Protocol for Prevention of Recurrence of Crohn's Disease by Fecal Microbiota Therapy (FMT)

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1. General Information

Protocol title
Prevention of Recurrence of Crohn's Disease by Fecal Microbiota Therapy (FMT)

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2. Background Information

Name and description of the investigational product

Fecal Microbiota Therapy (FMT)

Summary of Findings from Relevant Studies

Ulcerative colitis (UC) and Crohn's Disease (CD) are the two forms of inflammatory bowel disease (IBD) that lead to chronic intestinal inflammation. The natural history of these conditions is marked by recurrent episodes of disease exacerbation, leading to abdominal pain, diarrhea, weight loss and rectal bleeding. The inflammation in CD is confined predominantly to the ileum and colon, geographic sites with the highest concentrations of commensal bacteria in the body. This association has led to many questions about the role of intestinal bacteria in the pathogenesis of this chronic disease. In patients with Crohn's Disease (CD), a change in the ecology of this bacterial flora is observed, when compared to healthy individuals (1). This presence of a so-called "colitogenic flora may play a key role in propagating the intestinal inflammation seen in CD. Patients with CD develop less microbial diversity, and an overgrowth of species such as *Proteobacteria* and *Bacillus Firmicutes*, and patients with active CD flares have been shown to have predominantly more *Streptococcus spp*. and *Lactobacillus spp*. and less *bifidobaceria* in the inflamed tissue (2). It has been proposed that a spectrum of "colitogenic" flora in susceptible individuals triggers a sustained inflammatory response that leads to tissue destruction and disease.

Currently-approved therapies for CD are selected to suppress the immune response to dysbiosis, rather than address the triggers themselves. Despite advances in therapy over the last 20 years, there remain a significant number of patients who live with active symptoms and have a poor quality of life. In addition, available therapies do not provide sustained remission, leading up to 60% of patients with Crohn's disease to require surgery during their disease course (3). Annually, 10,000 patients with Crohn's disease (CD) undergo intestinal resection in the U.S., and many of them will later experience disease recurrence (4). Patients who require surgery at an early age, smokers and those with perforating phenotype are all at highest risk for recurrence; in recent trials this occurred in up to 85% of patients within 12 months of surgery (5). Human and animal studies have reported that dysbiosis occurs in the intestine after surgery, and reduced bacterial species diversity is associated with the subsequent risk of disease recurrence (6,7). An intervention at the microbiome level, before chronic inflammation is re-established, may diminish the ecological niche that some pro-inflammatory bacteria may acquire due to host defects in bacterial sensing. Supporting this concept is the evidence that post-operative antibiotics reduce the risk of endoscopic and clinical recurrence in patients with CD (8). Although anti-TNF agents have been shown to be highly effective at preventing resumption of inflammation, not every patient needs, or wants, to commit to continuous prophylactic anti-TNF therapy after surgery. Given the significant costs, and rare serious side-effects, of anti-TNF therapy, alternative effective strategies are also needed that target other instigators of post-operative recurrence. Our prior work highlighted the efficacy of antimicrobial therapy, and the limitations of anti-TNF agents, as post-operative prophylaxis (9,10).

Fecal Microbiota Therapy (FMT) is a microbiome-based treatment that could correct the intestinal dysbiosis in CD. FMT, also known as "fecal transplantation", "human probiotic infusion", "stool transplant," or "fecal transfer," involves collecting stool from healthy pre-screened donors and administering the components of this material to an individual with disease. Case series and reports of almost 400 patients since 1958 suggest that FMT is not only safe, but may be effective for a variety of gastrointestinal conditions including IBD (11). Fecal transplantation, by oral delivery, has been reported to enhance microbial diversity and restore ecological homeostasis in patients with C.difficile-associated colitis. Therefore, FMT could provide a safe and effective means of correcting ileal dysbiosis in the post-surgical setting, and preventing recurrence of CD. patients

