Weill Cornell Medicine NewYork-Presbyterian

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PROTOCOL

A randomized, placebo-controlled clinical trial examining the efficacy of Fecal Microbiota Transplantation (FMT) and subsequent dietary fiber in patients with moderate ulcerative Colitis

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Participating Sites:

Study Enrollment and Treatment
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Table of Contents

Statement of Compliance

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the Weill Cornell Medical College Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM.

List of Abbreviations

AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
CTSC	Clinical Translational Science Center
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
FDA	Food and Drug Administration
FMT	Fecal Microbiota Transplantation
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HUD	Humanitarian Use Device
IB	Investigator Brochure
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
UC	Ulcerative Colitis
UIRTSO	Unanticipated Problem Involving Risks to Subjects or Others
WCM	Weill Cornell Medicine

1. Protocol Summary

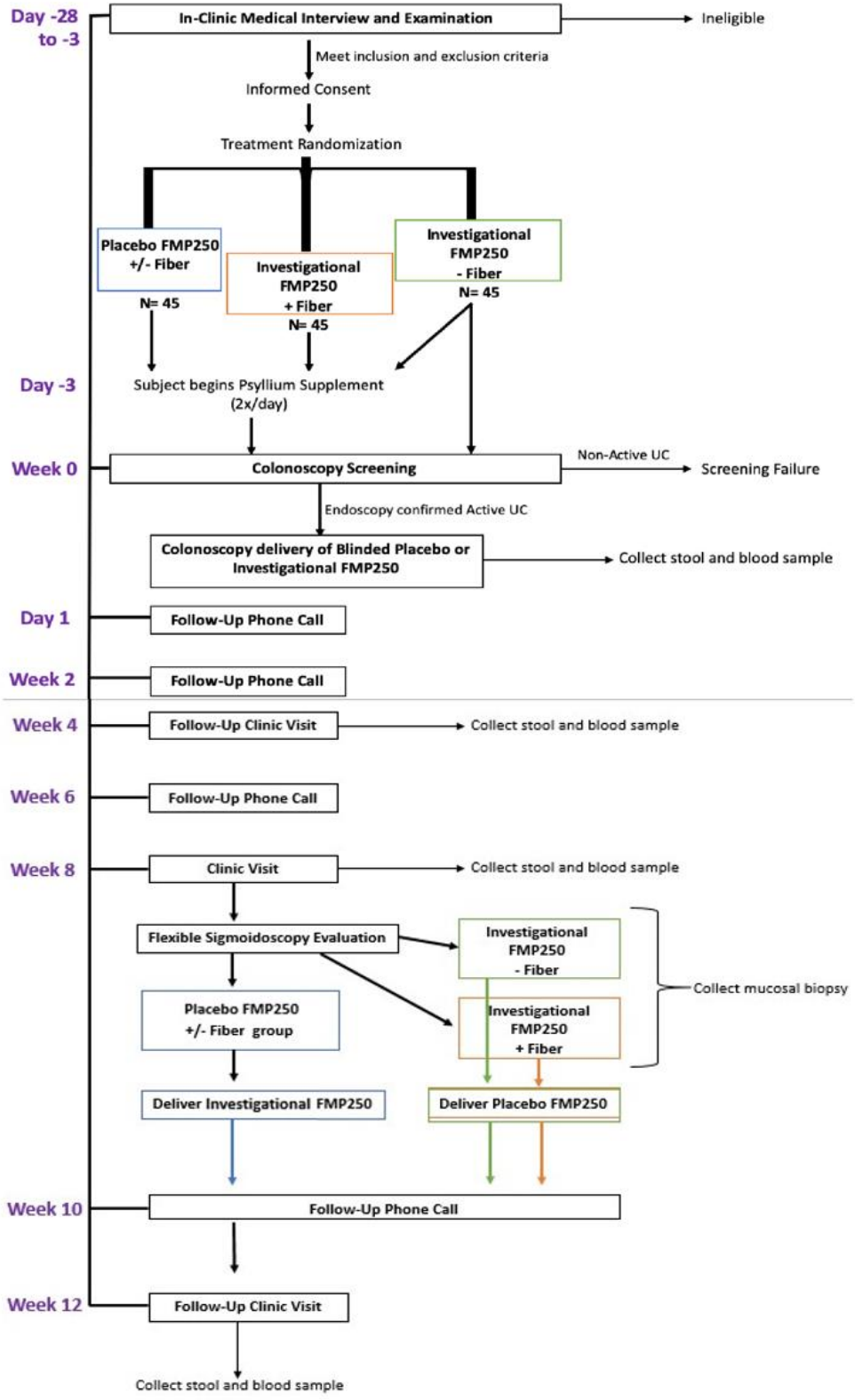
Full Title:	A randomized, placebo-controlled clinical trial examining the efficacy of Fecal Microbiota Transplantation (FMT) and subsequent dietary fiber in patients with moderate ulcerative Colitis
Short Title:	MINDFUL
Clinical Phase:	II
Principal Investigator:	Randy Longman, MD PhD
Study Description:	A double-blind, randomized, placebo-controlled clinical trial examining the efficacy and safety of Fecal Microbiota Transplantation (FMT) and high fiber supplementation in patients with active mild to moderate Ulcerative Colitis (UC). All enrolled subjects will provide serological, stool and mucosal specimen at each clinic visit to help further define the alterations in microbial profiles and immune cell function in response to psyllium fiber after FMT treatment.
Sample Size:	N=135, 45 subjects per study arm
Enrollment:	This study will enroll 135 subjects and screen up to 150 subjects.
Study Population:	All male and female participants at least 18 years of age with prior history of mild to moderate Ulcerative Colitis and willing to undergo standard of care colonoscopy to assess active disease for study eligibility.
Enrollment Period:	2019-2023
Study Design:	This is a randomized, double-blind, placebo-controlled clinical trial with the following treatment assignments:

1. Investigational FMP250 (one-time) at week 0
    a. Subjects in this group will also blindly receive placebo FMP250 at week 8 by flexible sigmoidoscopy.
2. Investigational FMP250 (one-time) at week 0 + Psyllium fiber (2x/day for 8 weeks)
    a. Subjects in this group will also blindly receive placebo FMP250 at week 8 by flexible sigmoidoscopy.
3. Placebo FMP250 (one-time) at week 0 with or without Psyllium fiber (2x/day for 8 weeks)
    a. Subjects in this group will also blindly receive investigational FMP250 at week 8 by flexible sigmoidoscopy.

Subjects will blindly receive the investigational or placebo FMP250 treatment only if they meet all inclusion and exclusion criteria during the day 0 screening colonoscopy. Subjects will receive a follow-up phone call or return for a clinic visit every 2 weeks post-FMT until week 12. At week 8 post-FMT, all subjects will be evaluated by flexible sigmoidoscopy in the clinic. Stool and blood samples will be collected for research from subjects at day 0 prior to FMT, week 4 post-FMT, week 8 post-FMT, and

	week 12 post-FMT. Mucosal biopsies will also be taken during the initial colonoscopy at day 0 and during the follow-up flexible sigmoidoscopy at week 8. Subjects randomized into the placebo cohort will receive investigational FMP250 and subjects randomized into the investigational cohort will receive placebo FMP250 by flexible sigmoidoscopy at the week 8 clinic visit (after week 8 endpoint data are collected). All subjects will return 4 weeks later at week 12 for a clinic visit. All subjects will be contacted for follow-up phone calls every subsequent 6 months for the next year.
Description of Site(s) Enrolling Participants:	The Jill Roberts Center for Inflammatory Bowel Disease Gastroenterology and Hepatology at David H. Koch Center Weill Cornell Medicine/ New York Presbyterian Hospital 1283 York Avenue, 9th Floor New York, NY 10065
Study Duration:	2019-2023
Participant Duration:	12 weeks + 1 year follow up
Study Drug Name:	FMT Lower Delivery Microbiota Preparation (FMP250)
Intervention Description:	Subjects will receive up to 250cc of blinded investigational or placebo FMP250 delivered by colonoscopy once at day 0. Placebo treatment group will receive investigational FMP250 while the investigational treatment groups will receive placebo FMP250 by flexible sigmoidoscopy at week 8.

1.1 Study Schematic



1.2 Study Objectives

1.2.1 Primary Objective

To assess if a dietary prebiotic supplementation (psyllium husk powder) in addition to FMT is superior to FMT or prebiotics alone to achieve clinical response in patients with mild to moderate Ulcerative Colitis compared to FMT or prebiotic alone.

1.2.2 Secondary Objective(s)

To assess if a dietary prebiotic supplementation in addition to FMT compared to either alone is superior in achieving clinical remission, endoscopic response or endoscopic remission, histologic response or remission rates.

To assess clinical response / remission and endoscopic response and remission of Fecal Microbiota Transplantation (FMT) for the management of active mild to moderate Ulcerative Colitis compared to placebo.

1.2.3 Exploratory Objective(s)

To define the microbial determinants of successful microbial manipulation therapy from mucosal, blood and stool samples collected at day 0 prior to FMT and week 8 post-FMT.

To define the impact of diet on the clinical and microbiome outcomes of Fecal Microbiota Transplantation (FMT) for the management of active mild to moderate Ulcerative Colitis compared to FMT or prebiotic alone.

2. Background

2.1 Ulcerative Colitis

Ulcerative colitis (UC) is a type of inflammatory bowel disease (IBD) characterized by recurring episodes of inflammation limited to the mucosal layer of the colon. This chronic disease may even extend to all divisions of the large intestine and in 95% of its cases it involves the rectum[1]. The highest prevalence of UC is reported in Europe (505 cases per 10,000 in Norway) and North America (286 per 100,000 in USA)[2] with approximately 38,000 new cases each year[3]. The severity of this illness ranges from mild well-controlled symptoms to severe uncontrolled manifestations which require hospitalizations, blood transfusions, surgical interventions, and may even cause death.

Current treatment for UC relies heavily on drug therapies to target host factors and immune suppression for the management of symptoms, prevention of relapses, and induction of remission. Aminosalicylates are the first line therapy for newly diagnosed mild to moderate UC. Although safe and effective in mild to moderate UC, few alternatives exist, and non-compliance is commonplace. Patients who relapse often require escalation to immunomodulators or steroid therapy, which similarly have limited safety profiles. Steroids are efficient for induction therapy; however, they are known to have significant side effects and do not provide benefit for maintenance therapy. Immunomodulators, such as azathioprine and 6-mercaptopurine, similarly have a significant side

effect profile and limited efficacy in inducing remission. They increase the risk of lymphoma and other malignancies, and may result in bone marrow toxicity and hepatotoxicity[4,5]. Mainstay of treatment for patients with UC who fail 5-ASA therapy are anti-tumor necrosis factor drugs (anti-TNFs), anti-integrin therapy (vedolizumab) and the janus kinase inhibitor tofacitinib, which are often efficacious with a clinical response rate reported to be as high as 70%[6]. Aside from vedolizumab, these therapies carry serious potential adverse effect profiles[7-9]. Furthermore, all have significant cost. Although there are numerous medications available for the management of UC, patients commonly become steroid-dependent and/or refractory to medical management and eventually require surgery[10]. Patients with poorly controlled UC are often desperate for a different method to control their symptoms due to the tremendous pain and suffering, loss of productivity, and disease-associated financial burdens.

Patients with IBD, including UC, harbor various genetic variants in genes regulating immune system function[11]. These variants can increase susceptibility to abnormal immune responses to microorganisms within the gut resulting in persistent inflammation and the debilitating inflammation of UC. Although the etiology of UC is not well understood, the presence of certain beneficial bacteria can prevent disease in experimental animal models of colitis while the loss of these bacteria or overgrowth of other types can trigger induction of inflammatory responses and debilitating symptoms of IBD[12]. The vast majority of treatment modalities for UC target host factors of inflammation. Despite substantial research efforts to understand the role of commensal bacteria in disease and pathogenesis, the therapeutic role for microbial manipulation in active UC is less well defined. Although antibiotics are used in the treatment of infectious complications of UC, their role for induction or maintenance therapy is unsupported by several different clinical studies. Therapeutic manipulation of intestinal microbiota can be achieved by other methods than antibiotics.

2.2 Fecal Microbiota Transplant (FMT)

FMT is an emerging therapy that transfers healthy donor fecal bacteria to patients suffering from GI illnesses with the goal of re-establishing a healthy intestinal bacterial community in those patients[13]. FMT has shown to be effective in the management of various diseases, most notably Clostridium difficile infections (CDI). A randomized control trial from 2013 in the New England Journal of Medicine evaluated the use of FMT in the management of CDI. The results were promising: an overall cure of 15 out of 16 patients (94%)[14].

There are 3 major clinical trials that have looked at the safety and efficacy of FMT for the management of UC. In the first randomized, placebo controlled clinical trial by Rossen et. al, 50 patients with active UC (23/25) received FMT (donor stool) or placebo (autologous stool) via nasoduodenal delivery twice during the 12 weeks study period[15]. Analysis showed 41% vs 25% efficacy with no statistical differences between the groups[15]. Moayyedi et al. enrolled 75 study participants who received donor FMT or placebo (water) weekly enemas for 6 weeks[16]. 24% of patients who received FMT showed clinical response compared with 5% in placebo group and the difference between the groups was significant[16]. Paramsothy et al.'s study delivered donor FMT or placebo in 85 (42/43) patients via colonoscopy followed by 5 times per week enema for 8 weeks[17]. Primary outcome was reached by 27% of patients from FMT group compared with 8% in placebo group with significant differences between the groups[17]. These clinical findings indicate that despite the variation of delivery and dosage, FMT appears to be safe and effective for induction and remission of UC and can be included as an adjunctive therapeutic modality for management of the disease.

