The ICON Study:
Inflammatory Bowel Disease and Recurrent Clostridium difficile Infection: Outcomes after Fecal Microbiota Transplantation

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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.

We intend to prospectively study the clinical and microbial outcomes of FMT in patients with IBD-CDI. The overall objective of our study is to collect robust data and create a tissue and data repository to understand the effects FMT has on this unique subgroup of IBD patients during initial follow up using clinical and microbiome analyses. Our central hypothesis is that FMT is effective for the treatment of recurrent CDI in patients with IBD and FMT will not lead

to adverse IBD outcomes in a majority of patients. The following aims will allow us to test the hypothesis and investigate the therapeutic potential of this targeted treatment.

2. Objectives and Aims:

2.1 Specific Aims:

- **Specific Aim 1**: Assess the efficacy of FMT at eradicating CDI in patient with IBD-CDI
- **Specific Aim 2**: Assess IBD clinical outcomes post FMT
- **Specific Aim 3**: Determine the impact of FMT on the intestinal microbiome of patients with IBD-CDI via 16s ribosomal RNA sequencing

2.2 Study Objectives:

Primary Objectives:
To assess the efficacy of FMT at eradicating CDI in patient with IBD-CDI

Secondary Objectives

- Assess IBD clinical outcomes post FMT
- Determine the impact of FMT on the intestinal microbiome of patients with IBD-CDI via 16s ribosomal RNA sequencing
- Determine is role of bile acid profiles on efficacy of FMT

2.3 Study Outcomes:

2.31 Primary Clinical Endpoint:

- **FMT Failure at Week 8:** Defined as a positive stool PCR and EIA (2-step testing approach) as well as diarrhea (>=3 loose stools in 24h period, defined as BSS 6-7, x 3 days).

2.32 Secondary Clinical Endpoints

IBD clinical outcomes following FMT 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 or maintained response.

- IBD flare is defined as an increase in Mayo or HBI score by 2 from baseline in the absence of CDI (negative EIA testing). If active disease at baseline, worsening of disease is defined as a increase in either HBI or Mayo 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 difficle 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).

Secondary Microbial Endpoints:

- 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

Secondary Metabolomic Outcomes: Bile salt 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** will be analyzed using the metabolomics platform targeting bile acids using liquid chromatography tandem mass spectrometry (LC-MS) to measure endogenous bile salts and their metabolite levels in fecal supernatant. Water soluble metabolites will be extracted from feces as described by Saric et al while lipids will be extracted from lypophilized samples using isopropanol. Water soluble metabolites will be measured using ion pairing chromatography and hydrophilic interaction chromatography methods, and lipids and bile acids will be measured using C4 and C18 reversed phase chromatography methods. MultiQuant software (AB SCIEX) will be used for automated peak integration and manual review of peak quality prior to statistical analyses. The GenePattern (Broad Institute) and IPA (Ingenuity Systems) software will be used to analyze and visualize results.

2.33 **Safety Endpoints:**

Primary Safety Outcomes Measures

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

Secondary Safety Outcome Measures:

- Proportion of participants with an AE through week 8 (±5 days)
- Proportion of participants with an SAE through week 8 (±5 days)
- Proportion of participants with a SAE at month 6 (±14 days) phone safety assessment

3. STUDY DESIGN:

This is an open-label single-arm pilot study to measure the microbiological and clinical impacts of FMT in patients with IBD-CDI. We will prospectively enroll 50 IBD-CDI patients from 4 tertiary care FMT referral centers. 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 (See Appendices for OpenBiome Quality and Safety Program as well as donor screening examples as well as Study Schema).

3.1 Donors: OpenBiome donors are rigorously assessed and monitored.

- Donor candidates are screened with comprehensive evaluation of medical histories, behavioral risks, and current health status.
- **Laboratory Screening:** Donor candidates are screened for 20 stool and serological tests at a CLIA-certified laboratory. Less than 20% of those screened become qualified donors
- **Continuous Requalification:** Qualified donors are under medical monitoring through the entire donation window and are fully rescreened every 60 days
- **Quarantine Procedure:** Prior to release, donated material is quarantined for 60 days in between two full panel screens at a CLIA certified laboratory. After passing a first battery of tests, a donor may donate specimens for a 60-day window. All material made from these specimens is held in quarantine until a second battery of tests is administered. The material from this 60-day window is released only if and when the donor passes this second battery of tests.

