VA Cooperative Studies Program #2004

Microbiota or Placebo After Antimicrobial Therapy for Recurrent *C. difficile* at Home (MATCH)

Statistics Analysis Plan

Version 1.2

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1. Introduction

1.1 Overview

1.1.1 Overview of Statistical Analysis Plan

This Statistical Analysis Plan (SAP) is intended to be a comprehensive and detailed description of the strategy, rationale, and statistical techniques that will be used in the monitoring and analysis of the data collected in this study.

1.1.2 Background of the CSP #2004 Study

Clostridium difficile infection (CDI) is one of the most common nosocomial infections and is increasingly seen in non-hospitalized patients. Although more than 90% of patients have symptom resolution with a course of standard antimicrobial therapy, subsequent recurrence rates range from 15-30% (after the first CDI episode) to 40-50% (after the second and subsequent episodes). Fecal microbiota transplantation (FMT) has shown promise as an adjunct to standard antimicrobial therapy, reducing recurrence among FMT recipients to 15%. The recent successful administration of FMT via oral capsule provides an opportunity to deliver FMT via a non-invasive and convenient method, which also allows for effective blinding. With the VA having a high burden of recurrent CDI, there has been considerable interest in FMT from both providers and patients. The availability of FMT is site-dependent, with some VA facilities performing the procedure, others referring patients to community-based providers, and others having no mechanism of providing FMT. Furthermore, the lack of strong evidence for the efficacy of CDI treatment has led to regulatory uncertainty, with the Food and Drug Administration requiring an Investigational New Drug application (IND) for research involving FMT, but exercising "enforcement discretion" regarding the IND requirement for treatment of CDI with FMT.

1.2 Study Objectives and Hypothesis

1.2.1 Primary Objective

The study's primary objective is to compare the incidence of recurrent (definite or possible) CDI following prior successful treatment with one course of standard antimicrobial therapy) or death

within 56 days of randomization, among participants receiving FMT vs. those receiving placebo capsules.

Definite CDI recurrence is defined as: new onset of more than 3 loose or watery stools in 24 hours for 2 consecutive days not explained by another diagnosis, with laboratory confirmation of *C. difficile* from a stool specimen by EIA toxin test.

Possible recurrence is defined identically as above but WITHOUT laboratory confirmation of *C. difficile* (no specimen, not tested or negative test).

To operate the definition:

> Possible CDI recurrence is defined as CDI symptoms present (a Form 9 is filled) + Adjudicated as "Yes, CDI recurrence" regardless of lab results.
>
> Definite CDI recurrence is defined as CDI symptoms present (a Form 9 is filled, with a "Yes" answer for item B.1, B.2 or B.3 in Form 9) + Toxin positive regardless of adjudication results.

Our primary hypothesis is that Veterans receiving FMT after standard antimicrobial therapy will have reduced rates of CDI recurrence compared to those receiving placebo.

1.2.2 Secondary Objectives

Secondary objectives include FMT vs. placebo comparisons of occurrences of components of definite or possible CDI and other manifestations of CDI:

i. The incidence of CDI recurrence (definite or possible) or death within 6 months of randomization;
ii. The incidence of definite CDI recurrence within 56 days after randomization;
iii. The incidence of possible CDI recurrence within 56 days after randomization;
iv. Death within 56 days;
v. Episodes of diarrhea that is negative for C. difficile by EIA toxin test and PCR within 56 days after randomization;
vi. Episodes of diarrhea that is negative for *C. difficile* by EIA toxin testing but positive by PCR within 56 days

vii. Abdominal pain which is related to the onset of diarrhea among those possible recurrent CDI episodes;
viii. Urgency among those possible recurrent CDI;
ix. Fecal incontinence among those possible recurrent CDI;
x. The number of CDI recurrences (definite or possible) within 56 days post randomization;
xi. The number of CDI recurrences (definite or possible) within 6 months post randomization; and
xii. Self-reported quality of life within 56 days post randomization.

1.2.3 Safety Objectives

We will monitor the incidence, severity, and relatedness of serious adverse events and complications within 6 months to evaluate the safety of FMT. In the six months following study treatment, we will review electronic medical records and communicate with subjects via telephone to evaluate for possible transmission of infectious agents or development of new conditions theoretically linked to alterations in gut microbiota.

1.2.4 Exploratory Analyses

The following exploratory analyses are proposed:

i. Characterization and comparison of the colonic microbiome, before and after FMT/placebo administration;
ii. Comparison of the post-FMT colonic microbiome to the donor microbiome;
iii. Comparison of the post-FMT microbiome of individuals who experience; and recurrence vs. the microbiome of those not experiencing recurrence.

1.3 Outcome Measurement

1.3.1 Primary Outcome

The primary outcome for this trial was selected to reflect the circumstances that currently lead clinicians and patients to consider FMT, and to provide a result that is clinically relevant. Since

the great majority of patients referred for FMT are undertaking the procedure to reduce the risk of subsequent CDI recurrence, the primary outcome was chosen to clearly assess the efficacy of FMT in preventing CDI recurrence.

The primary outcome is definite or possible CDI recurrence, or death within 56 days of randomization.

Definite recurrence is defined as any of the following:

- The new onset of more than three loose or watery stools in 24 hours for two consecutive days not explained by another diagnosis.
- Other clinical symptoms including ileus, toxic megacolon, or colectomy.

PLUS

- Laboratory confirmation of *C. difficile* from a stool specimen by EIA toxin test.

Possible recurrence is defined using the same clinical manifestations as above, but WITHOUT laboratory confirmation of *C. difficile* (stool test not sent, negative result, or uninterpretable result).

To operate the definition:

Possible CDI recurrence is defined as CDI symptoms present (a Form 9 is filled) + Adjudicated as "Yes, CDI recurrence" regardless of lab results.

Definite CDI recurrence is defined as CDI symptoms present (a Form 9 is filled, with a "Yes" answer for item B.1, B.2 or B.3 in Form 9) + Toxin positive regardless of adjudication results.

1.3.2 Secondary Outcomes

i. The incidence of CDI recurrence (definite or possible) or death within 6 months of randomization;
ii. The incidence of definite CDI recurrence within 56 days after randomization;
iii. The incidence of possible CDI recurrence within 56 days after randomization;
iv. Death within 56 days since randomization;

v. Episodes of diarrhea that is negative for C. difficile by EIA toxin test and PCR within 56 days after randomization;
vi. Episodes of diarrhea that is negative for C. difficile by EIA toxin testing but positive by PCR within 56 days
vii. Abdominal pain which is related with the onset of diarrhea among those possible CDI recurrent cases;
viii. Urgency among those possible CDI recurrent cases;
ix. Fecal incontinence among those possible recurrent CDI;
x. The number of CDI recurrences (definite or possible) within 56 days post randomization;
xi. Number of CDI recurrences (definite or possible) within 6 months:
    - The number of CDI recurrences within 6 months for a patient is the count of separate CDI recurrences from randomization to 6 months after randomization; and
xii. Quality of life at day 56:
    - We will use a brief assessment of both overall and gastrointestinal health status, using a previously validated instrument (see study protocol).

1.3.3 Safety Outcomes

Because of the limited information regarding long-term safety of FMT, safety outcomes will be collected until 6 months after FMT/placebo is administrated.

Safety outcomes to be collected include:

i. Serious adverse events, with a focus on SAEs involving hospitalization (new or prolonged);
ii. Adverse events which may be related to FMT treatment. This includes adverse events which Site Investigators consider related/possibly related to the study treatment, diarrhea, fever, abdominal pain and all other adverse events which occur within 14 days of study treatment (since an aggregate analysis of events temporally linked to treatment could show a causal relationship when compared to placebo);

iii. Infectious transmissions which are plausibly linked to FMT therapy; and
iv. Development of new conditions potentially linked to alterations in gut microbiota.

