute myeloid leukemia (AML; newly diagnosed or relapsed/refractory)
- Cohort B: Allo-HCT patients

  - Any T-replete allogeneic transplant regimen
- Sexually active females of childbearing potential and males with partners of child-bearing potential must agree to use adequate birth control until at least six months post-FMT/placebo
- Voluntary in-person written consent; or, remote consent via phone or electronic system. Remote consent will be documented with wet ink signature or e-signature using a 21 CFR Part 11 compliant system such as REDcap before performance of any study-related procedure not part of normal medical care.

5.2 Exclusion Criteria

- Planned continuation of antibacterial antibiotics (with the exception of antibiotics used for Pneumocystis carinii prophylaxis) after the first neutrophil recovery (ANC > 1,000)
- Subjects with severe food allergies
- Subjects with a history of chronic aspiration
- Pregnant or breast feeding. The FDA has not classified this agent into a specified pregnancy category. Females of childbearing potential must have a blood test or urine study within 14 days prior to registration to rule out pregnancy

6 Patient Registration

Registration will occur after the patient has consented and eligibility is confirmed, but before any treatment has been administered. To be eligible for registration to this study, the patient must meet each criteria listed on the eligibility checklist (found in appendix I) based on the eligibility assessment documented in the patient's medical record.

6.1 Study Enrollment

Upon completion of the screening evaluation, eligibility confirmation and obtaining either written, telephone, or electronic consent, the Study Coordinator or designee will enroll the patient on study in OnCore system. Co-enrollment on other studies is permitted.

6.2 Randomization

Patients will be randomized on a 2:1 ratio of FMT versus placebo in OnCore to complete enrollment.

6.3 Timing of initial study treatment

Patients will be consented before or within 7 days of starting chemotherapy [Cohort A] or before transplant Day 0 [Cohort B]. Patients will receive initial study treatment (FMT/placebo) either inpatient or outpatient, once their ANC count is greater than 1000. Additionally, if all antibacterial antibiotics have been discontinued (with the exception of antibiotics used for Pneumocystis carinii prophylaxis) for at least 2 days and all acute

toxicities have resolved to grade 2 or lower, study therapy will begin within 7 days after discontinuation of antibacterial antibiotics. To receive the study therapy, treatment eligibility will be confirmed based on the eligibility assessment (outlined in section 7.1 below and in appendix II) and documented in the patient's medical record. Patients will be permitted to co-enroll on other studies.

6.4 Timing of Additional Study Treatments

If patients are retreated with antibacterial antibiotics within the 3 month period after randomization, they may repeat FMT/placebo, up to two additional times, for a total of three treatments. Repeat FMT/placebo will begin after completion of each antibacterial antibiotic course, once the patient's ANC count is greater than 1000, antibacterial agents (with the exception of antibiotics used for Pneumocystis carinii prophylaxis) have been discontinued for at least 2 days, and all acute toxicities have resolved to grade 2 or lower. Treatment eligibility must be reconfirmed (using the eligibility assessment in appendix II) before each additional study treatment and documented in the patient's medical record.

6.5 Missed Additional Study Treatments

If patients who receive additional antibacterial antibiotics are unable to receive an additional study treatment for the following reasons:

- They are travelling and unable to return to the University of Minnesota clinic in the permitted study window.
- They receive additional antibacterial antibiotics at their home provider clinic and are unable to return to the University of Minnesota clinic in the permitted study window
- Additional special prohibitive circumstances are present and discussed with the PI

the study treatment will be considered skipped, but not a deviation, and patients will continue to be followed on study. Patients will be eligible for additional treatments within the 3 month period after randomization.

If patients are unwilling to receive additional study treatments, they will be removed from the study, no further labs will be drawn, and no further samples will be collected.

Further details on study removal are shown in section 7.5.

6.6 Patients Who Do Not Begin Study Treatment

If a patient is registered to the study, and is later found not able to begin the study treatment, for any reason, the patient will be taken off study. The Study Coordinator or designee will update OnCore of the patient's non-treatment status. The patient will be replaced to fulfill enrollment requirements.

7 Treatment Plan

In order to provide optimal patient care and to account for individual medical conditions, investigator's or treating physician's discretion may be used in the prescribing of all supportive care drug therapy (i.e. acetaminophen, diphenhydramine, etc.).

Each FMT treatment will consist of ~5.0 x 10^{11} bacteria divided in 4-6 capsules given either inpatient or outpatient. Trehalose-containing capsules (excipient alone) will be used as placebo. The following administration criteria need to be met:

7.1 FMT/Placebo Administration Criteria

In instances where meeting the criteria for a specific subject is equivocal, the treating clinician and PI will collaborate to make a determination. This consultation should be documented.