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 via the clinicaltrials.gov website (This may be via E-mail or phone call depending on patient preference)

Study procedures will take place at all four sites including Brigham and Women's Hospital, Brown University, Indiana University and Mt. Sinai Hospital.

3.2.1 Inclusion criteria:

- Adults age 18 or greater
- Confirmed recurrent CDI by positive PCR or EIA toxin test defined at ≥ 2 episodes and vancomycin failure within one year with the most recent being within the past 3 months.
- Confirmed diagnosis of IBD with colonic involvement (ulcerative colitis, Crohn's colitis or ileocolitis or indeterminate colitis) for ≥ 3 months
- Undergoing FMT via colonoscopy for CDI as part of standard medical care

3.2.2 Exclusion Criteria:

- Unable or unwilling to undergo a colonoscopy
- Inpatient status
- Anticipated immediate or upcoming surgery within 30 days
- Need for continued non-anti-CDI antibiotic therapy
- History of total or subtotal proctocolectomy
- Isolated ileal or small bowel disease
- Pregnancy or lactation
- 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
- 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
- Known concurrent HIV, Hepatitis B or C infection
- Concurrent PSC
- Patients with WBC< 3.0 x10^{9th}/L at baseline
- Patients with platelet count < 100 x10^{9th}/L
- Patients with initial elevation of AST or ALT > 1.5 times above normal limit at baseline
- Non - steroidal anti-inflammatory medications (NSAIDs) as long-term treatment, defined as use for at least 4 days a week each month
- Treatment with vancomycin or metronidazole for more then 60 days prior to enrollment
- Prior FMT within one year

3.3 Subject Withdrawal Criteria: Since this is a single treatment, pilot study, subjects will be withdrawn primarily prior to FMT.

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)
- Inclusion criterion not fulfilled
- Other reasons (must be noted)
- 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 week 2 adverse event screening, 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. We will not utilize advertisement material or other informational materials for patients beyond the consent form and the posting on clinicaltrials.gov. 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, and they will be encouraged to discuss participation with family members and health care providers. Patients will receive parking vouchers at each visit to cover the cost of parking.

If patients reach out to us via the provided E-mail or phone number located at the clinicaltrials.gov website, 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 via email or phone call (with patient permission) to confirm medical diagnosis. Once patient's medical and treatment history are thoroughly vetted with the primary care physician, we will ask the physician to further discuss the study with the patient to minimize "undue influence" and ensure appropriateness for participation. When we are given the approval of the physician to enroll the patient in the study, we will then schedule the standard screening visit to re-review medical history (inclusion and exclusion criteria) and perform informed consent. (See below)

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 and 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.

5. STUDY INTERVENTION

5.1 Product Description:

Fecal Microbiome Transplant (FMT)

FMT is the process by which processed donor microbiota material is transplanted into recipients, in this study specifically by lower gastrointestinal delivery (colonoscopy or flexible sigmoidoscopy). 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 administered via colonoscopy to the ileo-colonic mucosa as part of the patients standard care.

Donor Procedures (OpenBiome):

See Attached BBMF for full donor procedure details

5.2 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. Units will be shipped to each site and local site storage at -20°C or -80°C will be permitted for up to 6 months.

5.3 Accountability Procedures:

The site principal investigator (PI) (or designee) will maintain an accurate record of the receipt of the test materials as shipped by Openbiome, including the date received. 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.

The location, volume and number of FMT donor solutions will be maintained in a log by the research team. The principal investigator will be responsible for accurate record and tracking of all FMT solutions.

6. STUDY SCHEDULE

A schematic representation of the study schedule can be found in the appendix 9.

Visit 1 (Week -2): Screening – potential subjects will undergo the following screening procedures one to two weeks prior to FMT to determine if they meet the recipient selection criteria.

1. Medical record review to confirm diagnosis and treatment history
    a. **Demographic:** age, body mass index, race, 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 phenotype (Montreal classification), clinical disease activity assessment using patient reported outcomes of abdominal pain, stool frequency and presence of rectal bleeding. For UC modified Mayo with recall of the previous 3 days and SCCAI scores will be assess. For CD, HBI scores and CCAI 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. Symptom assessment and physical exam by study physician

3. Laboratory assessments:
    a) **Blood**: CBC, CRP, albumin and creatinine, HIV, Viral hepatitis and Syphilis
    b) **Stool:** Calprotectin (first stool of the morning), microbiome analysis. Stool will be collected on chronic anti-CDI therapy
4. Stool and blood will be banked for bile salt metabolomics and future analysis
5. Urine Pregnancy Test
6. If not currently on anti-CDI therapy Vancomycin should be started for a minimum of 10 days prior to FMT with instruction to hold for 48 hours prior FMT.

