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Defining Optimal treatment for recurrent *Clostridioides difficile* infection (OpTION Study): A randomized, double-blind comparison of three antibiotic regimens for patients with a first or second recurrence

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Abbreviations: *C. difficile* infections (CDI), CDI composite outcome (CDI-COM), Clinical Research Pharmacy Coordinating (CRPCC), Corporative Study Program Coordinating Center (CSPCC), Cooperative Studies Program (CSP), Clinical Science Research Development (CSR&D), Diarrhea composite outcome (D-COM), Fecal microbial transplant (FMT), Fidaxomicin (FDX), Family wised error rate (FWER), Interactive Web-Based Response System (ITTRS), Interactive Web-Based Response System (IWRS), Multi-arm Multi-stage (MaMs), Optimal treatment for recurrent *C. difficile* infection (OpTION), Patient centered outcome (PCO), recurrent CDI (rCDI), Vancomycin (VAN), Vancomycin taper and pulse (VAN-T/P)

HIGHLIGHTS

- Treatment recommendations for recurrent *C. difficile* vary among guidelines
- Current recommendations are also based on low-quality evidence
- CSP 596 will determine comparative efficacy of FDX, VAN, and VAN-T/P, informing care
- Novel methods included a pilot phase and modifications to reduce recruitment barriers
- Protocol modifications addressed evolving CDI management and the COVID-19 pandemic

ABSTRACT:

Background: Although many large, randomized controlled trials (RCT) have been conducted on antibiotic therapy for patients with primary *C. difficile* infections (CDI), few RCTs have been performed for patients with recurrent CDI (rCDI). In addition, fecal microbial transplant (FMT) is neither FDA-approved or guideline-recommended for patients with pauci-rCDI (first or second recurrences). Therefore, a rigorous RCT of sufficient size was designed to determine the optimal treatment among three antibiotic regimens in current practice for treatment of pauci-rCDI.

Methods: VA Cooperative Studies Program (CSP) #596 is a prospective, double-blind, multi-center clinical trial of veteran patients with pauci-rCDI comparing fidaxomicin (FDX) 200 mg twice daily for 10 days and vancomycin (VAN) 125 mg four times daily for 10 days followed by a 3-week vancomycin taper and pulse (VAN-T/P) regimen to a standard course of VAN 125 mg four times daily for 10 days. The primary endpoint is sustained clinical response at day 59, with sustained response measured as a diarrhea composite outcome (D-COM) that includes symptom resolution during treatment (before day 10) without recurrence of diarrhea or other clinically important outcomes through day 59.

Discussion: CSP study 596 is designed to compare three current antibiotic treatments for recurrent CDI that are in clinical practice, but which lack high-quality evidence to support strong guideline recommendations. The design of the study which included a pilot phase initiated at six sites with expansion to 24 sites is described along with protocol modifications based on early trial experience and clinical realities including the COVID-19 pandemic.

Keywords: *C. difficile, recurrence, clinical trial, study design, clinical treatment, veterans*

Trial Registration: This study is registered with clinicaltrials.gov (Identifier: NCT02667418)

1. Introduction

The high symptom recurrence rate following successful antibiotic treatment of initial *Clostridioides difficile* infection (CDI) is distressing [1]. First recurrences are often followed by additional recurrences. Some patients will develop multiple recurrent episodes that typically respond to treatment with either vancomycin (VAN) or fidaxomicin (FDX) but develop recurrent diarrhea within weeks of completing treatment for the previous episode. Best management of first and second recurrent CDI episodes (referred to as pauci-recurrent CDI) to prevent further recurrences is not known. The updated 2021 Infectious Disease Society of America and Society for Healthcare Epidemiology of America (IDSA/SHEA) guidelines for CDI management gave a conditional recommendation for fidaxomicin (FDX) but acknowledged that vancomycin was an acceptable alternative [2]. The recommendations for recurrent CDI were based on low quality evidence and gave the same three options for treatment of a first recurrence that were included in the earlier guideline: repeated treatment with VAN or FDX or a vancomycin taper and pulse (VAN-T/P) regimen [3]. In contrast, the recent American College of Gastroenterology (ACG) guidelines recommend either VAN-T/P or FDX for first recurrence based on treatment given for the initial episode and FMT for those experiencing a second or further recurrence [4]. To improve the quality and consistency of treatment recommendations, the OPTION study (Cooperative Studies Program, CSP #596) was designed as a randomized, double blinded, three-arm treatment trial to compare treatment with VAN-T/P or FDX standard dosing with VAN standard dosing. The study is currently enrolling patients; Herein, we describe the study design and protocol modifications and adjustments made based on experience with a pilot program and the COVID-19 pandemic.

