Safety of Fecal Microbiota Transplantation (FMT) for Recurrent or Refractory C. Difficile Infection in Patients with Solid Tumors

MSK THERAPEUTIC PROTOCOL

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Please note: All listed above must have completed the mandatory Human Subjects Education and Certification and Good Clinical Practice Certification Programs

OneMSK Sites	
Site Name	**Site's Role**
Manhattan	All Protocol Activities

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a therapeutic protocol for use of FMT in adult (≥18 years old) patients with solid tumor who are diagnosed with recurrent or refractory *C. difficile* infection (CDI). Recurrent infection is defined as CDI episode occurring > 2 weeks after the index episode that was successfully treated with a single course of antibiotic therapy as outlined in IDSA guidelines. Refractory CDI is persistent diarrhea without resolution during therapy. Patients will be recruited from the Gastroenterology and Infectious Diseases clinics or referred from other clinics at Memorial Sloan Kettering Cancer Center (MSKCC) over a one-year period. The primary endpoint is safety of FMT and the secondary endpoint is recurrence of diarrhea following FMT during a follow up period of 6 months. Eligible patients will undergo FMT and be monitored at 24 hours, 2 weeks, 4 weeks and 6 months for safety. Stool samples will be obtained from patients prior to the FMT procedure (preferably at the initial visit), 24 hours, 1 week, 2 weeks, 4 weeks, and 6 months post-FMT. Patients will not be required to return to clinic for the 24-hour, 2 week, and 6 month post-FMT visits. Patients will be provided with "at-home" stool collection kits for all time points. These kits will include all of the materials and instructions for patients to collect and ship their stool specimens from home. Two 3-mL EDTA tubes of whole blood will be drawn at the initial visit (pre-FMT), 1 week, and 4 weeks post-FMT. Stool and blood samples will be de-identified and labeled with the patient's study ID, date and time of collection and shipped to Finch Therapeutics, Inc. in order to investigate the connections between cancer, immunity, and the microbiome.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

- **Primary Endpoint:** The primary end point of the study is safety of FMT in patients with solid organ malignancy. Safety will be assessed by monitoring solicited adverse events (fever, vomiting, diarrhea, abdominal pain, and bloating) and infections that occur within 2 weeks of the FMT procedure. These infections will include (1) blood stream infection deemed to be secondary to gastrointestinal translocation defined as fever and positive blood cultures or (2) aspiration pneumonia defined as fever with new cough. Infection related to FMT will be determined by clinical assessment of symptoms, physical examination, laboratory values including microbiologic studies and radiographic findings. Unsolicited adverse events will be monitored through the duration of the study.
- **Secondary Endpoint**: The secondary outcome of the study is recurrence of *C. difficile*-associated diarrhea. Proportion of first recurrent diarrhea following FMT will be evaluated at 2 weeks, 4 weeks and 6 months following initial FMT.