Our collaborative team recently completed a pilot study at Weill Cornell Medicine aimed at assessing the safety, clinical efficacy, and microbial engraftment of single FMT delivery by colonoscopy for active UC[18]. We performed a single-center, prospective, open-label pilot study to evaluate the safety and

efficacy of two-donor fecal microbiota preparation (FMP) delivery by colonoscopy. The primary outcome was clinical response at week 4 with secondary endpoints including clinical remission, mucosal healing at week 4 and safety profile. Overall, 34 patients were screened, and 20 patients were enrolled. Seven patients (35%) achieved a clinical response (Mayo score ≥ 3 and a bleeding subscore ≤1) by week 4. Three patients (15%) were in clinical remission at week 4 (Mayo score ≤2 and no subscore >1), and two of these patients (10%) achieved mucosal healing (endoscopy subscore of 0). Paired analysis showed a significant improvement in Mayo score (Median decrease of 1.5, p = 0.03) and endoscopic subscore (Median decrease of 0.5, p = 0.002).

Further microbiome analysis revealed that signatures of donor-derived microbiota correlate with clinical response[18]. Taxonomic analysis revealed enrichment of *Ruminococcus*, *Odoribacter*, and *Christensenellaceae* in healthy donors and responders, but absent in patients with active disease. In contrast, patients who did not respond to treatment had failed to eradicate *Fusobacteria*, *Finegoldia* and *Collinsella*. To determine the fecal microbial composition and function at species/strain level, we performed metagenomic sequencing of a complete set of three samples (donor, recipient pre, recipient post) from three responder patients, who had met the primary endpoint of our pilot FMT trial. Relative abundances of microbial species were determined by Metaphlan2 and protein encoding genes profiling were determined by HUMAnN2 pipeline. Analysis of the previously identified transferrable genus of *Ruminococcus* revealed, that of the several species and strains present in the patient samples, abundance of only *Ruminococcus* torques was significantly enriched in responders. Collectively, this data revealed that response to single *colonoscopic* delivery correlated with engraftment of key species of transferrable bacteria in the responder patients. Further studies are required to determine factors that enhance the engraftment of these bacteria and increase the efficacy of this therapy.

2.3 Dietary Fiber Supplementation

Dietary supplements are important factor that may regulate engraftment of beneficial donor bacteria. Short-chain fatty acids, such as butyrate, are important colonic metabolites provided by diet-based carbohydrates fermented by commensal bacteria in the gut microbiota[19-21]. Butyrate has been well characterized by in vitro studies to protect the epithelium against pathogens by upregulating mucins, the antimicrobial peptides responsible for the mucosal layer, and by increasing the expression of tight junction proteins to reduce intestinal permeability[19]. Butyrate is an inhibitor of nuclear factor NF-κB, a transcription factor necessary for the expression of pro-inflammatory proteins[20], and an immunomodulator of macrophages, dendritic cells (DC), and T cells[19]. Studies in animal models demonstrate that supplemental butyrate upregulates regulatory T cells and ameliorates intestinal inflammation[22,23]. Recent studies evaluated the use of various fiber-based diets in animal models of IBD with indigestible fibers having strongest effect on mucosal inflammation[23-25]. These curative properties substantiate the potential role of a post-transplant fiber therapy as necessary to prolong remission and de-escalate immunosuppressive treatments by promoting microbial engraftment and mucosal healing.

Efficacy of dietary fiber for management of IBD has been long investigated using fiber rich diet or fiber supplements, largely with variable effects. Several clinical trials have demonstrated the therapeutic benefit in UC patients with psyllium having significant effect for maintenance of remission and germinated barley for active UC[20]. Importantly, none of the studies reported disease exacerbation or early relapse in patients with IBD. Therefore, controlled data demonstrating the effect of fiber as a prebiotic regulator of engraftment and FMT outcome in UC has yet to be explored.

2.4 Rationale

The current standard of care for ulcerative colitis relies heavily on medications targeting host factors for the management of symptoms, prevention of relapses, and induction of remission. Although there are numerous medications available for the management of UC, patients commonly become steroid-dependent and/or refractory to medical management. FMT is an emerging treatment modality for UC. Although the clinical efficacy of FMT for UC is variable, our preliminary results suggest that response may correlate with the engraftment of key beneficial microbiota[18]. Therefore, our study is aimed at determining the role of supplemental fiber as a mechanism to enhance the efficacy of FMT. Results from this study have the potential to offer pioneering data on the ability of prebiotics to shape microbial engraftment. This intervention has the potential to impact FMT in UC and microbial manipulation therapy more broadly.

Thus, the overall goal of this study is to test the role of supplemental psyllium in the clinical outcome and microbial engraftment of FMT for ulcerative colitis.

2.4.1 FMP Lower Delivery Microbiota Transplant (FMP250)

In our previous single-center, prospective, open-label pilot study, we sourced our two-donor fecal microbiota preparation (FMP) from OpenBiome and found that FMP delivery by colonoscopy not only was safe but also efficacious in improving clinical response as a therapeutic alternative for UC patients. Therefore, we propose to source OpenBiome's FMT Lower Delivery Microbiota Preparation (FMP250) as the investigational drug in this clinical trial.

2.4.2 Psyllium Husk Powder

Highly viscose, gel-forming soluble fibers have been found to lower elevated serum cholesterol concentrations, improve glycemic control, and have stool regularity benefits[28]. We are interested in utilizing a fiber that can provide regularity benefits to aid in stool passage. Regularity benefits are attainable by soluble gel-forming fibers if they are able to resist fermentation and have a high-water retention capacity. We have chosen psyllium as our dietary supplement to pair with FMP250 because it is a non-fermented, natural fiber that is viscose, gel-forming, and soluble and is an FDA-approved over the counter product. Psyllium is composed of stackable polymer chains, which contribute to its viscosity, that crosslink to form a gel to promote water retention in the colon, which causes a softer stool by protecting it against dehydration. The fiber will help the stool remain whole and bulky throughout its passage in the large intestine. We chose psyllium over a very similar fiber called b-glucan because various RCTs demonstrated that fermentable fibers in the colon caused no effect on stool composition. Interestingly, psyllium has the capacity to provide regularity benefits by two mechanisms. It can either soften stool or increase bowel movements for constipation but more importantly for this study, it is able to harden stool and decreased bowel movements for diarrhea.

Psyllium husk powder will be purchased commercially by WCM investigators and provided to subjects in the fiber treatment assignment if they meet all inclusion criteria during their screening visit, excluding the endoscopic criteria.

2.5 Risk/Benefit Assessment

2.5.1 Known Potential Risks

2.5.1.1. FMT-related: (adapted from OpenBiome FMP250 Investigator Brochure V4.0):

The following adverse reactions have been reported in scientific literature to be commonly caused by FMT material within 24 hours post-procedure:

- Transient diarrhea, abdominal cramps/discomfort, and nausea
- Fever, bloating, belching, vomiting, borborygmi
- Constipation and flatulence
- Flares in IBD patients

These symptoms are usually self-limiting and of short duration. They may also be attributable to the delivery modality (e.g. colonoscopy or upper endoscopy) or underlying disease.

According to Openbiome and/or peer-reviewed literature, the following serious adverse events are potential risks that have been observed by FMT-based products (not specifically Openbiome) or included based on biological plausibility:

1. Infection
    a. Bacterial infections from multi-drug resistant organisms (MDROs) (i.e. extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, vancomycin-resistant enterococci (VRE), carbapenem-resistant Enterobacteriaceae (CRE), and methicillin-resistant Staphylococcus aureus (MRSA))
    b. Shiga Toxin-Producing E. Coli (STEC) Infections
    c. Enteropathogenic E. Coli (EPEC) Infections
    d. SARS-CoV-2 Infection
    e. Diverticulitis, bacteremia, cytomegalovirus colitis, fever, diarrhea encephalophagy and pancytopenia, Influenza B and diarrhea, norovirus gastroenteritis
    f. Monkeypox Infection
2. Aspiration from upper GI delivery of FMT
3. GI complications (i.e. diarrhea, abdominal pain, appendicitis, peritonitis, IBD flare, and diverticulitis)
4. Allergy/Anaphylaxis
5. Autoimmune disorders
    a. Exacerbation of pre-existing autoimmune conditions
    b. Development of Rheumatoid arthritis, Sjogren's disease, peripheral neuropathy, idiopathic thrombocytopenic purpura
6. Non-infectious disease transmission (i.e. obesity, metabolic syndrome, cardiovascular disease, neurologic disorders, psychiatric conditions and malignancy)

2.5.1.2. Psyllium-related

The FDA {CFR - Code of Federal Regulations Title 21} recommends sufficient liquid consumption when taking dried psyllium husk to avoid any potential risk for choking. In geriatric patients, some rare side effects may include abdominal discomfort, nausea, mild abdominal cramps, griping, and faintness[34]. Additionally, our investigators hypothesize that bloating could occur as a side effect.

2.5.2 Known Potential Benefits

2.5.2.1. FMT-related

Our previous pilot study found 35% of subjects clinically responded and 15% went into clinical remission when evaluated at the 4 weeks post-FMT[18]. Similar clinical trials found improvement in clinical response in subjects treated with FMT when compared to the placebo groups[15-17]. However, we cannot and do not guarantee that subjects will receive any benefits from this study. We hope the information learned from this study will benefit other patients with ulcerative colitis in the future.

2.5.2.2. Psyllium-related

Various dietary fiber interventions report that it may be beneficial for IBD patients, however, their results do not consistently demonstrate alleviation of disease activity and/or inducement of clinical remission[31]. Therefore, we cannot and do not guarantee that subjects will receive any benefits from psyllium in combination with FMP250. We hope the information learned from this study will benefit other patients with ulcerative colitis in the future.

2.5.3 Assessment of Potential Risks and Benefits

Ulcerative colitis remains a major medical problem. Steroids, immunosuppressants, and biologic therapies are the mainstay of therapy for active disease. These medications are all associated with a range of side effects. Recent studies have demonstrated the potential efficacy of FMT for the treatment of mild to moderate UC. Although some risks exist including procedural risk associated with colonoscopic delivery, this emerging therapeutic strategy appears to be more effective than placebo in inducing clinical remission. This study will additionally assess the use of psyllium husk as a prebiotic supplement to enhance the efficacy of FMT. We do not anticipate additional risk associated with psyllium.

A FMT placebo arm with psyllium supplement is required to assess the potential clinical efficacy of psyllium alone and to serve as a placebo control for FMT. The placebo arm is required in order to determine the efficacy of FMT + psyllium over psyllium alone. However, at the end of the study, investigational FMT will be provided for patients in the psyllium + placebo arm.

Importantly, no SAEs have been found in any previous FMT intervention, including our pilot study, to be *definitely* attributed to the investigational drug. Therefore, we believe the potential benefit

of clinical and endoscopic response or remission from FMT concurrently with psyllium supplementation outweighs the risks.

2.6 Correlative Studies Background

Our collaborative team recently completed a pilot study at Weill Cornell Medicine aimed at assessing the safety, clinical efficacy, and microbial engraftment of single FMT delivery by colonoscopy for active UC[18]. We performed a single-center, prospective, open-label pilot study to evaluate the safety and efficacy of two-donor fecal microbiota preparation (FMP) delivery by colonoscopy. The primary outcome was clinical response at week 4 with secondary endpoints including clinical remission, mucosal healing at week 4 and safety profile. Overall, 34 patients were screened, and 20 patients were enrolled. Seven patients (35%) achieved a clinical response (Mayo score ≥ 3 and a bleeding subscore ≤1) by week 4. Three patients (15%) were in clinical remission at week 4 (Mayo score ≤2 and no subscore >1), and two of these patients (10%) achieved mucosal healing (endoscopy subscore of 0). Paired analysis showed a significant improvement in Mayo score (Median decrease of 1.5, $p = 0.03$) and endoscopic subscore (Median decrease of 0.5, $p = 0.002$). The present will test the hypothesis that prebiotic supplementation with psyllium will increase that clinical response rate over FMT alone. Furthermore, the current study will assess additional impact on clinical and endoscopic remission rates as well as placebo FMT.

Further microbiome analysis revealed that signatures of donor-derived microbiota correlate with clinical response[18]. Taxonomic analysis revealed enrichment of *Ruminococcus*, *Odoribacter*, and *Christensenellaceae* in healthy donors and responders, but absent in patients with active disease. In contrast, patients who did not respond to treatment had failed to eradicate *Fusobacteria*, *Finegoldia* and *Collinsella*. To determine the fecal microbial composition and function at species/strain level, we performed metagenomic sequencing of a complete set of three samples (donor, recipient pre, recipient post) from three responder patients, who had met the primary endpoint of our pilot FMT trial. Relative abundances of microbial species were determined by Metaphlan2 and protein encoding genes profiling were determined by HUMAnN2 pipeline. Analysis of the previously identified transferrable genus of *Ruminococcus* revealed, that of the several species and strains present in the patient samples, abundance of only *Ruminococcus* torques was significantly enriched in responders. Collectively, this data revealed that response to single *colonoscopic* delivery correlated with engraftment of key species of transferrable bacteria in the responder patients. This study will therefore evaluate the hypothesis that psyllium prebiotic supplementation will change the species engraftment.