with IBD (Crohn's disease or Ulcerative Colitis) who have undergone FMT have experienced sustained clinical, endoscopic, and histologic remission in case series and open label trials (12). An expert group recently recommended that well-designed clinical studies of FMT in patients with CD should also be undertaken. There is much enthusiasm in the CD community for FMT, and many patients are already opting to try FMT for their CD as an alternative to immunosuppressants. There have been a number of website bulletin boards on which there are active discussions by patients who have received fecal microbiota transplantation. In our review, these discussions reveal that some patients are now trying this treatment strategy at home without medical supervision or from unlicensed clinics. Cumulatively, these data highlight the need for a thoughtfully designed study of fecal microbiota transplantation for Crohn's disease, to provide data on its effects on the host microbiome, safety and tolerability.

We recently completed a pilot study of FMT to treat active Crohn's disease (IND#15409), and have presented the results at an international meeting (13). In this 12-month study at one site, we enrolled 20 patients with active Crohn's disease, refractory to conventional therapy, and treated them with open-label FMT (from frozen donor pool) via colonoscopy (NCT01847179). Following FMT, there was a significant change in HBI ($p < 0.0001$, **Figure 1 A**); fifty-four percent (6/11) of patients were in clinical remission at week 12 defined as an HBI < 5 and no escalation in CD related medications[3]. Following FMT, there was a shift in recipient microbiome towards donor samples with fewer disease-associated taxa present. Deep shotgun metabolomics sequencing of a single donor:recipient pair demonstrated that 99.5% of the donor microbiome was found in 56% of the recipient's microbiome post FMT, while only 10% of the pre-FMT microbiome remained (**Figure 1B)**. This study confirmed the safety of administering FMT in patients with active CD.

Figure 1

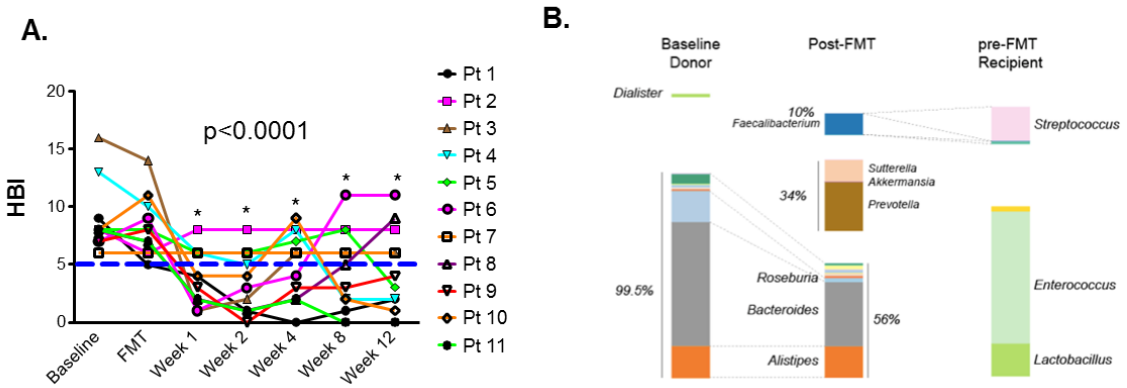

Figure 1. HBI scores in 11 patients with 12 week follow-up to date (A). Composition of the gut microbiome in a donor:recipient pair before and after FMT (B)

Given the clinical unmet need for safe, cost-effective interventions to prevent recurrence of Crohn's disease after surgery, we propose a randomized controlled trial to evaluate the efficacy of FMT to prevent recurrence of Crohn's disease in adult patients.

Summary of the Known and Potential Risks and Benefits to Human Subjects

Almost 400 patient outcomes have been reported from case series and case reports of patients who received FMT for colitis, and no serious adverse events have been noted. This included patients with Inflammatory Bowel Disease followed for up to 13 years. No infections transmitted from donor to recipient have been reported (14).

