Perelman School of Medicine
University of Pennsylvania

Open Label, Randomized, Multicenter, Comparative Effectiveness Trial of Specific Carbohydrate and Mediterranean Diets to Induce Remission in Patients with Crohn's Disease

Principal Investigator *James D. Lewis, MD, MSCE*
Perelman School of Medicine
Gastroenterology
720 Blockley Hall, 423 Guardian Drive
Philadelphia, PA 19104
215-573-5137
lewisjd@mail.med.upenn.edu

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List of Abbreviations

For example: LIST OF ABBREVIATIONS-list alphabetically.

AE: Adverse event

DCC: Data Coordinating Center

DMC: Data Management Center

DM: Diabetes Mellitus

DMS: Data Management System

DSMB: Data Safety Monitoring Board

FCP: Fecal Calprotectin

SCD: Specific Carbohydrate Diet

MSD: Mediterranean Style Diet

PPRN: Patient-Preferred Research Network

Study Summary

Title	Randomized, Multicenter, Comparative Effectiveness Trial of Specific Carbohydrate and Mediterranean Diets to Induce Remission in Patients with Crohn's Disease
Short Title	DINE-CD
IRB Number	825907
Phase	N/A
Methodology	Open Label Randomized Clinical Trial
Study Duration	3 years
Study Center(s)	Multicenter trial of up to 50 sites
Objectives	*Primary:* 1. To compare the effectiveness of the Specific Carbohydrate Diet and a Mediterranean style diet to induce symptomatic and clinical remission in patients with Crohn's disease. 2. *Secondary:* 1. To compare the effectiveness of the Specific Carbohydrate Diet and a Mediterranean style diet to reduce mucosal inflammation in patients with active Crohn's disease. Mucosal inflammation will be assessed by measuring the concentration of calprotectin in the feces (FCP). 2. To compare the effectiveness of the Specific Carbohydrate Diet and a Mediterranean style diet to reduce systemic inflammation in patients with active Crohn's disease. Systemic inflammation will be assessed by measuring the concentration of C reactive protein (CRP). 3. To compare the effectiveness of the Specific Carbohydrate Diet and a Mediterranean style diet to improve the following symptoms in patients with Crohn's disease: a) fatigue, b) pain, c) joint symptoms. *4.* To determine the proportion of patients who continue the study diets when prepared food is no longer provided without cost and the reasons for discontinuation of the diets.
Number of Subjects	*194 participants to be enrolled across all sites*

Main Inclusion and Exclusion Criteria	*Inclusion Criteria:* ◦ Age ≥18 ◦ Documented diagnosis of Crohn's disease ◦ sCDAI >175 and <400 ◦ Access to a computer with internet and the ability to complete daily online surveys ◦ Capable of providing consent to participate *Exclusion Criteria* ◦ Pregnancy ◦ Hospitalized patients or surgery planned within 6 weeks ◦ Ostomy or known symptomatic intestinal stricture ◦ Use of the Specific Carbohydrate Diet within 4 weeks of screening ◦ Start or change* dose of thiopurines, natalizumab, vedolizumab or methotrexate(w/in 12 weeks) or anti-TNF or ustekinumab (w/in 8 weeks) of screening ◦ Start or change* in dose of any 5-ASA medication within 2 weeks of screening ◦ Use of antibiotics within 2 weeks of screening ◦ Start or change* corticosteroids within 1 week of screening or dose >20mg prednisone or equivalent ◦ Baseline stool frequency >4 bowel movements/day when well ◦ BMI<16 or ≥40 ◦ Celiac disease, recent c diff colitis, or diabetes ◦ Albumin<2.0mg/dl (if measured as part of routine clinical care) * Exception for treatment failures: if a subject is determined to fail on any of the following standard lines of treatment at the treating investigator's discretion, subjects may screen for study intervention based upon the following wash out periods: 4 weeks for thiopurine and methotrexate and 8 weeks for natalizumab, vedolizumab, anti-TNF, or ustekinumab.
Investigational Product (drug, biologic, device, etc.)	Specific Carbohydrate Diet – up to 3000 calories provided to the participant per day.
Duration of administration (if applicable)	6 weeks
Reference therapy	Mediterranean Diet – up to 3000 calories provided to participant per day
Statistical Methodology	The primary analyses for the RCT will use 2-sided tests of statistical significance and will be performed using the intention-to-treat principle. The primary analysis will compare the proportion of patients who achieve a symptomatic remission at week 6 using the Cochran-Mantel-Haenszel (CMH) chi square test . All patients who are withdrawn or lost to follow-up prior to week 6 will be considered treatment failures. The MSD will be considered the reference group for all analyses.
Safety Evaluations	*Not applicable*

Data and Safety Monitoring Plan	A Data Safety and Monitoring Board (DSMB) will oversee the safety of the study.

1. Background and Study Rationale

1.1 Introduction

This study will be conducted in full accordance with all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations. This protocol is designed to compare the effectiveness of two dietary interventions for patients with Crohn's disease (CD). This randomized controlled trial (RCT) will provide the strongest evidence to date as to whether a commonly used restriction diet known as the Specific Carbohydrate Diet (SCD) is superior to a Mediterranean style diet (MSD) that has been demonstrated to have numerous other health benefits. The two diets will be compared in terms of their ability to resolve the symptoms that characterize this debilitating disease; and as secondary objectives, we will evaluate the ability of the diets to reduce inflammation of the bowel, systemic inflammation and other symptoms of the disease.

1.2 Background and Relevant Literature

CD is a chronic, debilitating disease with no cure that affects more than 500,000 Americans, with peak incidence in the 2nd and 3rd decades of life[1-6]. Cardinal symptoms of CD are abdominal pain, diarrhea, and weight loss. Most patients with CD will require at least one bowel resection – many require multiple resections[7,8]. The most feared complication of repeated bowel resections is short gut syndrome, causing chronic diarrhea, life threatening malnutrition and dehydration. Other complications of CD include mouth sores, eye problems (e.g. uveitis and episcleritis), arthritis and arthralgia, erythema nodosum, pyoderma gangrenosum, kidney stones, and blood clots. The currently available medical therapies are only effective for a fraction of the patients with CD (described below). Furthermore, the medications used to treat CD also may increase the risk of life threatening complications such as serious infections or cancer[9-17]. Sadly, despite the advances in medical therapy, patients with CD, particularly those with persistently active symptoms, have high rates of disability[18-23], reduced quality of life[24-27], and reduced life expectancy relative to the general population[28].

1.2.1 Therapeutic strategies for Crohn's disease

Numerous medications are efficacious in the treatment of CD, nearly all of which suppress the immune system (reviewed in[29-31]). The most effective of the currently available medications are antibodies directed against tumor necrosis factor α (anti-TNF) used in conjunction with a second immunosuppressant medication (either a thiopurine or methotrexate). However, even with this approach remission rates are <60%[32] and substantially wane over time[33,34]. Moreover, chronic immunosuppression is associated with numerous adverse effects including uncommon but potentially fatal adverse reactions, particularly lymphoma and serious infections[9-17]. Concerns about these uncommon but life threatening adverse effects strongly influence patients' choice of medical therapies[35-37]. As such, there is great interest in and need for alternative treatment strategies that are not based on immunosuppression.

Like for many intestinal diseases, it has been suggested for decades that dietary patterns may influence the course of CD. Indeed, this is among the most frequently asked question by patients. Furthermore, the majority of patients report intolerance to specific food items[38,39] and many follow nutritionally compromised diets[40], yet less than half have seen a nutritionist[41]. Thus, understanding the role of diet on the natural history of CD is of major public health interest. Unfortunately, there have been few high quality studies that specifically addressed this question.

1.3 Name and Description of the Investigational Product

The Specific Carbohydrate Diet was popularized by Elaine Gottschall in the book Breaking the Vicious Cycle[42]. The menu created for participants randomized to the SCD will follow the detailed descriptions in the book for which foods are allowed and not allowed. The SCD restricts all but simple carbohydrates. The only carbohydrates permitted are monosaccharides: glucose, fructose, and galactose. Fresh fruits and vegetables are universally acceptable with the exception of potatoes and yams. Certain legumes (i.e. lentils, split peas) are permitted, however others (i.e. chickpeas, soybeans) are not. No grains are permitted in the SCD. Saccharin and honey are permitted in addition to moderate use of sorbitol and xylitol. Canned fruits and vegetables are not permitted due to possible added sugars and starches. Unprocessed meats are permitted in the SCD without limitation. However processed, canned, and most smoked meats are restricted due to possible sugars and

starches used in additives. Milk is not permitted in the SCD due to lactose content. However, certain lactose free cheeses are permitted as is homemade lactose-free yogurt. See Appendix K for a detailed description of the menu for participants on the SCD.

1.4 Clinical Data to Date in Adults and Children

Dietary interventions are an attractive adjunct or alternative to immunosuppression therapy for CD. Exclusive enteral nutrition (EEN) with elemental, semi-elemental and defined formula diets are commonly used in the treatment of pediatric CD, particularly in Canada, Japan and Europe[43-45]. Commercially available formulae have proved efficacious in treating symptoms and intestinal inflammation in CD in addition to supporting nutritional needs (Figure 1 adapted from Cochrane review).[46-48]However, the effectiveness is greatest when used as the exclusive source of nutrition.[47,49] When compared head to head against corticosteroids, both resulted in improved symptoms, but only EEN resulted in healing of the mucosal inflammation which characterizes CD[46]. This approach has the advantage of avoiding the need for immunosuppression medications but is difficult to maintain long term. For maintenance of remission, a diet in which half of the daily calories were from an elemental supplement resulted in a nearly 50% reduction in CD relapse rates compared to a regular diet[50], suggesting that less extreme dietary interventions may be beneficial as well.

Two recent systematic reviews have addressed this question. The first reviewed 23 RCTs of fiber supplementation in IBD[51]. Although meta-analysis was not possible, the authors concluded that the role of fiber is intriguing and merits further investigation in adequately powered clinical trials. The second systematic review examined dietary interventions more broadly[52]. Although summary measures of efficacy were not calculated, the authors concluded that exclusion diets such as the specific carbohydrate diet (SCD) and the low FODMAP (fermentable oligo-, di-, and monosaccharides and polyphenols) were the most promising. This is consistent with systematic evaluations that show that the majority of patients believe diet affects the course of their disease[53,54] and the countless testimonials of patients who have tried SCD and other restriction diets as treatment for CD.

Fiber supplementation and restriction diets are completely different strategies to manage CD, though exclusion diets are more closely related to EEN and are the focus of this proposed study. In our prior qualitative review, we documented that most restriction diets had little clinical evidence to support their efficacy[55]. However, several recent small studies have provided important evidence that use of the SCD both improves symptoms and reduces bowel inflammation. For example, Suskind et al. reported the effectiveness of the SCD in 7 children with CD who were not receiving any immunosuppressive therapies[56]. All had clinical improvement by 3 months and in those whose inflammatory markers were measured, there was notable improvement. Cohen et al. completed a more rigorous evaluation of the SCD[57]. Ten children with CD received SCD as primary therapy. Video capsule endoscopy was completed at baseline and after 12 weeks of diet therapy; mucosal inflammation was quantified with the Lewis score (LS). There was significant improvement overall, with 4 of 10 achieving complete mucosal healing (LS<135) and 6 of 10 achieving clinical remission. Thus, like EEN, the SCD demonstrated meaningful clinical improvement and mucosal healing in this uncontrolled study. Several other notable small trials of restriction diets have also demonstrated improved disease activity and prolonged time to relapse[58-64]. Some of these were either derived from or have similarities to the SCD[61,64]. For example, Olendzki studied a diet that was derived specifically from the SCD and reported clinical improvement in 24 of 27 patients (89%) who attempted the diet[64]. Sigall-Boneh and colleagues noted clinical remission in 33 of 47 (70%) children and young adults treated with a restriction diet with or without caloric supplementation with a defined formula diet, including 6 of 7 patients who used the diet without supplemental nutrition from a defined formula. Of those with baseline elevated CRP, 70% had complete normalization, while 11 of 15 (73%) with colonoscopy or small bowel imaging demonstrated mucosal healing. The restriction diet resembled the SCD as condiments, sauces, gluten, dairy, processed meats and foods, and canned foods were all forbidden. Taken together, these small clinical trials have begun to provide evidence to support the testimonials of patients regarding the effectiveness of the SCD.

One might ask why all patients would not at least try the SCD as an adjunctive therapy for CD. The answer lies in the challenge associated with following this diet and the lack of strong endorsement by guidelines[30,31,65] such that many clinicians do not routinely recommend this to their patients. In preparing for this proposal, we queried potential participating sites if they made specific dietary recommendations. Four of 25 (16%) answered yes – only one routinely recommending the SCD. Rather, in the absence of

strong data in favor of a specific elimination diet (such as the SCD), most clinicians recommend that their patients with CD follow a generally healthy, balanced diet.

The MSD is a well-balanced diet that is much easier to follow than the SCD and is consistent with the United States Department of Agriculture and World Health Organization recommendations. Numerous cohort studies, randomized controlled trials, and systematic reviews support the efficacy of this diet to reduce inflammation[66], cardiovascular disease[67,68], cancer[69], and mortality[70]. This is particularly important for patients with CD, as a recent meta-analysis linked CD with an increased risk of cardiovascular disease[71]. Notably, the MSD entails higher fiber intake and appreciably lower red meat intake than the average American diet, and is associated with higher fecal concentrations of short chain fatty acids[72], thus supporting its role as an adjunctive therapy for CD. Additional supportive evidence comes from several small studies. Rajendran used food specific IgG4 levels guide a personalized exclusion diet[62]. Eggs and beef were the most commonly excluded foods. The 29 patients on the exclusion diet experienced a significant reduction in symptoms and reduction in the ESR as compared to pretreatment levels. The major limitation of this study was the absence of a control group. Stronger evidence for the MSD comes from work by Chiba et al.[63], who in a small study (N=22) demonstrated superiority of the semi-vegetarian versus an omnivorous diet to maintain clinical remission (94% vs. 33%)[63]. It should be noted that this was not a randomized trial but rather allowed patients to choose whether or not to continue on the diet after discharge. Together, these studies lend support to the therapeutic potential of the MSD for CD in addition to the overall health benefits associated with this diet.

The MSD was selected as the alternative diet based on 1) the strong evidence of its role in overall health, 2) the easier implementation in routine life, 3) evidence that characteristics of the diet including higher fiber and lower red meat intake may be specifically beneficial for patients with CD, and 4) consistency with recommendations to follow a well-balanced diet. The MSD is backed by strong evidence supporting improved health outcomes in many other domains, including cardiovascular, neurodegenerative disease and cancer. [66-70]

1.4.1 Gaps in Evidence: High quality evidence for the optimal diet once patients are diagnosed is lacking (PCORI Methodology Criterion 1)

As documented in CCFA Partners, patients routinely modify their diets in an attempt to improve symptoms[42,43.] Unfortunately, the current evidence base to guide how patients with CD should modify their diet is suboptimal, reflecting a disconnect with patients' demand for high quality data to inform this question. This also results in inconsistent messages being transmitted to patients. We recently systematically reviewed the recommendations available to patients on the internet[44]. We reviewed the top 30 hits on Google and Bing for the search strings "Crohn's disease diet" and "ulcerative colitis diet". There was enormous variability in the recommendations across the websites. For example, 24% of websites said to include any fruit, while 44% said to avoid any fruits. Thus, patients and their physicians face substantial uncertainty about the best diet for CD. The purpose of this study is to fill the evidence gap. Here we describe existing evidence that supports the need for comparative effectiveness trials of dietary interventions.

1.5 Patient-Centeredness (PCORI Methodology Criterion 3)

1.5.1 Generation and prioritization of the research question by patients from the CCFA Partners Patient-Powered Research Network (PPRN).

Prior to launching CCFA Partners, it was apparent in the medical literature that patients with IBD were deeply interested in the role of diet. We previously demonstrated that the benefits of therapy outweigh the harms for most patients[79,80]. Yet fear of these risks is a major deterrent to patients considering such therapy[35]. Rather, if given a choice of an equally effective nutritional intervention versus a medical therapy, patients with CD overwhelmingly prefer a nutritionally based therapy[81]. Indeed, and alternative medicine (CAM) has been tried by approximately 50% of patients with IBD, with 5-10% using the SCD82. Commonly reported reasons for CAM use are to improve symptoms and provide the patient with greater control of the disease[82]. Beyond what can be measured in a structured scientific experiment, our patients demonstrated their demand for nutrition-based therapies with their actions. For example, in 2014, 3008 patients registered for a CCF produced live webinar on nutrition and IBD and

5360 patients viewed the recording of the webinar. Similarly, in 2014, approximately 6400 patients visited the Diet Module of the I'll Be Determined Website (www.ibdetermined.org), representing 27% of all visitors to the website.

Once the PPRN was launched, we began to collect research questions proposed by patient members. Our interactive patient portal includes a Research section that engages patients in proposing research questions, and discussing and voting upon research questions proposed by others. This process of crowdsourcing generates a dynamic set of patient-generated research priorities. By a large margin, diet was the patient originated study question that generated the greatest support from the PPRN members (Table 1). From the first 69 questions proposed and 900 votes cast to endorse questions, two of the three most endorsed questions were directly related to diet (combined 211 votes of support) and the third question was on the effectiveness of a probiotic formulation, a topic closely related to diet.

Table 1. Questions receiving the most support from PPRN members (from 69 questions proposed and 900 votes cast).

Question proposed by PPRN patient member	Votes in support
We should compare individuals who manage their disease with medications and those who manage their disease with popular diets in the IBD community, such as Specific Carbohydrate Diet, FODMAP, Paleo, etc.	131
Research the validity of VSL#3 probiotic in controlling flare ups or as a factor in remission	96
Compare symptoms of IBD patients who consume dairy and those who avoid dairy	80

With knowledge of this, we reached out to two patient members of the PPRN, both of whom had actively discussed and endorsed the question, to solicit further input that would allow our team of scientists to fully understand the aspects of this question that were most important to the patients. (Note, the patient who proposed the question is a member of the PPRN Patient Governance Council and suggested the inclusion of other network members in this proposal.) The patients clarified that both were successfully using diet as their primary therapy for their CD but wanted more evidence to guide what is the most effective diet. With their help, through a series of conference calls, we finalized the research question. Our jointly established research goal is to determine the comparative effectiveness of two commonly used diets by patients with CD, the SCD and the MSD.