2. Materials and Methods

2.1 Objectives and Outcomes

2.1.1 Objectives

The primary objective is to determine whether FDX and/or VAN-T/P are superior to standard VAN for sustained clinical response in diarrhea composite outcome (D-COM) by day 59 in patients with a first or second recurrence of CDI. Day 59 was chosen to coincide with 28 days after discontinuation of treatment in the VAN-T/P arm and assess response at the same time in all 3 treatment arms. If both FDX and VAN-T/P are found to be superior to VAN, then the non-inferiority of VAN-T/P to FDX will be assessed as a secondary objective. Secondary objectives include: 1) comparison of sustained clinical response rates (D-COM) at 28 days post end of therapy and at day 90; 2) comparison of sustained clinical response rates in *C. difficile* composite outcome (CDI-COM) at 28 days post end of therapy, at day 59 and at day 90; 3) comparison of symptom resolution rate by day 10; and 4) comparison of diarrhea CDI recurrence rates at 28 days post therapy, at day 59 and at day 90. The study was initiated with a Pilot Phase (6 sites, 42 participant target), with aims to: 1) evaluate compliance with and efficiency of a daily patient stool diary; 2) develop a patient-centered outcome questionnaire; and 3) assess the recruitment rate.

2.1.2 Outcomes

The primary outcome is sustained clinical response at study day 59 defined as a diarrhea composite outcome (D-DOM). This includes outcomes that are meaningful to patients; specifically, symptom resolution during treatment without any of the following events assessed

on day 59: 1) Diarrhea recurrence; 2) Other non-fatal clinical events including severe abdominal pain related to current diarrhea illness, toxic megacolon, and colectomy; and 3) Death. Secondary outcomes include a CDI composite outcome (CDI-COM) defined as D-COM with confirmation of recurrent CDI by a positive stool assay; D-COM and CDI-COM at 28 days post-therapy; D-COM and CDI-COM at day 90; rate of symptom resolution; diarrhea recurrence and diarrhea recurrence with confirmation of recurrent CDI following initial symptom resolution; D-COM and CDI-COM among subgroups (infection [or not] with the BI/027/NAP1 strain, number of previous CDI episodes [1 or 2] within 6 months of enrollment, receipt [or not] of concomitant antibiotics at any time during the study, sustained clinical response correlated to Horn's and ATLAS severity scores [5,6]); and change in patient reported C.diff Health Related Quality of Life [7] from baseline to end of treatment and to time of primary outcome assessment (day 59).

Study medications are FDA-approved for use in CDI and expected off-target side effects are minimal. Patient safety is monitored by 1) laboratory tests (CBC and serum chemistry panels) during treatment; 2) documenting adverse events (AEs) determined to be related to study treatment; 3) treatment discontinuation due to AE; and 4) documenting all serious adverse events (SAEs) [8][Ref: VHA Directive 1058.01 and/or 21 CFR 312.32].

2.2 Study Design

OPTION is a prospective, multi-center, double-blind, randomized trial. Patients are randomly assigned equally into one of three treatment groups: a 10-day course of oral VAN (125 mg QID, considered standard of care at the time of study initiation [3,9]; or a 31-day course of VAN-T/P (including standard plus 21-day taper and pulse phase, 125 mg once daily for 7 days, once every other day for 7 days, and once every third day for 7 days), or a 10-day course of FDX

(200 mg BID) (see Figure 1). There is no consensus on an optimal tapered-pulse regimen, but experts emphasize the importance of the 'pulsed" every other day and every third day part of the regimen [10].

2.2 Participants

OPTION was designed to enroll and randomize veteran patients aged 18 and above with confirmed current diagnosis of first or second recurrent CDI at enrollment. Inclusion and exclusion criteria were carefully considered to identify appropriate participants while avoiding likely confounding conditions and modified when necessary during the trial (**Table 1**). CDI diagnosis is determined by diarrhea (based on stool frequency) and laboratory confirmation of *C. difficile* including the detection of free stool toxin or toxigenic *C. difficile* by nucleic acid amplification testing (PCR or LAMP). Given some recurrences occur after an 8-week recurrence window identified by standard rCDI surveillance definitions [11,12], the window was extended to a 90 day follow up period (**Table 2**). During the COVID-19 pandemic the criteria were modified to exclude patients with active COVID-19. Patients were eligible for enrollment based on recovery from COVID-19 as defined by CDC guidance for discontinuation of transmission-based precautions [13].

2.3 Assessment

Participants are closely monitored first for a response to treatment, then for development of diarrhea or CDI recurrence, and concomitant medication use thereafter. After randomization, follow-up contact occurs every 5-7 days with either a phone call or clinic visit, totaling 5 clinic

visits and 10 follow-up phone calls (see **Table 3**). Specific physical exams and lab assessments are waived if there is no need for confirmation/corroboration of a specific compliant and to minimize risk of COVID-19 exposure.

