Fecal Microbiota Transplantation (FMT) For *C. difficile* Infection (CDI) in Solid Organ Transplant (SOT) Recipients

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Principal Investigator & IND Sponsor: Nasia Safdar, MD, PhD

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PROTOCOL VERSION HISTORY

Version	Date	Comment
1.0	**13AUG2018**	**Initial version**
1.1	29AUG2018	Amendment per FDA
2.0	24Jul2019	Amendment per FDA and Steering Committee
3.0	12Mar2020	Amendment
4.0	24Aug2020	Amendment
5.0	05Jan2021	Amendment – FMT route of administration

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1.0 STATEMENT OF COMPLIANCE

The signature below constitutes that the research will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitment.

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

PRINTED OR TYPED NAME	SIGNATURE	DATE
Nasia Safdar, MD, PhD	Nasia Safdar	8/13/2018
Principal Investigator(s)		

2.0 LIST OF ABBREVIATIONS

AE	Adverse Event
CCC	Clinical Coordinating Center
CDC	Centers for Disease Control and Prevention
CDI	*Clostridioides difficile* infection
CFR	Code of Federal Regulations
CRF	Case Report Form
DCC	Data Coordinating Center
DSMB	Data & Safety Monitoring Board
eCRF	Electronic Case Report Forms
FDA	Food & Drug Administration
FMT	Fecal Microbiota Transplantation
FRGNB	Fluoroquinolone-resistant Gram-negative Bacteria
FSTRF	Frontier Science & Technology Research Foundation
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HMP	Human Microbiome Project
ICH E6	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice
IgG	Immunoglobulin G
IND	Investigational New Drug
IRB	Institutional Review Board
KAAS	Kyoto Automated Annotation Server
KEGG	Kyoto Encyclopedia of Genes and Genomes
KO	KEGG orthology
MARCH	Midwest Area Research Consortium for Health
MDRO	Multiple-drug resistant organism
MOP	Manual of Procedures
MRSA	Methicillin-resistant *Staphylococcus aureus*
N	Number (typically refers to subjects)
NG	Nasogastric
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
OTU	Operational taxonomic unit
PCR	Polymerase chain reaction
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SC	Steering Committee

SOC	Standard of care
SOT	Solid Organ Transplant
US	United States
UW	University of Wisconsin-Madison
VRE	Vancomycin-resistant *Enterococcus*

3.0 TERMINOLOGY

Fecal Microbiota Transplantation (FMT) is a procedure to restore *Clostridioides difficile* infection (CDI) impaired gut microbiome by instillation of stool from a healthy donor into the intestine of a CDI patient. There are multiple routes of administration for FMT: colonoscopy, enema, nasogastric tube or oral. In this study, FMT will be administered orally, using human stool that is freeze-dried and encapsulated, and administered to subjects as capsules to be swallowed. The formulation of encapsulated fecal microbiota being used in this study is called MTP-101-C.

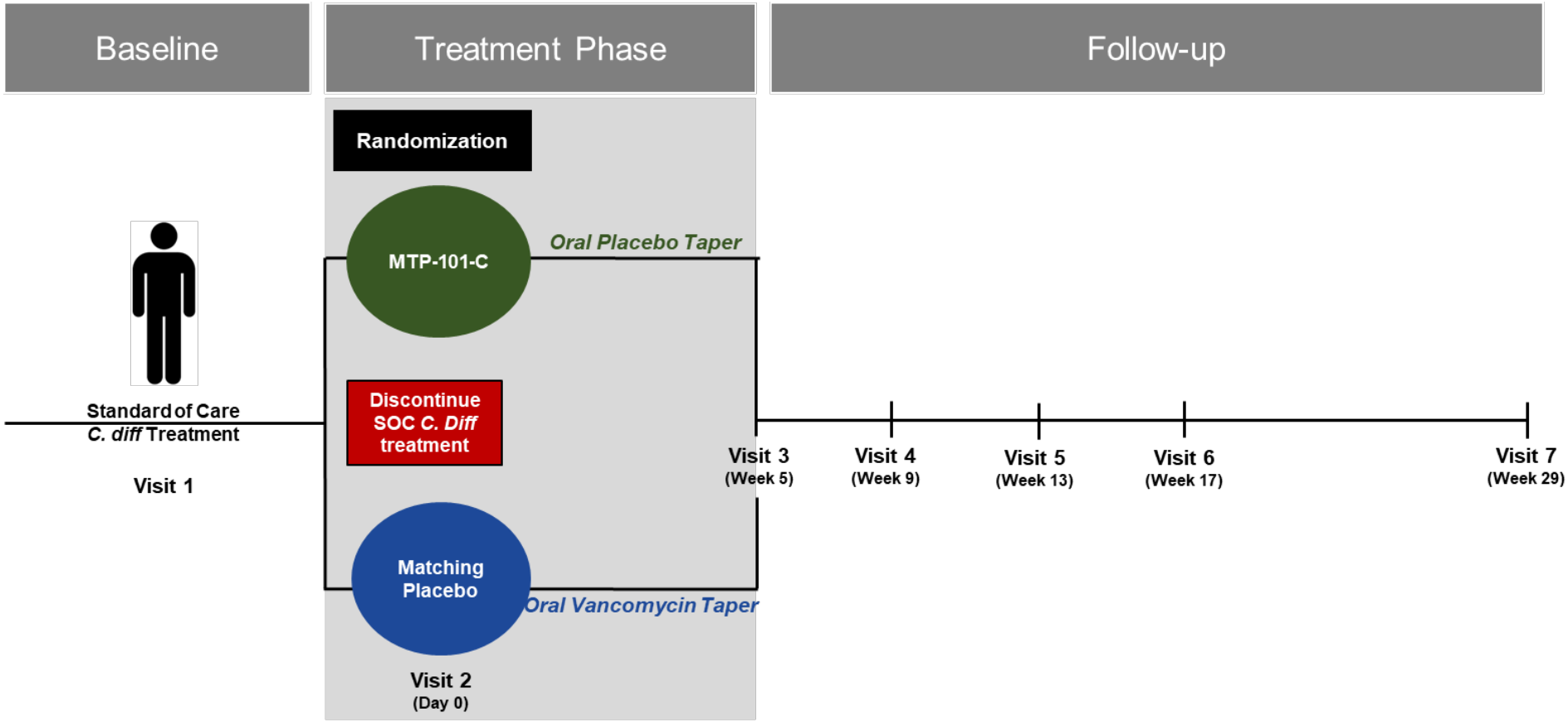
Throughout this protocol, the term FMT will refer to the fecal microbiota transplantation procedure. The terms MTP-101-C and encapsulated fecal microbiota will be used to describe the investigational product.

4.0 STUDY SUMMARY

Full Title:	Fecal Microbiota Transplantation (FMT) for *C. difficile* Infection (CDI) in Solid Organ Transplant Recipients
Short Title:	RECOVER
Protocol Number:	2018-1056
ClinicalTrials.gov:	NCT03617445
IND Number:	To Be Determined
IND Sponsor	Nasia Safdar, MD, PhD
Funding Source:	U01AI125053, National Institute of Allergy and Infectious Diseases (NIAID)
Phase:	Phase II
Précis:	A multisite, randomized, double-blind, doubly placebo-controlled phase II trial comparing the safety and efficacy of fecal microbiota transplant (FMT) versus oral vancomycin for prevention of CDI recurrence in solid organ transplant (SOT) recipients
Study Center(s):	Five sites in the United States
Objective(s):	• **Primary Objective:** Evaluate the safety and efficacy of FMT compared to oral vancomycin for the prevention of CDI recurrence in SOT recipients • **Secondary Objectives:** – Assess the CDI-related quality of life in SOT recipients treated with FMT compared with oral vancomycin – Compare the change in gut microbiota using multiple metrics of microbiota structure and function and to evaluate the association between the change in gut microbiota and recurrence of CDI – Evaluate the short- and medium-term safety of FMT in SOT patients

	– Compare the effects of FMT and oral vancomycin on intestinal colonization by multidrug-resistant organisms other than *C. difficile* in SOT recipients.
Main Eligibility Criteria:	Adult Solid Organ Transplant (SOT) recipients with at least a first recurrence of CDI.
Study Product:	MTP-101-C: screened, freeze-dried, encapsulated fecal microbiota from healthy human donors.
FDA Status	The Food & Drug Administration (FDA) considers MTP-101-C an investigational new drug (IND).
Reference Therapy:	125 mg oral vancomycin every 6 hours for 10 days, followed by 125 mg oral vancomycin every 12 hours for 7 days, followed by 125 mg oral vancomycin once daily for 7 days, followed by 125 mg oral vancomycin every 3 days for 14 days.
Sample Size:	A total of 158 subjects will be recruited from 5 study sites (i.e., approximately 30 subjects per site).
Study Duration	Study enrollment and follow-up will occur over 4 years. The duration of the study for each subject is approximately 30 weeks.

4.1 Schematic of Study Design



5.0 KEY PERSONNEL

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6.0 INTRODUCTION

6.1 Background

Clostridioides difficile (*C. difficile*) is a pathogen of major public health importance, especially in individuals with comorbid conditions such as solid organ transplantation (SOT). The Centers for Disease Control and Prevention (CDC) estimate that 165,000 serious *C. difficile* infections (CDI) occur in the US annually, at a cost of 1.3 billion dollars, resulting in 28,000 deaths.[1,2, 3] National data show that rates of *C. difficile* infection among hospitalized patients aged ≥65 years have increased 200%. The incidence and adverse outcomes of CDI are greatly amplified in the setting of SOT, due to healthcare exposure, antibiotic use and immunosuppression, all of which are ubiquitous in SOT recipients[4]. In recent years, CDI has been increasingly recognized as an important etiology of diarrhea in this population. An estimated 14-16% of SOT recipients develop CDI, compared with 1-2% of general non-SOT inpatients. The consequences of CDI in the SOT population are dire: higher rates of fulminant colitis, treatment failure, recurrence and mortality. At UW-Madison, the third largest abdominal transplant program in the country, the recurrence/relapse rate in SOT recipients is 35%; this is largely due to a combination of 1) impaired host immunity and 2) reduced diversity and health of the normal gut microbiota due to immunosuppression, surgical procedures and devices, repeated exposures to healthcare and antibiotic use. There are currently no effective treatment options to prevent further recurrence of CDI in SOT recipients. Usual care recommended in national guidelines involves oral vancomycin which has low efficacy for prevention of recurrence with side effects of gut dysbiosis and promotes vancomycin-resistant enterococci.

A novel approach that has recently gained attention is restoration of the CDI impaired gut microbiome by instillation of stool from a healthy donor into the intestine of a CDI patient. This treatment, called Fecal Microbiota Transplantation (FMT) has been found in non-comparative studies to reduce CDI recurrence dramatically with a reported efficacy of over 95%[5-9]; its efficacy in SOT recipients has not been studied and cannot be extrapolated from results in the non-SOT population because SOT recipients are a unique study population due to profound immunosuppression, frequent antibiotic use and frequent opportunities for exposure to CDI all of which markedly, repeatedly and persistently disrupt the gut microbiome. Thus, this critical gap in the field needs to be addressed by a trial of FMT in SOT recipients with CDI. The FMT may be delivered via any of several routes; oral, via nasogastric (NG) tube, enema or colonoscopy. All routes have good efficacy with 80% reported for oral encapsulated product compared with 90% for FMT via enema or colonoscopy.[5-9]

6.2 Rationale

There have been recent published randomized controlled trials (RCTs) in this area, and thus far, have included non-SOT recipients, performed FMT by way of NG tube rather than oral route with one study reporting an over 85% success rate compared with oral vancomycin taper (30% success rate) in 26 patients with recurrent CDI in the Netherlands.[10] While these results are very encouraging, there are a number of reasons why a RCT of FMT in SOT recipients is needed. These include the following:

- The aforementioned RCT had a very small sample size and an unplanned interim analysis resulted in premature termination of the study. This approach was criticized in multiple letters to the editor on the grounds that “small, index trials such as this one are vulnerable to exaggerated treatment effects; there may have been inequalities among the three treatment groups in terms of either the number of pretreatment recurrences of *C. difficile* infection or post-treatment exposure to an antimicrobial agent or proton-pump inhibitor (both of which are well-defined risks for recurrence).”[11]
- The cure rate in the control group treated with vancomycin was half of that reported in two randomized trials and it was this unexpectedly low cure rate in the control group that produced an inflated estimate of the efficacy of FMT thus leading to the trial's early termination.
- The route of FMT in that study was by nasogastric tube which has a higher risk of side effects than other delivery routes. Given the far fewer side effects expected with oral administration,

the optimal route of FMT deserves further study. A recent systematic review found equivalent outcomes in case series using FMT by fecal enema or colonoscopy.[12] Oral FMT has largely similar efficacy to enema/colonoscopy and high patient acceptance.

- The SOT population is at high risk for recurrent CDI due to age and comorbid illnesses and therefore potentially promising therapies such as FMT should be studied in this population.
- Follow-up in previous studies ranged from 1 week to 8 weeks; a standardized approach to follow-up for at least 12 weeks is needed to detect recurrence of CDI.
- Given multiple possible causes of diarrhea in the SOT population and a higher prevalence of *C. difficile* colonization which may be mistakenly diagnosed as CDI, objective blinded assessment of outcomes is essential. The SOT population is also at risk for potential adverse events from FMT by transmission of pathogens and potential precipitation of rejection of the solid organ. Thus, trials of FMT in non-SOT patients cannot be applied to SOT recipients.

An adequately powered, multisite, double-blind placebo controlled study of FMT versus oral vancomycin in SOT recipients followed for 30 weeks with outcomes of recurrence and rigor in addressing safety and rejection will address all of the aforementioned shortcomings.

A review of www.clinicaltrials.gov yielded 27 FMT trials for the treatment of CDI. Only a few are evaluating administration by enema, one in the VA population is assessing FMT via oral route but no trials are assessing safety and efficacy in SOT recipients. Thus, the proposed study will be the first to evaluate the safety and efficacy of FMT for CDI treatment in this patient population.

7.0 STUDY OBJECTIVES AND ENDPOINTS

7.1 Primary Objective

The primary objective is to compare the effects of FMT and oral vancomycin on the recurrence of CDI in SOT recipients in a randomized controlled trial.

7.2 Secondary Objectives

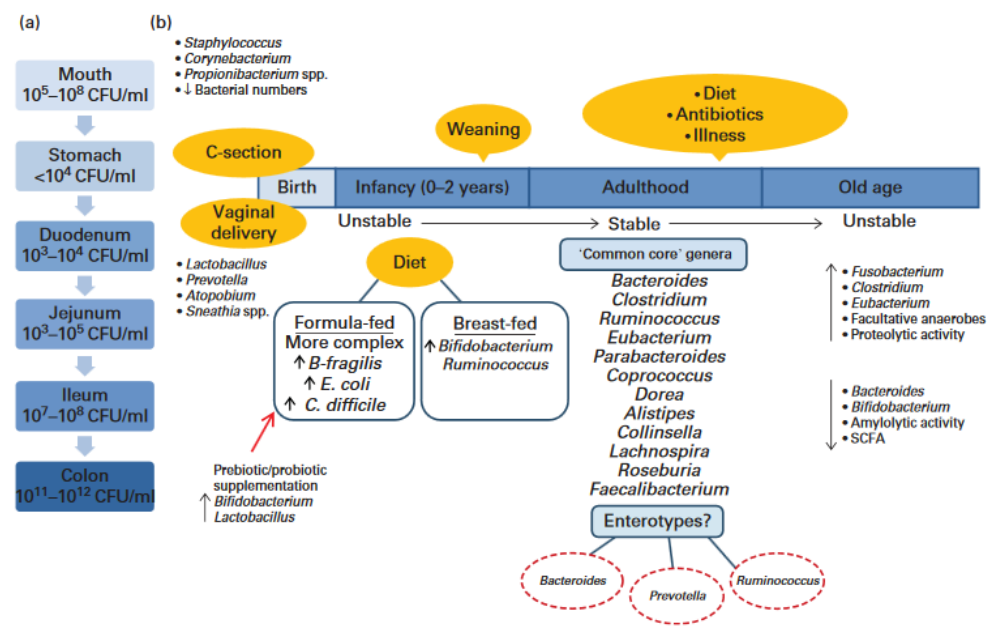
7.2.1 Secondary Objective #1

Secondary Objective #1 is to assess Quality of Life (QoL) in SOT recipients with CDI. Patients with recurrent CDI have a markedly compromised quality of life. There is a dearth of data on CDI-related QoL in SOT recipients. A validated instrument, Cdiff-32, will be used to assess CDI-related QoL comparing the FMT arm with the oral vancomycin arm.[1]

7.2.2 Secondary Objective #2

Secondary Objective #2 is to compare the change in gut microbiota using multiple metrics of microbiota structure and function and to evaluate the association between the change in gut microbiota and recurrence of CDI.

