A Randomized Controlled Trial to compare the effectiveness of Fecal Microbiota Transplantation (FMT) in combination with Bezlotoxumab compared to FMT and placebo for the prevention of CDI recurrence in patients with Inflammatory Bowel Disease and Recurrent Clostridium difficile Infection

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STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practices (GCP) as required by the following:

- United States Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, and 21 CFR Part 312);
- International Conference on Harmonization (ICH) E6; 62 Federal Register 25691 (1997);

Compliance with these standards provides public assurance that the rights, safety and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Lead Principal Investigator:

Signed: _____ Date: _____

Name, Title

1. Background and Significance:

Over the last decade, there has been an increase in the incidence and severity of *Clostridium difficile* infection (CDI) that has been attributed to a more virulent and treatment refractory strain[1,2]; and its impact has been especially pernicious on inflammatory bowel disease (IBD) patients.[3-5] The prevalence of CDI in the IBD population was noted to be 2.5 to 8-fold higher with a 10% lifetime chance of getting the infection. [6-8] Since 1998, CDI related IBD hospitalizations have doubled and inpatient hospital mortality rose significantly from 5.9% to 7.2%.[9] Further, the in-hospital death rate of IBD patients is nearly five times greater when complicated by CDI.[9] **Following an initial course of anti-CDI therapy, the CDI recurrence rate is 4.5-fold higher, and the prevalence of toxigenic *C. difficile* carrier state is 8-fold greater in IBD patients compared to non-IBD**. [9] While it is not clear whether Clostridium difficile can cause IBD, it may elicit an IBD flare and worsen disease severity as well as clinical course.[9] In a retrospective study, *C. difficile* positive ulcerative colitis patients were twice as likely to be hospitalized, eight-times as likely to be seen in the emergency room and had nearly doubled colectomy rates compared to C. difficile negative ulcerative colitis patients for up to a year following the index hospitalization.[10] It has been argued that C. *difficile* colonization is a marker of underlying IBD severity rather than a trigger for disease deterioration.[11] Additionally, recently reported CDI-related colectomy rates have been surprisingly low.[12-14] It appears that emergent colectomies in CDI-IBD are more often performed for medically refractory IBD than for toxic complication of CDI.[10] Nevertheless, CDI-IBD patients tend to improve on anti-CDI therapy suggesting that prompt eradiation of CDI may prevent colectomy, at least in the short term.

Recent advances in fecal microbiota transplantation (FMT) are changing the CDI treatment paradigm. Four randomized trials and numerous case reports in > 500 patients suggested a nearly 90% cure rate of FMT for the therapy of recurrent CDI with negligible adverse events.[15-18] These studies, however, included only a few IBD patients.[19] Kelly and colleagues demonstrated an overall cure rate of 94% in immunosuppressed patients but a 14% IBD exacerbation rate after FMT.[20] It was hypothesized that the flare up could have been precipitated by CDI infection versus natural disease progression, and/or FMT administration. More recently Khoruts et al showed patients with IBD were more likely to fail FMT.[21] Questions surrounding the safety and efficacy of FMT in IBD and immunocompromised patients with concurrent CDI persist and, more importantly, the effect of FMT on IBD disease course in the setting of CDI remains unknown. While the field moves forward exploring the use of FMT to treat IBD, showing early promise in ulcerative colitis, the unique population of IBD patients, specifically those with colonic disease and CDI, remains poorly understood. To effectively treat these patients and to decide where to position FMT in the treatment paradigm, further exploration of the impact FMT may have on CDI and IBD outcomes is crucial. Prospective data is currently lacking.

Additionally, Bezlotuxumab (Bezlo), a fully human monoclonal antibody that binds to *C. difficile* toxin B, is indicated to prevent recurrence of CDI in adults at risk for recurrent CDI (rCDI).[22] In the MODIFY I/II Phase 3 trials, a single infusion of bezlotuxumab resulted in a significantly lower rate of rCDI compared with placebo over 12 weeks.[23] Unlike other Phase 3 CDI trials, individuals with IBD were eligible to participate. The post-hoc analysis of MODIFY I/II investigated the CDI-related outcomes of participants with CDI complicating IBD. In

MODIFY I and MODIFY II, 44 participants had IBD: 23 (52.3%) had ulcerative colitis, 18 (40.9%) Crohn's disease, and three (6.8%) non-characterized IBD. In this recent pot- hoc analysis half as many bezlotoxumab-treated versus comparator-treated participants experienced recurrent CDI (rCDI) (26.7% vs 53.8%) representing a 27.2% absolute reduction (95% CI −57.9, 9.6) (unpublished). This data suggests that adding Bezlo in this population may have added benefit.

We therefore intend to prospectively study the clinical and microbial outcomes of FMT in combination with Bezlotuxumab in patients with IBD-CDI compared to FMT and placebo. Our central hypothesis is that FMT in combination with Bezlo will be more effective for the treatment of recurrent CDI in patients with IBD compared to FMT and placebo and will lead to improved IBD outcomes in a majority of patients

2. Objectives and Aims:

2.1 Specific Aims:

Specific Aim 1:
To assess the efficacy of FMT in combination with Bezlotuxumab (Bezlo) for the prevention of CDI recurrence in patients with IBD-CDI compared to FMT + placebo.

Hypothesis: The combination of FMT with Bezlotuxumab will result in fewer CDI recurrences then FMT and placebo

Specific Aim 2:
Assess IBD clinical outcomes post CDI in IBD-CDI patients who received FMT and Bezlo compared to FMT and placebo.

Hypothesis: IBD patients with CDI who receive FMT and Bezlo will have less IBD decompensation (escalation of meds, hospitalization, surgery) then patients who receive FMT and placebo for the prevention of CDI recurrence.

Specific Aim 3:
Determine the impact of Bezlo on the intestinal microbiome of patients with IBD-CDI via 16s ribosomal RNA sequencing and shotgun sequencing.

Hypothesis: IBD patients with CDI who receive FMT and Bezlo will have increase microbiome diversity compared to FMT and placebo.

2.2 Study Outcomes:

2.31Primary Outcome:

CDI Recurrence by Week 8: Defined as a positive Stool GDH and EIA (2-step testing approach) as well as diarrhea (>=3 loose stools in 24h period, defined as BSS 6-7, x 3 days)

within 8 weeks of receiving FMT.

2.32 Secondary Endpoints

IBD clinical outcomes at 1, 8 and 12 weeks post FMT with respect to disease activity, changes in medical therapy and need for surgery, and percent that maintained remission.

- **De Novo IBD flare** is defined as a Mayo or HBI score >= 4 in the absence of CDI (negative EIA testing) if Mayo or HBI were 2 or less at baseline.
- **Worsening of disease** pertains to those with active disease at baseline. Active disease is defined as a baseline Mayo or HBI score >= 4 and worsening of disease is defined as an increase in either HBI or Mayo by 2 or more at week 12
- **IBD improvement** is defined as a decrease in Mayo or HBI score by 2 or more at week 12 compared to baseline.
- Change in calprotectin at 12 weeks compared to baseline
- Resolution of diarrhea defined as 3 or less BMs in a day at Bristol Stool Scale of 5 or less.

Clostridium difficile outcomes: Stool will be tested at week 1, 8, and 12 post FMT regardless of symptoms.

- **Asymptomatic Clostridium difficile colonization rates:** defined as the percentage of patients EIA negative and PCR positive in the absence of diarrhea
- Rates of PCR positive EIA negative patients in the presence of ongoing diarrhea will also be measured (see patient treatment strategy).

Microbial Outcomes:

- Changes in recipients' fecal microbial diversity at 1, 8, 12 weeks after FMT relative to baseline
- Comparison of recipients' fecal microbial diversity at baseline to donor diversity.
- Correlation between microbial diversity and clinical outcomes

Metabolomic Outcomes : Metabolomic profiles of the samples and associated community structure of the fecal microbiome will be assessed as a measure of the interplay between host and gut microbiota.