For each study treatment administration, FMT/placebo capsules shall be administered if the following criteria are met:

7.1.1 Inclusion Criteria

- Neutrophil recovery: ANC > 1,000, checked within the last 7 days
- All anti-bacterial antibiotics have been discontinued for at least 2 days. (excluding antibiotics used for Pneumocystis carinii prophylaxis)
- Acute toxicities have resolved to grade 2 or lower
- Negative pregnancy test result for females of child bearing potential

7.1.2 Exclusion Criteria

- Unable to swallow capsules
- Disease has relapsed/progressed after original consent
- Active infection
- [Cohort B] GVHD on treatment

Participants who are not eligible to receive the first dose of study product will be taken off study and replaced.

7.2 Study Drug Administration

The oral capsules of FMT/placebo will be administered to patients directly by trained clinical research staff. The protocol for capsule FMT/placebo administration includes:

1) Only clear liquids, medications, or light snacks by mouth for at least 2 hours prior and 2 hours after FMT/placebo. Crackers or other light snacks to manage nausea or other side effects are permitted.

2) Swallow capsules with at least one glass of plain tap water.
3) Remain upright for 2 hours after the capsule administration.

Patients will be monitored for 15 minutes after taking the first FMT/Placebo. They will be given a study drug reaction diary to log side effects every day for one-week post FMT/placebo dose.

In addition, a member of the study team will contact the patients by telephone 1, 3 (+/-1), and 7 (+/- 3) days after each FMT/placebo administration to monitor for adverse events (AEs) to include: fever, abdominal pain, diarrhea, constipation, and bloating

7.3 Management of Selected Expected Toxicities

1) Fever within 7 days after FMT/placebo: Patients with fever will be evaluated in the emergency room or in clinic same day. Standard institutional algorithms for treatment fever in immunosuppressed patients will be applied.
2) Vomiting within 8 hours after FMT/placebo: This will be treated similar to nausea and vomiting for other reasons, using medications such as ondansetron or prochlorperazine. If not controlled by these measures, the patient will be referred to the emergency room.

7.4 Duration of Treatment

The FMT/placebo capsule will be administered orally up to 3 total times within the 3 month period after randomization either inpatient or outpatient. Patients may receive additional treatments (#2 - #3) after each new course of antibacterial antibiotics. Each administration will occur at the time of neutrophil recovery (ANC > 1000) as long as antibacterial antibiotics (with the exception of antibiotics used for Pneumocystis carinii prophylaxis) have been discontinued for at least 2 days and all acute toxicities have resolved to grade 2 or lower.

7.5 Duration of Study Participation

Evaluable patients will be followed for 9 months after randomization unless:

- Consent is withdrawn
- Routine treatment follow-up is discontinued due to failing health, re-transplant, or other reason
- Patients who fail to comply with receiving additional FMT/placebo after antibacterial antibiotics.
- The treating physician decides at some point that ongoing participation is not in the patient's best interest

In these cases, patients will be followed for toxicity, but will not have study samples obtained.

8 Schedule of Patient Activities

8.1 Required Clinical Care Activities

Below are standard of care evaluations which are performed as part of the parent protocols. Results of these evaluations will be extracted from the BMT Database.

		Administration 1-3		
Activity	Initial Assessment*	Pre FMT/placebo Assessment (w/in 7 days)	¥4 weeks post first FMT /placebo (+/- 7 days)	9 months after randomization (+/- 14 days)
Clinical evaluation	X	X	X	X
Weight	X		X	X
Medical history	X	X	X	X
Physical exam and vital signs	X	X	X	X
Medications	X	X	X	X
Disease relapse**		X		
Adverse events assessment		X	X	X

¥ Activities are from the time of the most recent FMT/placebo administration. If the patient receives additional FMT/placebo administration, the clock will "restart"

*Prior to consenting

**No procedures will be done to determine remission/relapse status for this study *per se*. However, if the existing information shows relapse, the patient will not receive further treatment and further samples will not be collected.

8.2 Research Related

			Administration 1-3[¥]					
	Prior to Treatment (chemotherapy or HCT)	When ANC > 1000	[¥]1 day, and 3 (+/- 1 day) days post FMT/placebo	[¥]1 week post FMT /placebo (+/- 3 days)	[¥]10 days FMT /placebo (+/- 3 days)	[¥]4 weeks post FMT /placebo (+/- 3 days)		9 months after randomization (+/- 14 days)
Consent	X (by day 7 of chemotherapy or before day 0 of transplant)							
Eligibility Screening	X (by day 7 of chemotherapy or before day 0 of transplant)	X						
Randomize to FMT or Placebo	X (within 3 days after consent)							
FMT/placebo		X						
Serum pregnancy test	X	X						
Stool Sample **	X (by day 7 of chemotherapy or before day 0 of transplant)	X (at count recovery within 7 days of ANC>1000)			X	X		X
Serum Sample **10 ml of serum** (red top tube)	X (by day 7 of chemotherapy or before day 0 of transplant)	X (at count recovery within 7 days of ANC>1000) [ff]				X[µ]		X
Blood: 6 mL (yellow-top tubes)	X (by day 7 of chemotherapy or before day 0 of transplant)	X (at count recovery within 7 days of ANC>1000) [ff]				X[µ]		X
GVHD Assessment								X
Research staff may review toxicities/drug diary with patients either at SOC visits or via telephone as per most current COVID-19 guidelines [£]			X[ß]	X[ß]		X[€]		X[€]

¥ Samples are from the time of the most recent FMT/placebo administration. If the patient receives additional FMT/placebo administration, the clock for stool, but not blood/serum, collection will “restart”

** Sample will be collected only if patient has a bowel movement. Missed samples will not be considered a deviation.

ß Study staff will review drug reaction diary with patient. If a subject reports an adverse event that warrants further investigation, an unscheduled clinic visit will be initiated.