Figure 1: Variations in microbial numbers across the length of the gastrointestinal tract by age.[2]



(a) Variations in microbial numbers across the length of the gastrointestinal tract. (b) Selected features affecting the establishment and maintenance of the microbiota and factors influencing the composition of the microbiota. Micro-organisms are listed where their abundance is related to a particular environmental factor. difficile

The human intestine is colonized by 10^{13} to 10^{14} microbes, the vast majority of which belong to the phyla Firmicutes and Bacteroidetes. The composition of the human intestinal microbiota is individual-specific at the species level and is stable over time in healthy adults.[2] The composition and activities of the microbiota may be influenced by numerous factors including chronic conditions, age, diet, and antibiotic treatment.[3-5] For example, obesity and inflammatory bowel disease cause significant alterations in the

microbiome.[6] Similarly, the microbiota of older people displays greater inter-individual variation than that of younger adults (Figure 1).[3]

7.2.2.1 The Relationship between CDI and Gut Microbiota

Perturbations to the gut microbiota may result in a loss of colonization resistance against *C. difficile*. Although CDI is commonly associated with antibiotic use, the precise alterations to the microbiota associated with CDI have only recently been examined. For example, Schubert *et al.* used a variety of antibiotic perturbations to generate a diverse array of gut microbiota structures, which were then challenged with *C. difficile* spores. They observed that *C. difficile* resistance was the result of multiple microbiota members interacting in a context-dependent manner. They found that populations associated with the Porphyromonadaceae, Lachnospiraceae, Lactobacillus, and Alistipes were protective, while populations associated with Escherichia and Streptococcus had high levels of *C. difficile* colonization. Their results showed that multiple diverse assemblages act in concert to mediate colonization resistance.[7]

7.2.2.2 Relationship of CDI with Fecal Cytokines and Serum Antibody Immunity

Recent data suggest that outcomes of CDI may be modulated by inflammation, as measured by high levels of fecal cytokines[8-11] or fecal lactoferrin[12] rather than bacterial burden alone. High IgG serum antibody to toxin A correlates with milder symptoms of CDI compared to patients with low IgG serum antibody to toxin A.[13] In SOT recipients, in particular, hypogammaglobulinemia plays an important role in predisposing to CDI.[14-16] CXCL-5/ENA-78,[11] and CXCL-8/IL-8 (Quantikine R&D Systems, Minneapolis, MN), levels of quantitative lactoferrin and serum IgG to toxin A will be measured.

7.2.2.3 Impact of FMT on Gut Microbiome

FMT rapidly replenishes the gut microbiota and the recipient microbiota becomes similar to that of the donor.[17-19] In particular, FMT is known to alter the recipient microbiota in a number of ways. First, introducing a fecal microbiota from healthy donors that has greater diversity than that of the recipient encourages the establishment of specific taxa within CDI patients and allows for alteration of the patient microbiota that effectively minimizes the effects of CDI. Under this model, specific microbes from the FMT are able to colonize and establish in CDI patients, a concept known as engraftment.[20] Importantly, the engraftment of FMT bacteria can further help to reprogram the gut microbiota of CDI patients by allowing for other microbes to colonize the gut from other sources (e.g. diet, the environment) and reestablish a highly-diverse healthy gut microbiota. We anticipate that overall gut microbiota health, as determined by diversity metrics, abundance indicators, and the ability of FMT microbes to engraft, will improve in the recipients of FMT. In contrast, patients treated with vancomycin are expected to have long lasting deleterious effects on the normal gut microbiota by limiting the ability of a healthy gut microbiota to establish.[21]

7.2.3 Secondary Objective #3

Secondary objective #3 is to evaluate the short- and medium-term safety of FMT in SOT patients. The literature supports the safety of FMT in non-SOT recipients delivered by any route; however, the safety of FMT in SOT recipients has not been systematically evaluated, particularly with regard to non-infectious outcomes, such as graft function and rejection. Our study will provide much needed data on FMT safety in SOT, which will be essential for any therapeutic development for recurrent CDI for this population.

7.2.4 Secondary Objective #4

Secondary objective #4 is to compare the effects of FMT and oral vancomycin on intestinal colonization by multidrug-resistant organisms other than *C. difficile* in SOT recipients. The normal gut microbiota poses resistance to invasion by pathogenic organisms. Once the normal gut microbiota is impaired by CDI, surgery, being immunocompromised, or antibiotics, pathogenic organisms may establish a niche of colonization and later manifest as infection. In the healthcare setting, to which SOT recipients are frequently exposed, these pathogens are invariably multidrug resistant, and include vancomycin-resistant *Enterococcus* (VRE), fluoroquinolone-resistant Gram-negative bacteria (FRGNB), methicillin-resistant *Staphylococcus aureus* (MRSA) and most recently, the subject of several news reports and editorials, the dreaded carbapenem-resistant *Enterobacteriaceae,* which are resistant to virtually all anti-infectives. There is currently no effective way to eradicate gastrointestinal colonization by these multidrug resistant organisms. In SOT recipients, infections caused by these pathogens are associated with major morbidity and mortality.[22, 23] Our previous studies on infections in SOT recipients found that 25% had gastrointestinal colonization by VRE, 10% by MRSA, and over 30% by FRGNB.[24, 25] We will study colonization of VRE, MRSA, and FRGNB because these are major causes of infections in SOT recipients and are all gut-associated pathogens. The potential benefit of FMT for eradication of non-CDI enteric pathogens has been shown in case reports; our study will provide a robust assessment of the role of FMT for non-CDI multidrug-resistant organisms.

There is scant data on outcomes of FMT for CDI in immunocompromised patients [37-39] and data specific to outcomes of FMT for CDI in SOT recipients is limited to two descriptive case series.[38, 40] Considerations unique to SOT recipients that may impact the role of FMT in CDI are nutritional status, co-infections, long-term effect of FMT on graft function, and cumulative immunosuppression. Data on these factors will be collected and incorporated in analyses.

7.3 Primary Outcome Measure

The primary outcome measure is recurrence of CDI in SOT recipients with recurrent CDI as a dichotomous variable. Recurrence of CDI is defined as diarrhea (≥3 loose stools that take the shape of the container in a 24-hour period) for 2 consecutive days with a positive stool test for *C. difficile* toxin by ELISA within a 60-day period following completion of treatment. Recurrent CDI will be assessed using stool diary and will be monitored by regular phone calls by study staff to determine signs and symptoms of diarrhea during the 24-week assessment period following enrollment (60 days for recurrence and 24 weeks to assess fecal microbiome). For subjects with diarrhea, a stool collection to determine *C. difficile* will be performed as part of standard of care.

7.4 Secondary Outcome Measures

7.4.1 Secondary Outcome Measure #1

Cdiff32 (Appendix 16.2), a validated instrument for CDI-related quality of life, will be completed at baseline (visit 1), end of study treatment (visit 3), end of follow-up (visit 7), and early termination.

7.4.2 Secondary Outcome Measure #2

Change in microbiota will be measured using multiple metrics of microbiota structure and function, as detailed below.

7.4.2.1 Multiplex sequencing of amplicons generated from bacterial 16S rRNA genes
Genomic DNA will be extracted from feces using a bead-beating protocol.[47] We will generate multiplexed barcoded amplicons from the variable region V3-V4 of

bacterial 16S rRNA genes, and perform 2x250 paired-end sequencing using an Illumina MiSeq, as previously described.48 This technology allows analysis of >300 samples in parallel.

7.4.2.2 Composition and structure of the gut microbiota

The composition and structure of the gut microbiota will be determined via 16S rRNA gene analysis. Two analyses will be performed, including an operational taxonomic unit (OTU) analysis, which determines the specific taxa of bacteria present in a microbiota and their relative abundances, and a Bray-Curtis dissimilarity analysis,[49] which quantifies the compositional dissimilarity between microbial communities in terms of both total diversity and phylogenetic distance and visualized as a principal component analysis (PCA). An important consideration for the establishment of a healthy gut microbiota is the specific taxa capable of colonizing CDI patients treated with FMT. Therefore, identifying broad groups of bacteria strongly correlated with post-FMT microbiota will help understand which groups colonize the gut of CDI patients. A downstream correlation analysis will be performed on total community structure (Bray-Curtis dissimilarity and relative abundance) and composition using analysis of similarity (ANOSIM) in R. Taken together, these analyses will determine which specific OTUs are found to contribute significantly to the overall composition of the microbiota that established in CDI patients after FMT treatment.

7.4.2.3 *Metagenomic analysis*

Shotgun metagenomics will be performed on all fecal DNA samples using a Illumina Hi-Seq 500 (paired-end 2x250). All sequences passing quality control (QC) will be assembled using MEGAHIT 50 to generate contigs and used to predict open reading frames using the program prodigal.[51] This library of genes within a given sample will serve as the basis for all downstream analyses using our metagenomics data, as follows:

- *Strain-level identification using metagenomics:* A key study goal is to determine if specific strains of bacteria are found to colonize CDI patients treated with FMT, and thereby minimize the effects of CDI. After FMT, the conventional hypothesis is that bacterial strains present in the FMT are capable of establishing within CDI patients and proliferating (engraftment). However, an alternative hypothesis is that the initial engraftment of FMT bacteria allows for the colonization of bacteria from other sources (e.g. environment, diet) and thereby facilitate reprogramming to a healthy gut microbiota. Detecting these fine-scale taxonomic resolutions is not possible with current Illumina-based 16S rRNA analysis. To address this, metagenomics data will be used to compare against both metagenomics data generated from the FMT itself, and the Human Microbiome Project (HMP, http://hmpdacc.org/), which contains over 3,000 genomes of human-associated bacterial strains, including over 800 from the gut alone. First, all reads generated from metagenomics sequencing will be compared against a custom database generated from the HMP and FMT samples using the phylogenetic binning program kraken.[52] A single-nucleotide polymorphism (SNP) analysis will then be conducted to determine if a given read can be identified as belonging to specific strains/species of gut-associated human microbes. This analysis will result in the following outcomes; (a) which specific strains from the FMT treatment can colonize CDI patients; and (b) what non-FMT related microbes are capable of colonizing CDI patients.

- *Function of the gut microbiota:* Metagenomic data also provides the opportunity to determine if specific genes are associated with the successful establishment of a healthy microbiota in CDI patients treated with FMT. The predicted ORF translations from the assembled metagenomes will be subjected to functional annotation using the Kyoto Encyclopedia of Genes and Genomes (KEGG) Automated Annotation Server (KAAS) to annotate each predicted protein according to the KEGG orthology (KO).[53] These will be mapped back to their respective metabolic pathways and normalized based on metagenome size. Comparisons between metagenomes will be conducted using chi-square test to determine if a given sample is enriched for genes within a specific pathway. A correlation analysis across samples using a pairwise comparison employing Spearmann's rank correlation will be conducted to determine which metagenomes are most similar to each other. Further comparisons will be conducted against the FMT-derived metagenomes and those pathways encoded by the HMP. In this way, not only will genes important in colonization be determined, but those derived from the FMT will also be identified as well.

- *Microbiologic methods:* Culture and polymerase chain reaction (PCR) will be used to recover MRSA, VRE and FRGNB. Molecular typing will be employed to show strain relatedness between the isolates at baseline and at the subsequent time points for these organisms and *C. difficile*.

- *Stool lactoferrin and cytokines:* For each stool collected, *C. difficile* will be cultured and PCR will be used for toxin-- quantitation. All isolates will be stored for future strain typing and characterization. Fecal cytokines will be assayed using ELISA. Levels of CXCL-5/ENA-78,24, CXCL-8/IL-8 and quantitative lactoferrin will be compared between treatment arm, with the anticipation that subjects assigned to FMT will have lower levels of cytokines and lactoferrin.

- *Blood sample analysis for antibodies to C. difficile toxin A:* Each subject will contribute 2-3 blood samples to examine if there are differences in serum antibody levels between treatment groups. Standard commercially available methods will be used to assess antibody levels (IgG to toxin A).

- *Correlative outcomes:* Diversity of the gut microbiota will be determined using either the reciprocal of Simpson's index or the Shannon's index. The reciprocal of Simpson's index takes into account both the number of species present and the abundance of each species. It has been used frequently in microbiota studies and is considered a standard measure of microbiota diversity. The Shannon's index is a complementary index of diversity that considered both the abundance and evenness of species. Metagenomic data as well as cytokines, CXCL-5/ENA-78 and CXCL-8/IL-8, levels of quantitative lactoferrin and serum IgG to toxin A will be determined using methods described above.

7.4.3 Secondary Outcome Measure #3

The following variables will be used to assess short- and medium-term safety of FMT in SOT patients:

Short term safety outcomes include:

- bloodstream infection from FMT
- immune phenomenon

Medium term safety outcomes:

- rejections
- malignancy
- metabolic syndrome
- organ function
- infections other than CDI
- viral (EBV, CMV) infections
- fungal infections
- hospitalizations
- emergency department visits

7.4.4 Secondary Outcome Measure #4

Intestinal colonization by multidrug-resistant organisms other than *C. difficile* in SOT recipients will be assessed by microbiologic methods as dichotomous variables. Stool specimens will be cultured and PCR will be used to recover methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), and fluoroquinolone-resistant Gram-negative bacteria (FRGNB). Molecular typing will also be used to show strain relatedness between the isolates at baseline and at subsequent time points.

Following enrollment, subjects will complete a daily stool diary during the course of therapy with follow-up visits at day 34, week 9, week 13, week 17, and week 29.

8.0 STUDY DESIGN

8.1 General Design

This phase II multi-site randomized, double-blind, doubly placebo-controlled trial will compare the safety and efficacy of fecal microbiota transplantation (FMT) versus oral vancomycin for prevention of CDI recurrence in solid organ transplant (SOT) recipients.

The study population will consist of 158 adult SOT recipients with at least a first recurrence of CDI. Recurrence of CDI is defined as diarrhea (3 or more loose stools) in a 24-hour period for 2 consecutive days with a positive stool test for *C. difficile* toxin within a 180-day period following completion of treatment.

Subjects will be enrolled while receiving *C. difficile* treatment as standard of care, they will be monitored and those that achieve symptomatic response between Day 4 and Day 7 of *C. difficile* treatment will be randomized to one of two treatment arms as follows:

- Arm 1: Single dose of MTP-101-C and vancomycin matching placebo taper.
- Arm 2: Single dose of MTP-101-C matching placebo and vancomycin taper.

MTP-101-C/Matching Placebo: Subjects will take a single dose at Visit 2. A single dose consists of 5 capsules, each swallowed individually with water.

Vancomycin/Matching Placebo: Subjects will take one capsule by mouth every 6 hours for a total of 10 days (10 days is inclusive of the 4-7 days of *C. difficile* treatment taken prior to Visit 2), after which they will undergo a taper as described in section 9.7.2.

Subject accrual will occur over four years at 5 U.S. sites. Subjects will complete 7 study visits over the course of approximately 30 weeks. Each subject will provide six stool samples and two to four blood specimens.

8.2 Rationale for Intervention

8.2.1 Rationale for Frozen, Freeze-dried Stool

Recent studies have shown that frozen stool FMT works as well as fresh stool[41, 42] and may be stored for up to 12 months.

8.2.2 Rationale for Universal Donors

The choices for a donor for FMT include a household or non-household member or other individual known to and selected by the recipient versus a universal anonymous or non-anonymous donor. There are pros and cons to each of these options but the main limitation of the approach where the donor selected by the recipient is logistical. Many of our patients that have undergone FMT have not been able to identify a donor. Even for those that have selected a donor, it has taken several weeks to get the donor tested and the procedure scheduled due to issues of transportation, challenges in taking time off from work, etc. Compare this to the universal donor, where testing is performed frequently and stool is collected and frozen until such time as it may be used. Recent studies have shown that frozen stool is perfectly adequate for FMT compared with fresh stool. This study will utilize universal donors that are screened and tested. More than one donor may be used for this trial.

8.2.3 Rationale for Encapsulated Fecal Microbiota versus Other FMT Delivery Modes

FMT may be delivered by enema, colonoscopy, nasogastric (NG) tube, and oral encapsulation of stool. Encapsulated fecal microbiota was selected for this RCT

because ingestion of a single dose of encapsulated fecal microbiota (~ 5 x 10^{11} bacteria) is ~ 80% successful in terminating the cycle of recurrent *Clostridioides difficile* infection (rCDI) in patients who have failed multiple attempts to achieve cure with antibiotics alone.[29, 30]The encapsulated fecal microbiota in this RCT, MTP-101-C, is an investigational drug that has been used since 2015 for treatment of rCDI under the 2013 FDA enforcement discretion policy, which allows FMT for treatment of rCDI that failed standard therapies.

8.3 Study Risk/Benefit Assessment

8.3.1 Known Potential Risks & Risk Minimization

- **Vancomycin:** Oral vancomycin is the standard of care treatment for CDI. When administered orally, vancomycin is poorly absorbed, and ingestion does not result in significant levels of drug in the body. The most common side effects associated with oral vancomycin are nausea, stomach pain, and low potassium levels in the blood. Less common side effects include peripheral edema, tiredness, fever, headache, diarrhea, gas, vomiting, urinary tract infection, and back pain. Rare but serious side effects include kidney failure, decrease in platelets, hearing problems, and vasculitis. Additionally, there is risk of developing antibiotic resistance including vancomycin resistant enterococcus (VRE). Risk minimization will include surveillance for VRE colonization at study visits and communication between subjects and study staff; and specimen collection and analysis.