1.5.2 This research will focus on outcomes of primary interest to patients with CD

The proposed research will focus on two primary outcomes, resolution of the symptoms that characterize active CD and interfere with daily activities and reduction of bowel inflammation. Each of these is important to patients in their own right. Diarrhea, abdominal pain, and decline in overall wellbeing are the most common presenting symptoms for patients with CD[83,84] (i.e. presence of these symptoms overcomes the inertia to ignore one's health). In our ongoing PCORI-funded study within CCFA Partners, we have confirmed that patients with CD have substantial disutility for these symptoms of CD. We surveyed 1250 patients with CD with discrete choice experiments (DCEs) using methods of conjoint analysis to estimate patients' utilities for treatment outcomes. Within the DCE, patients were asked to choose between two treatment options, each of which was described in terms of the following attributes: duration and severity of symptoms (including diarrhea, abdominal pain and general wellbeing), duration of use of steroids, and absolute increase in risk of severe infections, cancer, and need for bowel resection surgery. Our preliminary analysis demonstrates the strong negative preferences that patients have for active CD symptoms and steroid use and that the disutility is strongly tied to duration of symptoms (i.e. short periods of mild to moderate symptoms and/or steroid use are tolerable while longer periods or severe symptoms are not). We have considered this in designing our study, particularly the inclusion criteria and trial duration.

We will also examine resolution of inflammation as measured with a fecal marker, calprotectin (FCP). This biomarker is a strong predictor of another outcome of importance to patients – the duration that they will remain free of symptoms of CD. It has been repeatedly demonstrated that patients with IBD who have an elevated FCP concentration have earlier relapse of disease[85]. Thus, we will use this

biomarker as a surrogate for future disease course. Importantly, we have demonstrated that patients highly value time in remission using similar DCE methodology. In this study, patients are willing to accept substantial risks of serious infection (approximately 18% per year) or lymphoma (approximately 0.75% per year) in exchange for 5-years without symptoms[86].

Thus, this study will focus on resolution of clinical symptoms and a biomarker that predicts likelihood of relapse of the disease, two outcomes confirmed to be of high importance to patients with CD. Of course, we will also measure other patient reported outcomes using tools such as Patient Reported Outcome Measurement System (PROMIS) measures.

1.6 Dose Rationale

Participants will be asked to exclusively eat the diet to which they are assigned for a total of 12 weeks. The primary outcome will be assessed at six weeks. Six weeks was chosen for two main reasons. We felt it was unlikely that patients would stay on a diet for more than 6 weeks if they did not observe a benefit. Additionally, in Breaking the Vicious Cycle, it is stated that one month is sufficient to know if the SCD is working[42].

2 Study Objectives

This RCT is designed to address the following primary aim and a number of secondary aims which are considered exploratory in nature:

2.2 Primary Objectives

1. To compare the effectiveness of the Specific Carbohydrate Diet and a Mediterranean style diet to induce symptomatic and clinical remission in patients with Crohn's disease.
    - Hypothesis 1. Patients following the SCD will be more likely to experience resolution of CD symptoms than patients following a MSD.
2.

2.3 Secondary Objectives

1. To compare the effectiveness of the Specific Carbohydrate Diet and a Mediterranean style diet to reduce mucosal inflammation in patients with active Crohn's disease. Mucosal inflammation will be assessed by measuring the concentration of calprotectin in the feces (FCP).
2. To compare the effectiveness of the Specific Carbohydrate Diet and a Mediterranean style diet to reduce systemic inflammation in patients with active Crohn's disease. Systemic inflammation will be assessed by measuring the concentration of C reactive protein (CRP).

3. To compare the effectiveness of the Specific Carbohydrate Diet and a Mediterranean style diet to improve the following symptoms in patients with Crohn's disease: a) fatigue, b) pain, c) joint symptoms.
4. To determine the proportion of patients who continue the study diets when prepared food is no longer provided without cost and the reasons for discontinuation of the diets.

3 Investigational Plan

3.2 General Design

This is a randomized, multicenter, comparative effectiveness trial of SCD and MSD to induce remission in patients with Crohn's Disease. Participants will be screened for eligibility criteria and if eligible, enrolled into the trial. Participants will continue on the diet to which they are randomized for 6 weeks with all food being provided to the participant during this time period. Participants will complete brief daily online surveys throughout their entire study participation, from consent to week 12. These will be used to calculate scores for the Short Crohn's Disease Activity Index (sCDAI). The primary outcome will be assessed at week 6 at an in-person visit. From weeks 7 to 12 participants will be asked to adhere to their randomized study diet on their own. At week 12 participants will be evaluated at an in-person visit.

3.2.1 Informed Consent and Screening (PCORI Methodology Criterion 3)

Participants will be identified through review of clinical appointment schedules and chart review or through physician referral. Study participants will also be recruited through the CCFA Partners PPRN, an engaged and activated cohort of more than 14,000 adult patients with IBD who contribute to research by providing patient-generated health data through online surveys and other modalities and have agreed to be contacted to participate in additional observational, interventional, and translational studies.[73] Once identified as potentially eligible based on self-reported symptoms and medication use, we will be able to contact these patients to assess their interest in the study and refer them to a participating center in their region to undergo screening and enrollment in this study.

No data collection or other study procedures will take place until the participant provides verbal or written informed consent to participate in the research study.

The informed consent, screening, and baseline data collection which make up visit 1 can occur on the same day or be completed across several days. Participants will be pre-screened for nominal eligibility prior to the baseline visit or at the baseline visit. A pre-screening script will be used for determining nominal eligibility over the phone prior to the baseline visit.

The following screening and baseline data will be collected: participants' height, weight and vital signs, their medical history, diet history, their symptoms and any medication they may be taking. Their blood will be drawn to measure hsCRP and hematocrit levels. At some sites, two additional tubes of blood may be drawn for plasma. A physical exam will be done to obtain CDAI score. Participants will collect a stool sample no more than 28 days prior to start of the study diet and no more than 28 days after the date of initial consent (either in verbal or written form). Female participants will be asked to take a urine pregnancy test. Participants' charts will be reviewed and abstracted to obtain information for eligibility. One 24-hour dietary recall will be completed after the screening visit prior to start of the study diet. A dietitian from the University of Pennsylvania will contact the participant to complete this. The participant will complete daily online surveys regarding their Crohn's disease symptoms in order to calculate an sCDAI score. Participants will also be instructed about these online surveys they will receive throughout the study and when to collect stool samples.

The participant will ship their stool sample to Dr. Gary Wu's lab at the University of Pennsylvania. Penn will send an aliquot of stool to LabCorp to measure FCP. Remaining sample will be aliquoted and stored in the biobank managed by the CCF. *See section 7.8 Stool Processing for more information.*

The participant must complete 5 to 7 days of sCDAI symptom recording (the daily online surveys) before randomization and the start of study diet. They should not complete the 5-7 days of sCDAI symptom recording more than 14 days prior to start of study diet. Also, the participant must complete 5-7 consecutive days of sCDAI symptom recording no more than 14 days after nominal eligibility is determined.

Medical records may need to be requested for potential participants identified through CCFA Partners who are not already a patient at one of the participating clinic sites. Only the medical records necessary to determine eligibility should be requested. The Data Coordinating Center will provide a medical records release form for sites to use.

3.2.2 Study Intervention Phase

Randomization will occur after eligibility is confirmed AND the baseline stool sample is received at the University of Pennsylvania.
To determine the participant's randomization, the Site Coordinator must first confirm receipt of the stool sample at Penn and then confirm the participant's eligibility based on Visit 1 data collection and document both in the Data Management System (DMS). Upon documentation of both in the DMS, the DMS will automatically provide the Site Coordinator with the participant's assigned diet.

The Site Coordinator will inform the participant of their assigned diet in person or over the phone.

Participants will be provided instructions about how and when they will receive their study diet meals and will be assisted with registering with the vendor that provides the study diet meals. Participants will follow the study diet for 6 – 12 weeks. The first 6 weeks the food will be provided from the study meal vendor. The second 6 weeks the participant will be responsible for following the study diet on their own.

3.2.3 Follow-Up Phase

Participants will receive daily online surveys to complete for up to 16 weeks starting after consent. During weeks 1-6 participants will receive all of their meals shipped directly from the food vendor to the participant. At week 3 participants will receive an online survey via email or text about their satisfaction with the study diet. On Day 42 (+ or – 3 days) participants will come into the clinic for a visit that will involve: collection of information about their symptoms which will be used to obtain an sCDAI score, a physical exam to obtain CDAI score, one tube of blood drawn to measure hsCRP and one for HCT, possibly a third tube of blood drawn for plasma (for applicable sites only), providing information about adverse events, medications, joint symptoms, providing health status information (physical, mental and social) to obtain a PROMIS score, and being weighed. They will take a satisfaction survey about the study diet. They will collect one stool sample during days 38-40 and will ship it to Dr. Gary Wu's laboratory at the University of Pennsylvania. On a randomly selected day during week 6, participants will be interviewed by a dietitian over the phone who will ask them about what they ate on the previous day.

During weeks 7-12, participants will no longer receive prepared meals, but will adhere to their study diet on their own. Participants will be given recipes and instructions about how to prepare study diet meals on their own. Participants will also receive an online survey about their satisfaction with the study diet during week 9.

On Day 84 (+ or – 3 days), participants will come into the clinic for a visit that will involve: collection of information about their symptoms which will be used to obtain an sCDAI score, a physical exam to obtain CDAI score, one tube of blood drawn to measure hsCRP and one for HCT, providing information about adverse events, medications, joint symptoms, providing health status information (physical, mental and social) to obtain a PROMIS score and being weighed. Participants will take a satisfaction survey about the study diet online and they will complete a Diet History Questionnaire online.. The participant will collect one stool sample during days 80-82 and ship it to Dr. Gary Wu's lab at the University of Pennsylvania. On a randomly selected day during week 12, a dietitian will contact participants by phone to ask them about what they ate on the previous day. Participants complete the study at the end of the week 12 visit.

Site Coordinators may call participants as needed to remind them of their upcoming study visits, sample collections, and online surveys.

3.3 Allocation to Interventional Group

Participants who meet all eligibility requirements, provide a baseline stool sample, and complete 5 to 7 days of sCDAI online surveys, will be randomly assigned to one of the study diets in a 1:1 ratio of SCD:MSD. The randomization will be stratified based on whether the participant is currently using a biologic therapy for CD. As such, there will be two strata as follows:

Biologic Therapy
Yes
No

Randomization will be blocked using variable block sizes ranging from 2 to 4. A study biostatistician at the DCC will generate the randomization scheme which will be incorporated into the study data management system. Once the randomization form is completed in the data management system it will generate the participants' study diet assignment.

3.4 Study Endpoints

3.4.1 Primary Study Endpoints

3.4.1.1 Symptomatic remission

Symptomatic remission will be assessed at 6 weeks. This is defined by patient reported outcomes (PROs) focusing on the cardinal symptoms of CD - diarrhea, abdominal pain, and general wellbeing. These have been combined into the Short Crohn's Disease Activity Index (sCDAI) which provides a composite measure of the PROs. Symptomatic remission will be defined as a sCDAI <150[74] in the absence of the need for increasing corticosteroid dose or initiation of new therapies for CD during the study period. Participants who withdraw from the study prior to week 6 will be categorized as failing to achieve symptomatic remission and other related outcomes.

3.4.2 Secondary Study Endpoints

3.4.2.1 Clinical Remission

As a secondary clinical outcome, we will measure the CDAI at baseline, 6 weeks and 12 weeks. Clinical remission will be defined as a CDAI<150 in the absence of the need for increasing corticosteroid dose or initiation of new therapies for CD during the study period[75].

3.4.2.2 Other patient reported outcome measures

The same data elements included in the sCDAI have been combined into two item (stool frequency and abdominal pain) and three item patient reported outcome measures using the original weights derived from the full CDAI. Optimum cut-points for CDAI remission were mean daily stool frequency ≤1.5, abdominal pain ≤1, and general well-being score of ≤1 (areas under the ROC curve 0.79, 0.91 and 0.89, respectively).PRO2 and PRO3 values corresponding to CDAI scores of 150, 220, and 450 points were 8, 14, and 34 and 13, 22, and 53 respectively, and the corresponding values for CDAI changes of 50, 70, and 100 points, were 2, 5, and 8 and 5, 9, and 14, respectively[76]. We will examine the individual components of these PROs to determine the proportion of each group that met the optimum cutpoint for remission that met the PRO2 definition of remission. Finally, we will determine the proportion of each group with a reduction in the PR02 and PRO3 that corresponds to 100 point reduction in the CDAI.

The Patient Reported Outcome Measurement System (PROMIS) questionnaire contains several measures previously shown to correlate with disease activity and to have construct validity in CD[27]. These include measures of fatigue, pain interference, social aspects, and sleep. See appendix H for a copy of this survey.

A subset of core variables found in the Multi-dimensional Health Assessment Questionnaire (MD-HAQ) will be used to assess physical function and joint pain[77,78], as well as RADAI Arthritis screening questions. See appendix I for a copy of these surveys

We will screen for inflammatory back pain using criteria developed by Sieper et al[79]. and assess symptom severity with the Bath AS Functional index[80] in those who screen positive. See appendix J for a copy of these criteria.

3.5 Primary Safety Endpoints [if applicable]

Not applicable.

4 Study Population and Duration of Participation

4.1 Inclusion Criteria

1. Age ≥18
2. Documented diagnosis of Crohn's disease
3. sCDAI score >175
4. Documentation of receipt of a baseline stool sample by the data coordinating center and hsCRP.

5. Access to a computer with internet and the ability to complete daily online surveys
6. Capable of providing consent to participate
7. Able to receive weekly food shipments delivered every Friday for 6 weeks

4.2 Exclusion Criteria

1. Pregnancy
2. sCDAI >400
3. Hospitalized patients
4. Anticipated need for surgery within 6 weeks of randomization
5. Use of the Specific Carbohydrate Diet within 4 weeks of screening
6. Start or change*** dose of thiopurines (azathioprine and 6-MP), methotrexate, natalizumab, or vedolizumab within 12 weeks prior to screening
7. Start or change*** dose of anti-TNF agents (including infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi) or ustekinumab within 8 weeks prior to screening.
8. Start or change in dose of any 5-ASA medications within 2 weeks of screening.
9. Start or change dose of corticosteroids within 1 week of screening or a dose >20mg/day prednisone or equivalent*
10. Use of antibiotics (other than topical formulations) for any reason within 2 weeks prior to screening
11. Known symptomatic intestinal stricture.
12. Presence of an ostomy
13. Baseline stool frequency >4 bowel movements/day when well
14. BMI <16
15. BMI ≥40
16. Celiac disease
17. Documented C difficile colitis within four weeks of screening
18. Diabetes Mellitus requiring medication
19. Albumin<2.0mg/dl, within 4 weeks of screening (if tested as part of routine clinical care)
20. Known allergy to tree nuts or peanuts
21. Other conditions that would be a contraindication to any of the study diets or preclude the participant from completing the study.
22. Currently participating in another clinical trial of a drug to treat IBD or a dietary therapy for any indication.

*Patients may continue these medications at stable dose for the first six weeks and budesonide may be used at any dose. After the 6th week in the study, patients may taper their steroid dose. The study will provide a recommended taper schedule.
**Loading/induction doses of biologic type medication will be considered a stable doses.
***Exception for treatment failures: if a subject is determined to fail on any of the following standard lines of treatment at the treating investigator's discretion, subjects may screen for study intervention based upon the following wash out periods: 4 weeks for thiopurine and methotrexate and 8 weeks for natalizumab, vedolizumab, anti-TNF, or ustekinumab.

4.3 Participant Recruitment

Participants will be recruited at multiple centers around the U.S. Participants will be identified by reviewing clinic schedules each week and reviewing charts of likely eligible patients. Patients may be approached via telephone or when they come to the clinic for a clinical visit. Participants may agree to consent at the time of their clinic visit or may return to the clinic on another day to be consented. In some cases, a verbal consent via telephone may be done prior to an in-person visit where a full in-person consent process will be completed. Participants may also be recruited through CCFA Partners and referred to a participating clinic.

4.4 Duration of Study Participation

Participation in the study will last a minimum of 13 weeks from the time participants consent and are screened, for those who complete the study protocol. Adherence to the study diet will take place for up

to 12 weeks. Participation may last up to 16 weeks if the maximum time between screening and randomization is allowed.

4.5 Total Number of Subjects and Sites

It is expected that 230 participants will need to be enrolled (defined as having provided informed consent to participate in this research study) to achieve a final sample size of 194 participants. Recruitment will end when approximately 194 participants have been randomized.

4.6 Vulnerable Populations

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

5 Study Intervention

5.1 Description

The study intervention is the Specific Carbohydrate diet (SCD). The study diet is based on the detailed descriptions of allowable food in the book Breaking the Vicious Cycle[42], by Elaine Gottschall. We will use this list of allowed foods to create the menu of food items for the participants randomized to receive the SCD. The SCD restricts all but simple carbohydrates. The only carbohydrates permitted are monosaccharides: glucose, fructose, and galactose. Fresh fruits and vegetables are universally acceptable with the exception of potatoes and yams. Certain legumes (i.e. lentils, split peas) are permitted, however others (i.e. chickpeas, soybeans) are not. No grains are permitted in the SCD. Saccharin and honey are permitted in addition to moderate use of sorbitol and xylitol. Canned fruits and vegetables are not permitted due to possible added sugars and starches. Unprocessed meats are permitted in the SCD without limitation. However processed, canned, and most smoked meats are restricted due to possible sugars and starches used in additives. Milk is not permitted in the SCD due to lactose content. However, certain lactose free cheeses are permitted as is homemade lactose-free yogurt.

The control diet is a Mediterranean Style Diet. This is a well-balanced diet that is consistent with the United States Department of Agriculture and World Health Organization recommendations. The MSD entails higher fiber intake and appreciably lower red meat intake than the average American diet. It involves a high intake of olive oil, fruit, nuts, vegetables, and cereals; a moderate intake of legumes, fish, seafood, and poultry; a low intake of dairy products, red meat, processed meats, and sweets; and wine in moderation, consumed with meals.[29] Red and processed meats, soda drinks, bakery goods, sweets, pastries, and spreadable fats are not permitted on this diet. Wine is allowed only with meals and no more than two 5 oz. glasses per day.[69]

5.2 Intervention Regimen

Participants will be provided with fully prepared meals from Healthy Chef Creations (HCC) totaling a minimum of 2500 calories. Participants do not have to eat all of the food provided. Beverages will not be provided, but participants will be provided with a list of recommended beverages. Participants will receive these meals for six weeks. Some of the meals will require heating.

During weeks 7 through 12 participants will be asked to adhere to their randomized diet by preparing their own meals and snacks or by purchasing the meals from HCC. Participants will be provided with detailed instructions and recipes for preparing their food.