A recent randomized controlled trial of 17 patients treated with FMT (given by duodenal lavage) for *Clostridium difficile* infection reported their short-term adverse events. Immediately after the duodenal lavage, patients had diarrhea (in 94%), cramping (in 31%) or belching (in 19%) which all resolved within 3 hours in all cases (15). During follow-up, three patients who were treated with donor feces (19%) had constipation. These adverse events have not been noted when FMT is administered by colonoscopy. In our pilot study in patients with active Crohn's disease, no serious adverse events have been noted, over 6 months of follow-up (13). No other adverse events related to study treatment were reported. On the basis of these data, the following risks can be assumed for FMT;

Known Risks of FMT

- Altered bowel pattern (diarrhea, constipation)
- Cramping
- Belching
- Colonoscopy risks – intestinal perforation (1:5000), bleeding, altered bowel habit

Potential Risks of FMT

- Transmission of pathogenic bacteria, viruses, fungi
- Transmission of allergens
- Alteration in intestinal metabolism

Potential Benefits

- Restoration of fecal diversity
- Prevention of intestinal inflammation
- Prevention of clinical symptoms

Description of and justification for the route of administration, dosage, dosage regimen, and treatment period

Route of Administration

Donor fecal microbiota material will be administered in two formats; via colonoscopy as a solution, and encapsulated with glycerol and cocoa butter in HMCP capsules. For the initial dose, FMT in solution will be sprayed in the terminal ileum via a colonoscope. This route of administration for the initial dose has been selected for a number of reasons;

- Recurrence of inflammation in CD always develops in the region of the anastomosis between the ileum and colon (~2 inches long). This is the area where dysbiosis has been noted as a precursor to macroscopic inflammation. Colonoscopic delivery ensures delivery of FMT to the sites of disease recurrence. The rate of engraftment of donor microbiota when delivered via the oral route is unknown.
- The colonoscopic route of administration has been associated with ~80% efficacy in treating patient with *Clostridium difficile* colitis.

Prior studies, including ours (see above) have reported that changes in luminal microbiota diversity after a single colonoscopic delivery of FMT are not sustained. In order to enhance the probability of sustained changes in luminal microbiota post loading FMT, we propose weekly ingestion of an oral form of fecal-derived microbiota for the 6 months of the trial. This approach has been used successfully in a recent trial to treat *Clostridium difficile* colitis, where fecal matter from healthy donors were pipetted into acid-resistant hypromellose capsules for delivery to the colon (Youngster I 2014). This was associated with a 70% success rate in treating *Clostridium difficile* colitis

Dosage Form

1. Initial dose - filtered solution of donor stool (50 g) homogenized with sterile saline 90 mL.
2. Maintenance dose – six capsules of fecal material taken once per week (550µl of fecal material in size 00 gelatin capsule)

Dosing Regimen
Single initial dose of 90mL of fecal solution. This will be administered at least 30 days after the ileo-cecal resection, but within 50 days of the surgery.
Weekly dose of 6 capsules of fecal material (total 3300µl of fecal material per week)

Statement that the trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirements
This trial will be conducted in compliance with the protocol, good clinical practice, and FDA requirements.

Description of the Population to be Studied
Adult patients with ileo-colonic Crohn's disease who have undergone recent ileo-cecal resection.

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3. Trial Objectives & Purpose

Objectives

The objective of this trial is to assess if FMT can reduce the risk of endoscopic recurrence of CD in patients after intestinal resection. The specific outcomes of FMT we will examine are;

1. Endoscopic appearance
2. Clinical symptoms
3. Safety & tolerability
4. Microbial diversity

Hypothesis

Our hypothesis is that FMT will prevent establishment of a “pro-inflammatory” microbiome after surgery, leading to a reduced probability of recurrence of macroscopic inflammation. In addition we hypothesize that FMT will be safe and well-tolerated in these patients.