3. Study Design

3.1 Overall Design

Hypothesis: A high fiber diet will promote the engraftment of healthy donor microbiota and increase the efficacy of FMT in UC patients. If successful, this proposal will help us to define the role for dietary fiber supplementation in promoting microbial determinants of successful FMT and enhance the clinical efficacy of FMT for UC.
Study Phase: II
Study Design: Double-blinded, randomized, placebo-controlled clinical trial
Study Drug: FMT Lower Delivery Microbiota Preparation (FMP250)
Study Arms:

Group 1: Investigational FMT

- Subject will receive investigational FMT once at day 0 colonoscopy
- Subject will receive placebo FMT once at week 8 flexible sigmoidoscopy
- Observed for 12 weeks

Group 2: Investigational FMT + psyllium fiber

- Subject will receive investigational FMT once at day 0 colonoscopy
- Fiber supplementation of 1 teaspoon 2x/day for 8 weeks
- Subject will receive placebo FMT once at week 8 flexible sigmoidoscopy
- Observed for 12 weeks

Group 3: Placebo FMT with or without psyllium fiber

- Subject will receive placebo FMT once at day 0 colonoscopy
- Half of subjects will be randomized to receive fiber supplementation of 1 teaspoon 2x/day for 8 weeks
- Subject will receive investigational FMT once at week 8 flexible sigmoidoscopy
- Observed for 12 weeks

Site:

Weill Cornell Medical Center / New York Presbyterian Hospital (Clinical Facility)

- The Jill Roberts Inflammatory Bowel Disease Center at David H. Koch Center

Weill Cornell Medicine Belfer Research Building (Research Laboratory Facility)

- The Jill Roberts Institute for Research in Inflammatory Bowel Disease

Methods to Minimize Bias:

1. Randomization Bias
    a. A series of randomized blocks of fixed size will be generated with a 1:1:1 allocation ratio. This will provide assurance that after a given block has completed subject enrollment, there will the same number of subjects assigned to each of the three study arms. Additionally, the specific number of subjects within any randomization block (i.e., block size) will be blinded to all investigators to avoid any risk for unblinding treatment arms prior to the primary endpoint evaluation.
2. Unblinding Bias
    a. Clinicians are blinded throughout the study so they will assess the clinical response at week 8 and will be unblinded only once this independent scoring is completed for all 135 enrolled subjects. This will reduce the risk of potential bias by the clinician as all treatment groups will receive treatment (blinded investigational or placebo FMP250) at week 8 by flexible sigmoidoscopy.

3.2 Scientific Rationale for Study Design

The ability to manipulate the human gut microbiome and alter mucosal and systemic immunity remains a central question in the study of IBD. We have previously completed a pilot study for FMT at Weill Cornell and have the clinical research infrastructure and clinical expertise to recruit patients, characterize their response, and complete the data analysis. Work from our lab and others has defined the role for specific bacteria in inducing immune responses in mouse models. We also have defined diagnostic signatures of microbial profiles associated with inflammatory disease phenotype in humans

including rheumatoid arthritis and IBD. Emerging clinical data provides evidence for the clinical efficacy of FMT in patients with ulcerative colitis (UC). Preliminary data from our own research suggests that engraftment and/or particular microbial species correlate with clinical outcome, however the factors that determine microbial engraftment are not well defined. Therefore, we designed a randomized, double-blind, placebo-controlled study to examine the possibility of improving the clinical outcome and microbial engraftment of FMP250 by using prebiotic fiber supplementation in active UC patients. Study subjects will be randomized into three groups: (1) *FMP250+Fiber*, (2) *FMP250-Fiber*, and (3) *PlaceboFMP250 with or without Fiber*. Given that fiber alone has not shown significant benefits previously in many UC studies[27], we hypothesize that subjects given *PlaceboFMP250+Fiber* will allow us to assess the placebo rate for FMT (*FMP250only* vs. *PlaceboFMP250+Fiber*). Also, considering that we will utilize single donor FMP250 samples, comparing subjects given *FMP250only* and *FMP250+Fiber* will allow us to scientifically assess primary endpoints of the impact of prebiotic supplement on engraftment and efficacy. PlaceboFMP250-Fiber will remove any risk of unblinding and will maintain the integrity of our double blinded study.

Additionally, previous reports have suggested that dietary effects of fiber can have critical effects on the microbiome[28]. Moreover, these effects can, in part, be mediated by the impact on T cell repertoire and function[29]. These pre-clinical data may have a critical impact on the efficacy of FMT in UC, but human data are limited. To address this limitation, we will perform metagenomic sequencing on donor and recipient samples from this trial to assess the potential impact on beneficial bacterial strain engraftment. Also, as we have previously done, immune cell characterization will be performed to assess the potential impact of fiber on T cell function.

3.3 Justification for Dose

FMP250 is 250cc of healthy fecal homogenates and a standard size offering for FMT prepared by OpenBiome. It is also the standard dosage used for FMT treatment of *C. Difficile* infection. Single dose delivery of FMP250 was chosen as per our previous pilot study and due to supply cost constraints.

3.4 End of Study Definition

A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit, at week 12 depending on treatment assignment or the last scheduled procedure shown in the Schedule of Assessments (SoA), Section 6.1. The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

4. Subject Selection

4.1 Study Population

Subjects with a diagnosis of ulcerative colitis who meet the inclusion and exclusion criteria and are willing to undergo a standard of care colonoscopy to confirm their eligibility to participate in this study.

4.2 Inclusion Criteria

1. Male or Female ≥ 18 years of age.
2. Documentation of prior history of mild to moderate UC.
3. Endoscopy confirmed active UC ≥ 15 centimeters at day 0 screening colonoscopy.

a. As defined by a total Mayo scoring of 4-10 with an endoscopic sub-score ≥ 1 and a stool frequency or rectal bleeding sub-score of ≥ 1.

4. Patients must have a descending intact colon.
5. Patients taking steroid or biologic therapy must be on a stable dose for 4 weeks prior to screening and maintained throughout the trial.
6. Eligible patients willing to undergo serological and fecal screening testing prior to FMT to document baseline status:
    a. Urine Testing
        i. Pregnancy test (women with childbearing potential)
    b. Blood Testing
        i. B-HCG (research purposes)
        ii. CBC, ESR, CRP, and BMP (standard of care)
        iii. HIV, type I and II (standard of care)
        iv. Hepatitis A B C Profile (standard of care)
        v. RPR (treponema pallidum) (research purposes)
        vi. CMV IgM (standard of care)
        vii. Quantiferon-TB (standard of care)
    c. Stool Testing
        i. Calprotectin (standard of care)
        ii. Clostridium Difficile Toxin PCR (standard of care)
        iii. Ova & parasites (standard of care)
        iv. Gastrointestinal Pathogen PCR Panel (standard of care)
            1. *Campbylobacter* species
            2. *Plesiomonas Shigelloides*
            3. *Salmonella* Species
            4. *Vibrio* Species
            5. *Vibrio cholerae*
            6. *Yersinia Enterocolitica*
            7. Enteroaggregative *E. coli* (EAEC)
            8. Enterpathogenic *E. coli* (EPEC)
            9. Enterotoxigenic *E. coli* (LT/ST)
            10. Shigalike toxin producing *E.coli I* (STX/ST2)
            11. *Cryptosporidium*
            12. *Cyclospora caretanensis*
            13. *Entamoeba Cayetanensis*
            14. *Giardia*
            15. *Adenovirus* F 40/41
            16. *Astrovirus*
            17. *Norovirus* GI/GII
            18. *Rotavirus A*
            19. *Sapovirus*
            20. *GID* PCR INTERP

7. Patients must discontinue anti-rCDI antibiotics (e.g. vancomycin, fidaxomicin) 48 hours prior to FMT delivery procedure.

4.3 Exclusion Criteria

1. Biopsy proven Crohn's disease
2. UC patients with severe disease (defined as a total mayo score >10)
3. Clinical complications requiring emergent management (e.g. stricture, bowel obstruction, perforation and/or abscess)
4. Concurrent *C. difficile* or other infections
5. Primary sclerosing cholangitis
6. Prior history of FMT
7. Treatment for malignancy within past 5 years
8. Active or latent tuberculosis
9. Clinically meaningful laboratory abnormalities
    a. Hb: < 8
    b. ALT: greater than 3x the ULN (upper limit of normal)
10. History of anaphylactic reactions to food allergens or allergy to psyllium husk
11. Pregnancy or lactation
12. Probiotic use in the 4 weeks prior to screening and for the duration of the trial
13. Subject having any other condition that, in the opinion of the investigator, would jeopardize the safety or rights of the subject participating in the study, would make it unlikely for the subject to complete the study, or would confound the study.

4.4 Lifestyle Considerations

During this study, subjects will not be specifically instructed to restrict any lifestyle considerations. However, a 24—hour diet recall will be conducted during our screening clinic visit (day -28 to -3) with a clinical nutritionist/registered dietician or study physician at Jill Roberts IBD Center in efforts to accurately observe and record each subject's daily eating patterns. See **Section 6.1.1.** for more details.

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial and have potentially been randomized into a treatment assignment but do not meet all inclusion criteria, specifically the endoscopy scoring for active disease at the day 0 standard of care colonoscopy. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) at the day 0 standard of care colonoscopy may be rescreened at a later time.

4.6 Strategies for Recruitment and Retention

This clinical trial will recruit potential participants from the Jill Roberts Center for Inflammatory Bowel Disease and related facilities of New York Presbyterian Hospital/Weill Cornell Medical Center where our investigators are members of the medical staff. The Jill Roberts Center for IBD is a high-volume practice, led by our investigator Dr. Ellen Scherl, with over 4,000 IBD patients and with a full-time clinical research team dedicated to investigator-initiated studies. Our clinical research personnel are responsible for the recruitment, screening, enrollment and allocation of participants in study groups. We anticipate to identify and screen approximately 150 potential study participants from within our practice but will subsequently enroll 135 subjects. We expect the accrual rate to be approximately 40 to 50 subjects per year.

Recruiting efforts for this study will not target potential participants based on their gender, race, or ethnicity. Recruitment strategies will include submitting a summary of the study to clinicaltrials.gov and to the Jill Roberts IBD Center Website: https://jillrobertsibdcenter.weillcornell.org/research-and-clinical-trials/clinical-trials.

Subjects will not be compensated with financial incentives at any point during the study.

5. Registration Procedures

5.1 Subject Registration (WCM only)

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

5.2 Subject Registration (Sub-sites)

Not Applicable.

6. Study Procedures

6.1 Schedule of Assessments

Table 1. Schedule of trial events

	Day -28 to -3	Day 0	Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Off Study[d]
Informed consent	X									
Demographics	X									
Medical history	X									
Concurrent medication	X ---------- ----- X									
Treatment Randomization	X									
Physical exam	X				X		X		X	
Vital signs + Height + Weight	X				X		X		X	
B-HCG (serum pregnancy test) (research purposes)	X									

Urine Pregnancy Test (standard of care and research purposes)		X[c]					X			
CRP: C-Reactive Protein (standard of care)	X*						X			
ESR: Erythrocyte Sedimentation Rate (standard of care)	X*						X			
CBC[a] (standard of care)	X*						X			
CMP[b] (standard of care)	X*						X			
Blood: HIV screen (standard of care)	X*									
Blood: Hepatitis A B C Profile (standard of care)	X*									
Blood: RPR (*Treponema pallidum*) (research purposes)	X									
Blood: CMV IgM (standard of care)	X*									
Blood: Quantiferon-TB (standard of care)	X*									
Fecal Calprotectin (standard of care)	X*						X			
Stool: Ova &parasites (standard of care)	X*									
Stool: *Clostridium Difficile* Toxin PCR (standard of care)	X*									
Stool: Gastrointestinal Pathogen PCR Panel[e] (standard of care)	X*									
Screening Colonoscopy (standard of care)		X								
Blinded (Investigational or Placebo) FMP250 Treatment		X								
Follow-up Flex sigmoidoscopy (standard of care)							X			
Blinded Investigational FMP250 (research purposes)							Placebo group only			
Blinded Placebo FMP250 (research purposes)							Investigational group only			
Mucosal Biopsy Collection (research purposes)		X					X			
Blood and Stool Collection (research purposes)	X---------X				X		X		X	
Follow-Up Phone calls (research purposes)			X	X		X		X		X
Diet Recall with Clinical Nutritionist or study MD (research purposes)	X									
Psyllium Fiber Supplements (research purposes)	X----------X									
Adverse event evaluation	X ----------X									

*: These standard of care laboratory tests must be done during the screening period. However, if the subject consents on page 5 of the informed consent form, recent laboratory results may instead be used if the subject had them conducted within 2 weeks of signing consent.

a: Complete Blood Count (WBC count, RBC count, Hb, Hct, platelet count)
b: Comprehensive Metabolic Panel (glucose, calcium, sodium, potassium, CO_2, chloride, BUN, Creatinine)
c: Urine pregnancy test (women of childbearing potential) as standard of care for colonoscopy
d: Off-study evaluation for the following year.
e: Gastrointestinal Pathogen GI Panel (Campbylobacter species, *Plesiomonas Shigelloides*, *Salmonella* Species, *Vibrio* Species, *Vibrio cholerae*, *Yersinia Enterocolitica*, Enteroaggregative *E. coli* (EAEC), Enterpathogenic *E. coli* (EPEC), Enterotoxigenic *E. coli* (LT/ST), Shigalike toxin producing *E.coli* I (STX/ST2), *Cryptosporidium*, *Cyclospora caretanensis*, *Entamoeba Cayetanensis*, *Giardia*, *Adenovirus* F 40/41, *Astrovirus*, *Norovirus* GI/GII, *Rotavirus* A, *Sapovirus*, GID PCR INTERP)