- **Vancomycin Matching Placebo:** The vancomycin matching placebo capsules used in this study will be composed of Microcrystalline Cellulose (MCC), NF. MCC is a purified, partially depolymerized cellulose, obtained as a pulp from fibrous plant material. It is widely used in vitamin supplements and tablets, and the likelihood for adverse reaction is virtually none. There are no obvious foreseeable risks associated with the ingestion of the placebo capsules.

- **Fecal Microbiota Transplantation (FMT):** The most common risk associated with FMT's is abdominal discomfort (e.g., nausea, bloating, cramping, diarrhea). There is also a risk of inadvertent transmission of infectious organisms (bacteria, viruses, fungi, parasites) or MDRO contained in the stool as well as allergic reactions to constituents (antigens) contained in the donor stool. There is also a risk of transmission of non-infectious disease, e.g., immune dysregulation, energy metabolism dysregulation, malignancy, neurologic disease, and psychiatric disorder. It is unknown if FMT will impact the risk of rejection, organ function, malignancy, hospitalizations, and emergency department visits. The potential long-term effects of alterations in gut microbiome are unclear.

- **MTP-101-C:** While there have been no adverse events linked to MTP-101-C, a number of risks exist. These include:
    - Risk of infectious disease transmission: FMT has been associated with pathogen transmission, including Shiga-toxin producing Escherichia coli (STEC), Enteropathogenic E. coli (EPEC), norovirus. Although the donor material is tested for these pathogens, tests may be false negative. In addition, the current testing may not capture all important pathogens that could be transmitted. Similarly, although the donor screening and testing protocol is designed to mitigate risk of SARS-CoV-2 transmission, this risk cannot be eliminated with 100% certainty given the possibility of false negative tests.

- Risk of transmitting multi-drug resistant organisms: FMT has been associated with transferring Extended Spectrum Beta-Lactamase (ESBL) Enterobacteraceae.8 This risk is mitigated by excluding health care workers who have contact with patients as donors and donor material that tests posititive for ESBL, carbopenem-resistant Enterobacteraceae, vancomycin-resistant Enterococcus, methicillin-resistant Staphylococcus aureus.
- Risk of transferring risk of non-infectious diseases: Intestinal microbiota is integral to human physiology and its composition can affect the functions of the immune system, energy metabolism, and nervous system. Therefore, there is a theoretical risk that the new intestinal microbiota formed in part with the donor microbes can increase risks for autoimmunity, allergies, obesity, cancer, neurologic and psychiatric disorders. This risk is mitigated by excluding donors with these conditions.There is also a screening and testing protocol for SARS-CoV-2 in donors.

- **MTP-101-C Matching Placebo:** The MTP-101-C matching placebo is prepared using identical capsules and contain the equivalent amount of trehalose lyoprotectant. The rest of the content is made up with carboxymethylcellulose. There are no known risks for the placebo capsules.

- **Blood Draw:** The risks of drawing blood from a vein include discomfort at the site of puncture; possible bruising and swelling around the puncture site; rarely an infection; and, uncommonly, faintness from the procedure.

8.3.2 Potential Benefits to the Subjects

The potential benefits to research subjects associated with this study include the possible treatment of recurrent CDI.

If this study is able to show a therapeutic benefit of FMT in SOT patients, the community at large would benefit by the availability of a non-antibiotic based management option for CDI.

8.4 End of Study Definition

A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit (Visit 7) as outlined in Section 10.12, Study Calendar.

9.0 SUBJECT SELECTION

9.1 Inclusion/Exclusion Criteria

Eligibility will be determined by inclusion and exclusion criteria below and confirmed by medical record review as necessary.

Inclusion Criteria
1. Willing to provide written informed consent.
2. Willing to comply with all study procedures and be available for the duration of the study.
3. Ability to take oral medication.
4. Male or female, at least 18 years of age.
5. Solid organ transplant recipient.
6. Has recurrent *C. difficile* infection. A *C. difficile* recurrence is defined as: • Positive *C. difficile* testing in stool (confirmed via medial record review) AND • Diarrhea (≥ 3 loose stools over 24 hours) during the 180-day period following completion of treatment for prior CDI episode.
7. History of positive IgG testing to cytomegalovirus (CMV) and Epstein Barr Virus (EBV) for subject or organ donor
8. Clinical response to 4-7 days of *C. difficile* treatment for the current CDI episode. Clinical response is defined as ≥25% reduction of diarrhea.
9. Females of childbearing potential must have a negative urine or serum pregnancy test at baseline and prior to randomization. A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria: ▪ Has not undergone a hysterectomy or bilateral oophorectomy; or ▪ Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).
10. Women of childbearing potential in sexual relationships with men must use an acceptable method of contraception[§] from 30 days prior to enrollment until 4 weeks after completing study treatment. Males must agree to avoid impregnation of women during and for four weeks after completing study treatment through use of an acceptable method of contraception. [§]Note: Includes, but is not limited to, barrier with additional spermicidal foam or jelly, intrauterine device, hormonal contraception (started at least 30 days prior to study enrollment), intercourse with men who underwent vasectomy.

Exclusion Criteria
1. Major bowel resection surgery within 90 days of randomization.
2. Active chronic intestinal disease (e.g. Crohn's disease, ulcerative colitis).
3. History of total colectomy or bariatric surgery.
4. Known or suspected toxic megacolon and/or known small bowel ileus.
5. Concomitant antibiotic use within 48 hours of Visit 2. Antibiotic *C. difficile* treatment, topical antibiotics and SOT prophylaxis (e.g., trimethoprim-sulfamethoxazole) are permitted.
6. Dysphagia: oropharyngeal, esophageal, functional, neuromuscular (e.g. stroke, multiple sclerosis, ALS), or patient shows evidence of dysphagia when the 'safety test' capsule is administered.
7. Gastroparesis
8. Unwilling to withhold probiotics for duration of study. Probiotics include supplements, prescriptions, and non-prescriptions. Foods (like yogurt) are permitted.
9. Neutropenia, ≤500 neutrophils/mL [abstracted from the medical record and resulted within 30 days of Visit 1].
10. Symptomatic co-infection with another intestinal pathogen as determined by chart review.

11. Concurrent intensive induction chemotherapy, radiation therapy or biological treatment for active malignancy. Patients on maintenance chemotherapy may be enrolled only after consultation with medical monitor.
12. Any severe food allergy, defined as a history of anaphylaxis, systemic urticarial or angioedema attributed to a food and requiring current avoidance precautions.
13. Expected life expectancy <6 months.
14. Use of investigational drugs, biologics, or devices within 30 days prior to randomization.
15. Women who are pregnant, lactating or planning on becoming pregnant during the study.
16. Not suitable for study participation due to other reasons at the discretion of the investigators.

9.2 Recruitment

Prospective subjects will be identified through routine surveillance of electronic medical records using patient census and infection control lists. Providers will also be asked to refer patients from outpatient clinics (e.g., transplant clinic). Inpatient subjects will first be approached in person by someone involved in their clinical care. This is also true for those patients approached in a clinic setting.

Advertisements will be posted in public locations and on the internet. Letters will be sent to potentially eligible subjects identified through electronic medical records.

9.3 Retention Strategies

Strategies for retention include:

- Frequent phone contact throughout the 6 month follow-up study period. Subjects will receive a call 1-3 days after randomization (Visit 2) to assess for AEs, review concomitant mediations and remind them to complete daily stool diaries. Between Visit 3 and Visit 7, study staff will attempt weekly phone contacts for the aforementioned purposes as well as to assist with subject retention (e.g., study visit and stool collection reminders).
- Flexible study visit windows (i.e. +/- 7 days) to accommodate subject schedules.
- Offering subjects the option to complete Visits 4, 5, 6, and 7 over the phone or in person.
- Subjects will receive reimbursement for each completed study visit, a maximum total of $500.

9.4 Early Termination and Withdrawal

Subjects are free to withdraw from participation in the study at any time upon request. Participants with a CDI recurrence after randomization will be terminated early.

The Principal Investigator (PI) may discontinue or withdraw a subject from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject
- Disease progression which requires discontinuation of the study intervention
- If the subject is no longer an appropriate candidate for participation

Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced by randomizing a new subject to meet the accrual goal. Replacement participants will be assigned a new study ID. Subjects who sign the informed consent form, are randomized and receive the study intervention, then subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

10.0 STUDY INTERVENTION

10.1 Study Intervention Description

10.1.1 MTP-101-C

The U.S. Food & Drug Administration (FDA) requires an investigational new drug (IND) for the use ofMTP-101-C) to treat *C. difficile* infection not responding to standard therapies.

MTP-101-C is prepared from stool of healthy human donors, who are screened and tested for infectious and non-infectious diseases. Raw stool is homogenized and filtered to separate the microbiota, which is then frozen in the presence of a lyoprotectant (trehalose), freeze-dried and encapsulated in hypromellose capsules. Each capsule contains ~ 1×10^{11} bacteria. The capsules are acid-resistant and likely dissolve > 2 hours following ingestion in the small bowel or proximal colon.

MTP-101-C will be provided by the University of Minnesota Microbiota Therapeutics Program, and will be shipped on dry ice directly to study sites. MTP-101-C capsules should be stored frozen at -80°C.

10.1.2 MTP-101-C Matching Placebo

The MTP-101-C matching placebo is prepared using identical capsules and contain the equivalent amount of trehalose lyoprotectant. The rest of the content is made up of carboxymethylcellulose. Placebo capsules will be provided by University of Minnesota Microbiota Therapeutics Program and shipped on dry ice directly to study sites.

10.1.3 Vancomycin

Vancomycin is a tricyclic glycopeptide antibiotic that inhibits bacterial cell wall formation. Oral vancomycin is FDA-approved as first line treatment for CDI and is recommended for severe and recurrent CDI. Commercially available vancomycin capsules will be procured and over-encapsulated to look similar to placebo by an FDA-registered pharmaceutical manufacturing facility.

10.1.4 Vancomycin Matching Placebo

The vancomycin matching placebo will be composed of Microcrystalline Cellulose (MCC), NF. Placebo capsules will be procured and/or prepared by an FDA-registered pharmaceutical manufacturing facility.

10.2 Source

10.2.1 MTP-101-C/Matching Placebo Capsules

The University of Minnesota Microbiota Therapeutics Program will distribute MTP-101-C and matching placebo capsules to the study sites directly. Each shipment will include a temperature-monitoring device to verify maintenance of the cold chain during transit, as well as a packing slip. On delivery of the investigational product to the site, the person in charge of investigational product receipt will follow the instructions given in the Manual of Procedures, including checking that the cold chain was maintained during shipment (i.e., verification of the temperature indicator). The contents of the shipment will then be reviewed and verified against the packing slip, and will be documented as instructed by the Clinical Coordinating Center (CCC).

If the temperature-monitoring indicator reflects that the cold chain has been broken, the entire shipment must be immediately quarantined, the investigational product must not be administered, and the site investigator or responsible person should contact the CCC for instructions on how to properly discard the product. See the Manual of Procedures for further information on processing temperature deviations during shipment.

Sites will be responsible for ensuring appropriate receipt, use, disposition and reconciliation of the investigational product as outlined in the Manual of Procedures.

10.2.2 Vancomycin/Matching Placebo

As noted in sections 9.1.3 and 9.1.4, an FDA-registered pharmaceutical manufacturing facility will be responsible for procuring and over-encapsulating oral vancomycin and matching placebo, and subsequently shipping drug to each clinical site

10.3 Packaging and Labeling

10.3.1 Labeling of MTP-101-C and Matching Placebo Capsules

Each dose of MTP-101-C and matching placebo is packaged in an individual sealed container. The label lists the following information:

- Microbiota Transplant or Matching Placebo
- # capsules
- Bottle # xxxx
- Store refrigerated
- Caution: New Drug-Limited by Federal Law to Investigational Use

10.3.2 Vancomycin/Matching Placebo

Vancomycin and matching placebo capsules will be shipped to sites from an FDA-registered pharmaceutical manufacturing facility, and subsequently packaged by each site's investigational drug pharmacy into prescription bottles, containing the appropriate number of capsules indicated for the subject. Bottles will be labeled with subject name, study ID, date dispensed, and dosage instructions (Figure 4). Labels will reflect each site's local context information (e.g., site PI, phone number).

Figure 4: Vancomycin/Matching Placebo Capsules Label Example

Name _____ Date _____
Subject ID# _____ RPh: _____
Vancomycin/Matching Placebo 125 mg Capsules #50 Capsules
Directions:
Take one capsule by mouth as instructed on the Medication Diary. Swallow capsules whole.
FOR INVESTIGATIONAL USE ONLY IND# TBD
Fecal Microbiota transplantation for C. difficile Infection (CDI_ in Solid Organ Transplant Recipients.
Nasia Safdar, MD PhD
***
Site # _____
Site PI and Location:
_____
_____
_____
Site Contact Phone# _____

10.4 Preparation

10.4.1 MTP-101-C/Matching Placebo Capsules

The investigational drug pharmacy or designees at each site will prepare MTP-101-C and matching placebo as follows:

- Check product for tampering and/or exposure to high temperatures
- Thaw prior to administration, taking care to avoid freeze-thaw cycles and excessive humidity, using one of the following methods: A) Transfer to 4°C refrigerator until thawed, and store up to 30 days; B) Place at room temperature until thawed, and store up to 4 days.

Warning: Capsules should never be refrozen, or exposed to excessive humidity. If thawed, and not used within the prescribed amount of time based on storage temperature, the material should be disposed of. Freeze-thaw cycles may compromise stability or viability of the product.

9.4.2 Vancomycin/Matching Placebo

After receiving oral vancomycin and matching placebo from an FDA-registered pharmaceutical manufacturing facility, drug will be further prepared by each site's investigational drug pharmacy as detailed in section 9.3.2.

10.5 Storage and Stability

Investigational product must be stored separately from normal hospital stocks and must be stored in a securely locked area accessible only to authorized trial personnel until dispensed. The temperature must be monitored and documented on the appropriate form for the entire time that the investigational product is at the trial site. If the storage temperature deviates from the permitted range, the investigational product must not be administered, and the site investigator or responsible person should contact the CCC for further instructions.

10.5.1 MTP-101-C/Matching Placebo Capsules

Thus far, stable integrity of bacteria in MTP-101-C has been demonstrated following:

- 20 months of storage at -80°C
- 12 months of storage at -20°C (laboratory freezer, no auto-defrost feature)
- One month at 4°C
- Four days at 25°C (room temperature)

Importantly, the microbiota experienced no interim freeze-thaw cycles in the stability experiments and remains at the steady indicated temperature for the stated period of time. Theoretically, humidity represents the greatest threat to the integrity of the product. MTP-101-C and matching placebo capsules should be stored at -80°C for up to 20 months whenever possible, but may also be stored for 12 months at -20°C in a laboratory freezer without an auto-defrost feature.

10.5.2 Vancomycin/Matching Placebo

Store at controlled room temperature, 59° to 86°F (15° to 30°C).

10.6 Accountability

The person in charge of product management at the site will maintain records of product delivery, site inventory, and product disposal or return. The DMC/study monitors will verify each site's

product accountability records against the record of administered doses in the eCRFs, the source documents, and the communication from the online randomization program.

In case of any expected or potential shortage of product during the trial, the investigator or an authorized designee should alert the CCC as soon as possible, so that a shipment can be arranged. In the event of a quality issue, the site should quarantine the investigational product and contact CCC for further instructions.

10.7 Dosing and Administration

10.7.1 MTP-101-C/Matching Placebo Capsules

- *C. difficile treatment* will be stopped the day of the procedure (Visit 2).
- Blinded nurse will administer MTP-101-C and matching placebo.
- Administration of MTP-101-C should not coincide with concurrent treatment with antibiotics.
- If possible, do not take proton pump inhibitors or H2 blocker medications that block or diminish stomach acid production for 12 hours prior to MTP-101-C.
- No solid food should be present in the stomach at the time of treatment. Solid food should be avoided for at least 4 hours prior to ingestion of capsules and can be resumed 2 hours after ingestion of capsules. Clear liquids are allowed at all times.
- Drink at least one glass of water or another clear liquid after taking the capsules.
- Remain upright for at least 2 hours after taking the capsules.

10.7.2 Vancomycin/Matching Placebo

Subjects will receive one 125 mg vancomycin capsule or one matching placebo every 6 hours for a total of 10 days (inclusive of the 4-7 days of *C. difficile* treatment taken prior to visit 2), followed by 125 mg oral vancomycin or placebo every 12 hours for 7 days, followed by 125 mg oral vancomycin or placebo once daily for 7 days, followed by 125 mg oral vancomycin or placebo every 3 days for 14 days.

10.8 Randomization and Blinding

This will be a randomized, double-blind, doubly placebo-controlled trial. Eligible subjects will be randomized in a 1:1 ratio stratified by site. Study staff will randomize subjects through a web-based program that assigns the subject an identification number and treatment arm.

To maintain the blind, the MTP-101-C matching placebo capsules will mimic the MTP-101-C capsules in appearance, and the vancomycin matching placebo capsules will mimic the vancomycin capsules in appearance.