4. Trial Design

This is an open-label trial to study the rates of endoscopic recurrence of CD in patients after ileo-cecal resection. We will prospectively enroll 50 CD patients at least 30 days after ileo-cecal resection, and allow them to choose to receive either FMT or no therapy for 6 months. Subjects in the FMT arm will start treatment within 50 days of the surgery, but at least 30 days from the surgery, to ensure adequate healing has occurred at the anastomotic site, and to allow time for recognition of any early post-operative complications that might exclude patients from the trial.

Primary Clinical Endpoint

Proportion of patients in each arm of the trial who develop endoscopic recurrence within 6 months of ileo-cecal resection. “Endoscopic recurrence” will be defined as a Rutgeert’s score of >/= to i2.

Secondary Endpoints

Microbial Endpoints;

- Recipients’ fecal microbial diversity and metabolic profiles at 2, 4, 8, 10, 12, 16, 20 and 26 weeks after FMT, when compared to baseline

Inflammatory Endpoints;

- Percentage of patients with normal anastamosis (Rutgeerts score 0) at week 26
- Mean CRP at week 26

Clinical Endpoints;

- Mean Harvey Bradshaw Index (HBI) score at week 26
- Percentage of patients in clinical remission (those with an HBI score at week 26 <5)

Safety Endpoints;

- Number and nature of adverse events at week 4, 12, 26 and 52
- % of patients with adverse events reported at week 4, 12, 26 and 52

Steps to Minimize Bias

To minimize bias in the primary endpoint, endoscopic images from the week 26 colonoscopy will be reviewed and scored by a researcher who will be blinded to the treatment allocation (central reader).

Trial Treatment
The treatment for this trial will be an initial aliquot of donor stool in 90ml of sterile saline, followed by weekly ingestion of six capsules of encapsulated fecal material. These will be provided by the Microbiome Health Research Institute at Massachusetts Institute of Technology as described in their Drug Master File (15543).

Dosage Form
1. Initial dose - filtered solution of donor stool (50 g) homogenized with sterile saline 90 mL.
2. Maintenance dose – six capsules of fecal material taken once per week (550µl of fecal material in size 00 gelatin capsule)

Dosing Regimen
Single initial dose of 90mL of fecal solution
Weekly dose of 6 capsules of fecal material (total 3300µl of fecal material per week)

Packaging
Fecal solution will be acquired in plastic bottles, and enscapsulated fecal material in blister packs from the Microbiome Health Research Institute at Massachusetts Institute of Technology, as described in their Drug Master File (15543).

Labeling
See Drug Master File (15543).

Sequence & Duration of Trial Periods
An outline of the study timeline and measurements is shown in Appendix 1

Recipient Procedures;
Week -1; Screening – potential subjects will undergo the following screening procedures one week prior to FMT to determine if they meet the recipient selection criteria;
- medical record review to confirm diagnosis and treatment history
- Harvey Bradshaw Index (HBI) score to determine disease activity score (Appendix 2)
- stool sample to exclude current infections (bacterial culture, ova & parasites, Clostridum difficule toxin)
- standard of care blood tests for baseline and infection screening (CBC, LFTs, Renal profile, CRP, ESR)
- stool sample for microbiome analysis (MIT)

Women of child-bearing potential will be counseled by study clinicians, that those who choose to the treatment arm will be requested to avoid pregnancy by hormonal or barrier methods from time of screening for 7 months (duration of FMT therapy and one month lag afterwards).
Eligible subjects will then have the option to be in either treatment or control arm.