6.1.1 Screening Visit (Days -28 to -3)

- Informed consent
- Medical history
- Medication history
- Physical exam
- Blood Testing
  1. B-HCG (research purposes)
  2. CBC, ESR, CRP, and CMP (standard of care) *
  3. HIV, type I and II (standard of care) *
  4. Hepatitis A B C Profile (standard of care) *
  5. RPR (treponema pallidum) (research purposes)
  6. CMV IgM (standard of care) *
  7. Quantiferon-TB Gold Plus, 1 Tube (standard of care) *
- Stool Testing
  1. Calprotectin (standard of care) *
  2. Clostridium Difficile Toxin PCR (standard of care) *
  3. Ova & parasites (standard of care) *
  4. Gastrointestinal Pathogen PCR Panel (standard of care) *
     - *Campbylobacter* species
     - *Plesiomonas Shigelloides*
     - *Salmonella* Species
     - *Vibrio* Species
     - *Vibrio cholerae*
     - *Yersinia Enterocolitica*
     - Enteroaggregative *E. coli* (EAEC)
     - Enterpathogenic E. *coli* (EPEC)
     - Enterotoxigenic *E. coli* (LT/ST)
     - Shigalike toxin producing *E.coli I* (STX/ST2)
     - *Cryptosporidium*
     - *Cyclospora caretanensis*
     - *Entamoeba Cayetanensis*
     - *Giardia*
     - *Adenovirus* F 40/41
     - *Astrovirus*
     - *Norovirus* GI/GII
     - *Rotavirus* A
     - *Sapovirus*

- GID PCR INTERP

- Treatment Randomization (blinded to clinician and subject)
  1. Fiber treatment groups must receive psyllium dietary supplements (2 teaspoons/day) to begin on day -3
- Diet Recall with Clinical Nutritionist/Registered Dietician or study MD
  1. A subjective dietary record will be assessed anytime during the screening period (day -28 to -3), either by an clinic or phone call consult, in conjunction with the registered dietitian (RD). This meeting will aim to capture detailed information about food and beverages consumed over a certain (typical) period of time as an estimate of usual intake. The discussion may begin with the RD asking the subject "Could you please walk me through a typical day in terms of what you eat and drink from the time you wake up until you go to sleep?" The RD may then assess what the subject normally eats on a regular weekday, and give them the opportunity to tell them a few different options they might have for breakfast, lunch and dinner as well as snacks (if their days vary). They may also review what kinds of fruits and vegetables they consume most commonly, as well as get a sense of how much added sugar is likely in the subject's diet.
- Stool and blood samples taken for research purposes
  - This can be collected anytime during the screening period or on the day of the screening colonoscopy, prior to blinded FMT treatment, but if the subject is randomized to receive psyllium fiber, then this should be collected before day -3 when they begin the fiber supplementation.

*: These standard of care laboratory tests must be done during the screening period. However, if the subject consents on page 5 of the informed consent form then recent laboratory results may instead be used if the subject had them conducted as standard of care within 2 weeks of signing consent.

6.1.2 Treatment Phase

Eligible subjects will be randomly assigned to one of the three (Placebo or Investigational FMP250 +/- Psyllium) treatment groups. A series of randomized blocks of fixed size will be generated with a 1:1:1 allocation ratio. This will provide assurance that after a given block has completed subject enrollment, there will be the same number of subjects assigned to each of the three study arms.

Treatment assignment will be done during the screening visit because participants randomized to receive fiber supplementation must be provided two psyllium bottles to begin consumption 3 days prior the colonoscopy.

6.1.2.1 Screening Colonoscopy (Baseline, Week 0 Day 0)

- Urine pregnancy test as standard of care
- Standard of Care Colonoscopy for diagnostic purposes
  1. Mucosal biopsies taken for diagnostic and research purposes
- FMT delivery by colonoscopy for research purposes

1. If active disease, study physician will blindly administer placebo or investigational FMP250

- Stool and blood samples taken for research purposes, if not previously collected during screening period (days -28 to -3).

6.1.2.2 Clinic Visit 3 (Week 8 ± 5 day(s))

- Medical history (AE evaluation)
- Medication history
- Physical exam
- Urine pregnancy test for research purposes
- Flexible Sigmoidoscopy for diagnostic purposes
  1. Mucosal biopsies taken for research purposes
  2. Subjects in placebo group blindly receive investigational FMP250 .
  3. Subjects in investigational groups blindly receive placebo FMP250
- Stool and blood samples taken for research purposes
- Standard of Care Testing
  1. Fecal Calprotectin
  2. Serological CBC, ESR, CRP, and CMP

6.1.3 Follow-up Phase

6.1.3.1 Phone Consults (+/- 2 days)

- Day 1
- Week 2
- Week 6
- Week 10
- Every subsequent 6 months for the next year

6.1.3.2 Clinic Visits

- **Visit 2 (Week 4 ± 3 day(s))**
  - Medical history (AE evaluation)
  - Medication history
  - Physical exam
  - Stool and blood samples taken for research purposes

- **Visit 4 (Week 12 ± 5 day(s))**
  - Medical history (AE evaluation)
  - Medication history
  - Physical exam
  - Stool and blood samples taken for research purposes

6.1.4 COVID-19 Study Modifications

If necessary, video visits will be recorded in the deviation log and will be submitted to the IRB at the continuing review. Additionally, sample collection for research purposes may also be obtained by having essential research personnel mail the subject a 'Fedex clinical pak' prepackaged for exempt human specimen and provided with mailing instructions via phone. All shipping associated costs will be paid for by the research study's account and a Fedex pick up from the subject's home will be arranged to support "social distancing" practices. As per Fedex recommendations, the subject will leave the package on their door step to minimize interaction with essential Fedex personnel.

7. Study Intervention

7.1 Study Intervention/Device Description

7.1.1 Investigational and Placebo FMP250

The proposed intervention will deliver 250 milliliters of FMP250 by colonoscopy to the investigational FMP250 treatment groups at day 0. The placebo treatment group will instead receive the placebo FMP250 by colonoscopy at day 0 and then the investigational FMP250 by flexible sigmoidoscopy at week 8.

Investigational FMP250 is biologically active human fecal material that is pre-screened, tested, quarantined, stored, packaged, and labeled by OpenBiome. Placebo FMP250 is a control unit made of glycerol, saline, and food dye that is stored, packaged, and labeled identically to the investigational FMP250, to ensure blinding during delivery. Weill Cornell Medicine has contracted OpenBiome to supply 135 investigational FMP250 and 135 Placebo FMP250 directly to the Longman laboratory at Weill Cornell Medicine over the course of the study.

7.1.2 Psyllium Husk Powder

All subjects assigned to the fiber treatment arms will be required to take 1 teaspoon (approximately 5 grams) of psyllium husk powder twice a day (morning and night) for 8 weeks, beginning 3 days prior to Week 0 screening colonoscopy. To simplify, enrolled participants will consume approximately 10g of psyllium per day for 59 days.

The FDA characterizes psyllium seed husk as the dried form of a psyllium seed coat[33].

7.2 Availability

FMP250 is an investigational drug that will be purchased by WCM investigators from OpenBiome.

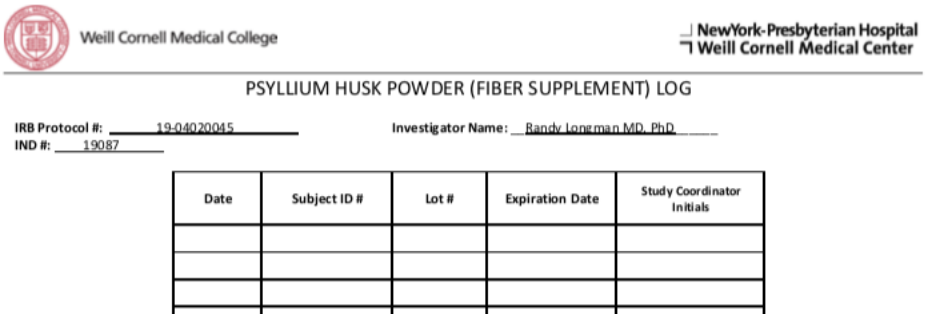
Psyllium Husk Powder, Organic is an FDA approved prebiotic fiber product that will be commercially sourced from NOW® Foods by WCM investigators for the purpose of our study. Any of the following information provided about their prebiotic product is accessible on their website: https://www.nowfoods.com/supplements/psyllium-husk-powder-organic.

7.3 Acquisition and Accountability

Psyllium Ordering and Shipping – Investigator-appointed Weill Cornell research staff will order *Psyllium Husk Powder, Organic* 12 oz. bottles, Item# 5966, UPC# 733739059666. This unit size

contains sufficient psyllium for the four-week psyllium regimen, therefore each subject will receive two bottles for the required 8 week supplementation. Details regarding the ordering and shipping process will depend on the company selected to commercially supply this product. Bulk shipments will be ordered preceding subject enrollment into the study. The quantity of units will be determined by the availability of the commercial provider.

Psyllium Inventory Records – The research coordinator for this study will maintain a careful record of the inventory. This included product arrival dates, expiration dates, lot numbers, and each unit's subject assignment on a *Psyllium Tracking Log*. This form is required by the FDA, must be kept in a safe place and filled out for all units in the possession of the investigator and/or appointed staff. An example of this form is shown below:



Weill Cornell Medical College

NewYork-Presbyterian Hospital
Weill Cornell Medical Center

PSYLLIUM HUSK POWDER (FIBER SUPPLEMENT) LOG

IRB Protocol #: 19-04020045 Investigator Name: Randy Longman MD, PhD
IND #: 19087

Date	Subject ID #	Lot #	Expiration Date	Study Coordinator Initials

FMP250 Ordering and Shipping – Investigator-appointed Weill Cornell research staff will order units of Investigational or Placebo FMT material by either (1) submitting orders via an OpenBiome specialized online order form, or (2) placing shipment orders directly via phone calls or emails with the OpenBiome Clinical Research Associate assigned to the trial.

OpenBiome Clinical Research Associates:

Jonathan Watson
P. 617-575-2201 ext. 794
E. jwatson@openbiome.org

Sally Kim
E. sally@openbiome.org

The initial shipment will need approximately 4-6 weeks to fill due to the internal review process of the study protocol, IRB approval, IND approval, and fully-executed contract conducted at OpenBiome. Upon approval, all subsequent shipments of the study agent will be expected to arrive 5-7 days after the original order is placed.

FMP250 Inventory Records – Investigator-appointed Weill Cornell research staff will maintain a careful record of the inventory and disposition of all agents received from OpenBiome with the *Material Tracking Log*, an example is pictured below, provided with each shipment by OpenBiome. This form should be kept in a safe space and must be filled out for all units. Once completed, it must be returned to OpenBiome prior to ordering the next shipment.

A	B	C	D	E	F	G	H	I
Item	Unit ID	Expiration Date	Ship Date	Date Received	Frozen on Receipt	Unit Status	Administering Physician	Follow-Up Form Given to Physician
FMP250	0001-0001-01	2/16/15	8/16/14		❑ Yes ❑ No	❑ Used ❑ Destroyed		❑ Yes ❑ No

7.4 Formulation, Appearance, Packaging, and Labeling

7.4.1 Investigational FMP250 Formulation and Appearance

Investigational FMP250 is 25 grams of pre-screened and tested human donor stool diluted and homogenized in 12.5% glycerol and normal saline buffer. The solution is then filtered to 330 microns and aliquoted directly into sterile 250mL high-density polyethylene bottles.

Potential OpenBiome donors are extensively screened for eligibility prior to stool collection by completing an informed consent, a Donor Health Questionnaire (DHQ), an in-person interview, and a clinical examination by one of their healthcare professionals. During this eligibility screening, OpenBiome evaluates the potential donor's infectious risk factors, potential microbiome-mediated conditions, general health status, in addition to their breastfeeding status and risk for pregnancy. If patients have completed and satisfied the requirements, OpenBiome then requires serological, stool, and nasal swab testing to be conducted.

There is an extensive standard operating procedure, which can be found in the OpenBiome IB, that is followed to ensure production and process controls. Therefore, once these have been fulfilled, the filtered stool is aliquoted, labelled, and frozen at -20 and then to -80 degrees Celsius. Donor stool is collected at the beginning of a 60-day window and is not shipped for clinical use until the donor undergoes the screening process again. This secondary screening process requires the donor to be cleared by two clinicians, and their stool to be evaluated by a quality assurance officer at the end of the collection window. Donors satisfying all secondary screening criteria will be cleared for stool shipment.

7.4.2 Placebo FMP250 Formulation and Appearance

Placebo FMP250 is a placebo control unit made of a sterile-filtered solution with 12.5% glycerol and normal saline buffer in addition to added brown food dye. Once the placebo ingredients are homogenized, the solution is sterile filtered through a .02um inline filter and aliquoted directly into sterile 250mL high-density polyethylene bottles. Bottles are labelled with a unique identifier and stored at -80ºC storage until the placebo lot has passed bioburden testing at which point material is released for use in clinical research trials. Considering the placebo product is masked by food coloring, it should be indistinguishable from the investigational FMP250 by appearance.

7.4.3 *Psyllium Husk Powder, Organic* Formulation and Appearance

This product is comprised of organic soluble fiber from powdered psyllium seed husks. This commercially available fiber supplement is also corn-free, dairy-free, egg-free, gluten-free, sugar-free, soy-free, nut-free, non-GMO, kosher, low sodium, organic and vegan/vegetarian. Natural color variation (beige to light brown) may be different between different units.