1.3.4 Outcome Measurements in Exploratory Analyses

We believe that evaluating the gut microbiome is important, particularly in the context of this large trial incorporating a placebo control. Prior work demonstrating similarity between the post-transplant microbiome and the donor microbiome suggests that "engraftment" of the donor microbiome is important for clinical success. However, since these data come from uncontrolled studies, this hypothesis has not been rigorously tested. The microbiome component can give us valuable insight into the mechanism of the resulting effect. If a clear correlation between recurrent CDI and failure to engraft is demonstrated, this would clarify the mechanism whereby FMT confers its benefit. Conversely, if subjects with engraftment of the donor microbiome recur at a similar rate as do those without engraftment, this would suggest that other factors may be contributing to recurrence.

A stool sample for the assessment of the colonic microbiome will be obtained at the time of randomization and 56 days after administration of FMT/Placebo. The first sample will be transported to the central laboratory performing the microbiome characterization by the Study Coordinator, whereas the second sample will be mailed to the same laboratory by the subject via a pre-paid mailer.

Shannon index (diversity) and the abundance-based coverage estimate (ACE) (richness) will be the outcome measurements to evaluate microbiome.

The following exploratory analyses are proposed:

i. Characterization and comparison of the colonic microbiome of individuals with CDI randomized to FMT and placebo, before and after FMT/placebo administration;
ii. Comparison of the post-FMT colonic microbiome of individuals randomized to FMT and placebo to the donor microbiome; and

iii. Comparison of the post-FMT microbiome of individuals that experience a recurrence to the microbiome of those not experiencing recurrence.

1.4 Patient Characteristics

1.4.1 Screened Population

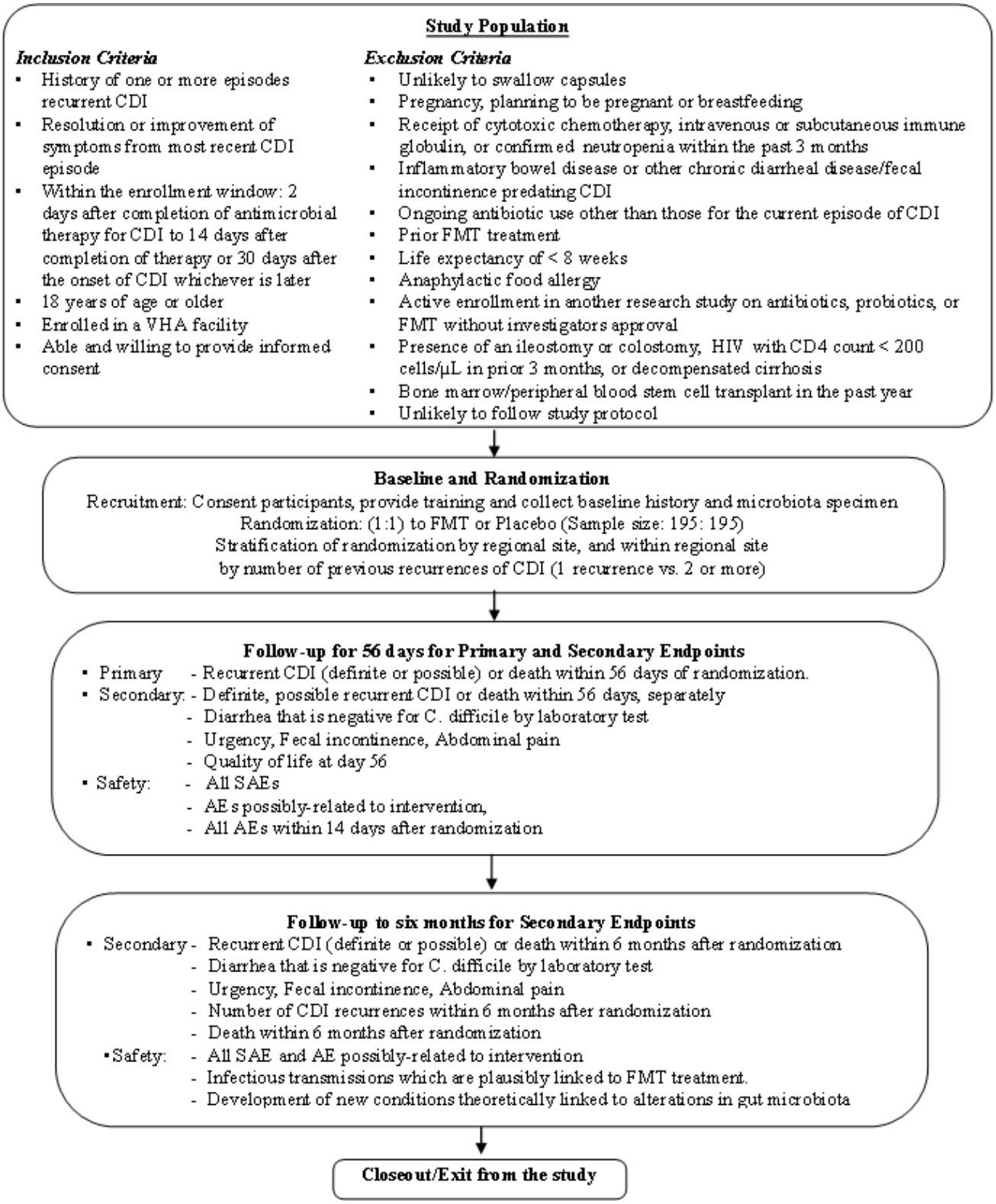
A relatively novel method of enrollment will be used in this study, with central Study Coordinators identifying eligible participants in the entire VA system. The identification of eligible participants will be accomplished using multiple strategies, as outlined below, which include electronic case finding and direct referrals from clinical providers.
Our main strategy for recruitment is through electronic case finding of all new diagnoses of CDI across the VA using Corporate Data Warehouse (CDW) support through VA Informatics and Computing Infrastructure (VINCI), which is updated daily. An incident case of CDI will be identified through electronic monitoring of orders for C. difficile testing, lab results, diagnostic codes for outpatient and inpatient visits, and prescriptions. The system has been successfully refined and is transition to an automated system. It is planned to run weekly or bi-weekly. The Study Coordinators will screen cases found through this automated system, and will then utilize the patient's electronic medical record to assess for inclusion/exclusion criteria using national Computerized Patient Record System (CPRS) access via Compensation and Pension Records Interchange (CAPRI).

If the patient appears eligible at initial screening, a Study Coordinator (SC) will contact the patient's provider and ask the provider or a member of their care team to obtain permission for the SC to initiate contact via telephone. If the patient agrees to be contacted, the SC will contact the patient, provide information about the study and, if the patient is interested in participating, mail an informed consent form for the patient to review.

1.4.2 Enrolled/Randomized Participants

Participants qualified to be randomized within CSP #2004 must meet all eligibility criteria. The Inclusion and Exclusion criteria are detailed in the Study Protocol and Operations Manual and are summarized as follows (Table 1).

Table 1. Study Flowchart



2. Statistical Approaches

2.1 Study Design Summary

2.1.1 Effect Size

Sample size calculations were initiated with a determination of what improvement in the rate of recurrence would be sufficiently large to be considered clinically significant. For a high-risk procedure, the benefit must be substantial enough to outweigh the potential risks. In the case of FMT, approximately 500 cases have been reported in the medical literature, with few reports of harm. Those that were reported were largely related to the route of delivery - including a fatal aspiration event associated with colonoscopy, and peritonitis associated with administration of FMT via an indwelling gastric tube. Since the protocol proposal is FMT administration via capsules, which confers substantially lower risk, it is appropriate to consider a 15%-20% reduction in the CDI recurrence rate as clinically significant. An absolute improvement (reduction) of 15% was selected as the threshold for clinical significance, meaning that if the placebo group had a recurrence rate of 35%, the FMT group would have to achieve a rate of 20% for the difference in rates to be considered clinically significant.