Week 0; *Treatment & Control Arm*
- Urine pregnancy test (HCG) for females of child-bearing age (during admission process, prior to colonoscopy)
- Initial Fecal Transplant via colonoscopy for treatment arm (none for control arm). Biopsies will be taken at the time of colonoscopy

Week 1; *Treatment Arm*
- Ingestion of first oral FMT capsules in clinic, under observation
- Follow-up phone call to assess for adverse events 4 hours later

Week 2, 4, 8, 10, 12, 16, 20 and 26: (Treatment & Control Arms)

- Stool sample for microbiome analysis (MIT)

Weeks 4, 12, 26; (Treatment & Control Arms) ;
Follow-up assessment of

- clinical scores
- adverse event screening,
- standard of care blood tests screening (CBC, LFTs, Renal profile, CRP, ESR)

Week 26: (Treatment & Control Arms);
Efficacy end-point evaluation;

- Urine pregnancy test (HCG) for females of child-bearing age (prior to colonoscopy)
- colonoscopy and Rutgeert's score of anastomosis images (Appendix 3). Biopsies will be taken at the time of the colonoscopy

Week 52 (Treatment & Control Arms)

- Final safety assessment; phone interview to screen for adverse events.

Written instructions will be given to all subjects for stool collection methods (Appendix 4).

Stopping Criteria

Adverse events will be specifically monitored at 4, 12, 26 and 52 weeks after FMT by direct patient interviews, or by reporting from clinical sites of adverse events at any time in-between. A data safety and monitoring board (DSMB, Appendix 5) will review all patient data to ensure optimal patient safety and precautions for subjects with CD treated with FMT. A severity grade for adverse events (Appendix 6) and subject symptom diary used (Appendix 7). The DSMB will meet a minimum of 2 times: after treatment of the first 20 subjects, and after treatment of all 44 subjects. Study will be stopped under the following circumstances;

- recurrence of CD symptoms in any more than 3 of the first 10 patients treated (increase by >5 points from baseline of mean HBI score after FMT)
- detection of new pathogenic intestinal infection in stool samples in any patient treated.
- any unexpected serious adverse event that that DSMB determines is of significant clinical impact, and probably related to FMT

In addition, any subject who develops a serious adverse event that is judge to be probably, possibly or definitely related to FMT therapy will receive no further FMT treatment. They will remain in the trial for adverse event follow-up.

Accountability Procedures for the Investigational Product

The location, volume and number of all FMT donor solutions will be maintained in a log by the research team. The principal investigator will be responsible for accurate record and tracking of all FMT solutions. Logging of FMT solution used for administration will be performed using a two-person process.

Data to be Recorded Directly on the CRFs

Data will be obtained from patient directly, and their electronic health record as follows;
Demographics - age, gender
Disease history - disease phenotype, disease location, duration of disease, medication history, surgical history, symptoms
Endoscopic scores

Adverse Events

5. Selection & Withdrawal of Subjects

Inclusion Criteria

Patients - Patient enrollment will be done via referral of appropriate patients from the study sites. Patients will be included if they meet all the following criteria:

- Adults (age > 18)
- Confirmed diagnosis of Crohn's disease, based on endoscopy, histology and imaging (confirmed by Study PI for each site)
- Ileo-cecal resection or terminal ileal resection for CD at least 30 days prior to enrollment in the trial.
- Resection margins & anastomosis free of active inflammation based on histology and surgical description (confirmed by Study PI for each site)
- No therapy to prevent post-operative recurrence of CD. A 30-day wash-out period for anti-TNFs, thiopurines, antibiotics will be required prior to enrollment.

Risk factors for post-operative recurrence will not be a requirement for study eligibility, as we expect most clinicians and their high-risk patients will opt to start anti-TNF therapy post-operatively, rather than enroll in a clinical trial. However, we expect some patients in this category will opt to try FMT before committing to anti-TNF prophylaxis. All enrolled subjects will be categorized as either 'high-risk' of recurrence (current smoker / perforating phenotype / prior ileal resection), or 'low-risk'.