5.3 Receipt

Participants will receive shipments of food to their home (or another location, if desired) each week via tracked courier from HCC. Shipments will occur on Fridays. These shipments will contain breakfast, lunch, dinner and two snacks for each day of the week. The food will be delivered fresh (not frozen) with sufficient ice packs to remain on a door step until later that evening. Each shipment will contain instructions on how to reheat the meal (if needed), whether or not the meal can be frozen and how long the meal can be kept under refrigeration before consumed. Additionally, each shipment will contain contact information for customer service representatives of HCC. The representatives can be contacted for any questions about the food, its ingredients, preparation instructions etc.

5.4 Storage

Each meal or snack will be labeled with the storage requirements for that meal (freeze, refrigerate, keep at room temperature). Proper preparation with regard to reheating will also be included on a label on each meal/snack.

5.5 Preparation and Packaging

All of the meals and snacks for this study will be prepared by HCC in a single kitchen. All participants, regardless of the clinical center from which they were recruited, will receive their meals from HCC directly to their homes via tracked courier. Food will arrive in a cardboard box with the food inside surrounded by freezer packs. The box will have a label reading "Perishable."

5.6 Administration and Accountability

HCC will provide a monthly report detailing all of the food deliveries including the date they were delivered and to whom. This report will include information on whether additional meals needed to be delivered to replace damaged shipments or shipments not received.

5.7 Subject Compliance Monitoring

Adherence to the assigned diet will be assessed using three 24-hour dietary recalls administered by trained dietitians on randomly selected days. This assessment will occur once between screening and start of study diet, once during week 6 and once during week 12. We will also have participants complete a diet history questionnaire (DHQ) at baseline and week 12. The DHQ asks about food eaten in the past 30 days. Therefore, the week 12 DHQ will be used in addition to the 24 hour dietary recall to assess adherence to the assigned diet.

5.7.1 Return or Destruction of Investigational Product

Participants will be allowed to keep all meals that are delivered to their homes. If meals are past their expiration date or if they are unwanted by the participant, the participant will be responsible for disposing of the meals.

6 Study Procedures

6.1

			Study diet provided Weeks 1-6		Self-adherence to diet, food not provided Weeks 7-12	
Week	**-28 to -1**	**0**	**1-5**	**6**	**7-11**	**12**
Visit	**1**			**2**		**3**
	In-Person	**In-Person Or Phone**	**Online**	**In-Person**	**Online**	**In-Person**
Informed Consent	X	X*				
Eligibility	X					
Medical History	X					
Diet History Questionnaire	***					X
Urine Pregnancy	X					
Randomization		X				

sCDAI (symptoms collected daily throughout study)	X***		X	X	X	X
CDAI	X			X		X
Physical Exam	X			X		X
Stool Collection	X			X		X
Fecal Calprotectin	X			X		X
Blood draw for hsCRP, HCT	X			X		X
Blood draw for plasma**	X			X		
PROMIS measures	X			X		X
Joint symptoms	X			X		X
Adverse events	X			X		X
Medications	X			X		X
One dietary recall (over the phone)	X			X		X
Satisfaction with diet			X (week 3)	X	X (week 9)	X
Weight	X			X		X
Height	X					
Vitals	X					

*Verbal informed consent may be obtained to allow for some screening steps to begin prior to the in person visit. Written informed consent must still be obtained at the in person screening visit.

**Plasma collection may not apply to all clinic sites.

*** These measures will be completed online prior to the first visit.

6.2 Study Intervention Phase and Follow Up Phase

6.2.1 Recruitment and Pre-Screening

Site Coordinators and/or Investigators will identify potential participants via review of their medical record. The Site Coordinator (SC) may contact the participant either in person or over the phone to discuss the study, complete a verbal or in-person informed consent, and ask and record pre-screening questions to determine nominal eligibility. No data will be recorded without at least verbal consent. The SC will immediately enter the pre-screening information, including the participant's contact information and mailing information, into the study data management system (DMS). The Site Coordinator will either complete the screening visit (Visit 1) at that time if the consent was done in person or will schedule a screening visit for a later date (if initial contact and consent was over the phone).

The DMS will automatically alert the Data Coordinating Center (DCC) of the new nominally eligible participant and will ship one stool collection kit to their home for the baseline stool sample collection. The database will begin automatically emailing or texting the daily sCDAI surveys to the participant.

6.2.2 Visit 1

The informed consent, screening, and baseline data collection which make up visit 1 can occur on the same day or be completed across several days.

At Visit 1 the Site Coordinator and/or Site Investigator must collect the following:

- Informed Consent (if not done so already)
- Medical History
- Urine Pregnancy
- Diet History Questionnaire (see below for more information)
- 24-hour dietary recall (see below for more information)
- Medications
- Joint Symptoms
- PROMIS Measures
- Physical Exam
- Vitals
- Height and weight
- Short Quality of Life in Inflammatory Bowel Disease Questionnaire (SIBDQ)
- CDAI
- sCDAI (see below for more information)
- Adverse Events
- Blood draw to measure hsCRP, hematocrit, and to collect plasma (see below for more information)
- Stool Collection (see below and section 7.8 for more information)
- Provide study instructions

sCDAI: A minimum of 5 and maximum of 7 days of patient reported symptoms will be required to compute the sCDAI to determine eligibility. The participant will accomplish this via daily online surveys sent to the participant after at least a verbal consent is obtained. The sCDAI is computed using the following equation where *L* is the number of liquid or very soft stools, *A* is the rating of abdominal pain (0-3, none to severe), *W* is the rating of general wellbeing (0-4, generally well to terrible), *n* is the day of follow-up, and *d* is the number of days of data used to compute the sCDAI[82].

$$sCDAI = 44 + \frac{7}{d} * \left(\left(2 * \sum_{n=1}^{d} L \right) + \left(5 * \sum_{n=1}^{d} A \right) + \left(7 * \sum_{n=1}^{d} W \right) \right)$$

Stool Collection: The participant must collect a stool sample no more than 28 days from the date the participant will start the study diet and no more than 28 days after the initial form of consent. Participants at the University of Pennsylvania may bring the sample with them to visit 1. All other participants must ship the sample to the University of Pennsylvania in materials the DCC ships to the participant's home. *See section 7.8 Stool Processing for more information.*

Diet History Questionnaire (DHQ): The participant will complete an online Diet History Questionnaire at home prior or immediately following the visit in the clinic. Alternatively, the participant may complete it at their visit if a computer with internet is available. It will take approximately 30 minutes to complete. The DMS will email the participant the link to the questionnaire as well as their username and password to access the questionnaire.

24-hr Dietary Recall: A dietitian from the University of Pennsylvania will call the participant at home to ask them what they ate the day before. This should be completed on a random day between screening and the start of study diet.

FCP: Upon receipt of the stool sample, laboratory staff at the University of Pennsylvania will send a small amount of the sample to LabCorp for a baseline measurement of FCP. LabCorp will report the results to the Data Coordinating Center (Penn).

Blood draw: one tube of blood will be drawn for measuring hsCRP and one for hematocrit. Two additional tubes may be drawn for plasma collection. Blood tubes and other collection materials will be

provided to the sites. After blood is drawn, the Site Coordinator will spin the tubes of blood in a centrifuge using instructions provided from the Data Coordinating Center. They will package the spun tubes in materials provided and will place the blood sample for hsCRP and hematocrit in a LabCorp lockbox at their site. If the site does not currently have a LabCorp lockbox, LabCorp will install one. The Site Coordinator must contact LabCorp to inform them there is a sample for them to pick up. A LabCorp driver will pick up the sample. The blood samples for plasma will be stored at the site in a -80° C freezer and shipped in batch to Biostorage at the end of the study. See the Manual of Procedures for processing instructions for plasma.

Steroid Equivalency chart:

Cortisone	25mg
Hydrocortisone	20mg
Prednisone or Prednisolone	5mg
Methyl prednisone	4mg
Dexamethasone	0.75mg

Randomization will occur after eligibility is confirmed and a stool sample is receieved..
To determine the participant's randomization, the Site Coordinator must first confirm receipt of the stool sample at Penn and then confirm the participant's eligibility based on Visit 1 data collection and document both in the Data Management System (DMS). Upon documentation of both in the DMS, the DMS will automatically provide the Site Coordinator with the participant's randomization.

The Site Coordinator will inform the participant of their randomized diet in person or over the phone.

The DCC will be alerted to the participant's eligibility and randomization, after which they will ship two more stool collection kits to the participant's home for the remainder of the study.

6.2.3 Visit 2 (week 6 visit)

The following will be conducted at Visit 2 (week 6):

- 24-hour dietary recall (see below for more info)
- Medications
- Joint Symptoms
- PROMIS Measures
- Physical Exam
- Weight
- CDAI
- SIBDQ
- sCDAI (same as for visit 1)
- Adverse Events
- Blood draw to measure hsCRP, hematocrit, and to collect plasma
- Stool Collection
- Online Diet Satisfaction Survey (completed at home)

FCP: same as for visit 1

24-hr Dietary Recall: A dietitian from the University of Pennsylvania will call the participant at home to ask them what they ate the day before. This should be completed on a random day during week 6.

Blood draw: Blood draw: one tube of blood will be drawn for measuring hsCRP and one drawn for hematocrit. One additional tube may be drawn for plasma. The samples will be processed in the same manner as in Visit 1.

Stool collection: participants must collect one stool sample during days 38-40.

Recommended Steroid Taper after week 6: participants who are on steroids may taper after week 6. The following tapering schedule is to be used but can be modified by the treating physician in response to symptoms or in the case of special circumstances (e.g. a slower taper may be used for patients with a history of long-term steroid use):

20mg/day for one week → 15mg/day for one week → 10 mg/day for one week → 5 mg/day for one week → 2.5 mg/day for one week → off

6.2.4 Visit 3 (week 12 visit)

The following will be conducted at Visit 3 (week 12):

- Diet History Questionnaire (same as for visit 1)
- 24-hour dietary recall (see below for more info)
- Medications
- Joint Symptoms
- PROMIS Measures
- Physical Exam
- Weight
- CDAI
- SIBDQ
- sCDAI (same as for visit 1)
- Adverse Events
- Blood draw to measure hsCRP and hematocrit Stool Collection
- Online Diet Satisfaction Survey (completed at home)

FCP: same as for visit 1

24-hr Dietary Recall: A dietitian from the University of Pennsylvania will call the participant at home to ask them what they ate the day before. This should be completed on a random day during week 12.

Stool Collection: participants must collect one stool sample during days 80-82.

6.2.5 End of Study Visit

The end of study visit will take place at week 12 or at the visit where the participant withdraws or is withdrawn from the study. This visit will include a physical exam to obtain CDAI score. An sCDAI score will also be calculated. Participants will be asked to collect a stool sample at home and ship it to Penn. Stool will be shipped from Penn to LabCorp to obtain an FCP result. Participants will be asked to complete a DHQ, SIBDQ,a 24-hour dietary recall, and provide information about adverse events, medications, joint symptoms and provide health status information (physical, mental and social) to obtain a PROMIS score. Participants will also be weighed and have their blood drawn to measure hsCRP and hematocrit.

6.3 Rescue Therapy [if applicable]

Participants will remain under the care of their treating gastroenterologist while in the study. If their symptoms worsen, participants will contact their treating gastroenterologist and follow any recommendations with regard to changes in therapy for their Crohn's disease. Participants whose worsening symptoms require a change in the current treatment for Crohn's disease will be considered study treatment failures and will be withdrawn from the study. See Section 6.5 for subject withdrawal information.

6.4 Unscheduled Visits

Unscheduled visits could potentially occur if a participant experiences an Adverse Event that requires medical evaluation.

6.5 Subject Withdrawal

Participants may withdraw from the study at any time.

Participants may be withdrawn at the discretion of the investigator prior to randomization for the following reasons:

.

- Failure to provide the baseline stool sample
- Failure to complete at least 5 of the 7 baseline sCDAI surveys

Participants will be withdrawn from the study if they experience worsening symptoms requiring a change in their Crohn's disease treatment,the initiation of an antibiotic for gastrointestinal symptoms, and/or an increases of greater than 10mg/day of prednisone or equivalent for a non-gastrointestinal condition*.
**Please see section 6.2.2 for equivalency chart*

Participants who have been randomized to one of the two diets and withdraw early from the study should complete an end of study visit and provide a stool sample at the time of withdrawal as described in section 6.2.5.

If the participant wishes to discontinue the study diet early for reasons not related to worsening Crohn's Disease (e.g., they don't like the diet), they will be asked to remain in follow-up and complete the next in-person visit at the target date of that visit (either week 6 or week 12). This will be the end of study visit.

7 Study Evaluations and Measurements

7.1 Medical History

The following information may be obtained from a combination of the participant's medical charts and/or self-report:

- Medical and surgical history
- Crohn's disease history
- Medication use
- Hospitalizations
- Laboratory test results – albumin and C. difficile colitis

7.2 Demographic information

Gender, date of birth and race will be collected from each participant. Medication use will be collected at each visit.

7.3 Current Symptoms

Participants' current symptoms, both Crohn's disease-related and otherwise, will be collected at each visit. Crohn's symptoms will also be collected through daily online surveys. Patient reported outcomes using PROMIS and other measures will be assessed at each visit.

7.4 Concomitant Medication

Medication use will be collected at each visit. Participants will be permitted to taper their steroid dose after week 6 following the recommended tapering schedule in section 6.2.4.

7.5 Vital Signs

Participants will be weighed on a scale in the clinic at each visit. Participant's height will be measured at Visit 1 using a stadiometer. Participants' seated temperature, heart rate, and blood pressure will be measured at Visit 1.

7.6 Laboratory Evaluations

Fecal Calprotectin - This biomarker is a strong predictor of an outcome of importance to patients, the duration that they will remain free of symptoms of CD. It has been repeatedly demonstrated that patients with IBD who have an elevated FCP concentration have earlier relapse of disease[83]. Thus, we will use this biomarker as a surrogate for future disease course. FCP assays will be completed by LabCorp at baseline, 6 weeks, and 12 weeks.
The DCC will provide the Site Investigators with their participants' FCP results from LabCorp after all of the participants have completed the last study visit upon request.

High Sensitivity C-Reactive Protein (hsCRP) – this is a biomarker in the blood that is a measure of inflammation in the body. Participants will have their blood drawn at baseline, week 6, and week 12. The Site Coordinator will spin the blood according to lab instructions, place the blood sample in the LabCorp lockbox at their site and inform LabCorp via phone of the blood sample. LabCorp will then pick up the sample for transport to their laboratory. Coordinators will be provided with detailed instructions for this.

Hematocrit will be measured by LabCorp at each visit as part of calculating a Crohn's Disease Activity Index (CDAI) score.

7.7 Plasma Collection

Two tubes (4 tsp) of blood will be drawn and centrifuged at baseline and week 6 for plasma separation and collection. . The plasma samples will be stored for future research use related to this study and other relevant health related questions. Possible use of the plasma samples include testing for serological markers or metabolites. Further blood sample processing, storage, and shipping information for the local sites can be found in the DINE-CD Study Manual of Procedures.

7.8 Pregnancy Testing

Female participants will take a urine pregnancy test at screening if they have not yet reached menopause or if they have not had a hysterectomy.

7.9 Stool Sample Collection

Stool samples will be collected on the days described above in sections 3.2.1 and 3.2.3. We will ask participants to categorize their samples on the Bristol Stool Chart scale. Stool collection kits, including pre-paid shipping labels, will be prepared by the DCC in advance and shipped to the participant (or given in person for participants at the University of Pennsylvania). Participants should collect a baseline sample within 28 days prior to the start of study diet and no more than 28 days from the initial form of consent. Participants should collect a sample for visit 6 during days 38-40 and for week 12 during days 80-82. They will ship the samples to Dr. Gary Wu's lab at the University of Pennsylvania. Shipping will be pre-paid by the Data Coordinating Center.

7.10 Sample preparation, processing, and storage

Stool sample collection kits will be prepared at the DCC and sent directly to the participants' homes from the DCC. Participants will collect their samples at home, put a sample amount of stool into one 10 ml Sarstedt spoon-top vial with 5mL of 100% ethanol, and ship back the ethanol aliquot and remaining sample to the DCC. At all visits the lab will also aliquot some sample into a container provided from LabCorp labeled with participant ID and Date of Birth and send to LabCorp for FCP testing. Remaining de-identifiied sample labeled with the unique study ID number will be aliquoted into 4 empty 10mL Sarstedt spoon-top vials and one stock tube. The four frozen aliquots, one ethanol aliquot and one stock tube will be stored in a -80°C freezer. Once the lab has enough to create a batch shipment, they will ship aliquots in batch to Biostorage Technologies, a biobank who contracts with CCF to store CCF study samples. Samples from this study will be stored there for later use.

Four tubes of blood will be collected at baseline, three tubes will be drawn at week 6, and two tubes will be drawn week 12. All will be centrifuged according to instructions from the DCC. Two tubes will be packaged and placed in the site's LabCorp lock box for pick-up by LabCorp staff (applicable at all visits). These sample will be tested by LabCorp for hsCRP and HCT. The third and fourth tubes at baseline and

week 6 will be for plasma separation. Plasma will be aliquoted and frozen within one hour of collection in a -80°C freezer at the site. Plasma samples will be stored locally in a -80 freezer and shipped in batch to Biostorage at the end of the study. Processing, storage, and shipping instructions can be found in the DINE-CD Manual of Operating Procedures.

7.11 Other Evaluations, Measures

24-hour dietary recalls will be used to assure adherence with the study diet. A trained dietitian will administer a phone interview to determine what participants have eaten on the randomly selected days (described above in Section 3.2.3).

An online, confidential, Diet History Questionnaire (DHQ) will be used to assure adherence with the study diet and will be completed at baseline and week 12. Patients will complete the online questionnaire at home immediately prior to or immediately following their baseline and week 12 visit. Alternatively, they may be able to complete it in the clinic if a computer with internet access is available. We will use the National Cancer Institute's web-based DHQ II questionnaire that asks about food eaten in the past 30 days. There is no patient identifying information in the DHQ. Patients log into the questionnaire with a unique code and password. The DCC will download an Excel file containing study participants' questionnaire responses from a secure https website accessible only by certain study staff at the DCC.

Study diet satisfaction surveys will be administered via an online questionnaire at the time points described in section 3.2.3. This will be a brief survey that will allow for free text comments from participants about their satisfaction and overall experience with the assigned diet.

The Patient Reported Outcome Measurement System (PROMIS) questionnaire contains several measures previously shown to correlate with disease activity and to have construct validity in CD[27]. These include measures of fatigue, pain interference, social aspects, and sleep.

A subset of core variables found in the Multi-dimensional Health Assessment Questionnaire (MD-HAQ) will be used to assess physical function and joint pain[77,78].