Comorbid conditions and CDI disease severity are assessed at baseline. From randomization to day 10, the Investigator assesses the participant for treatment failure or resolution of diarrhea for 48 consecutive hours compared to the participant's baseline. Beyond day 10, participants meeting the symptom resolution criteria are evaluated for recurrence at each follow-up contact point based on the participant's stool diary entries and after discussion with the participant. Assessment of sustained clinical response is specifically conducted at days 38, 59, 90, and at the unscheduled visit for recurrence.

The patient diary is the primary data collection tool to assess for study medication consumption (up to day 31), symptom resolution, sustained clinical response and/or diarrhea/CDI recurrence (**Figure 2**).

Treatment failure is defined as worsening of CDI after 3 days of treatment which may include progression of CDI into fulminant disease (i.e., toxic megacolon), or increased daily unformed bowel movements compared to the participant's baseline. Symptom resolution is defined as improvement or resolution of diarrhea (≤ 3 unformed bowel movements over 24 hours) for 48 consecutive hours compared to the participant's baseline. Recurrent diarrhea is defined as having >3 loose or semi-formed stools over 24 hours for 48 consecutive hours (after symptom resolution, beyond day 10). Recurrent CDI is defined as recurrent diarrhea with confirmation of toxigenic *C. difficile* or its toxin by stool testing. Quality of life is assessed via a patient-centered outcome questionnaire [7] supplemented with questions about participant concern

of financial impact of the disease developed through a semi-structured interview process implemented during the study pilot phase.

Blood samples are collected to assess safety events and include blood count, serum creatinine, albumin and liver functions. Stool specimens are collected and shipped to a central reference laboratory for subsequent culture and strain typing of the recovered *C. difficile* isolates by restriction endonuclease analysis (REA) [14].

2.4 Recruitment

In 2016, a pilot phase was initiated at six sites to evaluate compliance with and efficiency of a stool patient diary, develop a patient-centered outcome questionnaire, and assess recruitment rates. In 2018, the study was expanded to 24 sites with a goal of recruiting a total of 549 patients (including the pilot phase). In 2021, as the result of the COVID-19 pandemic and slowing of recruitment rates a design modification was made to achieve a more realistic recruitment goal of 459 patients.

Recruitment strategies include reviews of the hospital microbiology laboratory results of stool testing for *C. difficile* and patient electronic medical records for patients with positive tests to identify recurrent CDI episodes, as well as active tracking of patients with first CDI episodes to identify recurrence (most helpful given the ~20% risk of recurrence for patients with a first CDI episode). Positive stool *C. difficile* tests notifications and electronic notifications of oral VAN orders were built into the electronic medical record. Notification of oral VAN orders identified patients treated empirically for recurrent CDI or where treatment was initiated simultaneously with request for a stool specimen.

2.4.2 Additional Barriers to Recruitment Identified

Changes in the epidemiology, diagnostic algorithms, clinical guidelines, clinical practice and the COVID-19 pandemic have impacted CDI recruitment during this trial. Rates of CDI and healthcare associated (HCA) CDI declined nationally 24% and 36%, respectfully from 2011 to 2017 [15]. A widely epidemic strain of *C. difficile* variously termed ribotype 027, restriction endonuclease type BI and North American pulse field type NAP1, responsible for a major portion of all CDI cases during the first decade of the 21st century, declined from 31% in 2011 to 15% in 2017 for HCA CDI and from 19% to 6% for community CDI [15].

The use of nucleic acid amplification tests (NAAT, which detect the presence of a toxin-producing strain of *C. difficile* in stool) for diagnosis of CDI increased markedly from 55% of laboratories in 2011 to 83% in 2017. NAAT testing had been demonstrated to be 50% or more sensitive compared to stool toxin testing in the diagnosis of CDI and raised concern that it was too sensitive and was resulting in overdiagnosis of CDI [16]. As a result, diagnostic algorithms were adopted in some laboratories that included tests for *C. difficile* toxin in stool (a much less sensitive test than NAAT) resulting in a decrease in CDI diagnoses in these institutions. Although NAAT testing without pre-screening for symptoms has led to overdiagnosis of CDI, enrollment in OPTION requires symptomatic criteria in addition to positive stool *C. difficile* testing as well as documentation of a prior episode of CDI that was treated followed by response and recurrent symptoms after treatment, making the concern for overdiagnosis less relevant and supporting NAAT only testing for this study.