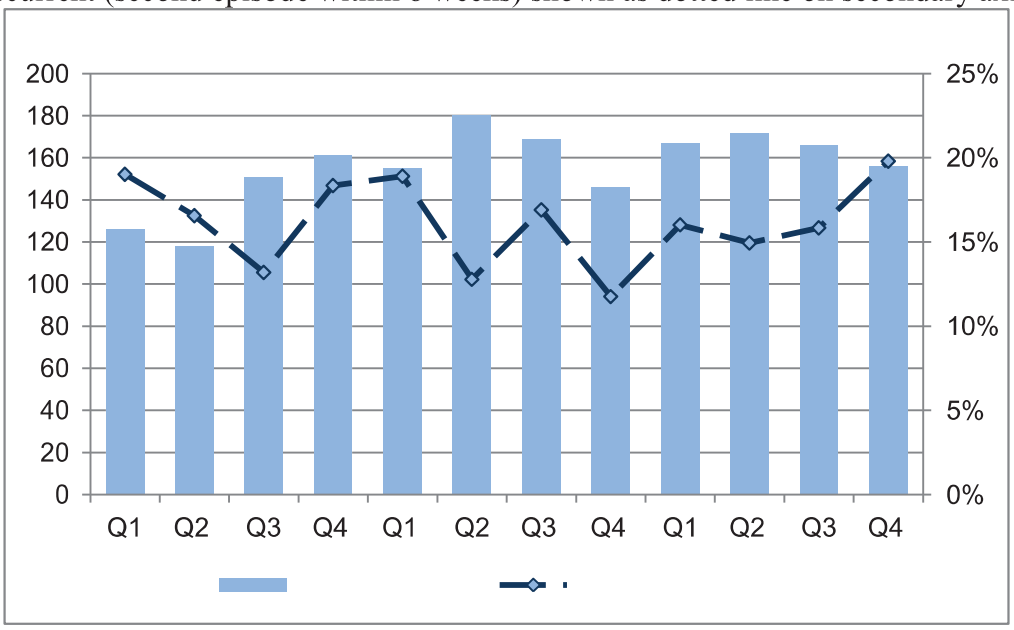
3.0 BACKGROUND AND RATIONALE

CDI is the most frequent bacterial cause of healthcare-associated diarrhea accounting for 15-25% of antibiotic associated-diarrhea. It is a major cause of morbidity and mortality and has increased to epidemic proportions over the past decade to an incidence of 10.4 cases per 1,000 patient admissions (1). Increases in incidence have been paralleled by an increased mortality rate from 1.2% in 2000 to 2.3% in 2004 (2). This increase in incidence, severity, recurrence rate and mortality has been associated with emergence of a new highly virulent and resistant strain referred to as NAP1 (3).

Immunocompromised patients, especially those undergoing treatment for cancer, are at particular risk of developing CDI. Disruptions in intestinal microbiota and immune responses as a consequence of anti-neoplastic therapy, frequent and longer hospital stays and exposure to broad-spectrum antibiotics increase the risk for CDI in this population.

The CDI rates at MSKCC are twice the average for NYS medical centers and higher incidence of CDI among cancer centers has been well-described (4). Recurrent CDI is a particularly common and challenging problem at MSKCC often managed with lengthy courses of oral vancomycin causing frequent delays or interruption in delivery of oncologic care. At MSKCC, approximately 20% of patients experience recurrence within the first 8 weeks of their index CDI episode. The number of new and recurrent (within 8 weeks) cases at MSKCC from 2011-2013 is shown in Figure 1 below. Approximately 30% of patients with CDI develop subsequent infections.

Figure 1- Number of new cases of CDI at MSKCC shown as bars (primary axis) and percentage recurrent (second episode within 8 weeks) shown as dotted line on secondary axis



2011 2011 2011 2011 2012 2012 2012 2012 2013 2013 2013 2013
New Cases % Cases Recurrent

Current practice guidelines by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) focus on metronidazole- and vancomycin- based regimens. First recurrence is managed similarly to an initial episode. Vancomycin in a tapered and/or pulsed regimen is recommended for second and subsequent relapses (5). However up to 60% of patients, especially patients over 70 years of age, do not respond to this treatment strategy or develop further recurrence once vancomycin is stopped often necessitating maintenance doses of vancomycin administered over months and years for symptom control until a more durable and sustained therapeutic option such as FMT is feasible and readily available (6).