2.1.2 Expected Recurrence Rate after Standard Antimicrobial Therapy

CDI recurrence rates after antimicrobial treatment are well-described for the initial episode; unfortunately, subsequent rates of recurrence are less well known. Data regarding subsequent rates of recurrence derive from a few RCTs that included subjects with a previous episode of CDI, and several observational studies. Two RCTs comparing fidaxomicin to vancomycin for the treatment of CDI have been reported, each containing a subgroup of patients with a prior episode of CDI (the rest experiencing their first episode). A subsequent publication assessed the difference in recurrence by treatment arm in those with prior CDI. The overall recurrence rate for those with prior CDI was 27% (36% vancomycin vs. 20% fidaxomicin: P = .045). Another trial compared high-dose vancomycin vs. low-dose vancomycin vs. metronidazole for the treatment of recurrent CDI, each with the addition of a probiotic (*Saccharomyces boulardii*) vs. placebo. In this study, the overall recurrence rate was 45%. Among the six different treatment arms, five treatment arms had recurrence rates between 45% and 51%; the combination of *S. boulardii* and high-dose vancomycin had a recurrence rate of 17% (3/18). Finally, in the trial of FMT vs. two

vancomycin-based control groups, the combined recurrence rate in the vancomycin groups was 73% (19/26).

Data from observational studies on subsequent recurrence after treatment of recurrent CDI is variable, both in terms of results and the population studied. In contrast to the RCTs which predominantly studied patients being treated for their first episode of recurrence, many of the observational studies reported on patients with multiple episodes of recurrence. Reporting and publication bias is a significant concern, since successful experiences may be more likely to be submitted and accepted for publication. Those caveats aside, there is still valuable information regarding recurrence rates to be gained from this literature. An older case series describes no recurrence (after a mean of 6 months follow-up) among 22 patients treated with vancomycin using a tapered/pulsed dosing strategy, whereas another study evaluating tapered or pulsed dose vancomycin reported a 38% recurrence rate (10/26). Finally, a small case series described successful treatment without recurrence in 7 of 8 patients using vancomycin followed by a course of rifaximin. Details of these studies are summarized in Table 2.

Table 2. Studies reporting antimicrobial treatment of recurrent CDI and subsequent recurrence rates

Study	Study type	N	Population	Treatment	Recurrence rate
Cornely 2012	RCT	128	Patients with 1st recurrence of CDI	Vancomycin or fidaxomicin	27%
Surawicz 2000	RCT	170	Patients with 1st recurrence of CDI	High-dose vancomycin, low-dose-vancomycin, or metronidazole, all with *S. boulardii* vs. placebo	45%
van Nood 2013	RCT	26	Patients with recurrent CDI (1-9 episodes)	Vancomycin or vancomycin plus bowel lavage	73%
Pepin 2006	Retrospective cohort	463	Patients with 1st recurrence of CDI	Vancomycin or metronidazole	33%
McFarland 2002	Retrospective cohort	26	Patients with recurrent CDI (1-14 episodes)	Vancomycin taper/pulsed dose	38%
Tedesco 1985	Case series	22	Patients with multiple relapses	Vancomycin taper/pulsed dose	0%
Johnson 2007	Case series	8	Patients with recurrent CDI (4-8 episodes)	Vancomycin followed by rifaximin	13%

The three largest studies report recurrence rates of 27%, 33%, and 45%. All of these included only patients with a first recurrence of CDI; subsequent recurrence rates are typically higher. Importantly, the placebo arm of the recently presented RCT (Kelly, oral presentation) had a recurrence rate of 37%, although the precision of this estimate is limited by the sample size of 24. **Accordingly, we believe that 35% is a conservative estimate for an expected recurrence rate after treatment with standard antimicrobial therapy**. If enrolled participants have a history of multiple recurrences, the recurrence rate is likely to be in the 40%-50% range.

Expected recurrence rates after FMT have recently been systematically reviewed and summarized. The overall recurrence rate, including case series and RCTs of all FMT delivery methods, is 15%. The single published series regarding capsule delivery of FMT reported a recurrence rate of 30% (6/20), with another series (presented in abstract form only) reporting no recurrences in 29 patients (Abstract 89. Fecal microbiome transplantation (FMT) via oral fecal microbial capsules for recurrent *Clostridium difficile* infection (rCDI) Session: Oral Abstract Session: New Considerations in *C. difficile* Prevention and Treatment/ October 2, 2013, IDWeek, San Francisco). Given the overall recurrence rate for FMT of 15%, the data from the published study of capsule-delivered FMT indicating a recurrence rate of 30%, and taking into account the unpublished study, **we believe that anticipating a 20% recurrence rate after standard antimicrobial therapy followed by FMT is appropriate.**

2.1.3 Sample Size of the Primary Outcome

Accordingly, sample size was estimated using the following assumptions:

1) Recurrence rate of standard antimicrobial therapy followed by placebo of 35%
2) Recurrence rate of standard antimicrobial therapy followed by FMT of 20%
3) Two-sided significance level of 0.05
4) Overall drop-out rate of 5%.

Using the method described in Fleiss for comparing two proportions, a total sample size of 390 provides 90% power to find an absolute difference of 15% in the recurrence rate with the addition of FMT to standard antimicrobial therapy for recurrent CDI.

Table 3. Sample Size Estimation Table

Recurrent CDI or All-Cause Mortality by Day 56			Power		
Placebo (Control Arm)	FMT (Experimental Arm)	Absolute Reduction	0.80	0.85	0.90
45%	35%	10%	792	905	1059
	30%	15%	343	392	457
	25%	20%	187	213	248
40%	30%	10%	749	857	1004
	25%	15%	320	366	427
	20%	20%	173	191	229
35%	23%	12%	471	539	629
	20%	15%	290	333	390
	17%	18%	196	223	259
30%	22%	8%	992	1134	1326
	15%	15%	255	291	339
	12%	18%	168	192	223

Using the assumption in Table 3 above of a target sample size of 390, the following scenarios were considered as sensitivity power analyses:

- If the recruitment rate is lower than anticipated, the study will still maintain 82% power to detect an absolute reduction of 15% with a sample size of 300 (77% of the target sample size).
- If the control group event rate was lower than anticipated (30%), the study would maintain 90% power to detect an absolute reduction of 14%.
- If the effect size is smaller than hypothesized, the study would still maintain 80% power to detect an absolute reduction of 13% while the control event rate maintains as 35%.

In summary, the anticipated rate of recurrent CDI following standard antimicrobial therapy is 35%; the study is powered to detect a clinically significant difference of 15%. As previously discussed, this difference is chosen based on the non-invasive nature of the intervention, as well as favorable safety data from the > 500 cases of FMT reported in the literature. The rate of recurrence will be affected by the mixture of patients enrolling; if most enroll after their first recurrence, the rate of subsequent recurrence may be slightly lower, whereas if most enroll after multiple recurrences, 35% is likely an underestimate. Using the above assumptions, the

previously specified 90% power with a two-sided significant threshold of 0.05, and a 5% drop-out rate, the total sample size is 390 participants.

2.2 Interim Monitoring and Analysis

2.2.1 Overview

Interim monitoring will be performed by the West Haven Cooperative Studies Program Coordinating Center (WH-CSPCC) and will focus on recruitment, baseline comparability of treatment groups, protocol adherence, completeness of data, accrual of primary endpoint events (i.e., information accrual), safety, and treatment efficacy. The WH CSPCC will provide the basis for reporting to the Data Monitoring Committee (DMC) as well as the interim reports to the DMC, which will meet for two scheduled interim analyses.