- **Stool and Serum** metabolomics profiling will be using liquid chromatography tandem mass spectrometry (LC-MS) will be measured at baseline, week 1, 8, and 12

Tolerability Outcomes:

Early Tolerability:

- Proportion of participants with an AE through day 7 (±3 days)
- Proportion of participants with a SAE through day 7 (±3 days)

Late Tolerability:

- Proportion of participants with an AE through week 12 (±5 days)
- Proportion of participants with an SAE through week 12 (±5 days)
- Proportion of participants with a SAE at month 6 (±14 days) phone safety assessment

3. STUDY DESIGN:

This is a randomized controlled trial to assess the clinical and microbiological impacts of FMT in combination with Bezlotoxumab compared to FMT and placebo in patients with IBD-CDI. We will prospectively enroll up to 150 IBD-CDI patients from 5 tertiary care FMT referral centers in order to have 120 who complete the trial to account for drop out. Patients will be randomized 1:1 to either receive FMT and placebo or FMT in combination with Bezlotoxumab. Donor stool from healthy donors will be obtained from OpenBiome. OpenBiome is a nonprofit 501(c)(3) organization that provides hospitals with screened, filtered, and frozen material ready for clinical use. Patients will be enrolled and followed prospectively for 12 weeks post therapy. Stool and blood samples as well as clinical data will be collected at baseline, week 1, 8 and 12.

3.1 Donors: Donor stool from healthy donors will be obtained from OpenBiome. Please see attached Investigator Brochure (BBMF # 17195) for full donor screening procedures.

3.2 Patients: Patient enrollment will be done via two methods:

1) Referral of appropriate patients from the GI clinic, primary care offices or inpatient service.
2) Patient initiated communication with investigator: This may be via clinicaltrials.gov website, direct e-mail or phone call

Subjects for this study will be recruited at 5 sites: Brigham and Women's Hospital, Indiana University, Brown University/Women's Collaborative, Mount Sinai Health System, and NYU Langone Health. All 5 sites are tertiary care FMT referral centers.

3.2.1 Inclusion criteria:

- Adults age 18 or greater
- ≥ 2 episodes confirmed recurrent CDI defined as the presence of diarrhea (Bristol 6 or 7 for 48 hours and a confirmatory test for CDI). Preferred testing will be a two-step method using GDH/EIA toxin, though PCR will be accepted based on hospital availability with the most recent episode occurring within the prior 3 months
- Confirmed diagnosis of IBD (ulcerative colitis, Crohn's disease or indeterminate colitis)
- Undergoing FMT via colonoscopy for CDI as part of standard medical care

3.2.2 Exclusion Criteria: to be confirmed either by medical records or by patient self-reporting if records are not available

- Unable or unwilling to undergo a colonoscopy
- Inpatient status, though patients can be screened while inpatients, the must be outpatient for the planned colonoscopy.
- Anticipated immediate or upcoming surgery within 30 days

- Need for continued non-anti-CDI antibiotic therapy
- History of total proctocolectomy
- Female patients who are pregnant or breastfeeding or plan to become pregnant in the next 6 months.
- Patients who are unable to give informed consent
- Participation in a clinical trial in the preceding 30 days or simultaneously during this trial
- Severe food allergy (anaphylaxis or anaphylactoid-like reaction)
- Life expectancy < 6 months
- Unable to adhere to protocol requirements
- Patient who have received an FMT in the past year
- Any condition that the physician investigators deems unsafe, including other conditions or medications that the investigator determines that it will put the subject at greater risk from FMT
- Patient who is diagnosed with class 3 or 4 Heart Failure
- Lab value of WBC <3.0 x $10^3/mm^3$, Platelets <100 x $10^3/mm^3$, ALT or AST > 1.5 x institutional ULN
- If a patient is heavily immunosuppressed, defined as being on 3 or more immunosuppressants, and is negative for CMV or EBV exposure measured by IgG

3.3 Subject Withdrawal Criteria:

A participant may choose to withdraw from this study at any time, for any reason, without consequence.

A participant may be withdrawn from the study by the Investigators for the following reasons:

- Severe or intolerable adverse event
- Lack of participant cooperation
  - Participants request to withdraw from study
  - Lack of compliance (fails to attend the follow-up visits as agreed)
  - Technical / logistical reasons (relocation)
- Colonoscopy cannot be completed for technical reasons due to inability of endoscopist to complete the exam or patient intolerance of procedure.
  a. These patients will only be followed-up for 2 weeks for adverse event screening (either via clinic visit or phone call based on patient preference), as they will not have received FMT. These subjects will be replaced, as they will not be considered “treated”.

3.4 Study Termination

In the unlikely event that significant safety concerns arise, the principal investigator, can terminate or halt the study pending review by the DSMB. In addition, this study may be halted early based on interim safety and efficacy analyses as per the DSMB charter or FDA recommendations (See further details below).

4. Subject Enrollment

4.1 Recruitment Procedures:

Gastroenterologists at each facility, including attending physicians and fellows, will be informed of the study's aims and inclusion criteria. These doctors will inform the principal investigator or site lead investigators of patients who meet the study criteria and who may be good candidates for the study. The treating gastroenterologist will introduce the study to the potential patient and request the patient's permission to be approached by study staff. Patients will be given as much time as they need to decide. They will be given a copy of the consent form to take home, read, and consider if they choose to, or the consent form will be emailed to them if the initial conversation takes place over the phone. They will be encouraged to discuss participation with family members and health care providers. If they are interested in participating in a screening/consent visit will be scheduled.

The trial will be posted on clinicaltrials.gov. If patients reach out to us via the provided E-mail or phone number located at the clinicaltrials.gov website, or directly reach out to the study team via any mechanism, we will pre-screen them using questions from the provided E-mail/phone script. If the patient's responses do not indicate any exclusion criteria being met, then we will contact their primary care provider or GI provider via email or phone call (with patient permission) to confirm medical diagnosis. If no records exist for exclusion criteria patient report will be accepted.

4.2 Consent Procedures:

The treating gastroenterologist will introduce the study to the potential patient and request the patient's permission to be approached by study staff. With the treating gastroenterologist's permission, either a physician investigator or study coordinator will describe the research study in detail, including participation and risks and alternative courses of treatment, and answer any questions or concerns that the patient may have. Patients will be given as much time as they need to consider participation before signing the consent form.

Subjects will be drawn from the investigators own practices of patients eligible for FMT for clinical care. In order to avoid coercion, study staff will reinforce that participation is voluntary and that their decision will not affect the medical care that they receive now or in the future. If patients seek more time to consider participation, they will be given a copy of the consent form and encouraged to discuss the study with family, friends, PCP, or others. Study staff will follow-up to see if any questions or concerns have not been addressed. A physician investigator will obtain informed consent signatures.

If patients initiate contact with the study team and the initial phone screen suggests eligibility they will be provided with the consent form via email to review. They will be re-contacted in a few days so that any questions may be answered. If they would like to proceed a screening visit will be set up.

5. STUDY INTERVENTION

5.1 Fecal Microbiome Transplant (FMT)

All patients enrolled in the trial will undergo an FMT as part of clinical care. FMT is the process by which processed donor microbiota material is transplanted into recipients, in this study specifically by colonoscopy. The aim is to reconstitute the normal intestinal microbial flora in recipients.

The treatment for this trial will be a filtered solution of donor fecal microbiota (50 g) homogenized with sterile saline resulting in a 250 mL slurry. This will be administered as a single topical treatment via colonoscopy to the ileo-colonic mucosa as part of standard care.

Donor Procedures (OpenBiome): See Investigator Brochure BBMF 17195 for full donor procedure details

Product Storage

Product will be screened and produced at Openbiome. Produced material will be stored at -80°C and each unit will have a date of production printed on it for tracking purposes. Studies have been conducted to ensure long-term bacterial viability following the freezing process based on studies conducted by Hamilton et. al and Young et. al.[22] Units will be shipped to each site from Openbiome and local site storage at -20°C or -80°C will be permitted for up to 6 months as done for clinical care FMTs.