€ Patients will be asked whether or not they have gained weight or been newly diagnosed with conditions such as pre-diabetes, diabetes, hypertension, obesity, or autoimmune conditions

ff Prior to first FMT/placebo only

µ Only after study drug administration #1, whether or not clock has reset for other study procedures

£ Telephone calls may be more frequent if clinically indicated

Research sample collection is tied to the clinical care schedule of events and their associated window for performance. Therefore, if a clinical time point does not occur or is altered, the research related time point will be adjusted (or eliminated) as appropriate. It is recognized that with novel therapies as used in this study, the timing of protocol directed research samples may miss important patient specific events. For this reason, up to 3 extra samples for a total of 180 ml of blood may be drawn at additional time points that are not specified above.

9 Study Drug Information

Single donor lots of minimally manipulated microbial material in lyophilized form, derived from human feces will be provided by the Molecular and Cellular Therapeutics (MCT) facility at the University of Minnesota.

9.1 Fecal Microbiota - lyophilized

Dosage form: capsules for oral administration
Concentration or strength: ~1.0 x 10^{11} per capsule
Total dosage: ~5 capsules
Single-use or multiuse container: Single Use
Manufacturer information: UMN Microbiota Therapeutics Program. FMT capsules will be manufactured at the Molecular and Cellular Therapeutics, University of Minnesota, 1900 Fitch Avenue, St. Paul, MN 55108

The following elements apply:

9.1.1 Accountability

UMN Microbiota Therapeutics Program, the manufacturer, will maintain product records for the manufacturing process through delivery of the product to the sponsor-investigator. The Molecular and Cellular Therapeutics facility will maintain product accountability records from receipt through dispensing the product to the sponsor-investigator. The sponsor-investigator will record administration of the product to each subject.

9.1.2 Handling

Qualified personnel, familiar with aseptic technique and procedures that ensure the quality of the agent and minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and, when applicable, safe disposal of the agent. The encapsulated lyophilized product will be administered directly to patients for oral use by trained staff.

9.1.3 Ordering

UMN Microbiota Therapeutics Program will deliver the lyophilized fecal microbiota preparation to the trained study staff for administration to the subject.

9.1.4 Destruction and Return

Unused agent will be disposed of according to approved institutional standard of practice.

9.2 Fecal Microbiota - lyophilized

9.2.1 Description

The lyophilized product is manufactured by diluting the fecal slurry to 2.9-8.6 x 10^{10} microbes per milliliter with sterile phosphate buffered saline (PBS) and amended with a sterile trehalose solution to a final concentration of 10%. A 35ml aliquot of the suspension is distributed to a stainless steel tray and lyophilized. The lyophilized powder is manually filled into capsules, which are stored with a dessicant at -60°to -80°C in a mechanical freezer. The single dose is defined as 5 x 10^{11} bacteria in variable number of capsules (typically 4-6).

9.2.2 Toxicology

Thus far, the capsule FMT product has been used exclusively in patients with multiply recurrent C. difficile infection who have failed to cure the infection with antibiotics alone. No adverse events attributable to the product were noted in the initial published experience with 49 patients [11]. This experience has since been extended to 108 patients with no adverse events attributable to the product.

9.2.3 Supplier

The microbiota capsules and placebo are manufactured by the Microbiota Therapeutics Program in accordance with IND 15071 (Sponsor-Investigator is Khoruts). The manufacturing is done in accordance with cGMP protocols in the Molecular and Cellular Therapeutics (MCT) building on the St. Paul campus. The capsules are kept in MCT until they are released to Dr. Khoruts in accordance with release criteria. Following release the capsules are kept at -80oC in Dr. Khoruts' Lab freezer in the Wallin Medical Biosciences Building.

9.2.4 Storage and stability

Lyophilized preparations will be stored in a desiccated condition at -60°to -80°C in a mechanical freezer.

Stability testing, described in the updated IND 15071, includes microbial cell membrane integrity that shows no loss of cell viability various temperatures up to 6 months. The data includes testing at room temperature for 4 days, which suggests no loss of activity is anticipated when the product is taken out of storage and brought into clinic. In vivo stability testing was done by clinical potency of the product in curing C. difficile infection over at least one year.

9.2.5 Handling, Ordering, Accountability, Destruction and Return.

See section 9.1.