Visit 2 (Week 0): 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.
2. Clinical disease activity assessment using patient reported outcomes of abdominal pain, stool frequency and presence of rectal bleeding (Mayo and SCCAI for UC and short CDAI and HBI for CD)
3. Biopsies for histology

72 Hours: Study phone call

1. IBD clinical outcomes: Assessment of disease activity scores, diarrheal assessment form, and review of patient symptom assessment sheet
2. AEs related or possibly related to FMT

Visit 3,4,5 (Weeks 1, 8, 12 +/- 3 days): Patients will be evaluated in the clinic for the following for follow-up assessment of clinical scores and adverse event screening

1. **Assessment of efficacy of FMT**: Assessment of diarrheal symptoms as well as testing for CDI by EIA and PCR regardless of symptoms at week 1, 8 and 12 post FMT.
2. **IBD clinical outcomes:** Assessment of disease activity scores, ie. Modified Mayo score, SCCAI, short CDAI and HBI, changes in medical therapy including need for corticosteroids and need for surgery
3. **Assessment for related AEs to FMT** will occur at each visit using NIH criteria. Related AES include:
    - Bloating, distention
    - Diarrhea
    - Constipation
    - Abdominal pain
    - Fever
    - bacteremia
    - infection transition

4. Laboratory assessments:
    - **Blood**: CBC, CRP, albumin and creatinine,
    - **Stool:** CDI testing (as above), Calprotectin, microbiome analysis. All samples will be shipped to BWH which will serve as the central lab for this study for stool analysis.
    - Stool and blood will be banked for bile salt metabolomics and future analysis

Week 26 +/- 7 days): Study Phone Calls. Patients will be called to assess the following:

3. IBD clinical outcomes: Assessment of disease activity scores, changes in medical therapy including need for corticosteroids and need for surgery
4. AEs related or possibly related to FMT
5. Patients will mail in samples for microbiome analysis

Week 26: 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 through year 5 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:

- Clinical and safety assessment by study nurse / physician, specifically evaluating adverse events related to the intervention.

- Data collection at visit:

    - Interim medical history with focus on IBD

- Concomitant medication
- Changes in stool consistency (Bristol Stool Scale) and frequency
- Clinical evaluation using standard, structured assessment
- Vital signs: Temperature, heart rate, blood pressure, weight (if available)
- General health status
- Adverse events (NIH criteria)

- Stool collection for 16S sequencing, CDI testing and fecal calprotectin

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:

- Interim medical history with focus on IBD
- Concomitant medication
- Changes in stool consistency (Bristol Stool Scale) and frequency
- Clinical evaluation using standard, structured assessment
- Vital signs: Temperature, heart rate, blood pressure, weight (if available)
- General health status
- Adverse events (NIH criteria)

- Stool collection for 16S sequencing, CDI testing and fecal calprotectin

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**	**FMT Failure**	**Treatment Course**
Diarrhea	**+**	**+**	**Yes**	Anti-CDI Therapy including antibiotics or repeat FMT
Diarrhea	+	-	No	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 at stable doses. Rescue pathway for IBD subjects with worsening disease during the study period to be determined by the clinician investigator and based on standard of clinical practice.
This may include, but is not limited to the following;

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

7. Specimen Handling and Shipping

All patients will be assigned a unique barcode number / participant ID. All participants enrolled in the study will have a study identifier posted in their file and will have barcode labels available to the study staff. All stool samples will be treated under strict infection control procedures which includes gloves to be worn at all times when handling samples and strict handwashing before and after handling specimens. Stool from every site will be shipped overnight to Brigham and Women's Hospital, which will serve as the central lab for this study, on ice packs to maintain temps of 2-8°C. The samples will be processed and all testing will be performed at the BWH clinical laboratory. Additionally samples will be aliquoted at BWH into various media including RNA later, glycerol and flash frozen aliquots for banking.