We will screen for inflammatory back pain using criteria developed by Sieper et al.[79] and assess symptom severity with the Bath AS Functional index[80] in those who screen positive.

We will assess quality of life using a Short Quality of Life in Inflammatory Bowel Disease Questionnaire (SIBDQ) at all visits.

Patient's most recent colonoscopy results prior to the time of randomization will also be collected for those subjects with accessible records. Additionally, any colonoscopies conducted during the study or within 6 weeks of the termination visit may be requested at the opinion of the Principle Investigator.

7.12 Efficacy Evaluations

Crohn's Disease Activity Index(CDAI), PRO2 and PRO3 measures[85], and Short Crohn's Disease Activity Index (sCDAI)[74] will be used to determine if participants' symptoms have improved or worsened with the intervention. The sCDAI assesses clinical remission as defined by patient reported outcomes focusing on the cardinal symptoms of CD - diarrhea, abdominal pain, and general wellbeing. The CDAI uses patient reported measures, similar to the sCDAI, but also uses findings from a physical exam and laboratory measures.

8 Statistical Plan

8.1 Primary Endpoint

<u>The primary outcome will be measured at 6 weeks after the start of the study diets.</u> Specific aim 1 will focus on the outcomes that are most important to patients, specifically the control of the cardinal symptoms of CD. We will assess clinical remission as defined by patient reported outcomes (PROs) focusing on the cardinal symptoms of CD - diarrhea, abdominal pain, and general wellbeing. These have

been combined into the Short Crohn's Disease Activity Index (sCDAI) which provides a composite measure of the PROs. Symptomatic remission will be defined as a sCDAI <150[74] in the absence of the need for increasing corticosteroid dose or initiation of new therapies for CD during the study period. Participants who withdraw from the study prior to week 6 will be categorized as failing to achieve symptomatic remission and other related outcomes.

The sCDAI was derived from the Crohn's Disease Activity Index[86] , the standard disease activity index for CD clinical trials in adults for the last several decades[87]. The original index includes the number of liquid stools per day, abdominal pain, general wellbeing, extraintestinal complications of CD, use of Lomotil or opiates for diarrhea, anemia, weight loss, and the presence of an abdominal mass on physical exam. The CDAI has increasingly fallen out of favor as it combines PROs with physical exam, medication use, and laboratory data[88]. As such, investigators validated the sCDAI which patients can complete using a simple web-based survey tool without an office visit or blood draw[74,82]. The sCDAI uses the same scale as the full CDAI, such that scores <150 define remission, 150-219 mild activity, 220-450 moderate activity, >450 severe activity. The correlation between the full CDAI and sCDAI for baseline scores and score change was 0.90 and 0.96, respectively[74]. Our research team has subsequently demonstrated that the sCDAI can be accurately measured with less than 7 days of data, thereby reducing participant burden[82] (IR-1). Indeed, we have utilized this abbreviated version of the sCDAI as part of the CCFA Partners PPRN since its inception and in our ongoing RCT of a high vs. low red meat diet for patients with quiescent CD that is being conducted within the CCFA Partners PPRN.

The primary outcome will be measured at 6 weeks. The 6 week study duration was selected for the following reasons:

a. Our stakeholders informed us that they would be unlikely to continue trying a dietary therapy if they did not observe a benefit within 6 weeks.
b. In Breaking the Vicious Cycle, it is stated that one month is sufficient to know if the SCD is working.
c. The practical implications of not allowing changes to the medical therapy for patients with active CD for much longer than 6 weeks could be a major disincentive to enrollment.

8.2 Secondary Endpoints

Markers of inflammation

We will compare the proportion of patients who achieve reduction in FCP to less than 250ug/g and by greater than 50% from baseline. Fecal concentration of calprotectin, a calcium binding protein found in neutrophilic granulocytes, will be measured by LabCorp. FCP concentration is correlated with endoscopic findings of mucosal inflammation and decreases following initiation of medications in active CD[90,91]. There is no single standard to define mucosal healing with FCP[92-94]; a recent meta-analysis identified 250 µg/g as the optimal cut point for endoscopically defined inflammation among patient with IBD[95,96]. There are a number of important reasons to measure FCP in this study. From the patient's perspective, FCP predicts the risk of recurrence of symptoms for those who have achieved clinical remission through medical or surgical therapy[90,97,98]. Equally as important, to achieve optimal adoption of dietary strategies into the management of CD will require convincing treating physicians of the effectiveness of the diet. Increasingly, physicians are demanding evidence that CD treatments improve inflammation in addition to symptoms[88]. Thus, FCP is a biomarker that predicts an important outcome for patients and for physicians it can be used to document reduction in mucosal inflammation.

We will use hsCRP as a marker of systemic inflammation. We can compare the proportion of patients who have hsCRP below the upper limit of normal and mean levels of hsCRP as outcome measures.

Secondary clinical outcomes and combined outcomes

As a secondary outcome, we will assess the proportion of patients achieving combined clinical remission and reduction in FCP using the same criteria described above.

As a secondary clinical outcome, we will measure the Crohn's Disease Activity Index (CDAI) at baseline, 6 weeks and 12 weeks. Clinical remission will be defined as a CDAI<150 in the absence of the need for increasing corticosteroid dose or initiation of new therapies for CD during the study period.

The same data elements included in the sCDAI have been combined into two item (stool frequency and abdominal pain) and three item patient reported outcome measures using the original weights derived from the full CDAI referred to as PRO2 and PRO3[76]. Optimum cut-points for CDAI remission were mean daily stool frequency ≤1.5, abdominal pain ≤1, and general well-being score of ≤1 (areas under the ROC curve 0.79, 0.91 and 0.89, respectively).PRO2 and PRO3 values corresponding to CDAI scores of 150, 220, and 450 points were 8, 14, and 34 and 13, 22, and 53 respectively, and the corresponding values for CDAI changes of 50, 70, and 100 points, were 2, 5, and 8 and 5, 9, and 14, respectively[76]. We will examine the individual components of these PROs to determine the proportion of each group that met the optimum cutpoint for remission that met the PRO2 definition of remission. Finally, we will determine the proportion of each group with a reduction in the PR02 and PRO3 that corresponds to 100 point reduction in the CDAI.

The Patient Reported Outcome Measurement System (PROMIS) questionnaire contains several measures previously shown to correlate with disease activity and to have construct validity in CD[27]. These include measures of fatigue, pain interference, social aspects, and sleep.

A subset of core variables found in the Multi-dimensional Health Assessment Questionnaire (MD-HAQ) will be used to assess physical function and joint pain[77,78] as well as a RADAI Arthritis screening questionnaire.

We will screen for inflammatory back pain using criteria developed by Sieper et al.[79] and assess symptom severity with the Bath AS Functional index[80] in those who screen positive.

8.3 Sample Size and Power Determination

The study is designed to enroll 97 patients into each of the treatment arms. With 97 participants per group, the study will have 80% to 90% power with a type 1 error of 5% to detect a difference of 20% in effectiveness of the two diets depending on the success rate in the reference arm. Our PPRN Patient Governance Council met and determined that a smaller difference is unlikely to justify the challenges of following a strict restriction diet.

8.4 *Statistical Methods*

A formal data analysis plan will be prepared as a separate document. The following sections summarize the planned analyses.

8.4.1 Baseline Data

The initial analyses will utilize descriptive statistics to define the characteristics of the study cohort. Continuous variables will be described as medians and interquartile ranges. Categorical variables will be defined as proportions. Formal statistical comparisons of these descriptive variables will be performed comparing the two arms of the study using the Wilcoxon rank sum test for continuous variables and the chi squared or Fisher's exact test for categorical variables [99]. Because any unbalance in the two groups is by definition a chance occurrence, these analyses will be used to highlight areas of substantial unbalance between the study arms.

8.4.2 Efficacy Analysis

Analysis of the primary outcome: The primary analyses for the RCT will use 2-sided tests of statistical significance and will be performed using the intention-to-treat principle.[100] Thus, patients will be classified according to the study arm that they were assigned, regardless of the amount of food from the assigned diet consumed. The primary analysis will compare the proportion of patients who achieve a symptomatic remission (aim 1) at week 6 using the Cochran-Mantel-Haenszel (CMH) chi square test, which is equivalent to the score test derived from the conditional logistic regression. [99] All patients who are withdrawn or lost to follow-up prior to week 6 will be considered treatment failures. The MSD will be considered the reference group for all analyses. Although randomization should minimize unbalance between the groups, it is still possible that unbalance may occur. As such, we will use stratified analyses and logistic regression analysis to adjust for potential unbalance between the two groups as observed in

the descriptive analyses.[101] Age, sex, smoking status, duration of CD, presence of disease involving the colon and/or rectum, use of corticosteroids during the trial, current use of biologic therapy, and current use of immunomodulator therapy will be examined individually for potential confounding of the main outcome using logistic regression analysis. All variables that affect the crude estimate of the relative risk of effectiveness by 10% or greater will be included in the final model[102].
Stratified analyses will be used to assess for treatment effect heterogeneity based on the following variables: presence of documented inflammation at baseline (defined as FCP>250 mcg/g, hsCRP >5 mg/L.Although pre-specified, we have not powered the study for these subgroup analyses and as such they will be considered hypothesis generating. Therefore, we will report the overall results as well as results for each subgroup. We note that the strongest a priori hypothesis for treatment effect heterogeneity is with the presence or absence of inflammation. We hypothesize that the SCD may appear relatively more effective among those patients without active inflammation than among those with confirmed active inflammation at baseline.

Analysis of secondary outcomes (Secondary Aim 2):
The secondary outcomes of clinical remission as assessed by the CDAI, PRO2, PRO3 reduction of hsCRP by >50% and to <5 mg/L, reduction of FCP by >50% and to a value of <250mcg/g and combined clinical remission and resolution of inflammation will be analyzed using the same methods described for the primary outcomes.

The secondary outcomes of fatigue, sleep quality, social aspects and pain interference will be measured using PROMIS short forms using the same methods as previously employed within CCFA Partners[27,103]. PROMIS items are calibrated using a T score such that 50 is the mean for the general US population with a standard deviation of 10. Higher scores reflect greater level of the domain. We will compare PROMIS scores at baseline and at the end of the trial using a t-test. If there are meaningful differences in baseline scores between the treatment arms, comparison of the PROMIS measures at the end of follow-up will be adjusted for the baseline value using linear regression.

Analysis of data from weeks 7 – 12 (Secondary Aim 3): After week 6, participants will need to provide for the meals on their own if they choose to remain on the diet. This provides an opportunity to further assess the combined feasibility of the diets in the real world and patients' satisfaction with following the diet. Utilizing results from 24-hour dietary recalls, we will determine the proportion of patients assigned to each arm who elect to remain on the diet through week 12. We will also determine the proportion of patients who were able to discontinue steroid use by week 12 among the subgroup who were taking steroids in weeks 1-6. Finally, we will assess reasons for discontinuation of the diet among those who did not continue. Comparisons will be made using the CMH test following the principle of intention to treat. The analysis will be repeated among the subgroup of participants who achieved remission by week 6. These results will be qualitatively compared to the free text data on satisfaction and personal experience with the diets.

Change from baseline stratified by treatment arm: For continuous outcome measures, such as sCDAI, PRO2, PRO3, and FCP, we will compare the week 6 and week 12 values to the baseline value using the Wilcoxon sign rank test, a nonparametric paired test. These analyses will be conducted separately for each treatment group. Imputation of missing data for this analysis will assume the worst case scenario that the outcome measure was worse during follow-up than at baseline. (Note that approach to missing data for other analyses are described below).

Approach to missing data (**PCORI Methodology Standard MD1-5**): Our study design will minimize missing data by requiring participants to continue to provide data and samples in order to continue to receive the study diets without cost. In addition, we will employ reminder methods that were developed in our current CCFA Partners RCT and will collect symptoms daily, but have documented that less frequent data collection is adequate[82]. It is possible that missing follow-up data will be more common among participants who did not have reduced symptoms, particularly those whose symptoms worsened. There are several approaches to missing data in clinical trials. Complete case analysis violates the principle of

intention to treat and as such will not be employed. For continuous measures, last observation carried forward (LOCF) is the most commonly used, but it is not necessarily the most conservative[104]. Baseline observation carried forward (BOCF) may be more appropriate, particularly in circumstances where the outcome would be expected to return to the baseline level if the treatment is discontinued[104]. The European Medicines Agency recommends picking the most conservative approach depending on the individual trial, favoring a responder analysis (i.e. converting continuous variables to dichotomous variables) and categorizing all dropouts as treatment failures[104]. We will use this approach in analyses for aims 1 and 2. For the continuous variables in the secondary outcomes, we will use BOCF as the most conservative approach. Sensitivity analyses will compare results of our BOCF analysis with that obtained using LOCF or multiple imputation methods. All results will be interpreted and reported after taking into account the results of the sensitivity analyses, applying the principle put forth by the EMA to not favor the "experimental" arm, which in this RCT would be the SCD.

8.4.3 Safety Analysis

All subjects entered into the study and randomized at the baseline visit will have detailed information collected on adverse events for the overall study safety analysis.

8.5 Subject Population(s) for Analysis

As a comparative effectiveness study, the primary efficacy and safety analysis will use the principle of intention to treat such that all randomized patients will be included in the group that they were randomized to, regardless of the level of adherence with the assigned diet.

9 Safety and Adverse Events

9.2 Definitions

9.2.1 Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

9.2.2 Serious Adverse Event

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event (not life threatening but may require intervention; for example drug overdose, drug abuse, a seizure not resulting in hospitalization)

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

9.2.3 Expected Adverse Events

As a short term study of two diets, there are few expected risks of the two interventions. These include allergic reaction to a component of the food, intolerance of the food other than as an allergic reaction, and worsening of Crohn's disease manifested as any of the following: worsened abdominal pain, worsened diarrhea, bowel obstruction, penetrating complications such as fistula or abscess. In addition, worsening of extraintestinal manifestations of Crohn's disease is possible, such as worsening arthropathy, mouth sores, skin rashes including pyoderma gangrenosum and erythema nodosum, and ocular manifestations such as episcleritis or uveitis. The Crohn's disease related adverse events would not be considered to be caused by the diets, but rather as a consequence of failure of the diet based therapy to induce disease remission. Some exacerbations of Crohn's Disease may result in hospitalization and/or the need for surgery. In rare circumstances, exacerbations of Crohn's disease may be life-threatening.

9.3 Recording of Adverse Event (AE)

At each contact with the subject from the screening visit to the end of study visit, the Site Investigator or Site Coordinator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately on the AE case report form (CRF). The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause.

Related, treatment-emergent serious and severe adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome, which may include resolution or stable outcome.

9.4 Relationship of AE to Study

The relationship of each adverse event to the study procedures should be characterized by the Site Investigator and recorded on the case report form. The relationship to the study intervention will be classified as definitely related, possibly related, not related, or unknown. For reporting purposes, an Adverse Event is considered "related to participation in the research" if the cause of the event is deemed possibly related or definitely related to the investigational product or a procedure that was performed for the purposes of the research.

9.5 Reporting of Serious Adverse Events and Unanticipated Problems

A Serious Adverse Event or Unanticipated Problem (see definition below) is required to be reported to the relying IRB within 10 days. If the adverse event involved a death and indicates that participants or others are at increased risk of harm the investigators are required to submit a report to the relying IRB within 3 days.

Non-medical Unanticipated Problems that should be reported to the IRB may include complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team, breach of confidentiality, incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study, or premature completion of the entire study for any reason.

Serious Adverse Events or Unanticipated Problems will be reported to the relying IRB using either a Reportable Event form from the relying IRB, or by writing a narrative including the minimum necessary information listed below. If not all information is known within the reporting timeframe, the site investigator should still complete a Reportable Event form or narrative within the timeframe with the information available and inform the relying IRB that a follow-up report will be provided when all information is known.

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study intervention was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

If an event does not meet the definition above of a Serious Adverse Event or Unanticipated Problem, a narrative summary of events that occurred should be submitted to the relying IRB at the time of Continuing Review, including a rational for why the event(s) was not reportable within 10 days.

Any known serious adverse event that occurs after the study period and is considered to be possibly or definitely related to the study intervention or study participation will be recorded and reported to the PI, the sponsor, and the relying IRB immediately.

9.5.1 Follow-up SAE report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the relying IRB. The site investigator is responsible for ensuring that all SAEs are followed until either resolved or stable.

9.5.2 Investigator reporting: notifying the study sponsor (Penn)

Site investigators should report serious adverse events and unanticipated problems meeting the 3 day reporting requirement (as defined in section 9.5) to the University of Pennsylvania Sponsor by phone and via the data management system. Phone notification should be within 24 hours of the site investigator becoming aware of the serious adverse event. Notification via the DMS should be done within 72 hours. In the case where the DMS form cannot be fully completed with 72 hours, a partially completed form should be entered into the DMS within 72 hours, and a completed form should be entered as soon as is possible. Report SAE's by phone to:

James D. Lewis, MD
Phone: (215) 573-5137

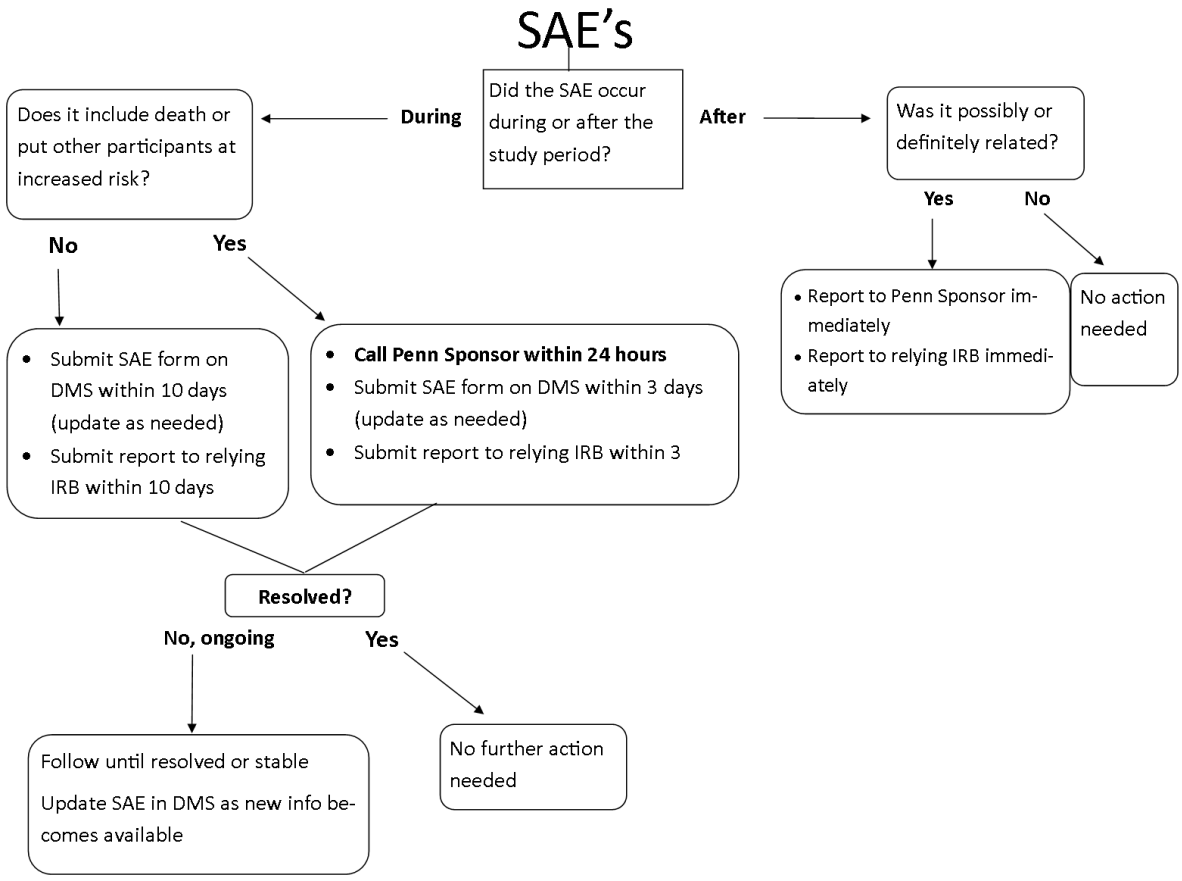
In the event Dr. Lewis cannot be reached, report SAEs to
Meenakshi Bewtra, MD
Phone: (215) 746-4922

Or
Adam Hawkins (215) 746-4218 or Lisa Nessel (215) 573-6003

SAE's that do not meet the 3 day reporting requirement (i.e., do not involve death or indicate that participants are at increased risk) should be reported to the sponsor within 10 days via the data management system only. No phone call will be required.