Exclusion Criteria

Patient - Patients will be excluded for any of the following:

- Diagnosis of indeterminate colitis
- Women who are pregnant or nursing
- Patients who are unable to give informed consent
- Patients who are unable or unwilling to undergo colonoscopy with moderate sedation (>ASA class II)
- Patients who have previously undergone FMT
- Patients who have a confirmed malignancy or cancer
- Participation in a clinical trial in the preceding 30 days or simultaneously during this trial
- Probiotic use within 30 days of start date
- Decompensated cirrhosis
- Congenital or acquired immunodeficiencies e.g. neutropenia
- Chronic kidney disease as defined by a GFR <60mL/min/1.73m2 44
- History of rheumatic heart disease, endocarditis, or valvular disease due to risk of bacteremia from colonoscopy
- Active infections, including, but not limited to, surgical infections or abscesses
- History of severe food allergies
- Any condition, based on clinical judgement, that may make study participation unsafe. In particular, post-operative anastomotic leaks or fistula

Subject Withdrawal Criteria

Patients – patients will be withdrawn under the following circumstances;

- Colonoscopy for FMT cannot be completed for technical reasons due to inability by endoscopist to reach terminal ileum, or patient intolerance of procedure, or pregnancy. These patients will only be followed-up for week 2 adverse event screening, as they will not have received FMT. These subjects will be replaced, as they will not be considered "treated".
- Patient withdraws their consent for study protocols, follow-up visits or contacts
- Any subject who develops a serious adverse event that is judge to be probably, possibly or definitely related to FMT therapy will receive no further FMT treatment. They will remain in the trial only for adverse event follow-up.

Subjects who require rescue treatment will be censured for the analysis of primary end-point. They will however continue to be followed for 6 months for evaluation of safety outcomes.

6. Treatment of Subjects

Trial Treatment

The initial treatment for this trial will be administration of an initial single infusion of fecal solution to the terminal ileum. Treatment will begin at least 30 days after ileo-cecal resection, but within 50 days of surgery, in the treatment group.

Subsequent FMT administration will be in the form of capsules of frozen FMT material ingested orally once a week. Each subject will ingest six FMT capsules once every seven days for the 6 months of treatment in the trial. The first ingestion will be undertaken in the clinic, where subjects will be monitored for adverse events for 1 hour. A follow-up phone call will be undertaken 4 hours later to screen for adverse events. At this visit, and at weeks 4, 12 subjects will be provided with blister packs of FMT capsules for their subsequent doses. They will be instructed to store the blister packs in a sealed bag (provided) in a domestic freezer at -20^0C until each weekly ingestion. A full instruction document for patient is included as Appendix 8.

Medications Permitted

During the follow-up period after enrollment (6 months), subjects should not take any medications that may prevent recurrence of CD; antibiotics, thiopurines, anti-TNFs, mesalamine. Rescue pathway for CD subjects with clinical recurrence during the study period to be determined by the clinician investigator and based on standard of clinical practice. This may include, but is not limited to the following;

i. Oral steroids (if not already receiving them or failing them)
ii. Rectal therapy (5-ASA or steroids)
iii. IV steroids
iv. Hospitalization
v. Anti-TNF therapy
vi. Surgery

7. Assessment of Efficacy

Primary Clinical Endpoint;

Proportion of patients in each arm of the trial who develop endoscopic recurrence within 6 months of ileo-cecal resection. "Endoscopic recurrence" will be defined as a Rutgeert's score of >/= to i2.

Secondary Endpoints:

Microbial Endpoints;

- Recipients' fecal microbial diversity and metabolic profiles at 2, 4, 8, 10, 12, 16, 20 and 26 weeks after FMT, when compared to baseline

Inflammatory Endpoints;

- Percentage of patients with normal anastamosis (Rutgeerts score 0) at week 26
- Mean CRP at week 26

Clinical Endpoints;

- Mean Harvey Bradshaw Index (HBI) score at week 26
- Percentage of patients in clinical remission (those with an HBI score at week 26 <5)

Safety Endpoints;

- Number and nature of adverse events at week 4, 12, 26 and 52
- % of patients with adverse events reported at week 4, 12, 26 and 52

8. Assessment of Safety

Patient safety monitoring schedule - although there have been no reported serious adverse events associated with fecal microbiota transplantation (FMT) in patients with recurrent refractory Clostridium difficile or Crohn's disease (CD), we will have a special data safety and monitoring board (DSMB) to ensure optimal patient safety and precautions for subjects with CD treated with FMT. Adverse events will be specifically monitored at 4, 12, 26 and 52 weeks after FMT by direct patient interviews, or by reporting from clinical sites of adverse events at any time in-between. The DSMB will meet a minimum of 2 times: after treatment of the first 20 subjects, and after treatment of all 44 subjects. A copy of the DSMB charter is located in Appendix 5.