Specimens will be closely tracked during transportation using the barcode labeling and log books. Formal hand-overs with recording of specimen barcodes in tracking logbooks will be required during the transport of specimens from study sites to Brigham and Women's Hospital.

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:

	Severity

Symptom that is clinically more severe than participant's baseline	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 use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated; limiting instrumental activities of daily life	Symptoms interfering with self-care activities of daily life; obstipation with manual evacuation indicated	Life-threatening consequences (e.g. obstruction, toxic megacolon); urgent intervention indicated	Death

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 occurring from the time of FMT until 6 months following FMT and will be assessed for related 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.

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. A specific SAE CRF will be provided. In case of a SAE, this form will be completed and reviewed by the PI as an initial report, and 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 to DMID 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. The DSMB may conduct a safety interim analysis after 50% of patients have received an FMT.

9. STATISTICAL CONSIDERATIONS

This is a pilot, open label study to determine the efficacy of FMT in patients with IBD-CDI.

9.1 Primary endpoint: Failure of FMT at 8 weeks

Proportion of participants who failed FMT, 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 50 patients was determined to ensure sufficient accuracy in the estimation of the primary outcome of cure rate. In one of our prior studies found that the 3-month cure rate of CDI was 79% among patients with an established history of IBD for at least 3 months.[22] Additionally, in our preliminary data on post FMT testing, 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] Assuming a 75% cure rate, our sample size of 50 patients provides accuracy with a 13% margin of error in the estimation of the cure rate at the 95% confidence level.

In our prior study, the IBD disease activity score had an improvement of 3 points in the Ulcerative Colitis Clinical Score (UCCS) at 3 months post FMT with a standard deviation of 3.5, yielding an effect size of 0.86. Among patients with Crohn's disease, the Harvey-Bradshaw Index (HBI) had an improvement of 4 points with a standard deviation of 8.2, yielding an effect size of 0.49.[14,22] Assuming a conservative effect size of 0.4, our sample size of 50 patients provides 80% power for detecting such an effect in the change of IBD clinical outcomes based on a paired-sample t-test at the alpha level of 0.05. In addition, for the estimation of adverse event rate related to FMT, this sample size provides accuracy with no more than 10% margin of error at the 95% confidence level, assuming a true adverse event rate of no more than 10%.

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 electronic CRFs. Original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, laboratories, and medico-technical departments involved in the clinical trial. Original source documents will be maintained by each site.

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. 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 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 electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each subject enrolled in the study. 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, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. 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 40% and 70% 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 (except for future use consent forms) 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, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained. Consent forms for future use 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 study PI or designated personnel at BWH.

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. Potenial Risks and Benefits

14.1 Risks

14.1.1 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
- 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 FMT you 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.

14.1.2 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.

14.1.3 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.

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

14.1.5. 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

As this is a pilot study, it is difficult to quantify the expected benefits.

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16. 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: Crohn's Disease Activity Index

Crohn's Disease Activity Index	
Number of liquid stools (daily for 7 days)	x 2
Abdominal pain (none = 0, mild = 1, moderate = 2, severe = 3)	x 5
Sense of well-being (well = 0, slightly below par = 1, poor = 2, very poor = 4, terrible = 4)	x 7
Number of complications (arthritis/arthralgia, iritis/uveitis, erythema nodosum/pyoderma gangrenosum, aphthous stomatitis, anal fissure/fistula or abscess, fever > 37.8° C)	x 20
Taking diphenoxylate or loperamide (no = 0, yes = 1)	x 30
Abdominal mass (no = 0, questionable = 1, present = 5)	x 10
Hematocrit (males: 47 – HT%, females: 42 – Ht%	x 6
Weight (1 – weight / standard weight x 100). Add or subtract according to the sign	x 1
Total	

Appendix 4: Simple Clinical Colitis Activity Index:

Ulcerative Colitis (SCCAI):

1) **Bowel frequency (day)**
   - ❶ 1 to 3
   - ① 4 to 6
   - ② 7 to 9
   - ③ more than 9
2) **Bowel frequency (night)**
   - ❶ None -->0
   - ② 1 to 3
   - ③ 4 to 6
3) **Urgency of defecation**
   - ❶ None
   - ① Hurry
   - ② Immediately
   - ③ Incontinence
4) **Blood in the stool**
   - ❶ None
   - ① Trace
   - ② Occasionally Frank
   - ③ Usually Frank
5) **General wellbeing**
   - ❶ Very well
   - ① Slightly below par

