APPENDIX C. PROTOCOL

A Randomized Controlled Trial of Encapsulated Fecal Microbiota for Vancomycin Resistant Enterococcus Decolonization

Full title: Phase II randomized, double blind, placebo-controlled, parallel group trial of encapsulated fecal microbiota transplantation for vancomycin resistant enterococcus decolonization

Sponsor: Microbiome Health Research Institute, d/b/a OpenBiome

OpenBiome Sponsor Representative Principal Clinician:

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IND Number: 17312

ClinicalTrials.gov Identifier: NCT03063437

Privileged and Confidential

Not for distribution

September 9, 2019

STATEMENT OF COMPLIANCE

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

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

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

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

PRINCIPAL CLINICIAN SIGNATURE PAGE

Protocol Title: Phase II randomized, double blind, placebo-controlled, parallel group trial of encapsulated fecal microbiota transplantation for vancomycin resistant enterococcus decolonization

Version Date: September 9, 2019

I acknowledge that I have read and understand the protocol named above and agree to conduct the study according to the protocol named above. I also agree and will adhere to terms and procedures in accordance with United States Food and Drug Administration (FDA)/International Council for Harmonisation (ICH) guidelines, including all federal and locally applicable regulations and laws.

I assure that the study drug supplied by OpenBiome will be used only as described in the protocol named above.

_____ _____

Signature Date

APPENDIX C. TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CDAD	*Clostridium difficile* Associated Diarrhea
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CFR	Code of Federal Regulations
CRE	Carbapenem-Resistant Enterobacteriaceae
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
ESBL	Extended-Spectrum Beta-Lactamases
FMT	Fecal Microbiota Transplantation
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
N	Number (typically refers to participants)
PHI	Protected Health Information
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
VRE	Vancomycin Resistant Enterococcus

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PROTOCOL SUMMARY

Title:	A Randomized Controlled Trial of Encapsulated Fecal Microbiota for Vancomycin Resistant Enterococcus Decolonization
Phase:	II
Population:	Vancomycin resistant enterococcus (VRE) identified by stool culture in the past 14 days among adults.
Sample size	46 (1:1 randomization) - 23 in the treatment group and 23 in the placebo group).
Number of sites:	Multi-center study at 2 tertiary academic medical centers (Indiana University and University of Wisconsin).
Study duration:	Approximately 1 year.
Description of Agent:	Encapsulated fecal microbiota preparation (formulation FMP-402). Please refer to OpenBiome BBMF # 17300, Section I, H. Sourced from human-derived microbes. Please refer to OpenBiome BBMF # 15543, Section F.

Study Objectives:

To investigate the efficacy and safety of FMP-402 to decolonize VRE.

Primary Objectives:

- To determine the VRE decolonization rate of FMP-402 versus placebo.
- To evaluate the safety profile for FMP-402 versus placebo.

Secondary Objectives:

- To determine the VRE infection rate of FMP-402 versus placebo.
- To evaluate the decolonization rate of antibiotic resistant bacteria (ARB) for FMP-402 versus placebo.
- To determine the composite ARB infection rate for FMP-402 versus placebo.
- To evaluate the time to VRE colonization and infection.
- To evaluate the VRE decolonization rate for FMP-402 versus placebo among immunocompromised patients.
- To evaluate VRE decolonization rate for FMP-402 versus placebo among those 65 years and older.

Exploratory Objectives:

- To evaluate the microbiome disruption index (MDI) by 16s rRNA sequencing): MDI-community and MDI-species (day 3, day 10, week 4).
- To evaluate the trends in VRE type/strain-level engraftment using whole genome sequencing among those colonized.

Study Endpoints/Outcome Measures:

Primary Efficacy Outcome Measure:

- Proportion of participants with VRE decolonization at day 10 (±3 days) after randomization.
    - VRE decolonization is defined by absence of VRE on stool culture using standard clinical laboratory techniques.

Secondary Efficacy Outcome Measures:

- Proportion of participants with VRE infection at day 3 (±2), day 10 (± 3), week 4 (±5 days) after randomization.
    - VRE infection will be defined as an associated bacteremia, urinary tract infection, or wound-related infection.
- Proportion of participants with other antibiotic resistant bacteria (ARB) colonization at day 10 (± 3) after randomization. ARB testing will be conducted with Acuitas™ MDRO test (OpGen) or similar PCR assay platform.
    - ARB will be defined as: a) carbapenem-resistant enterobacteriaceae (CRE) by PCR; b) extended-spectrum beta-lactamase (ESBL) producing organism by PCR; c) *C. difficile* by PCR.
- Proportion of participants with antibiotic resistant bacteria (ARB) colonization at day 10 (± 3) after randomization. ARB testing will be conducted with Acuitas™ MDRO test (OpGen) or similar PCR assay platform.
    - ARB will be defined as: a) carbapenem-resisant enterobacteriaceae (CRE) by PCR; b) extended-spectrum beta-lactamase (ESBL) producing organism by PCR; c) *C. difficile* by PCR; d) VRE

- Proportion of participants with composite ARB infection at day 3 (±2), day 10 (± 3), week 4 (±5 days) after randomization and time (in days) when ARB infection occurs.
    - ARB infection will be defined as VRE, CRE, ESBL or *C. difficile*-associated clinical infection in keeping with standard clinical practices.
- Time (in days) from randomization until the study day when VRE colonization and infection occurs.
- Proportion of participants with VRE decolonization among immunocompromised patients at day 10 (± 3) after randomization.
- Proportion of participants with VRE decolonization among 65 years or older at day 10 (± 3) after randomization.

Primary Safety Outcome Measures:

- Proportion of participants with an adverse event (AE) through day 10 (±3 days) after randomization.
- Proportion of participants with a severe adverse event (SAE) through day 10 (±3 days) after randomization.
- Proportion of participants with newly acquired transmissible infectious diseases which are considered adverse events of special interest (AESI) through day 10 (±3 days) after randomization.

Secondary Safety Outcome Measures:

- Proportion of participants with an AE through week 4 (±5 days) after randomization.
- Proportion of participants with an SAE through week 4 (±5 days) after randomization.

- Proportion of participants with newly acquired transmissible infectious diseases which are considered adverse events of special interest (AESI) through week 4 (±5 days) after randomization.

- Proportion of participants with a SAE at month 6 (±14 days) phone safety assessment after randomization.

Exploratory Outcome Measures:

- Proportion of participants with microbial engraftment assessed by MDI (MDI-community and MDI-species) measured by 16s ribosomal RNA at day 3, day 10, week 4 after randomization.

- To evaluate the trends in VRE type/strain-level engraftment using whole genome sequencing among those colonized.

- **Description of Study Design:**

This multi-center, randomized, double blind, placebo-controlled, parallel group trial will compare the efficacy and safety of oral FMP-402 to decolonize VRE. Participants will be 18 years of age or older with VRE on stool assessment within the last 14 days before randomization. Participants must meet inclusion criteria and have no exclusion criteria prior to randomization.

Participants will then be randomized in a 1:1 ratio to 1 of 2 treatment groups:

- FMP-402: Encapsulated fecal microbiota sourced from human-derived microbes generated by healthy, screened donors. Dosing regimen will be a single 30 capsule dose. Patients will be nil per os (NPO) for a minimum of 2 hours prior to administration, and 1 hour post-administration.

- Placebo: Oral placebo will be identical to the investigational product but will not contain product microbes. Placebo capsules will consist of glycerol and saline. Dosing regimen will be a single 30 capsules dose. Patients will be NPO for a minimum of 2 hours prior to administration, and 1 hour post-administration.

Participants will be assessed for:

a) Clinical and safety assessment will occur at day 3 (±2) after randomization. This will use a structured case report form (CRF) at an in-hospital assessment or telephone assessment if the patient is discharged.

b) Clinical and safety assessment will occur at day 10 (±3 days) after randomization. This will use a structured CRF at an in-hospital assessment or clinic assessment if the patient is discharged.

c) Clinical and safety assessment will occur at week 4 (±5 days) after randomization. This will use a structured CRF at an in-hospital assessment or a telephone assessment if the patient is discharged.

d) Safety follow-up will occur at month 6 (±14 days) (structured telephone questionnaire) after randomization. All attempts will be made to complete safety follow-up for participants who received the study product, but discontinued participation in other study procedures, for the duration of the planned follow-up period.

e) Unscheduled visit: At the time of a VRE infection (for participants who experience an infection) or a serious AE, an unscheduled visit will be attempted (optional). If this is not possible, clinical data will be collected from the patient's most responsible physician, allied healthcare team and medical records.

Stool samples will be collected at:

a) Screening

b) Enrollment

c) Day 3 (±2) after randomization

d) Day 10 (±3) after randomization

e) Week 4 (±5) after randomization

f) Unscheduled visit: At the time of VRE infection (for participants who experience an infection) or a serious AE. Stool samples will attempt to be collected (optional). Additionally, VRE isolates from the site of associated VRE infection (blood, urine, wound) will attempt to be collected (optional) during a suspected VRE infection if no residual sample that was obtained clinically is available.

Information regarding the co-administration of any oral or parenteral antimicrobial agents or probiotics, any acid blockers (H2 blockers and PPIs) or any antiperistaltics will be recorded through follow-up.

Estimated Time to Complete Enrollment:

11 months

Participant Inclusion Criteria

Participants eligible to participate in this study must meet the following inclusion criteria:

1. Adults 18 years or older at the time of enrollment.
2. Able to provide signed and dated informed consent.
3. Identified as VRE-positive by a stool culture within last 14 days.
4. 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.
5. 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.

*Includes, but is not limited to, barrier with additional spermicidal foam or jelly and vasectomy.