Accountability Procedures:

The site principal investigator (PI) (or designee) will maintain an accurate record of the receipt of the materials shipped by Openbiome, including the date received, the freezer the material is in, and number of FMT donor solutions currently available for use. In addition, the laboratory technician based at OpenBiome will maintain a log of all clinical materials dispensed for the study. Each site will maintain their material as they do for clinical use otherwise.

5.2 Bezlotoxumab:

Bezlotoxumab is a human monoclonal antibody that binds to Clostridium difficile toxin B, indicated to reduce recurrence of Clostridium difficile infection (CDI). It is a single IV infusion, dosed at 10mg/kg, infused over 60 mins. Drug vials will be provided by Merck and Co and will be shipped directly to the research pharmacy at each site. The research pharmacy will prepare the IV solution and the equivalent placebo which will constitute a normal saline infusion. Accountability logs and temperature logs will be maintained by the research pharmacies at each site.

6. STUDY SCHEDULE

A schematic representation of the study schedule can be found in the appendix 6.

Visit 1: Screening – potential subjects will undergo the following screening procedures no more than 4 weeks prior to FMT to determine if they meet the recipient selection criteria.

1. Medical record review will be done to confirm diagnosis and inclusion criteria. Records

will be reviewed for exclusion criteria, however if not available patient self-report will be accepted. The following data will be documented at baseline visit:

a. **Demographic:** age, height, gender, weight, race, significant past medical history, and smoking status
b. **Disease related**: IBD diagnosis, age at IBD diagnosis, IBD medication history and medication at the time of FMT, surgical history, disease location and phenotype (for Crohn's), and clinical disease activity assessment. For UC modified Mayo with recall of the previous 3 days will be used. For CD, HBI scores will be used.
c. **Diarrheal symptom assessment**: Average daily Bristol score, number of daily BMs.
d. **CDI history**: inciting antibiotic, Number and approximate date of previous CDI episodes, previous positive stool tests—dates, PCR versus EIA , CDI treatment courses (metronidazole, vancomycin, vancomycin taper, or fidaxomicin), CDI related prior hospitalizations and number of CDI related hospitalizations.

2. Baseline symptom assessment using diary and targeted physical exam by study physician or nurse

3. Laboratory assessments:
   a) **Blood**: CBC, CRP, CMP, HIV, Viral hepatitis, Syphilis, and ONLY subjects who are heavily immunosuppressed will also be screened for CMV and EBV exposure via IgG.
   b) **Stool:** Calprotectin, microbiome analysis. Stool will be collected on chronic anti-CDI therapy
4. Stool and blood will be banked for metabolomics and future analysis
5. Urine Pregnancy Test if applicable. If patients are post-menopausal this will be documented and pregnancy test is not needed
6. If not currently on anti-CDI therapy Vancomycin should be started for a minimum of 4 days prior to FMT with instruction to hold for 48 hours prior FMT.

Once patient has passed screening and all labs have been reviewed colonoscopy will be scheduled and the patient will be randomized. The master randomization list will be housed at BWH by an unblinded member of the team who will communicate with each sites pharmacy as patients are enrolled

Visit 2: Fecal Transplant - the following baseline assessments will be made in enrolled subjects on day of scheduled FMT;

1. Urine pregnancy test (HCG) for female patients if applicable. If patients of post-menopausal this will be documented, and pregnancy test is not needed .
2. Clinical disease activity assessment depending on disease (Mayo for UC and HBI for CD)
3. Endoscopic scores will be documented
4. Biopsies for histology will be done for clinical care to assess disease activity

Visit 3. Bezlotoxumab infusion. This can take place on the same day of the FMT. This infusion

will take place over 60 mins. If not possible to occur of the same day of FMT then the infusion can occur after the screening visit labs have been completed and results released, but prior to wash out period. The infusion will not occur post FMT

Visit 4: Study phone call (72 hours post FMT +/- 1 day)

1. Clinical disease activity assessment depending on disease (Mayo for UC and HBI for CD)
2. AE assessment

Visit 5,6,7 (Week 1, 8, 12 +/- 3 days post FMT): Patients will be evaluated in the clinic for follow-up assessments. The following will be documented:

1. **Assessment of efficacy**: Assessment of diarrheal symptoms as well as testing for CDI by GDH/EIA and PCR regardless of symptoms at week 1, 8 and 12 post FMT.
2. **IBD clinical outcomes:** Clinical disease activity assessment depending on disease (Mayo for UC and HBI for CD), any changes in medical therapy including need for corticosteroids and need for surgery or hospitalizations
3. **Assessment for related AEs to FMT** or **Bezlo** will occur at each visit using NIH criteria. Related AES include but are not limited to:
    - Bloating, distention
    - Diarrhea
    - Constipation
    - Abdominal pain
    - bacteremia
    - infection transition
    - headache
    - nausea
    - pyrexia

4. Laboratory assessments:
    - **Blood**: CBC, CRP, CMP (to be done locally)
    - **Stool:** CDI testing (as above), Calprotectin, microbiome analysis. All stool samples from each site will be shipped overnight to BWH which will serve as the central lab for this study for the stool analysis.
    - Stool and blood will be banked for metabolomics and future analysis
5. Vital Signs and targeted physical exam
6. List of current concomitant medications

Visit 8 (Week 26 +/- 7 days post FMT): Study Phone Call. Patients will be called to assess the following:

1. IBD clinical outcomes: Assessment of disease activity scores, changes in medical therapy including need for corticosteroids and need for surgery or hospitalizations

2. AE assessment
3. Patients will mail in samples for microbiome analysis only

Patient obligations in the study will end at week 26 however the patient's medical record will be followed prospectively for evaluation of IBD outcomes and procedures done for clinical care for 1 year post-enrollment.

6.1 Early Termination Visit:
In the case of an early termination, study staff will complete an 'Early Termination CRF', if possible, and the following will be assessed:

1. **Assessment of efficacy**: Assessment of diarrheal symptoms as well as testing for CDI by GDH/EIA and PCR regardless of symptoms
2. **IBD clinical outcomes:** Clinical disease activity assessment depending on disease (Mayo for UC and HBI for CD), any changes in medical therapy including need for corticosteroids and need for surgery or hospitalizations
3. **Assessment for related AEs to FMT or Bezlotoxumab** will occur at each visit using NIH criteria. Related AES include but are not limited to:
    a. Bloating, distention
    - Diarrhea
    - Constipation
    - Abdominal pain
    - bacteremia
    - infection transition
    - headache
    - nausea
    - pyrexia

4. Laboratory assessments:
    a. **Blood**: CBC, CRP, CMP (to be done locally)
    b. **Stool:** CDI testing (as above), Calprotectin, microbiome analysis. All stool samples from each site will be shipped overnight to BWH which will serve as the central lab for this study for the stool analysis.
    c. Stool and blood will be banked for metabolomics and future analysis
5. Vital Signs and targeted physical exam

6.2 Unscheduled Visit: At any point during the study if patients experience worsening of symptoms they may be brought in by study staff for an unscheduled visit for an assessment. This visit will include:

1. **Assessment of efficacy**: Assessment of diarrheal symptoms as well as testing for CDI by GDH/EIA and PCR regardless of symptoms at week 1, 8 and 12 post FMT.
2. **IBD clinical outcomes:** Clinical disease activity assessment depending on disease (Mayo for UC and HBI for CD), any changes in medical therapy including need for corticosteroids and need for surgery or hospitalizations
3. **Assessment for related AEs to FMT or Bezlotoxumab** will occur at each visit using NIH criteria. Related AES include but are not limited to:

a. Bloating, distention
- Diarrhea
- Constipation
- Abdominal pain
- bacteremia
- infection transition
- headache
- nausea
- pyrexia