The 2017 IDSA/SHEA CDI clinical guidelines [3] offered weak recommendations for treatment of recurrent CDI with low to moderate quality of evidence. A guideline summary in JAMA [17] over-simplified the recommendations, necessitating a clarification letter to the editor [18]

highlighting the low evidence quality informing recommendations and the need for further research. Clinician confusion was evidenced by OPTION site investigators, questioning if it remained ethical to treat recurrent CDI with standard VAN therapy.

As clinical practice evolved, use of VAN oral prophylaxis to prevent subsequent CDI recurrence among patients diagnosed with CDI who were taking antibiotics appeared to increase. Limited retrospective observational studies and an open-label trial have been published supporting its use [19,20] suggesting that oral VAN can prevent recurrence of CDI and reduce the number of patients available for study enrollment.

An additional clinical practice change has been to treat recurrent diarrheal symptoms as recurrent CDI by prescribing treatment (usually with VAN) without the benefit of repeat testing to confirm recurrence of CDI. We have been able to partially mitigate this practice by monitoring oral VAN orders and requesting that the provider obtain CDI stool testing so that patients with a positive test can be considered for enrollment in OPTION.

Finally, the COVID-19 pandemic markedly curtailed recruitment in OPTION. All VA clinical research enrollment was halted from March to August 2020. When the national hold was lifted, local sites were still required to have permission from their local Institutional Review Board to resume recruitment, and many sites due to ongoing COVID-19 were unable to obtain permission to reopen. OPTION was particularly affected by the pandemic because the majority of our local site investigators are infectious disease trained physicians whose clinical activity was required to address COVID-19 patients.

2.5 Randomization and blinding

Participants and all study personnel at the recruitment sites are blinded to treatment allocation. Randomization is based on a permuted block scheme stratified by site. Eligible veterans are randomly assigned equally to one of three treatments: VAN, FDX or VAN-T/P. For each participant, an Interactive Touch Tone Randomization System (ITTRS; maintained by the VA Perry Point CSP Coordinating Center) is used to generate a randomization code and an Interactive Web-Based Response System (IWRS; maintained by the VA CSP Clinical Research Pharmacy Coordination Center) generates the Drug Assignment Certificate

2.6 Treatment

Study medication is started on the day of randomization. Eligible participants receive 1) a 10-day course of oral VAN (125 mg four times daily), or 2) a 31-day course of VAN-T/P which includes a 21-day taper and pulse phase (125 mg once daily for 7 days, once every other day for 7 days, and once every third day for 7 days) following first 10-day treatment of oral VAN (125 mg four times daily), or 3) a 10-day course (200 mg twice daily) of FDX. All participants receive two blister cards containing 31 total days of therapy. Blister cards contained encapsulated (FDX), over-encapsulated (VAN), or placebo arranged to align with the assigned treatment arm. All participants were instructed to take one capsule four times a day for the first 10 days, and one capsule a day on days 11-31 to maintain treatment blinding.

Participants experiencing adverse effects determined to be possibly related to the study drug can be removed from active treatment by the local study investigators in collaboration with the participant's primary providers. Participants who discontinue the study drug are asked to continue with safety assessments until the end of the study. Study participants who fail to respond to treatment or have subsequent diarrhea recurrence or experience complications

(including toxic megacolon, colectomy, or severe abdominal pain related to current diarrhea illness that requires re-treatment for CDI) in the follow up period are transitioned to the care of their primary care physicians for subsequent management.

2.7 Statistical Methods

2.7.1 Overall Statistical Approach

The main objective of this study is to determine whether 1) FDX and/or 2) VAN-T/P is superior to standard VAN for sustained clinical response in diarrhea composite outcome (D-COM) by day 59. This is assessed through two hypotheses, namely, H_1 [H_{10}: $\delta_1=P_1 - P_0 =0$ vs. H_{11}: $\delta_1 \neq 0$], and H_2 [H_{20}: $\delta_2=P_2 - P_1=0$ vs. H_{21}: $\delta_2 \neq 0$].

2.7.2 Sample size and power considerations

We anticipated D-COM rates of 31% (P_0) in the VAN arm and 47% (P_1, P_2) in both the FDX and VAN-T/P arms. To arrive at these estimates, we first calculated recurrent CDI and sustained cure rates reported for VAN and FDX [21] and VAN-T/P [22]. These were then converted to D-COM rates using data from a study that recorded both diarrhea and confirmed CDI recurrence rates [23]. The EAST version 6.5 multi-arm multi-stage (MaMs) module was used for power analysis, which allows sample size calculation comparing multiple treatment arms to a common control for a binary outcome utilizing a generalization of a single-step Dunnett's test [24,25] with an unpooled variance. The study originally planned to recruit 549 participants to obtain 91% global power to detect a 16% absolute difference (31% vs. 47%) in D-COM for at least one comparison (VAN-T/P vs. VAN, FDX vs. VAN) at a family wise error rate (FWER) of 0.05 level (2-sided). Given experience with recruitment challenges during the COVID-19 pandemic, an

adjustment to the sample size was made to enhance study feasibility. With the adjustment, a target of 459 participants was determined with a reduced global power of 85% using the same assumptions as above. This sample size has adjusted for 2 interim looks and 3% missingness rate of D-COM by day 59.