Participant Exclusion Criteria

Participants will not be able to participate if they meet any of the following exclusion criteria:

1. Female patient who are pregnant, lactating or planning on becoming pregnant during study.

Female patients of childbearing potential will undergo a pregnancy test, and be excluded from the study if positive.

2. Inability (e.g. dysphagia) to or unwilling to swallow capsules.
3. Active antibiotic-resistant bacteria (ARB) or gastrointestinal infection at time of enrollment.
4. Patient received antibiotics or probiotics in the last 48 hours. Patients will be eligible to enroll if antibiotic therapy is discontinued for at minimum 48 hours prior to randomization. Does not include antibiotics used for prophylaxis or topical antibiotics.
5. Requires continued antibiotic use or anticipates antibiotic use in the upcoming 4 weeks. Does not include antibiotics used for prophylaxis or topical antibiotics.
6. Unwilling to withhold probiotics for a minimum of 48 hours prior to providing a screening stool sample.
7. Known or suspected toxic megacolon and/or known small bowel ileus.
8. Major gastrointestinal surgery (e.g. significant bowel resection) within 3 months before enrollment. This does not include appendectomy or cholecystectomy.
9. History of total colectomy or bariatric surgery.
10. Admitted to or expected to an intensive care unit for medical reasons (not just boarding). Patients residing in a nursing home, long-term care facility or rehabilitation center may be enrolled.
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. Unable or unwilling to comply with protocol requirements.
13. Expected life expectancy < 6 months
14. Previous FMT or microbiome-based products at any time excluding this study.
15. Patients with a history of severe anaphylactic or anaphylactoid food allergy.

16. Solid organ transplant recipients ≤ 90 days post-transplant or on active treatment for rejection.
17. Neutropenia (≤500 neutrophils/mL) or other severe immunosuppression. Anti-TNF will be permitted. Patients on monoclonal antibodies to B and T cells. glucocorticoids, antimetabolites (azathioprine, 6-mercaptopurine, methotrexate), calcineurin inhibitors (tacrolimus, cyclosporine) and mycophenolate mofetil may be enrolled only after consultation with the medical monitor.
18. If at risk for CMV/EBV associated disease (at investigator's discretion, e.g. immunocompromised), negative IgG testing for cytomegalovirus (CMV) or Epstein Barr Virus (EBV).
19. A condition that would jeopardize the safety or rights of the subject, would make it unlikely for the subject to complete the study, or would confound the results of the study.

C.1. KEY ROLES

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C. 2. BACKGROUND AND SCIENTIFIC RATIONALE

C.2.1 Background

VRE colonization as a public health threat

Antibiotic-resistant organisms are a major public health threat with over 2 million Americans infected each year.[1] Over half of these infections are transmitted in healthcare settings, where the widespread use of antibiotics selects for resistance and creates a stable pool of vectors, enabling the transmission of resistant organisms. Among resistant organisms, Vancomycin resistant enterococcus (VRE) is designated as a "serious threat" by the CDC and a major public health challenge both clinically and economically.[1] There are an estimated 20,000 VRE cases and 1,300 associated deaths annually, which account for approximately 30% of all healthcare-acquired infections.[1] Beyond the poor clinical outcomes among patients with VRE, there is a significant economic burden rooted in hospitalization costs driven by an increased length

of stay and the use of more costly antimicrobial agents.[2,3] Evidence suggests that a VRE infection increases a patient's length of stay by 17 days, increases healthcare costs by $81,208 per patient and carries a median hospital mortality of 75% versus 29% in an otherwise matched control group.[3]

The gastrointestinal tract is the reservoir for VRE, where it persists for a mean duration of 26 weeks.[4] VRE colonization is a significant and growing problem in healthcare settings. A National Healthcare Safety Network survey (2006-2007) identified 33% of enterococci in US healthcare settings that were vancomycin resistant.[5] A recent study suggested 8.8% (95% CI: 7.1-10.6%) of patients admitted to the ICU were VRE colonized and an additional 8.8% (95% CI: 6.9-11.0%) will become colonized during their admission.[6] Transplant patients are at higher risk of VRE colonization with up to 13.3% of liver transplant patients colonized.[7,8]

VRE colonization is a prerequisite for VRE infection. A 2013 meta-analysis reports 10.2% of VRE colonized patients will develop VRE infections compared to less than 2% of non-colonized patients.[6,9] Additionally, VRE colonization is associated with higher mortality rates (24.6% versus 17.1%), a 25% increase in total admission days, and a 22% increase in hospital costs compared to matched controls.[10] In addition to direct patient outcomes, patients colonized with VRE serve as a vector for VRE transmission, posing a risk to other vulnerable hospitalized patients and healthcare workers.[11]

Current approaches to preventing transmission of VRE are both expensive and ineffective. Current standard of care does not include any intervention or technology to eliminate VRE in colonized patients. While contact precautions and isolation procedures are used to reduce transmission, lack of routine screening in many settings means that colonized patients may not be identified. Furthermore, such protocols can be costly to implement and challenging to ensure compliance, resulting in limited success. While reducing carriage of antibiotic-resistant bacteria (ARB) by prevention measures alone is possible, the CDC has reported that "nearly all studies reporting successful [multi-drug resistant organism] MDRO control employed a median of 7 to 8 different interventions concurrently or sequentially."[12] Indeed, at high levels of colonization, prevention methods such as adhering to hand-washing protocols and antibiotic stewardship have been shown to have very limited, if any, impact on infection rates.[11] For these reasons, there is a significant need for an inexpensive, safe intervention that can rapidly eliminate colonization and thereby interrupt the chain of transmission.

C.2.2 Scientific Rationale

Scientific principles support FMT for elimination of VRE colonization

FMT, has been shown to be a highly effective and safe intervention for treatment of recurrent *C. difficile* infection (CDI). A recent systematic review and pooled analysis reports FMT was 83% effective in the treatment of recurrent CDI, with few reported adverse events.[13] Although not fully elucidated, the hypothesized mechanism of FMT for CDI is that normal colonic microbiota outcompete and competitively exclude *C. difficile*.[14]

In a recent commentary, Halpin and McDonald from the CDC highlighted the ecological principles and preliminary research suggesting that FMT may also be effective for eliminating enteric colonization with VRE.[15] Similar to CDI, VRE colonization is known to be induced by microbial dysbiosis.[16] Furthermore, vancomycin-resistance is known to carry a fitness defect for the organism carrying this gene, making it a prime target for a microbial intervention such as FMT, a procedure which infuses microbiota that will competitively exclude VRE. In vitro competition assays with enterococci have demonstrated a 4% fitness defect of VanA relative to sensitive enterococci.[17] Similarly, expression of VanB-type resistance results in reduced fitness in vitro, as well as reduced colonization ability and dissemination in gnotobiotic mice.[18] More recently, genetic analyses identified two distinct evolutionary clades within *E. faecium*: Clade A, which includes subclade A1, commonly associated with hospital-acquired infections, and Clade B, associated with healthy human microbiota.[19] When strains from clade A and clade B were co- introduced in a murine gastrointestinal tract, Clade B strains were better able to persist.[20] Introduction of commensal microbiota may also help to eliminate VRE infection through direct effects such as nutrient depletion, or immune-mediated factors such as stimulation of TLR signaling and restoration of intestinal REGIIIγ expression.[14,21]

Importantly, the role of FMT in eradicating VRE is also supported by FMT administration in murine models. Transfer of healthy colonic microbiota from antibiotic-naive mice to animals that have been treated with antibiotics and colonized with VRE reversed dysbiosis and eliminated VRE infection within 14 days.[22]

Clinical data supports FMT for elimination of ARB

A number of case reports suggest that FMT may be able to decolonize patients colonized with ARB, including VRE. In a case report of FMT performed on a patient suffering from CDI along with high levels of VRE colonization and a history of VRE infection, Stripling and colleagues reported a reduction in *Enterococcus* along with dramatic clinical improvement, including no further VRE infections.[23] Three case reports and a case series also reported decolonization of other ARB following FMT, including Carbapenem-resistant *enterobacteriaceae* (CRE), Extended-spectrum beta-lactamases (ESBL) and Methicillin-resistant *Staphylococcus aureus* (MRSA) enteritis.[24–27] A recent study of

20 patients with recurrent CDI treated with FMT by colonoscopy demonstrated a reduction in the overall abundance and diversity of resistance genes (resistome) in the gut microbiota post-FMT.[28] Finally, among 8 recurrent CDI patients, VRE colonization density decreased by 2-6 logs 8 weeks after receiving a microbial therapeutic.[29]

Evidence from a multi-center retrospective analysis

Our group performed a multicenter retrospective analysis was performed using stool samples from recurrent CDI patients treated with FMT (n=31) or autologous FMT as a control from a previous trial (n=18). VRE was assessed using a PCR-based assay targeting VanA (Acuitas® MDRO Gene Test). Colonization was defined as positive result at any dilution. VRE decolonization was defined as absence of VRE colonization post-FMT among a patient colonized with VRE pre-FMT. Among this cohort, 16 patients were VRE colonized; 9/9 (100%) in the FMT group tested VRE-negative compared to 3/7 (43%) in the control group (p=0.02, Fisher's Exact Test). Two of these patients were treated with a single dose of 30 FMT capsules, while the rest received FMT via traditional modalities (Appendix 16.1).

C.2.3 Potential Risks and Benefits

There are risks associated with conducting this study; however, OpenBiome and its clinical affiliates possess a unique set of resources and expertise to mitigate these risks. To clarify, the risks described below are generalized to FMT therapies that are delivered endoscopically. There is no data available that is specific to FMT therapies that are delivered orally, with is the case for FMP-402. It is expected that the risks of oral FMT therapy will be significantly reduced because many of the risks of FMT therapy delivered via endoscope are due to the procedure itself, not the drug that is delivered.