10.9 Unblinding Procedures

Unblinding will be done in emergent circumstances where the identity of the study medication needs to be known. All efforts will be made to maintain blinding except in the case of urgent medical necessity. If a subject needs to be unblinded, the study staff should contact the medical monitor prior to any unblinding procedures and refer to the Manual of Procedures for further instruction.

10.10 Study Intervention Compliance

The MTP-101-C/matching placebo capsules will be taken under direct supervision by research

staff; thus adherence is not a concern.

Several measures will be used to assess oral vancomycin adherence, including:

- Drug accountability by study staff at Visit 3.
- Subjects will be provided a dose diary to record administration of vancomycin/matching placebo capsules according to prescribed schedule.

For reporting non-compliance, refer to section 14.4 (Protocol Deviations).

10.11 Concomitant Therapy

No other drugs potentially useful in the treatment of CDI should be given during the study unless they are specifically given because of a primary treatment failure or recurrence. Drugs to control diarrhea (e.g., loperamide) must also be withheld. Subjects may continue to take transplant-related medications, provided they are not for acute rejection.

Table 1: Concomitant Medications Not Permitted During the Study

Antibiotics/Antivirals#	Anti-Diarrheals	Other
• Nitazoxanide • Rifampin	• Atropine/diphenoxylate • Bismuth subsalicylate • Loperamide	• Probiotics • ≥80 mg of prednisone or other treatment for acute transplant rejection

#Topical antibiotics/antivirals are allowed.

11.0 STUDY VISITS AND PROCEDURES

11.1 Screening and Enrollment

The Screening and Enrollment visits and procedures are described in detail below.

11.1.1 Prescreening

Prescreening activities may include medical record review to verify limited inclusion criteria (e.g., adult SOT recipient prescribed *C. difficile* treatment for a CDI recurrence). Potentially eligible outpatients will be contacted by letter or phone to inform them of the study. Potentially eligible inpatients will be asked by member of their clinical care team if they would be interested in learning about a research study. Outpatient telephone recruitment will be preceded by a recruitment letter, unless a patient is fully eligible to enroll in the study. If a patient is fully eligible, they may be contacted without first sending a recruitment letter in order to enroll a patient within the required timeframe.

11.1.2 Informed Consent

The informed consent process will be conducted following all federal and institutional regulations relating to informed consent. Informed consent will be obtained prior to conducting any study related activities. The consent process will occur in-person or via telephone. The informed consent process will be performed as follows:

1. The investigator or designee will review the consent form and discuss the study in detail with the potential research subject.
2. The study team member will explain the study, its risks and benefits, and what would be required of the research subject
3. The research subject will be given the opportunity to take the consent form home so that he or she may discuss it with family members, friends, clergy, or others when possible.

4. The subject will have the opportunity to ask questions and have all questions answered by the study coordinator and/or PI.
5. The informed consent document must be signed and dated by the research subject.
6. The study team member will review the informed consent document to ensure that all fields that require a response are complete (i.e. checkbox marked yes or no, etc.) as applicable.
7. The person obtaining consent (POC) must sign and date the informed consent document.
8. The research subject will be given a copy of the signed and dated informed consent. The original signed informed consent is kept in the subject's research chart or medical record in accordance with each site's institutional policy/practice.

11.1.3 Screen Failure and Re-enrollment

Not applicable.

11.2 Visit 1 (Baseline)

- Obtain written informed consent
- Obtain demographics and contact information
- Review concomitant medications
- Review medical history
- Social history: smoking status
- Perform chart abstraction
- Perform targeted physical examination
- Measure height, weight and vital signs (temperature, respiratory rate, heart rate, and blood pressure)
- Blood draw (if necessary)
- Urine or serum pregnancy testing in women of childbearing potential
- Assess inclusion/exclusion criteria
- Administer Quality of Life Questionnaire (Cdiff32)
- Dietary history (may be collected at Visit 2)
- Dispense stool collection kit and instructions
- Schedule visit 2.
- Instruct subject to hold *C. difficile* treatment for at least 6 hours but not more than 24 hours on the day of randomization.
- Instruct subject to avoid eating solid food for at least 4 hours prior to visit 2.

11.3 Visit 2 (Randomization)

- Confirm subject withheld SOC *C. difficile* treatment for at least 6 hours but no more than 24 hours
- Confirm subject has not eaten solid food for at least 4 hours
- Review concomitant medications, changes in medical history, assess AEs
- Perform chart abstraction
- Urine or serum pregnancy testing in women of childbearing potential
- Blood draw
- Retrieve subject-collected stool specimen (if necessary)
- Administer safety capsuleConfirm eligibility
- Randomize subject via the internet using Stars (Statistical Registration & Randomization System)
- Blinded nurse administers MTP-101-C/matching placebo capsules and monitors subject for 30 minutes following administration

- Dispense oral vancomycin/matching placebo and instruct subject on use
- Dispense stool collection kit and instructions
- Dispense stool diary
- Schedule follow-up phone call and visit 3
- Subjects will be asked to complete a specific stool diary, for 7 days post-FMT, that in addition to recording every bowel movement, they will also be asked to record if they experience any of the following adverse events: fever, vomiting, abdominal pain, bloating, flatulence, diarrhea, constipation, and (for 7 days post-FMT). Subjects will be asked to return this completed diary at Visit 3.

11.4 Study Drug Administration Follow-up Call

- Subjects will be contacted by phone 1-3 days after randomization (Visit 2) to assess for AEs, review concomitant medications, and remind subjects to complete daily stool diaries.

11.5 Visit 3 (in-person)

- Review concomitant medications, changes in medical history, assess AEs
- Perform chart abstraction
- Perform targeted physical examination
- Measure weight and vital signs (temperature, respiratory rate, heart rate, and blood pressure)
- Blood draw
- Retrieve subject-collected stool specimen (if necessary)
- Collect and review daily stool dairies
- Collect unused study medication and perform accountability
- Administer Quality of Life Questionnaire (Cdiff32)
- Dispense stool collection kit and instructions
- Dispense additional stool diaries
- Schedule visit 4

11.6 Visit 4 (in-person or phone call)

- Review concomitant medications, changes in medical history, assess AEs
- Perform chart abstraction
- Retrieve subject-collected stool specimen (if necessary)
- Collect and review daily stool dairies (if phone call, participants may provide at next visit or mail to study coordinators)
- Collect unused study medication and perform accountability if not collected at Visit 3
- Dispense stool collection kit and instructions
- Dispense additional stool diaries as necessary
- Schedule visit 5

11.7 Visit 5 (in-person or phone call)

- Review concomitant medications, changes in medical history, assess AEs
- Perform chart abstraction
- Retrieve subject-collected stool specimen (if necessary)
- Collect and review daily stool dairies (if phone call, participants may provide at next visit or mail to study coordinators)
- Dispense stool collection kit and instructions
- Dispense additional stool diaries as necessary
- Schedule visit 6

11.8 Visit 6 (in-person or phone call)

- Review concomitant medications, changes in medical history, assess AEs

- Perform chart abstraction
- Retrieve subject-collected stool specimen (if necessary)
- Collect and review daily stool dairies (if phone call, participants may provide at next visit or mail to study coordinators)
- Dispense stool collection kit and instructions
- Dispense additional stool diaries as necessary
- Schedule visit 7

11.9 Visit 7 (in-person or phone call)

- Review concomitant medications, changes in medical history, assess AEs
- Perform chart abstraction
- Blood draw (if in-person)
- Retrieve subject-collected stool specimen (if necessary)
- Collect and review daily stool dairies
- Administer Quality of Life Questionnaire (Cdiff32)

11.10 Telephone Contact

Between Visit 3 and Visit 7, study staff will attempt weekly phone contacts to assess for AEs, review concomitant medications, and remind subjects to complete daily stool diaries. If contact with the patient is unsuccessful, study staff must document their attempt(s) to contact the participant.

11.11 Unscheduled Visit

Unscheduled Visits occur at the time of diarrhea or suspected CDI recurrence (≥3 loose stools that take the shape of the container in a 24-hour period). Data collection for unscheduled visits will be collected in addition to early termination visit if recurrence is confirmed. Study staff will complete a recurrence CRF for each episode of CDI. This CRF will be used to track duration of the episode, type, dosage, and duration of antibiotics. Data points for infectious episode:

- Date
- Preliminary diagnosis
- Antibiotic/s
  - Name
  - Formulation (IV, suspension, capsules)
  - Dosage
  - Prescribed duration
  - Final (actual) duration of antibiotics
  - Change in antibiotics regimen
- Concomitant medication (name, dose, route of administration, duration)
- Hospital admission (yes/no)
  - Name of facility
  - Department where participant was admitted (ward / step down/ ICU)
  - Relevant Medical Procedures
    - Colonoscopy (including preparation)
    - Intestinal surgery
    - Dialysis
    - Other
- Final diagnosis

11.12 Early Termination and Withdrawal

Subjects have the right to withdraw from the study or discontinue study treatment at any time. If a subject decides to end his or her participation, the PI and study staff will invite the subject to complete the Early Termination Visit. Participants who meet the primary endpoint of recurrence will complete the early termination visit.

At this visit, the following procedures will occur:

- Review concomitant medications, changes in medical history, assess AEs
- Perform chart abstraction
- Blood draw
- Retrieve subject-collected stool specimen (if necessary)
- Collect and review daily stool dairies
- Administer Quality of Life Questionnaire (Cdiff32)
- Collect unused study medication and perform accountability if not collected previously

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

- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods. These contact attempts should be documented in the subject's study file.
- If the subject continues to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up. The withdrawn date is the last day of attempted contact.

11.13 Study Calendar

	Baseline	Study Treatment			Follow-up					
Procedure (Visit Window)	**Visit 1[11]** (Day -7 to Day -1)	**Visit 2[11]** (Day 0)	**Study Drug Admin. Follow-up Call** (Day 1 to Day 3)	**Visit 3** (Day 31 to Day 38)	**Visit 4[9]** (Week 9 ± 7 days)	**Visit 5[9]** (Week 13 ± 7 days)	**Visit 6[9]** (Week 17 ± 7 days)	**Visit 7[9]** (Week 29 ± 7 days)	**Unsched.**	**Early Term.**
Informed Consent	X									
Demographics	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Medical History[1]	X									
Inclusion/Exclusion Criteria	X	X								
Physical Examination, Height, Weight & Vital Signs[2]	X			X						
Urine or Serum Pregnancy Test (if applicable)	X	X								
Stool Collection[3]	- - - - - - - - X - - - - - - -			X	X	X	X	X	X	X
Stool Assessments[4]	- - - - - - - - X - - - - - - -			X	X	X	X	X	X	X
C. difficile Toxin A Blood Draw[5]		X		X				X[12]		X
CBC w/ diff Blood Draw[5]				X						
CMV/EBV Antibodies Blood Draw	X[6]									
Quality of Life Questionnaire (Cdiff32)	X			X				X		X
Safety Capsule		X								
Adverse Event Monitoring		X	X	X	X	X	X	X	X	X
Daily Stool Diary[10]			- - - - - - - -

1. Baseline medical history to include type of transplant, date of transplant, donor characteristics, cytomegalovirus status, Epstein Barr Virus status, rejection episodes, induction immunosuppression, probiotic use, social history (smoking status). Confirm positive stool C difficile toxin test.
2. Targeted physical exam to include assessment of heart, lung and abdomen. Height will be measured at Visit 1 only. Weight will be measured at Visit 1 and Visit 4. Vital signs to include temperature, respiratory rate, heart rate, and blood pressure.
3. Subject to collect stool sample within specified window. Specimen may be brought to study visit or shipped.
4. Stool will be processed at UW-Madison research laboratory for microbiology analysis, toxin assays and microbiome analysis.
5. Blood obtained at visits 2, 3, 7 and Early Term will be processed for IgG antibodies to *C. difficile* Toxin A. CBC with differential will also be assessed at visit 3.
6. Antibodies to CMV and EBV will be assessed at Visit 1 if not previously documented.
7. Between Visit 3 and Visit 7, study staff will attempt weekly phone contacts to assess for AEs, review concomitant medications and remind subjects to complete daily stool diaries as well as to assist with subject retention.
8. The following variables will be abstracted from the medical record at each study visit: rejection episodes, maintenance immunosuppression, nutritional status, bowel habits, organ function assessment, metabolic parameters, bloodstream infections, viral and fungal infections, hospitalizations, emergency department visits, gastric acid suppression, antibiotic use, FMT history, concomitant medications, and safety endpoints.
9. Visits may be conducted in-person or via telephone call.
10. Dispense 7-day post-FMT Stool Diary and Stool Diary at visit 2 for subject to complete at home.
11. Visits 1 and 2 may occur on the same day.
12. If subject chooses to complete visit 7 remotely, *C. diff* Toxin A blood sample will not be collected.

11.14 Study Procedures

11.14.1 Physical Examination and Vital Signs

At visits 1 and 3, a targeted physical exam including heart, lung, abdomen, and weight. Height will be measured at Visit 1 only. Vital signs to include temperature, respiratory rate, heart rate, and blood pressure.

11.14.2 Urine or Serum Pregnancy Test

Females of childbearing potential must have a negative urine or serum pregnancy test at baseline (Visit 1) and prior to randomization (Visit 2). Samples should be processed by each sites' clinical laboratory or research staff.

11.14.3 Stool Collection

A total of 6 stool samples will be self-collected by participants or perirectal swabs collected by study staff if stool sample(s) cannot be produced. Subjects may choose to: A) collect samples within the 24 hours proceeding their scheduled visits and bring to their appointment; or B) collect samples within the allotted visit window and ship directly to the UW infectious disease research laboratory. Reference MOP for additional detail.

11.14.4 Stool Assessments

Stool specimens collected to coincide with visits 2-7 will be processed at the UW Infectious Disease Research Lab for microbiology, toxin (TechLab *C. difficile* TOX A/B II) and microbiome analysis. Note: the positive *C. difficile* test required for eligibility will be assessed from medical record review. Reference MOP for additional detail.

11.14.5 Blood Assessments

A total volume of approximately 25 ml (4 teaspoons) of blood will be collected during the study.

11.14.5.1 IgG Antibodies to *C. difficile* toxin A
Approximately 5 ml of blood will be drawn at visits 2, 3 and 7 to assess antibodies to *C. difficile* toxin. After initial processing at the site, serum will be removed and sent to a commercial lab. Reference MOP for additional detail.

11.14.5.2 IgG Antibodies to CMV and EBV
If historical laboratory results for antibodies to CMV and EBV are not available, approximately 5 ml of blood will be drawn at visit 1.

11.14.5.3 Complete Blood Count (CBC) with differential
Approximately 5 ml of blood will be drawn at visit 3 and processed at each site's clinical laboratory. Reference MOP for additional detail.

11.14.6 Quality of Life Questionnaire (Cdiff32)

Health-related quality of life will be assessed at visits 1, 3 and 7 using Cdiff32, a validated instrument specific for patients with CDI.

11.14.7 Safety Capsule Administration

Subjects will ingest one inert 'safety' capsule under direct supervision of the study nurse at visit 2. The safety capsule is identical to the MTP-101-C matching placebo and will minimize risk to study participation by determining subjects' tolerance for consuming capsules.

11.14.8 MTP-101-C/Matching Placebo and Vancomycin/Matching Placebo at Visit 2

At visit 2, subjects will receive a single dose of MTP-101-C or matching placebo. A single dose consists of 5 capsules, each swallowed individually with water. Reference section 9.7.1 and MOP for additional detail.

At visit 2, subjects will also receive oral vancomycin or matching placebo capsules to be taken according to the prescribed schedule. Reference section 9.7.2 and MOP for additional detail.

11.14.9 Daily Stool Diary

Subjects will complete a daily stool diary starting at visit 2 through the end of the study (visit 7). The modified Bristol stool consistency scale will be used for diarrhea assessment. At visit 2, subjects will be asked to complete a specific stool diary for 7 days post FMT that will assess the following adverse events: fever, vomiting, abdominal pain, bloating, flatulence, diarrhea, constipation, and rectal bleeding.

11.14.10 Chart Abstraction

The following data will be abstracted at baseline: transplant, date of transplant, donor characteristics, cytomegalovirus status, Epstein Barr Virus status, rejection episodes, induction immunosuppression. The following variables will be abstracted at each study visit: rejection episodes, maintenance immunosuppression, nutritional status, bowel habits, organ function assessment, metabolic parameters, bloodstream infections, viral and fungal infections, hospitalizations, emergency department visits, gastric acid suppression, antibiotic use, FMT history, concomitant medications, and safety endpoints.

12.0 DATA COLLECTION, HANDLING AND RECORD KEEPING

The PI will be responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will 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.

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. Frontier Science, a not-for profit clinical research organization that has extensive experience on data management and quality control, will be responsible for these activities to support the study.

12.1 Types of Data

Data for this study will include safety, laboratory, and endpoint measures: diarrhea, demographics, comorbidity, medications, transplant related factors, *C. difficile* lab results, other multidrug-resistant organism results and fecal microbiome assessment.