For a flow chart outlining SAE reporting to the sponsor, please see Image 1 below.

Image 1. SAE Flow Chart



9.6 Medical Monitoring

9.6.1 Data and Safety Monitoring Plan

To identify and mitigate potential risks to research subjects, we will inquire with participants at each contact if they are experiencing any adverse events. We do not expect that there will be many as the intervention is normal, healthy food.

As mentioned above, SAE's will be reported to the Principal Investigator at the University of Pennsylvania. Additionally, we will employ a Data Safety and Monitoring Board (DSMB). Please see the section below for details about the DSMB..

9.6.2 Data Safety Monitoring Board

We will convene a DSMB prior to the initiation of the study. The DSMB membership will include 3 total members consisting of: 1 biostatistician, 1 experienced clinical investigator with knowledge of CD, and 1 patient representative. The DSMB will have full authority to recommend suspending the study at any time if concerns arise about the safety of the study. Formal meetings of the DSMB will be planned to occur prior to the enrollment of the first patient, after one-third of patients are enrolled, after two-thirds of patients are enrolled, and at the conclusion of the trial. DSMB meetings will follow the standard format of an open session including the DSMB members and the investigators, followed by a closed session of the DSMB at which unblinded data can be reviewed, followed by another open session if required. The DSMB will render a decision to continue the trial as is, continue the trial with modifications, suspend the trial until modifications can be implemented, or to permanently suspend the trial. The study team will provide support to the DSMB to generate meeting minutes. The meeting minutes will be provided to the IRB and to PCORI.

SAE reports will be sent as they occur to the chair of the DSMB for review.

10 Study Administration, Data Handling and Record Keeping

10.2 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.3 Data Collection, Source and Accuracy (PCORI Methodology Standard IR-1)

Clinical data will be captured through a combination of means. Baseline characteristics of the participants and follow-up data on adverse events and physician derived components of the CDAI will be collected by the local investigator and recorded in the study database using double data entry by the clinical sites. We will use double data entry to minimize data entry errors. Baseline and follow-up data on symptoms and medication use will be collected directly from patients through the CCFA Partners PPRN web portal. Symptom data will be collected daily via surveys emailed or texted directly to the patients. Diet satisfaction and diet history will be collected via online surveys emailed to the participant at certain time points. Patient-reported medication use will be confirmed with the local investigator. Adherence to the diet will be assessed using 24 hour dietary recall data collected by trained dietitians.

10.3.1 Data Coordinating Center (DCC)

The University of Pennsylvania will serve as the Data Coordinating Center for this study. The DCC will develop all data collection instruments in collaboration with the steering committee and the DMC. The DCC will be charged with assuring data is entered and that data are complete and accurate. The DCC will also be charged with data and safety monitoring and coordinating all meetings of the DSMB.

10.3.2 Data Management Center(DMC)

The Biostatistics Core of the Center for Gastrointestinal Biology and Disease at the University of North Carolina Chapel Hill will serve as the Data Management Center. The DMC will be charged with creating, managing, and housing the data management system.

Site Coordinators will collect data on source documents and will complete double data entry onto electronic CRFs in the data management system created by the DMC Participants will collect data via direct data capture. All of the data will be maintained, archived, retrieved and distributed (except for the source documents completed by the Site Coordinators), by a computer system. The use of electronic records will increase the speed of data collection and exchange. Electronic records permit economical storage of study data and ease of accessibility and analysis. Data management and data quality systems will be built into the system. The DCC will have password-required access to the data management system where they can export data. The local sites will have password-required access to the data management system as well but they will only have access to their site's data and they will not be permitted to export the data.

The Data Management Center (DMC) at the CGIBD at the University of North Carolina will track the data collection, provide data security, control for confidentiality of study data, maintain computer backups to protect data until study closure and archive study data according to FDA requirements (21 CFR 11). Electronic signatures will be linked to each entry.

All computer systems and programs will be password protected, and all electronic communications of study and other confidential information will be encrypted. Personnel at the CGIBD have extensive training and experience using electronic data systems. Good computer security practice (restricting physical access to machines, prohibition of password sharing, and logging off computers after work hours or when away from the machine) will be required of all study personnel.

Standard Operating Procedures exist for users of the DMS. The DMS will be housed on an https secure website in order to protect the study participants' information. Only authorized persons are authorized for data entry and access. Data security systems require password protected identification codes for data entry and provide protection against data manipulation. The database is located on a server protected by firewalls. Access to the database server will not be allowed by users on computers outside of the firewall-protected zone. Virus protection software is installed on each study machine. System access to computer systems will be audited. Redundant backups and off-site backup storage will allow for quick restoration of data in the unlikely event that a hardware failure, disaster, or security breach should occur. Servers and backups will be located in a secured location with access limited to authorized personnel.

Standardized study management reports will be generated monthly during the recruitment phase of the study. These reports will be used to track study progress including patient enrollment, randomization, compliance, patient status changes, and study events. The data will be reported for each Study Center individually and summarized for the study as a whole. Every six months, a standardized report will also be generated for the DSMB meeting. This report will include additional information on clinical events and adverse events that is coded by treatment group. Other than the DSMB, the study statistician and statistical analyst, no study personnel will see this report.

10.3.3 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, subject files, and records kept at the food dispensing company, and at the laboratories. Any forms or documents with participants' identifying information placed in the participant's study file will be kept locked using a double lock system (for example, a locked filing cabinet in a locked office) and only certain members of the study team will have access to those forms.

Study staff at the local sites will have access to their participants' PHI. They will not have access to other sites' participant PHI or participant data, with the exception that the research team at the University of Pennsylvania may see other sites' participant PHI and data to facilitate participants' receipt of study food and problem solving.

10.3.4 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained.

Data on CRFs will be collected via double data entry using a secure web-based database designed by and housed in the University of North Carolina. The eCRFs will be the source document in some cases. These eCRFs will not include PHI or participants' identifiable information. Instead, eCRFs will be labeled with a unique study identification number and PHI will be kept separate.

If a space on the CRF is left blank because the procedure was not done or the question was not asked, type "N/D". If the item is not applicable to the individual case, type "N/A".

10.4 Records Retention

Study documents and records will be retained for 7 years after the last participant has completed the last visit, unless otherwise notified by the DCC.

11 Study Monitoring, Auditing, and Inspecting

11.2 Study Monitoring Plan

Most of the data to be collected in this study will be collected directly from participants through our web-based data entry system. For specific aim 1, the primary outcome is derived from patient reported data. For specific aim 2, the primary outcome is derived from the measurement of the concentration of fecal calprotectin, which will be done by a commercial laboratory LabCorp. Such data are not subject to monitoring other than for completeness. This will be done by the data analysts.

We will monitor the sites for compliance with regulatory documentation and for compliance with the study protocol, particularly as it relates to inclusion criteria. We will utilize a system whereby the local investigator team prints, redacts if needed, and uploads into our data management system source documents that demonstrate the eligibility of the participants. Study monitors will then remotely review these documents for compliance with the study protocol, send queries to the local sites, resolve outstanding queries, and document the level of adherence with the study protocol. Any findings that demonstrate a protocol deviation will be reported to the Penn IRB or local IRB, as appropriate. Similar methods will be employed for reviewing the participating sites regulatory binder. We will provide each site with an electronic storage area where their regulatory documents can be stored and then reviewed by the monitors. Data quality monitoring will be implemented after the second patient is enrolled at the site. Eligibility criteria and consent process will be monitored for all participants. If deemed necessary, on site monitoring will be employed.

11.3 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities.

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Ethical Considerations

This study will be conducted in accordance with applicable US Government regulations and international standards of Good Clinical Practice. This protocol, any amendments and any study instructions and data collection instruments will be submitted to a properly constituted Ethics Committee or Institutional Review Board, in agreement with local legal prescriptions for formal approval of the study conduct. The decision of the Ethics Committee or Institutional Review Board concerning the conduct of the study will be made in writing to the investigator and a copy of the decision will be provided to the Penn Data Coordinating Center before commencement of the study. Continuing review will be required through the Penn Institutional Review Board or other local reviewing entities at the recruiting centers.

12.2 Risks

The intervention in this trial poses little risk to participants. The prescribed diets are consistent with many dietary recommendations to minimize consumption of “processed” foods. There is a theoretical risk of delaying a change in the patient’s medication regimen while trying the study diets. However, the duration of the primary intervention period is only 6 weeks and we will exclude patients who are hospitalized for their CD, require in excess of 20mg per day of prednisone or the equivalent, or for whom the treating physician believes that surgery will be required within 6 weeks. There is minimal risk of phlebotomy, including bruising or fainting. However, nearly all of these patients would be expected to undergo phlebotomy for clinical reasons at the same time.

As with all research, there is the risk of loss of confidentiality of the data. Within the clinical trial, all data collected will be collected in a manner consistent with Good Clinical Practice. The case report forms (CRFs) will be electronic, avoiding the risk of paper forms. Access to the data will be limited to the research team, including the investigators, the research coordinator, and the data analysts. Electronic data will be

stored on servers within the University of North Carolina. Access to the server is password protected. The servers are backed-up nightly to prevent loss of information.

No vulnerable populations are included in this study.

12.3 Benefits

Participants may benefit from participation in this trial if the dietary intervention reduces their symptoms of CD and the related inflammation. If either study diet is demonstrated to be superior to the other, it is anticipated that many patients with CD would elect to follow a similar diet.

12.4 Risk Benefit Assessment

The leading unanswered question for patients with IBD is what diet to eat. Ultimately, regardless of the results, we will provide an answer to the question, "What should I eat?" If either of the diets is demonstrated to be superior, then we can confidently recommend that diet to patients with active CD. If neither diet is found to be superior, the default recommendation will be to follow a "healthy" and well-rounded diet such as the MSD. This is a low risk study, so the risks to subjects are reasonable in the context of the information to be gained.

12.5 Informed Consent Process / HIPAA Authorization

The Informed Consent and HIPAA Authorization will be combined into one form. The Research Coordinator or Investigators at the local site will obtain informed consent. The consent process will take place in a private space in the clinic where the patient sees their gastroenterologist. Participants will be permitted to provide consent at the time of the consent discussion or they will be required to come back to provide written informed consent at the screening visit. They may be initially verbally consented over the phone prior to collection of pre-screening information, with a later date scheduled to complete the in-person consent. During the consent process, participants will be encouraged to ask questions. Ample time will be dedicated to answering all of the participants' questions to make sure they understand the study. They will be permitted to think about whether they want to participate, review the consent form on their own and discuss it with whomever they like and sign the consent form at a later visit. Potential participants will be reminded that the study is voluntary and they are not required to participate. Both the participant and the person obtaining consent will sign the consent form. A copy of the consent will be provided to the participant.

To participate in this study, participants will be required to join the Crohn's and Colitis Foundation's (CCF) online patient research network called CCFA Partners. This research network is an online group of adult patients with Inflammatory Bowel Disease (IBD) who agree to contribute to IBD-related research. It does not cost anything to join. By signing up to be a member of CCFA Partners, participants agree to be contacted for potential participation in other IBD research studies, and to provide information regarding their health through online questionnaires. Completion of online questionnaires and participation in other research studies is voluntary and not required for participation in DINE-CD. They can opt out of any questionnaire and can decline any research study. They can also withdraw at any time from CCFA Partners.

13 Study Finances

13.1 Funding Source

This study is funded through the Crohn's and Colitis Foundation and the Patient Centered Outcomes Research Institute (PCORI).

13.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research. Only sites with a Conflict of Interest Policy will be permitted to participate. Exceptions to this may be made on a case by case basis and only with permission from the University of Pennsylvania's Conflict of Interest Standing Committee and other applicable regulatory bodies. Each local site will be required to follow their institution's Conflict of Interest Policy Related to Research.

13.3 Subject Stipends or Payments

Participants will not be compensated for their participation in this research study.

14 Collaborative Effort (PCORI Methodology Criterion 2. Technical Merit)

The proposed study is a unique collaboration between CCFA Partners, AR-PoWER, and ImproveCareNow (ICN) and will also leverage the infrastructure of the Mid-South CDRN.
We will invite interested ICN centers to participate in the trial through the recruitment and follow-up of their young adult patients (who will simultaneously be co-enrolled into the CCFA Partners PPRN). We will also work with ICN to disseminate study findings. ICN is submitting a related proposal to use n-of-1 methodology to study the impact of the SCD in pediatric CD. If both proposals are funded, this will offer a unique opportunity to compare two different study designs to answer related questions in related populations (adult and pediatric CD).

Our partnership with the AR-PoWER PPRN takes advantage of the fact that many patients with CD have co-morbid arthritis and related conditions and studies to evaluate the impact of diet on arthritis have been prioritized by patients in the AR-PoWER network. Our partnership with AR-PoWER will enable us to study the effects of our dietary interventions on joint symptoms using a series of PROs selected in collaboration with AR-PoWER patients and scientists. This will provide important preliminary data of both the effectiveness and feasibility of future dietary studies in rheumatology patients. We will also partner with the AR-Power PPRN to disseminate our study findings, as appropriate.
The Mid-South CDRN will provide informatics, administrative, and regulatory support for this study at two of CDRN sites: Vanderbilt and the University of North Carolina at Chapel Hill.

15 Publication Plan and Dissemination of Results (PCORI Methodology IR-6)

The results will be submitted to PCORI for review according to their guidelines for final reports. In addition, the results will be submitted for publication as a full length manuscript to a peer reviewed journal, allowing for complete description of the key methodology and results. The results will also be made available through the clinicaltrials.gov website. We will also utilize the PPRN infrastructure as all 3 PPRNs have developed dissemination strategies through their Phase I efforts, and will be refining and expanding such strategies over the course of Phase II.

We also have the support of the CCF to assist in the dissemination of our study results across multiple stakeholders-- nurses, dietitians, physicians and other allied health professionals. The CCF routinely hosts local, regional, and national patient and provider educational events. Additionally, the CCF hosts live webinars, publishes multiple brochures and newsletters, and maintains an active website. Total contacts are estimated at over 500,000 individuals each year (personal contact, Laura Wingate, CCF September 13, 2015).
Finally, we will work with our patient collaborator and active IBD blogger (thegreatbowelmovement.org), Ms. Meyer, to further disseminate the findings to patients and healthcare practitioners.

16 Appendices

- Appendix A: Protocol Signature Page
- Appendix B: Study Procedures Flowchart/Table
- Appendix C: Data Safety Monitoring Plan
- Appendix D: Stool Kit Preparation SOP
- Appendix E: Stool collection instructions for Patients
- Appendix F: DSMB Charter
- Appendix G: Analytic and Statistical Plan
- Appendix H: PROMIS Measures
- Appendix I: RADAI Arthritis screening and RAPID 3 Questionnaire
- Appendix J: Inflammatory back pain screening questions and Bath AS Functional index
- Appendix K: Menu Samples

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Appendix A

Protocol Signature Page

I will provide copies of the **DINE-CD Study** protocol (v5.4 2019.Apr.10), any subsequent protocol amendments and access to all information furnished by the sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational drug and the study protocol.

I agree to conduct this clinical trial according to the protocol described herein. I also agree to conduct this study in compliance with applicable federal, state and local regulations, Guidelines for Good Clinical Practice (GCP), and with the requirements of my Institutional Review Board. I understand that I may not implement this protocol without first receiving written IRB approval.

Furthermore, I understand that I cannot make any changes to this protocol. (The only exception being an action needed to remove a subject from immediate harm, with subsequent notification to the study PI and IRB.)