2.7.3 Data analysis for the primary outcome

The primary outcome D-COM will be analyzed using a Z-statistic for equality of proportions for each comparison based on the modified intent-to-treat (mITT) population, which includes all randomized participants who received at least one dose of study treatment medication and met study inclusion criteria. Z-statistic comparing the *i*th (*i*=1,2) treatment arm (VAN-T/P, FDX) with the control (VAN) at the *j*th look (*j*=1, 2 and 3) is given below:

$$Z_{ij} = \frac{\hat{P}_{ij} - \hat{P}_{0j}}{\sqrt{\frac{\hat{P}_{ij}(1-\hat{P}_{ij})}{n_{ij}} + \frac{\hat{P}_{0j}(1-\hat{P}_{0j})}{n_{0j}}}}$$

Here $\hat{P}_{ij}$ and $\hat{P}_{0j}$ are respectively the sample proportions for treatment *i* and control arm from data collected up to the *j*th look. In comparison of proportion of sustained D-COM in the VAN-T/P group or FDX group to that of the VAN group, two-sided p-value for each comparison will be compared to the efficacy boundary in P-value scale at interim looks 1, 2 and final look. The proportion difference and repeated 95% confidence interval for δ_i (difference in proportions for the *i*th comparison) at look *j* (*i*=1, 2; *j*=1, 2 and 3) is:

$$\hat{P}_{ij} - \hat{P}_{0j} \pm c_j \sqrt{\frac{\hat{P}_{ij}(1-\hat{P}_{ij})}{n_{ij}} + \frac{\hat{P}_{0j}(1-\hat{P}_{0j})}{n_{0j}}},\ c_j \textit{ is the efficacy boundary on the Z scale}.$$

Primary analyses will be followed by exploratory analyses, using logistic regression modeling, to account for the effects of baseline covariate (e.g., prior CDI episode, CDI severity,

underlying comorbid conditions, strain) and concomitant antibiotics use during study. D-COM will also be evaluated for a per protocol analysis population, defined as participants in the mITT analysis who are 80% compliant with study drug.

Participants who fail to achieve symptom resolution by day 10 or dropout prior to day 59 due to study-drug related adverse events or because they felt the study drug was ineffective and their symptoms were not improved will be considered as failures to achieve day 59 D-COM. Participants who achieve symptom resolution by day 10 but subsequently have CDI symptoms sufficient to warrant clinical determination of CDI and are withdrawn from the study for re-treatment for CDI despite not having two consecutive days of >3 diarrhea stools will be considered as failures for day 59 D-COM. Participants who terminated prior to day 59 for unknown reasons or reasons unrelated to the study treatment will be handled by multiple imputation methods. Additional sensitivity analyses, assuming all participants with previously imputed values are non-responders, will be performed. Completer analysis will also be done based on participants who remained in the study through the 59-day follow-up period.

2.7.4 Interim analysis.

Two interim analyses, considering stops for efficacy, have been planned when 40% and 70% of participants have been randomized and have completed their day 59-dayfollow-up for the primary outcome. To preserve Type-I error, an O'Brien-Fleming stopping boundary for efficacy will be used. If an unplanned interim analysis is conducted, efficacy boundaries will be recomputed additionally. We will confer with the Data Monitoring Committee (DMC) members for trial stopping guidelines based on findings from the interim analysis.

2.8 Data collection and management

The DataFax clinical trial data management system (by DF/Net Research) is used for data collection via paper case report forms (CRFs) (in the pilot phase) as well as electronic data capture (EDC) via iDataFax (current version 2016) (in the expansion phase). CRFs are reviewed for protocol adherence and data consistency; data queries are submitted for items that fail checks. Quality Control reports listing all unresolved data queries and aggregated data quality reports including information on each recruiting site are generated periodically for review (e.g., number of participants, visits, queries, etc.).

2.9 Ethical considerations

The study is being conducted in compliance with the Guidelines for Good Clinical Practice and CSP Guidelines. The Study protocol and Informed Consent Form have been approved by the Coordinating Center's Human Rights Committee and VA Central Institutional Review Board. All participants give written informed consent and HIPAA authorization. Surrogate consent is not allowed. Personal information about potential and enrolled participants is collected, shared, and maintained in a confidential fashion. The Food and Drug Administration has determined that OPTION is exempt from investigational new drug requirements.