For this trial, an adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a biologic product; such an occurrence does not necessarily have to have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product whether or not considered related to the medicinal product. A serious adverse event (SAE) is defined as any untoward medical occurrence that results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is an important medical event that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes previously mentioned. Adverse events will be determined by a toxicity grading scale (Appendix 6). In accordance with applicable policies of the BIDMC Institutional Review Board (IRB), the investigator-sponsor will report, to the IRB, any observed or volunteered Unanticipated Problem that is determined to be 1) unexpected); 2) related or at least possibly related to study participation; and 3) suggests that the research places subjects or others at a risk of unknown harm or addition/increased frequency of harms (including physical, psychological, economic, legal, or social harm) than was previously known or recognized. Unanticipated problems may be adverse events, protocol deviations, noncompliance or other types of problems, but MUST meet all of the criteria listed above. Unanticipated problem reports will be submitted to the IRB in accordance with the respective IRB procedures.

Patients will be asked to document their symptoms using the symptom diary card (Appendix 7) as a memory aide. Subjects will be asked to complete a symptom diary card 1 week prior to colonoscopy FMT and on the day of colonoscopy FMT treatment to assess their baseline. They will then be asked to complete a symptom diary card daily for the first seven days post colonoscopy FMT and then weekly thereafter for 26 weeks. The symptom diary card will help the patient monitor and keep track of adverse events. 6 months after the last dose of oral therapy, the patient will receive a final follow-up phone call.

In addition the DSMB may convene additional meetings if necessary to ensure the ongoing monitoring and safety of the subjects treated with FMT. The internal DSMB will include the following individuals: Dr Ciaran Kelly (Gastroenterology – BIDMC, Chair),
Dr. David Yassa (Infectious Diseases – BIDMC),
Dr. Mark Osterman (Gastroenterology – University of Pennsylvania)

All events will be reported directly to the DSMB and the Institutional Review Board (IRB) in accordance with Harvard University policy: Investigators will promptly report to the IRB all unanticipated problems involving risks to human subjects or others under Title 21 of the Code of Federal Regulations (21 CFR 312.32) part 56 (Institutional Review Boards), part 312 (Investigational New Drug Application), and part 812 (Investigational Device Exemptions). Harvard Medical School policy is consistent with guidance set forth by the Office for Human Research Protections (OHRP) (presented January 15, 2007) http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm and the FDA (presented January 14, 2009) http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf when determining what related events require review by the Institutional Review Board. Any serious AEs also will be evaluated by the DSMB for review and determination of whether the trial should continue.

All subjects will be followed for an additional six months following the end of their treatment. Subjects that did not experience a AEs or SAEs will receive a telephone call to monitor their current symptoms and quality of life. For subjects that did experience a AE or SAE that was found to be connected to the FMT treatment, we ask that they return to our medical center for an exam with their gastroenterologist. All treatment and outcome of AEs will be documented on the CRF and summarized in the CSR. All AEs will be followed to resolution or stabilization by the study physician.

9. Statistics

Power Calculations

Assuming 60% endoscopic recurrence in the control arm, and 20% in the FBT arm, the study would require 22 patients in each arm (Total N=44) to have 80% power. These assumptions are based on endoscopic recurrence data from the Reguiero trial, which represents typical patient populations coming to ileo-colectomy at tertiary referral centers[16]. This cohort could be enrolled from 4 participating sites (N=11 per site) that perform >30 ileo-cecal resections per annum.