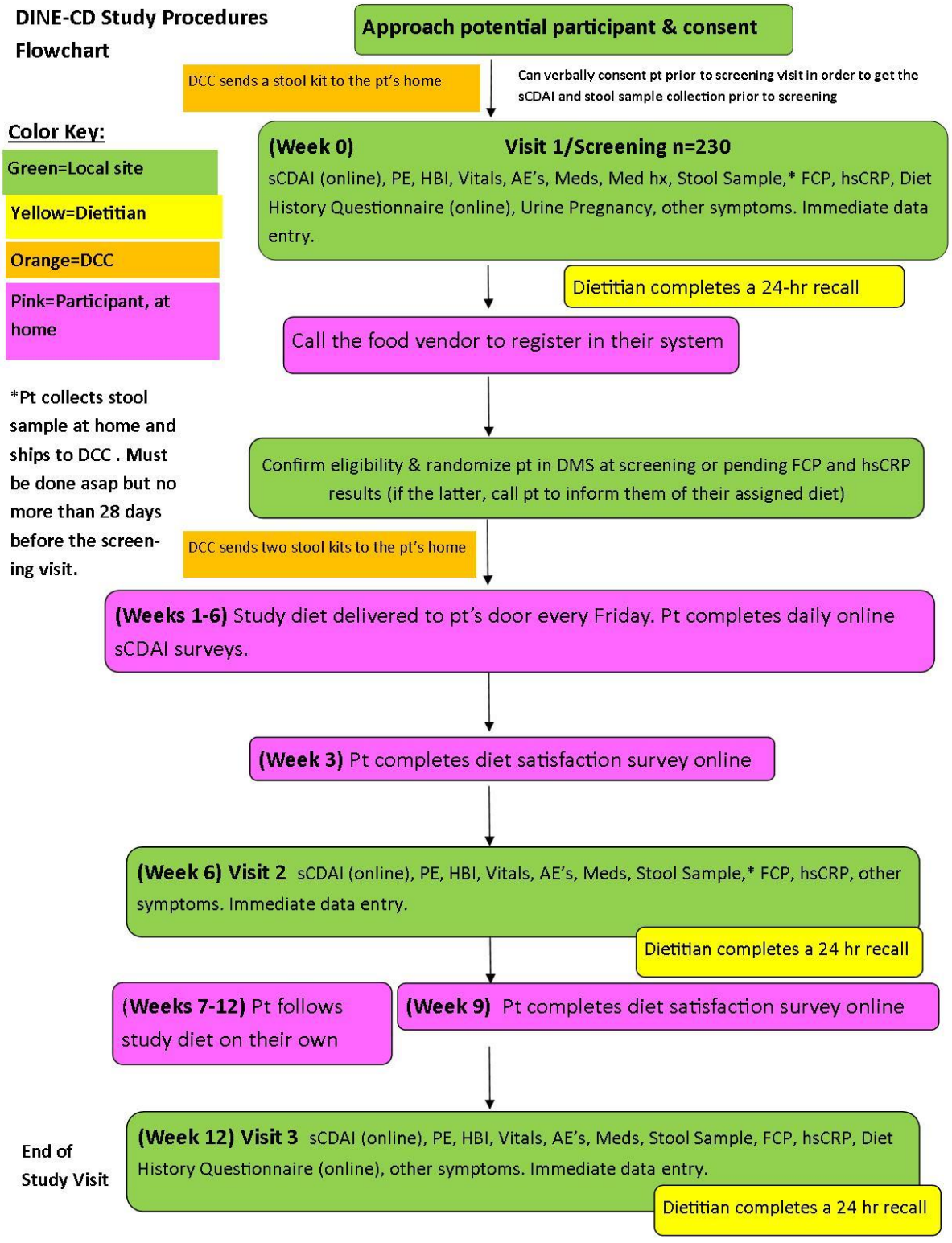
CLINICAL SITE INVESTIGATOR:_____ _____
(Signature) ***(Date)***

_____
NAME: (Please Print)

_____
INSTITUTION:

Instructions: Upon signature, please upload a copy of this form to the DMS.

Appendix B


DINE-CD Study Procedures Flowchart
Approach potential participant & consent
DCC sends a stool kit to the pt's home
Can verbally consent pt prior to screening visit in order to get the sCDAI and stool sample collection prior to screening
Color Key:
Green=Local site
Yellow=Dietitian
Orange=DCC
Pink=Participant, at home
(Week 0) Visit 1/Screening n=230
sCDAI (online), PE, HBI, Vitals, AE's, Meds, Med hx, Stool Sample,* FCP, hsCRP, Diet History Questionnaire (online), Urine Pregnancy, other symptoms. Immediate data entry.
Dietitian completes a 24-hr recall
Call the food vendor to register in their system
*Pt collects stool sample at home and ships to DCC . Must be done asap but no more than 28 days before the screening visit.
Confirm eligibility & randomize pt in DMS at screening or pending FCP and hsCRP results (if the latter, call pt to inform them of their assigned diet)
DCC sends two stool kits to the pt's home
(Weeks 1-6) Study diet delivered to pt's door every Friday. Pt completes daily online sCDAI surveys.
(Week 3) Pt completes diet satisfaction survey online
(Week 6) Visit 2 sCDAI (online), PE, HBI, Vitals, AE's, Meds, Stool Sample,* FCP, hsCRP, other symptoms. Immediate data entry.
Dietitian completes a 24 hr recall
(Weeks 7-12) Pt follows study diet on their own
(Week 9) Pt completes diet satisfaction survey online
End of Study Visit
(Week 12) Visit 3 sCDAI (online), PE, HBI, Vitals, AE's, Meds, Stool Sample, FCP, hsCRP, Diet History Questionnaire (online), other symptoms. Immediate data entry.
Dietitian completes a 24 hr recall

Appendix C

Data and Safety Monitoring Plan

Randomized, Multicenter, Comparative Effectiveness Trial of Specific Carbohydrate and Mediterranean Diets to Induce Remission in Patients with Crohn's Disease

James Lewis, M.D., M.S.C.E., Principal Investigator
Perelman School of Medicine at the University of Pennsylvania

1. Overview

1.1. Purpose of the study

This is a randomized, multicenter, comparative effectiveness trial of SCD and MSD to induce remission in patients with Crohn's Disease. The primary study objectives are

1. To compare the effectiveness of the specific carbohydrate diet and a Mediterranean style diet to induce symptomatic and clinical remission in patients with Crohn's disease.
2.

Secondary objectives include:

1. To compare the effectiveness of the specific carbohydrate diet and a Mediterranean style diet to reduce mucosal inflammation in patients with active Crohn's disease. Mucosal inflammation will be assessed by measuring the concentration of calprotectin in the feces (FCP).
2. To compare the effectiveness of the Specific Carbohydrate Diet and a Mediterranean style diet to reduce systemic inflammation in patients with active Crohn's disease. Systemic inflammation will be assessed by measuring the concentration of C reactive protein (CRP).

3. To compare the effectiveness of the specific carbohydrate diet and a Mediterranean style diet to improve the following symptoms in patients with Crohn's disease: a) fatigue, b) pain, c) joint symptoms.
4. To determine the proportion of patients who continue the study diets when prepared food is no longer provided without cost and the reasons for discontinuation of the diets.

Participants will be screened for eligibility criteria and if eligible, enrolled into the trial. Participants will continue on the diet to which they are randomized for 6 weeks with all food being provided to the participant during this time period. Participants will complete daily online surveys throughout their entire participation. From consent to the last study visit, participants may complete up to 15 weeks of daily online surveys. The primary outcome will be assessed at week 6 at an in-person visit. From weeks 7 to 12 participants will be asked to adhere to their randomized study diet on their own. At week 12 participants will be evaluated at an in-person visit.

The study is designed to enroll 97 patients into each of the treatment arms. Specific aims 1 and 2 will be considered separately and no reduction in type 1 error will be applied for multiple testing. With 97 participants per group, the study will have 80% to 90% power with a type 1 error of 5% to detect a difference of 20% in effectiveness of the two diets depending on the success rate in the reference arm. Our PPRN Patient Governance Council met and determined that a smaller difference is unlikely to justify the challenges of following a strict restriction diet.

1.2. Adherence statement.

The Data and Safety Monitoring Plan (DSMP) outlined below will adhere to the protocol approved by the University of Pennsylvania IRB.

2. Adverse Events

2.1. Definitions

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event (not life threatening but may require intervention; for example drug overdose, drug abuse, a seizure not resulting in hospitalization)

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

2.2. Expected Adverse Events

As a short term study of two diets, there are few expected risks of the two interventions. These include allergic reaction to a component of the food, intolerance of the food other than as an allergic reaction, and worsening of Crohn's disease manifest as any of the following: worsened abdominal pain, worsened diarrhea, bowel obstruction, penetrating complications such as fistula or abscess. In addition, worsening of extraintestinal manifestations of Crohn's disease is possible, such as worsening arthropathy, mouth sores, skin rashes including pyoderma gangrenosum and erythema nodosum, and ocular manifestations such as episcleritis or uveitis. The Crohn's disease related adverse events would not be considered to be caused by the diets, but rather as consequence of failure of the diet based therapy to induce disease remission.

These risks are specified in the protocol and informed consent form.

2.3. Recording of Adverse Event (AE)

At each contact with the subject from the screening visit to the end of study visit, the Site Investigator or Site Coordinator will seek information on adverse events by specific questioning and, as appropriate, by examination. Every event that is reported to either the principal investigator or the designated research associates by the subject or medical staff caring for the subject and which meets the criteria will be documented. Information on all adverse events will be recorded immediately on the AE case report form (CRF). We will document a description of the event, the date the event occurred, its relation to the investigational product or study procedures (not related, possibly related, definitely related, unknown), the grade of severity (normal, mild, moderate, severe), whether it is resolved or ongoing, and if resolved, the resolution date. The site investigator will be required to review each AE and initial on the AE form that they have reviewed it. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause.

Related, treatment-emergent serious and severe adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome, which may include resolution or stable outcome.

2.4. Relationship of AE to Study

The relationship of each adverse event to the study procedures should be characterized by the Site Investigator and recorded on the case report form. The relationship to the study intervention will be classified as definitely related, possibly related, not related, or unknown. For reporting purposes, an Adverse Event is considered "related to participation in the research" if the cause of the event is deemed possibly related or definitely related to the investigational product or a procedure that was performed for the purposes of the research.

2.5. Reporting of Serious Adverse Events and Unanticipated Problems

A Serious Adverse Event or Unanticipated Problem (see definition below) is required to be reported to the relying IRB within 10 days. If the adverse event involved a death and indicates that participants or others are at increased risk of harm the investigators are required to submit a report to the relying IRB within 3 days.

Non-medical Unanticipated Problems that should be reported to the IRB may include complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team, breach of confidentiality, incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study, or premature completion of the entire study for any reason.

Serious Adverse Events or Unanticipated Problems will be reported to the relying IRB using either a Reportable Event form from the relying IRB, or by writing a narrative including the minimum necessary information listed below. If not all information is known within the reporting timeframe, the site investigator should still complete a Reportable Event form or narrative within the timeframe with the information available and inform the relying IRB that a follow-up report will be provided when all information is known.

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study intervention was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

If an event does not meet the definition above of a Serious Adverse Event or Unanticipated Problem, a narrative summary of events that occurred should be submitted to the relying IRB at the time of Continuing Review, including a rational for why the event(s) was not reportable within 10 days.

Any known serious adverse event that occurs after the study period and is considered to be possibly or definitely related to the study intervention or study participation will be recorded and reported to the PI, the sponsor, and the relying IRB immediately.

2.5.1. Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the relying IRB. The site investigator is responsible for ensuring that all SAEs are followed until either resolved or stable.

2.5.2. Investigator reporting: notifying the study sponsor (Penn)

Site investigators should report serious adverse events and unanticipated problems meeting the 3 day reporting requirement (as defined in section 9.5) to the University of Pennsylvania Sponsor by phone and via the data management system. Phone notification should be within 24 hours of the site investigator

becoming aware of the serious adverse event. Notification via the DMS should be done within 72 hours. In the case where the DMS form cannot be fully completed with 72 hours, a partially completed form should be entered into the DMS within 72 hours, and a completed form should be entered as soon as is possible. Report SAE's by phone to:

James D. Lewis, MD
Phone: (215) 573-5137

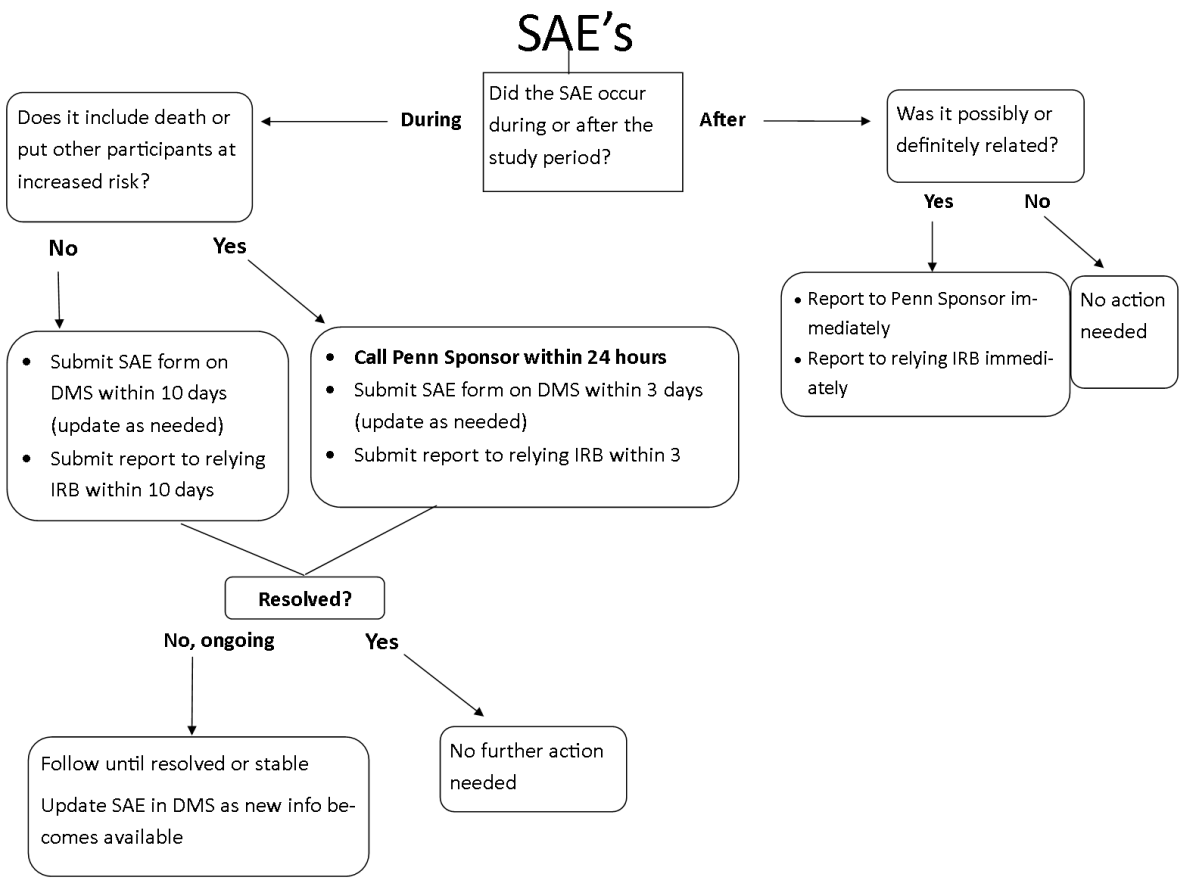
In the event Dr. Lewis cannot be reached, report SAEs to
Meenakshi Bewtra, MD
Phone: (215) 746-4922

Or
Adam Hawkins 215-746-4218 or Lisa Nessel (215) 573-6003

SAE's that do not meet the 3 day reporting requirement (i.e., do not involve death or indicate that participants are at increased risk) should be reported to the sponsor within 10 days via the data management system only. No phone call will be required.

For a flow chart outlining SAE reporting to the sponsor, please see Figure 1 below.

Figure1. SAE Flow Chart



3. Safety Review Plan and Monitoring

Principal Investigator (PI): Adverse events will be reviewed by the PI and the members of the DSMB. As described above, the PI will review all SAE reports in real time. Every quarter, reports of adverse events will be tabulated for review by the PI. The adverse events will be categorized by MedDRA categories at increasingly levels of granularity. The PI is also responsible for overall monitoring of the progress of the study, including enrollment, retention, data completeness, and site monitoring.

A Data and Safety Monitoring Board (DSMB) will be assembled prior to enrolment of the first participant in the trial. The DSMB will consist of at least 5 members. Three members will constitute a quorum. Members of the DSMB shall have no financial, scientific, or other conflict of interest with the study. Collaborators or associates of the investigators in this trial are not eligible to serve on the DSMB. Written documentation attesting to absence of conflict of interest is required. Please see the DSMB charter for further details.

The DSMB will meet once prior to the start of recruitment. Subsequently, the DSMB will meet annually with the first meeting occurring no later than once 50% of the total accrual goal has been met. . The DSMB may request an emergency meeting at any time and for any reason. At each DSMB meeting, review of progress will include updates on enrollment, retention, data completeness, and site monitoring. The DSMB members will also review all reported adverse events, including SAEs.

Overall progress of the trial will be reported to PCORI according to the standard PCORI progress report template.

The study investigators will obtain a renewal of the IRB approval for all participating sites at least once each year. Were the IRB approval to lapse at any site, no further research activity shall take place at that study site until approval renewal is obtained.

4. Informed Consent

Informed consent will be obtained from each subject at entry into the study. No study activities will occur until Informed Consent occurs. The participants may be verbally consented initially, with a formal in-person consent process completed in person. At both the verbal and in-person consent the entire study, study procedures, and intervention will be explained to the participant as well as the risks involved to the participant in participating. They will be given time to read over the study information and discuss it with their doctor, family, or friends, if they would like. They will also be given the opportunity to ask any questions to the study team and they will be provided with the contact number for the Office of Research Affairs if they have questions about their rights as a research participant. They will be made duly aware that participation in the research study is voluntary and they do not lose any of their rights by participating. If the participant would like to participate in the study, they will be asked to sign and date the consent form. The study staff obtaining consent will also sign and date the consent form and provide a copy to the participant.

Verbal Informed consent may occur if a potential participant is identified via chart review prior to their upcoming clinic visit. In this case, the Research Coordinator will ask the potential participant's gastroenterologist if he or she may contact the potential participant about the study. If permission is granted, the Coordinator will call the potential participant and gain their interest in the trial. If they are interested and would like to provide a stool sample, complete surveys about their current Crohn's disease symptoms and complete a screening visit at the time of their upcoming clinic visit, then the Coordinator will complete a verbal consent process with the potential participant. Upon coming into the clinic, the Coordinator will complete an in-person informed consent process with the participant.

5. Data Quality and Management

A. Describe measures taken to insure data integrity and protection of databases.

The Biostatistics Core of the Center for Gastrointestinal Biology and Disease at the University of North Carolina Chapel Hill will serve as the Data Management Center. The DMC will be charged with creating, managing, and housing the data management. The DCC will be charged with assuring data is entered and are complete and accurate. The DCC will also be charged with data and safety monitoring and coordinating all meetings of the DSMB.

Site Coordinators will complete minimal data entry immediately after each participant's visit, utilizing a double data entry system to minimize error and ensure data quality.

With the exception of the minimal visit data, most of the data to be collected in this study will be collected directly from participants through our web-based data entry system. For specific aim 1, the primary outcome is derived from patient reported data. For specific aim 2, the primary outcome is derived from the measurement of the concentration of fecal calprotectin, which will be done by a commercial laboratory LabCorp. Such data are not subject to monitoring other than for completeness. This will be done by the data analysts.