2.10 Study Monitoring

Periodic (monthly – quarterly) central monitoring reports are reviewed to track site performance on recruitment, protocol adherence, data quality and adverse events. Risk-based indicators, including informed consent critical findings, recruitment, withdrawals, data reporting

and quality, protocol deviations, and medication compliance, are reviewed to determine potential critical-to-quality factors specific to this trial.

A Data Monitoring Committee reviews study progress reports at least annually to monitor safety and efficacy of study treatments and provide recommendations to the CSP Director. An Executive Committee monitors protocol adherence, site performance, and data quality, inquires with sites about performance challenges, and makes decisions about site probation, termination, and replacement.

The trial is audited by the VA Site Monitoring, Auditing, and Resource Team (SMART) for compliance with GCP. Monitoring is a collaboration of onsite site visits conducted by SMART Monitors, and remote monitoring performed by SMART and Hines Coordinating Center Quality Assurance RNs.

3. Discussion

The Centers for Disease Control and Prevention recently updated estimates on CDI burden in the U.S. [15]. Despite a 24% decrease from their earlier report, they still estimated 462,100 cases annually and the burden of first CDI recurrences was unchanged, with 31,300 and 38,500 recurrences for community-associated and healthcare-associated cases, respectively, in 2017 [15]. Recurrent CDI remains an important treatment challenge and guidelines on management are hampered by insufficient evidence. Available RCTs have been underpowered, lack appropriate comparators, or fail to address current treatment options. In addition, new antibiotics under development for CDI have failed to reach the clinic [26-29]. In the last decade, fecal microbial transplant (FMT) has been used increasingly as an adjunctive treatment for recurrent CDI, but is not recommended for patients with pauci-rCDI (first or second recurrences) and still lacks FDA

approval. Therefore, OPTION was designed as a rigorous RCT by the VA Cooperative Studies Program to determine the optimal treatment among three antibiotic regimens in current practice for treatment of pauci-rCDI.

The OPTION pilot phase refined the primary data collection tool and a patient-centered outcome questionnaire and assessed the recruitment rate. The study protocol was modified to remove non-essential barriers to recruitment, expand the CDI recurrence window to three months, allowed for one prior treatment with any of the study treatment arms, and expanded the recruitment window allowing 72 hours of prior antibiotic treatment for the enrolling CDI episode (Table 2).

Despite extensive planning and pilot phase, numerous recruitment barriers have been encountered. Barriers include changes in diagnostic testing strategies, evolving treatment guidelines, empiric treatment of recurrent CDI without confirmation by stool testing, increased use of prophylaxis with vancomycin, and the COVID-19 pandemic which temporarily suspended clinical research and also likely changed the epidemiology of CDI, particularly among hospitalized patients. Despite these barriers, the OPTION protocol was adapted with alternate recruitment strategies adopted to allow for ongoing study enrollment as well as a new global power analysis allowing for a more realistic target enrollment goal. The research question remains valid and results from this study should help determine the optimal treatment for pauci-recurrent CDI. Lessons learned during the study will guide future clinical trials for CDI that have been challenging given the ever-changing epidemiology, treatment practices, and diagnostics for CDI.

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Declaration of Competing Interests: The authors declare no commercial, financial or any other conflict of interest in this research.

Ethics approval and consent to participate: The study has been approved by the VA Central IRB (cIRB) (IRB# 1613088). Patients provide written informed consent at the time of enrollment

Availability of data and materials:

De-identified data may be available to other VA and non-VA researchers under certain conditions and consistent with the informed consent and CSP policy which prioritize protecting subjects' privacy and confidentiality possible. It is the policy of the CSP that outcome data will not be revealed to the participating investigators until the study is completed to safeguards against possible biases affecting the data collection. No individual participating investigator has any inherent right to perform analyses or interpretations or to make public presentations or seek publication of any or all of the data other than under the auspices and approval of the Executive Committee.

Authors' Contributions: S.J., D.N.G., X.L. designed the study and prepared the manuscript. All authors contributed to the manuscript and read and approved the final version. The authors express deep appreciation to Fred M. Gordin for his insight, enthusiasm, and contributions to the planning of this study as well as his role on the executive committee until his untimely passing on March 18, 2018.

Disclaimer: The opinions herein are those of the individual authors and the contents do not represent views of the U. S. Department of Veterans Affairs or the US government.

X.L. is currently an employee of AbbVie, however this publication was neither originated nor managed by AbbVie, and it does not communicate results of AbbVie-sponsored Scientific Research. Thus, it is not in scope of the AbbVie Publication Procedure (PUB-100).