Statistical Analysis Plan

For the primary end-point, chi-square test (or Fisher's exact test if any cell number <5) will be used to compare the proportion of patients in each arm who exhibit endoscopic recurrence (Rutgeerts score $\geq$ i2) at 6 months. A p value <0.05 will be considered significant.

For the secondary end-points, dichotomous variables will be summarized using frequency tables or proportions, and compared using chi-square of Fisher's exact test. Continuous variables will be expressed as mean values ± standard error, and compared using unpaired, two-tailed Student's t-tests and one-way analysis of variance (ANOVA) for multiple group comparisons. Data that lack normality will be analyzed using non-parametric tests (Mann-Whitney). P-values < 0.05 will be considered significant, after correction for multiple tests. Data will be analyzed using JMP software (SAS, Cary, NC). For microbial diversity, we will apply a set of downstream statistical tests to the resulting microbial, viral, gene, pathway, and metabolite abundances. Transformed data from groups will be compared using Bray–Curtis similarity, multidimensional scaling, and analysis of similarity (ANOSIM) (Primer E, Plymouth,UK). ANOSIM will also be used to compare

intersubject and intrasubject TRFLP profile similarities. Analysis of variance (ANOVA) will be used to compare relative abundance of specific TRFLP pattern elements between each group of subjects. These tests will take into account covariates included in available or collected sample metadata (age, family history, treatment, environmental/demographic data, and diet) by leveraging our LEfSe univariate biomarker discovery method and its multivariate successor MaAsLin. Such statistical tests will provide a measure of expected reproducibility of predicted microbial biomarkers that is not attainable by unsupervised ordination methods (e.g. Principle Coordinates Analysis) as provided by other software such as QIIME.

10. Direct Access to Source Data/Documents

The investigator will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents.

11. Quality Control and Quality Assurance

Good Clinical Practice will be adhered to in screening, preparation and administration of donor stool. All research staff are trained in Responsible Conduct of Research of clinical trials.

12. Ethics

Special Ethical Considerations: None
Subject Confidentiality: as described above
Placebo Use: N/A
Exclusion of Children and Women of Childbearing Capacity: This is a pilot study to establish safety and tolerability in adults and women who are not pregnant or nursing. Future studies will potentially include children and childbearing-women
Exclusion of Vulnerable Populations: N/A
Plans for Scientific Review: The PI and co-investigators will be responsible for overseeing scientific review.
In accordance with Harvard Medical School policy, all investigators have completed a COI statement. There are no relevant COI for this study.

13. Data Handling and Recordkeeping

Electronic data will be uploaded to a secure server hosted at the primary study site. Electronic data will be stored in the site's shared drive on a secure server behind the site's firewall. Only those individuals granted access to the CD research shared drive will have access to this data. Patient information will be coded and the coding legend will be maintained in a password-protected PC in the investigator's locked office. Only investigators will retain the electronic code linking samples to PHI for patients. Original consent forms and other paper charts will be kept in a secured locked cabinet in the study coordinators office . Data will be stored through the Harvard-affiliated RedCap program. This will allow security of data and accuracy of clinically collected information.

Research stool samples will be shipped on the day of collection with unique study numbers that do not identify patients by name, date of birth or medical record number (completely de-identified). Once received, researchers at the Broad Institute will re-code samples for an additional level of security. Analyzed stool products will be stored at the Broad Institute for the duration of the study. Only investigators at BIDMC will retain the code linking blood samples to PHI. There is very minimal risk of loss of confidentiality relating to the shipment or storage of stool samples.

14. Financing and Insurance

This clinical trial is funded by a grant from the Harvard Institute for Translational Immunology (HITI) and Finch Therapeutics.

15. Publication Policy

The PI will be responsible for publishing any findings. Results are expected to be published six months following the conclusion of the study. The study team will be responsible for compiling all necessary results in preparation for publication.