FMT involves the reconstitution of normal flora by stool transplant from a healthy donor and has shown to be effective in treating recurrent CDI with cure rates of up to 98%. CDI is associated with the use of antimicrobial agents that alter the normal bacterial flora of the gastrointestinal tract so as to permit colonization and subsequent proliferation by *C.* difficile. FMT involves administration of fecal material from a healthy individual (donor) into an affected patient to restore the normal diversity of the human gut microbiome. Transplantation of human stool was first described in 1958 for the treatment of fulminant pseudomembranous enterocolitis (7). Since that time, FMT has been used in recurrent CDI, inflammatory bowel disease, irritable bowel syndrome and chronic constipation. For the management of recurrent CDI it has been shown to be practical, safe and highly efficacious in a number of case series and clinical trials. In 2013, a randomized controlled trial looking at the efficacy of FMT versus vancomycin for the treatment of recurrent CDI was published by van Nood et al in the New England Journal of Medicine (8). It showed that resolution of CDI occurred in 13 of 16 (81%) patients in the FMT group compared to 4 of 13 (31%) patients receiving vancomycin alone. There were no significant differences in adverse events between the FMT and standard antibiotic groups (8).

The NEJM study excluded immunocompromised patients due to the theoretical risk of infectious complications from the infusion of bodily fluids. However, there have been no infectious complications directly attributable to FMT in the literature to date. In 2014, Kelly et al published a multicenter retrospective series on the use of FMT in immunocompromised patients with recurrent CDI in the American Journal of Gastroenterology (9). Cases included 75 adult and 5 pediatric patients treated with FMT for recurrent/refractory CDI. Reasons for immunocompromised state included HIV/AIDS, solid organ transplant, malignancy, immunosuppressive therapy for inflammatory bowel disease, and other medical conditions/medications. The most common reason for immunocompromise was treatment for inflammatory bowel disease (36 out of 80 patients). Seven patients were immunocompromised due to cancer and treatment with antineoplastic agents. The overall CDI cure rate was 89%, similar to the outcome reported in the NEJM study suggesting that this form of therapy would be as efficacious among persons undergoing treatment for cancer. No infections related to FMT specifically transmissible pathogens or related to gut translocation were reported in this series. The major weaknesses of the study are its retrospective design and the limited number of cancer patients studied. Due to the lack of prospective trials looking at the safety of FMT in patients with malignancy, this procedure is not currently performed at MSKCC. Therefore it is important to conduct a systematically designed prospective study with clear inclusion and exclusion criteria, donor selection and screening protocols for a more thorough evaluation of the safety of FMT in this population.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This study is a prospective study and the primary end point is safety of FMT among patients with solid organ malignancy. Patients with recurrent or refractory CDI who meet study eligibility criteria, as detailed below, will consent to undergo either colonoscopy or upper endoscopy with infusion of stool admixture. Safety will be assessed by monitoring infections that occurred within 2 weeks of the FMT procedures. These will include (1) blood stream infection deemed to be secondary to gastrointestinal translocation or (2) aspiration pneumonia. Aspiration pneumonia will be attributed to FMT if it occurs within 24-72 hours following upper endoscopy or colonoscopy. A bloodstream infection will be attributed to FMT if there is no other source of infection (i.e., UTI, cholangitis) after a full infectious workup. Criteria for infection will be the same regardless of whether patients underwent colonoscopy or upper endoscopy for FMT

Patients will be assessed at 24-hours, 1 week, 2 weeks, 4 weeks and 6 months following FMT for adverse events (AEs), serious adverse events (SAEs) and *C. difficile* associated diarrhea recurrence. Based on IDSA/SHEA guidelines, patients will not be routinely tested for *C. difficile* if they do not have symptoms. They will be tested only if they develop diarrhea or other symptoms suspicious for recurrence. The secondary endpoint is recurrence of *C. difficile* associated diarrhea. Proportion of first recurrent diarrhea will be evaluated at 2 weeks, 4 weeks, and 6 months following initial FMT.

Additionally, stool samples will be collected at the pre-FMT, 24-hours, 1 week, 2 weeks, 4 weeks, and 6 months post-FMT visits. Two 1-gram stool aliquots will be utilized. One aliquot will be flash frozen at -80C or -20C and the other aliquot will be homogenized into glycerol buffer and then frozen at -80C or -20C. Two 3-mL EDTA tubes of whole blood will also be drawn during each patient's initial visit (pre-FMT), 1 week, and 4 weeks post-FMT. Stool and blood specimens will be de-identified and labeled with the patient's study ID, date and time of collection and sent to Finch Therapeutics, Inc. for further analysis. 16s rRNA transcription will be performed on each stool specimen provided. Stool specimens and blood samples will be shipped on dry ice.