Tables

Table 1. Inclusion and exclusion criteria*

Inclusions	Exclusions
• Informed consent obtained and signed • Veteran age ≥ 18* • If female, participant must not be pregnant or nursing. Negative pregnancy test required for females <61 years of age or without prior hysterectomy unless they were documented as post-menopausal* • Confirmed current diagnosis of CDI, determined by having 1) >3 loose or semi-formed stools over 24 hours AND 2) A positive stool assay for *C. difficile*: EIA positive for toxin A/B; or Cytotoxin assay; or Nucleic Acid Amplification Test (NAAT, PCR or LAMP) based detection of toxigenic *C. difficile* • Current episode represents the first recurrent episode of CDI within 3	• Inability to provide informed consent • Inability to take oral capsules • Receipt of >72 hours of antibiotics considered effective in the treatment of CDI including vancomycin, fidaxomicin, metronidazole, rifaximin, or nitazoxanide* • Prior infusion of bezlotoxumab within the previous 6 months* • Known presence of fulminant CDI, including hypotension, severe ileus or GI obstruction or incipient toxic megacolon • Receipt of more than one treatment course of oral vancomycin, more than one treatment course of vancomycin followed by a taper/pulse, and more than one treatment course of fidaxomicin, since the primary episode of CDI as defined above (i.e., one course of any of the above 3 treatment options is allowable)* • Known allergy to vancomycin or fidaxomicin • Acute or chronic diarrhea due to inflammatory bowel disease or other cause

months of the primary CDI episode in a patient who has not had CDI in the 6 months prior to the primary episode OR a second recurrent CDI episode occurring within 3 months of the first recurrent episode, as defined above*

- -At least one of the previous CDI episodes must have been confirmed by a stool assay for *C. difficile*

that would confound evaluation of response to CDI treatment

- Anticipation of need for long term systemic antibiotic treatment (beyond 7 days)
- Patients with an active diagnosis of COVID-19 will be excluded from the study, but patients who have recovered (per current CDC guidance on discontinuation of transmission-based precautions) can be included in the study.*

*Denotes inclusion, exclusion criteria that were clarified or modified after study initiation (changes outlined in Table 2).

399 Table 2. Protocol modifications

Date	Modification
01/06/2016	• Participant self-report diary condensed and simplified
12/02/2016	• Extension of the allowable window for CDI recurrence from 8 weeks to 3 months • Allowance of one prior vancomycin taper/pulse regimen • Removal of requirement for physical exams on days 31, 59, & 90
02/02/17	• Open-ended patient centered outcome (PCO) questionnaire replaced by a recently published and validated PCO with responses rated on a 5-point Likert scale: (C.diff32) [7]
12/01/2017	• Expansion of recruitment window from 48 to 72 hours of prior antibiotics. • Ability to recruit from CBOCs and nearby VA facilities • Permission to travel to participant to conduct follow-up visits in situations where it would be prohibitive for the participant to travel
06/26/2018	• Infusion of bezlotoxumab within 6 months added as an exclusion.
06/26/2019	• Shared enrollment of participants on other CSP intervention studies approved during long-term follow up phase and after the completion of the active phase (intervention and safety monitoring) for those studies
02/13/2019	• Third recruitment strategy approved for identifying patients with first CDI episodes and actively following them for recurrence • Allowance of physical exams conducted by accredited examiner to be substituted for the physical exam by study personnel
09/10/2020	• Exclusion of patients with active COVID-19, but allowance for enrollment of patients who have recovered from COVID-19 as

	defined by CDC • Day 10 physical exam and day 10 and 31 blood draw can be waived when the visit would result in increased risk of harm to patient and no need for confirmation/corroboration of a specific complaint
11/12/2021	• Due to the suspension of recruitment by the COVID-19 pandemic in mid-March 2020 and its significant impact on the slow recruitment after the sites resumed recruitment activities, the target enrollment was reconsidered with a new power analysis reducing the sample size to 459

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Table 3. Schedule of Assessment Measures

Visit	day 0	Call 1 (day 5)	day 10	Call 2 (day 17)	Call 3 (day 24)	day 31	Calls 4, 5, 6 (day 38, 45, 52)	day 59	Calls 7, 8, 9, 10 (days 66, 73, 80, 87)	day 90	Unscheduled Visit for Recurrence
Eligibility & Randomization	X										
Informed Consent	X										
Demographics	X										
Past Medical History	X										
Medication Use	X	X	X	X	X	X	X	X	X	X	X
Targeted Physical Exam	X		X***			X*		X*		X*	X
Laboratory Assessments	X		X***			X***					
Severity/Horn's Assessment	X										
Stool Sample	X										X
Pregnancy Test	X										
Study Diaries	X	X	X	X	X	X	X	X	X	X	X
Collection of Study Diary			X			X		X		X	X
Patient Centered Outcome	X		X					X			
Adverse Events	X	X	X	X	X	X	X	X			(AE-SAE follow up closed out)
Assessment of Treatment Failure & Symptom Resolution			X								
Assessment of Recurrence & Sustained Clinical Response							X (day 38)	X		X	X
Drug Dispense	X		X								

* Physical exam will only be performed on days 31, 59, and 90 if the participant history indicates need for confirmation/corroboration of a specific complaint.