9.3 Placebo

The placebo (Trehalose-containing capsules) will be provided by the University of Minnesota Microbiota Therapeutics Program. The placebo capsules are manufactured by the Microbiota Therapeutics Program in accordance with IND 15071 (Sponsor-Investigator is Khoruts). The manufacturing is done in the Molecular and Cellular Therapeutics (MCT) building on the St. Paul campus. The capsules are kept in MCT until they are released to Dr. Khoruts in accordance with release criteria. Following release the capsules are kept at -80oC in Dr. Khoruts' Lab freezer in the Wallin Medical Biosciences Building.

10 Correlative/Special Studies

10.1 Specimen Collection and Transport To Processing Laboratory

All participants will undergo stool and blood sample collection for microbiota-related studies (bacterial DNA sequencing of stool/serum, ELISA of serum for citrulline/LPS/I-BABP/I-FABP/Flagellin, patient's germline genetic variants in PBMCs relevant to gut barrier) at the schedule indicated in the Study Activity Calendar (Section 8). Samples will be collected in the inpatient setting until the patients are discharged from the hospital. Stool samples after discharge from the hospital will be collected at home and either brought to clinic or mailed to the lab. Note, for patients co-enrolled on biospecimen collection trials, such as MT2017-12, this trial will have priority on specimens if the sample collection dates overlap.

10.2 Initial specimen processing, storage, and shipping

PBMC and serum samples will be stored frozen in the Translational Therapy Lab ("TTL"). Stool samples will be stored in Dr. Staley's lab, in a -80^0 freezer. The samples will be stored for further analyses until no longer needed up to a maximum of 10 years from the study's end. Samples will be de-identified and labelled with a bar code.

While participants are hospitalized, stool specimens are collected by the bedside nurse, similar to how stool specimens would be collected for diagnostic purposes. For outpatient collections, each participant is given an instruction sheet with pictures demonstrating simple but proper technique to collect samples at home. Participants are provided with sample collection kits and optional specimen pans. The participants mail their samples to the laboratory (cost covered by study) or store them in their home freezer and bring them to the clinic at the time of their next visit. Research stool samples are collected only at the time of bowel movement and no laxatives will be used to facilitate bowel movements. The

participants will record the time and date of collection. Stool samples will then be kept in patient's own freezer until they bring the samples to clinic in a provided cooler or picked up by one for the study coordinators. A patient has the right to withdraw consent at any time by informing a member of the study staff, their treating physician, or by following the instructions provided in the HIPAA document. If this occurs, any remaining identifiable research sample(s) will be destroyed and no further clinical data will be collected from the medical records for this study.

Samples will be labeled with a Sample ID that can be linked back to the subject, study timepoint, and date of collection. Receipt of all samples will be verified by a clinical research associate and/or a clinical research nurse. All received, processed, and stored stool samples will be logged into the repository database maintained by Dr. Staley's lab. All received, processed, and stored blood samples will be logged into the Freezerworks™ database maintained by TTL.

10.3 Analytical Method

After DNA extraction, stool samples will undergo 16S rRNA amplicon sequencing of the V4 region at the University of Minnesota Genomics Center on Illumina MiSeq lane, followed by taxonomic annotation by Dr. Staley (Department of Surgery). Samples will be processed and annotated using mothur software, and taxonomic classifications will be made based on the Ribosomal Database Project [12]. Microbiota engraftment will be determined using SourceTracker software [13], as described previously [14] [15]. This software uses a Bayesian modeling approach to describe the percent of microbial community similarity in patient samples to those of the donor sample based on the presence and distribution of shared taxa. PBMCs will be sequenced using PCR probes targeted for genetic polymorphisms of interest (e.g., haptoglobin) at the University of Minnesota Genomics Center. Serum will be analyzed for biomarkers of gut barrier integrity, function, and inflammation (e.g., LPS, flagellin, citrulline, I-FABP, amphiregulin) at the Cytokine Reference Laboratory using standard ELISA or Luminex assays.

11 Event Monitoring, Documentation and Reporting

Toxicity and adverse events will be classified and graded according to NCI's Common Terminology Criteria for Adverse Events V 5.0 (CTCAE) and reported on the schedule below. A copy of the CTCAE can be downloaded from the CTEP home page. (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50)

11.1 Event Terminology

Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Serious Adverse Event: An adverse event is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Unexpected Event: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

Major and Minor Clinical (Protocol/Patient) Deviations as defined by the Masonic Cancer Center:

Major Deviations:
A deviation or violation that impacts the risks and benefits of the research; may impact subject safety, affect the integrity of research data and/or affect a subject's willingness to participate in the research. Deviations that place a subject at risk, but do not result in harm are considered to be major deviations.

Minor Deviations:
A deviation or violation that does not impact subject safety, compromise the integrity of research data and/or affect a subject's willingness to participate in the research.

11.2 Event Documentation

Patients will be monitored for adverse events from the first dose of study treatment until nine months after randomization as per the schedule in section 8.2. After that time point, events meeting the definition of serious and at least possibly related to study treatment will be documented upon knowledge.

Routine AE reporting will occur via data entry into the study eCRF. AEs reported through expedited processes (e.g., reported to IRB, FDA, etc.) must also be reported in routine study data submissions.