2.2.2 Monitoring Recruitment

The WH-CSPCC will monitor the recruitment process to assure early recognition of lower than anticipated performance and to identify reasons for inadequate performance for the trial. To assist in this process, the WH-CSPCC will produce weekly data monitoring reports (Appendix Tables 1-8) to include number of screening forms completed, reasons for non-matriculation into the study, number of informed consent documents signed, and number of randomizations, overall and by month. The same reports will be made available to the DMC at each of its meetings. Predicted total patient accrual for the full study will be extrapolated from the accumulated data.

2.2.3 Monitoring Safety

Trial safety will be monitored by Site Investigators, WH-CSPCC and the CSPCRPCC, throughout the study. Safety reports will be submitted to the DMC approximately every 6 months after enrollment begins, or more frequently, if requested by the DMC. For reports included in the DMC closed session, serious adverse events will be summarized by treatment group, and relatedness to the assigned interventions.

Site Investigators will review and evaluate adverse events, their relatedness and severity without un-blinding study group assignment. The relatedness between an adverse event and study

therapy will be assessed in terms of reasonable attribution to the study intervention (No, Possibly, Yes). The severity of adverse events will be classified in terms of general AE descriptions including diarrhea, abdominal pain, nausea, vomiting which doesn't fit SAE criteria and SAEs. Among the SAEs, the severity will be reported and monitored in term of serious reasons (Death, Life-threatening, Hospitalization or Prolongation of Hospitalization, Significant disability/incapacity Congenital anomaly/Birth Defect or Other condition) as well as SAE outcome (ongoing, resolved, resolved with sequelae and fatal).

For SAE that are reported as at least possibly related to study therapy or any suspected or proven transmission of infection from possible FMT product, the CSPCRCC and WH-CSPCC will communicate with the DMC for further discussion and recommendation. If it is necessary, the therapy assignment can be unblinded.

In general, the proportion of participants experiencing an AE as well as the AE incidence rate in each treatment arm will be calculated. The same data will be generated for SAE. If the DMC finds the proportion or incidence rate of AEs/SAEs unacceptably higher in one treatment group compared to another, it may consider recommending that either the trial be stopped, or the protocol be modified.

2.2.4 Monitoring Efficacy Outcomes

Two interim analyses of the primary outcome (recurrent CDI or death) are planned, after which the DMC will decide whether to recommend the trial to continue. The DMC will have discretion to request additional or differently scheduled interim analyses. The first interim analysis will be done when at least 195 subjects have been enrolled and followed for more than 56 days (50% accrual of primary outcome information), and the second when at least 292 subjects have been enrolled and followed for more than 56 days (75% accrual of primary outcome information). For both interim analyses, a stopping rule with a wide boundary such as the Haybittle and Peto method will be used. It is suggested that the significance level for the interim analyses will be 0.001 and the two-sided significance level for the final analysis will be 0.05. The inflation of the overall type I error will be negligible. At the first interim analysis, there will be approximately 82% power to detect an 18.5% absolute reduction in the primary outcome relative to the placebo

arm (based on a placebo rate of 35%). At the second interim analysis, there will be approximately 85% power to detect a 16% absolute reduction in the primary outcome relative to the placebo arm (again assuming a 35% primary outcome rate in the placebo arm).

At the time of the two interim analyses, a futility analysis will be performed to assess the likelihood of eventual success based on the observed data. The conditional power to fulfill the study will be provided to the DMC. If the conditional power is low, such as less than 10% per observed trend, then the DMC may recommend stopping the study. In both interim analyses especially the second one, if the conditional power is between 60% to 80% with a more than 5% treatment effect, then the DMC may recommend continuing with an adjustment to the sample size and extension of the trial.

In addition to these futility analyses for the primary endpoint, the observed laboratory confirmed event rate is monitored from the initiation of the trial and compared with the primary event rate. When considering the futility analyses, the DMC may also consider the laboratory confirmed evidence of futility (i.e., secondary outcomes) and would reserve the option of recommending early termination of the trial for futility or continuing with a possible adjustment to sample size.

2.2.5 Monitoring Protocol Adherence

Protocol adherence will be monitored to assure early identification of poor performance in the trial. Periodic reports will be provided to the Executive Committee and to the DMC at each of its meetings. Specific parameters to be monitored include:

- Randomization of ineligible participants
- Treatment allocation errors
- Failure to complete required follow-up assessments on time
- Loss and withdrawal rates

2.2.6 Sample Size Re-estimation

In CSP #2004, the sample size assumptions regarding the control group event rate, the effect size and dropout rate will be re-evaluated at two interim analysis time to determine whether the estimated sample size is sufficient. If necessary, the sample size will be re-estimated based on the accumulated data under the condition that the observed treatment is above 5% and

conditional power based on observed trend is above 60%. This information will be presented to the DMC who will make a recommendation to the WH-CSPCC on whether the sample size for the trial should be amended to achieve the study objectives.

3. Final Statistical Analysis

3.1.1 Overview

All primary analyses will be according to the principle of intent-to-treat; i.e., subjects will be analyzed according to their original treatment assignment regardless of protocol adherence.

3.1.2 Baseline Comparability

In order to assess the adequacy of randomization, the baseline characteristics to be compared and summarized include: age, birth sex, race, ethnicity, marital status, education, military service history, surgical history, medical history including diabetes, coronary artery disease, chronic liver disease, chronic kidney disease, hematologic cancer, solid-organ cancer, systemic antibiotics, solid organ or bone marrow transplant, and number of prior CDI episodes experienced, nursing home status and usage of probiotic supplements in the past 12 months. The baseline laboratory information includes serum creatinine, serum albumin, WBC, HGB, and platelet count. The distribution of baseline patient characteristics between groups will be evaluated using descriptive statistics. *A priori* baseline variables which will be used for covariate adjustment include age, sex, number of prior CDI episodes, and immunodeficiency.

3.1.3 Analysis of Primary Outcome Measure

The primary outcome (recurrent CDI or death within 56 days) will be summarized in terms of incidence rate with 95% confidence interval by treatment arm. Absolute treatment difference with 95% confidence interval will also be summarized. A generalized linear model will be used to make treatment comparisons since it is appropriate for a binary endpoint and can be adjusted for covariates and tested for interactions. Based on the study design, treatment arm, as well as a previous recurrence of CDI (1 vs. ≥ 2) will be considered as fixed effects, and the status of having a recurrence of CDI or death will serve as the outcome. The odds ratio of having a primary outcome in terms of FMT treatment to the placebo with 95% confidence interval will

also be provided. The primary hypothesis will be tested by the above generalized linear model with treatment adjusted for study group assignment. Treatment by number of prior CDI episodes interactions will be examined in exploratory analyses. A p-value of 0.05 will be used for all interaction tests and sub-group analyses of the primary outcome.

As an exploratory analysis of the primary outcome, we will test the treatment effect adjusted for study design as well as a set of pre-specified baseline covariates to examine their influence on the treatment comparison. Treatment by covariate interactions will be examined for the following baseline covariates: gender, race (white vs. other), age, number of prior CDI episodes, and immunosuppression status. A p-value of 0.05 will be used for all interaction tests and sub-group analyses of the primary outcome.

Another exploratory analysis, Kaplan-Meier survival curves, adjusted for censoring due to loss to follow-up, will also be used to evaluate treatment effects for time to first recurrent CDI within 56-days. A log-rank test will be used to test the effect of treatment.

Chi-square test in the difference of primary incidence rate will also be processed as an exploratory analysis.