12.2 Data Collection

12.2.1 Source Documents and Access to Source Data/Documents

Most data will be recorded on structured electronic case report forms (eCRFs) at clinical sites; other data will be sent electronically to the DCC from the lab. Drafts of the study eCRFs will be prepared by the DMC and reviewed and approved by the study team.

The information collected on eCRFs will be self-coding whenever possible. Brief instructions for completing the form will be given for each eCRF. Additional instructions, including those for standard data formats (e.g., dates, justification, and zero-filling), will be included in the MOP. All of the data collected on CRFs will be visit-driven. At scheduled protocol-defined visits (screening, baseline, and weeks12 and 24) and protocol-specific data (e.g., clinical, laboratory, medication, adherence, adverse effects) will be recorded. Protocol-specified clinical events (e.g., adverse events or deaths) will be reported as they occur.

The lab will send data files to the DCC, which then logs the data into the central repository. The data management will be coordinated by Frontier Science.

The DCC will be located in the Department of Biostatistics and Medical Informatics of the University of Wisconsin-Madison, with a subcontract at Frontier Science & Technology Research Foundation office (Amherst NY). UW-Madison will be responsible for oversight of the DCC activities with specific responsibilities for statistical methods, and FSTRF will be responsible for data management, quality control and trial monitoring support.

12.2.2 Data Collection Forms

Standardized data collection forms (e.g., source documents, case report forms, standardized assessment forms, etc.) are used to ensure data collected are consistent and compliant with the protocol and IRB application.

Data collection is the responsibility of study team members under the supervision of the principal investigator. The principal investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the recorded and reported data.

All data collection forms must be completed in a legible manner; any missing data will be explained. Data entry errors will be corrected with a single line through the incorrect entry and the correct data is entered above/near the correction. All changes will be initialed and dated.

Data collection forms are maintained in the subject files and retained as described in the Record Retention section.

12.2.3 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 PI or designee.

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

12.3 Data Capture Methods

Clinical data (including AEs, concomitant medications, and reactogenicity data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant Internet Data Entry System (IDES) provided by Frontier Science. 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.

12.3.1 Data Management Software System(s)

OpenClinica will be the clinical trial data management system (CTDMS) for this trial. It is a web-based CTDMS thus it can be accessed from most locations in the world to support multi-center studies. OpenClinica is FDA 21 CFR Part 11 compliant and supports Good Clinical Practice (GCP) via differentiated user roles and privileges, password and user authentication security, electronic signatures, secure sockets layer (SSL) encryption, and a comprehensive auditing record and monitoring of access and data changes.

Based on the differentiated roles and privileges, subject data will only be available to the specific site which has enrolled the subject and entered data. All clinical data required by the protocol is entered using a unique subject assigned number and no personal identifying information is entered or stored other than dates of birth and service.

All data entered through OpenClinica will be stored on servers provided by OpenClinica, LLC which maintains all data in a SAS 70 Type II audit certification and meets ISO 17799 standards for information security. Access to OpenClinica on their servers is limited, via login credentials, to authorized users for the web interface only. Customers have no access to the server itself. All OpenClinica employees are granted access only to computer and networking areas necessary to perform their duties. Each installation is separate, and cannot be accessed from any other installation. Connection to a hosted instance is encrypted by means of secure socket

layer. The application server and database server are secured via firewall, hardened to remove nonessential access credentials, and strong password compliance. Hosted systems are constantly monitored for latencies and intrusion.

12.4 Data Confidentiality

12.4.1 Confidentiality of Subject Records

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, 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 of the sponsor.

All research activities will be conducted in as private a setting as possible.

All the staff participating in this project must complete human subjects protections, Good Clinical Practice (GCP), and HIPAA training.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). All subjects will sign an informed consent document and HIPAA authorization that includes specific privacy and confidentiality rights. Study data will be maintained per federal, state, and institutional data policies.

The investigator(s) will ensure that the identities of subjects are protected by using coded subject information. The subject log with identifying information, linking subjects to their study-specific identification number, will be maintained electronically on a secure network server that is password-protected with access provided only to authorized study personnel.

Authorized representatives of the following groups may need to review this research as part of their responsibilities to protect research subjects: authorized representatives of the NIAID, representatives of the IRB, DSMB, DCC staff, regulatory agencies or study product suppliers. The clinical study site will permit access to such records.

12.5 Records Retention

Study records will be retained for a minimum of 7 years after study completion.

12.6 Specimen Banking

All samples collected from this study will be labeled with a subject ID and maintained in secure freezer space located UW Infectious Disease Research Lab. Laboratory and freezer access is limited to authorized personnel.

Subjects will be given the option to allow their tissue to be stored for future research and may withdraw their tissue at any time. Subjects may withdraw their tissue by contacting the PI. If the patient withdraws consent, the subject’s data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

13.0 ASSESSMENT OF SAFETY

13.1 Adventitious Findings

Not applicable.

13.2 Adverse Event (AE) Definition

Adverse event (AE) means any untoward or unfavorable medical occurrence in a human subject or others that happens during or after participation in a research study.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline. These AEs will be entered into the electronic data capture system (EDC).

For the purposes of this study, baseline symptoms will be collected prior to the administration of the study intervention. Only those symptoms identified as new or worsened compared to the baseline assessment will be recorded as an AE. In addition, only those abnormal laboratory values or physical examination assessments that are considered clinically significant will be recorded in the study documents.

13.3 Serious Adverse Event (SAE) Definition

An adverse event is considered "serious" if, in the view of either the investigator or sponsor, meets any of the following criteria:

- Results in death
- Are life-threatening (Refers to an AE in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically, might have caused death if it were more severe.)
- Requires an inpatient hospitalization or prolongation of an existing hospitalization
- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.)
- Results in a congenital anomaly/birth defect, constitute, based upon appropriate medical judgment, an event that may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed above.

13.4 Unanticipated Problem (UP) Definition

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

- The incidence, experience, or outcome is unexpected given the research procedures described in protocol-related documents (e.g., the study protocol, the consent documents, the Investigator's Drug Brochure) and the characteristics of the subject population being studied. An event may be considered unexpected if it exceeds the nature, severity, or frequency described in the study-related documents, Investigator's Drug Brochure, product labeling, or package insert.
- The incidence, experience, or outcome is related or probably related to participation in the research study. Probably related means the incidence, experience, or outcome is more likely than not to be caused by the research study procedures.
- The occurrence of the incidence, experience, or outcome suggests that the research places subjects or others at a greater risk of harm (physical, psychological, economic, or social) than was previously known or recognized.

13.5 Classification of an Adverse Event

13.5.1 Severity of Event

All AEs will be assessed by the clinician using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5. For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild (grade 1)** – Events require minimal or no treatment and do not interfere with the subject's daily activities.
- **Moderate (grade 2)** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe (grade 3)** – Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.
- **Life threatening (grade 4)** - The patient was at risk of death at the time of the event.
- **Fatal (grade 5)** - The event caused death.

13.5.2 Relationship to Study Intervention

For all collected AEs, the clinician who examines and evaluates the subject will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – Clearly related to the study procedures and other possible contributing factors can be ruled out.
- **Probably Related** – Likely related to the study procedures and the influence of other factors is unlikely.
- **Possibly Related** – Possibly related to the study procedures and there are other factors that could be equally likely.
- **Unlikely to be related** – Doubtfully related to the study procedures and there is another likely cause.
- **Unrelated** – Clearly not related to the study procedures and/or evidence exists that the event is definitely related to another cause.

13.5.3 Expectedness to Study Intervention

The PI will be responsible for determining whether an AE is expected or unexpected in relation to the intervention.

For investigational drug and device studies, an AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in the clinical protocol, device manual, investigator's brochure, investigational drug brochure, the package insert(s), the IRB application, or the informed consent document.

13.6 Collection and Reporting of AEs, SAEs & UPs

Study subjects will be instructed to contact the study staff if any serious or unexpected adverse event occurs. Reported AE's will be recorded in detail in an AE case report form.

Adverse events will be identified with subjects on weekly telephone calls and study visits. Any adverse events will be discussed with the PI and will be reviewed to determine whether a change in protocol is necessary.

All adverse events and serious adverse events should be recorded on the Adverse Event Log, Serious Adverse Event Log, and in OpenClinica, within 24 hours.

AE/SAEs that meet the definition of an unanticipated problem will be reported to the IRB within 14 business days. Events that are immediately life threatening, severely debilitating to other current subjects or resulted in a death will be reported to the IRB Chair or IRB Director via telephone or email within 24 hours (1 business day) of site awareness.

AE/SAEs that meet the definition of suspected, unexpected serious adverse reactions will be reported to the FDA no later than 15 calendar days after determining the information qualifies for reporting or within 7 calendar days for any unexpected fatal or life-threatening suspected adverse reactions as outlined in 21 CFR 312.32

13.7 Stopping Rules

13.7.1 Study Stopping Rules

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study sites, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Safety data in patients with solid organ transplants is limited. The most common adverse events in solid organ transplant recipients who have received FMT treatment have been nausea, bloating, cramping, and diarrhea. Additionally, there is the risk of inadvertent transmission of infectious organisms contained in the donor stool as well as allergic reactions to antigens contained in the donor stool. It is unknown if FMT will impact the risk of rejection, organ function, malignancy, hospitalizations, and emergency visits.

Circumstances that may warrant termination or suspension include, but are not limited to:

- An infection in any subject in which the probable cause is the study treatment
- Determination of unexpected, significant, or unacceptable risk to subjects when a causal relationship with the study treatment is probable
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

The DSMB may be unblinded to judge whether a specific adverse event meets the stopping rules listed above.

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the applicable federal and institutional regulatory authorities.

13.7.2 Subject Stopping Rules

Refer to section 8.4, Early Termination and Withdrawal.

14.0 STUDY ANALYSIS

14.1 Statistical Hypothesis

This five-site trial in 158 SOT recipients with at least a first recurrence of CDI is designed to test the hypothesis that FMT will result in less recurrence of CDI compared with oral vancomycin.

14.2 Primary Efficacy Objective

The primary efficacy objective is to compare the effects of FMT and oral vancomycin on the recurrence of CDI in SOT recipients. The primary analysis will be performed according to the intention-to-treat principle.. The primary efficacy analysis will be based on the primary endpoint of CDI recurrence in a 60-day period as a dichotomous variable. The primary comparison between the two treatment arms will be based on a Cochran-Mantel-Haenszel chi-square test accounting for stratification by clinical site at a significance level of 0.05. A log binomial model with treatment as model term while adjusting for potential confounders such as age, sex, race/ethnicity, comorbidities, exposure to healthcare system, clinical site, and type of transplant organ as per NIH Rigor and Reproducibility standards will be used to estimate the relative risk or risk ratio of CDI recurrence with 95% confidence interval. As a secondary analysis, time to recurrence of CDI as time to event data will be compared using log-rank test stratified by clinical site, and its survival distribution estimated using Kaplan-Meier method.[21] A Cox proportional hazards regression model stratified by clinical site will be used to estimate a hazard ratio with 95% confidence interval.[57]

14.3 Primary Safety Objective

The primary safety objective is to evaluate the short- and medium-term safety of FMT. The frequency and proportion of short- and medium-term adverse outcomes will be summarized and compared using chi-square test for dichotomous and Jonckheere-Terpstra test for ordinal data.

14.4 Secondary Objectives

14.4.1 Secondary Objective 1

The Secondary Objective 1 is to compare the CDI-related quality of life of SOT recipients. The CDI-related quality of life (QoL), as measured using Cdiff32, will be compared using longitudinal mixed effects regression model with treatment and time, and treatment by time interaction as model terms while adjusting for potential confounders.

14.4.2 Secondary Objective 2

The secondary objective 2 is to compare the change in gut microbiota using multiple metrics of microbiota structure and function and 2) to evaluate the association between the change in gut microbiota and recurrence of CDI.

The change in diversity indices between the treatment groups will be compared using t-test and analysis of covariance. With the effective sample size of 158, there is 0.80-0.90 power to detect the treatment effect size of 0.51-0.59, where the treatment effect size is defined as the difference in mean change in diversity indices between the two groups divided by the standard deviation. Cytokines and levels of lactoferrin and serum IgG to toxin A will also be compared between the treatment groups. As a secondary analysis, the longitudinally measured diversity indices will be analyzed using linear mixed models with treatment and time and treatment by time interactions as model terms, while adjusting for potential confounders. Depending on the distribution of the diversity index, a normalizing transformation may be necessary or a nonparametric test such as Wilcoxon rank sum test used instead. Association

between clinical outcome of CDI recurrence and the change in gut diversity and microbiota data (both 16S rRNA and metagenomics) will be assessed using the Cox regression model for time to CDI recurrence with treatment and gut diversity as a time-varying covariate as model terms, while adjusting for potential confounders and using either Bray-Curtis dissimilarity with ANOSIM (16S rRNA) or chi-square test (metagenomics).

14.4.3 Secondary Objective 3

The third secondary objective is to compare the effects of FMT and oral vancomycin on intestinal colonization by multidrug-resistant organisms other than *C. difficile* in SOT recipients. The primary analysis will compare the prevalence of colonization by each multidrug-resistant organism at 24 weeks between the two groups, using Mantel-Haenszel chi-square test accounting for stratification by clinical site at a significance level of 0.05. The longitudinally measured prevalence of colonization over time will be analyzed using generalized linear mixed models with treatment and time, and treatment by time interactions as model terms while adjusting for potential confounders. Although Specific Aim 3 is exploratory, a power of > 0.90 for detecting the prevalence of 0.1 vs 0.3, 0.05 vs 0.25, and 0.05 vs 0.3, is expected for FMT and vancomycin given the sample size of 158.

14.5 Sample Size Justification

The primary endpoint of the study is the recurrence of CDI over 60 days from randomization defined as a dichotomous outcome. With the probability of 60-day recurrence denoted by p_V and p_F, respectively, for the SOC vancomycin (V) arm and the FMT (F) arm, the primary objective of the study will be evaluated by testing the null hypothesis H_0:p_V=p_F using a two-tailed two-sample test at a significance level α=0.05 against the alternative hypothesis H_1:$p_V \neq p_F$ with power 1-β=0.9 to detect the decrease in the probability of 60-day recurrence ($\Delta_p = p_V - p_F$) of 0.3. The table below gives the sample size estimates under different drop-out rates. Assuming a random drop-out rate of 20%, we propose a sample size of **158** based on p_V=0.60-0.70 and p_F=0.30-0.40. If the probability of 60-day recurrence on vancomycin (p_V) is <0.60 or >0.70, the study will have a slightly higher power than 0.90.

14.6 Subject Population(s) for Analysis

The study will enroll 158 subjects who meet the inclusion and exclusion criteria over the course of 4 years from five domestic clinical sites.

Drop-out rate	Probability of 60-day recurrence on vancomycin (p_V)						
	0.50	0.55	0.60	0.65	0.70	0.75	0.80
15%	138	144	150	150	150	144	138
20%	146	154	158	158	158	154	146
25%	156	164	168	168	168	164	156

The efficacy analyses of the trial will be based on the intention-to-treat principle, to include all subjects randomized. For those subjects who fail to return for evaluation of the primary and secondary efficacy endpoints, a method of multiple imputation will be used to impute the missing endpoints[26] or other method for missing data such as principal stratification[27] will be used for longitudinal outcomes. Multiple imputation will follow the standard approach: 1) generate complete datasets multiple times using a log-binomial regression model based on the available data; 2) analyze the multiply imputed datasets using the same model; 3) and combined the results for statistical inference.

All randomized subjects who underwent the protocol treatment of either MTP-101-C or oral vancomycin, the so-called Per-Protocol Analysis Set, will be included in all safety analyses. A supportive analysis of the efficacy endpoints will be performed using the Per-Protocol Analysis Set.

14.7 Statistical Methods

Statistical methods will follow the established good statistical practice adopted by a wider community of statisticians in clinical research. All statistical data analyses will be performed using the latest version of SAS (SAS Institute, Inc., Cary NC) and R (The R Foundation, Vienna, Austria) to provide validation of all analyses as per NIH Rigor and Reproducibility standards.

14.7.1 Demographics and Baseline Characteristics

Summary tables and graphs of all randomized subjects, subject disposition and reasons for withdrawal, demographics, and baseline CDI characteristics will be produced. Baseline subject characteristics will be summarized using descriptive statistics such as mean and standard deviation, or median and interquartile range for quantitative measurements, frequency and proportion for binary or categorical measurements, graphics such as box plots and empirical distribution functions, and assessed for balance between the two dose groups.

Appropriate categorical data analysis methods such as chi-square test or Jonckeere-Terpstra test will be used to determine if the two treatment groups are balanced and comparable with respect to demographic and baseline characteristics.[7] Student's t-test or Wilcoxon rank-sum tests will be used to determine if the two treatment groups are balanced with respect to baseline continuous covariates.

14.7.2 Efficacy Analysis

Primary Efficacy Analysis: The primary analysis will be performed according to the intention-to treat principle. The primary efficacy analysis will be based on the primary endpoint of CDI recurrence in a 60-day period as a dichotomous variable. The primary comparison will be based on a Mantel-Haenszel chi-square test accounting for stratification by clinical site at a significance level of 0.05. A log-binomial regression model with treatment as model term while adjusting for potential confounders such as age, sex, comorbidities, exposure to healthcare system, clinical site, and type of transplant organ will be used to estimate the relative risk or risk ratio of CDI recurrence with 95% confidence interval. As a secondary analysis, time to recurrence of CDI as time to event data will be compared using log-rank test stratified by clinical site, and its survival distribution estimated using Kaplan-Meier method. A Cox proportional hazards regression model stratified by clinical site will be used to estimate the hazard ratio of recurrence of CDI with 95% confidence interval.