We will monitor the sites for compliance with regulatory documentation and for compliance with the study protocol, particularly as it relates to inclusion criteria. We will utilize a system whereby the local investigator team prints, redacts, and uploads into our data management system source documents that demonstrate the eligibility of the participants. Study monitors will then remotely review these documents for compliance with the study protocol, send queries to the local sites, resolve outstanding queries, and document the level of adherence with the study protocol. See the table below for the list of source documents that the monitors will review for each inclusion/exclusion criteria. Any findings that demonstrate a protocol deviation will be reported to the Penn IRB or local IRB, as appropriate. The first remote monitoring visit will occur after a site enrolls its first 4 participants. After that, remote monitoring visits will occur each time 6 more participants are enrolled (for example, visits will occur after the 4th, 10th, 16th, 22nd participant, etc).

Similar methods will be employed for reviewing the participating sites regulatory binder. We will provide each site with an electronic storage area where their regulatory documents can be stored and then reviewed by the monitors. Eligibility criteria and consent process will be monitored for all participants. If deemed necessary, on site monitoring will be employed.

Source Documents that will be reviewed by the study monitors for protocol compliance are outlined in the following table.

Data type	Source Document to review
Age	Demographics from medical record
Medications	Office notes from 16 weeks prior to randomization and medication list up to 16 weeks prior to randomization
Clostridium Difficile	Any stool sample testing in medical record within 4 weeks prior to the screening visit
Diabetes Mellitus requiring medication	Medication list and problem list/diagnosis list in medical record
hsCRP	Blood draw results done by the study at the screening visit, at week 6 and week 12
Albumin	Blood draw results in medical record within 4 weeks prior to the screening visit
BMI	Physical exam source document done at the screening visit
FCP	FCP result done by the study at baseline (stool

	must be collected within 28 days prior to start of study diet), at week 6 and week 12
sCDAI score	sCDAI score in the DMS at baseline from at least 5 days of symptom recording
Intestinal Stricture	Imaging in the last year and two office notes – the office note closest to the screening visit and the office note immediately preceding that visit

Data quality checks will be built into the DMS, such that nonsensical data will prompt the Site Coordinators to check for accuracy, certain questions will be required for form completion, and skip patterns will be in place. We will also implement a data quality monitoring system after the second patient is enrolled that will report on form completeness and on the timeliness of form completion. Data quality checks will continue monthly throughout the study by the Data Coordinating Center. Data queries will be sent from the DCC to the local sites.

Reports on form completion, missing data reports so that we are aware of patterns of missing data early on in the study, logic checks will be completed throughout the study. Reminders will be automatically sent to the sites from the DMS for upcoming visit target dates 14 days prior to the visit target date. Another reminder will be sent in advance of visit window closing dates. Not only are we going to check for missing data we are going to proactively manage the data to avoid missing data.

B. Describe measures taken to insure data integrity and protection of databases.

All computer systems and programs will be password protected, and all electronic communications of study and other confidential information will be encrypted. Personnel at the CGIBD have extensive training and experience using electronic data systems. Good computer security practice (restricting physical access to machines, prohibition of password sharing, and logging off computers after work hours or when away from the machine) will be required of all study personnel.

Standard Operating Procedures exist for users of the DMS. Only authorized persons are authorized for data entry and access. Data security systems require password protected identification codes for data entry and provide protection against data manipulation. The database is located on a server protected by firewalls. Access to the database server will not be allowed by users on computers outside of the firewall-protected zone. Virus protection software is installed on each study machine. System access to computer systems will be audited. Redundant backups and off-site backup storage will allow for quick restoration of data in the unlikely event that a hardware failure, disaster, or security breach should occur. Servers and backups will be located in a secured location with access limited to authorized personnel.

6. Confidentiality

As mentioned in the section above, participant information will be kept on secure servers and electronic communication of information will be encrypted. Samples and CRFs will be labeled with a unique study identifier to protect participants' confidentiality. Only members of the study team will have access to the web application. Source documents will be kept separately from CRFs. Paper forms with participants' identifiers will be kept secure in a double lock system such as a locked filing cabinet in a locked office.

Appendix D

DINE-CD SOP: Assembly of Stool Sample Collection Kits

Version: 1

Date: August 19, 2016

This SOP outlines the assembly of stool sample collection kits at the Data Coordinating Center.

If you have any questions, please contact Adam Hawkins ahawkeye@upenn.edu or 215-746-4218

To be done in advance, or on a continuous basis, by lData Coordinating Center

Materials for ONE Specimen Collection kit:

A. (1) White stool collection bucket + lid + frame
B. (1) Therapak Styrofoam shipper
C. (1) Gallon-size Ziploc bag
D. (1) Biohazard label
E. (1) Exempt Human Specimen label
F. (1) Study label
G. (1) Stool Collection form
H. (1) Stool Collection Instructions for participants
I. (1) UPS/FedEX Shipping label to ship to the participant's home (if applicable)
J. (1) UPS/FedEX Shipping label for the participant to ship the sample to the University of Pennsylvania
K. (1) Black canvas bag (for Penn participants)
L. (1) Additional Black canvas bag (for Penn participants who will bring the stool sample with them to their visit)

*You will also need mailing tape

1. Print and obtain a study label with the participant's study ID number on it
2. Get a white stool collection bucket and place a study label on it.
3. Print a Stool Collection form and record the participant's ID number on it and date of birth.
4. Place the white bucket with the lid on it, the Ziploc bag, the Stool Collection form and Stool Collection instructions for participants into the Styrofoam shipper.
5. Obtain a UPS/FedEx Shipping label with the following name and address as the sender and recipient:
   Name: Lillian Chau
   Address: 421 Curie Blvd
   936 BRB II/III
   Philadelphia, PA 19104
6. Insert the shipping label into a plastic sleeve
7. Place the shipping label and sleeve from step 6 inside the Styrofoam cooler so that the participant can use it after they receive the kit. Close the lid. Place the frame in the box and gently fold it over the lid of the Styrofoam cooler, making sure it doesn't break.
8. Seal the box with mailing tape.
9. You need to print/obtain another shipping label that will have your address as the sender and the participant as the recipient.

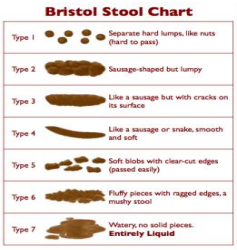
10. Place this label on the outside of the box (either in a sleeve or not; if you use a sleeve, you can instruct the participant to use this same sleeve when it is their turn to ship. Taking the sleeve off may damage the integrity of the box making it unacceptable to ship).
11. Place the Biohazard Label and Exempt Human Specimen label on the outside of the shipper cardboard box on a different side than the shipping label.
12. Arrange for courier pick-up or drop off the box at a courier pick-up location or store.

STOOL COLLECTION INSTRUCTIONS

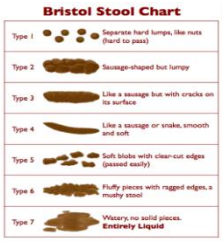
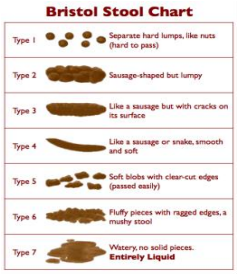
Please collect your first stool sample as soon as possible on a Sunday, Monday, Tuesday, or Wednesday following the instructions below. Do not collect a sample on Thursday, Friday, or Saturday. You will need to schedule your sample to be picked up by UPS as soon as possible after you collect it so that it is shipped soon after collection (see step 16 on page 3 below).

Contact your study coordinator if you notice any of the pieces of the kit below are missing or if you have any questions as you complete the stool collection.

Each stool collection kit contains:

	One stool collection bucket with a frame, a lid, and a label on the outside.
	One gallon-size plastic storage bag
	Four gel ice packs
	One Therapak Shipper: a Styrofoam cooler and lid inside a cardboard box, equipped with a Biohazard label, an Exempt Human Specimen label, an Excepted Quantities label and a plastic specimen bag.
	One spoon-top labeled vial filled with 5mL ethanol
	One Stool Collection form to document date and time of collection and date of birth (further instructions for filling out the form are located on the form)

	**STEP 1.** Put the gel ice packs in your freezer at home as soon as you get your kit so they are already frozen when you are ready to collect your sample(s).
	**STEP 2**. When you are ready to collect the sample, raise the toilet seat. Pass urine into the toilet first, if necessary. **Do not let urine or water from the toilet get into the collection bucket.** Place the stool collection frame on the back of the toilet bowl. All four corners of the collection frame should be supported by the toilet bowl. Place collection bucket in the frame.
	**STEP 3**. Place the toilet seat down. Do **not** urinate into the collection bucket and do **not** let urine or water touch the stool sample. Deposit your stool directly into the collection bucket. **STEP 4**. After collecting your sample, remove the collection bucket from the frame. Discard the frame.
	**STEP 5.** Take the lid off of the spoon-top vial. Scoop a small amount of stool from the sample and place this into the vial. Only scoop enough to fill the scoop. It does not need to be a heaping scoop. Screw the tap on the vial tightly. Shake the vial to make sure the sample comes off the spoon.
	**STEP 6.** Write the date on the label on the outside of the vial. Place the vial in the plastic bag labeled, "Biohazard" and seal the bag.

	**STEP 7.** Put the lid on the stool collection bucket and write the date of collection on the label on the outside. Place it in the gallon size Ziploc plastic bag and seal the bag.
	**STEP 8.** Complete the Stool Collection form. Record the date and time of collection on the Stool Collection Form. Also record your Date of Birth if it is not already recorded there by the Study Coordinator. Lastly, choose the type on the Bristol Stool scale that most represents your sample and record it in the space provided.
	**STEP 9.** Put the frozen gel ice packs in the Styrofoam cooler. **STEP 10.** Put the two plastic bags containing your samples into the cooler.
	**STEP 11.** Fold the Stool Collection form and place it on top of the samples. Put the lid of the cooler on top. **STEP 12.** Close the flaps on the box. The sample is ready to be provided to study staff. ******The next steps are for shipping the sample to the study lab at the University of Pennsylvania ******
	**STEP 13:** Seal the box with tape to prepare for shipping **STEP 14:** Place the shipping label that was included in the cooler in the label pouch on the outside of the box, replacing the used label. **STEP 15:** Make sure the Biohazard sticker, the "Exempt Human Specimen," sticker and the sticker with a red capital letter "E" are on the box. **STEP 16:** Call 1-800-PICK-UPS to arrange a pick-up of the sample. Place the sample outside your home for the courier to pick up. You will not need to be there when they pick it up. All pick up fees will be paid for by the study. If you collect a sample at night, have it picked up the next morning.

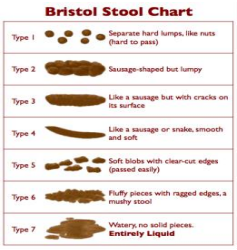
STOOL COLLECTION INSTRUCTIONS

For your 2nd and 3rd stool samples in the study, we need you to collect a sample during the following date ranges:

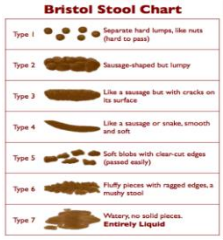
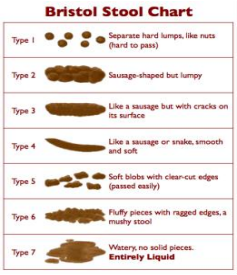
- Between mm/dd/yyyy [insert day 38] and mm/dd/yyyy [insert day 40] AND
- Between mm/dd/yyyy [insert day 80] and mm/dd/yyyy [insert day 82]

Contact your study coordinator if you notice any of the pieces of the kit below are missing or if you have any questions as you complete the stool collection.

Each stool collection kit contains:

	One stool collection bucket with a frame, a lid, and a label on the outside.
	One gallon-size plastic storage bag
	Four gel ice packs
	One Therapak Shipper: a Styrofoam cooler and lid inside a cardboard box, equipped with a Biohazard label, an Exempt Human Specimen label, an Excepted Quantities label and a plastic specimen bag.
	One spoon-top labeled vial filled with 5mL ethanol
	One Stool Collection form to document date and time of collection and date of birth (further instructions for filling out the form are located on the form)

	**STEP 1.** Put the gel ice packs in your freezer at home as soon as you get your kit so they are already frozen when you are ready to collect your sample(s).
	**STEP 2**. When you are ready to collect the sample, raise the toilet seat. Pass urine into the toilet first, if necessary. **Do not let urine or water from the toilet get into the collection bucket.** Place the stool collection frame on the back of the toilet bowl. All four corners of the collection frame should be supported by the toilet bowl. Place collection bucket in the frame.
	**STEP 3**. Place the toilet seat down. Do **not** urinate into the collection bucket and do **not** let urine or water touch the stool sample. Deposit your stool directly into the collection bucket. **STEP 4**. After collecting your sample, remove the collection bucket from the frame. Discard the frame.
	**STEP 5.** Take the lid off of the spoon-top vial. Scoop a small amount of stool from the sample and place this into the vial. Only scoop enough to fill the scoop. It does not need to be a heaping scoop. Screw the tap on the vial tightly. Shake the vial to make sure the sample comes off the spoon.
	**STEP 6.** Write the date on the label on the outside of the vial. Place the vial in the plastic bag labeled, "Biohazard" and seal the bag.

	**STEP 7.** Put the lid on the stool collection bucket and write the date of collection on the label on the outside. Place it in the gallon size Ziploc plastic bag and seal the bag.
	**STEP 8.** Complete the Stool Collection form. Record the date and time of collection on the Stool Collection Form. Also record your Date of Birth if it is not already recorded there by the Study Coordinator. Lastly, choose the type on the Bristol Stool scale that most represents your sample and record it in the space provided.
	**STEP 9.** Put the frozen gel ice packs in the Styrofoam cooler. **STEP 10.** Put the two plastic bags containing your samples into the cooler.
	**STEP 11.** Fold the Stool Collection form and place it on top of the samples. Put the lid of the cooler on top. **STEP 12.** Close the flaps on the box. The sample is ready to be provided to study staff. ******The next steps are for shipping the sample to the study lab at the University of Pennsylvania ****** *(if you are a participant at the University of Pennsylvania and this is your week 6 or week 12 sample, you may bring you sample to your study visit.)*
	**STEP 13:** Seal the box with tape to prepare for shipping **STEP 14:** Make sure there is a shipping label on the outside of the box (should have been already put on the box by study staff) **STEP 15:** Make sure the Biohazard sticker, the "Exempt Human Specimen," sticker and the sticker with a red capital letter "E" are on the box. **STEP 16:** Call 1-800-PICKUPS to arrange a pick-up of the sample. Place the sample outside your home for the courier to pick up. You will not need to be there when they pick it up. All pick up fees will be paid for by the study.

Appendix F

DSMB Charter

Randomized, Multicenter, Comparative Effectiveness Trial of Specific Carbohydrate and Mediterranean Diets to Induce Remission in Patients with Crohn's Disease

James Lewis, M.D., M.S.C.E., Principal Investigator

Perelman School of Medicine at the University of Pennsylvania

1. Introduction

This Data and Safety Monitoring Board charter is for a clinical trial titled, "Randomized, Multicenter, Comparative Effectiveness Trial of Specific Carbohydrate and Mediterranean Diets to Induce Remission in Patients with Crohn's Disease" with a short title Dietary Intervention in Crohn's Disease (Dine CD). This study is being funded by the Patient-Centered Outcomes Research Institute (PCORI) and the Crohn's and Colitis Foundation (CCF). The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to the investigator sponsor, Dr. Lewis, and the CCF to monitor patient safety and evaluate the efficacy of the intervention.

2. MEMBERSHIP

The Data Safety Monitoring Board will consist of at least 5 members. Three members will constitute a quorum. Members of the DSMB shall have no financial, scientific, or other conflict of interest with the study. Collaborators or associates of the investigators in this trial are not eligible to serve on the DSMB. Written documentation attesting to absence of conflict of interest is required.

Dr. Naihua Duan, Professor Emeritus of Biostatistics (in Psychiatry) at Columbia University has been selected to serve as the DSMB Chairperson. He is responsible for overseeing the meetings and developing the agenda in consultation with the PI and the Administrative PI, Angela Dobes, MPH of the CCF. Orna Ehrlich, CCF's Senior Director, Professional Education will serve as the DSMB Executive Secretary (ES) and is the contact person for the DSMB. Other PCORI and CCF officials may serve as ex-officio members of the DSMB. The University of Pennsylvania shall provide the logistical management and financial support for the DSMB.

3. RESPONSIBILITIES

3.1. Responsibilities of the DSMB

The initial responsibility of the DSMB will be to approve the initiation of this clinical trial. After this approval, and at periodic intervals during the course of the trial, the DSMB responsibilities are to:

- review the research protocol and plans for data safety and monitoring, including all proposed revisions;
- evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial sites, and other factors that may affect study outcome;
- consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- protect the safety of the study participants;

- report on the safety and progress of the trial;

- make recommendations to the CCF, the Principal Investigator (PI), and, if required, to the Institution Review Boards (IRBs) concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;

- ensure the confidentiality of the trial data and the results of monitoring;

- assist the PI and CCF by commenting on any problems with study conduct, enrollment, sample size and/or data collection.

3.2. Responsibilities of the Data Management Center

The Biostatistics core of the Center for Gastrointestinal Biology and Disease at the University of North Carolina Chapel Hill will serve as the Data Management Center (DMC). The DMC will be charged with creating, managing, and housing the data management system.

All data will be created, modified, maintained, archived, retrieved and distributed by a computer system. The use of electronic records will increase the speed of data collection and exchange.
The Data Management Center (DMC) at the CGIBD at the University of North Carolina will track the data collection, provide data security, control for confidentiality of study data, maintain computer backups to protect data until study closure and archive study data according to FDA requirements (21 CFR 11). Electronic signatures will be linked to each entry.

All computer systems and programs will be password protected, and all electronic communications of study and other confidential information will be encrypted. Personnel at the CGIBD have extensive training and experience using electronic data systems. Good computer security practice (restricting physical access to machines, prohibition of password sharing, and logging off computers after work hours or when away from the machine) will be required of all study personnel.

Standard Operating Procedures exist for users of the DMC. Only authorized persons are authorized for data entry and access. Data security systems require password protected identification codes for data entry and provide protection against data manipulation. The database is located on a server protected by firewalls. Access to the database server will not be allowed by users on computers outside of the firewall-protected zone. Virus protection software is installed on each study machine. System access to computer systems will be audited. Redundant backups and off-site backup storage will allow for quick restoration of data in the unlikely event that a hardware failure, disaster, or security breach should occur. Servers and backups will be located in a secured location with access limited to authorized personnel.