Participants who cannot be contacted by day 56 will have their CDI status updated based on information in the medical record. Participants who completely withdraw from the study will have their last assessment (recurrent CDI or not) carried forward, whereas those partially withdrawing (i.e., allowing medical record review) will have their CDI status updated based on information in the medical record. Participants who do not withdraw from the study but are lost to follow-up will have their CDI status updated based on information in their medical record. In the meantime, the study team will contact that participant's previous treating physicians and primary care physicians for information about possible recurrent CDI. Survival status on patients who cannot be contacted by day 56 will be obtained using the VA Beneficiary Identification and Records Locator System (BIRLS), the National Center for Health Statistics' National Death Index database and the Social Security Administration's Death Master File. With the above follow-up process, we will include every randomized participant for the final analysis of primary

endpoint. In the meantime, a sensitivity analysis will be performed on the primary endpoint by assuming those participants who cannot be contacted by day 56 as having a recurrent CDI.

3.2 Analysis of Secondary Outcomes

3.2.1 Recurrence of CDI or death within 6 months

The first secondary outcome (recurrent CDI or death within 6 months) will be summarized using incidence with 95% confidence interval (FMT vs placebo arm). Treatment group comparisons will be based on generalized linear model. The odds ratio (FMT vs placebo) of having a recurrent CDI or death within 6 months (95% confidence interval) will be provided. Kaplan-Meier survival curves, adjusted for censoring due to loss to follow-up, will also be used to evaluate treatment effects for time to first recurrent CDI within 6-months. The Cox proportional hazards model will also be used to test the effect of treatment adjusted for the study design. The proportional hazard assumption will be tested by visual examination of log (log) plots, to assure the validity of this analysis. If the assumption is not valid, appropriate adjustments will be made, such as adding time by covariate interaction terms or use of stratification.

Missing data due to early withdrawal or loss to follow-up will be handled in the same way as for primary outcome analysis.

3.2.2 Definite Recurrent CDI, Possible Recurrent CDI, Diarrhea with Negative CDI

Secondary outcomes such as definite recurrent CDI, possible recurrent CDI and diarrhea with negative CDI will be summarized and analyzed the same way as the primary endpoint. Each of these endpoints is designed to address one unique research question. Between treatment group analysis will be carried out using an alpha-level of 0.05, without adjusting for multiple comparisons for each endpoint.

possiblePossible3.2.3 Death within 56 Days

Death within 56 days will be summarized using incidence rate (95% confidence interval) by treatment. This study outcome will be analyzed the same way as the primary outcome.

3.2.4 Death within 6 Months

Death within 6 months will be summarized using incidence rate (95% confidence interval) by treatment. Kaplan-Meier survival curves, adjusted for censoring due to loss to follow-up, will be used to evaluate the treatment effects for 6-month all-cause mortality. Treatment group comparisons will be carried out using the log-rank test. The Cox proportional hazards model will also be used to test the effect of treatment adjusted for study treatment assignment. The proportional hazard assumption will be tested by visual examination of log (log) plots, to assure the validity of this analysis. If the assumption is not valid, appropriate adjustments will be made, such as adding time by covariate interaction terms or use of stratification.

3.2.5 Urgency, Fecal Incontinence, and Abdominal Pain

Urgency, fecal incontinence, abdominal pain, severity of abdominal pain, and number of episodes of abdominal pain will be summarized using descriptive statistics by treatment arm. Chi-square test will be applied to all categorical endpoints to test treatment effect. ANOVA as well as Log-rank test will be applied on severity of abdominal pain to test the treatment effect.

The summaries and tests described above will be compiled for CDI cases. Similar reports will be generated for possible recurrent CDI cases, definite recurrent CDI and PCR negative cases separately.

The summary will be done for diarrhea that is negative for *C. difficile* by PCR, number of CDI recurrences within 6 months, and quality of life at day 56; between treatment groups will be carried out using an alpha-level of 0.05, without adjusting for multiple comparisons.

3.2.6 Number of Definite or Possible CDI Recurrences by 6 Months

The number of definite CDI recurrences by 6 months will be summarized using mean (standard deviation) by treatment group and analyzed using an ANOVA model. This variable will also be categorized into three levels of discrete ordinal measurement – none, one, and more than one. A generalized linear model with a cumulative logit link function will be used to investigate the effects of treatment on the number of CDI recurrences. Otherwise, a weighted-least-squares analysis will be used to assess the mean score of number of CDI recurrences for each treatment

arm. As for the primary outcome, treatment comparisons will be adjusted for both the study arm assignment and the pre-specified set of baseline covariates.

Similar analyses will be used for the number of possible CDI recurrences by 6 months.

In terms of counting episodes of recurrent CDI, two episodes within 8 days of onset time will be treated as a single episode.

3.2.7 Quality of life at day 56

Quality of life, Gastrointestinal Quality of Life Index, (a continuous measurement) will be summarized by visit time (baseline or 8-week) and treatment arm. The differences between the two treatment arms at week 8 will be analyzed using a linear model. Since some of the censoring, such as death, may be informative, analyses both with and without adjusting for the possibility of informative censoring will be conducted. First, the analysis will be done on the observed quality of life, regardless of whether the censoring is informative or not. Then, a lower score will be given to those missing due to death and the data adjusted for the informative censoring as a sensitivity analysis.

3.3 Analysis of Safety Outcomes

3.3.1 Serious Adverse Events (SAE)

All randomized participants will be included in the SAE analyses.

The number of SAEs and proportion of participants experiencing an SAE up to six months will be summarized by treatment arm, MedDRA System Organ Class and Preferred Terms. The treatment comparison of SAE incidence (total number of SAE during the entire study time) will be made using a Poisson regression model where total actual follow-up time will serve as the exposure variable. The treatment comparison in incidence of subject having SAE will be made using a Chi-square test. SAE criteria, SAE outcome and attribution to the study intervention, severity, and SAE leading to discontinuation from the study will be tabulated by treatment arm.

SAEs occurring in the first 48 hours or 14 days after randomization will be summarized and analyzed in a similar way as described above.

3.3.2 Adverse Events (AE)

In this study, the following specific AEs occurring at day 2 and day 14 are collected: diarrhea, abdominal pain, vomiting, nausea, fever, bloating, gas/flatulence, belching, fatigue, constipation and anorexia. Their severity and ongoing status are also collected. For each AE, the total number of AE and the proportion of participants experiencing that AE at day 2 and day 14 will be summarized by treatment arm. The severity and current status will be summarized in terms of count and proportion by treatment. All treatment comparisons will be made using a Chi-square test. For each AE event, only participants providing a valid answer will be included in the summary and analysis.

Other reported AEs will be summarized and analyzed in a similar way as the study SAEs.

3.3.3 Analysis of Exploratory Outcomes

The Shannon index (diversity) and the abundance-based coverage estimate (ACE) (richness) will be used as endpoints in the following exploratory analyses that aim at evaluating the microbiome of patients pre- and post-treatment:

i. Characterization and comparison of the colonic microbiome of individuals with CDI randomized to FMT and placebo, before and after FMT/placebo administration;
ii. Comparison of the post-FMT colonic microbiome of individuals randomized to FMT and placebo to the donor microbiome; and
iii. Comparison of the post-FMT microbiome of individuals that experience a recurrence to the microbiome of those not experiencing recurrence.

Collected stool samples will be used to extract DNA, quantify and amplify microbial communities, and use 16S rRNA gene profiling using V5 + V6 hypervariable regions sequencing on the Illumina MiSeq platform to characterize the microbial community structure. Taxonomic classification will be performed using Version 14 data release from the Ribosomal Database Project. Specifically, we will be quantifying microbial diversity using two validated indices to

characterize microbial diversity and richness with the Shannon index (diversity) and the abundance-based coverage estimate (ACE) (richness) respectively. These two indices are calculated to assess parametric and non-parametric diversity. The Shannon index is scored between 0 and 7 while the ACE ranges from 0 to 8000.

Student t-test (paired and unpaired), Pearson and Spearman correlations will be used to assess and compare pre- and post FMT, and donor-recipient scores. Our hypothesis is that post- FMT samples will show increased diversity and richness compared to pre-FMT; that post-FMT changes will resemble the microbiota composition of donor specimens; and that post-FMT changes will be sustained over 6 months.