Patients will receive $50, in the form of a gift card, after completing the following visits:

- 24 hours post FMT
- 7 days post FMT
- 14 days post FMT
- 6 months post FMT

4.2 Intervention

Study subjects will undergo FMT with healthy donor stool provided by OpenBiome, a nonprofit 501(c)(3) organization that provides clinicians and hospitals with screened, filtered and frozen stool to be used for FMT (9). Materials are ordered through the OpenBiome website and shipped within 5 business days. Materials are concentrated and packaged for either colonoscopic (250mL format) or nasogastric (30mL format) administration.

The protocol for administration of donor stool is identical to those used in prior randomized studies. Fecal therapy consists of a lavage with bowel prep.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Stool is a heterogeneous substance, composed primarily of bacteria and water. It also contains viral and fungal organisms, undigested food, bile, bilirubin, cholesterol, inorganic salts, dead cells and mucus from the lining of the intestinal wall. The exact composition of human stool varies from person to person and from day to day.

In order to ensure the safety of its product, OpenBiome maintains a rigorous screening process for its donor stool. First, donor candidates are screened with comprehensive evaluation of medical histories, behavioral risks and current health status. They are also screened for 20 stool and serological tests at a CLIA-certified laboratory. Qualified donors are under medical monitoring for the entire donation window and are fully re-screened every 60 days. Prior to release, donated material is quarantined for 60 days in between two full panel screens at a CLIA-certified laboratory. All adverse events are reported to OpenBiome, which maintains an unpaid, independent clinical advisory board.

A summary of OpenBiome donor screening, testing and monitoring programs can be found in the appendix of this application.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- ≥18 years old
- Patients with solid organ malignancy who have received chemotherapy within the past six months.
- Clinical and microbiologic relapse of *C. difficile* associated diarrhea after at least one course of adequate antibiotic therapy or refractory disease that does not respond to treatment.
    - At least 10 days of vancomycin at least 125mg QID, or metronidazole 500mg TID
    - *C. difficile* associated diarrhea is defined as:
        - ≥3 loose or watery stools per day for at least 2 consecutive days or ≥8 loose stools in 48 hours and
        - Positive *Clostridium difficile* PCR
- Life expectancy of >3 months.

6.2 Subject Exclusion Criteria

- Expected prolonged compromised immunity
    - HIV infection with CD4 count <240
    - History of hematopoietic stem cell transplant (HSCT)
    - Hematologic malignancy
    - ANC <1000/mm^3
- Contraindications to anesthesia for procedure
    - Serious cardiopulmonary comorbidities

  - Inability to tolerate anesthesia
  - HGB <8 g/dL
- Risk of bleeding during procedure
  - PLT <50,000 K/mcL
  - INR >1.5 INR
- Pregnancy
  - Pregnant patients will be excluded from this study.
- Gastrointestinal (GI) contraindications
  - Inflammatory bowel disease
  - Active fistula
  - Small bowel obstruction
  - Ileus
  - Gastroparesis
  - Nausea and vomiting
  - Gastrointestinal surgery within the previous 3 months

7.0 RECRUITMENT PLAN

Patients referred to the Infectious Disease or Gastroenterology clinics for the management of recurrent or relapsed CDI will be approached for recruitment for this study. Patients being treated in other divisions or departments at MSKCC may also be referred for this study by contacting the PI or Co-PI. Patients admitted in the hospital may also be recruited for the study if the primary service requests a formal Gastroenterology or Infectious Disease consultation. Potential FMT patients will be referred to Dr. Mendelsohn and undergo a medical interview and physical exam to determine study eligibility.