Secondary Efficacy Analyses: The CDI-related quality of life (QoL), as measured using Cdiff32, will be compared using longitudinal mixed effects regression model with treatment and time and treatment by time interaction as model terms while adjusting for potential confounders.

The prevalence of colonization by each of three multidrug-resistant organisms, VRE, MRSA and FRGNB, at 24 weeks will be compared between the FMT and vancomycin groups using a Mandel-Haenszel chi-square test accounting for stratification by clinical site. Although this analysis is exploratory, a power of >0.90 for detecting the prevalence of 0.1 vs 0.3, 0.05 vs 0.25, and 0.05 vs 0.3, is expected for FMT and vancomycin, given the sample size of 158. In addition, the prevalence of colonization over time will be analyzed using generalized linear mixed models with treatment and time and treatment by time interactions as model terms while adjusting for potential confounders.

14.7.3 Safety Analysis

The frequency and proportion of short- and medium-term adverse outcomes will be summarized by tables and graphs and compared using chi-square test for dichotomous and Jonckheere-Terpstra test for ordinal data.

All inferential statistical tests of safety data will use two-sided statistical tests with a significance level at 0.05 without adjustment for multiplicity. The format and content of all tables and graphs summarizing adverse event, vital signs and laboratory data will adhere to standard good statistical practice.

Adverse events will be summarized in multiple tables and graphs by treatment group:

- Incidence Table: summary of the incidence of any adverse event,
- Serious Adverse Event Table: summary of the incidence of serious adverse events

Shifts in laboratory tests are compared between treatments in terms of numbers of subjects showing an increase, decrease, and no change, with respect to the normal range. Changes from baseline to week 24 (calculated as final value minus baseline value) will also be compared between treatments. Inferential analyses will use Wilcoxon rank-sum tests for continuous variables and chi-square test for categorical variables. All early termination laboratory results will be considered final laboratory results.

The percent of subjects showing clinically relevant changes from baseline in laboratory tests will be compared between the two treatment groups. Significant laboratory changes from baseline within treatment group as determined by Student t-test will be listed.

14.7.4 Analysis of Correlative Endpoints

The change in diversity indices between the treatment groups will be compared using t-test and analysis of covariance. Depending on the distribution of the diversity index, a normalizing transformation may be necessary or a nonparametric test such as Wilcoxon rank sum test used instead. With the sample size of 158, there is 0.80-0.90 power to detect the treatment effect size of 0.51-0.59, where the treatment effect size is defined as the difference in mean change in diversity indices between the two groups divided by the standard deviation. Metagenomic data as well as cytokines, CXCL-5/ENA-78 and CXCL-8/IL-8, levels of quantitative lactoferrin and serum IgG to toxin A will also be compared between the FMT and vancomycin groups using appropriate two-sample tests depending on the statistical distributions for these endpoints.

As a secondary analysis, diversity indices over time will be analyzed using linear mixed models with treatment and time and treatment by time interactions as model terms, while adjusting for potential confounders. Association between clinical outcome of CDI recurrence and the change in gut diversity and microbiota data (both 16S rRNA and metagenomics) will be assessed using the Cox regression model for time to CDI recurrence with treatment and gut diversity as a time-varying covariate as model terms, while adjusting for potential confounders and using either Bray-Curtis dissimilarity with ANOSIM (16S rRNA) or chi-square test (metagenomics).

14.8 Subgroup Analysis

Many baseline characteristics are known to be prognostic or suspected confounders for the clinical outcomes in the CDI study population, including age, sex, race/ethnicity, status of

hospital stay, clinical site, and type of transplant organ. Internal consistency of the primary efficacy analysis will be assessed in subgroups defined by these covariates. Heterogeneity will be assessed using interaction tests of treatment by these baseline covariates. Any interaction test resulting in a heterogeneity p-value < 0.15 will be further evaluated for clinical plausibility.

14.9 Handling Missing Data

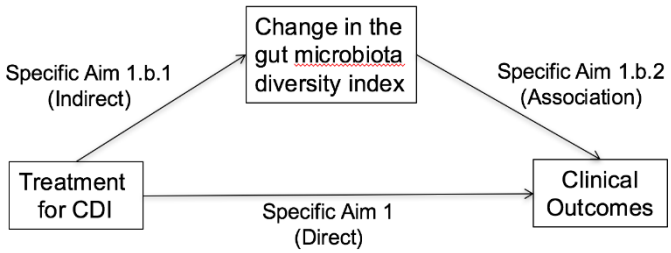
Not all subjects will have their stool samples, stool diaries, and QoL data available for analysis, and there will inevitably be missing data. Most methods for handling missing data assume that the data are missing at random, which may not be a valid assumption. Reasons for missing data will be documented and evaluated. If the missing data are extensive, model-based approaches will estimate their effects under various assumptions regarding missingness. For longitudinal data, principal stratification will be used for missing data. Missing data analysis will follow the guideline promulgated in the National Research Council report.[28]

14.10 Exploratory Analysis

Marginal analyses, separately, of the clinical outcomes for the primary objective and the change in diversity of the gut microbiota for the secondary objective may not fully capture the effects of FMT treatment. In order to better understand the effects of FMT clinically and biologically, joint statistical models for the gut microbiota diversity index at baseline and weeks 1, 4, 8 and 12 and time to recurrence of CDI will be developed.

In addition, mediation analysis will be performed to understand whether the effects of FMT is directly on the clinical outcomes without mediation of the gut microbiota diversity or indirectly through modulation of the gut microbiota diversity index instead (Figure 5). A publicly available R package, mediation, will be used to perform the required mediation analysis (http://cran.r-roject.org/web/packages/mediation/index.html).

Figure 5: Direct and indirect effects of treatment with gut microbiota modulation and association between the change in diversity index and clinical outcomes.



14.11 Interim Analysis

No interim analysis for efficacy is planned.

14.12 Multiplicity of Endpoints and Multiple Testing

Considering the nature of the study, observed significance level, the so-called p-value, less than 0.05 will be taken to indicate statistical significance without adjustment for multiple testing involved with subgroup analysis. Statistical significance will be assessed in a hierarchical manner starting with the primary endpoint followed by the secondary endpoints in the order of appearance in Section 6.4.

15.0 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

15.1 Quality Management

All sites will have a plan in place for assuring the quality of the research being conducted and will have SOPs in place for quality management. Frontier Science will be responsible for data management which includes quality control. Relative to quality control, their role will be the following:

- On an ongoing basis, perform QA/QC of submitted clinical and laboratory data, primarily through automated facilities.
- On an ongoing basis, collect data from other instruments and/or other sources collaborating in the study.
- On a daily basis, monitor computer processes and the database to ensure that all systems are operating correctly. These include data transmission and update operations, and the operations of the system software supporting and managing the study database.
- Monitor the registration & randomization system on a daily basis. Monitor accruals and, working with the study statistician, ensure that the study dosing schema is executed properly.
- Provide 24X7 user support for the data management systems. Provide backup to the registration & randomization system if there is a failure or if a site is temporarily unable to directly enter a subject.
- Provide training in data management issues and software to staff as needed
- Assist the project statistician with database retrievals and resolve any data inconsistencies identified by the statistician, querying sites as necessary.
- Produce periodic reports for the PI, study sites, and other study collaborators as requested. Generally, sites will receive operational reports, the PI and designees will receive administrative and site performance reports, while others will receive function-specific reports.
- Generate reports on schedules and as needed; develop additional reports as required.

15.2 Safety Oversight

The Midwest Area Research Consortium for Health (MARCH) Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to the Principal Investigator and NIAID to monitor subject safety, data quality and to evaluate the ability of the study to achieve its research goals. The DSMB will meet at a minimum of every 6 months, during the four-year accrual period. Additional meetings may be convened as necessary.

The MARCH DSMB operates according to an established charter and is comprised of a core group of individuals, representing each MARCH institution. All members have clinical trials experience, are independent of the study, and have no financial ties to the trial outcome. Members have diverse expertise in disciplines including laboratory science, clinical medicine, statistics, epidemiology, and/or research ethics. Ad hoc members may be added as warranted.

The DSMB members will review protocol-specific reports prepared by the DCC. Reports will include an overview of study objectives, a review of actual and projected accrual rates, an evaluation of subject demographics for balance of randomization, data quality (e.g., missed visits, late visits) and a summary of the number and seriousness of adverse events.

The DSMB will make recommendations to the Principal Investigator that could include actions of continuation, modification, suspension, or termination. The Principal Investigator will forward the communication of the DSMB recommendations and all pertinent regulatory information to the FDA, appropriate Institutional Review Board(s), and the Sponsor when applicable.

The DSMB will review all serious adverse events and will halt the study for any serious adverse event assessed as at least possibly related to the study product or any suspected or confirmed transmission of an infection from the study product to a study recipient. In the event of a study halt for DSMB review, the FDA will be notified within 48 hours.

15.3 Study Monitoring

The DMC/Frontier Science monitors will be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures (SOPs) to ensure that trial is conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice (ICH E6), and all applicable federal, state, provincial, and local laws, rules, and regulations relating to the conduct of the clinical trial.

During the trial, the DMC and Frontier Science monitors will utilize on-site, remote and risk-based monitoring to ensure that the protocol and good clinical practices (GCPs) are being followed as described in detail in a separate quality assurance document/monitoring plan. At regular intervals during the clinical trial, each site will be contacted, through on-site monitoring visits, webinars or telephone calls, by a Frontier Science monitor to review trial progress, Investigator and patient compliance with protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient Informed consent for 100% of patients, source data verification, patient recruitment and follow-up, adverse event documentation and reporting (including timeliness), trial treatment administration, patient compliance with the regimens, pharmacy review/accountability, concomitant therapy use and quality of data.

The DCC will determine data accuracy using a number of statistical-based approaches to identify potential data errors. Source documents, such as documentation of entry criteria, may be queried and reviewed by members of the DMC to identify data irregularities and to confirm that the data recorded on the case report forms is accurate. Any site found to be Unacceptable or Acceptable/Needs Follow-up on monitoring is required to submit a written response and/or corrective action plan to the DMC within 21 days of the receipt of the final monitor findings. Sites that fail to meet the standards for acceptable performance will undergo follow-up action, which will be determined by the severity of the discrepancies and may include repeat on-site monitoring, probation, or suspension. For-cause monitoring will occur if irregularities are identified, and if necessary will be supplemented by site visits by members of theDMC. The Investigator and the clinical site will allow the monitors and appropriate regulatory authorities direct access to source documents to perform this verification.

The Clinical Site may be subject to review and/or inspection by the Institutional Review Board (IRB), the US Food and Drug Administration (FDA), and/or to quality assurance audits performed by the NIAID or the DMC.

It is important that the Investigator(s) and the relevant clinical site personnel be available during the monitoring period and possible audits or inspections, and that sufficient time is devoted to the process.

15.4 Protocol Deviations

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

It is the responsibility of the Principal Investigator/site investigator/study staff to use continuous

vigilance to identify and report deviations. The Principal Investigator is responsible for assessing whether the deviation constitutes noncompliance as defined by the reviewing IRB and if so, reporting it within the required time frame(s).The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

For this trial, subject non-compliance with MTP-101-C/matching placebo or oral vancomycin/matching placebo (e.g., missed dose) is considered a protocol deviation. Incomplete 7-Day Post-FMT Stool Diaries are deviations. Incomplete Stool Diaries after the 7-days post-FMT are not deviations but study staff must reeducate subjects on completion and use of the diary and document reeducation.

15.5 Publication Plan

Publication of the results of this trial will be governed by policies and procedures developed by the Steering Committee. No results will be released publicly before completion of the final analysis regarding the primary endpoint of this study without the approval of the NIAID, and the Steering Committee. Any presentation, abstract, or manuscript will be made available for review by the principal investigators and the NIAID prior to submission.

This study will comply with the NIH Public Access Policy, which requires submission of final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central.

16.0 MULTISITE RESEARCH COMMUNICATION PLAN

16.1 Statement of Compliance with NIH Single IRB Policy

In accordance with the NIH Policy on the use of a single IRB for multisite research, a single IRB will provide IRB review under 45 CFR 46 of all human subjects' research at all collaborating sites.

16.2 UW-Madison Health Sciences IRB

The UW-Madison Health Sciences IRB will serve as the single IRB of record for all sites.

16.3 Participating Sites Agreement to Rely on sIRB

Only sites who agree to rely on UW-Madison Health Sciences IRBs Office as the single IRB will participate.

16.4 Communication between Sites and the sIRB

16.4.1 Roles

- Reviewing IRB: Responsible for addressing questions related to the Reviewing IRB's policies and procedures and review status for a ceded study
- Clinical Coordinating Center (CCC): Main entity responsible for communication with the Reviewing IRB and facilitating communication between relying site study teams and the Reviewing IRB regarding the ceded study
- Relying Site Reliance Point of Contact (POC): Main person or entity responsible for communication with the Reviewing IRB and local study team regarding the ceded study (e.g., personnel in the local IRB office or local human research protection program personnel)
- Relying Site Study Team POC: Main person responsible for communication with the Clinical Coordinating Center regarding the ceded study

16.4.2 Lead Study Team POC (or CCC) Responsibilities

The Lead Study Team will be the primary POC for communication to and from the Reviewing IRB. Site-specific information from the relying sites will be provided to the lead study team and then submitted to the Reviewing IRB. All communication from the Reviewing IRB will flow from the Reviewing IRB to the Lead Study Team POC to the CCC to the Relying Study Team POC. This includes (but is not limited to) the following:

- Preparing and submitting the study-wide application for initial IRB review and study- wide amendments to the Reviewing IRB
- Preparing and submitting the site-specific applications and site-specific amendments to the Reviewing IRB that address site variations in study conduct, informed consent language, HIPAA Privacy Rule requirements (if applicable), subject identification and recruitment processes (including recruitment materials), and any other applicable components of the research
- Providing documentation of IRB determinations to relying site study teams
- Providing copies of IRB-approved materials to the lead study team
- Providing copies of the most current versions of IRB-approved materials to relying site study teams in a timely manner
- Providing the consent form template to relying site study teams

- Providing relevant Reviewing IRB policies to the study teams
- Obtaining and collating study-wide information for continuing review to the Reviewing IRB
- Submitting continuing review progress report to the Reviewing IRB
- Reporting reportable events to the Reviewing IRB (e.g., unanticipated problems, noncompliance, subject complaints)
- Providing the Reviewing IRB with required information when a study is closed

16.4.3 Relying Study Team Responsibilities

Relying Study Team POC will be responsible for communicating with the Relying Site POC for:

- Site-specific research applications (if any)
- Obtaining site-specific approvals (if any)

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17.0 APPENDICES

17.1 Quality of Life Questionnaire (Cdiff-32)

CDI-HRQOL study/ patient questionnaire

HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRE FOR *CLOSTRIDIUM DIFFICILE* INFECTION (*C. diff* infection)

How to fill the questionnaire

The following questions are about your state of health over the last 7 days. Each question has five different responses. For each statement, please circle or check the corresponding box for the response that best describes your feelings. Please respond to all questions even if you think some are similar. Please do not leave any question unanswered. If you make a mistake, cross out the wrong answer and circle or check the corresponding box for the one that best applies to you. Thank you for your participation.