C.2.3.1 Potential Risks

In the first randomized controlled trial on FMT, mild diarrhea (94%), abdominal cramping (31%) and belching (19%) were observed on the day of colonoscopic infusion; however, these symptoms resolved within 3 hours. Of note, in follow-up three patients who were treated with donor feces (19%) had constipation. No other adverse events related to the study treatment were reported.[36] Recently, Osman et al presented effectiveness and safety data from a 2,050 patient cohort among OpenBiome recipients. The data suggests that among the 42 suspected adverse events, 0 were definitely related to FMT material based on NIH criteria after a comprehensive investigation (Appendix 16.2).

There is a paucity of data on long-term follow-up related to FMT. Brandt et al conducted a retrospective multi-center study (n=77) with a follow up varying

between 3 to 68 months and reported 7 deaths. However, none related to FMT.[37] A recent systematic review on the safety of FMT, suggests there are risk including: infectious (fever, bacteremia), autoimmune disease (peripheral neuropathy, Sjogren's syndrome, idiopathic thrombocytopenic purpura and rheumatoid arthritis, inflammatory bowel disease flare among patients with ulcerative colitis) and other studies have suggested a link to metabolic syndrome.[38, 39] However, comprehensive screening of donors should decrease any potential future risk. Donors are highly selected with only 2.8% of candidate donors qualifying to donate after screening both infectious disease and microbiome-mediated disease (Appendix 16.3).

C.2.3.2 Potential Benefits

Studies have suggested that FMT may be able to decolonize patients colonized with VRE, and in turn, the prevention of VRE associated infection. As described previously, our group has demonstrated in a retrospective study that allogenic FMT is able to decolonize VRE significantly more than autologous FMT (Appendix 16.1). Additionally, a number of case reports have reported decolonization of ARB following FMT, including carbapenem-resistant Enterobacteraciae (CRE), extended spectrum beta-lactamase (ESBL)-producing *Escherichia coli* and methicillin-resistant *Staphylococcus aureus* (MRSA) enteritis.[23-29]

C.3. OBJECTIVES

C.3.1 Study Objectives

To investigate the efficacy and safety of FMP-402 to decolonize VRE.

Primary Objectives:

- To determine the VRE decolonization rate of FMP-402 versus placebo.
- To evaluate the safety profile for FMP-402 versus placebo.

Secondary Objectives:

- To determine the VRE infection rate of FMP-402 versus placebo.
- To evaluate the decolonization rate of antibiotic resistant bacteria (ARB) for FMP-402 versus placebo.
- To determine the composite ARB infection rate for FMP-402 versus placebo.
- To evaluate the time to VRE colonization and infection.
- To evaluate the VRE decolonization rate for FMP-402 versus placebo among immunocompromised patients.
- To evaluate VRE decolonization rate for FMP-402 versus placebo among those 65 years and older.

Exploratory Objectives:

- To evaluate the microbiome disruption index (MDI) by 16s rRNA sequencing): MDI-community and MDI-species (day 3, day 10, week 4).
- To evaluate the trends in VRE type/strain-level engraftment using whole genome sequencing among those colonized.

C.3.2 Study Outcome Measures

C. 3.2.1 Efficacy Outcome Measures

Primary Efficacy Outcome Measure:

- Proportion of participants with VRE decolonization at day 10 (±3 days) after randomization.
    - VRE decolonization is defined by absence of VRE on stool culture using standard clincal laboratory techniques.

Secondary Efficacy Outcome Measures:

- Proportion of participants with VRE infection at day 3 (±2), day 10 (± 3), week 4 (±5 days) after randomization.
    - VRE infection will be defined as an associated bacteremia, urinary tract infection, or wound-related infection.
- Proportion of participants with other antibiotic resistant bacteria (ARB) colonization at day 10 (± 3) after randomization. ARB testing will be conducted with Acuitas™ MDRO test (OpGen) or similar PCR assay platform.
    - ARB will be defined as: a) carbapenem-resisant enterobacteriaceae (CRE) by PCR; b) extended-spectrum beta-lactamase (ESBL) producing organism by PCR; c) *C. difficile* by PCR.
- Proportion of participants with antibiotic resistant bacteria (ARB) colonization at day 10 (± 3) after randomization. ARB testing will be conducted with AcuitasTM MDRO test (OpGen) or similar PCR assay platform.
    - ARB will be defined as: a) carbapenem-resisant enterobacteriaceae (CRE) by PCR; b) extended-spectrum beta-lactamase (ESBL) producing organism by PCR; c) C. difficile by PCR; d) VRE

- Proportion of participants with composite ARB infection at day 3 (±2), day 10 (± 3), week 4 (±5 days) after randomization and time (in days) when ARB infection occurs.
    - ARB infection will be defined as VRE, CRE, ESBL or *C. difficile*-associated clinical infection in keeping with standard clinical practices.
- Time (in days) from randomization until the study day when VRE colonization and infection occurs.
- Proportion of participants with VRE decolonization among immunocompromised patients at day 10 (± 3) after randomization.
- Proportion of participants with VRE decolonization among 65 years or older at day 10 (± 3) after randomization.

C.3.2.2 Safety Outcome Measures

Primary Safety Outcome Measures:

- Proportion of participants with an AE through day 10 (±3 days) after randomization.
- Proportion of participants with a SAE through day 10 (±3 days) after randomization.
- Proportion of participants with newly acquired transmissible infectious diseases which are considered adverse events of special interest (AESI) through day 10 (±3 days) after randomization.

Secondary Safety Outcome Measures:

- Proportion of participants with an AE through week 4 (±5 days) after randomization.
- Proportion of participants with an SAE through week 4 (±5 days) after randomization.
- Proportion of participants with newly acquired transmissible infectious diseases which are considered adverse events of special interest (AESI) through week 4 (±5 days) after randomization.
- Proportion of participants with a SAE at month 6 (±14 days) phone safety assessment after randomization.

C.3.2.3 Exploratory Outcome Measures

- Proportion of participants with microbial engraftment assessed by MDI (MDI-community and MDI-species) measured by 16s ribosomal RNA at day 3, day 10, week 4 after randomization.
- To evaluate the trends in VRE type/strain-level engraftment using whole genome sequencing among those colonized.

C.4. STUDY DESIGN

This multi-center, randomized, double blind, placebo-controlled, parallel group trial will compare the efficacy and safety of oral FMP-402 to decolonize VRE. It will be performed in collaboration with Indiana University and the University of Wisconsin. A study schematic can be found in the Appendix 17.1.

Study Population: Participants will be 18 years of age or older with VRE on stool assessment within the last 14 days before randomization. Participants must meet inclusion criteria (Section 5.1) and have no exclusion criteria (Section 4.2) prior to randomization.

Subjects will then be randomized in a 1:1 ratio with random permuted blocks (size of 2 or 4) at each site to either the intervention or control group.

Intervention: FMP-402 - Encapsulated fecal microbiota sourced from human-derived microbes generated by healthy, screened donors. Dosing regimen will be a single 30 capsule dose. Patients will be nil per os (NPO) for a minimum of 2 hours prior to administration, and 1 hour post-administration. Patients may consume water during capsule administration.

Dosing Rationale
The dosing rationale is driven by the successful VRE decolonization of 2 patients with recurrent CDI following a single dose of 30 OpenBiome FMT capsules and the success of this dose among recurrent CDI patients presented by our group (Appendix 16.1).

Capsule Tolerability
Clinically, there have been no reported concerns regarding the number of administered capsules among >300 recurrent CDI patients treated, even among elderly and medically complex patients. Specifically, elderly patients who commonly manage polypharmacy find tolerability of 30 capsules easier than younger patients without experience administering pills. Overall, mean time of 30 capsule administration is approximately 20 minutes (range 10-30 minute) (Allegretti, unpublished data). To mitigate safety risks with capsules, in an eligible

patient thought to be a capsule candidate, a single inert 'test capsule' is administered at screening under direct observation, and any evidence of dysphagia is a contraindication for capsule administration.

Control: Placebo - Oral placebo will be identical to the investigational product but will not contain product microbes. Placebo capsules will consist of glycerol and saline. Dosing regimen will be a single 30 capsules dose. Patients will be NPO for a minimum of 2 hours prior to administration, and 1 hour post-administration.

C.5. STUDY ENROLLMENT AND WITHDRAWAL

C.5.1 Participant Inclusion Criteria

Participants eligible to participate in this study must meet the following inclusion criteria:

1. Adults 18 years or older at the time of enrollment.

2. Able to provide signed and dated informed consent.

3. Identified as VRE-positive by a stool culture within last 14 days.

4. 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.

5. 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.

C.5.2 Participant Exclusion Criteria

Participants will not be able to participate if they meet any of the following exclusion criteria:

1. Female patient who are pregnant, lactating or planning on becoming pregnant during study. Female patients of childbearing potential will undergo a pregnancy test, and be excluded from the study if positive.
2. Inability (e.g. dysphagia) to or unwilling to swallow capsules.