8.0 PRETREATMENT EVALUATION

Potential FMT patients will undergo a medical interview to determine eligibility for the treatment and a physical exam will be performed. Only patients 18 years of age or older will be treated under this FMT protocol. Serologic testing will be done on all patients to document baseline status prior to FMT including: HIV 1 & 2, Hepatitis A Ab, Hepatitis B surface Ag, Hepatitis B surface Ab, Hepatitis B core Ab, Hepatitis C Ab, and RPR.

Female patients of childbearing potential (aged 18-50) will have a urine or blood pregnancy test within one week prior to the FMT procedure to ensure eligibility. Patients who are pregnant will not be permitted to receive FMT. A baseline stool sample will also be collected.

9.0 TREATMENT/INTERVENTION PLAN

Table of Assessments (Note there is a +/- 48 hour window for each visit):

	Initial Visit	Day of FMT	24 hour post FMT	7 days post FMT	14 days post FMT	4 weeks post FMT	6 months post FMT
Medical interview	X	X				X	
Physical exam	X	X				X	
Upper endoscopy or colonoscopy		X					
Telephone call			X	X	X		X
Blood tests (CBC and other routine tests)	X	X					
Urine or blood pregnancy test[3]		X					
EKG[2]		X					
At-home stool collection	X		X[1]	X[1]	X[1]	X	X[1]
Whole blood collection (two 3-mL tubes)	X			X		X	

1. You will be reimbursed after you complete each of these visits. If you are in clinic during these visits, you may be asked to provide a sample while in clinic. If you provide a sample in clinic, you will not be required to submit an additional at-home collection and you will still be reimbursed.

2. EKG can be performed on the Initial Visit, or the Day of FMT, or any time between these two visits.

3. Urine or blood pregnancy tests can be completed within one week prior to the FMT procedure.

At-home stool collection and shipment can be performed at each of the visits. Each kit will include:

- 1 x stool homogenizer vial containing 5ml RNAlater preservative
- 1 x 7ml plastic transfer pipette
- 1 x disposable spatula
- 1 x pair of large latex free nitrile gloves
- 2 x small re-sealable bag, one labeled with a biohazard sticker
- 1 x Pre-addressed, postage paid bubble mailer containing a strip of absorbent fabric
- 2 x Fe-Col flushable paper stool catcher with instructions

Patients will be provided instructions (see Finch Therapeutic, Inc. Home Stool Collection Directions) on how to collect and ship samples. No PHI will be recorded during this process.

9.1 Preparation of Stool for FMT Infusion

- Feces obtained through OpenBiome will be shipped to MSKCC.
- Samples will be sent on dry ice, in double-containment vessels, with temperature indicators to ensure that samples have not thawed during transportation.
- Upon arrival material will be immediately transferred to a -80 or -20^{0}C freezer. Material may

be stored for up to 6 months.

- Thawing process:
  - For colonoscopic administration of 250cc sample: thaw for 1 hour in a 30°C water bath or thaw for 4 hours at room temperature or thaw overnight in a 4°C refrigerator.
  - For upper endoscopic administration of 30cc sample: thaw for 15 minutes in a 30°C water bath or thaw for 45 minutes at room temperature or thaw overnight in a 4°C refrigerator.
  - Once thawed, the material is ready for immediate administration.
  - After thawing, material may remain at room temperature for up to 4 hours (or refrigerated/on ice for up to 8 hours).
  - Samples should never be re-frozen. If thawed and not used within 8 hours, the material will be disposed of as a hazardous waste product.