CDI-HRQOL study/ patient questionnaire

DAILY ACTIVITIES

Over the last 7 days, because of your *C. diff* infection,

1. Have you had any difficulties and/or disruption carrying out your daily activities?

☐1	☐2	☐3	☐4	☐5
Not at all	A little bit	Moderately	Quite a bit	Extremely

2. Have you had any difficulties carrying out your leisure activities like gardening, walking, etc?

☐1	☐2	☐3	☐4	☐5
Not at all	A little bit	Moderately	Quite a bit	Extremely

3. Has it taken you longer to perform certain tasks at work (including work in the home)?

☐1	☐2	☐3	☐4	☐5
Not at all	A little bit	Moderately	Quite a bit	Extremely

4. Has your *C. diff* infection prevented you from leaving your house?

☐1	☐2	☐3	☐4	☐5
Never	Rarely	Sometimes	Often	Always

ANXIETY

5. Are you afraid that your *C. diff* infection could come back again?

☐1	☐2	☐3	☐4	☐5
Not at all	A little bit	Moderately	Quite a bit	Extremely

6. Are you afraid that your *C. diff* infection could get worse in the future?

☐1	☐2	☐3	☐4	☐5
Not at all	A little bit	Moderately	Quite a bit	Extremely

7. Are you afraid that the next time you'll need antibiotics, your *C. diff* infection will appear again?

☐1 ☐2 ☐3 ☐4 ☐5

CDI-HRQOL study/ patient questionnaire

Not at all	A little bit	Moderately	Quite a bit	Extremely

Over the last 7 days,

8. Have you been worried about not knowing when the next diarrhea would arise?

☐1	☐2	☐3	☐4	☐5
Never	Rarely	Sometimes	Often	Always

DIET

9. Are you afraid that certain food will worsen your *C. diff* infection?

☐1	☐2	☐3	☐4	☐5
Not at all	A little bit	Moderately	Quite a bit	Extremely

Over the last 7 days, because of your *C. diff* infection,

10. Have you felt frustrated about what you can eat and when?

☐1	☐2	☐3	☐4	☐5
Not at all	A little bit	Moderately	Quite a bit	Extremely

CDI-HRQOL study/ patient questionnaire

SLEEP

Over the last 7 days,

11. Because of your *C. diff* infection, have you had trouble sleeping?

☐1	☐2	☐3	☐4	☐5
Never	Rarely	Sometimes	Often	Always

12. Because of your *C. diff* infection have you been woken up from sleep?

☐1	☐2	☐3	☐4	☐5
Never	Rarely	Sometimes	Often	Always

CDI-HRQOL study/ patient questionnaire

DISCOMFORT

Over the last 7 days,

13. Have you been bothered by abdominal pain?

☐1	☐2	☐3	☐4	☐5
Not at all	A little bit	Moderately	Quite a bit	Extremely

14. Have you been bothered by flatulence (wind)?

☐1	☐2	☐3	☐4	☐5
Not at all	A little bit	Moderately	Quite a bit	Extremely

15. Have you been bothered by a bloated stomach?

☐1	☐2	☐3	☐4	☐5
Not at all	A little bit	Moderately	Quite a bit	Extremely

16. Have you avoided wearing some clothes (tight clothes, dress, light-colored clothes ...)?

☐1	☐2	☐3	☐4	☐5
Never	Rarely	Sometimes	Often	Always

17. Have you been bothered by the smell caused by your *C. diff* infection related diarrhea?

☐1	☐2	☐3	☐4	☐5
Never	Rarely	Sometimes	Often	Always

18. Have you been bothered by how much time you spend on the toilet?

☐1	☐2	☐3	☐4	☐5
Never	Rarely	Sometimes	Often	Always

COPING WITH DISEASE/ HEALTH PERCEPTION

Note! The following sentences are statements. Please indicate whether you agree or disagree with these statements.

19. Despite my C diff infection I can live a normal life.

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

CDI-HRQOL study/ patient questionnaire

CONTROL OF DISEASE

20. I feel that I am not in control of my *C. diff* infection.

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

21. I have no idea what I should do when I have my *C. Diff* infection?

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

CDI-HRQOL study/ patient questionnaire

IMPACT OF STRESS

22. I believe that any stress can worsen my *C. diff* infection.

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

CDI-HRQOL study/ patient questionnaire

DYSPHORIA

23. I feel irritable because of my *C. diff* infection.

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

24. I feel isolated from others because of my *C. diff* infection.

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

25. I feel depressed because of my *C. diff* infection

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

26. I feel my life is less enjoyable because of my *C. diff* infection.

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

27. I worry about transmitting my *C. diff* infection to my family and/or friends.

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

28. I feel much stressed because of my *C. diff* infection.

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

CDI-HRQOL study/ patient questionnaire

RELATIONSHIPS

29. Because of my *C. diff* infection, I have difficulty being around people I do not know.

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

30. My *C. diff* infection is affecting my closest relationships.

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

CDI-HRQOL study/ patient questionnaire

SOCIAL REACTION

31. I feel like I irritate others because of my *C. diff* infection.

☐1	☐2	☐3	☐4	☐5
Totally disagree	Mostly disagree	Don't know	Mostly agree	Totally agree

32. How would you rate your overall quality of life during the past week (that is, how have things been going for you)?

☐1	☐2	☐3	☐4	☐5
Very bad: could hardly be worse	Pretty bad	Good and bad part about equals	Pretty good	Very well: could hardly be better

17.2 Stool Diary

17.2.1 7-Day Post-FMT Stool Diary

Please use this specific stool diary for the first 7 days after the FMT procedure.

Dates for use: ___/___/___ **to** ___/___/___ (Fill in specific dates)

Date: Please fill in the date as MM/DD/YYYY. Please record every bowel movement you have during this study. If you have more than one bowel movement on the same day please record each stool on a separate line.

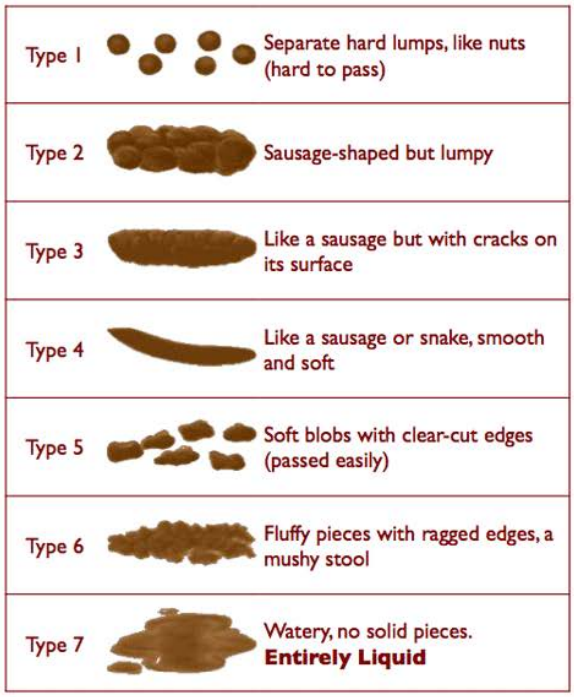
Time of Stool: Please fill in the time you have a bowel movement. Please circle AM (before noon) or PM (noon or later) as appropriate.

Stool Consistency: Please circle a numerical value (Type) based on the Bristol Stool Chart below for each stool. Circle NA if you do not pass any stool on this date. **Call [Coordinator] at [XXX-XXX-XXXX if you have three or more loose stools (Type 5-7 on Bristol Stool Chart) in any 24-hour period.**

Symptoms: Please use this section to indicate if you experience any of the symptoms listed in the section (**fever, vomiting, abdominal pain, bloating, flatulence, diarrhea, constipation, or rectal bleeding**). Also, please Include how you rank the symptom severity (mild, moderate, or severe), and include any medications you may have taken for the symptom(s) and when the symptom(s) went away (if applicable).

Mild: Did not keep me from going about normal activities.
Moderate: Kept me from doing some of my normal activities.
Severe: Really noticed the symptom, it kept me from doing activities that I needed or wanted to do.

Bristol Stool Chart



Subject Number:_____ **Study Site:** _____

Subject Signature: _____ **Date:** _____

Date: Days 1-7 post FMT	Time of stool	Stool consistency (Circle one)	Symptoms (if applicable) : Please indicate if experiencing: Fever, vomiting, abdominal pain, bloating, flatulence, diarrhea, constipation, or rectal bleeding
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	

17.2.2 Stool Diary

Instructions on how to complete this diary are below. Call your coordinator with questions.

Please track all of your stools while you are on this study. Each date should have at least one entry. If you have more than one bowel movement on the same day please record each stool on a separate line.

Date: Please fill in the date as MM/DD/YYYY.

Time of Stool: Please fill in the time you have a bowel movement. Please circle AM (before noon) or PM (noon or later) as appropriate. Leave blank if you do not pass any stool on this date.

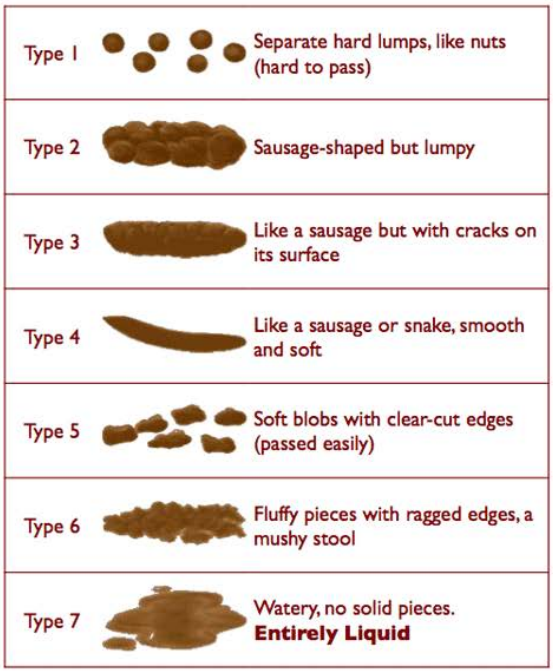
Stool Consistency: Please circle a numerical value (Type) based on the Bristol Stool Chart below for each stool. Circle NA if you do not pass any stool on this date. Call your coordinator if you have three or more loose stools (Type 5-7 on Bristol Stool Chart) in any 24-hour period.

Subject Initials: Please initial after completing each study day's documentation.

Comments: Use comments section to record additional information. Record any symptoms you may experience after you began taking the study medication. Include how you rank the symptom severity (mild, moderate, or severe), any medications you may have taken for this symptom and when the symptom went away (if it resolved).

Mild: Did not keep me from going about normal activities.
Moderate: Kept me from doing some of my normal activities.
Severe: Really noticed the symptom, it kept me from doing activities that I really needed or wanted to do.

Bristol Stool Chart



Study: RECOVER

Subject Number:_____ **Study Site:** _____

Please call your research coordinator _____ at phone number _____ if you have three or more loose stools (Type 5-7) within 24 hours.

Date	Time of stool	Stool consistency	Comments (if applicable)
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	
_____ MM/DD/YYYY	_____ AM PM	1 2 3 4 5 6 7 NA	

Subject Signature: _____ Date: _____

17.3 Subject Instructions for Stool Collection

Research Study: RECOVER

Instructions for Stool Collection

Thank you for donating this important sample.

1. **Please wash hands.**

PLEASE DO NOT pass the stool directly into the toilet.
PLEASE DO NOT pass the stool directly into the collection vial.
PLEASE DO NOT urinate on the stool sample.

2. **Place the tub and frame into the toilet to collect the stool sample.**

- **Remove the lid from the plastic collection tub or 'margarine tub", and put the tub through the round hole in the frame.**
- **Lift the toilet seat, place the tub, and frame along the back edge of the toilet, so the long straight side is facing the center of the toilet.**
- **Sit on the toilet as usual and have the bowel movement into the collection tub.**

3. **Put on gloves and use the wooden tongue depressor to scoop out about four tablespoons of stool and put this into the sterile plastic container.**

- Close the top of the sterile container tightly to avoid leakage.
- Record date and time of collection on the outside of container. Container will be pre-labeled with subject number.
- Discard used 'margarine tub' with the lid on, in the regular trash.

4. **Place the container in the biohazard bag, seal bag tightly. Then place into paper bag for transport.**

5. **Store the sample at refrigerator temperature until transported to the lab. Please transport/ship specimen as soon as possible and within 24 hours of collection. PLEASE DO NOT freeze specimen.**

Infectious Disease Research Lab H4-663 CSC Madison, WI 53792
PH: 608/263-6962 600 Highland Avenue, MC5158 FAX: 608/263-8713

17.4 Medication Diary

Study: RECOVER

Subject Initials: ___ ___ ___ **Subject Number:** ___ ___ ___ ___ **Study Site:** _____

Study Drug: 125mg vancomycin or placebo capsule

Dose Instructions: Take one capsule by mouth once every 6 hours for ___ days, then every 12 hours for 7 days, then 1 capsule per day for 7 days, and then 1 capsule every 3 days for 14 days. There may be extra capsules in your bottle. Only take amount directed by your study team. Do not open or crush capsules. If you miss a dose please record it was not taken and resume next dose if further doses are scheduled. Store capsules at room temperature and leave in original container. If you vomit and are able to see the capsule please take another capsule as soon as possible and make a note in the diary.

Call your study team with any questions, if your other antibiotic treatment changes, or if you have three or more loose stools (5-7 on Bristol Stool Scale) in a 24 hour period.

Please bring any unused study drug or empty container and this form to your next clinic visit.

How to complete this form:
Date: Please fill in the date as MM/DD/YYYY

Study capsule taken: Please circle yes if one study capsule was taken, no if study capsule was not taken. Please document reason in notes section if scheduled study capsule was not taken.

Comments: Please use the comments section to record additional information.

Signature: Please sign and date after completing this page or taking your last capsule

There may be blank lines on this form when you are finished taking your study capsules.

Day	Date	One study capsule taken?	Comments (if applicable)
One Capsule Every 4 Hours for ___ Days			
Day 0	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
Day 1	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
Day 2	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
Day —	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
Day —	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	

Subject Signature: _____ **Date:** _____

Please call [Coordinator], Study Coordinator, at [XXX-XXX-XXXX] if you have any questions.

Page ___ of ___

Study: RECOVER

Subject Initials: ___ ___ ___ Subject Number: ___ ___ ___ ___ Study Site: _____

Study Drug: 125mg vancomycin or placebo capsule

Dose Instructions: Take one capsule by mouth once every 6 hours for ___ days, then every 12 hours for 7 days, then 1 capsule per day for 7 days, and then 1 capsule every 3 days for 14 days. There may be extra capsules in your bottle. Only take amount directed by your study team. Do not open or crush capsules. If you miss a dose please record it was not taken and resume next dose if further doses are scheduled. Store capsules at room temperature and leave in original container. If you vomit and are able to see the capsule please take another capsule as soon as possible and make a note in the diary.

Call your study team with any questions, if your other antibiotic treatment changes, or if you have three or more loose stools (5-7 on Bristol Stool Scale) in a 24 hour period.

Please bring any unused study drug or empty container and this form to your next clinic visit.

How to complete this form:

Date: Please fill in the date as MM/DD/YYYY

Study capsule taken: Please circle yes if one study capsule was taken, no if study capsule was not taken. Please document reason in notes section if scheduled study capsule was not taken.

Comments: Please use the comments section to record additional information.

Signature: Please sign and date after completing this page or taking your last capsule

There may be blank lines on this form when you are finished taking your study capsules.

Day	Date	One study capsule taken?	Comments (if applicable)
Day ___	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
Day ___	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
2 Capsules per Day for 7 Days			
Day ___	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
Day ___	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
Day ___	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
Day ___	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
Day ___	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	

Subject Signature: _____ **Date:** _____

Please call [Coordinator], Study Coordinator, at [XXX-XXX-XXXX] if you have any questions.

Page ___ of ___

Study: RECOVER

Subject Initials: ___ ___ ___ Subject Number: ___ ___ ___ ___ Study Site: _____

Study Drug: 125mg vancomycin or placebo capsule

Dose Instructions: Take one capsule by mouth once every 6 hours for ___ days, then every 12 hours for 7 days, then 1 time per day for 7 days, and then 1 time per day every 3 days for 14 days. There may be extra pills in your bottle. Only take amount directed by your study team. Do not open or crush capsules. If you miss a dose please record it was not taken and resume next dose if further doses are scheduled. Store capsules at room temperature and leave in original container. If you vomit and are able to see the capsule please take another capsule as soon as possible and make a note in the diary.

Call your study team with any questions, if your other antibiotic treatment changes, or if you have three or more loose stools (5-7 on Bristol Stool Scale) in a 24 hour period.

Please bring any unused study drug or empty container and this form to your next clinic visit.

How to complete this form:

Date: Please fill in the date as MM/DD/YYYY

Study capsule taken: Please circle yes if one study capsule was taken, no if study capsule was not taken. Please document reason in notes section if scheduled study pill was not taken.

Comments: Please use the comments section to record additional information.

Signature: Please sign and date after completing this page or taking your last capsule

There may be blank lines on this form when you are finished taking your study capsules.

Day	Date	One study capsule taken?	Comments (if applicable)
2 Capsules per Day for 7 Days			
Day ___	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
Day ___	_____ MM/DD/YYYY	Yes No	
	_____ MM/DD/YYYY	Yes No	
1 Capsule per Day for 7 Days			
Day ___	_____ MM/DD/YYYY	Yes No	
Day ___	_____ MM/DD/YYYY	Yes No	
Day ___	_____ MM/DD/YYYY	Yes No	
Day ___	_____ MM/DD/YYYY	Yes No	
Day ___	_____ MM/DD/YYYY	Yes No	
Day ___	_____ MM/DD/YYYY	Yes No	
Day ___	_____ MM/DD/YYYY	Yes No	
1 Capsule per Day Every 3 Days for 2 Weeks			
Day ___	_____ MM/DD/YYYY	Yes No	
Day ___	_____ MM/DD/YYYY	Yes No	
Day ___	_____ MM/DD/YYYY	Yes No	
Day ___	_____ MM/DD/YYYY	Yes No	
Day ___	_____ MM/DD/YYYY	Yes No	

Subject Signature: _____ Date: _____

Please call [Coordinator], Study Coordinator, at [XXX-XXX-XXXX] if you have any questions.