3. Active antibiotic-resistant bacteria (ARB) or gastrointestinal infection at time of enrollment.
4. Patient received antibiotics in the last 48 hours. Patients will be eligible to enroll if antibiotic therapy is discontinued for at minimum 48 hours prior to randomization. Does not include antibiotics used for prophylaxis or topical antibiotics.
5. Requires continued antibiotic use or anticipates antibiotic use in the upcoming 4 weeks. Does not include antibiotics used for prophylaxis or topical antibiotics.
6. Unwilling to withhold probiotics for a minimum of 48 hours prior to providing a screening stool sample.
7. Known or suspected toxic megacolon and/or known small bowel ileus.
8. Major gastrointestinal surgery (e.g. significant bowel resection) within 3 months before enrollment. This does not include appendectomy or cholecystectomy.
9. History of total colectomy or bariatric surgery.
10. Admitted to or expected to an intensive care unit for medical reasons (not just boarding). Patients residing in a nursing home, long-term care facility or rehabilitation center may be enrolled.
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. Unable or unwilling to comply with protocol requirements.
13. Expected life expectancy < 6 months
14. Previous FMT or microbiome-based products at any time excluding this study.
15. Patients with a history of severe anaphylactic or anaphylactoid food allergy.
16. Solid organ transplant recipients ≤ 90 days post-transplant or on active treatment for rejection.
17. Neutropenia (≤500 neutrophils/mL) or other severe immunosuppression. Anti-TNF will be permitted. Patients on monoclonal antibodies to B and T cells. glucocorticoids, antimetabolites (azathioprine, 6-mercaptopurine, methotrexate), calcineurin inhibitors (tacrolimus, cyclosporine) and mycophenolate mofetil may be enrolled only after consultation with the medical monitor.
18. If at risk for CMV/EBV associated disease (e.g immunocompromised), negative IgG testing for cytomegalovirus (CMV) or Epstein Barr Virus (EBV).
19. A condition that would jeopardize the safety or rights of the subject, would make it unlikely for the participant to complete the study, or would confound the results of the study.

C.5.3 Treatment Assignment Procedures

C.5.3.1 Randomization Procedures

Participants who fulfill the criteria for randomization, will be randomized on a 1:1 basis with a with random permuted blocks (size of 2 or 4) to receive FMP-402 or placebo. Participant's randomization will be carried out by a bioinformatician based at OpenBiome using random number generation software to create a randomization schedule.

C.5.3.2 Masking Procedures

This is a double blinded placebo controlled trial where both the participant and treating physicians will be blinded. FMP-402 or placebo will be dispensed by OpenBiome thereby maintaining blinding of study clinician. Packaging will be identical and consist of the same saline and glycerol buffer used in FMT processing without the addition of microbiota.

Under normal circumstances, the blind should not be broken. The blind should be broken only if specific emergency treatment would be dictated by providing the treatment the participant was receiving. In such cases, the site PI must contact the Medical Monitor to request that the blind be broken. For participants who require unblinding, this information will be captured in the case report form (CRF).

The randomization schedule will be maintained by OpenBiome. Study participants or legal guardians will remain blinded and not be provided any information until all participants have completed the trial.

C.5.3.3 Reasons for Withdrawal

A participant may withdraw from the study at any time for any reason, without any consequence. A participant may be withdrawn from the study by the site PI for the following reasons:

Adverse event that may make it no longer in the best interest of the subject to continue participation in the study

Participant choice (withdrawal of consent)

Protocol violation/non-compliance

Pregnancy

Lost to follow up

Other (must be noted)

C.5.3.4 Handling Withdrawals

The primary reason for withdrawal from the study will be recorded on the Study Status CRF page. Participants will be encouraged to complete the Early Termination Visit. The Early Termination Visit procedures are listed. Although participants are free to withdraw at any time, participants will be encouraged to remain in the study for follow-up safety evaluation. Every attempt should be made to follow all AEs and SAEs ongoing at the time of early withdrawal to resolution or until stabilized. If possible, a final stool sample will be collected at the Early Termination Visit. Intention-to-treat analysis will be utilized according to best practices in clinical trials. Attempts will be made to complete safety follow-up for all subjects who have received the study product, including those who have discontinued participation in other study procedures, for the duration of the planned follow-up period.

Participants who are withdrawn from the study after randomization but before intervention or placebo will be replaced. Possible reasons for participant withdrawal after randomization include but are not limited to:

- Participants who are started on a new course of antibiotics after randomization and before intervention/placebo
- Unrelated participant death

C.5.3.5 Termination of Study

In the unlikely event that significant safety concerns arise, the PIs can terminate or halt the study pending review by the DSMB. In addition, this study may be halted early based on the DSMB charter or FDA recommendations.

C.6. STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

C.6.1 Study Product Description

FMP-402 is encapsulated fecal microbiota sourced from human-derived microbes. The human source generating the fecal microbes has been extensively screened for infectious pathogens and microbiome mediated diseases using a standardized process (found in OpenBiome's BBMF # 15543, Section F). Additionally, the capsule delivery vehicle enables *targeted deposition* of the investigational active pharmaceutical ingredient into the colon.

C.6.2 Formulation

C.6.2.1 Encapsulated fecal microbiota preparation (formulation FMP-402)

This formulation is encapsulated fecal microbiota sourced from human-derived microbes generated by healthy, screened donors, as described in OpenBiome's

[redacted]

BBMF # 17300

[redacted].

C.6.2.2 Placebo

Placebo capsules will be identical in appearance to FMP-402 capsules but will not have human feces, [redacted]

processed as described in OpenBiome's BBMF # 17300 [redacted].

C.6.3. Product Storage and Stability

Produced material will be stored at -80°C and each unit will have a date of production printed on it for tracking purposes. Studies have been conducted to ensure long-term bacterial viability following the freezing process based on studies conducted by Hamilton et. al and Youngster et. al.[40,41] Local site storage at -20°C will be permitted for up to 6 months.

FMP-402 is currently undergoing stability testing, therefore expiration dates will not be provided with each unit. Instead, storage requirements will be provided via correspondence from the manufacturing company, Finch Therapeutics. Results from ongoing stability testing will be provided by Finch Therapeutics to partner sites, through OpenBiome, on an anticipated monthly basis. If units are determined to be unstable, Finch Therapeutics will communicate with OpenBiome to destroy the relevant units.

C.6.4 Dosage, Preparation and Administration of Study Intervention/Investigational Product

Participants will receive a single dose of 30 FMP-402 or placebo capsules. The dosing rationale is driven by the successful VRE decolonization for 2 patients with recurrent CDI and co-colonization of VRE following a single dose of 30 OpenBiome FMT capsules. Participants will undergo capsule administration by the following process:

- Document Review: Confirmation/review of exclusion criteria/contraindications as previously described.
- Safety Capsules: Direct observed capsule test, where participants will ingest one inert, size 00 'safety' capsule under direct supervision of the study physician/nurse.
- Dietary instructions: Patients should maintain a clear liquid diet the day of administration and should fast (NPO) for a minimum of 2 hours prior to administration
- Capsule administration:
    a. Patient should ingest 30 capsules (FMP-402 or placebo) under the direct observation of a physician/nurse. Patients may have water during capsule administration.
    b. Patient should ingest capsules after extraction from freezer, and no longer than 60 minutes after removal.
    c. Patients should remain fasting (NPO) for 1 hour following ingestion but may then return to a full diet.

C.6.5 Accountability Procedures for the Study Intervention/Investigational Product

The site principal investigator (PI) (or designee) will maintain an accurate record of the receipt of the investigational materials as shipped, including the date received. One copy of this receipt will be returned to OpenBiome when the contents of the investigational materials shipment have been verified. In addition, the unblinded laboratory technician based at OpenBiome will maintain a log of all clinical trial materials (FMP-402 and placebo) dispensed. This clinical trial material accountability record will be available for inspection at any time.

C.6.6 Modification of Study Intervention/Investigational Product for a Participant

If the participant is unable to complete the full dose of FMP-402 or placebo, the following modification will take place. The dose will be recorded and the remainder of capsules will be offered to participant the same day at the discretion of the treating physician. Intention-to-treat analysis will be utilized according to best practices in clinical trials.

C.6.7 Assessment of Participant Compliance with Study Intervention/Investigational Product

FMP-402 or placebo capsules will be consumed under direct supervision of study staff.

C.6.8 Concomitant Medications/Treatments

Given the participants with VRE colonization and who are most at risk for VRE infection are patients with multiple comorbidities, all medications will be accepted in this study, at the discretion of the treating physician. This includes, but is not limited to:

1. Anti-hypertensive therapies
2. Heart failure medications
3. Diuretics
4. Laxatives
5. Topical medications
6. Anti-depressants
7. Statins
8. Diabetic medication
9. NSAID
10. Acid-blockers
11. Anticoagulants
12. Opioids
13. Iron supplementation
14. Anti-TNF will be permitted. Patients on monoclonal antibodies to B and T cells. glucocorticoids, antimetabolites (azathioprine, 6-mercaptopurine, methotrexate), calcineurin inhibitors (tacrolimus, cyclosporine) and mycophenolate mofetil may be enrolled only after consultation with the medical monitor.

Participants will be eligible to enroll 48 hours after their last dose of antibiotics; however, topical and prophylactic antibiotics will be permitted. Participants are also eligible to enroll 48 hours after their last dose of probiotics.

C.7. STUDY SCHEDULE

A schematic representation of the study schedule can be found in Appendix 17.2.

C.7.1 Screening (Visit 1)

Screening will take place with both passive and active systems. From a passive system perspective, VRE positive stool samples will be identified by each sites

laboratory and compiled lists of candidate participants distributed for study evaluation. Patients previously marked VRE positive in the medical records will also be approached for study evaluation. From an active system perspective, individuals at high-risk for VRE colonization including but not limited to those discharged from ICU to ward after a greater than 3 days stay, undergoing chronic dialysis, have an oncology or stable organ transplant history will be approached for consent to screen for VRE.[42] Awareness about the study will be raised by standard, approved recruitment techniques and discussions with key stakeholdes including clinical microbiology, infectious diseases and laboratory medicine teams. Past VRE positive patients in the health system may also be eligible to participate, provided that they fulfill eligibility criteria, and will be contacted by the research staff and invited to participate via an invitation letter/telephone follow-up call (UW) or with an invitation via telephone call (IU).

If patients are interested in participating in the study, and have been discharged from the hospital, stool samples can be submitted for screening for VRE colonization with a waiver of consent documentation. Patients being seen in any ambulatory setting in the health system are eligible if they are known to be VRE or at risk of having VRE.