4. Laboratory assessments:
    a. **Blood**: CBC, CRP, CMP (to be done locally)
    b. **Stool:** CDI testing (as above), Calprotectin, microbiome analysis. All stool samples from each site will be shipped overnight to BWH which will serve as the central lab for this study for the stool analysis.
    c. Stool and blood will be banked for metabolomics and future analysis
5. Vital Signs and targeted physical exam
6. List of current concomitant medications

6.3 Patients Treatment Strategy: The below treatment strategy will be utilized based on results obtained at each visit.

Symptoms	**Step 1: PCR**	**Step 2: EIA**	**CDI recurrence**	**Treatment Course**
Diarrhea	**+**	**+**	**Yes**	Anti-CDI Therapy including antibiotics or repeat FMT
Diarrhea	+	-	No	Likely colonization, treatment at Clinician discretion
Diarrhea	-	-	No	No CDI, evaluate for other causes of diarrhea and treat accordingly
No Diarrhea	+	+	No	Clinician discretion
No Diarrhea	+	-	No	Asymptomatic Carriage, No anti-cdi tx needed
No Diarrhea	-	-	No	No treatment needed

6.4 Medications Permitted

During the follow-up period after FMT, subjects may remain on their co-existing medications. Rescue pathway for IBD subjects with worsening disease during the study period will be discussed with the patients primary GI and the clinician investigator and will be based on standard clinical practice.
This may include, but is not limited to the following;

i. Oral steroids (if not already receiving them or failing them)
ii. Rectal therapy (5-ASA or steroids)
iii. IV steroids
iv. Biologic therapy
v. Immunomodulators

If it is determined surgery is needed for the treatment of IBD that will be decided with the patients primary GI. If this occurs prior to week 12 the patient will be withdrawn from the study.

7. Specimen Handling and Shipping

All patients will be assigned a unique participant ID. Each site will have IDs unique to that site. All stool samples will be handled with gloves and strict handwashing before and after handling specimens will be performed. Stool from every site will be shipped overnight to Brigham and Women's Hospital, which will serve as the central lab for this study. The stool will be shipped on ice packs to maintain temps around 2-8°C. The samples will be processed once received, and results will be reported back to each site same day. Additionally, blood and stool samples will be aliquoted at BWH and banked. BWH will not be performing the blood analysis however one EDTA tube will be shipped with the stool sample to be banked.

Specimens will be closely tracked during transportation using FedEX labeling and tracking.

8. ASSESSMENT OF SAFETY

Safety will be assessed by the frequency and severity of adverse events (AE)

8.1 Definition of an Adverse events (AE)

Adverse events (AEs) will be recorded at each regular scheduled study visit in the study patient record (source document) as well as on a specific AE CRF.
An AE is any untoward medical occurrence in a study patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product, e.g.:

- any new clinical diagnosis
- any symptom that requires medical clarification or leads to in-patient admission (surgery or accident)
- any suspected adverse drug reaction (ADR)
- any symptom that appears on the study patient's medical records

- any event related in time with the application of the study medication and affecting the health of the study patient (including laboratory value changes)

If there is any doubt as to whether a clinical observation is an AE, the event should be reported. AEs must be graded for severity and relationship to study product.

8.2 NIH Grading of Severity of the Event

AEs will be assessed by the clinician using the NIH protocol defined grading system (see Appendix). Briefly, the criteria for estimating adverse event severity grade:

- Grade 1 (Mild): events require minimal or no treatment and do not interfere with the patient's daily activities.
- Grade 2 (Moderate): events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Grade 3 (Severe): events interrupt a patient's usual daily activity.
- Grade 4 (Potentially life threatening): Events result in inability to perform basic selfcare functions or the need for medical or surgical intervention to prevent permanent disability or death.
- Grade 5 (Death)

8.3 NIH Adverse Event Relatedness

The clinician's assessment of an AE's relationship to test FMT is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.
The following NIH guidelines of relatedness are used:

- Related: The adverse event is related to the FMT material – i.e. an event that follows a reasonable temporal sequence from administration of the FMT material, follows a known or expected response pattern to the FMT material, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the patient's clinical state.
- Possibly Related: The adverse event follows a reasonable temporal relation to FMT administration, however, symptom may be related to other factors.
- Not Related – The adverse event is not related to the FMT material. - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible

8.3.1. Solicited mild to moderate adverse events: In addition to open-ended questions on adverse events meeting the above definitions, specific potential adverse events will be inquired about during the follow up period:

Symptom that is clinically more severe than participant's baseline	Severity				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Fever*	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	>39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)	>40.0 degrees C (>104.0 degrees F) for <=24 hrs	>40.0 degrees C (>104.0 degrees F) for >24 hrs	Death
Diarrhea	Increase of <4 stools per day over baseline pre-FMT; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Abdominal Pain	Mild pain	Moderate pain; limiting instrumental activities of daily life	Severe pain; limiting self care activities of daily life	n/a	n/a
Bloating	No change in bowel function or oral intake	Systemic, decreased oral intake; change in bowel function	n/a	n/a	n/a
Constipation	Occasional or intermittent symptoms; occasional	Persistent symptoms with regular use of laxatives	Symptoms interfering with self-care activities of	Life-threatening consequences (e.g. obstruction, toxic	Death

	use of stool softeners, laxatives, dietary modification, or enema	or enemas indicated; limiting instrumental activities of daily life	daily life; obstipation with manual evacuation indicated	megacolon); urgent intervention indicated	

There are a few potential risks of fecal microbiota transplantation (FMT) including the transmission of antibiotic-resistant bacteria and E. Coli bacteria. Antibiotic resistant bacteria are bacteria that are resistant to some antibiotics. The two strains of E. Coli that subjects may contract include Enteropathogenic E. Coli (EPEC) and Shiga Toxin producing E. Coli (STEC) that may cause Diarrhea among other symptoms. These bacteria could be transmitted through FMT and could cause serious infection or death.

The FMT subjects will receive 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.

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 could be transmitted through stool and could cause serious infection or death. It is possible or healthy, Asymptomatic stool donors to potentially be infected with SARS-CoV-2.

The FMT provided by Open Biome also undergoes regular stool, blood, and nasal screenings for many different infectious agents, including a nasal swab test for SARS-CoV-2 at a minimum of every 30 days. Each FMT is only made available when these screens do not detect these infectious agents in the donor at each of these time points. Donors also undergo regular clinical assessments for any risk factors associated with carrying SARS-CoV-2, such as review of recent travel to areas considered high risk for the virus, including visiting certain healthcare facilities, or other behaviors which may increase the risk of exposure. OpenBiome will continue to update its screening guidelines and procedures as addition data, assays, and information becomes available. Subjects who received FMT from stool donations provided prior to December 1st, 2019, it is believed that the risk of SARS-CoV-2 virus being present in the FMT is very low and therefore no testing for the virus has been performed. Though precautions have been taken to lessen the risk of SARS-CoV-2 transmission via FMT, the scientific community is still learning about SARS-CoV-2 and COVID-19, and there may be additional risks that are unknown at this time.

8.3.2. Serious Adverse Events

- An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
  - Death;
  - Life-threatening adverse event*;
  - Inpatient hospitalization or prolongation of existing hospitalization;
  - A congenital anomaly/birth defect;
  - Persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life function.

  **Life-threatening adverse event. An adverse event is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event which, had it occurred in a more severe form, might have caused death.*

  Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Any adverse event or suspected adverse reaction that meets the criteria for serious adverse event will be:

- recorded on the appropriate SAE CRF
- followed through resolution by a study clinician
- reviewed and evaluated by a study clinician

8.3.3 Unsolicited Adverse Events

On enrollment in the study, the study participants will be instructed to contact the site PI if an AE occurs. All unsolicited non-serious adverse events will be collected from the time of FMT until 6 months following FMT and will be assessed for relatedness as outlined in section 8.3. Patients will be given a patient diary with date, time, details and action taken to help with data collection. Patients will bring this diary to the site PI for evaluation at each follow-up visit and will be instructed to seek immediate medical attention if indicated.