9.2 FMT Procedure

- Patient preparation
  - Subjects will receive vancomycin as clinically indicated.
  - If donor stool will be administered via colonoscopy, patients will undergo bowel lavage with bowel purge.
  - 1-2 hours prior to endoscopy, patient may take 2 loperamide tablets to aid in the retention of administered donor stool.
- Method of FMT infusion
  - Procedure will be performed within the GI/endoscopy suite at MSKCC.
  - Based on discussion between the patient and the physician, the stool recipient will undergo either an upper endoscopy with or without placement of a nasoduodenal tube or a colonoscopy with stool infusion.
  - During the procedure donor feces will be infused either into the small intestine if the patient is undergoing upper endoscopy or infused into the colon if the patient elects to have colonoscopy instead.
  - The patient will be encouraged to retain the stool for as long as possible (optimally 1 hour).

  Female patients should not become pregnant or breastfeed an infant within 4 weeks of treatment by FMT. In order to reduce risk of pregnancy, the patient and her partner will be asked to use an acceptable method of birth control during this time period. The patient should remain on an acceptable method of birth control for 6 months after FMT treatment.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Patients will be closely monitored throughout the endoscopic procedure by both the GI endoscopist and anesthesiologist following standard procedure protocol. Vital signs are measured continuously while the patient is sedated. Following endoscopy, patients are carefully monitored in the PACU and discharged home only when stable and asymptomatic.

Solicited and unsolicited AEs will be elicited and reviewed at the 24 hour, 1 and 2 week phone calls as well as at the 4 week office visit. Patients will be contacted via telephone by a member of the clinical team at approximately 6 months after the FMT to record any SAEs, new medical conditions

or diagnoses, or changes in medical conditions, diagnoses or medications since last study contact. The time window for each time point listed is +/- 48 hours, with the exception of the first, 24 hour, time point. The time window for the 24 hour time point is +48 hours post FMT. For FMT procedures that occur on a Friday, contacting the patient on the following Monday is considered to be within the allotted time window. Stool samples will also be collected prior to the FMT procedure, 24 hours, 1 week, 2 weeks, 4 weeks, and 6 months post-FMT. For each time-point, at-home stool collection will be permitted. Blood samples will be collected pre-FMT, 1 week, and 4 weeks post-FMT.

The safety of patients will be monitored during each contact with patients.

11.0 TOXICITIES/SIDE EFFECTS

Based on the current literature the risk from FMT is minimal. There are 3 areas of risk to patients associated with this treatment: (1) physical risks related to upper endoscopy or colonoscopy, (2) theoretical risks (infectious and otherwise) related to FMT, and (3) psychological or other risks related to confidentiality and loss of privacy.

Risks of ingestion of bowel lavage on the day prior to FMT procedure include risk of dehydration and minor electrolyte imbalances. Standard endoscopy risks include the risk of bowel perforation, bleeding, infection, and adverse cardiopulmonary events related to sedation. The infusion of the liquid fecal matter will prolong the procedure by less than 5 minutes. If administered via upper endoscopy it carries a small additional risk of aspiration. Upper endoscopy and colonoscopy are generally very well tolerated. Side effects such as gaseous distention and sore throat resolve within several hours.

There have been no infectious complications directly attributable to FMT reported in the literature to date. However, since the process involves infusion of one person's bodily fluids into another, transmission of an infectious agent or disease remains a theoretical possibility. Risks will be minimized by the rigorous donor-selection process and pre-procedural stool and blood studies used by OpenBiome.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Patients will be encouraged to contact the clinical team immediately if they experience recurrence of diarrhea so that stool can be tested for *C. difficile* and treatment with anti-CDI therapy can be initiated if necessary. Patients will only submit stool specimens for *C. difficile* testing if they experience symptoms suggestive of relapse. Testing to confirm cure in asymptomatic patients is not indicated.

Patients will be contacted via telephone by a member of the clinical team 24 hours, 7 days, 14 days post FMT and again 6 months post FMT. Regardless of symptoms, all subjects will be scheduled for a follow up visit at 4 weeks post FMT. Patients will be instructed to inform the treating physician of any infectious symptoms or new medical conditions which develop after FMT.