Prior estimates from the literature suggest that the mean Shannon index for pre- and post FMT will be 1.68+0.75 and 3.37 $\pm$0.46 respectively. Assuming half the study participants agree to provide an additional sample for characterization of stool microbiome (n=200) we would have >95% power to estimate assess pre- and post FMT differences.

Additional analyses may include: differences in microbiota diversity (community composition) using analysis of similarity (ANOSIM), other diversity indices (number of operational taxonomic unit (OTU) sequences (S obs), sequencing coverage estimation, UniFrac analysis, ANOSIM analysis, principal coordinate analysis (PCoA), Mantel tests, Kruskal – Wallis analysis), and analysis of molecular variance (AMOVA) will be performed.

4. Ground Rules and Data Handling Conventions

4.1 Baseline Definitions or Conventions

Baseline will be defined as the last assessment taken prior to or at the randomization and the assignment of study treatment. These assessments are usually captured in the participant's subject's electronic medical record or updated during the randomization visit.

4.2 Handling of Missing Data

For data summaries, descriptive statistics will be calculated using available data. The number of missing data values will be reported for major data items and presented by reporting the number of values that were available and/or the number of missing responses. Missing data can occur through loss to follow-up, or missed contact, etc.

For recurrent CDI incident data at day 56, participants who cannot be contacted by day 56 will have their CDI status updated based on information found in the medical record. Participants who completely withdraw from the study will have their last assessment (recurrent CDI or not) carried forward, whereas those partially withdrawing (i.e., allowing medical record review) will have their CDI status updated based on information in the medical record. In this way there should be no missing data for incidence of recurrent CDI at day 56, which is the CDI portion of the primary study endpoint as the primary analysis. In the meantime, a sensitivity analysis will be performed on the primary endpoint by assuming those participants who cannot be contacted by day 56 as having a recurrent CDI.

For the survival outcome, no missing data is expected since we perform a time to event analysis.

Quality of life will be measured at two different time points, day 1 and day 56. A longitudinal linear model will be used for the analysis. For this analysis, missing data due to death can be handled through imputation method. Missing due to loss of follow-up other than death will be treated as missing.

For safety data such as SAE, the study team will periodically check the participant's VA electronic medical record through CPRS or CDW to capture all VA hospitalization records and report those related SAEs. If a non-VA hospitalization is recorded in CPRS or CDW, it will also be reported with the available information. A similar process will be used for AEs. The number of missing SAE or AE data is expected to be minimal because of the utilization of the electronic medical record. All safety data will be summarized and analyzed using reported valid data.

4.3 Description of Protocol Deviations

The frequency of protocol deviations will be tabulated by protocol deviation category and treatment group. The number and category of protocol deviations will also be summarized by protocol violation type and site.

4.4 Datasets/Programs/Variables

Raw Datasets: Raw datasets will be created for each study case report form (Forms 1-7, 9-17). CRFs are transmitted to WH-CSPCC via iDataFax and will be processed through internal and external data checking, validating, and quality control procedures. Each CRF is then exported to our local server as a CSV file. CSV files will be read by SAS programs to create SAS datasets for each CRF. The iDataFax data management tools are used to create and manage the updating and checking of these datasets.

4.5 Analysis Datasets

Programs will be developed to create analysis datasets that will facilitate production of tables and figures for interim reports and final analyses. These files include:

- Screening Activities — Screening.sas7bdat
- Demographic, Baseline and Participant Status — Demo.sas7bdat
- All participant Follow-up — FollowUp.sas7bdat
- Evaluation CDI — EvaluationCDI.sas7bdat
- Efficacy — Efficacy.sas7bdat
- Safety (AE/SAE) — Safety.sas7bdat

DEMO: Demographic, Baseline Data and Participant Status dataset – One record per enrolled participant. Includes screening data (Form 2), baseline data, QoL (at baseline only) (Forms 4 – 7), randomization (Randomization Assignment), and termination data (Form 17 Exit) for all randomized patients. Value added fields include all survival times, study time, and others.

FOLLOW-UP: Data collected at regular follow-up contact – One record per regular follow-up contact for each randomized participant, therefore creating multiple records per randomized participant. Follow-up data includes Forms 10-16.

EVALUATION CDI: Data collected in Form 9. Value added fields include indications of primary endpoint, possible recurrent CDI, definite recurrent CDI, possible CDI with negative lab result. consolidated death within 56 days, and consolidated death within 180 days

EFFICACY: Demo Data and Evaluation CDI data – One record per enrolled participant. It merges demographic data with CDI evaluation data and includes the value-added fields such as primary endpoint, possible recurrent CDI, definite recurrent CDI, possible CDI with negative lab result, consolidated death within 56 days, and consolidated death within 180 days. Primary and secondary endpoints and baseline information are included for major efficacy analyses.

SAFETY: Adverse Event dataset that includes all reported adverse events and serious adverse events. There is one record per adverse event record including the initial report and all follow-ups. Value added fields include MedDRA coding terms.

4.6 Programming Specifications and Software

Programming for data summaries and analyses will be primarily performed using SAS v9.3 or v9.4 on the UNIX AIX platform. Programming specifications and documentation will be completed according to the study data management plan and WH-CSPCC work instructions.

4.7 Validation of Statistical Programs

This study may adapt programs which have been validated for use in other studies at WH-CSPCC. If so, program validation may include review of the result and testing of the adapted program using study data. New statistical programs will be drafted, tested, and validated by a biostatistician or a programmer before use.

Appendix

CSP #2004 MATCH

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CSP #2004

Table 1: Number of Potential Participants Screened, Eligible, and Randomized by Month

Month	No. Screened	No. Eligible	No. Randomized	Cumulative No. Screened	Cumulative No. Eligible	Cumulative No. Randomized
1						
2						
3						
…						
36						

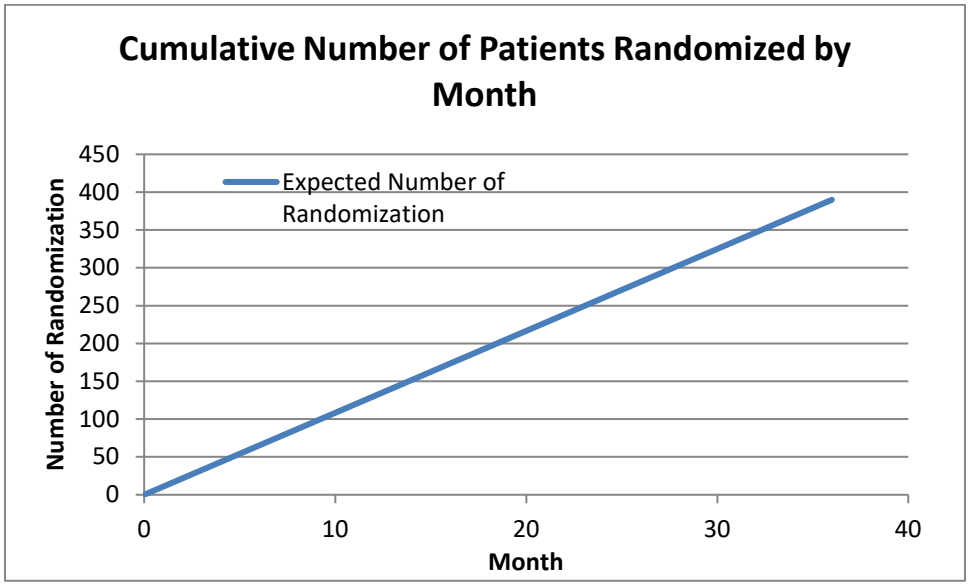
CSP #2004

Table 2: Cumulative Number of Patients Screened, Eligible and Randomized by Site

Site	Cumulative No. Screened	Cumulative No. Eligible	Cumulative No. Randomized
Minneapolis			