8.3.4. New-Onset Related Chronic Medical Condition

Study FMT related chronic medical conditions occurring from the time of the FMT until 6 months following FMT. Specifically, new-onset chronic medical conditions potentially related to FMT such as weight gain, glucose intolerance, autoimmune conditions, and metabolic syndrome will be monitored for. This is be done via patient report.

8.4 Reporting of Adverse Events

Study participants will be instructed to contact the study nurse or doctor if any serious or unexpected adverse event occurs. Study staff will enquire, about using a generally worded question, about AEs at each study visit. Reported AE's will be recorded in detail in an AE CRF. AE information to be collected in the AE CRF:

- Nature of the event
- Time of onset: date, time
- Concomitant treatment: product (generic name), indication, dosage, dosage interval, presentation, mode of administration, administration regimen
- Duration of the AE
- Severity
- Seriousness
- Causality
- Outcome

The course and outcome of the adverse event will be commented on as follows:

- Recovered without sequelae
- Not yet recovered
- Recovered with sequelae
- Fatal

Any SAE (including death, irrespective of the cause) occurring during the study will be immediately reviewed by the PI, i.e. within 24 hours and referred to the DSMB. In case of a SAE, the information will be reviewed by the PI and reported to the DSMB chair. If the SAE is judged by the DSMB to be related to the treatment, a report will be sent to the IRB of the site and OpenBiome. The report must contain a detailed description of the symptoms observed and the concomitant treatment administered. Furthermore, the investigator must comment on a possible causative relationship between the AE and the trial medication. Each SAE must be followed until it is resolved or can be explained satisfactorily.

For non-serious adverse reactions the site PI will complete and submit a report to the lead PI. All non-serious adverse reactions will be reviewed by the DSMB at their regular meeting and or ad/hoc depending on the clinical case at the discretion of the site PI and lead PI.

In accordance with safety requirements, the study PI will inform the local IRB and will make sure that the involved persons will obtain adequate information. The following instructions must be heeded:

- In the case of an intolerable SAE, the study patient must, at the decision of the investigator, be withdrawn from the clinical trial, and symptomatic treatment must be administered.
- The measures taken must be recorded on the CRF.
- In accordance with local legislation, the investigators will submit copies of the final SAE-report to the Regulatory Authorities concerned, if necessary.

8.5 Follow-up of Subjects after Adverse Events

AEs will be followed until resolution or stability even if this extends beyond the study-reporting period. Resolution of an AE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.
Follow-up procedures, evaluations, and outcomes will be recorded on the subject's case report forms.

8.6 Halting Rules

8.6.1. Study enrollment halting rules

Enrollment in the study will be suspended for conduct of a safety review by the DSMB in the case of:

- A Grade 3 AE of the same organ system deemed related to the study intervention in three or more of the randomized participants in a study treatment group.
- Any serious adverse event of an enrolled participant related to the study intervention, including transmission of a pathogen from donor to recipient.
- An overall pattern of symptomatic, clinical, or laboratory events that the lead PI considers related to study product and that may appear minor in terms of individual events, but that may collectively represent a serious potential concern for safety.

8.6.2. Individual's halting rules

Subjects who meet any of the following criteria must be assessed by the PI to determine if it is in the subject's best interest to stop the study product(s):

- Subject choice (Withdrawal of consent)
- Participant's non-compliance.
- Development of a significant medical condition and/or participation in the study is no longer in the best interest of the subject.

8.7 Safety Oversight

8.7.1. Data and Safety Monitoring Board (DSMB)

Safety oversight will be under the direction of a DSMB. The DSMB is an independent group of experts who will advise the study investigators. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for subject safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations concerning the continuation, modification, or termination of the trial. The DSMB will be composed of at least 3 voting members. The membership will include a chairperson with prior DSMB experience. There will also be members with clinical expertise in the medical area and subject population being studied. All DSMB members will be separate and independent of study personnel participating in this trial and should not have scientific, financial or other conflict of interest related to the trial. Procedures for DSMB data reviews will be defined in the DSMB Charter that will include DSMB membership, responsibilities, and the scope and frequency of data reviews. The study should be reviewed by the DSMB at least annually otherwise will plan to meet after 30, 60, 90 and 120 patients are enrolled.

9. STATISTICAL CONSIDERATIONS

9.1 Primary endpoint: CDI recurrence by 8 weeks

Proportion of participants who experience a CDI recurrence, defined as the presence of diarrhea and a positive CDI PCR and EIA toxin test by week 8 post FMT.

9.2 Sample size

Our sample size of 120 patients was determined to ensure sufficient accuracy in the estimation of the primary outcome of cure rate. In one of our current studies we found that the 3-month cure rate of CDI post FMT was 80% among patients with an established history of IBD. [23] Additionally, we preliminary found that out of 44 IBD patients who underwent FMT for recurrent CDI, the cure rate was found to be 77% at 4 weeks and 75% at 8 weeks.[24] The post-hoc data from MODIFY I and II we see a 27% reduction rate in CDI recurrence among IBD patients treated with bezlo.

Assuming a conservative effect size of 0.2, our sample size of 120 patients provides 80% power for detecting such an effect in the change of cure rates based on a paired-sample t-test at the alpha level of 0.05. This assumes a 75% cure rate in the FMT group and a 95% cure rate in the FMT + Bezlo group. However to allow for patient dropout we will plan to enroll up to 150 to ensure 120 patients complete the trial.

9.3 Final Analysis Plan

Categorical data will be described using descriptive statistics (proportions and percentages). Continuous data will be described using means and standard deviations (normally distributed data) or using medians and interquartile range (non-parametric data). Appropriate comparative statistical tests will be chosen based in the variable types (categorical, dichotomous, continuous) and distribution (parametric, non-parametric) and will be used to describe significant differences between intervention and control groups. Where appropriate, point estimates and confidence intervals will be reported. The p-value will be two tailed with a significance level of 0.05.

10. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with institutional requirements for the protection of confidentiality of subjects. Forms for use as source documents will be derived from the paper CRFs. Original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, pharmacy dispensing records. Original source documents will be maintained by each site. Copies of study paper CRFs will be sent to the BWH for manual entry of data into the master electronic CRF. This will allow BWH to check for accuracy and completeness of CRFs from each site. Original source data will not be sent to BWH.

11. QUALITY CONTROL AND QUALITY ASSURANCE

The site-PI's and study coordinators based at the sites are responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress

and protocol compliance. The overall PI will have direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring. Additionally, auditing by the by local and regulatory authorities will occur at their discretion. The PI will ensure all study personnel are appropriately trained and applicable documentations are maintained on site.

The Principal Investigator, Dr. Jessica Allegretti, will assure the validity and integrity of the data and adherence to the IRB-approved protocols.

Study staff will review completed CRF's before each visit to ensure completeness of previous entries. Entries that need clarification will be reviewed by the PI, and the subject and/or treating gastroenterologist will be consulted if needed.

12. ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 Ethical Standard

The PI will ensure that this study is conducted in full conformity with principles of the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR 46, 21 CFR 50 and 56, and ICH E6; 62 Federal Regulations 25691 (1997), if applicable. The investigator's Institution will hold a current Federal Wide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research if applicable.

12.2 Institutional Review Board

Each participating institution will provide for the review and approval of this protocol and the associated informed consent documents, by an appropriate ethics review committee or IRB. Any amendments to the protocol or consent materials must also be approved before they are placed into use unless change is for the safety of the subject. Only those IRB members who are independent of the investigators should provide an opinion on study related matters. Verification of IRB approval of the protocol and the written informed consent will be transmitted by the investigator or designee prior to the shipment of clinical trial material. No deviations from or changes to the protocol will be initiated without prior approval of an appropriate amendment unless change is for the safety of the subject. Each participating institution is responsible for ensuring Continuing Review at least once a year and for keeping the IRB apprised of the progress of the study and any changes to the protocol.