IDSA/SHEA guidelines do not recommend routine *C. difficile* testing in patients who do not have symptoms because patients may be colonized and not develop disease. If continued symptoms of *C. difficile* associated diarrhea persist beyond after the procedure, patients will be tested for *C. difficile* via PCR. If tested positive diarrhea with a positive stool PCR), the procedure may be repeated up to two additional times. If patients have no improvement in symptoms within 7 days after initial FMT,

they will be considered for repeat FMT treatment. In addition, if one or more FMT treatments fail to result in clinical improvement, subjects will be assessed by one of the investigators for rescue therapy with antibiotics.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will be withdrawn from treatment protocol if they are lost to follow up following FMT. Every reasonable effort will be made to contact these patients to ensure they are receiving appropriate follow up care with documentation of any SAEs, AEs or changes in medical conditions, diagnoses or medications. They may also withdraw consent at any time if they no longer wish to participate in the study. Patients will also be excluded if they develop any of the exclusion criteria outlined in section 6.2.

14.0 BIOSTATISTICS

CDI is an increasingly common nosocomial antibiotic-associated infection that is associated with significant morbidity and mortality. Recurrence occurs in up to 25% of patients after initial CDI treatment. Current guidelines recommend a tapering dose of vancomycin after a second recurrence; however up to 60% of these patients do not respond. Recent studies published on the efficacy of FMT have shown success rates of 80-90% in patients with recurrent CDI. These studies also showed no significant adverse events or infectious complications in patients treated with FMT. Nevertheless, immunocompromised patients have been excluded from randomized controlled trials due to the theoretical risk of infection and other serious complications. A recently published retrospective study of FMT among immunocompromised patients further demonstrated its efficacy with few adverse events and no related infectious complications. To date there have been no prospective studies looking at the safety of FMT among immunocompromised patients. Specifically, in this study we aim to look at the safety of FMT among immunocompromised patients with solid organ malignancy.

The primary endpoint of this study is the safety of FMT among patients with solid organ malignancy. Safety will be assessed by monitoring two types of infections that occur within 2 weeks of the FMT procedure. These will include (1) blood stream infection deemed to be secondary to gastrointestinal translocation or (2) aspiration pneumonia. The study will be considered safe if at least 14 patients are able to complete FMT without infection within 2 weeks after the initial procedure. If we observe 2 or more patients with infection within 2 weeks after FMT, if any SAE is assessed as at least possibly related to FMT, or if there is any suspected or proven transmission of infection from FMT product to the recipient the trial would be stopped and FMT declared unsafe. The operating characteristics of this decision rule of stopping the trial are provided in the table below.

Probability of declaring FMT unsafe given the true rate of infection

	0.05	0.10	0.13	0.15	0.20
Prob of ≥ 2/15	17%	45%	60%	68%	83%

We will describe any other adverse events that patients may experience during the course of follow up.

For patients with repeated FMT, we will document any infection that occurs after the repeated FMT. However only infections mentioned above that occur within 2 weeks after the initial FMT will be counted as failure for the primary end point.

A secondary endpoint of the study is recurrence of *C. difficile* associated diarrhea. We will use summary statistics to describe proportion of first recurrent diarrhea at 2 weeks, 4 weeks and 6 months following initial FMT

Patients who are lost to follow-up prior to 2 weeks will be counted as treatment failures for the primary endpoint. Patients who are lost to follow-up prior to 2 weeks or 6 months following FMT will be considered inevaluable for the secondary endpoints and will be treated as missing data in the analysis of the secondary endpoints.

We plan to recruit 15 patients for this study. We will recruit over a one year period or until target enrollment.

Results obtained from the 16s rRNA sequencing performed by Finch Therapeutics, Inc. may be used for future publications.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

Not applicable.