If on probiotics at time of screening then patients will be advised to withhold probiotics for 48 hours prior to providing a sample.

C.7.2 Enrollment and Intervention Administration (Visit 2)

C.7.2.1 Enrollment

All VRE positive individuals will be equally eligible for enrollment into this study, provided they fulfill the eligibility criteria. A detailed consent process will be administered by study staff who are trained in consenting procedures. Potential participants who fulfill the eligibility criteria will undergo a detailed clinical assessment by study staff which will include demographics, medical history, dietary information and current medication. Data from this assessment may be from the participant/substitute decision maker, healthcare team and/or medical record.

- Data points at enrollment study visit:
    - General parameters:
        - Date of birth
        - Sex
        - Smoking status
        - Race
        - Ethnicity
    - Past medical history and allergies

        - A focused collection of past medical history (including common infections)
        - Charlson's Comorbidity Index
    - Current medication list
    - Antibiotic history
    - Dietary history
    - Social history
        - Country of birth, duration living in the U.S.
    - Travel history
    - Examination findings
        - Vital signs: temperature, height (measured or abstracted from medical records), weight (measured or abstracted from medical records), heart rate, blood pressure, waist circumference, respiration rate, oxygen saturation
        - Relevant review of systems
    - Overall assessment of current health
- Sample collection
    - Positive VRE stool sample collected within the previous 14 days to the Enrollment visit using a stool collection kit/hat or a rectal swab
- Formal aspects
    - Informed consent procedure
    - Verification of inclusion and exclusion criteria including administering 'test' capsule and documenting:
        - Safe to receive intervention (yes/no)
        - Able to swallow test capsule (yes/no)

- Participants that are at risk for EBV/CMV associated disease (at investigator's discretion, e.g. immunocompromised) will undergo EBV and CMV IgG testing, if double positive status (EBV+/CMV+) not already documented. If CMV/EBV testing cannot be conducted at the university hospital, non-university hospitals may be used to perform the testing. Any costs associated with CMV/EBV testing to determine eligibility for this study will be paid by study funds; the patient will not incur any charges. The research team will send results from outside laboratories via mail or secure fax from outside laboratories and will store the results in the patients' study chart, if applicable. If either is negative, the patient will be excluded. CMV/EBV testing may occur at the screening or enrollment visit.

C.7.2.2 Intervention Administration (Day 0)

After baseline clinical asssessment, stool sample has been collected and female participants of childbearing potential have been administered a urine pregnancy test and reported negative, the participant is eligible to undergo adminstration of the intervention (FMP-402 or placebo) in accordance with the randomization schedule. The intervention will be administered by the blinded study staff and the participant observed for 30 minutes following administration. In addition to the previously described baseline clinical assessment, pre-intervention vital signs (temperature, blood pressure, heart rate) and immediate post-intervention assessment will take place including any overt safety concerns and post-intervention vital signs if clinically indicated at the discretion of the study staff. Participants will be provided with information regarding monitoring for minor and severe adverse event related to the intervention administration. Participants will be encouraged to report any concerning symptoms to staff. Oral nutrition may commence 1 hour post-capsules administration.

C.7.3 Follow-Up (Visit 3, 4, 5, 6)

At day 3 and day 10 post-intervention, the study physician/nurse will perform a clinical assessment and administer a study questionnaire, which will specifically inquire about solicited and unsolicited symptoms of AEs. Access to the medical records may be utilized to capture salient changes in healthcare status. Participants will have a stool sample within each follow-up window.

At week 4 and month 6 study visits, participants will undergo a similarly structured study visit which includes a clinical assessment and AE focused questionnaire.

C.7.3.1 Visit 3 - Day 3 (±2 days)

Clinical and safety assessment will occur at day 3 (±2 days) after randomization. This will use a structured CRF at an in-hospital assessment or telephone assessment if the patient is discharged and unable to attend clinic. If this assessment is done over the phone, participants will be given instructions to mail in or drop off their stool sample, depending on their preference.

- Clinical and safety assessment by study nurse / physician, specifically evaluating adverse events related to the intervention.
- Data collection at visit:
    - Interim medical history with focus on infectious diseases
    - Concomitant medication

- Significant changes in diet
- Changes in stool consistency (Bristol Stool Scale) and frequency
- Clinical evaluation using standard, structured assessment
- Vital signs [if in-patient]: Temperature, heart rate, blood pressure, weight (will be obtained from medical record, if available, rather than collected specifically for research purposes), waist circumference, respiration rate, oxygen saturation
- General health status
- Adverse events (NIH criteria)

- Stool collection for 16S sequencing and ARB PCR

C.7.3.2 Visit 4 - Day 10 (±3 days)

Clinical and safety assessment will occur at day 10 (±3 days) after randomization. This will use a structured CRF at an in-hospital assessment or clinic assessment if the patient is discharged and unable to attend clinic.

- Clinical and safety assessment by study nurse / physician, specifically evaluating adverse events related to the intervention.
- Data collection at visit:
  - Interim medical history with focus on infectious diseases
  - Concomitant medication
  - Significant changes in diet
  - Changes in stool consistency (Bristol Stool Scale) and frequency
  - Clinical evaluation using standard, structured assessment
  - Vital signs [if in-patient]: Temperature, heart rate, blood pressure, weight (will be obtained from medical record, if available, rather than collected specifically for research purposes), waist circumference, respiration rate, oxygen saturation
  - General health status

- Adverse events (NIH criteria)

- Stool collection for 16S sequencing and ARB PCR

C.7.3.3 Visit 5 – Week 4 (±5 days)

Clinical and safety assessment will occur at week 4 (±5 days) after randomization. This will use a structured CRF at an in-hospital/clinic assessment or a telephone assessment if the patient is discharged and unable to attend clinic.

- Clinical and safety assessment by study nurse / physician, specifically evaluating adverse events related to the intervention.
- Data collection at visit:
    - Interim medical history with focus on infectious diseases
    - Concomitant medication
    - Significant changes in diet
    - Changes in stool consistency (Bristol Stool Scale) and frequency
    - Clinical evaluation using standard, structured assessment
    - Vital signs [if in-patient]: Temperature, heart rate, blood pressure, weight (will be obtained from medical record, if available, rather than collected specifically for research purposes), waist circumference, respiration rate, oxygen saturation
    - General health status
    - Adverse events (NIH criteria)
- Stool collection for 16S sequencing and ARB PCR

C.7.3.4 Visit 6 - Month 6 (±14 days)

Safety follow-up will occur at month 6 (±14 days) (structured telephone questionnaire) after randomization.

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

- Data collection at visit:
    - Interim medical history with focus on infectious diseases
    - Concomitant medication
    - Significant changes in diet
    - Changes in stool consistency (Bristol Stool Scale) and frequency
    - Clinical evaluation using standard, structured assessment
    - General health status
    - Adverse events (NIH criteria)

C.7.4 Early Termination Visit

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

- Clinical and safety assessment by study nurse / physician, specifically evaluating adverse events related to the intervention.
- Data collection at visit:
    - Interim medical history with focus on infectious diseases
    - Concomitant medication
    - Significant changes in diet
    - Changes in stool consistency (Bristol Stool Scale) and frequency
    - Clinical evaluation using standard, structured assessment
    - Vital signs [if in-patient]: Temperature, heart rate, blood pressure, weight (will be obtained from medical record, if available, rather than collected specifically for research purposes), waist circumference, respiration rate, oxygen saturation
    - General health status
    - Adverse events (NIH criteria)
- Stool collection for 16S sequencing and ARB PCR

Participants will be asked if study staff may follow participants passively using their medical records if clinical follow-up and/or stool collection is not viable.

All attempts will be made to complete safety follow-up for participants who received the study product, but discontinued participation in other study procedures, for the duration of the planned follow-up period.

C.7.5 Unscheduled Visit

At the time of VRE infection (for participants who experience an infection) or serious AE. Study staff will attempt to collect a stool sample (optional). Additionally, VRE isolates from the site of associated VRE infection (blood, urine, wound) will attempt to be collected (optional) for participants suspected to have a VRE infection.

- Study staff will complete an infection CRF for each ARB infection episode. 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 regime
    - 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

- For a serious AE (section 8.5), the details of reporting are outlined in Section 8.7

C.7.6 Stool Collection

Stool samples will be collected (or rectal swabs in keeping with VRE standard of care). If the visit is conducted over the telephone, participants will be given instructions on how to mail in or drop off their stool sample, depending on their preference:

a) Screening (only if status of VRE colonization is not already known)

b) Enrollment – if needed (VRE positive screened sample 14 days prior to Enrollment visit is acceptable).

c) Day 3 (±2) after randomization

d) Day 10 (±3) after randomization

e) Week 4 (±5) after randomization

f) At the time of VRE infection (for subjects who experience an infection) or serious AE. Stool samples will attempt to be collected (optional). Additionally, VRE isolates from the site of associated VRE infection (blood, urine, wound) will attempt to be collected (optional) for participants suspected to have a VRE infection.

C.8. ASSESSMENT OF SAFETY

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

C.8.1 Definition of an Adverse Event (AE)

Adverse events (AEs) will be recorded at each regular scheduled study visit in the study patient record (source document) as well as on a specific AE case report form (CRF).

An AE is any untoward medical occurrence in a study patient or clinical investigation participant administered a pharmaceutical product. An AE does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product, e.g.:

- any new clinical diagnosis

- any symptom that requires medical clarification or leads to in-patient admission (surgery or accident)
- any suspected adverse drug reaction (ADR)
- any symptom that appears on the study patient's medical records
- any event related in time with the application of the study medication and affecting the health of the study patient (including laboratory value changes)

If there is any doubt as to whether a clinical observation is an AE, the event should be reported. AEs must be graded for severity and relationship to study product. Adverse events of special interest (AESI) will be defined as newly acquired transmissible infectious diseases (e.g. newly acquired bacteremia).