Adverse events recorded in the case report forms include:

- All events considered possibly, probably or definitely related to study agent
- All events of fever, abdominal pain, diarrhea, constipation, and bloating (for 7 days after each dose of FMT/placebo). Refer to Appendix III.
- Grade 3 or higher unsolicited adverse events (for 28 days after each dose of FMT/placebo)
- New-onset chronic medical conditions potentially related to FMT (metabolic syndrome, glucose intolerance, autoimmune conditions, and weight gain) until 9 months after randomization. All serious adverse events.

11.3 SAE and Death Documentation

Any event meeting the definition of a serious adverse event (SAE) requires documentation using the SAE Report Form in OnCore. Refer to section 11.4 for the definition of events that must be reported to the FDA, Dr. Alexander Khoruts, and IRB in an expedited manner.

Deaths, including due to disease, during the treatment and 6 month follow-up period will be recorded as an SAE. Deaths due to disease should be recorded as a Grade 5 “Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease). In addition, the death date and cause must be reported in the patient follow-up tab in OnCore using the comment field in the survival status section to record the cause. Deaths only need to be reported in an expedited manner if they meet the criteria in section 11.5. Otherwise, they are reported at the time of IRB and FDA annual reporting.

11.4 Early Stopping Rule Documentation and Reporting

The following event counts toward an early study stopping rule and must be reported per Section 11.5:

- bloodstream infection within 1 week after FMT/placebo

An event that counts toward an early stopping rule does not necessarily constitute a SAE and should be reported as such only if they meet the criteria for reporting as defined in Section 11.5.

11.5 Expedited Event Reporting

Agency	Criteria for reporting	Timeframe	Form to Use	Submission address/email address
U of MN IRB	Unanticipated death of a locally enrolled subject(s); New or increased risk; Any adverse event that require a change to the protocol or consent form – refer to the IRB website for complete details	5 Business Days	RNI	Ethos
	Clinical deviations per current IRB reporting requirements		RNI	Ethos
FDA	Unexpected and fatal or unexpected and life threatening suspected adverse reaction	no later than 7 Calendar Days	SAE Report Form	Submit to CBER as an amendment to IND
	1) Serious and unexpected suspected adverse reaction or 2) increased occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure or 3) findings from other sources (other studies, animal or in vitro testing)	no later than 15 Calendar-Days		
	All other events per CFR 312.33	Submit as part of the IND annual report	Summary format	Submit as part of the IND annual report
SAE Coordinator	Events that meet the definition of an early study stopping rule	At time of reporting	Event Form	mccsaes@umn.edu
Ad Hoc DSMC	SAEs and suspected/confirmed transmission of pathogens.	5 Business Days	Report Form	Shernan Holtan sgholtan@umn.edu, Armin Rashidi arashidi@umn.edu and Alexander Khoruts khoru001@umn.edu
Medical Monitor	Events that meet the definition of an early study stopping rule	w/in 24 hours	Event Form	Byron Vaughn, MD bvaughn@umn.edu pgr: 612-899-4052

12 Study Data Collection and Monitoring

12.1 Data Management

This study will collect regulatory and clinical data using University of Minnesota CTSI's instance of OnCore® (Online Enterprise Research Management Environment). The Oncore

database resides on dedicated secure and PHI compliant servers. All relevant AHC IS procedures related for PHI compliant servers (as required by the Center of Excellence for HIPAA Data) apply to Oncore databases.

The data will be integrated and extracted to researchers through the CTSI Informatics team and will be delivered through secure and compliant mechanisms (e.g. AHC IE data shelter, BOX, sftp, etc). If data de-identification is needed, then compliant AHC IE data de-identification tools will be used. The informatics team will grant the IRB approved study team members access to data.

Additional data about correlative laboratory samples generated by the Masonic Cancer Center Translational Therapy Laboratory (TTL) from the protocol-directed correlative research samples is stored in their Laboratory Information Management System (LIMS).The LIMS database application is also stored on a production server located in the UMN datacenter (WBOB) and is managed by the Academic Health Center. Key study personnel are trained on the use of OnCore and will comply with protocol specific instructions embedded within the OnCore.

12.2 Case Report Forms

Participant data will be collected using protocol specific electronic case report forms (e-CRF) developed within Oncore based on its library of standardized forms. The e-CRF will be approved by the study's Principal Investigator and the Biostatistician prior to release for use. The Study Coordinator or designee will be responsible for registering the patient into OnCore at time of study entry, completing e-CRF based on the patient specific calendar, and updating the patient record until patient death or end of required study participation.

12.3 Data and Safety Monitoring Plan (DSMP)

The study's Data and Safety Monitoring Plan will be in compliance with the University of Minnesota Masonic Cancer Center's Data & Safety Monitoring Plan (DSMP), which can be accessed at http:// z.umn.edu/dmsp.

For the purposes of data and safety monitoring, this study is classified as high risk (investigator initiated IND protocol). Therefore, the following requirements will be fulfilled:

- At least quarterly review of the study's progress by the Masonic Cancer Center Data and Safety Monitoring Council (DSMC).
- The PI will comply with at least twice yearly monitoring of the project by the Clinical and Translational Science Institute monitoring services.