7.4.3 Manufacturing Addresses

OpenBiome
2067 Massachusetts Avenue
Cambridge, MA 02140
E. info@openbiome.org
P. (617) 575-2201

NOW Foods
395 S. Glen Ellyn Rd
Bloomingdale, IL 60108
P. (888-669-3663)

7.4.4 Product Labeling and Documentation

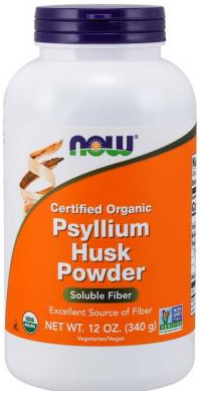
OpenBiome's IB indicates that each sample bottle is labeled with (1) the handling and storage warnings, (2) a lot number and (3) the expiration date based on the storage temperature (pictured below from left to right). The lot number is formatted as XXXX-YYYY-ZZ, where XXXX is the donor number, YYYY is the donation number, and ZZ marks the bottle number. Additionally all donor screening results will be provided in the stool shipment. Released placebo units are affixed with the same label as active FMP250 units, though the specialized lot numbers will allow for differentiation.

NOW® Foods brands each Psyllium Husk Powder, Organic plastic bottle with the following label. The label provides nutritional facts, suggested usage, ingredients, and a bar code for commercial use in addition to other details. The lot number and the expiration date are printed at the bottom of each individual unit (not pictured below).

7.5 Product Packaging and Handling

OpenBiome will package investigational and placebo FMP250 units in PET Corning bottles with HDPE screw-caps (pictured below). All units will be shipped by overnight carrier in dry ice inside a Styrofoam cooler with a WarmMarker temperature indicator attached to the lid. Upon arrival to the Longman laboratory, the package will be immediately checked for product tampering and temperature exposure. Each unit should be sealed and then stored promptly in a -20 or -80 Celsius degree freezer. The seal should not be broken unless the sample is going to be thawed the same day for delivery.

NOW® Foods packages each Psyllium Husk Powder, Organic product in a white plastic bottle with a sealed cap. The bottle is approximately 6.5 inches tall and 3.5 inches wide. Upon arrival to the Longman Laboratory, the package will be immediately checked for product tampering and accounted for by the *Psyllium Tracking Log* form.



7.6 Product Storage and Stability

Investigational and placebo FMP250 units must be stored in a freezer at all times until directly before use. The units are stable for up to 6 months at -20 degrees Celsius or 12 months at -80 degrees Celsius. Product stability is not compromised by freezer temperature shifts of up to five degrees Celsius.

NOW® Foods recommends their *Psyllium Husk Powder, Organic* product be stored in a dry and cool place after opening. We assume the same is recommended for its storage at WCMC, before its distribution to subjects.

7.7 Product Preparation

1. Thawing
    a. All FMP250 units must be thawed prior to use by one of the following methods:
        i. 1 hour in a 30-degree Celsius water bath
        ii. 4.5 hours at room temperature
        iii. 16 hours in a refrigerator
    b. Thawed material must be homogenized by mixing for 10 seconds before delivery

Any leftover FMP250 material must never be reused or refrozen. It should be immediately disposed according to internal WCMC/NYPH protocol.

7.8 Dosing and Administration

7.8.1 FMP250

Prior to colonoscopy subjects will be asked to undergo bowel prep and to fast the night before the procedure. Additionally, subjects will be provided anti-diarrheal agent(s) 1-2 hours prior to the procedure to aid with retention of the fecal transfer, which ideally would be for up to four hours.

The study intervention will only be infused through the working channel of the instrument during colonoscopy at the day 0 screening visit if the clinician confirms the subject meets the endoscopy dependent inclusion criteria. A 250cc dosage of the investigational or placebo FMP250 will be delivered in aliquots of 60cc but we also recognize that some fecal material may be lost during the transfer. During the week 8 flexible sigmoidoscopy, subjects that were randomized into the placebo group will receive a 250cc dose of investigational FMP250 and subjects that were randomized into the investigational group will receive a 250cc dose of placebo FMP250.

Once the FMP250 has been thawed, it is stable for administration for up to 4 additional hours at room temperature or 8 hours refrigerated.

7.8.2 Psyllium

Subjects randomized into the psyllium fiber treatment group will receive two bottles of the *Psyllium Husk Powder, Organic* product to begin consuming three days prior to the day 0 colonoscopy. They will be asked to take one teaspoon (approximately 5 grams) of this fiber supplement twice a day until their week 8 clinic visit which will be approximately 59 days. The twice a day dosage is advised to be taken once in the morning (e.g. breakfast) and once in the night (e.g. dinner) to help with subject compliance.

NOW® Foods recommends a tablespoon of this product to be mixed in at least a cup of liquid to avoid the risk of choking.

7.8.3 Dosing Delays/Dose Modifications

Not Applicable.

7.9 General Concomitant Medication and Supportive Care Guidelines

All concomitant medications will be recorded and/or updated on subject medication log throughout the course of the study and saved in subject binder and REDCap.

7.10 Duration of Therapy and Criteria for Removal from Study

Subjects assigned to the investigational FMP250 treatment groups will receive the FMT once at the day 0 colonoscopy and will subsequently receive the placebo FMP250 at week 8 to minimize unblinding bias between FMT treatment arms. Subjects assigned to the placebo FMP250 will also

receive the investigational drug once at the week 8 flexible sigmoidoscopy. The therapy is not given over a cycle or extended period of time.

Subjects assigned to the psyllium fiber treatment groups will take the fiber supplement twice daily beginning three days prior to the colonoscopy until the week 8 follow-up clinic visit. Subjects who do not comply to the recommended dose will not be removed from the study, however, they may not be evaluable for scientific analysis for this treatment group. In the case that a subject cannot tolerate the fiber supplement due to uncomfortable side effects, we recommend they decrease the dose to one teaspoon a day for a week before discontinuing the supplement altogether. Any subject tolerating the advised psyllium dose for less than one week will not be considered in this intention to treat trial as tolerating intervention, however, they will still continue with the FMT intervention. Importantly, subjects will be considered evaluable for scientific analysis in the *Fiber + placebo or active FMT* treatment group if they take the psyllium dosage for at least one-week post-FMT procedure up until the 4-week post-FMT clinic evaluation.

Study Termination Guidelines: A subject's follow-up in the study will end after one of the following applies:

- Subject's voluntary withdrawal
- Subject lost to follow-up
- Subject death
- Completion of all scheduled study follow-up clinical visits and phone calls

7.11 Duration of Follow Up

Subjects will receive subsequent follow-up phone calls every 6 months for the following year after completion from study (in-clinic visits) or until death, whichever occurs first. Subjects removed from study for unacceptable adverse events will be followed by the treating clinician and/or principal investigator until resolution or stabilization of the adverse event.

7.12 Measures to Minimize Bias: Randomization and Blinding

Randomization Bias:

A series of randomized blocks of fixed size will be generated with a 1:1:1 allocation ratio. This will provide assurance that after a given block as completed subject enrollment, there will be the same number of subjects assigned to each of the three study arms. Only the statistician and the study coordinator will have access to the randomization list. The dedicated research coordinator will assign the randomization code from the list for each subsequently enrolled patient (i.e., the statistician will give the list that contains the randomized blocks only to the research assistant).

Unblinding Bias:

Clinicians are blinded while they assess the clinical response at week 8 and will be unblinded only once all clinical evaluations at week 8 have been conducted for all 135 study participants. This will reduce the risk of potential bias by the clinician as all treatment groups will receive treatment (blinded investigational or placebo FMP250) at week 8 by flexible sigmoidoscopy.

Unblinding in the case of emergency (i.e. anticipated or unanticipated serious adverse event) is up to the discretion of the treating physician, particularly if it is medically necessary to know what treatment assignment the subject received. However, it is advised that the treating physician

discuss with the principal investigator prior to breaking protocol. The study coordinator will not delay or refuse unblinding if knowledge of the investigational drug is imperative for emergency treatment. The study coordinator will then immediately notify the PI of unblinding and will document the reason in the subject's folder and/or eCRF.

7.13 Study Intervention/Follow-up Compliance

Adherence to the protocol can be assessed and verified from logs, such as eligibility checklists and standard operating procedures (SOPs), that will be created by study coordinators and confirmed by the treating clinician throughout the course of the intervention. These logs will be based on the schedule of events detailed in **Section 6.1, Table 1.** to ensure the subject's compliance and that all data collection is successfully completed and reviewed at each visit. These paper forms will be stored in each subject's study binder.

In our previous pilot study, we also utilized single colonoscopic delivery of FMP250 and did not experience any loss to follow up due to our short-term follow-up clinic evaluation at 4 weeks post-FMT. Therefore, we anticipate our loss to follow-up rate to remain consistent in this new clinical trial. Considering patients will be blinded up until all study subjects complete week 8 evaluations, we expect them to comply with our follow-up clinic visits because the subject would want to ensure they received the investigational drug. However, if a patient does not respond after three contact attempts (either phone call and/or e-mail) by the study coordinator they will be labeled as a lost to follow-up.

In regard to safety-phone calls at 6-months and 1-year, subjects will be contacted three times (either phone call and/or e-mail). Should subject fail to answer, the investigator or designee will mail a certified letter to the subject's last known mailing address in order to regain contact.

8. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

8.1 Discontinuation of Study Intervention

Discontinuation from receiving FMP250 does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE). Certain AE/SAEs may result in a safety review and may cause for the discontinuation of the study intervention. See **Section 15.2.** for details on halting rules.

Discontinuation of Psyllium Husk Powder, Organic during the approximately eight-week course does not translate to discontinuation from this study. Any subject tolerating the advised psyllium dose for less than one week will not be considered as tolerating intervention, however, they will still continue with the FMT intervention. Therefore, the remaining study procedures should be completed as indicated in the study protocol. Further details on what to do if a subject does not finish the complete fiber supplement course can be found in **Section 7.10.**

The data to be collected at the time of study intervention discontinuation will include the following:

- Reason for discontinuation (escalation of care, not feeling well, surgery, etc.)

- All follow-up evaluations (AE/SAE reporting via phone calls, clinic visits) detailed in **Section 13**.

8.2 Participant Discontinuation/Withdrawal from the Study

Subjects are free to withdraw from participation in the study at any time upon notification. However, if a subject decides to stop participating in the study we encourage them to speak with the research coordinator or investigator first.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant lost to follow-up after several attempts to contact subject to schedule study visit.

Patients withdrawn because of SAEs, AEs or at the discretion of the physician will continue to receive treatment in accordance with current standard of care. Patients having AEs will be monitored with relevant clinical assessments, laboratory tests, imaging studies and procedures as determined by the treating physician.

The date and reason for participant discontinuation or withdrawal from the study will be recorded on an electronic Case Report Form (eCRF) created on REDCap. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

8.3 Lost to Follow Up

A participant will be considered lost to follow-up if he or she fails to return for 1 scheduled visits and is unable to be contacted by the study site staff. Every reasonable effort will be made to contact these patients to ensure they are receiving appropriate follow up care with documentation of any serious adverse effects (SAEs), adverse effects (AE) or changes in medical condition (for example, Mayo score), diagnoses or medications.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 1 week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent

methods). These contact attempts should be documented in the participant's medical record or study file.

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. Correlative/Special Studies

9.1 Laboratory Correlative Studies

9.1.1 Microbiome – Laboratory Correlative Study #1

9.1.1.1 Collection of Specimen(s): Fecal

9.1.1.2 Handling of Specimen(s): Frozen -80C

9.1.2 Lamina propria cells – Laboratory Correlative Study #2

9.1.2.1 Collection of Specimen(s): Biopsy

9.1.2.2 Handling of Specimen(s): Collected in PBS, Processed in Longman lab

9.1.3 Peripheral Blood – Laboratory Correlative Study #3

9.1.3.1 Collection of Specimen(s): Blood sample

9.1.3.2 Handling of Specimen(s): Processed in Longman lab

9.2 Special Studies

9.2.1 Special Correlative Study #1

9.2.1.1 Assessment

Microbial alterations, transferability and engraftment will be studied by sequencing DNA material at different timepoints. Previous studies have used reference genome alignments to evaluate microbial engraftment, however this approach does not determine taxonomy at the strain level, and therefore it is less accurate in defining the shared microbes between donor and patient. To overcome this issue metagenomics post-quality control sequences will be profiled using StrainPhlAn pipeline. To determine the degree of the engraftment, we will apply principal coordinates analysis to Bray-curtis distances. Wilcoxon signed-rank (paired) statistical tests will be used to evaluate the level of microbial similarity (Bray-curtis) between donor, pre-FMT and post-FMT. Given the dissimilar microbial composition observed in donor and pre-FMT samples in our preliminary data, we propose to use these microbial signatures to infer the origin of the post-FMT microbes. Briefly, bacteria shared among donor and pre-treatment samples will be removed from the model and the remained unique strains will be calculated. Machine learning models, Random Forest procedure, will be fitted in R-studio to predict bacterial engraftment and their persistence, as previously described.

9.2.2 Special Correlative Study #2

9.2.2.1 Assessment

Lamina propria mononuclear cells (LPMCs) are the key effectors within the mucosa. Numerous studies have characterized the contribution of bacterial signals to the effector functions of LPMCs, but the signatures associated with prebiotic supplementation are

limited. To characterize these profiles as we have done previously, LPMCs will be purified from digested endoscopic biopsy tissue and cryopreserved. We have optimized processing and freezing conditions to allow for efficient recovery and immune phenotyping by flow cytometry. These samples will then be used to phenotype innate and adaptive lymphocyte effector cell function. In addition, to profiling CD4+ T cell subsets by transcription factor (RORγt, T-bet, GATA-3, FoxP3) and intracellular cytokine production (IFNγ, IL-4, IL-17, IL-22), CD8+ T cells from the lamina propria and intra-epithelial lymphocyte fraction will be profiled.