C.8.2 NIH Grading of Severity of the Event

AEs will be assessed by the clinician using the NIH Common Terminology Criteria for Adverse Events (CTCAE) defined grading system (Appendix 17.3). Briefly, the criteria for estimating adverse event severity grade:

- **Grade 1, Mild:** Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2, Moderate:** Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
- **Grade 3, Severe:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- **Grade 4, Life threatening:** Places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.
- **Grade 5, Death**

C.8.3 Relatedness

All adverse events, regardless of relatedness should be reported. All adverse events should be evaluated for relatedness when reporting and documenting on the CRF.

The following guidelines of relatedness are used modified from the NIH guidelines:

☐ **Related:** The adverse event is related to the FMT material – i.e. an event that follows a reasonable temporal sequence from administration of the FMT material, follows a known or expected response pattern to the FMT material, that is

confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the patient's clinical state.

☐ **Not Related:** The adverse event is not related to the FMT material. - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

C.8.4 Solicited Adverse Events after FMT

In addition to open-ended questions on adverse events meeting the above definitions, specific potential adverse events will be inquired about during the follow up period (following intervention through to 6 months after randomization):

Symptom that is clinically more severe than participant's baseline	**Severity**				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Fever*	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	>39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)	>40.0 degrees C (>104.0 degrees F) for <=24 hrs	>40.0 degrees C (>104.0 degrees F) for >24 hrs	Death
Diarrhea	Increase of <4 stools per day over baseline pre-FMT; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN	Life-threatening consequences; urgent	Death

			or hospitalization indicated	intervention indicated	
Abdominal Pain	Mild pain	Moderate pain; limiting instrumental activities of daily life	Severe pain; limiting self care activities of daily life	n/a	n/a
Bloating	No change in bowel function or oral intake	Systemic, decreased oral intake; change in bowel function	n/a	n/a	n/a
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated; limiting instrumental activities of daily life	Symptoms interfering with self-care activities of daily life; obstipation with manual evacuation indicated	Life-threatening consequences (e.g. obstruction, toxic megacolon); urgent intervention indicated	Death

* Participants will be given a digital thermometer at the time of enrollment.

C.8.5 Serious Adverse Events

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the site PI or lead PI, it results in any of the following outcomes:

- Death
- Life-threatening adverse event*
- Inpatient hospitalization or prolongation of existing hospitalization
- A congenital anomaly/birth defect
- Persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life function
- Important medical events that, may not result in death, be life-threatening, or require hospitalization may be considered when, based

upon appropriate medical judgement, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

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

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

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

C.8.6 Unsolicited Adverse Events

On enrollment in the study, the study participants will be instructed to contact the site PI if an AE occurs. These unsolicited, unrelated non-serious adverse events occurring from the time of FMT until 6 months following FMT. Patients will be given a patient diary with date, , details and action taken to help with data collection. This diary be taken to the site PI for evaluation at each follow-up visit and patients instructed to seek immediate medical attention if indicated.

C.8.7 Reporting of Adverse Events

Study participants will be instructed to contact the study nurse or physician if any serious or unexpected adverse event occurs. Study staff will enquire about AEs at each study visit. Reported AE's will be recorded in detail in an AE CRF.

AE information to be collected in the AE CRF:

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

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

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

Any SAE (including death, irrespective of the cause) occurring during the study will be immediately reviewed by the site PI, i.e. within 24 hours and referred to the study medical monitor and lead PI.

If determined to be a SUSAR (suspected unexpected serious adverse reaction – SUSAR; Appendix 17.3 and 17.4) by the site PI, study medical monitor and lead PI, the event will be reviewed by the DSMB. Regulatory filing to the FDA or local IRB as per standard practices will occur.

In case of a SAE (non-SUSAR), the site PI will report the event to the study medical monitor and lead PI for review and compilation. The DSMB will review all SAE every 6 months or *ad hoc* depending on the clinical case at the discretion of the site PI, study medical monitor and lead PI. A specific SAE CRF will be provided similar to Appendix 17.3. The report must contain a detailed description of the symptoms observed and the concomitant treatment administered. Furthermore, the report must comment on a possible causative relationship between the AE and the trial medication. Each SAE must be followed until it is resolved or can be explained satisfactorily.

For non-serious adverse reactions (definitely related, possibly related, not related) the site PI will complete a report and submit it to the medical monitor and lead PI. All non-serious adverse reactions will be reviewed by the DSMB every 6 months or *ad hoc* depending on the clinical case at the discretion of the site PI, study medical monitor and lead PI.

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

- In the case of an intolerable SAE, the study patient must, at the decision of the site PI, be withdrawn from further treatment/placebo, and symptomatic treatment must be administered. The participant may opt to voluntarily providing sample for duration of study.
- The measures taken must be recorded on the CRF.
- In accordance with local legislation, the site PI will submit copies of the final SAE-report to the Regulatory Authorities concerned, if necessary.

C.8.8 Follow-up of Participants after Adverse Events

AEs will be followed until resolution or stability even if this extends beyond the study-reporting period. Resolution of an AE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

Follow-up procedures, evaluations, and outcomes will be recorded on the participant's case report forms.

C.8.9. Halting Rules

C.8.9.1 Study Halting Rules

Enrollment and administration of study intervention will be suspended pending a safety review by the DSMB to determine whether the study will be terminated or re-initiated in the following situations:

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

CBER will be notified of any study halt that occurs as a result of any of the above halting criteria.

C.8.9.2 Individual's Halting Rules

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

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

All attempts will be made to complete safety follow-up for participants who received the study product, but discontinued participation in other study procedures, for the duration of the planned follow-up period.

C.8.10 Safety Oversight

C.8.10.1 Data and Safety Monitoring Board (DSMB)

Safety oversight will be under the direction of a DSMB. The DSMB is an independent group of experts who will advise the study PIs. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations to the continuation, modification, or termination of the trial. The DSMB will be composed of at least 3 voting members. The membership will include a chairperson who has prior DSMB experience. One member will be an experienced gastroenterologist and one member will be an experienced infectious disease specialist. All DSMB members will be separate and independent of study personnel participating in this trial and should not have scientific, financial or other conflict of interest related to the trial. Procedures for DSMB data reviews will be defined in the DSMB Charter that will include DSMB membership, responsibilities, and the scope and frequency of data reviews. The DSMB will have access to unblinded treatment assignments during the closed session of their meetings. The study should be reviewed by the DSMB at least bi-annually. The DSMB may conduct a safety interim analysis after 50% of patients have enrolled in the treatment arm.

C.9. CLINICAL MONITORING

C.9.1 Site Monitoring Plan

Site monitoring is conducted to ensure that the human participant protection, study and laboratory procedures, study intervention administration, and data collection processes are of high quality. The lead PI (or delegate) will conduct a site-monitoring visit(s) as detailed in a monitoring plan. The PIs will permit authorized representatives of CDC, regulatory agency and/or an auditing body to inspect facilities and records relevant to this study, if needed.

Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, eCRFs, informed consent forms, medical and laboratory reports, and protocol compliance. Study monitors will meet with site PIs to discuss any problems and actions to be taken and document visit findings and discussions.

C.10. STATISTICAL CONSIDERATIONS

This is a randomized double blind, placebo controlled clinical trial to determine the safety and efficacy of FMP-402 on the decolonization of VRE.

C.10.1 Sample Size

Sample size (n=46) was calculated based on a conservative estimate of 85% decolonization in FMT group, 40% in control group with power=0.9 and alpha=0.05 in keeping with preliminary data and a conservative 15% drop-out rate.

C.10.2 Final Analysis Plan

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

C.11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 GCP, Section 4.9, and regulatory and institutional requirements for the protection of confidentiality of participants. Forms for use as source documents will be derived from the electronic CRFs. Additional source data include records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, imaging, and participant files and records kept at the pharmacy, laboratories, and medico-technical departments involved in the clinical trial.

C.12. QUALITY CONTROL AND QUALITY ASSURANCE

The site PI and delegates based at each site are responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress and protocol compliance. The site PI will provide direct access to all trial-related sites, source data/documents, and reports for the

purpose of monitoring and auditing, and inspection by local and regulatory authorities. The site PI will ensure all study personnel are appropriately trained and applicable documentations are maintained on site.

The site PI or delegate will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

C.12.1 Database QC

QC procedures regarding data entry will be implemented. Regular data quality control checks will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification and resolution.

C.13. ETHICS/PROTECTION OF HUMAN PARTICIPANTS

C.13.1 Ethical Standard

The site PI will ensure that this study is conducted in full conformity with principles of the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR 46, 21 CFR 50 and 56, and ICH E6; 62 Federal Regulations 25691 (1997), if applicable.

C.13.2 Institutional Review Board

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

C.13.3 Informed Consent Process

The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki and will adhere to the ICH Harmonised Tripartite Guideline for Good Clinical Practice. Informed consent should be

implemented before any protocol-specified procedures or interventions are carried out. Informed consent will be obtained in accordance with 21 CFR 50.25 and 45 CFR 46. Information should be presented both orally and in written form.

An site PIs or designee will describe the protocol to potential participants face-to-face. The Participant Information and Consent Form may be read to the participants, but, in any event, the site PIs shall give the participants ample opportunity to inquire about details of the study and ask any questions before the signing and dating the consent form.

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

Neither the site PIs, nor the trial staff, should coerce or unduly influence a participant to participate or continue to participate in the trial. The extent of the confidentiality of the participants' records must be defined, and participants must be informed that applicable data protection legislation will be followed. Participants and/or substitute decision maker/proxy must be informed that the monitor(s), auditors(s), IRB and regulatory authority(ies) will be granted direct access to the participant's medical records for verification of clinical trial

procedures and/or data without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations, and that, by signing a written informed consent form, the participant is authorizing such access. Participants and/or substitute decision maker/proxy must be informed that records identifying the participant will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available and, if the results of the trial are published, the participant's identity will remain confidential.