CSP #2004

Figure 1: Cumulative Number of Patients Randomized



CSP #2004
Table 3: Summary of Screening and Reasons for Not Eligible

Reason for Not Eligible	Number	Percent
INCLUSION CRITERIA		
Current episode of CDI being treated with standard antimicrobial treatment		
Prior episode of CDI within 90 days before the onset of the current CDI		
Age >= 18 years		
Willing and able to provide informed consent		
EXCLUSION CRITERIA :		
Inability to swallow capsules		
Pregnant or planning to become pregnant		
Receipt of cytotoxic chemotherapy, immune globulin, or confirmed neutropenia (absolute neutrophil count of < 1,000 cells/mL), within the past 3 months		
Inflammatory bowel disease or other chronic diarrheal disease/fecal incontinence predating CDI		
Ongoing antibiotic use		
Prior FMT		
Life expectancy of < 8 weeks		
Anaphylactic food allergy		
Active enrollment in another research study on antibiotics, probiotics, or FMT without investigators approval		
Inability to follow study protocol		

CSP #2004
Table 4: Distribution of Randomized Patients by Site and Stratification

Site	Randomization Stratification	Treatment 1		Treatment 2	
		N	%		
Minneapolis	Overall				
	1st recurrent CDI				
	>1 recurrent CDI				

CSP #2004
Table 5: Subject Study Status

Site	Description	Treatment 1		Treatment 2	
		N	%		
Minneapolis	No. of Randomized				
	Being followed				
	Exit from study				
	Completed 6-mo follow-up				
	Death				
	Lost to follow-up				
	Withdrew				
	Other				

CSP#2004
Table 6: Completeness of Expected Follow-up Forms by Site

Visits	Treatment 1		Treatment 2		Total	
	Expected	Completed (%)	Expected	Completed (%)	Expected	Completed (%)
Baseline						
Day 2						
Week 2						
Week 8						
6 Months						

CSP #2004
Table 7: Summary of Data Queries by Form Pack and Site

Form	Site 1		Site 2		Site 3	
	Total Queries	Unresolved Queries (%)	Total Queries	Unresolved Queries (%)	Total Queries	Unresolved Queries (%)
Form 1						
Form 2						
…						

CSP #2004
Table 8: Summary of Protocol Deviations by Treatment

Deviation Type	Treatment 1		Treatment 2	
	N	%	N	%

CSP #2004

Table 9: Baseline Demographic Characteristics by Treatment Assigned

Characteristic	Treatment 1		Treatment 2		Total	
	N	%	N	%	N	%
Mean Age (SD)						
Gender						
Male						
Female						
Race						
White						
Black or African-American or Negro						
American Indian or Alaskan Native						
Asian Indian						
Chinese						
Japanese						
Filipino						
Korean						
Vietnamese						
Other Asian						
Native Hawaiian						
Guamanian or Chamorro						
Samoan						
Other Pacific Islander						
Other						
Refused to Answer						
Ethnicity						
Not Hispanic						
Mexican, Mexican American, Chicano						
Puerto Rican						
Cuban						
Other Spanish, Hispanic or Latino						
Refused to Answer						
Hight (cm)						
Weight (kg)						
Education						
< High School Diploma						
High School diploma						

Technical Certificate						
Associate Degree						
Bachelor's Degree						
Master's Degree						
Ph.D. or Professional Dr						

CSP #2004
Table 10: Baseline Laboratory Assessments

Assessments	Treatment 1		Treatment 2		Total	
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N
Serum Albumin						
Serum Creatinine						
WBC						
Hemoglobin						
Hematocrit						
Platelet count						

CSP #2004
Table 11: Baseline Physical Examination

Assessments	Treatment 1		Treatment 2		Total	
	N	Mean (SD) Or %	N	Mean (SD) Or %	N	Mean (SD) Or %
Weight (lbs.)						
Height (inches)						
SBP (mmHg)						
DBP (mmHg)						
Heart Rate (beats/min)						
Respiration (breaths/min)						

CSP #2004
Table 12: Baseline Medical History

Assessments	Treatment 1		Treatment 2		Total	
	N	Mean (SD) Or %	N	Mean (SD) Or %	N	Mean (SD) Or %
Surgical History						
Appendectomy						
Gastric Bypass or Banding						
Resection of Small Bowel or Colon						
Other						
Medical History						
Diabetes						
Coronary artery disease						
Chromic liver disease						
Chronic kidney disease						
Hematologic cancer						
Solid-organ cancer						
Systemic antibiotics in last 6 months						
Others						
Resident in Nursing Home						
Number of prior episode of CDI						
1						
2						
3						
4						
>4						
Use of probiotics in the past 12 months						
Lactobacillus species						
Saccharomyces species						
Multiple agents						
Other probiotics						

CSP #2004

Table 13: Summary of Study Specific Adverse Events by Treatment at 48 Hours

Event	Description	Treatment 1		Treatment 2		Total		p-value
		Event Count	N (%)	Event Count	N (%)	Event Count	N (%)	
	Count of form received							
Diarrhea	No. event							
Abdominal pain	No. event							
	Severity: Mild							
	Moderate							
	Severe							
	Ongoing (yes)							
Vomiting	No. event							
	Severity: Mild							
	Moderate							
	Severe							
	Ongoing (yes)							
Nausea	No. event							
	Severity: Mild							
	Moderate							
	Severe							
	Ongoing (yes)							
Bloating	No. event							
	Severity: Mild							
	Moderate							
	Severe							
	Ongoing (yes)							
Gas/Flatulence	No. event							
	Severity: Mild							
	Moderate							
	Severe							
	Ongoing (yes)							
Belching	No. event							
	Severity: Mild							
	Moderate							
	Severe							
	Ongoing (yes)							

Fatigue	No. event							
	Severity: Mild							
	Moderate							
	Severe							
	Ongoing (yes)							
Constipation	No. event							
	Severity: Mild							
	Moderate							
	Severe							
	Ongoing (yes)							
Anorexia	No. event							
	Severity: Mild							
	Moderate							
	Severe							
	Ongoing (yes)							
Fever	No. event							
	Mean temperature							
	STD							

CSP #2004

Table 14: Summary Serious Adverse Events Reasons by Treatment

	Treatment 1	Treatment 2	All
	N (%)	N (%)	N (%)
No. of Randomized Participants	67	70	137
No. Serious Adverse Events after Randomization/Implantation	10	7	17
SAE Criteria			
Death	0 (0.0)	0 (0.0)	0 (0.0)
Life-threatening	0 (0.0)	0 (0.0)	0 (0.0)
Congenital Anomaly/Birth Defect	0 (0.0)	0 (0.0)	0 (0.0)
Hospitalization/Prolongation of Hospitalization	9 (90.0)	6 (85.7)	15 (88.2)
Disability - Incapacity	0 (0.0)	0 (0.0)	0 (0.0)
Other Event Considered Serious by LSI	1 (10.0)	2 (28.6)	3 (17.6)
SAE Attribution to the study intervention			
Not Attributed	9 (90.0)	6 (85.7)	15 (88.2)
Possibly Attributed	1 (10.0)	1 (14.3)	2 (11.8)
Yes, Attributed	0 (0.0)	0 (0.0)	0 (0.0)
SAE Outcome			
Death	0 (0.0)	0 (0.0)	0 (0.0)
Life-threatening	0 (0.0)	0 (0.0)	0 (0.0)
Severe	10 (100.0)	5 (71.4)	15 (88.2)
Moderate	0 (0.0)	2 (28.6)	2 (11.8)
Mild	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
SAE cause discontinuation from the study			
Yes	0 (0.0)	0 (0.0)	0 (0.0)
No	0 (0.0)	0 (0.0)	0 (0.0)

* More than one SAE Criteria can be checked per SAE. Therefore, percentages do not sum up to 100%.