16.0 DATA MANAGEMENT ISSUES

Patients will be followed and study data will be collected for 6 months post-FMT. A Research Study Assistant (RSA) will be responsible for source verifying all of the data, ensuring that phone follow-ups are documented, and for maintaining the study database. In addition to the institutional minimal dataset, the following study specific information will be collected: symptoms on the day of the FMT, 24 hours post-FMT, 14 days post-FMT, 4 weeks post-FMT and 6 months post-FMT. In addition to symptoms we will also elicit and record changes in medical conditions, diagnoses or

medications at each of the patient's study encounters. Stool studies for *C. difficile* PCR will also be recorded at any time points if tested as indicated by patient symptoms. All data for this study will be entered into the institutional Clinical Research Database (CRDB).

16.1 Quality Assurance

Throughout the life of the study, the research team comprising of the PI, RSA, and Clinical Research Supervisor (CRS) will meet regularly to monitor the progress of this study.

These meetings will serve to:

- Evaluate study progress/ accrual rate
- Track patients' progress
- Assess protocol compliance
- Review source documents for completeness
- Review adverse events
- Review data reports and any queries
- Review informed consent procedures
- Review patient eligibility
- Review and address any deviations/ violation from the protocol
- Discuss pending issues and outstanding actions
- Discuss corrective actions and administrative issues
- Discuss data storage and management issues

16.2 Data and Safety Monitoring

MSKCC's Data and Safety Monitoring (DSM) Plan was developed to comply with the NIH/NCI policy guidance: "NCI's Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by the NCI." The plan was reviewed and approved by the NCI in September 2001. It is established and monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://inside2/clinresearch/Pages/protocol-review-committees/data-and-safety-monitoring- committee.aspx. During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (i.e. NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

We will be monitoring closely throughout the study for potential side effects of the FMT. Common side effects are related to the colonoscopy or upper endoscopy procedure and include abdominal bloating or discomfort, nausea/vomiting, somnolence related to anesthesia and reaction at IV site. Less common risks include aspiration, bleeding, and bowel perforation. Patients will be observed closely in the recovery area for these adverse events immediately following the procedure. Potential long-term risks of FMT include transmission of infection and other chronic conditions such as diabetes, inflammatory bowel disease, irritable bowel syndrome and obesity. We will try to reduce this risk by using only stool that has been thoroughly tested and following OpenBiome's safety monitoring protocol closely. Patients can withdraw from the study at any time.

17.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in 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 (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent *and* is registered. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

An SAE must be reported to the IRB/PB within 5 calendar days of the event. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSK)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB AE report should be completed as above. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events will be used in assessing each adverse event. A sample of the grading scale is provided below.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

17.2.1

Both anticipated and unanticipated adverse events and problems will be formally monitored and recorded in the EMR. Unanticipated SAEs or problems will be reported to the hospital and university IRBs (as per local reporting requirements), the FDA (within 15 days; or 7 days for unexpected fatal or life threatening events or transmission of infectious agent). Anticipated and less serious AEs will be submitted annually in reports to the FDA.

We will specifically document and report to the FDA:

- Complications related to endoscopy (sedation-related, bleeding, perforation).
- Complications related to FMT (infection, inflammatory, allergic reaction).
- Solicited and unsolicited AEs will be assessed at follow up telephone contacts and clinic visits.
- Development of new symptoms or diagnoses (irritable bowel syndrome, inflammatory bowel disease, autoimmune disorder, or neurologic disorder) which may or may not be related to FMT will be elicited at the 6 month follow up telephone call and documented.

- Subjects who have an SAE that is possibly related to FMT will not receive a second FMT if they are determined to be at risk for a second SAE.
- FDA will be notified of any unexpected fatal or life-threatening suspected adverse reaction within 7 days after initial receipt of the information.
- FDA will be notified within 7 days if an infectious disease is possibly, probably, or definitely transmitted to a patient via FMT.
- All SAEs will be reported to the FDA within 15 days.
- All other AEs will be reported in an annual report to the FDA.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

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20.0 APPENDICES

1. OpenBiome Quality Metrics