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

C.13.4 Exclusion of Women, Minorities, and Children (Special Populations)

Children are excluded for safety reasons.

C.13.5 Participant Confidentiality

Participant confidentiality is held strictly in trust by the participating PIs, their staff, and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating participants.

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

The lead PI or delegate and the FDA may inspect all documents and records required to be maintained by the site PIs, including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

C.13.6 Study Discontinuation

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

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

C.13.7 Future Use of Stored Specimens

Any leftover stool specimens will be stored and may be used for future research, under a future protocol, to learn more about FMP-402. These specimens will be stored indefinitely after the study is completed. In the informed consent document, participants will be given an opportunity to choose whether or not their de-identified barcoded specimens are stored for future use. For participants who choose not to allow storage of their samples for future use, these samples will be destroyed at the end of the study.

There are no benefits to participants in the collection, storage and subsequent research use of specimens. Reports about future research done with participant's samples will NOT be kept in their health records, but participant's samples may be kept with the study records or in other secure areas. Participants can decide if they want their samples to be used for future research or have their samples destroyed at the end of the study. A participant's decision can be changed at any time before the end of the study by notifying the study doctors or nurses in writing. However, if a participant consents to future use and some of their stool has already been used for research purposes, the information from that research may still be used.
Samples may be shared with other investigators at other institutions with the consent of the lead PI. Each sample will be encoded (labeled) only with a barcode and a unique tracking number to protect participant's confidentiality.

Research using stored specimens may be conducted by other institutions. Any specimens and data provided to the receiving-institution will be coded. Unequivocally, neither individual personal identifiers nor the key linking coded data to individuals will be released to the receiving-institution. The use of any of these specimens for any future studies will only be performed after the lead PI has authorized the use of these specimens.

C.14. DATA HANDLING AND RECORD KEEPING

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

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant 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.

C.14.1 Data Management Responsibilities

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

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

C.14.2 Data Capture Methods

Clinical data (including AEs, concomitant medications, and solicited events data) and clinical laboratory data will be entered into a 21CFR11-compliant Internet Data Entry System, RedCap. 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.

C.14.3 Types of Data

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

C.14.4 Timing/Reports

Interim reports for the DSMB will be prepared when approximately 50% of treating participants complete enrollment and every 6 months. Interim statistical reports may be generated as deemed necessary and appropriate by the lead PI. Other safety summary reports may be generated for the DSMB. A final report will be prepared following the availability of all the clinical, safety and efficacy data.

C.14.5 Study Records Retention

Study files (except for future use consent forms) must be maintained for a minimum of two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in and ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the lead PI or designate, if applicable. It is the responsibility of the lead PI or designate to inform the site PIs when these documents no longer need to be retained. Consent forms for future use will be maintained as long as the sample exists.

C.14.6 Protocol Deviations

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

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, Section 5.1.1
- 5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

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

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

C.15. PROTOCOL REFERENCES

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C.16. PROTOCOL ABSTRACTS

C.16.1 Eysenbach et al. ID Week 2016

Abstract #59960
Title: Clearance of Vancomycin-Resistant Enterococcus Colonization with Fecal Microbiota Transplantation among Patients with Recurrent *Clostridium difficile* Infection

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Background: Vancomycin-resistant enterococcus (VRE) is a public health threat to hospitalized patients and gastrointestinal colonization with VRE is a major risk factor for active infection, including bacteremia. Fecal microbiota transplantation (FMT) is a well-tolerated and effective treatment for recurrent *C. difficile* (rCDI). Data from animal models and clinical case reports suggest that FMT may reverse dysbiosis and eliminate colonization with antibiotic-resistant organisms, including VRE; however, there is a paucity of clinical data. This study aims to determine whether FMT may decolonize VRE in rCDI patients treated with FMT.

Methods: A multicenter retrospective analysis was performed using stool samples from rCDI patients treated with FMT (n=31) or autologous FMT as a control (n=18). Material was accessed from 6 academic hospitals under existing research protocols. VRE was assessed using a PCR-based assay targeting VanA (Acuitas® MDRO Gene Test). Colonization was defined as positive result at any dilution. VRE decolonization was defined as absence of VRE colonization post-FMT among a patient colonized with VRE pre-FMT.

Results: Among the cohort, 9/31 (29%) of patients in the FMT group and 7/18 (39%) of patients in the control group were colonized with VRE at baseline. At the first time point measured post-FMT, 9/9 (100%) of colonized patients in the FMT group tested VRE-negative compared to 3/7 (43%) in the control group

(p=0.02, Fisher's Exact Test). On subgroup analysis, samples collected at ≤6 weeks, 5/5 (100%) patients in the FMT group and 3/7 (43%) controls were decolonized; for samples collected at >6 weeks, 4/4 (100%) in the FMT group and 6/7 (86%) in the control group were decolonized. These results from subgroup analyses were not statistically significant given the high rate of spontaneous VRE decolonization.

Conclusion: FMT may be able to eliminate gastrointestinal colonization with VRE. However, a well-powered RCT with short follow-up time points is necessary to prospectively examine colonization dynamics and clinical outcomes. These results from a heterogeneous retrospective cohort study suggest that FMT or related microbial therapies may be effective to prevent infection and transmission of VRE in high-risk settings.

C.16.2 Osman et al. ID Week 2016

Osman et al. ID Week 2016, "Safety and efficacy of fecal microbiota transplantation for recurrent Clostridium difficile infection"

Abstract #59497
Title: Safety and efficacy of fecal microbiota transplantation for recurrent *Clostridium difficile* infection from an international public stool bank: Results from a 2,050 patient multi-center cohort
Original Submission Date: May 17, 2016
Last Edited Date: May 18, 2016
Authors: Majdi Osman, MD MPH[1], Kelsey O'Brien, MPH[2], Zachery Stoltzner, BS[2], Kelly Ling, BS[1], Emily Koelsch, RN BSN[1], Nancy Dubois, MSN MBA[3], Adila Khoiri, MD[4], Kanchana Amaratunga, MD, MPH[5], Mark Smith, PhD[1] and **Zain Kassam**, MD MPH[1], (1)OpenBiome, Medford, MA, (2)Clinical Safety, OpenBiome, Medford, MA, (3)William F. Connell School of Nursing, Boston College, Chestnut Hill, MA, (4)Sydney Children's Hospital, Sydney, Australia, (5)Infectious Disease, The Ottawa Hospital, Ottawa, ON, Canada

Background
Clostridium difficile infection (CDI) is a public health threat and fecal microbiota transplantation (FMT) appears to be an effective therapy. Recently, universal stool banks have emerged to enable safe and seamless access to FMT. However, there is a paucity of real-world safety and efficacy data from stool banks.

Methods
Quality assurance data on CDI classification, FMT delivery modality and clinical efficacy was consecutively collected from 482 healthcare facilities across 50 U.S

states and 7 countries between January 16, 2014 and April 12, 2016. The primary outcome was physician-reported clinical cure as per standard of care follow-up. Safety data was assessed through mandatory adverse event (AE) reporting. Descriptive statistics and Chi-square analysis for binomial variables was conducted.

Results

Among consecutively collected reports, complete safety and efficacy data was returned for 2,050 patients, which were included in these analyses. Overall, the clinical cure rate from physician-reported data across all delivery modalities and CDI patient populations was 84.0%. The most common indication for FMT, recurrent CDI, had an 87.0% (1150/1322) clinical cure rate by lower gastrointestinal (GI) delivery (Figure 1). Across the entire cohort, 85.0% (n=1742) of patients were treated with 250mL lower GI delivery fecal microbiota preparation (FMP) and 15.0% used 30mL upper GI delivery FMP. FMT by colonoscopy (85.8% clinical cure, n=1441) was superior to upper endoscopy (74.1% clinical cure, n=201) ($p<0.01$). The relationship between fecal preparation type and efficacy was statistically significant ($p<0.05$), with 85.1% efficacy for 250mL preparations and 77.9% efficacy for 30mL preparations. CDI classification had a statistically significant impact on the rate of clinical efficacy (Figure 1). From a safety perspective, 42 AEs were reported; however, no AEs were determined to be "definitely related" to FMT, 3 were "possibly related" to FMT and 39 "not related" based on NIH criteria.

Conclusions

To our knowledge, this is the largest FMT study reported, and suggest in a large, real-world patient cohort that includes severe and refractory CDI patients, FMT from a public stool bank appears to be a safe and effective treatment for CDI not responsive to standard therapy.

Figure 1: Efficacy of FMT by *Clostridium difficile* infection classification and fecal microbiota preparation type

Clostridium. difficile infection Classification	Total			250 mL			30mL		
	N	Efficacy (%)	P-value	N	Efficacy (%)	P-value	N	Efficacy (%)	P-value
Recurrent	1542	85.9	<0.001	1322	87.0	<0.001	220	79.5	0.278
Mixed (e.g. recurrent and severe)	259	79.2	0.021	229	80.0	0.047	30	66.7	0.118
Refractory	159	74.2	<0.001	126	75.4	<0.01	33	69.7	0.228

Severe	90	83.3	0.85	65	81.5	<0.01	25	88	0.205

C.16.3 Dubois et al. ID Week 2015

Title: Prospective Assessment of Donor Eligibility for Fecal Microbiota Transplantation at a Public Stool Bank: Results From the Evaluation of 1,387 Candidate Donors

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1. OpenBiome
2. Massachusetts Institute of Technology
3. Broad Institute

Character count: 1,948/1,950

Background: Recurrent *Clostridium difficile* infection is a major public health threat and fecal microbiota transplantation is a promising therapy. Public stool banks have emerged to meet increasing demand, supplied with fecal material from rigorously screened, universal donors. However, limited data exists regarding best practices for donor assessment. Accordingly, we aim to outline a donor screening framework, capture etiology of exclusion, and quantify the number of qualified stool donors.