10. Measurement of Effect

10.1 Response Criteria

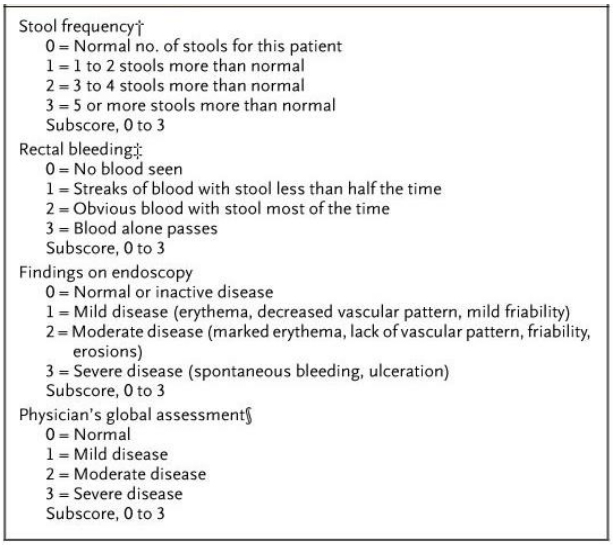
10.1.1 Primary Endpoint Assessments

10.1.1.1 Mayo Scoring System[30]

The Mayo Scoring System will be used for the assessment of ulcerative colitis activity. It is a composite score that ranges from 0-12 based on the following four categories: bleeding, stool frequency, physician assessment, and endoscopic findings. A partial Mayo Score ranges from 0-9 and can also be utilized if no endoscopic visualization is available to assess disease activity.

Study subjects will be evaluated by a full Mayo score at day 0 and week 8, and a partial Mayo score at the week 4 clinic visit. Both clinical response and remission will be evaluated at week 8 post-FMT. Clinical response is described as a reduction of the Mayo score by >3 points and >30% reduction from baseline with an accompanying decrease in the sub-score for rectal bleeding of at least 1 point. Clinical remission will be defined by Mayo score ≤ 2 without any sub-score >1, and Mayo endoscopic sub-score 0-1.

Table 2. Mayo Scoring System for the assessment of ulcerative colitis activity.



Stool frequency†
0 = Normal no. of stools for this patient
1 = 1 to 2 stools more than normal
2 = 3 to 4 stools more than normal
3 = 5 or more stools more than normal
Subscore, 0 to 3

Rectal bleeding‡
0 = No blood seen
1 = Streaks of blood with stool less than half the time
2 = Obvious blood with stool most of the time
3 = Blood alone passes
Subscore, 0 to 3

Findings on endoscopy
0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern, mild friability)
2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)
Subscore, 0 to 3

Physician's global assessment§
0 = Normal
1 = Mild disease
2 = Moderate disease
3 = Severe disease
Subscore, 0 to 3

* The Mayo score ranges from 0 to 12, with higher scores indicating more severe disease. Data are from Schroeder et al.[24]
† Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.
‡ The daily bleeding score represents the most severe bleeding of the day.
§ The physician's global assessment acknowledges the three other criteria, the patient's daily recollection of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

10.1.2 Secondary Endpoint Assessments

10.1.2.1 Biomarkers

Blood, stool, and mucosal samples will be processed and analyzed in the Longman Laboratory. The schedule and frequency of these collections are present in the Table of Events (Table 1). The total amount of blood collected for biomarker and safety evaluations will be specified in the Informed Consent Form.

10.1.2.2 Adverse Event Reporting

See Section **13** for more information on AE and/or SAE reporting for safety evaluation.

10.2 Duration of Response

Not applicable.

10.3 Progression-Free Survival

Not applicable.

10.4 Other Response Parameters

See Section **12.4** for a description of all other study endpoints.

11. Data Reporting / Regulatory Considerations

11.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled subjects.

11.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group-based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

11.2 Regulatory Considerations

11.2.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

Neither the Investigator nor BMS will modify or alter this protocol without the agreement of the other. All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IEC/IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill Cornell Medicine, updated documents will be provided to participating sites. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.2.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

11.2.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-GCP and local regulations, as applicable, from each potential subject or each subject's legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB/IEC requirements, applicable laws and regulations.

11.2.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.2.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the IP. In addition, all subjects' medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

12. Statistical Considerations

12.1 Sample Size and Analysis Plan

Prior studies and clinical experience involving FMT suggests a 27% response rate from a null rate of diet alone at 7%. Based on previous work[18], we estimate the effect size of clinical response to FMT+fiber in patients with IBD to be approximately double the FMT-alone group (i.e., 55% vs. 27%, respectively). Recruitment of ~135 subjects with 45 patients per arm was calculated assuming a 55% response rate at 8 weeks in the FMT+fiber arm and a 27% response rate at 8 weeks in the FMT-alone arm, with approximately 80% power to detect this difference (using a two-sided significance level of 0.05)[31]. We will conduct pairwise chi-square analysis between the study arms of interests to directly address the primary study objective to detect a difference in clinical response (i.e. FMT+ fiber versus FMT alone). The remaining two pairwise comparisons can be considered as secondary aims and thus no multiple comparison adjustment is needed.

Considering analyses will be performed based on intent to treat, any subject in the FMT alone (no psyllium) or the FMT with psyllium intervention groups with missing primary endpoint data at week 8 will be labeled as failed treatment (no change in clinical response from baseline). Therefore, subjects with missing data will have their baseline Mayo score carried forward to remain the same for the week 8 primary endpoint. For primary efficacy analysis, the populations FMT + psyllium vs. FMT alone (no fiber) will be compared by the chi-square test (pair-wise group comparisons will also be performed). Those characteristics found to be clinically different between groups at baseline using significance criteria of $p<0.05$ or known to be clinically important (e.g., in the event randomization provided insufficient balance between groups) will be incorporated into a multivariable logistic regression model of clinical response (i.e., binary outcome variable). This will facilitate estimating the independent effect of treatment group status on clinical response, after controlling for such factors, if any, that may differ between the two study arms at baseline. Sensitivity analyses for the primary endpoint will also be performed; in addition to carrying forward the baseline Mayo score for subjects with missing data at week 8, the minimum, median, and maximum Mayo score of subjects with available data at week 8 will be used (imputed) for subjects with missing data at week 8. Similarly, we will also explore multiple imputation techniques under varying assumptions of missingness (e.g., missing completely at random and missing at random). These multiple imputation techniques will rely on regression models to predict the missingness and missing values, and incorporate uncertainty through an iterative approach. For dealing with the possibility of data not missing at random, a worst-case analysis will be explored (i.e., missing data are replaced with the “worst” value under the not missing at random [non-ignorable] assumption). These sensitivity analyses will allow for an assessment of the consistency of the primary endpoint difference between groups under the varying assumptions for missing data at week 8.

Similar analyses will be conducted for secondary and exploratory endpoints (i.e., need for escalation, clinical remission, etc.). For secondary efficacy and safety analysis, comparison populations include: (i) FMT alone (no fiber) vs. placebo FMT alone (no fiber); (ii) FMT (with or without fiber) vs. placebo FMT (with or without fiber); (iii) placebo FMT with fiber vs. placebo FMT alone (no fiber); (iv) FMT with fiber vs. placebo FMT with fiber. All p-values will be two-sided with statistical significance evaluated at the 0.05 alpha level. Ninety-five percent confidence intervals for all parameters of interest will be calculated to assess the precision of the obtained estimates. Secondary analysis excluding subjects who discontinued the study treatment for reasons clearly not related to the study medications will also be performed. Treatment groups will be assessed at baseline with primary objective criteria. Balance between treatment groups will be assessed by ANOVA tests or Kruskal-Wallis tests for continuous variables and chi-square tests or Fisher’s exact tests for categorical variables.

12.2 Sample Size/Accrual Rate

We anticipate approximately 150 patients to be screened for inclusion into our study, however, 15 will likely be screening failures or dropouts. Therefore, we propose a sample size of N=135. We anticipate to accrue approximately 30-50 subjects/year over the course of our 4-year study duration.

12.3 Stratification Factors

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Not applicable.

12.4 Analysis of Endpoints

12.4.1 Analysis of Primary Endpoints

1. Clinical response at week 8 post-FMT, as defined by the reduction of the Mayo scoring system by >3 points (+30% reduction) with an accompanying decrease in the sub-score for rectal bleeding of at least 1 point (Section 10.1.2.2).

12.4.2 Analysis of Secondary Endpoints

a. Clinical remission at week 8 post-FMT, as defined by Mayo score ≤ 2 without any sub-score >1
b. Endoscopic response or remission, as defined as a Mayo endoscopic sub-score 0-1 with at least a 1-point reduction from baseline or a Mayo endoscopic sub-score of 0
c. Safety will be assessed by:
    1. Subject mucosal biopsies, stool and blood testing.
    2. Subject symptomatology via medical interview, physical exam, and Mayo score and change in standard UC medications.
    3. Number and type of treatment related adverse events
    4. Number and type of disease-related complications such as hospitalizations, surgeries and endoscopies, medical complications, and mortality.

12.4.3 Analysis of Exploratory Endpoints

1. Alterations in microbial profiles as defined by sequence of genetic material from fecal material
    a. Sample collection
        1. Up to 60cc of the recipient stool will be collected at the time of procedure.
        2. Up to 60cc of recipient stool will be collected at 4 and 8 weeks of follow up (as per protocol).
        3. Samples will be aliquoted and stored at -80C for batched analysis.
    b. Sequencing
        1. Fecal DNA extraction
            1. Fecal DNA will be extracted via phenol chloroformor, a commercially available resin binding column.
            2. DNA will be stored at -80C until sequencing.
            3. 16S rRNA amplicon libraries will be prepared for analysis by Illumina MiSeq or HiSeqor Roche 454 high throughput sequencing.

4. Genomic DNA libraries will be prepared using Illumina library preparation for sequencing on Illumina MiSeq or HiSeq.
5. Metabolomic analysis by mass spectrometry
6. Microbial strains will be isolated for genomic and functional analysis in vitro and in mouse models

2. Alterations in immune cell function from mucosal biopsies as defined by RNA sequencing and flow cytometry
   a. Sample collection: 4 biopsies will be collected into sterile saline for cellular analysis
   b. Biopsy will be removed of IEL fraction with dithiothreitol (DTT) followed by EDTA. Remaining tissue will be digested with collagenase and DNase and purified over a discontinuous percoll gradient to obtained lamina propria mononuclear cells.
      a. Stimulated and unstimulated will be analyzed by flow cytometry, transcriptional regulation, and cytokine production (including ELISA, cytometric bead array, or Luminex).
   c. Biopsy will be transferred to DNA extraction buffer and mechanically homogenized. Total DNA will be extracted by phenol chloroform as above. 16S library preparation and sequencing will be performed to determine mucosal associated bacteria

12.5 Interim Analysis

No interim analysis will be conducted for this study.

12.6 Reporting and Exclusions

12.6.1 Evaluation of Toxicity

All subjects will be evaluable for toxicity from the time of their first treatment with FMP250.

12.6.2 Evaluation of Response

All subjects included in the study will be assessed for response to treatment if they meet all inclusion and exclusion criteria, and then receive either placebo or investigational FMP250 treatment during the screening colonoscopy.

13. Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

13.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) is any untoward medical occurrence in a patient or clinical trial subject administered FMT that does not necessarily have to have a causal relationship with this treatment. It can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a FMT but does not

imply any judgment about causality. An adverse event can arise with any use of FMP250 (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

13.1.1 Investigational Drug, FMP250, Risks (Potential Adverse Events)

There may be risks for this therapeutic intervention which will be discussed with study participant by the research doctor. Risks from donor stool, such as serious blood-stream infection (rare) or fevers, abdominal cramping, bloating, diarrhea, and bloody stool (less likely). The potential risks associated with FMP250 may include but are not limited to the following:

- Transmission of infectious organisms (bacterial, viral, fungal) contained in the stool
    - Multi-Drug Resistant Organisms (MDROs)
        - A potential risk of fecal microbiota transplantation (FMT) is the transmission of antibiotic-resistant bacteria. These are bacteria that are resistant to some antibiotics. These bacteria could be transmitted through FMT and could cause serious infection or death.
        - The study drug, FMP250, that will be delivered by FMT is provided by OpenBiome, a universal stool bank where donors who provide stool for FMT undergo regular screening for certain antibiotic-resistant bacteria. Each FMT is only made available when these screens do not detect antibiotic-resistant bacteria in the donor before and after the stool donation. Donors also undergo regular clinical assessments for any risk factors associated with carrying antibiotic-resistant bacteria, such as recent use of antibiotics, visiting certain healthcare facilities, or certain travel activities.
    - Shiga Toxin-Producing E. Coli (STEC) and Enteropathogenic E. Coli (EPEC)
        - A potential risk of fecal microbiota transplantation (FMT) is the transmission of STEC and EPEC. STEC is a type of E. coli that can produce a toxin called Shiga toxin. Shiga toxin can be transmitted through FMT and can cause symptoms like abdominal pain, diarrhea (often bloody), vomiting, and mild fever. Most people develop symptoms within 3-4 days of acquiring the bacteria, and most get better within 5-7 days. EPEC is another type of E. coli that can be transmitted through FMT and is generally carried asymptomatically but can sometimes cause transient watery diarrhea, similar to traveler's diarrhea. Symptoms typically resolve in a matter of days.
        - The study drug, FMP250, that will be delivered by FMT is provided by OpenBiome, a universal stool bank where donors who provide stool for FMT undergo regular screening for these bacteria. Each FMT is only made available to delivery when these stool screenings do not detect EPEC or STEC in the donor before and/or after the stool donation.
    - SARS-CoV-2 Infection
        - A potential risk of fecal microbiota transplantation (FMT) is the transmission of SARS-CoV-2, a novel coronavirus that causes the disease COVID-19. Infection with SARS-CoV-2 may be transmitted through stool and may cause serious illness or death. It is possible for healthy, asymptomatic stool donors to potentially be infected with SARS-CoV-2.
        - The FMT you will receive is provided by OpenBiome, a universal stool

bank where donors who provide stool for FMT undergo regular stool, blood, and nasal screenings for many different infectious agents, including SARS-CoV-2, the virus that causes the illness called COVID-19. However, not all infectious agents are screened for and some infectious agents are as yet undiscovered. Each FMT unit is only made available for use when these screens do not detect the infectious agents for which we test. Donors also undergo regular in-person clinical assessments for any risk factors, including risk factors associated with carrying SARS-CoV-2, such as visiting certain healthcare facilities, or other behaviors that may increase the risk of exposure. However, because COVID-19 is so widespread, donors may be exposed or infected without having an identified risk factor for exposure. They may also have no symptoms of infection. OpenBiome continually updates its screening guidelines and procedures as additional data, tests, and information become available.If the FMT that you receive was made from stool donated after December 1st, 2019, the stool donor was tested for the presence of SARS-CoV-2 using a nasopharyngeal swab to conduct a viral RNA test. This kind of test looks for the specific genetic material that makes up the virus. If a donor tests positive for SARS-CoV-2, OpenBiome destroys any FMT units made from that donor in the 4 weeks (28 days) before their positive test result. The donor is also disqualified from providing stool donations for at least 8 weeks. To be re-instated in the stool donation program after 8 weeks, the donor must pass all screens. Although we cannot be absolutely certain, it is unlikely that SARS-CoV-2 is present in stool donations that were provided to OpenBiome on or prior to December 1st, 2019. For this reason, testing on donors prior to December 1st has not been performed. Though these precautions are taken to minimize the risk of SARS-CoV-2 transmission via FMT, the scientific and clinical community continues to learn more about SARS-CoV-2 and COVID-19. There are limits to the detection levels of laboratory tests, including those for SARS-CoV-2. Even with current screening and testing strategies, there may be additional risks that are unknown at this time. Although the donor screening tests we perform are likely to prevent you from receiving FMT from a donor who is infected with SARS-CoV-2, we cannot be absolutely certain that the stool you receive has not been contaminated with the SARS-CoV-2 virus.

  - Monkeypox Infection
    - A potential risk of fecal microbiota transplantation (FMT) is the transmission of monkeypox. Infection can cause symptoms including rash, fever, fatigue, myalgia, and respiratory symptoms which may be severe especially in immunocompromised patients. Studies have documented the presence of monkeypox virus DNA in rectal swabs and/or stool from infected individuals, but it is unknown whether monkeypox can be transmitted through stool or from asymptomatic infected individuals.
- Missed polyps, cancer, or other lesion (infusing donor stool interferes with visualization of colonic mucosa)
- Allergic reaction to antigens in donor stool

- Enhanced ulcerative colitis activity
- Theoretical increased risk of developing disease which may be related to donor gut bacteria (i.e. obesity, metabolic syndrome, autoimmune conditions, allergic/atopic disorders, neurologic disorders, and/or malignancy)

Many side effects go away shortly after the stool transplant is stopped, but in some cases side effects can be serious, long lasting or permanent. In reported experiments of subjects treated with FMT via colonoscopy no adverse effects were noted.

13.1.2 FMT Procedural Risks (Potential Adverse Events)

Based on the existing literature and the investigator's previous experience, the risks from FMT and dietary supplement ingestion are low. The usual risks of performing colonoscopy and flexible sigmoidoscopy still apply, as well as the minor risk associated with additional tissue biopsy procurement during flexible sigmoidoscopy and colonoscopy. These procedures are overall safe with few complications. Risks and side effects related to the delivery procedure include:

1. The risks of standard lavage include dehydration and minor electrolyte imbalances.
2. Standard colonoscopy and sigmoidoscopy include the risk of bowel perforation, bleeding, and adverse cardiopulmonary events related to sedation. (serious but less likely)
3. Many adverse effects of colonoscopy and sigmoidoscopy resolve shortly after the procedure has been completed, but in some cases abdominal discomfort and gaseous pain can persist for several hours. (common but mild)
4. Risks related to sedation. (less likely)

There may also be unpredictable side effects, other than listed above that. Other drugs may be given to make side effects that occur less serious and less uncomfortable.

13.1.3 Risk from colonoscopy and sigmoidoscopy (Potential Adverse Events)

Risks from colonoscopy and sigmoidoscopy include perforation (serious but less likely), abdominal discomfort during or after the procedure (common but mild), and risks related to sedation (less likely). The incidence of risk associated with biopsies taken as standard of care does not increase with additional biopsies taken for research. These risks include bleeding, intestinal perforation, and / or infection. Bleeding associated with biopsy generally resolves spontaneously, however, in the unlikely event of persistent bleeding, clips and / or cautery can be applied to stop the bleeding.

13.1.4 Risk from Medical Record Review (Potential Adverse Events)

Subjects will be asked about their medical history, usage of birth control, concurrent medication. There is a risk associated with the loss of privacy or confidentiality due to the probing of information. For example, if your identity as a participant in this study or your identifiable health information were disclosed to unauthorized persons, there is the possible risk of discrimination by employers or insurance providers.

13.1.5 Risk from Blood Draws (Potential Adverse Events)

Drawing blood from a vein may cause local pain, bruising, occasional lightheadedness, fainting, and very rarely, infection at the site of the blood draw. Rarely, blood clots may form and infections

may occur. If you feel faint, you should lie down right away to avoid falling down. You should let your study doctor or staff know if you have any of these problems.

13.1.6 Risk from Placebo (Potential Adverse Events)

In this research study, you may receive a placebo (inactive substance). If you receive the placebo, your condition may not change or may worsen.

13.1.7 Risk from Psyllium Husk (Potential Adverse Events)

The main concern with psyllium husk is the risk of choking, specifically if the product is not consumed with sufficient liquid. Our research physicians also hypothesize bloating may occur. The following rare side effects may be of concern for older adults: abdominal discomfort, nausea, mild abdominal cramps, griping, and faintness.

13.1.8 Risk from Anti-Diarrheal Agents (Potential Adverse Events)

Healthy adults usually don't experience side effects from antidiarrheal medicines. But side effects may be a concern if you are older or have health problems. Side effects of diphenoxylate/atropine may include: drowsiness, dizziness, headache, tiredness, restlessness, blurred vision, dry mouth, nausea, vomiting, upset stomach, loss of appetite, skin rash, or itching. Unlikely but serious side effects of diphenoxylate/atropine including: stomach or abdominal pain or swelling, severe nausea or vomiting, mental/mood changes (e.g., confusion, depression), or numbness and tingling of arms or legs. Side effects of loperamide may include: dizziness, drowsiness, tiredness, constipation, stomach pain, skin rash, or itching. Unlikely but serious side effects may also include severe constipation/nausea/vomiting, stomach or abdominal pain, or uncomfortable fullness of the stomach or abdomen.

There may also be side effects, other than listed above that we cannot predict. Other drugs may be given to make side effects that occur less serious and less uncomfortable. Many side effects go away shortly after the stool transplant is stopped, but in some cases side effects can be serious, long lasting or permanent

13.1.9 Risk for Women of Child-Bearing Potential

Participation in this the study may involve unknown risks to a pregnant woman, unborn baby or nursing infant. Subjects must not take part in this study if they are pregnant, plan to become pregnant during the research study period, or are breast-feeding a baby.

What do subjects need to know about reproductive health and/or sexual activity if they are in this study?

If a subject is sexually active, both men and women should use at least one effective means of birth control while participating in this research study. According to the World Health Organization and the United States Center for Disease Control and Prevention, the most effective forms of birth control include complete abstinence, surgical sterilization (both male and female), intrauterine devices (IUDs), and the contraceptive implant. The next most effective forms of birth control include injectables, oral contraceptive pills, the

contraceptive ring, or the contraceptive patch. Acceptable, but least effective, methods of birth control include male condoms (with or without spermicide) and female condoms.

If a subject becomes pregnant while participating in this research study, it is important that they tell the study doctor or other research team member immediately. The subject will be required to stop receiving study procedure/intervention for this study; however, other clinical care options will be discussed with them at that time if necessary and they will continue to complete the AE phone calls, week 4 clinic visit, and week 12 clinic visit as originally planned. The only difference will be that your week 8 assessment will be changed from a standard of care flexible sigmoidoscopy procedure into a clinic visit. This means you will do all other assessments, such as standard of care labs, research collection of blood and stool, physical exam, vital signs, height and weight measurements, etc. Therefore, the week 8 will no longer include a procedure, FMT blinded treatment, and biopsy collection for standard of care or research.

If a subject is considered to be postmenopausal, they are not required to use contraception while participating in this research study. Postmenopausal women rarely become pregnant.

13.1.10 Likelihood of Any Adverse Event

1. Very Likely
    a. Mild to moderate abdominal pain or gaseous discomfort during or after colonoscopy
    b. Fatigue on the day of the colonoscopy from sedatives
    c. Pain, bruising, feeling faint or slight risk of infection from blood draws
2. Less Likely
    a. Nausea with possible vomiting from ingestion of the standard lavage
3. Less Likely but Serious
    a. Transmission of infection from donor specimen
    b. Allergic reaction to unknown antigen present in donor stool
    c. Risks and side effects related to the colonoscopy or follow-up sigmoidoscopy including bleeding, bowel perforation and adverse cardiopulmonary events related to sedation
    d. Acquisition of antibiotic resistance or risk factors for chronic diseases such as diabetes, inflammatory bowel disease, obesity, or colon cancer

13.1.11 Adverse Event Characteristics and Related Attributions

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting in this study and reported to the primary investigator as frequently as adverse events occur. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- Attribution of the AE:
    - Definite – The AE *is clearly related* to the study treatment.
    - Probable – The AE *is likely related* to the study treatment.
    - Possible – The AE *may be related* to the study treatment.

- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

13.1.12 Recording of Adverse Events

All AEs, regardless of seriousness, severity, or causal relationship to FMT, will be recorded in the subject's medical record and/or subject specific AE log. The AE log will be maintained by the research staff and kept in the subject's research chart.

13.1.13 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.1.14 Reporting of AE to FDA

The following AEs will be specifically documented and reported to FDA within 15 calendar days if considered unexpected*:

1. Complications related to the colonoscopy, including sedation, perforation, or bleeding
2. Complications related to FMT (infection, inflammatory or allergic reactions)
3. Solicited and unsolicited AEs assessed via follow up telephone calls and clinic visits
4. Development of new symptoms or diagnoses (for example, irritable bowel syndrome, inflammatory bowel disease (IBD), autoimmune disorder, neurologic disorder) which may be related or unrelated to FMT will be elicited at follow-up calls and visits, documented and reported to the FDA

* According to the FDA, an AE 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.

13.1.15 Reporting Events to Participants

Based on our pilot study and the Investigator's Brochure by OpenBiome, all anticipated SAEs and AEs will be listed and made known to the subject in the informed consent. Any additions and/or changes to the list of potential SAEs or AEs will require an update of the informed consent to be approved by the IRB. Therefore, this would require subjects to be reconsented and made aware of any reported events.

13.1.16 Reporting of Pregnancy

If a female subject becomes pregnant during the 8-week period post-FMT, the physician must be notified as soon as possible and will document it in the subject's research binder or medical chart. The subject subsequently will cease further study procedures (week 8 flexible sigmoidoscopy) and blinded FMT intervention and will only continue to complete the safety follow-ups.

13.2 Definition of SAE

Serious adverse events (SAEs) are any adverse experience occurring during or after FMT that results in any of the following outcomes: death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

13.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:
http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.2.2 Reporting of SAE to FDA [For Protocols Where WCMC is the Sponsor-Investigator]

IND application sponsor-investigators must report any suspected adverse reaction or adverse reaction to study treatment that is both serious and unexpected. Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported expeditiously by the treating physician to the FDA in a written IND safety report within 7 calendar days following the initial receipt of the information. Examples of SAE may be any of the following:

i. death,
ii. a life-threatening adverse event,
    Note: An adverse event or suspected adverse reaction is considered life-threatening if, in the view of the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
iii. in-patient hospitalization or prolongation of existing hospitalization
    Note: Adverse events requiring hospital admissions that are less than 24 hours in duration do not meet this criterion. A scheduled hospitalization for a pre-existing condition that has not worsened during participation in the study does not meet this criterion. Pre-planned hospitalizations for an elective medical/surgical procedure or routine check-ups do not meet this criterion.
iv. a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
v. a congenital anomaly or 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 research subject and may require medical or surgical intervention to prevent one of the outcomes listed as serious

Any observation that is also an AE will be recorded in the medical record along with any actions taken. If not, all information will be available at the time of initial report and follow-up SAE reports will be completed and submitted. Anticipated and less serious adverse events will be submitted annually in reports to the FDA.

CDER INDs*:*
Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room 5901-B
Ammendale Road Beltsville, MD 20705-1266

13.2.3 Reporting of SAE to OpenBiome

OpenBiome requests any and all adverse event reports to be submitted through their online form: www.openbiome.org/adverse-events at the time of the annual FDA and IRB continuing review submissions. Once the form is submitted, a triage call may be set up with the report's author and a Finch medical professional to assess cases according to FDA ruling. Then, Finch/OpenBiome clinical staff may work with WCM clinical/research staff to determine the next steps in the investigation, which may or may not include reporting a Form FDA 3500. The Clinical Safety team at OpenBiome can also be directly reached at safety@openbiome.org or by phone at (617) 575-2201, option 9.