12.3 Informed Consent Process

The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki and will adhere to the ICH Harmonized Tripartite Guideline for Good Clinical Practice. Informed consent should be implemented before any protocol-specified procedures or interventions are carried out. Informed consent will be obtained in accordance with 21 CFR 50.25 and 45 CFR 46. Information should be presented both orally and in written form.

An investigator or designee will describe the protocol to potential subjects face-to-face. The Subject Information and Consent Form may be read to the subjects, but, in any event, the

investigator shall give the subjects ample opportunity to inquire about details of the study and ask any questions before the signing and dating the consent form.

Study staff must inform subjects and/or legal guardian that the trial involves research, and explain the purpose of the trial, those aspects of the trial that are experimental, any expected benefits, all possible risks (including a statement that the particular treatment or procedure may involve risks to the subject or to the embryo or fetus, if the subject is or may become pregnant or fathers a child, that are currently unforeseeable), the expected duration of the subject's participation in the trial, the procedures of the research study, including all invasive procedures, and the probability for random assignment to treatment groups. Subjects and/or legal guardian will be informed that they will be notified in a timely manner if information becomes available that may be relevant to their willingness to continue participation in the trial. They must also be informed of alternative procedures that may be available, and the important potential benefits and risks of these available alternative procedures. Subjects and/or legal guardian must receive an explanation as to whether any compensation and any medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained. Subjects and/or legal guardian must be informed of the anticipated financial expenses, if any, to the subject for participating in the trial, as well as any anticipated prorated payments, if any, to the subject for participating in the trial. They must be informed of whom to contact (e.g., the investigator) for answers to any questions relating to the research project. Information will also include the foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated. The subjects and/or legal guardian must be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or continue to participate in the trial. The extent of the confidentiality of the subjects' records must be defined, and subjects must be informed that applicable data protection legislation will be followed. Subjects and/or legal guardian must be informed that the monitor(s), auditors(s), IRB, and regulatory authority(ies) will be granted direct access to the subject's medical records for verification of trial procedures and/or data without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations, and that, by signing a written informed consent form, the subject is authorizing such access. Subjects and/or legal guardian must be informed that records identifying the subject will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available and, if the results of the trial are published, the subject's identity will remain confidential.

Consent forms must be in a language fully comprehensible to the prospective subjects. Informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject and the person who conducted the informed consent discussion. The signature confirms that the consent is based on information that has been provided and all questions have been answered to the prospective subject's satisfaction. Each subject's signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or the sponsor and Regulatory Compliance persons. The subject should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects, and should receive copies of any signed and dated consent form updates and any amendments to the written information provided to subjects.

12.4 Exclusion of Women, Minorities, and Children (Special Populations)

Children are excluded for safety reasons.

12.5 Subject Confidentiality

Subject confidentiality is held strictly in trust by the participating investigators, their staff, and the sponsor and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval from the sponsor.

The study monitor or other authorized representatives of the sponsor and FDA may inspect all documents and records required to be maintained by the Investigator, including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

12.6 Study Discontinuation

The PI has the right to terminate this study or an individual site's participation at any time. Reasons for terminating the study may include, but are not limited to, the following:

- Incidence or severity of adverse events indicates a potential health hazard;
- Data recording is inaccurate or incomplete;
- Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study.

12.7 Future Use of Stored Specimens

Any leftover blood and stool specimens will be stored and may be used for future research, under a future protocol, to learn more about fecal transplant in patients with IBD-CDI. These specimens will be stored indefinitely at the OpenBiome repository after the study is completed as well as at Brigham and Women's Hospital for future testing. In the informed consent document, subjects will be given an opportunity to choose whether or not their de-identified barcoded specimens are stored for future use. For subjects who choose not to allow storage of their samples for future use, these samples will be destroyed at the end of the study. All proposed research projects will be subject to approval by an IRB prior to release of any specimens. No human genetic tests will be performed on specimens.

There are no benefits to subjects in the collection, storage and subsequent research use of specimens. Reports about future research done with subject's samples will NOT be kept in their health records, but subject's samples may be kept with the study records or in other secure areas. Subjects can decide if they want their samples to be used for future research or have their samples destroyed at the end of the study. A subject's decision can be changed at any time before the end of the study by notifying the study doctors or nurses in writing. However, if a subject consents to future use and some of their blood and stool has already been used for research purposes, the information from that research may still be used.

De-identified samples and associated meta-data may be shared with other investigators at other institutions for academic purposes or industry collaborators pending an approved protocol and MTA. Each sample will be encoded (labeled) only with a barcode and a unique tracking number to protect subject's confidentiality.

Research using stored specimens may be conducted by other institutions. Any specimens and data provided to the receiving-institution will be coded. Unequivocally, neither individual personal identifiers nor the key linking coded data to individuals will be released to the receiving-institution.

13. DATA HANDLING AND RECORD KEEPING

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All data collection forms should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. Do not erase, overwrite, or use correction fluid or tape on the original.

Copies of the paper CRFs will be provided to BWH from the other participating site for use as source documents and maintained for recording data for each subject enrolled in the study. This will be entered into the eCRF by BWH staff only. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained.

13.1 Data Management Responsibilities

All source documents and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. Adverse Events must be graded, assessed for severity and causality, and reviewed by the site Principal Investigator or designee.

Data collection is the responsibility of the trial staff at the site under the supervision of the site Principal Investigator. During the study, the investigator must maintain complete and accurate documentation for the study.

13.2 Data Capture Methods

Clinical data (including AEs, concomitant medications, and solicited events data) and clinical laboratory data will be entered into a compliant Internet Data Entry System. The data system includes password protection and internal quality checks. Clinical data will be entered directly from the source documents.

13.3 Types of Data

Data for this study will include clinical, safety and microbiological outcome measures.

13.4 Timing/Reports

Interim reports for the DSMB will be prepared when approximately 25%, 50%, 75% and 100% of subjects complete enrollment. Interim statistical reports may be generated as deemed necessary and appropriate by the study PI. Other safety summary reports may be generated for the DSMB. A final report will be prepared following the availability of all the clinical, safety and efficacy data.

13.5 Study Records Retention

Study files must be maintained for a minimum of two years after the last approval. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor investigator prior to that time point, if applicable. Consent forms for future use of samples will be maintained as long as the sample exists.

13.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or protocol-specific MOP requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to the site PI.

All protocol deviations, as defined above, must be addressed in study subject source documents. A completed copy of the Protocol Deviation Form must be maintained in the Regulatory File, as well as in the subject's source document. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

14. Potential Risks and Benefits

14.1 Risks :

Fecal Microbial Therapy:

Known Risks of FMT

- Altered bowel pattern (diarrhea, constipation)
- Cramping
- Belching

Potential Risks of FMT

- Transmission of pathogenic bacteria, viruses, fungi
- Transmission of allergens
- Alteration in intestinal metabolism
- Inflammatory Bowel disease flare or exacerbation

Bezlotuxumab:
The most common adverse events reports include nausea, pyrexia and headache. However, there is an increased risk of heart failure in patients with a history of congestive heart failure (CHF). There is also a risk of an infusion reaction.

Privacy and Confidentiality:
This study involves the collection of personal health information. Accidental release of personal health information is a risk of participation in this study. Measures will be taken to protect the confidentiality of all subjects' information. These measures include keeping all information collected about the subjects' confidential, keeping information in locked rooms, and having physicians who are directly involved with a subject's clinical care involved in the study.

Colonoscopy:
Standard potential risks of the endoscopy procedure include discomfort, gastrointestinal bleeding either related or unrelated to biopsies, intestinal perforation, altered bowel habit. Complications of IV conscious sedation during the procedure include respiratory arrest, medication reactions, and aspiration. This is performed as part of clinical care.

Venipuncture:
Risks of having blood drawn include pain, bruising, or infection.

Pregnancy
The risks to fetuses and women who are pregnant are unknown. We will not be enrolling any pregnant of lactating women.