- The PI will oversee the submission of all reportable adverse events per section 11.4 to the Masonic Cancer Center's SAE Coordinator, the University of Minnesota IRB, Dr. Khoruts, and the FDA.

  In addition, at the time of the continuing review with the University of Minnesota IRB, a copy of the report with any attachments will be submitted to the Cancer Protocol Review Committee (CPRC).

Additional Monitoring:

A Data Safety Monitoring Committee (DSMC), consisting of a physician from each of the following disciplines: Infectious Diseases (1 individual), Gastroenterology (1 individual), and Hematology/Oncology (2 individuals) will meet ad hoc (either in person, or online) for SAEs and suspected/confirmed transmission of pathogens. These physicians will not be involved in the study other than participating in the DSMC. Assessment by at least 3 of these 4 physicians is required for each SAE.

SAEs and deaths will be reported to the DSMC on an ongoing basis; the study will be stopped for a safety evaluation by the DSMC if they have any concerns, or if a stopping rule is activated. The DSMC chair will be responsible for recording the summary of its various meetings and for reporting findings and/or recommendations to the study sponsor and to the funding agency.

The Medical Monitor will serve as the liaison between the DSMC and the Sponsor/ Investigator. The actual analyses will be conducted by the Study Biostatistician who will ensure that the unblinded analyses are not available to study investigators.

Medical Monitoring

An expert in Gastroenterology and Microbiome research, with specific expertise with FMT, will serve as the Medical Monitor. The external Medical Monitor will be separate from the Sponsor/Investigator and will not participate in any study procedures (e.g., screening of subjects, consenting of subjects, administration of FMT or study follow-up). The Medical monitoring will include a regular assessment of each stopping rule event. If a stopping rule event is considered to be related to the study agent, the DSMC will be notified.

Unblinding Procedures

If unblinding the study therapy is necessary to ensure a subject's safety, this will be done by the external medical monitor after review of the clinical events. The Sponsor/Investigator must be informed within 24 hours by phone, fax or email of the unblinding event, followed by a detailed written narrative within 48 hours of the event.

In other circumstances, the medical monitor may choose to unblind him/herself if there is concern based on the safety data that a type of adverse event may be associated with FMT treatment; in this case, the medical monitor will inform the study sponsor that he/she has unblended him/herself, but not of the treatment assignments.

IND Annual Reports

In accordance with regulation 21 CFR § 312.33, the sponsor-investigator, Dr. Holtan, will submit a progress report annually. The report will be submitted within 60 days of the anniversary date that the IND went into effect. A copy of the IND annual report will be submitted to Dr. Khoruts.

12.4 Study Monitoring

The investigator will permit study-related monitoring, audits, and inspections by the study's Principal Investigator/IND sponsor and/or any designees, the local IRB, government regulatory bodies, and University of Minnesota compliance groups. The investigator will make available all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.) will be available for trial related monitoring, audits, or regulatory inspections.

12.5 Record Retention

The investigator will retain study records including source data, copies of case report form, consent forms, HIPAA authorizations, and all study correspondence in a secured facility for at least 6 years after the study file is closed with the IRB and FDA.

12.6 Telephone and Electronic Consent Procedures

Given current COVID-19 restrictions, remote consent via phone or virtual visit will be permitted. Remote consent will be documented with either patients' hand-written signature or e-signature using a 21 CFR Part 11 compliant system, such as Redcap to minimize patient and staff contact. All electronic paperwork and health information will be securely stored in Redcap, OnCore or password protected files.

The REDCap database uses a MySQL database via a secure web interface with data checks used during data entry to ensure data quality. REDCap includes a complete suite of features to support HIPAA compliance, including a full audit trail, user-based privileges, and integration with the institutional LDAP server. The MySQL database and the web server will both be housed on secure servers operated by the University of Minnesota Academic Health Center's Information Systems group (AHC-IS). The servers are in a physically secure location on campus and are backed up nightly, with the backups stored in accordance with the AHC-IS retention schedule of daily, weekly, and monthly tapes retained for 1 month, 3 months, and 6 months, respectively. Weekly backup tapes are stored offsite. The AHC-IS servers provide a stable, secure, well-maintained, and high-capacity data storage environment, and both REDCap and MySQL are widely-used, powerful, reliable, well-supported systems. Access to the study's data in REDCap will be restricted to the members of the study team by username and password.

13 Study Endpoints

13.1 Primary Endpoint

To demonstrate the efficacy of FMT in AML patients and allo-HCT patients, as measured by the number of all infections within 4 months after the first study drug administration.