Methods: Enrollment was conducted prospectively over a 1-year period. Candidates were directed to an online registry to complete a pre-screening survey to rule out common exclusion criteria. Eligible participants were invited for a 109-point, in-person clinical assessment by a nurse or physician and overseen by an internal medicine specialist to exclude risk factors for transmissible diseases and potential microbiome-mediated conditions. Candidate donors completed stool and serologic screening by a CLIA-approved laboratory (Figure 1).

Results: Overall, 1,387 participants enrolled in the donor program. At Stage 1, candidates completed a pre-screen survey with 910 (66%) individuals excluded, commonly for abnormal body mass index, logistic constraints and recent antimicrobial use. At Stage 2, remaining participants underwent a clinical assessment with 403 (84%) participants excluded, most commonly for loss to follow-up with 235 (58%) candidates failing to attend an invited assessment.

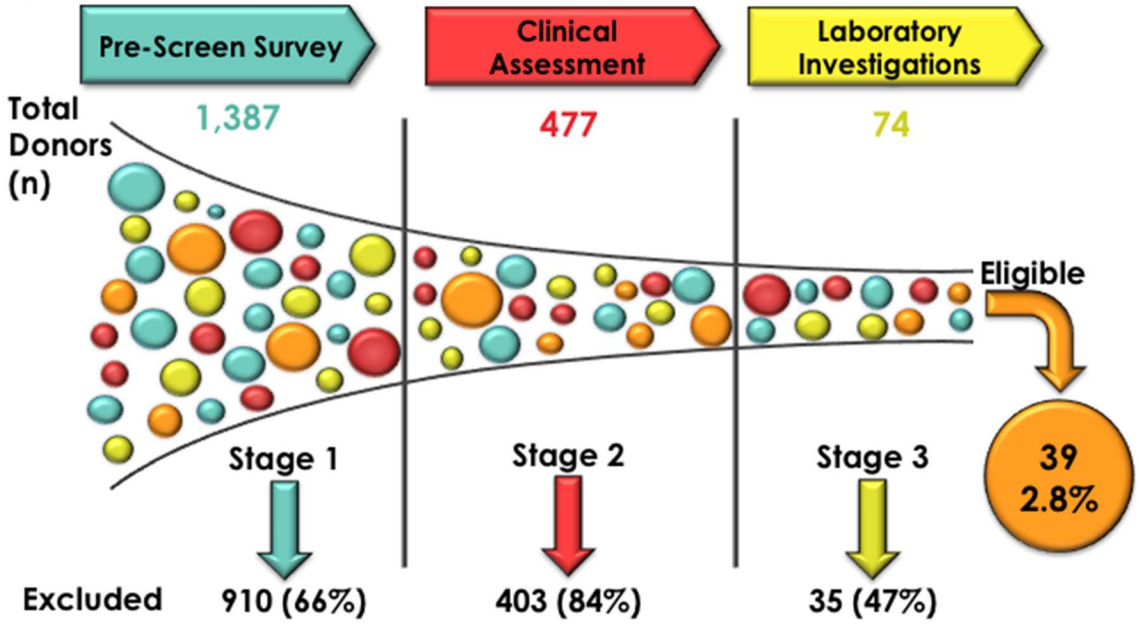
During the clinical interview, psychiatric illness, medications and infectious disease risk factors were identified as the most common reasons for exclusion. At Stage 3, remaining candidates underwent laboratory investigation with 35 (47%) candidates excluded, commonly for rotavirus and *C. difficile*. Overall, 39 participants qualified as stool donors resulting in a 2.8% acceptance rate (Figure 2).

Conclusions: Healthy, rigorously screened stool for use in FMT is rare with only 2.8% donors qualifying. An unanticipated, large number of asymptomatic potential donors were not eligible and logistics as well as loss to follow-up appear to be important factors for stool banks. Consensus-based guidelines are urgently needed to ensure safe standards for stool donors.

Figure 1. Stool and serologic screening panels

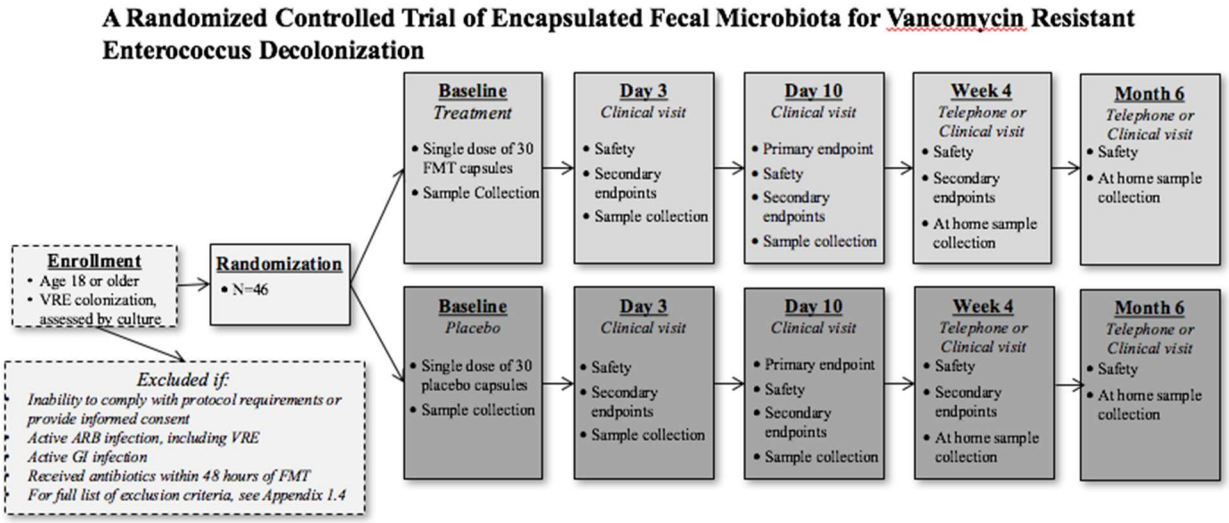
STOOL TESTING	SEROLOGIC TESTING
- PCR assay for *Clostridium difficile* toxin gene NAA - Culture-based assays for common enteric pathogens (including *Salmonella, Shigella, Campylobacter, Vibrio, E. coli* Shiga toxin EIA) - *Helicobacter pylori* fecal antigen EIA - Ova and parasites (including *Isospora*) - *Giardia lamblia* fecal antigen EIA - *Cryptosporidium* fecal antigen EIA - Acid-fast stain for *Cyclospora* - Microscopic exam for *Microsporidia* - Real-time PCR assay for fecal Norovirus - Rotavirus and Adenovirus (Type 40/41) fecal antigen EIA - Culture-based assay for fecal Vancomycin-Resistant Enterococcus (VRE)	- HIV antibody, type 1 and 2 - Hepatitis A (IgM) - Hepatitis B panel (HBsAg, anti-HBc [IgM and Total]) - Hepatitis C (HCV antibody) - *Treponema pallidum* (EIA with reflex to RPR) - HTLV 1 and 2 - Complete blood count with differential - Hepatic function panel (AST, ALT, ALP, bilirubin, albumin)

Figure 2. Donor eligibility workflow for an international public stool bank



C.17. STUDY DESIGN

C.17.1 Study Schematic



Primary Endpoint:
1. VRE clearance at day 10

Secondary Endpoints
2. Clearance of other antibiotic-resistant bacteria (i.e. CRE, ESBLs) at Day 3, Day 10, Week 4
3. VRE infection (i.e. bacteremia) at Day 3, Day 10, Week 4
4. Composite endpoint for clinical infections with antibiotic-resistant organisms and C. difficile (i.e. CDI-associated diarrhea) at Day 3, Day 10, Week 4
5. Microbiome disruption indices (MDI) (16S rRNA sequencing): MDI-community and MDI-species at Day 3, Day 10, Week 4
6. Trends in strain-level engraftment of patients colonized at Day 10, assessed by shotgun sequencing
7. Safety will be assessed up to six months using the guidelines in 21 CFR § 312.32.

C.17.2 Study Visit Table

	Screening[1] (Visit 1)	Enrollment [1] and FMT (Visit 2)	Follow-Up Visit Day 3 (Visit 3)	Follow Up Visit Day 10 (Visit 4)	Follow Up Visit Week 4 (Visit 5)	Follow Up Visit Month 6 (Visit 6)
Identified positive VRE stool sample	X					
Informed consent	X (if active screening)	X				
Baseline medical assessment		X				
Adverse events			X	X	X	X
Clinical and Safety Assessment[2]		X	X	X	X	X
Test capsule		X (as part of eligibility)				
FMP-402 or placebo		X				
Stool sample[3]		X	X	X	X	
ARB PCR testing		X	X	X	X	

1. Females of childbearing potential will undergo urine pregnancy test the day of invervention and participants that are at risk for EBV/CMV associated disease (at investigator's discretion, e.g. immunocompromised) will undergo EBV and CMV IgG testing, if double positive status (EBV+/CMV+) not already documented. If either is negative, the patient will be excluded.
2. Clinical and Safety Assessment may be in-hospital/clinic or telephone if the patient is discharged and unable to attend clinic
3. Stool samples (or rectal swab per standard of care for VRE) may also be collected at time of VRE infection.

C.17.3 NIH Common Terminology Criteria for Adverse Events (CTCAE)

Adverse Events Recording Form

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

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

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

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

Completed _____ Date _____

Name

C.17.4 Adverse Event Assessment Flow Chart