14.2 Potential Benefits:

The potential benefits include:
- Restoration of fecal diversity
- Reduction in intestinal inflammation
- Improvement in clinical symptom scores

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Assessment 4-weeks after fecal microbiota transplantation (FMT) is predictive of standard 8-week cure endpoint

. ACG; 2016; Las Vegas.

Appendix

Appendix 1.

Harvey-Bradshaw Index for Crohn's disease

Harvey-Bradshaw Index
General Well-Being (0=very well, 1=below par, 2=poor, 3=very poor, 4=terrible)
Abdominal Pain (0=none, 1=mild, 2=moderate, 3=severe)
Number of Liquid Stools per Day
Abdominal Mass (0=none, 1=dubious, 2=definite, 3=definite & tender)
Complications (1 per item)
Arthralgia
Uveitis
Erythema Nodosum
Apthous ulcers

Pyoderma Gangrenosum
Anal fissue
New Fistula
Abscess
TOTAL SCORE

Appendix 2. Mayo Score

Table 1: Mayo Scoring System for Assessment of Ulcerative Colitis Activity. [7,55]	
Stool frequency*	
0	Normal no. of stools for this subject
1	1 to 2 stools more than normal
2	3 to 4 stools more than normal
3	5 or more stools more than normal
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
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)
Physician's global assessment	
0	Normal
1	Mild disease
2	Moderate disease
3	Severe disease
*	Each subject serves as their own control.
**	Represents the most severe bleeding of the day.

Appendix 3: Record of Side Effects

Fecal Microbiota Transplantation - Record of Side Effects

This diary is one way researchers will get information from you regarding any possible problems or side effects in this study.

- **What you are going to do is simple.** Just keep a record of any unpleasant thing that happens to you while you are in the study, before, during, and after we have completed the stool transplant. We even want you to record things that do not seem to be part of the stool therapy, at all.

- **When do you start? When do you end?** You will record one entry 1-week prior and on the day of the transplant. You will then complete one entry per day for the first week following the treatment and then once a week thereafter for 12-weeks.
- **What do you look for? What do you report?** Any symptom or problem whether or not it may be from the medicine, stool therapy. This could include: fever, abdominal pain, a big belly, lots of gas, diarrhea, nosebleeds, and anything else you know is not quite right.
- **What will you do?** In the first 7 days after the transplant, you will report some of the specific things that have bothered you by checking the boxes in the diary (see below). You can also write any other problems that you may have had during that time. **Additionally, you will record your temperature once for each day for the first 7 days after the transplant, unless you feel hot. If you feel hot, please take your temperature again.** Please make sure to record the highest temperature taken that day if you take it more than once.

  Continue to record any problem up to 6 months after the transplant.

How will you record it? Like this…

EVENT	DATE OF ONSET	INTENSITY	ACTION TAKEN	MEDICATION	DATE RESOLVED
Fever	3/1/12	3	Missed 2 days of school	Tylenol-200mg	3/3/12
Sore throat	3/5/12	1	None	None	3/6/12

OTHER SYMPTOMS
Record each symptom at its ***worst*** level for each day.
For example, a sore throat that starts at 'Grade 1" but increases to 'Grade 2' should be recorded as 'Grade 2".

Examples of Grades:
Grade 1 – Mild: I noticed the symptom. It did not keep me from doing my normal activities.
Grade 2 – Moderate: I noticed the symptom and it kept me from doing some of my normal activities.
Grade 3 – Severe: I really noticed the symptom and it kept me from doing activities that I wanted or needed to do.
Grade 4 – Very severe: The symptom made me unable to perform basic self-care functions such as washing myself **OR** medical or surgical intervention was needed to prevent serious consequences.

Subject ID:_____

Date:____/____/_____ Check here is no side effects present. ☐
Highest temperature of the day:_____^{o}F Total Number of Stools:_____

Check if symptom present	Event	Date of Onset	Intensity	Action taken	Medications	Date Resolved
☐	Fever					
☐	Abdominal Pain					
☐	Diarrhea					
☐	Nausea/Vomiting					
☐	Blood in Stool					
☐	Other 1					
☐	Other 2					
☐	Other 3					

Grade 1 – Mild: I noticed the symptom. It did not keep me from doing my normal activities.
Grade 2 – Moderate: I noticed the symptom and it kept me from doing some of my normal activities.
Grade 3 – Severe: I really noticed the symptom and it kept me from doing activities that I wanted or needed to do.
Grade 4 – Very severe: The symptom made me unable to perform basic self-care functions such as washing myself **OR** medical or surgical intervention was needed to prevent serious consequences.

Appendix 4:

Adverse Events Recording Form

Record of adverse events:				
System:	**Present**	**Grade**	**Attribute**	**Describe reaction (refer to appendix 9)**
Systemic				
Infection				
Injection site reaction				
Skin/dermatologic				
Cardiovascular				
Gastrointestinal				
Neurologic				
Respiratory				
Musculoskeletal				
Genitourinary				
Ocular/Visual				
Endocrine/metabolic				
Laboratory AE:				
Hematologic				
Chemistry				
Urinalysis				

NIH Adverse Event Severity Grading Scale*		
Scale		*Description*
1	Mild	Symptoms causing no or minimal interference with usual social and functional activities
2	Moderate	Symptoms causing greater than minimal interference with usual social and functional activities
3	Severe	Symptoms causing inability to perform usual social and functional activities
4	Potentially life-threatening	Symptoms causing inability to perform basic self-care functions OR medical and operative intervention indicated to prevent permanent impairment, persistent disability, or death
5	Death	Fatal event related to adverse event

NIH Adverse Event Relatedness *	
Likely	*Description*
Definitely Related	The adverse event is clearly related to the investigational agent/procedure –i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state
Possibly related	An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.
Not related	The adverse event is clearly not related to the investigational agent/procedure – i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

**Source: NIH Adverse Event and Serious Adverse Event Guidelines, available online at https://www.nia.nih.gov/sites/default/files/niaaeandsaeguidelinesfinal011012_0.doc*

Completed _____ Date _____

Name

Appendix 5:

Charter, Data and Safety Monitoring Board for:
A Randomized Controlled Trial to compare the effectiveness of Fecal Microbiota Transplantation (FMT) in combination with Bezlotuxumab compared to FMT and placebo for the prevention of CDI recurrence in patients with Inflammatory Bowel Disease and Recurrent Clostridium difficile Infection

Version Date: Feb 2019

The DSMB will consist of a team of clinical researchers who are unaffiliated with this project.

These individuals will not be investigators in this study and will be experienced in conducting and interpreting clinical trials; they will review the efficacy and safety endpoints at the below stated time points. There will be 3 voting members on the DSMB:

Andrew Courtwright, MD, PhD: Critical Care/Ethics
Walter Chan, MD, MPH: GI
Joe Feurestein, MD: GI, IBD

The Charter is intended to be a living document. The DSMB may wish to review it at regular intervals to determine whether any changes in procedure are needed.

1. Responsibilities of the DSMB

The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study.

The DSMB is an independent group advisory and is required to provide recommendations about starting, continuing, and stopping the study. In addition, the DSMB is asked to make recommendations, as appropriate, to the about:

- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol and consent forms
- Participant safety
- Notification of and referral for abnormal findings

2. Scheduling, Timing, and Organization of Meetings

Data and Safety Monitoring Meetings

The DSMB will meet a minimum of 4 times: after treatment of the first 25%, 50%, 75% an 100% of patients have been recruited. In addition the DSMB may convene additional meetings if necessary to ensure the ongoing monitoring and safety of the subjects treated with FMT. Any serious AEs also will be evaluated by the DSMB for review and determination of whether the trial should continue. An example of the DSMB meeting minutes are at the end of this document. The study will not proceed at each of these time points until the DSMB gives approval to continue.