*** The day 10 physical exam and the day 10 and day 31 blood draw can be waived when the visit would result in increased risk of harm to the participant; and

404 if there is no need for confirmation/ corroboration of a specific complaint.

Figure Legends

Figure 1. Study Design

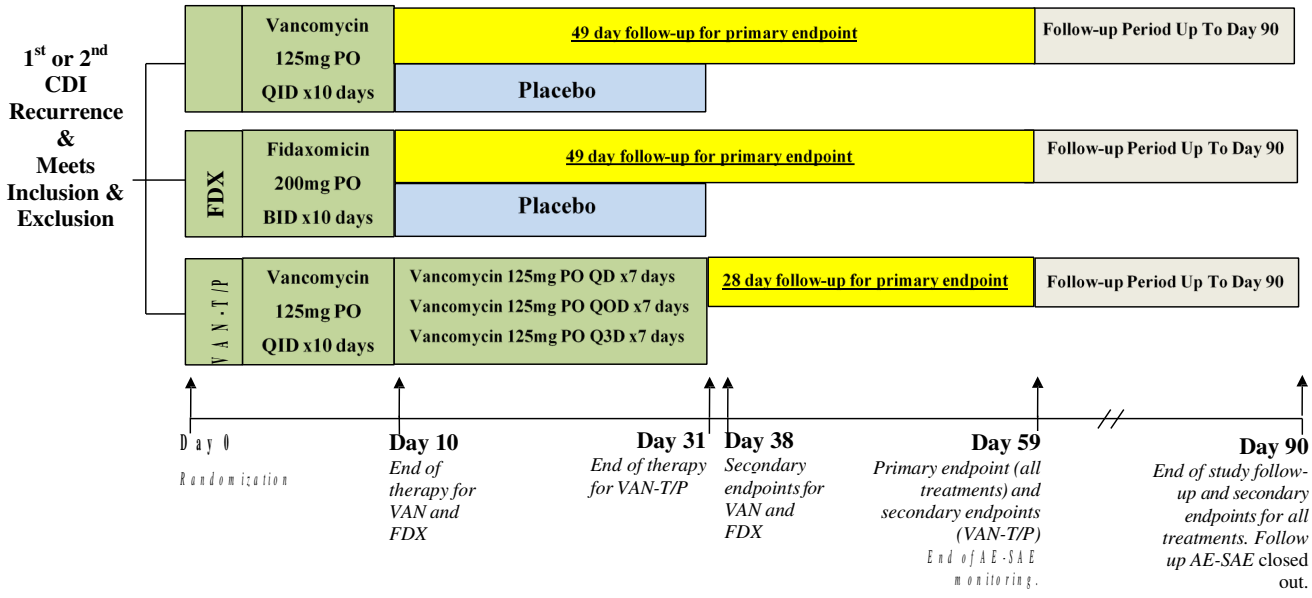

Figure 2. Patient Self-Reported Diary

Bristol Stool Chart

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on the surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges
Type 6		Fluffy pieces with ragged edges, a mushy stool **DIARRHEA**
Type 7		Watery, no solid pieces. **Entirely Liquid**

DAY x (day 1-10):

PARTICIPANT ID: _ _ _ _ _ _ _

DATE

Today's date: _____

STUDY DRUG

Did you take **all 4 capsules** today? ☐Yes ☐No

If **no**, specify number of capsules **missed**: _____ , and **explain:**

_____

_____

_____

BOWEL MOVEMENTS

How many bowel movements did you have today? _____

How many of these bowel movements were **loose or watery bowel movements** (DIARRHEA)? _____

If you feel your condition is not getting better, please notify the study doctor or coordinator immediately

DISCOMFORTS AND HEALTH CONCERNS

Have you had any of the following discomforts or health concerns today?

☐Yes ☐No, **if yes, please specify;** otherwise stop

Discomfort or Health Concern	Scale: 0=None, 1 = Mild, 2=Moderate, 3 = Severe			
Nausea	0	1	2	3
Abdominal (Belly) Pain	0	1	2	3
Rash	0	1	2	3
Bloating	0	1	2	3
Urgent Need to Have A Bowel Movement	0	1	2	3

COMMENTS *(optional)*

_____

_____

_____

_____

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