13.2.4 Protocol-Specific Exceptions to SAE Reporting

A suspected clinical endpoint event, regardless of when the event occurs, is not to be reported as an AE or SAE or reported in an expedited manner as an SAE. The suspected clinical endpoint event includes:

- Recurrent UC flare
- Initial response to therapy with initial reduction to Mayo score ≤3 with an accompanying decrease in the sub-score for rectal bleeding of at least 1 point or an absolute sub-score for rectal bleeding of 0 or 1

13.3 AE/SAE Follow Up

All SAEs and AEs reported during this study require the investigator to follow them until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the subject discontinues participation from the study. Resolution is defined as:

a. Resolved with or without residual effects
b. Return to baseline for a pre-existing condition
c. Fatal outcome; if autopsy is performed, the autopsy report must be provided to the sponsor.

13.4 Time Period and Frequency for Event Assessment

13.4.1. AE/SAE Monitoring

Each enrolled subject will be monitored for the occurrence of AEs, including SAEs, beginning immediately after FMT. The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. Subjects will be questioned at each follow up time-point about unsolicited and solicited AE on stool form and frequency, presence of abdominal pain, fevers and subjective well-being and/or examined (at day

1, 2, 6, 10 and 12 weeks post-FMT via phone call; 4 and 8 weeks post-FMT via office visit and review of patient diary for AE monitoring) by the treating physician for evidence of AEs. The questioning of subjects with regard to unsolicited adverse events will be generalized such as, "How have you been feeling since your last visit?". The following AEs will be solicited via phone calls and clinic visits by a study coordinator, along with the intensity of each:

1. Fever
    a. Mild: Temperature 37.7-38.6°C
    b. Moderate: Temperature 38.7-39.3°C
    c. Severe: Temperature 39.4-40.5°C
    d. Potentially Life Threatening: Temperature >40.5°C
2. Chills
    a. Mild: No or minimal interference with usual social and functional activities
    b. Moderate: Greater than minimal interference with usual social and functional activities
    c. Severe: Inability to perform usual social and functional activities
3. Fatigue/Malaise
    a. Mild: No or minimal interference with usual social and functional activities
    b. Moderate: Greater than minimal interference with usual social and functional activities
    c. Severe: Inability to perform usual social and functional activities
    d. Potentially Life Threatening: Incapacitating fatigue or malaise symptoms causing inability to perfume basic self-care functions.
4. Anorexia (loss of appetite)
    a. Mild: Loss of appetite without decreased oral intake
    b. Moderate: Loss of appetite with decreased oral intake without significant weight loss
    c. Severe: Loss of appetite with decreased oral intake associated with significant weight loss
    d. Potentially Life Threatening: Life threatening consequences or aggressive intervention indicated (TPN or tube feeding)
5. Abdominal Pain
    a. Mild: Pain causing no or minimal interference with usual social and functional activities.
    b. Moderate: Pain causing greater than minimal interference with usual social and functional activities.
    c. Severe: Pain causing no inability to perform usual social and functional activities.
    d. Potentially Life Threatening: Disabling pain causing inability to perform basic self-care functions or hospitalization (other than an emergency room visit) indicated.
6. Constipation
    a. Mild: Irregularity of bowel movements not requiring dietary modification, laxative or enema.
    b. Moderate: Persistent constipation requiring regular use of dietary modifications, laxatives or enemas.
    c. Severe: Obstipation with manual evacuation indicated
    d. Potentially Life Threatening: Life threatening consequences (i.e. obstruction)

7. Diarrhea
    a. Mild: Transient or intermittent episodes of unformed stools or increase of ≤3 stools over baseline per 24-hour period
    b. Moderate: Persistent episodes of unformed to watery stools or increase of 4-6 stools over baseline per 24-hour period
    c. Severe: Bloody diarrhea OR increase of ≥7 stools per 24-hour period or IV fluid replacement indicated
    d. Potentially Life Threatening: Life threatening consequences (i.e. hypotensive shock)
8. Nausea
    a. Mild: Transient (<24 hours) or intermittent nausea with no or minimal interference with oral intake.
    b. Moderate: Persistent nausea resulting in decreased oral intake for 24-48 hours
    c. Severe: Persistent nausea resulting in minimal oral intake for >48 hours or aggressive rehydration indicated (IV fluids).
    d. Potentially Life Threatening: Life threatening consequences (i.e. hypotensive shock)
9. Vomiting
    a. Mild: Transient or intermittent vomiting with no or minimal interference with oral intake.
    b. Moderate: Frequent episodes of vomiting with no or mild dehydration.
    c. Severe: Persistent vomiting resulting in orthostatic hypotension or aggressive rehydration indicated (IV fluids).
    d. Potentially Life Threatening: Life threatening consequences (i.e. hypotensive shock)

Study coordinators will report any and all AE/SAE to the treating clinician and/or PI and they will contact the subject for follow-up. Additionally, Subjects will also be instructed to contact the treating physician at any time point post-FMT to report symptoms experienced.

- Patients having AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the treating physician.
- AEs, actions taken as a result of AEs, and follow-up results must be recorded in the patient's medical record.
- In addition, patients will receive a follow up phone call 6-months post FMT and every subsequent 6 months for the next year to record any SAEs, new medical conditions and diagnoses, or changes in conditions or diagnoses since last study contact.

For all SAEs and AEs, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate, until final resolution or stabilization of the event(s).

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate electronic case report form (eCRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study coordinators will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

13.4.2. AE/SAE Assessment

13.4.2.1 Assessment of Severity

The severity of AEs will be assessed according to the following definitions:

- Mild: The AE is noticeable to the patient and/or the Investigator but does not interfere with routine activity.
- Moderate: The AE interferes with routine activity but responds to symptomatic therapy or rest.
- Severe: The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy.
- Life-threatening/disabling: The AE puts patient as risk of death. This does not refer to an event that may hypothetically have caused death if it were more severe.

13.4.2.2 Assessment of Causality

The physician must assess the relationship of any AE (including SAEs) to FMT, as related or not related, based on clinical judgment and using all available information, and may include consideration of the following factors:

a. Possible alternative causes of the AE, including the disease under treatment, pre-existing conditions, concomitant use of other drugs, and presence of environmental or genetic factors.
b. The temporal association between FMT exposure and onset of the AE.
c. Whether the manifestations of the AE are consistent with known actions or theoretical toxicity of FMT.

The causal relationship between FMT and the AE will be assessed using one of the following categories:

a. Not Related: An AE is not associated with FMT if:
    - An event that can be determined with certainty to have no relationship to the FMT.
    - Temporal relationship is lacking (i.e. the event did not occur within a reasonable time frame following administration of FMT)

- Other causative factors more likely explain the event (i.e. pre-existing condition, other concomitant treatments);

b. Definitely Related:
   - There is a positive temporal relationship (i.e. the event occurred within a reasonable time frame following FMT)
   - The AE is more likely explained by FMT than by another cause
   - Previously known toxicity of FMT.

c. Probably Related:
   - There is a positive temporal relationship (i.e. the event occurred within a reasonable time frame following FMT)
   - The AE is more likely explained by FMT than by another cause
   - Unlikely to be explained by patient's clinical state or other intervention.

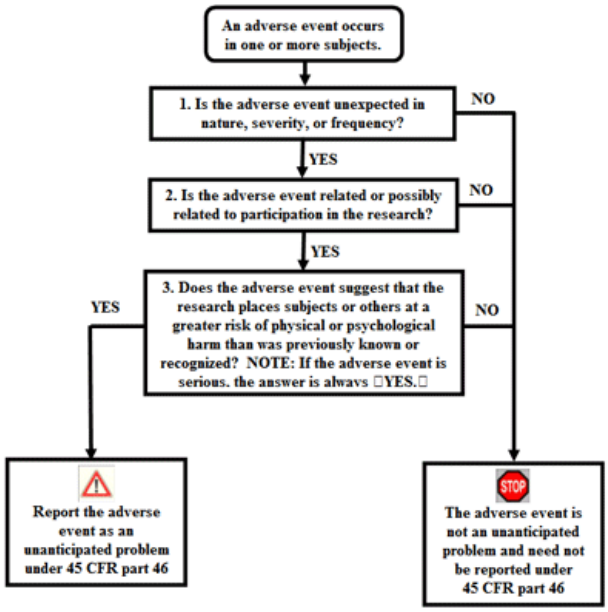
d. Possibly Related:
   - There is a positive temporal relationship (i.e. the event occurred within a reasonable time frame following FMT)
   - Event follows an expected response pattern to FMT, but event could have occurred secondary to a number of other factors.

14. Unanticipated Problems Involving Risks to Subjects or Others

14.1 Definition of Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.



14.1.2 Unanticipated Problem Reporting

The sub-investigators will report unanticipated problems (UPIRTSOs) to the reviewing Institutional Review Board (IRB) and to the lead principal investigator (PI). The UPIRTSO report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UPIRTSO;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UPIRTSO.

To satisfy the requirement for prompt reporting, UPIRTSOs will be reported using the following timeline:

- UPIRTSOs that are serious adverse events (SAEs) will be reported to the IRB within 1 week of the investigator becoming aware of the event.
- Any other UPIRTSO will be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), Food and Drug Administration (FDA), and the Office for Human Research Protections (OHRP) within one month of the IRB's receipt of the report of the problem from the investigator.

15. Data and Safety Monitoring Plan (DSMP)

A Weill Cornell Medicine Data Safety Monitoring Board (WCM DSMB) will monitor the data collected in this clinical trial on a quarterly basis to ensure the safety of enrolled subjects. The first periodic report to the DSMB will be within 3 months after enrolling the first subject and will be submitted through the

following link: https://research.weill.cornell.edu/integrity-compliance/research-support/human-research/data-safety-monitoringboard/make-submission. This monitoring plan was chosen for this clinical trial because it will be randomized and is intended to provide definitive information on the effectiveness and safety of FMTs and fiber supplements in active UC patients.

We will minimize the risk of UC relapse/flare by maintaining close clinical contact with all enrolled subjects. They will be encouraged to contact the clinical team if they experience recurrence of diarrhea, fever or abdominal pain so that further work up can be initiated, and escalation of standard therapy as appropriate. Solicited and unsolicited AEs will be recorded at day 1, week 2, week 6, week 10, week 12, 6 months, and every subsequent 6 months for 1-year post-FMT via phone calls and at 4 weeks, 8 weeks, and 12 weeks via clinic visit by any study team member. They will record any SAEs, new medical conditions/diagnoses or changes in medical conditions/medications since last study contact. If any events are noted during these follow-up evaluations, they will promptly be reported and reviewed by the treating physician and/or lead PI.

15.1. Plan for informed consent compliance

Written, informed consent will be obtained from each subject prior to the performance of any study procedures or assessments. Prior to enrolling a subject into the study, a designated member of the study team will explain the study protocol as outlined in the informed consent, procedures and objectives to the subject and/or authorized representative. When the subject, or legally authorized representative agrees to participation in the clinical trial, he/she or authorized representative must understand, sign and date the IRB approved Informed Consent Document which describes the study and potential discomforts, risks and benefits of participating. One copy of the consent form will be provided to the subject and one copy will be maintained with the subject's permanent medical records.

15.2. Plan for HIPAA compliance

We will minimize potential risks due to loss of confidentiality by having all information collected and handled by research staff trained to deal appropriately with sensitive clinical issues. Computer data files will be available only to authorized personnel and no names or obvious identifying information will be stored in data files. No participant will be identified in any report to the FDA. Further, when contacting participants for follow-up, no identifying information other than the first name of the caller will be used when leaving messages or speaking to anyone other than the patient him/herself. Written consent will be obtained to contact other persons for the purpose of locating the participant for follow-up and participants can refuse or revoke such consents. No information about participants will be released without their permission or where required by law.

15.3. Annual Reporting

The safety of patients will be monitored during each contact with patients. Both anticipated and unanticipated adverse events and problems will be formally monitored and recorded. Unanticipated serious adverse events 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 adverse events will be submitted annually in reports to the FDA.

The sponsor will provide the following for the annual report under 21 CFR 312.33(b);

1. Percentage of patients with at least one AE (within pre-specified time periods)
2. Percentage of patients with at least one SAE (within pre-specified time periods)
3. Percentage of patients who did/did not experience relapse in the 12 weeks post-FMT

15.4. Halting Rules

The DSMB will have the power to halt the treatment of patients under this protocol if it is determined that safety concerns exist. Any safety issues will be discussed with the research team and all reportable AEs will be communicated to the FDA as detailed above in IND amendment 1 Section 9 and 12. Specifically if the IND is halted for review, the FDA will be notified within 2 business days. Specific safety findings will result in temporarily suspending enrollment until a safety review is convened, the objective of which is a decision as to whether the study should continue per protocol, proceed with caution, be further investigated, be discontinued, or be modified and then proceed. Suspension of enrollment (for a particular group or for the entire study) is another potential outcome of a safety review.

Subsequent review of serious, unexpected, and related AEs by the DSMB, IRB, the sponsor, or the FDA or relevant local regulatory authorities may also result in suspension of further trial interventions/administration of FMT at our site. The FDA and study sponsor(s) retain the authority to suspend additional enrollment and study interventions/administration of FMT for the entire study, as applicable. Findings that will trigger a safety review are:

- Death
- Transmission of an infection from donor to subject via FMT
- If more than 10% of subjects experience the same Grade 3 Adverse Event
- If one or more subjects experiences a serious, unexpected adverse event
- Increased frequency of events (specifically, new diagnoses of inflammatory bowel disease in > 2 FMT treated subjects).

FDA will be notified by phone, email, or fax within 48 hours if the study is halted for review.

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