Safety Reporting

In accordance with applicable policies of the individual site Institutional Review Board (IRB), the investigator-sponsor will report, to the IRB, any observed or volunteered Unanticipated Problem that is determined to be 1) unexpected); 2) related or at least possibly related to study participation; and 3) suggests that the research places subjects or others at a risk of unknown harm or addition/increased frequency of harms (including physical, psychological, economic, legal, or social harm) than was previously known or recognized. Unanticipated problems may be adverse events, protocol deviations, noncompliance or other types of problems, but MUST meet all of the criteria listed above. Unanticipated problem reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable unanticipated problems will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the investigator-sponsor's receipt of the respective information. For Internal Fatal/Life-Threatening Unanticipated Problems, the PI should notify the IRB Chair by phone immediately and consider voluntarily halting subject enrollment.

Follow-up information to reported adverse event will be submitted to the IRB as soon as the relevant information is available. If the results of the investigator's follow-up investigation show that an adverse event that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the investigator will report the unanticipated problem to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

Grading and Attribution Methods for Adverse Events

Grading Scale

0 No adverse event or within normal limits
1 Mild adverse event – did not require treatment
2 Moderate adverse event – resolved with treatment
3 Severe adverse event – resulted in inability to carry on normal activities and required professional medical attention
4 Life threatening or disabling adverse event
5 Fatal adverse event

Attribution Scale

Definite: The adverse event is clearly related to the study drug
Probable: The adverse event is likely related to the study drug
Possible: The adverse event may be related to the study drug
Unlikely: The adverse event is doubtfully related to the study drug
Unrelated: The adverse event is clearly not related to the study drug

Appendix 6: Study Schema

Weeks	-2	72 Hrs	0	1	8	12	26
Labs							
CRP	x			x	x	x	
CMP	x			x	x	x	
CBC	x			x	x	x	
HIV	x						
Viral Hepatitis Panel	x						
Syphilis	x						
CMV and EBV IgG*	x						
Calprotectin	x			x	x	x	
C.diff GDH/EIA				x	x	x	
C.diff PCR				x	x	x	
Urine HCG	x		x				
Bank stool	x			x	x	x	x
Bank blood	x			x	x	x	
Metabolomics							
Blood	x			x	x	x	
Stool	x			x	x	x	
Stool 16S/DNA Extraction	x			x	x	x	x
Colonoscopy/FMT			x				
Bezlotoxumab/Placebo			x				
Clinical Indices							
HBI/Mayo	x	x	x	x	x	x	x
Bristol Score/Diarrhea score	x	x		x	x	x	
HPI	x						
Targets Physical Exam	x			x	x	x	
Adverse event Assessment		x		x	x	x	x

*only for patients severely immunocompromised (3 or most immunosuppressing drugs)

Appendix 7. PCP Phone Call Script

Hello is this Dr._____? My name is _____ and I am reaching out on behalf of Dr. Allegretti. I am a member of the study team investigating the use of on fecal microbiota transplant for the treatment of C.diff in the setting of IBD. We were contacted by your patient _____ who expressed interest in participating in our study. We wanted to know if you had some time to discuss your patient's medical history in order to confirm if they are eligible to participate in our study? It shouldn't take more than 5-10 minutes. We will require your office to fax over any documentation that confirms their medical history for our records. Would it be okay to set up a time to discuss?

Some additional information about the study:

Your patient will be receiving an FMT, which is the transfer of heavily screened donor stool that is delivered via a colonoscopy, in combination with Bezlotuxumab, a human monoclonal antibody indicated to reduce recurrence of C. Diff infection. In this study we are looking to assess the benefits of an FMT in combination with Bezlotoxumab on eradicating CDI in patients who also have IBD. We also hope to understand how the FMT will affect their IBD. This is crucial because patients with IBD are at higher risk of getting C Diff infections and this can worsen their IBD. Based on clinical trials we have seen a nearly 90% cure rate of C Diff. in patients without IBD with minimal side effects.

As stated earlier, we just need you to confirm a couple of things regarding your patient :

1) Does your patient have at least 2 confirmed CDI diagnoses within the past year and have they failed to resolve with Vancomycin treatment?
2) When was the last time the patient was prescribed antibiotics?
3) Do you have a record of the patient's date of IBD diagnosis and can you tell me more about the severity of their condition?
4) Are there any concerns you might have with your patient receiving an FMT via a colonoscopy?
5) Are there any other medical problems that your patient might have that you feel will be affected by the FMT?

Thank you for taking the time to discuss your patient's medical history with me. Our fax number is 617-732-9198. It was a pleasure speaking with you, please do not hesitate to contact me if you want to provide us with any other information or if you have any questions. You can call me at 617-525-7322 M-F during normal business hours. Have a good day.

Appendix 8: Pre-Screening Phone and Email Script for Patients

Hi, is this _____? My name is _____, I am a research coordinator in the Gastroenterology department at the Brigham. I wanted to thank you for your interest in the research study you inquired about, regarding fecal transplant in combination with Bezlotoxumab and its efficacy in getting rid of C Diff. infection in patients with IBD. I wanted to know if you had some time to discuss more details about the study? It shouldn't take more than 10 minutes, but it will require you to answer questions about your health and medical history to find out if you might qualify for the study. Some of the questions may make you feel uncomfortable, but you can stop at any time. I will also be recording your answers in writing, but I will only collect detailed contact information if you qualify for the study and want to schedule an in person visit. We will also take reasonable steps to protect the confidentiality of the information you provide during this conversation. Would it be okay with you to proceed?

Let me provide you with some more information about the study and then I can answer any questions that you might have.

An FMT is the transfer of heavily screened donor stool that is delivered via a colonoscopy. In this study we are looking to assess the benefits of an FMT on getting rid of CDI in patients who also have IBD. We also hope to understand how the FMT will affect your IBD. This is crucial because patients with IBD are at higher risk of getting C Diff infections and this can worsen IBD. Based on clinical trials we have seen a nearly 90% cure rate of C Diff. in patients without IBD with minimal side effects. We therefore would like to see how this would affect patients with IBD and C Diff.
The FMT you will be receiving will be done in combination with Bezlotoxumab. Bezlotoxumab is a drug taken as a single IV infusion over the course of 60 minutes. This portion of the study is placebo controlled so not every subject will receive Bezlotuxumab. The drug is meant to prevent the recurrence of C. Diff. infection and we hope to see if it helps to further prevent the chance of recurrence after FMT.
We are still recruiting for the study and all patients will be given an FMT via a colonoscopy. This study involves 5 visits to the Brigham and Women's hospital over 12 weeks and 2 over the phone check ins throughout the entirety of the study. If the FMT is not successful, you may have the option to receive another FMT in order to treat your C diff. infection. You will also be required to fill out symptom diaries and bring in stool samples at all visits. Prior to scheduling you in for a screening visit I do have a few questions to confirm your eligibility, but please feel free to ask me any questions that you might have at this point.

We just need some information about yourself? Pending your answers below we may need to contact your primary physician to confirm parts of your history. Would that be alright with you?

1) Do you have 2 or more confirmed CDI diagnoses?
2) Did you have a confirmed CDI diagnosis within the last 3 months?
3) Did one of the CDI infections fail to get resolved with Vancomycin treatment?
4) When was the last time you took antibiotics?
5) Do you have a confirmed diagnosis of IBD?
6) Are you comfortable receiving an FMT via a colonoscopy?
7) Are you comfortable receiving an IV infusion over the course of 60 minutes?
8) Do you have any medical problems that you are currently or have previously seen a doctor for?
9) What medications do you currently take?
10) Where are you located, and will you be able to get to Boston easily?

Thank you for answering my questions. That's all the information I need from you right now. Do you have any questions?
I will send you a copy of the consent form for you to read over and discuss with your physician and family members. If you decide to proceed we will then schedule you for a screening visit where we will review the consent form in person. May I please have the best email to contact you with? If you have any question you can call me at 617-525-7322 M-F 9am-5pm. Thank you so much for your time, it was a pleasure speaking with you!