13.2 Secondary Endpoints

13.2.1 FMT engraftment rate at 10 days and 4 weeks post each FMT and 9 months after randomization.

13.2.2 In the Allo-HCT cohort, the cumulative incidence of acute grade II-IV GVHD through day 180 post-HCT

13.2.3 The incidence of BSI through 1 week after each FMT

13.2.4 In both cohorts, the number of bacterial, viral, and fungal infections within 4 months after the first study drug administration

13.3 Correlative Endpoints

- The effect of FMT on gut barrier biomarkers

14 Statistical Considerations

14.1 Study Design

This is a randomized, double-blind, placebo-controlled clinical trial of Fecal Microbiota Transplant (FMT) procedure in 2 independent cohorts (72 AML patients undergoing

chemotherapy and 72 Allo-HCT patients). Participants in each cohort will be randomized to receive up to 3 treatments of FMT vs. placebo after each exposure to antibacterial antibiotics until 3 months after randomization. The primary endpoint is the number of all infections within 4 months after the first study drug administration. Interim safety analysis will be performed. Other endpoints are listed in section 13.

14.2 Power Analysis:

This is a phase II randomized study aiming for obtaining treatment effect data for further phase III study. Nevertheless, the power analysis was conducted for the designed sample sizes for two patient groups, the BMT and chemo group, separately. The unbalanced sample size between the intervention group (N=48) and the control group (N=24) was chosen in order to get reliable estimates for the intervention group for the use of future design of phase III trials. The infection rates of the controls in the BMT and chemo groups were estimated based on a pilot cohort (17 infectious events per 1440 patient-days, i.e., infection rate=0.013) and published data (infection rate=0.009 for days 30-180 post-transplant) [16], respectively. Two-sided tests for the ratio of two exponential rates [17] with a 120 days' follow-up were used for power calculation with PASS14 (NCSS, LLC). The power for a presumed 50% reduction in infection rate for the intervention group (i.e., the infection rate ratio of intervention vs. control = 0.5) was calculated.

14.3 Data Analysis Plan:

The infection data will be summarized using infection density for each treatment and each patient group. The recurrent infection data will be compared between the intervention and control using the Lin-Wei-Yang-Ying regression model [18] with intervention as the primary covariate, and then adjusting for additional patient/treatment-related characteristics in a multivariable regression model. Potentially informative censoring events such as death and second transplant will be taken into account with a sensitivity analysis using the method by [19].

14.4 Sample Size and Accrual

With ~70 cases of newly diagnosed and ~30 relapsed/refractory AML cases per year, 50% consent decline rate, and ~20% probability of being unevaluable after consenting, we expect to complete enrollment of the leukemia cohort in ~18-24 months. With ~100 allo-HCT cases per year, 50% consent decline rate, and ~20% probability of being unevaluable after consenting, we expect to complete enrollment of the HCT cohort in ~18-24 months.

14.5 Safety Monitoring

Continuously stopping rules are in place to stop the study in case there are excessive complications. In the case that the boundaries are crossed, the Principal Investigator will be

notified who will report it to the Masonic Cancer Center Data Safety Monitoring Committee and the Medical Monitor. The protocol will be reviewed by the Medical Monitor to determine if the protocol should be terminated. The stopping rule was developed using Pocock stopping boundaries [20]. The stopping rules will be applied separately for FMT arms in each cohort. We do not expect toxicity in placebo arms. Therefore we will not monitor for the two placebo arms.

Excess toxicity will be defined as bloodstream infection within 1 week after FMT. The goal is to construct a boundary based on toxicity such that the probability of early stopping is at most 10% if the toxicity rate is equal to 30%. Given these parameters, for each of FMT arms, the upper stopping boundary for toxicity is 4 out of 4, 5 out of 6, 6 out of 9, 7 out of 11, 8 out of 13, 9 out of 16, 10 out of 18, 11 out of 21, 12 out of 23, 13 out of 26, 14 out of 28, 15 out of 31, 16 out of 34, 17 out of 36, 18 out of 39, 19 out of 42, 20 out of 44, 21 out of 47, or 22 at any time. If the true toxicity rate is as high as 60%, the chance of early stopping is 99%; this will occur after 13th enrollments.

15 Ethical and Regulatory Considerations

15.1 Good Clinical Practice

The study will be conducted in accordance with the appropriate regulatory requirement(s). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

15.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted as a single site study where IRB approval has been obtained. The protocol, informed consent, written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

15.3 Informed Consent

All potential study participants will be given a copy of the IRB-approved Consent to review. The investigator or designee will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the Consent document; or consent

remotely over the telephone or electronically. Remote consent will be documented with either patient's hand-written signature or e-signatures using a 21 CFR Part 11 compliant system such as REDCap. Patients who refuse to participate or who withdraw from the study will be treated without prejudice.

16 References

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Appendix I – Eligibility Checklist for Initial Enrollment

A Randomized Placebo-Controlled Clinical Trial of Fecal Microbiota Transplantation in Patients with Acute Myeloid Leukemia and Allogeneic Hematopoietic Cell Transplantation Recipients

Eligibility Checklist – page 1 of 1

Study ID: 17170-UMN-_____

INCLUSION CRITERIA

A "NO" response to any of the following disqualifies the participant from study entry.