Data is arbitrary for explain the table set up only.

CSP #2004

Table 15: Summary of MedDRA Coding of Serious Adverse Events by Treatment

	Treatment 1			Treatment 2			All		
		N			N			N	
No. of Randomized Participants		67			70			137	
Total Subject-Year In Study		100.9			108.7			209.6	
No. Serious Adverse Events after Randomization		161			153			314	
No. Subjects with SAEs after Randomization		41			38			79	
SYSTEM ORGAN CLASS/Preferred Term	**No. of SAEs**	**No. of Subjs**	**% of Subjs**	**No. of SAEs**	**No. of Subjs**	**% of Subjs**	**No. of SAEs**	**No. of Subjs**	**% of Subjs**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1	1	1.5%	2	2	2.9%	3	3	2.2%
Autoimmune haemolytic anaemia	0	0	0.0%	1	1	1.4%	1	1	0.7%
Haemorrhagic anaemia	1	1	1.5%	0	0	0.0%	1	1	0.7%
Normochromic normocytic anaemia	0	0	0.0%	1	1	1.4%	1	1	0.7%
CARDIAC DISORDERS	67	28	41.8%	49	23	32.9%	116	51	37.2%
Cardiac failure congestive	32	20	29.9%	36	20	28.6%	68	40	29.2%
Atrial fibrillation	10	8	11.9%	2	2	2.9%	12	10	7.3%
Acute myocardial infarction	7	5	7.5%	1	1	1.4%	8	6	4.4%
Myocardial infarction	4	4	6.0%	1	1	1.4%	5	5	3.6%
Cardiomyopathy	3	3	4.5%	0	0	0.0%	3	3	2.2%
Cardiac arrest	1	1	1.5%	1	1	1.4%	2	2	1.5%
Coronary artery disease	2	2	3.0%	0	0	0.0%	2	2	1.5%
Ventricular fibrillation	1	1	1.5%	1	1	1.4%	2	2	1.5%
Acute left ventricular failure	0	0	0.0%	1	1	1.4%	1	1	0.7%
Angina pectoris	0	0	0.0%	1	1	1.4%	1	1	0.7%
Angina unstable	1	1	1.5%	0	0	0.0%	1	1	0.7%
Atrioventricular block complete	1	1	1.5%	0	0	0.0%	1	1	0.7%
Bradycardia	0	0	0.0%	1	1	1.4%	1	1	0.7%
Cardiac failure	0	0	0.0%	1	1	1.4%	1	1	0.7%
Cardiac failure acute	0	0	0.0%	1	1	1.4%	1	1	0.7%
Congestive cardiomyopathy	1	1	1.5%	0	0	0.0%	1	1	0.7%
Coronary artery occlusion	1	1	1.5%	0	0	0.0%	1	1	0.7%
Mitral valve incompetence	1	1	1.5%	0	0	0.0%	1	1	0.7%
Pulseless electrical activity	0	0	0.0%	1	1	1.4%	1	1	0.7%

CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	0	0.0%	1	1	1.4%	1	1	0.7%
Haemorrhagic arteriovenous malformation	0	0	0.0%	1	1	1.4%	1	1	0.7%
EAR AND LABYRINTH DISORDERS	1	1	1.5%	0	0	0.0%	1	1	0.7%
Vertigo	1	1	1.5%	0	0	0.0%	1	1	0.7%

Data is arbitrary for explain the table set up only.

CSP #2004
Table 16: Summary Other Adverse Events Reasons by Treatment

Event	**Treatment 1**		**Treatment 2**		**Total**	
No. Subject Enrolled						
Subject-year of follow-up						
No. AEs						
No. Subject with AE						
AE Attribution to Study Therapy						
Not Attributed						
Possibly Attributed						
Yes, Attributed						
Severity of AE						
Mild						
Moderate						
Severe						
Life-threatening						
Death						
AE still ongoing						
No						
Yes						
Cause discontinuation from the study						
No						
Yes						

CSP #2004

Table 17: Summary of Potential Recurrent CDI within 56 Days by Treatment Assigned

Description	Treatment 1			Treatment 2			Overall		
	n	N*	%	n	N*	%	n	N*	%
No. of Randomization									
No. of potential recurrent CDI (Form 9)									
No. of Possible recurrent CDI									
No. of Cases with Toxin+									
No. of Possible CDI or Cases with Toxin+									
No. of Cases with PCR+									
No. of Cases with Toxin - & PCR +									
No. of Cases with Toxin - & PCR -									

*N is number of form 9.

CSP #2004

Table 17A: Recurrent CDI or Death within 56 Days by Treatment Assigned

Primary Outcome (No. recurrent CDI of Death)	Treatment 1		Treatment 2		Odds Ratio (95% CI)	p-vale to test odds ratio =1
	R/N	%	R/N	%		
No. of Randomization						
No. of recurrent CDI (definite or possible) or Death						
No. of definite recurrent CDI						
No. of Death						
No. of possible recurrent CDI						

Table 17B: Recurrent CDI or Death within 6 Months by Treatment Assigned

Same lay out as table 17.

CSP #2004

Table 18: Number of Recurrent CDIs within 56 days by Treatment Assigned

Number of recurrent CDI	Treatment 1		Treatment 2		Odds Ratio (95% CI)	p-vale to test odds ratio =1
	R/N	%	R/N	%		
No. of Randomization						
Definite CDI						
0						
1						
Above 1						
Possible CDI						
0						
1						
Above 1						
Possible or Definite CDI						
0						
1						
Above 1						

Table 18A: Number of Recurrent CDIs within 6 Months by Treatment Assigned

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Table 19A: CDI Evaluation among Definite CDIs within 56 Days by Treatment Assigned

Description	Treatment 1			Treatment 2			Total		
	No	Yes	N/A	No	Yes	N/A	No	Yes	N/A
No. of Randomization									
No. of Subs with definite CDI									
Clinical Symptoms									
>3 loose stools per 24h for days									
Ileus									
Toxin megacolon									
Stool Specimen Collected									
Urgency									
Occasional urgency									
Frequent urgency									
Inability to control defecation									
Unintentional passing of stool									
Use pads or altered lifestyle									
Abdominal pain									
New pain or worsening									
Pain scale (mean, std)									
No. of episode pain/day (mean, std)									
Medical office visit									
Cause of abdominal pain									
With non-CDI cause									
Without clear non-CDI cause									
With criteria meeting primary endpoint									
Antibiotic use since randomization									

Table 19B: CDI Evaluation among Possible CDIs within 56 Days by Treatment Assigned
Table 19C: CDI Evaluation among Possible CDIs but not definite CDI within 56 Days by Treatment Assigned

CSP #2004

Table 20: Summary of Gastrointestinal QoL Score (GQoL) by Time Point and Treatment Assigned

GQoL Score	Treatment 1		Treatment 2		Difference of Treatment 1 – Treatment2	p-value
	N	Mean (SD)	N	Mean (SD)		
Baseline						
6 Months						

CSP #2004

Table 21: Summary of Colonic Microbiome by Time Point and Treatment Assigned

	Treatment 1		Treatment 2		Difference of Treatment 1 – Treatment2	p-value
	N	Mean (SD)	N	Mean (SD)		
Baseline time						
Colonic microbiome						
6 Months						
Colonic microbiome						

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Table 22A: Summary of Form 9 cases with clinical symptoms as B.1 (>3 loose/watery stools per 24 h for 2 consecutive days)

	PCR +	PCR -	PCR N/A	Total
Toxin +				
Toxin -				
Toxin N/A				
Total				

Table 22B: Summary of Form 9 cases with any of the three clinical symptoms (>3 loose/watery stools per 24 h for 2 consecutive days, or ileus, or toxic megacolon)

	PCR +	PCR -	PCR N/A	Total
Toxin +				
Toxin -				
Toxin N/A				
Total				