Page ___ of ___

17.5 Data Safety Monitoring Board Charter and Membership

MARCH Data and Safety Monitoring Board Charter
Version: v3; April 17, 2018
Adopted: April 20, 2018

Midwest Area Research Consortium for Health (MARCH)
Data and Safety Monitoring Board (DSMB) Charter

1.0 INTRODUCTION

The purpose of this Charter is to define the roles and responsibilities of the *MARCH Data Safety Monitoring Board (DSMB)*, delineate qualifications of the membership, describe the purpose and timing of meetings, and provide the procedures for ensuring confidentiality and proper communication. Changes to this Charter may not be made without approval by the *MARCH DSMB*. Protocol specific information should be included in an addendum or memorandum of understanding that must be reviewed by the *DSMB*.

The purpose of the *MARCH DSMB* is to provide researchers access to and utilization of an independent data and safety monitoring board for investigator-initiated human research studies for which such a Board has not already been designated. The primary actions of this *DSMB* are directed toward safety. It is anticipated that in most cases interim/stopping rules for efficacy will not be the primary focus of this *DSMB*.

The *DSMB* will be responsible for safeguarding the interests of trial participants during the trial, and for monitoring the overall conduct of the clinical trial. The *DSMB* will periodically review study results, evaluate the study interventions and procedures for adverse effects, determine whether the basic trial assumptions remain valid, and judge whether the overall integrity and conduct of the trial remain acceptable. Moreover, the *DSMB* may formulate recommendations relating to the selection/recruitment/retention of participants and their management, and compliance to protocol-specified regimens and the procedures for data management and quality control. The *DSMB* will make its recommendations to Principal Investigator and his/her designated *study leadership* and Sponsor which then has the prerogative to accept, reject, or modify those recommendations. Such recommendations by the *DSMB* will also be copied to MARCH central administration. It is the responsibility of the *Principal Investigator* to forward the communication of the *DSMB* recommended actions and all pertinent regulatory information to the FDA, appropriate Institutional Review Board(s), and the Sponsor when applicable.

Using the *DSMB* will require the use of a *DSMB* approved data management tool for the protocol under review. This may include systems such as the clinical research management software OnCore, or the research electronic data capture application REDCap. Administrative support for functioning of the *DSMB* will be provided through the resources of MARCH and the *Principal Investigator(s)*. Where possible, specific resources of the Sponsor will be employed. Remuneration for services of, and related to, the operations of the *DSMB* will be sought from the *Principal Investigator(s)* and/or Sponsor.

2.0 ORGANIZATION

2.1 Composition of the *DSMB*

The *DSMB* consists of a core group of individuals, representing each MARCH institution, who have expertise in laboratory science, clinical medicine and/or surgery, statistics, epidemiology, and/or research ethics. All members have experience and expertise in clinical trials. In the event that the Chair is unable to attend a meeting or has a conflict of interest, a core member of the *DSMB* will be designated as Vice-Chair. In addition, ad hoc members may be added to complement the expertise of the core *DSMB* members and provide the flexibility to serve the diverse research landscape of MARCH trials. An ad hoc member's role on the *DSMB* will be limited to a specific trial or trials in which their expertise is needed.

Input by the *Principal Investigator(s)*, other members of the protocol team, and/or Sponsor may also be required, and thereby be involved in the composition of the *Board* as *invited guests*. *Invited guests* may also include expert consultants whose presence is requested by the *DSMB*, protocol team or Sponsor at a specific meeting, as well as other individuals who would attend *DSMB* meetings as part of a mentoring or educational opportunity. *Invited guests* must be approved by the DSMB core members prior to attending DSMB meetings.

The *DSMB* will also include an *executive secretary* who will support the administrative responsibilities of the Board and will serve as a non-voting member.

2.2 Selection of *DSMB* Members

The *DSMB* Chair and its members are identified and selected by personnel from the MARCH Advisory Committee with input from the core members of the *DSMB*. The *Principal Investigator* and/or Sponsor may help to identify ad hoc members for the *DSMB* when a specific area of expertise is not already represented on the *Board*.

In the event that a member is unable to continue participation on the *DSMB*, a replacement will be found. Any member may be removed by a simple majority, due to poor attendance, verified conflict of interest, and/or inadequate demonstration of effort and/or professionalism.

3.0 RESPONSIBILITIES AND FUNCTIONS

The *DSMB* is responsible to the *Principal Investigator(s)* for oversight of the study data and safety considerations, and efficacy considerations as appropriate. The *DSMB* will be involved with the following:

- Review the study protocol and consent form(s), as well as any protocol amendments, and make recommendations to the *Principal Investigator(s)* and Sponsor with regard to changes. Protocol amendments will be reviewed to determine if any changes affect the role of the *DSMB*. Though recommendations may be made to the *Principal Investigator(s)* by the *DSMB*, their approval is not needed prior to the submission of a protocol amendment to the IRB(s) of record.

- Review overall data collection methods and safety monitoring procedures, and make recommendations for additions or adjustments.

- Define the safety and related parameters to be monitored, frequency of committee monitoring reviews, methods for review, and establish criteria for making recommendations to the *Principal Investigator(s)*.

The *DSMB* reviews data generated by the study and study safety events on a periodic basis and recommends any of the following actions to the study *Principal Investigator(s)*:

- Discontinue the study (with provisions for orderly discontinuation in accordance with good clinical practice).

- Discontinue treatment arm(s) of the study (with provision for orderly discontinuation).

- Suspend the study protocol or specific treatment arm(s) of the study. Subject visits should occur as scheduled to monitor subject safety, but new subjects are not to be enrolled until *DSMB* concerns have been appropriately addressed.

- Modify the study protocol. Modifications may include, but are not limited to, changes in inclusion/exclusion criteria, frequency of visits or safety monitoring, alterations in study procedures, adjustments in sample size, changes in duration of observation and follow up.

- Continue the study according to the protocol and any related amendments.

4.0 RESPONSIBILITIES OF THE Principal Investigator(s)

The *Principal Investigator(s)*, in collaboration with the trial Sponsor, is responsible to the *DSMB* for the following:

- Making resources available to the *DSMB* as are necessary to carry out its designated functions including use of clinical research management software, such as OnCore or the research electronic data capture application REDCap, to act as the data management tool for the protocol under review.
- Providing resources to create and maintain an independent Statistical Data Analysis Center to receive data from a Data Management Center. The Statistical Data Analysis Center prepares reports for the *DSMB*.
- Communicating all pertinent regulatory information to the Federal Food and Drug Administration (FDA) and other appropriate regulatory bodies.
- Adverse events (AEs) and serious adverse events (SAEs) will be reported to the *DSMB* within the same time frame as required for reporting to the IRB.
- Submitting IRB-approved changes of protocol that affect the safety or primary outcome(s) to the *DSMB*.
- Responding to the *DSMB's* recommended actions within ten working days from the date on the *DSMB* letter, when applicable. If the recommended action is discontinuation or suspension due to a safety issue, the *Principal Investigator(s)* must respond within two working days of receiving the *DSMB* letter.

5.0 RESPONSIBILITIES OF THE DATA MANAGEMENT CENTER

The Data Management Center, as designated by the Principal Investigator(s), will perform the following data coordinating responsibilities:

- Collect case report forms (CRF).
- Ensure the completeness and accuracy of all data collected to the extent required by the *DSMB* and the Sponsor; this includes CRF data, central-laboratory data and data from central endpoint review committees.
- Provide data sets to the Statistical Data Analysis Center utilizing all CRF data necessary for creating *DSMB* reports.

- Use of a *DSMB* approved data management tool, such as OnCore or REDCap.

6.0 RESPONSIBILITIES OF THE STATISTICAL DATA ANALYSIS CENTER

The Statistical Data Analysis Center (SDAC) is responsible for the overall data analysis preparation for review by the *DSMB*.

The SDAC will prepare Open and Closed reports, as applicable, for review by the *DSMB* based on data generated by the Sponsor and the Data Management Center. It also prepares reports based on supporting documentation for events and may receive copies of case report forms directly from study investigators for these events. Open SDAC Reports will contain aggregate data, while Closed SDAC Reports will display data by assigned intervention/treatment group(s).

These reports will contain data on recruitment and baseline characteristics, baseline comparisons of risk factors, compliance, safety and adverse effects, and interim analyses of efficacy (as applicable). *The SDAC will repeat these analyses until the completion of the trial.*

The SDAC Reports should provide information that is accurate, with follow-up that is complete to within two months of the date of each *DSMB* meeting. Where possible and as appropriate, SDAC Reports will adhere to CONSORT 2010 Statement Guidelines[1].

7.0 CONDUCT OF *DSMB* MEETINGS

7.1 Scheduled Meetings

The *DSMB* convenes prior to initiation of the study. Thereafter, the frequency of scheduled meetings depends on the overall risk profile of the study as well as study subject enrollment and safety event occurrences. Additional *ad hoc meetings* may be held at the discretion of the *DSMB*.

A scheduled face-to-face meeting of the core members of the *DSMB* should be convened at a single location once a year to discuss *DSMB* policies, processes, and procedures.

7.2 Quorum

A quorum consists of at least 5 *DSMB* members present at the scheduled or unscheduled meeting or participating by phone. The 5-member quorum should include a chair, a biostatistician and any member(s), including ad hoc, in which their expertise is required

for a specific protocol. If an ad hoc member is not available to attend the scheduled meeting, they may provide comments/concerns to the *DSMB* chair prior to the meeting.

7.3 Voting

The *DSMB* members vote on all recommendations intended to be submitted to the *Principal Investigator(s)*. To vote, a *DSMB* member must either be present at convened scheduled meetings or participate through conference calls. Each *DSMB* member has *one* vote, including the chair. SDAC staff do not have a vote. A member may abstain from voting, but their presence at the meeting still counts towards quorum. Members may also recuse themselves due to a conflict of interest, which will lower the quorum.

A simple majority of the quorum passes a proposal, motion, or recommendation that will be submitted to the *Principal Investigator(s)*. Ad hoc members are voting members unless otherwise specified. Expert consultants are deemed *invited guests* and therefore will not have the ability to vote. On a tie vote the proposal, motion, or recommendation is lost. Additional discussion and a new proposal, motion, or recommendation may be made.

The *DSMB* chair may propose an email vote for items not involving a continuation/ suspension/termination recommendation sent to the *Principal Investigator(s)*.

7.4 Meeting Format

Prior to implementation of the study, an initial meeting will be held between the *DSMB* and *Principal Investigator(s)* to review the protocol. Particular issues addressed will include but are not limited to study design, procedures, inclusion/exclusion criteria, and safety, efficacy and/or futility stopping rules.

Meetings held during the course of the study will consist of open and closed sessions. During the initial open portion of a meeting, the Sponsor and/or *Principal Investigator(s)* will make a brief presentation(s) and be available for questions from the *DSMB*.

The <u>open session</u> will only discuss aggregate data for primary concerns of safety and efficacy, as appropriate. Topics presented may include but not be limited to recruitment/enrollment/retention, adverse events, compliance, data accuracy, study design, stopping rules, and administrative issues.

The <u>closed session</u> will be restricted to the *DSMB,* including ad hoc members, and staff from the Statistical Data Analysis Center. *Invited guests* may be asked by the *DSMB* Chair to attend the closed session (e.g. expert consultant or NIH program official). The closed session will discuss accumulating data by assigned intervention/treatment group(s).

An executive session comprised of DSMB members, including ad hoc, and the executive secretary may be convened to discuss study issues independently.

In the event of relevant information revealed during the course of the study, ad hoc meeting(s) may be held as frequently as necessary. Any such meeting(s) will be called by the *DSMB* Chair.

7.5 Procedures for Sharing Recommendations with the Principal Investigator(s)

Any duly voted and passed *DSMB* recommendation(s) to the *Principal Investigator(s)* will be transmitted in writing to the *Principal Investigator(s)* within seven working days from the time of the meeting at which the recommendation was passed. *The Principal Investigator(s)* has the responsibility to communicate recommendations to the Sponsor and to the appropriate Institutional Review Board(s).

If a response is needed, the *Principal Investigator(s)* also has the responsibility of responding to the *DSMB's* recommended actions within ten working days from the date on the *DSMB* letter. If the recommended action is discontinuation or suspension due to a safety issue, the *Principal Investigator(s)* must respond within two working days of receiving the *DSMB* letter.

7.6 Meeting Minutes

Meeting minutes are prepared by the *executive secretary* based on the discussions during each *DSMB* meeting and may contain some data by treatment groups. The minutes are distributed in a timely manner after each meeting to the *DSMB* members, and reviewed and approved at the subsequent meeting or by email vote. They will not be forwarded to the *Principal Investigator(s)* or the Sponsor for review after each meeting.

At the end of the study and after treatment is unblinded, a copy of the minutes from the *DSMB* meetings may be forwarded to the *Principal Investigator(s)* upon request. It is the responsibility of the *Principal Investigator(s)* to share the meeting minutes with the Sponsor, if necessary.

7.7 Confidentiality

All members and *invited guests* of the *DSMB* will treat all data, notes, reports, discussions, and minutes as confidential. Each member will sign a Confidentiality Non-Disclosure Agreement that will accompany documentation that entails his/her responsibilities as a *DSMB* member. *Invited guests* will also be required to sign a Confidentiality Non-Disclosure Agreement.

7.8 Conflict of Interest Guidelines

Members of the *DSMB* are to be independent from the Sponsor, IRB/EC, regulatory agencies, *Principal Investigator(s)*, co-principal or sub-principal investigator, site investigator, site sub-investigator, Steering Committee membership, advisory board membership, clinical care of the study subjects, or any other capacity related to trial operations. Each member agrees not to serve as a paid consultant to the Sponsor during these same periods unless exempted by the *DSMB* chair. A member serving as an NIH consultant (e.g. study sections) or receiving NIH funds on unrelated project(s) would not be considered a conflict and would be exempted.

Other activities that may be viewed as constituting conflicts of interest are to be reported annually to the *DSMB* chair for review. These include; the participation of a member in educational activities supported by the Sponsor, the participation of members in other research projects supported by the Sponsor, and occasional scientific consulting to the Sponsor on issues not related to the product in the trial and for which there is no financial payment or other compensation.

These guidelines also apply to the member's spouse and dependents and to the Statistical Data Analysis Center staff. SDAC staff will hold and update annually conflict-of-interest statements from each *DSMB* member and SDAC staff.

DSMB members and SDAC staff who have a conflict of interest may answer *DSMB* member questions, but must remove themselves during sensitive discussions and will recuse themselves from voting, when applicable, on the protocol in which they have a conflict.

7.9 Indemnification

Indemnification for participation on the *DSMB* is the individual responsibility of each member of the *DSM*B.

REFERENCES

[1] Schultz KF, Altman DG, and Moher E for the CONSORT Group. Annals of Internal Medicine, 2010.152(11):726-733.

MARCH Data and Safety Monitoring Board Charter
Version: v3; April 17, 2018
Adopted: April 20, 2018

Version History			
Version	Date	Revisions	Adopted
v1	April 13, 2015	New	May 12, 2015
v2	June 2, 2016	Revised quorum definition, added vice-chair language, clarifying guests/ad hoc, voting clarifications, removal of appendices & added language to clarify when changes to charter are allowed	June 2, 2016
v3	April 17, 2018	Combined and split sections for better flow and consistency. Clarified 'summary notes' and responsibilities of the SDAC. Generalized review of outcome data – 'interim analyses of efficacy (as applicable)'. Minor grammatical updates.	April 20, 2018

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ADDENDUM – PROTOCOL SPECIFIC INFORMATION

MARCH DSMB Composition			
Chair:	Eric White, MD, MS	Professor of Internal Medicine, Division of Pulmonary & Critical Care Medicine	University of MI
Core Members:	Cathie Spino, Sc.D.	Research Professor of Biostatistics	University of MI
	Peter Schwartz, MD, PhD	Associate Professor of Medicine, Division of General Internal Medicine	Indiana University
	Sylk Sotto, EdD	Assistant Professor of Medicine & Vice Chair for Faculty Affairs and Diversity	Indiana University
	Rickey Carter, PhD	Professor of Biostatistics	Mayo Clinic
	Prasad Iyer, MD	Professor of Medicine, Division of Gastroenterology & Hepatology	Mayo Clinic
	Ryan Spellecy, PhD	Associate Professor of Bioethics and Medical Humanities & Associate Professor of Psychiatry and Behavioral Health	Medical College of WI
	John Connett, PhD	Professor, Division of Biostatistics	University of MN
	Mark Paller, MD, MS	Professor of Medicine, Division of Renal Diseases and Hypertension	University of MN
	Michael Para, MD	Professor of Internal Medicine, Division of Infectious Diseases	Ohio State University
	Peter Rahko, MD, FACP, FACC	Professor of Medicine, Division of Cardiovascular Medicine	University of WI-Madison
Ad Hoc Member(s):			
Additional Non-Voting Members:	Scott Hetzel, MS (SDAC Staff)	Researcher, Biostatistics and Medical Informatics (Creation of SDAC Reports)	University of WI-Madison
	Amy Siedschlag, MS (Executive Secretary)	Manager, MARCH DSMB (Administrative Support)	University of WI-Madison

Protocol Information		
Principal Investigator(s):		
Protocol Title:		
MARCH sites involved: (*Lead site)	☐ Indiana University ☐ Medical College of WI ☐ University of Minnesota ☐ University of WI-Madison	☐ Mayo Clinic ☐ University of Michigan ☐ The Ohio State University