② Poor
③ Very poor
④ Terrible

6) Extraintestinal manifestations of IBD (check all that apply; 1point for each):

□ Arthralgia
□Erythema nodosum
□ Uveitis
□ Pyoderma gangrenosum

Appendix 5: 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 6:

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 7:

Charter, Data and Safety Monitoring Board for
The ICON Study: Inflammatory Bowel Disease and Recurrent Clostridium difficile Infection: Outcomes after Fecal Microbiota Transplantation
Version Date: January 2017

1. Introduction

This Charter is for the Data and Safety Monitoring Board (DSMB) for the study **The ICON Study: Inflammatory Bowel Disease and Recurrent Clostridium difficile Infection: Outcomes after Fecal Microbiota Transplantation**

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

Stacy Kahn, Gastroenterology, Boston Children's Hospital
Joseph Feurestein, Gastroenterology, Beth Israel Deaconess
Hamed Khalili, Gastroenterology, Massachusetts General Hospital

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 members on the DSMB consisting of at least two gastroenterologists and one infectious disease specialist. The members of the DSMB are:

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.

2. 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

3. Scheduling, Timing, and Organization of Meetings

Data and Safety Monitoring Meetings
The DSMB will meet a minimum of 2 times: after treatment of the first 40% of patients have been recruited and after treatment of 70% of subjects. 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.

4. 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 8: Data and Safety Monitoring Meeting Minutes Template

Date:

Title of Protocol/IRB Number:

Principal Investigator/Designee:

Recommendations:

□ **Continue the trial without modification**

□ **Accrual:**
- □ Recommend study be closed because of slow accrual
- □ Continue to monitor study, but consider closure because of slow accrual

□ **Recommend study is amended/changed:**
- □ For patient safety reasons
  - □ Rate of adverse events
  - □ Early stopping of inferior therapy
- □ To extend accrual because of an event rate slower than expected

□ **Other:** _____

Signature/Principal Investigator or Designee:

_____

The DSMB will review adverse event data, other safety data, quality and completeness of study data, and enrollment data at each meeting to ensure proper trial conduct. At intervals, as noted above, the DSMB will also review formal interim analyses of the primary end point.

5. Reports of DSMB Deliberations

- Initial summary: The Director or designee will review this summary and approve or disapprove the recommendation(s), or request additional information. The recommendations will then be sent to the DCC, and the clinical investigators.

- Action plan: If the DSMB's recommendations require significant changes or follow-up, the BWH IRB staff will prepare an action plan outlining the steps required to implement the recommendations.

- Formal minutes: The DSMB Chair is responsible within 30 days of the meeting or call to present minutes to the IRB. These minutes are subject to FOIA requests and are prepared accordingly to summarize the key points of the discussion and debate, requests for additional information, response of the investigators to previous recommendations, and the recommendations from the current meeting. These minutes will be reviewed by IRB staff, key study personnel before being forwarded to the DSMB Chair for final review and approval. The DSMB Chair may sign the minutes or indicate approval electronically via email. Then, the minutes are sent to the BWH IRB for approval. Subsequently, the minutes are sent back to the IRB and the relevant investigators, and included in the materials for the subsequent DSMB meeting to be approved by voice vote at that meeting. Once they have been voted and approved by the Board, they are considered Final.

Appendix 9: Study Schema

Weeks	-2	72 Hrs	0	1	8	12	26
Labs							
CRP	x			x	x	x	
Albumin	x			x	x	x	
CBC	x			x	x	x	
BMP	x			x	x	x	
HIV	x						
Viral Hepatitis Panel	x						
Syphilis	x						
Calprotectin	x			x	x	x	
C.diff 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	
Bile Salt Metabolomics							
Blood	x			x	x	x	
Stool	x			x	x	x	
Stool 16S/DNA Extraction	x			x	x	x	x
Colonoscopy/FMT			x				
Clinical Indices							
HBI/Mayo/CDAI/SCCAI	x	x	x	x	x	x	x
Bristol Score/Diarrhea score	x	x		x	x	x	
HPI	x						
Physical Exam	x			x	x	x	
Adverse event Assessment		x		x	x	x	x
Phone Call		x					x