		Yes	No
1.	≥ 18 years	☐	☐
2.	Cohort A: Patients undergoing chemotherapy for acute myeloid leukemia (newly diagnosed or relapsed/refractory).	☐	☐ NA
3.	Cohort B: Allo-HCT patients ☐ Any T-replete allogeneic transplant regimen	☐	☐ NA
4	Sexually active females of childbearing potential and males with partners of child-bearing potential must agree to use adequate birth control until at least six months post-FMT/placebo	☐	☐
5	Voluntary written consent signed before performance of any study-related procedure not part of normal medical care	☐	☐

EXCLUSION CRITERION

A "YES" response to the following disqualifies the participant from study entry.

		Yes	No
1.	Planned continuation of antibacterial antibiotics (with the exception of antibiotics used for Pneumocystis carinii prophylaxis) after the first neutrophil recovery (ANC > 1,000)	☐	☐
2.	Subjects with severe food allergies	☐	☐
3.	Subjects with a history of chronic aspiration	☐	☐
4.	Pregnant or breast feeding. The FDA has not classified this agent into a specified pregnancy category. Females of childbearing potential must have a blood test or urine study within 14 days prior to registration to rule out pregnancy	☐	☐

Date consent form signed: _____

Having obtained consent and reviewed each of the inclusion/exclusion criteria, I verify that this participant is eligible.

_____

Signature of person verifying eligibility Date

Appendix II – Eligibility Checklist for FMT/placebo Administration

A Randomized Placebo-Controlled Clinical Trial of Fecal Microbiota Transplantation in Patients with Acute Myeloid Leukemia and Allogeneic Hematopoietic Cell Transplantation Recipients

Eligibility Checklist – page 1 of 1

Study ID: 17170-UMN-_____

INCLUSION CRITERIA

A "NO" response to any of the following disqualifies the participant from study entry.

		Yes	No
1.	Neutrophil recovery: ANC > 1,000, checked within the last 7 days		
2.	All anti-bacterial agents (with the exception of antibiotics used for Pneumocystis carinii prophylaxis) have been discontinued for at least 2 days	☐	☐
3.	Acute toxicities have resolved to grade 2 or lower	☐	☐
4.	Negative pregnancy test result for females of child bearing potential	☐	☐

EXCLUSION CRITERION

A "YES" response to the following disqualifies the participant from study entry.

		Yes	No
1.	Unable to swallow capsules	☐	☐
2.	Disease has relapsed/progressed after original consent	☐	☐
3.	Active infection at the time of screening	☐	☐
4.	[Cohort B] Active GVHD or being treated for GVHD at the time of screening	☐	☐

Date consent form signed: _____

Having obtained consent and reviewed each of the inclusion/exclusion criteria, I verify that this participant is eligible.

_____ _____

Signature of person verifying eligibility Date

Appendix III – FMT/Placebo Reaction Diary

The Diary is to be completed by the patient as a self-assessment for 7 days after each dose of FMT/Placebo.

A new diary must be started for each dose of FMT/Placebo.

For inpatients, the diary is completed by patient or study personnel.

Patient Number*		**Date of Study Drug**	**_____/_____/_____**	

Please answer all questions below daily for 7 days. Be sure to bring back this completed diary to your next clinic visit.

	Instructions	Day 1 Post Study Drug ___/___/____	Day 2 Post Study Drug ___/____/____	Day 3 Post Study Drug ___/____/____	Day 4 Post Study Drug ____/___/____	Day 5 Post Study Drug ___/___/____	Day 6 Post Study Drug ___/___/____	Day 7 Post Study Drug ___/___/_____
1. Do you have any stomach pain?	Check the pain box if present And tell us if the pain is mild, moderate or severe	☐ Pain Mild Mod Severe	☐ Pain Mild Mod Severe	☐ Pain Mild Mod Severe	☐ Pain Mild Mod Severe	☐ Pain Mild Mod Severe	☐ Pain Mild Mod Severe	☐ Pain Mild Mod Severe
2. Do you have any diarrhea?	Check: ☐Yes or ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No
3. Do you have any constipation?	Check: ☐Yes or ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No
4. Do you have any bloating?	Check: ☐Yes or ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No
5. Record your daily temperature upon waking (do not drink anything 5 minutes before taking your temperature)	Check: ☐Yes or ☐No If your temperature is 101°F for more than 24 hours notify your study doctor or research staff.	☐Yes ☐No _____°F Time: ____:____ AM / PM	☐Yes ☐No _____°F Time: ____:____ AM / PM	☐Yes ☐No _____°F Time: ____:____ AM / PM	☐Yes ☐No _____°F Time: ____:____ AM / PM	☐Yes ☐No _____°F Time: ____:____ AM / PM	☐Yes ☐No _____°F Time: ____:____ AM / PM	☐Yes ☐No _____°F Time: ____:____ AM / PM
Have you taken any additional medications?	List medicines, including herbal supplements you have taken.	_____ _____ _____	_____ _____ _____	_____ _____ _____	_____ _____ _____	_____ _____ _____	_____ _____ _____	_____ _____ _____