Standardized study management reports will be generated monthly during the recruitment phase of the study. These reports will be used to track study progress including patient enrollment, randomization, compliance, patient status changes, and study events. The data will be reported for each Study Center individually and summarized for the study as a whole. Every six months, a standardized report will also be generated for the DSMB meeting. This report will include additional information on clinical events and adverse events that is coded by treatment group. Other than the DSMB, the study statistician and statistical analyst, no study personnel will see this report.

3.3. Responsibilities of the Data Coordinating Center

The University of Pennsylvania will serve as the Data Coordinating Center for this study. The DCC will be charged with assuring data is entered and that data are complete and accurate. The DCC will also be charged with Data and Safety Monitoring. The DCC will organize all DSMB meetings.

4. BOARD PROCESS

The DSMB will at 50% of the accrual goal at at a minimum of annually.

Meetings shall be closed to the public because discussions may address confidential patient data. Meetings are attended, when appropriate, by the principal investigator and members of his/her staff.

Meetings may be convened as conference calls as well as in person.

An emergency meeting of the DSMB may be called at any time by the Chairperson or by the CCF or PCORI should questions of patient safety arise. The DSMB Chairperson should contact the PCORI project officer and the CCF's Chief Scientific Officer prior to convening an emergency meeting.

5. MEETING FORMAT

An appropriate format for DSMB meetings consists of an open, closed and executive session. This format may be modified as needed.

Open Session:
The voting members of the DSMB, the Executive Committee, the NIDDK staff, the principal investigator and members of his staff including the study biostatistician will attend the open session.

Issues discussed will include the conduct and progress of the study, including patient recruitment, data quality, general adherence and toxicity issues, compliance with protocol, and any other logistical matters that may affect either the conduct or outcome of the study. Proposed protocol amendments will also be presented in this session. **Patient-specific data and treatment group data may not be presented in the open session.**

Closed Session:
The closed session will be attended only by voting DSMB members, representatives from the NIDDK, and the study biostatistician. **The discussion at the closed session is completely confidential.**

Analyses of blinded outcome data are reviewed by masked intervention groups, including baseline characteristics, primary and secondary outcomes, adverse events, adherence and dropouts, and examination of any relevant subgroups. However, the DSMB may request unmasking of the data for either safety or efficacy concerns. Procedures to accomplish unmasking of either individual or treatment group data are to be specified in the DSMB plan.

Executive Session:
The executive session will be attended by voting DSMB members and the NIDDK executive secretary.

The DSMB will discuss information presented to it during the closed and open sessions and decide whether to recommend continuation or termination, protocol modification or other changes to the conduct of the study. The DSMB can become unblinded if trends develop either for benefit or harm to the participants.

Three members will be required for a quorum; however, any changes to the study will require a full vote of the DSMB.

Should the DSMB decide to issue a termination recommendation, full vote of the DSMB will be required. In the event of a split vote, majority vote will rule and a minority report should be appended. Reasons for early termination include:

- Serious adverse effects in entire intervention group or in a dominating subgroup;
- Greater than expected beneficial effects;
- A statistically significant difference by the end of the study is improbable;
- Logistical or data quality problems so severe that correction is not feasible.

Final Open Session (optional):
The final session may be attended by voting DSMB members, the principal investigator, the study biostatistician or other study members, and the NIDDK staff.

The Chair of the DSMB or the Executive Secretary shall report on the recommendations of the DSMB regarding study continuation and concerns regarding the conduct of the study. Requests regarding data presentation for subsequent meetings will be made. Scheduling of the next DSMB meeting may be discussed.

REPORTS

Interim Reports: Interim reports are generally prepared by the study statistician(s) and distributed to the DSMB and the NIDDK Project Officer at least 14 days prior to a scheduled meeting. These interim reports are numbered and provided in sealed envelopes within an express mailing package or by secure email as the DSMB prefers. The contents of the report are determined by the DSMB. Additions and other modifications to these reports may be directed by the DSMB on a one-time or continuing basis. Interim data reports generally consist of two parts:

> Part 1 (**Open Session Report**) provides information on study aspects such as accrual, baseline characteristics, and other general information on study status. This report is generally shared with all investigators involved with the clinical trial.
>
> Part 2 (**Closed Session Report**) may contain data on study outcomes, including safety data, and depending on the study, perhaps efficacy data. The Closed Session Report is considered confidential and should be destroyed at the conclusion of the meeting. Data files to be used for interim analyses should have undergone established editing procedures to the extent possible. Interim analyses of efficacy data are performed only if they are specified and approved in advance and criteria for possible stopping is clearly defined. This report should not be viewed by any members of the clinical trial except the designated study statistician.

Reports from the DSMB: A formal report containing the recommendations for continuation or modifications of the study, prepared by the ES with concurrence from the DSMB, will be sent to the PI. This report will also contain any recommendations of the NIDDK in reference to the DSMB recommendations. It is the responsibility of the PI to distribute this report to all co-investigators and to assure that copies are submitted to all the IRBs associated with the study.

Each report should conclude with a recommendation to continue or to terminate the study. This recommendation should be made by formal majority vote. A termination recommendation may be made by the DSMB at any time by majority vote. The NIDDK is responsible for notifying the PI of a decision to terminate the study. In the event of a split vote in favor of continuation, a minority report should be contained within the regular DSMB report. The report should not include unblinded data, discussion of the unblinded data, or any other confidential data.

Mailings to the DSMB: On a scheduled basis (as agreed upon by the DSMB) blinded safety data should be communicated to all DSMB members, the NIDDK project officer and the designated safety officer. Any concerns noted by the DSMB or the safety officers should be brought to the attention of the NIDDK Project Officer.

Access to Interim Data: Access to the accumulating endpoint data should be limited to as small a group as possible. Limiting the access to interim data to the DSMB members relieves the investigator of the burden of deciding whether it is ethical to continue to randomize patients and helps protect the study from bias in patient entry and/or evaluation.

CONFIDENTIALITY

All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

Appendix G

DINE-CD Analytic and Statistical Analysis Plan

This document will outline the analytic and statistical plan for the DINE-CD clinical trial.

1. Definitions and roles

Principal investigator – Dr. James Lewis at the University Pennsylvania will be the principal investigator for this clinical trial and will be responsible for oversight of all aspects of the trial.
Lead data analyst – Ms Colleen Brensinger at the University of Pennsylvania's Center for Clinical Epidemiology and Biostatistics (CCEB) will conduct all statistical analyses for this clinical trial.
Study biostatistician – Dr. Hongzhe Li at the University of Pennsylvania will serve as the lead biostatistician and will supervise the work of Ms. Brensinger.
Data coordinating center – Dr. Lewis and colleagues at the University of Pennsylvania will serve as the data coordinating center for this clinical trial.
Data management center – the University of North Carolina in collaboration with the CCFA Partners Patient Powered Research Network (PPRN) will build the data warehouse and database structure and will house all of the data from this trial.

2. Overview

This is a randomized, multicenter, comparative effectiveness trial of the specific carbohydrate diet (SCD) and a Mediterranean style diet (MSD) to induce remission in patients with Crohn's disease. The study is funded by PCORI, will be conducted in up to 50 centers throughout the United States over a period of three years.
The primary and secondary objectives of this clinical trial are the following:
Primary:

1. To compare the effectiveness of the specific carbohydrate diet and a Mediterranean style diet to induce symptomatic and clinical remission in patients with Crohn's disease.
2.
3. *Secondary:*
    1. To compare the effectiveness of the specific carbohydrate diet and a Mediterranean style diet to reduce mucosal inflammation in patients with active Crohn's disease. Mucosal inflammation will be assessed by measuring the concentration of calprotectin in the feces (FCP).
    2. To compare the effectiveness of the Specific Carbohydrate Diet and a Mediterranean style diet to reduce systemic inflammation in patients with active Crohn's disease. Systemic inflammation will be assessed by measuring the concentration of C reactive protein (CRP).
    3. To compare the effectiveness of the specific carbohydrate diet and a Mediterranean style diet to improve the following symptoms in patients with Crohn's disease: a) fatigue, b) pain, c) joint symptoms.
    4. To determine the proportion of patients who continue the study diets when prepared food is no longer provided without cost and the reasons for discontinuation of the diets.

The clinical trial will enroll 194 participants who will be randomly assigned in a 1 to 1 ratio to the two study diets. The main inclusion criteria are Crohn's disease with mild to moderately active symptoms as measured by the short CDAI (sCDAI) score greater than 175 and less than 400, and at least 18 years of age. The main exclusion criteria are the following:

- Pregnancy
- Hospitalized pts. or surgery planned within 6 wks
- Ostomy or known symptomatic intestinal stricture
- Start of thiopurines,natalizumab, vedolizumab or methotrexate(w/in 12 wks) or anti-TNF (w/in 8 wks)
- Start or change corticosteroids within 1 week of screening or dose >20mg prednisone or equivalent
- Use of antibiotics w/in 2 weeks of screening
- Start or change of dose of 5-ASA type medication w/in 2 weeks of screening
- Baseline stool frequency >4 bowel movements/day when well
- BMI<16 or ≥40
- Celiac disease, recent c diff colitis, or diabetes

- Albumin<2.0mg/dl (if part of routine clinical care)

The primary outcome measures will be assessed six weeks following randomization. Additional secondary outcome measures will be assessed 12 weeks following randomization. The study diets will be provided to the participants at no cost for the first six weeks following randomization. Subsequently, participants will be required to obtain their own food. However, participants will be provided with instructions on how to continue to follow the study diets during weeks 7 to 12 of the clinical trial.

3. Data Collection and Management

3.1. Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, subject files, and records kept at the food dispensing company, and at the laboratories.

3.2. Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained.
Data on CRFs will be collected via direct electronic data capture using a secure web-based database designed by and housed in the University of North Carolina. The eCRFs will be the source document in some cases. These eCRFs will not include PHI or participants' identifiable information. Instead, eCRFs will be labeled with a unique study identification number.
Study personnel are instructed that if a space on the CRF is left blank because the procedure was not done or the question was not asked, type "N/D". If the item is not applicable to the individual case, type "N/A".

3.3. Data access

TO BE COMPLETED WITH HELP FROM UNC
During the conduct of the trial, the data management team at the University of North Carolina and the lead data analyst at the University of Pennsylvania will have access to the raw study data. Standardized reports will be generated to allow data coordinating center to monitor recruitment and retention, completion of eCRFs, and for quality control purposes prior to the end of the trial. The analyst will prepare summary documents for the investigative team without separating the data by study group. The analyst will prepare separate files stratifying the data by study group for the data and safety monitoring board (DSMB).
At the conclusion of the trial, the data analyst and study biostatistician will prepare the analytic data files to be used in the final analyses. They will work with the data coordinating center and the data management team to resolve any outstanding queries prior to conducting the final analyses. Review of descriptive data of the combined cohort may be conducted with the data management team and the data coordinating center to facilitate data cleaning.
The analytic plan will be reviewed and agreed upon by the data coordinating center and study steering committee prior to conducting the final analyses. A copy of the locked final analytic data set will be preserved as a backup. All analyses will be conducted using fast computer programs such that no changes will be made to the locked final data set.

4. Data collection

Baseline and follow-up data will be collected through a combination of electronic CRFs completed by the participants and by the research team. The former will be used to collect symptoms used to define the PROs. The latter will be used to collect data on patient characteristics and adverse events.
Baseline data are described in the following table.

Variable	Variable name	Categorization
Age		Continuous

Sex		Male=0; Female=1
Race		Caucasian=0; Black=1; Asian=3; American Indian / Alaska Native=4; Pacific Islander / Hawaiian = 5; Multi racial = 6
Ethnicity		Non-Hispanic=0; Hispanic=1
Weight in Kg		Continuous
BMI		Continuous
Tobacco use		0=never; 1=former; 2=current
Current medications		
Current corticosteroid use		0=no; 1=yes
Current mesalamine use		0=no; 1=yes
Current azathioprine or 6MP use		0=no; 1=yes
Current methotrexate use		0=no; 1=yes
Current anti-TNF use		0=no; 1=yes
Current vedolizumab/natalizumab		0=no; 1=yes
Former medications		
Former corticosteroid use		0=no; 1=yes
Former mesalamine use		0=no; 1=yes
Former azathioprine or 6MP use		0=no; 1=yes
Former methotrexate use		0=no; 1=yes
Former anti-TNF use		0=no; 1=yes
Former vedolizumab or natalizumab		0=no; 1=yes
Disease distribution		
Ileum		0=no; 1=yes
Colon		0=no; 1=yes
Ileocolon		0=no; 1=yes
Duration of current flare		Continuous in days
Current symptoms		
Bowel frequency		Continuous
Abdominal pain rating		Ordinal
General Wellbeing		Ordinal
Fatigue (PROMIS)		Continuous
Sleep (PROMIS)		Continuous
Pain interference (PROMIS)		Continuous
Social Isolation (PROMIS)		Continuous
Baseline diet from DHQ		
Percent calories from Fat		Continuous
Percent calories from Carbohydrates		Continuous
Percent calories from Protein		Continuous
Gluten free diet		0=no; 1=yes
Other dietary descriptions – Charlene		
Back pain screening*		
Age at onset <40 years		0=no; 1=yes
Insidious onset		1=no; 0=yes
Improvement with exercise		0=no; 1=yes
Improvement with rest		1=no; 0=yes
Wake up in the second half of the		0=no; 1=yes

night with pain		
Bath Index if screen positive for back pain		Continuous

*If at least four out of these five parameters were fulfilled, the criteria had a sensitivity of 77.0% and specificity of 91.7% for axial spondyloarthritis in the patients participating in the workshop, and 79.6% and 72.4%, respectively, in the validation cohort.

Baseline and follow-up clinical data will be collected as described in the following table

Variable	Variable name	Categorization	Data source	When collected
Number of liquid or soft stools each day		Continuous	Participant	Daily
Abdominal pain		0=none; 1=mild; 2-moderate; 3=severe	Participant	Daily
General wellbeing		0=generally well; 1=slightly under par, 2=poor; 3= very poor; 4= terrible	Participant	Daily
Arthralgia		0=no; 1=yes	Investigator	0,6,12
Uveitis		0=no; 1=yes	Investigator	0,6,12
Erythema nodosum		0=no; 1=yes	Investigator	0,6,12
Abscess		0=no; 1=yes	Investigator	0,6,12
Pyoderma gangrenosum		0=no; 1=yes	Investigator	0,6,12
Fissure		0=no; 1=yes	Investigator	0,6,12
New fistula		0=no; 1=yes	Investigator	0,6,12
Abscess		0=no; 1=yes	Investigator	0,6,12
Aphthous ulcers		0=no; 1=yes	Investigator	0,6,12
PROMIS measures				
Pain Interference 6a short form		Continuous	Participant	0,6,12
v1.0 Fatigue 7a short form		Continuous	Participant	0,6,12
v1.0 Sleep Disturbance 8a short form		Continuous	Participant	0,6,12
V2.0 Social Isolation 4a				
RAPID-3		Continuous	Participant	0,6,12
BASFI*		Continuous	Participant	0,6,12

* Only if screen positive on back pain screen

4.1. Best Practices in Administration of PROMIS measures

- PROMIS self-report measures are intended to be completed by the respondent without help from anyone else.
- If respondents are unable to answer on their own, have someone else ("proxy") report on their behalf. Respondents requiring a proxy may include: young children, people in the early stages of dementia who may not recognize the extent of their impairment, people with cognitive or communication deficits, and people with severe disease burden. PROMIS Parent Proxy measures are available.
- Keep respondents' privacy in mind, but have staff readily available to help with any technology issues that may arise.
- It is acceptable for staff to define a term (e.g., "nausea"), but not to define a concept where the respondent's subjective interpretation is the goal of the question (e.g., "quality of life").
- Utilize the same method (e.g., computer, telephone, or paper) and mode (e.g., self vs. interviewer) of administration. However, this is not always possible, and PROMIS measures have produced similar scores when the method of administration varied. See the Forum for more information on **method / mode** effects.
- In clinical settings, give respondents the optimal time needed to capture the most relevant perspective and complete data (e.g., before/after clinician visit or in between visits). This may depend on the study aims and/or clinic work flow.
- The text and responses of PROMIS items cannot be altered in any way and still be considered a PROMIS item. Users are welcome to modify the items, but cannot refer to these modified items as PROMIS and we have no data about whether or not this modified version would have the same psychometric properties as the original PROMIS item. If you do modify items, please clearly specify in what ways the items were modified in any publications or other publicly disseminated work products.

There are multiple different versions of the PROMIS measures. The recommended shortform versions can be found at http://www.healthmeasures.net/applications-of-healthmeasures/in-research/selecting-a-healthmeasure. For pain interference, v1.0 Pain Interference 6a short form is recommended. For fatigue, v1.0 Fatigue 7a short form is recommended. For sleep, v1.0 Sleep Disturbance 8a short form is recommended. For social isolation, we selected a brief version (Social Isolation Short Form 4a). Scoring guidelines are included in the appendices. We will use the PROMIS Assessment Center Scoring Service to obtain the most accurate scores.

5. Analytic plan

5.1. Overview

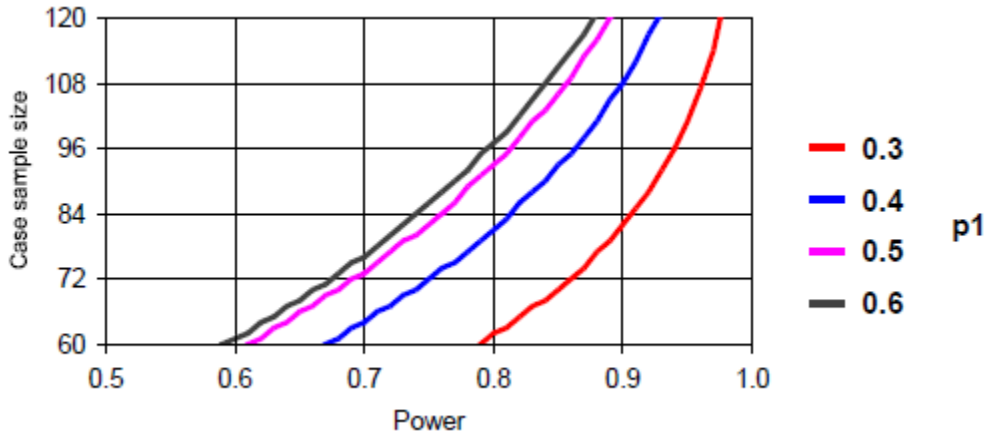
This clinical trial will examine the effects of a low risk intervention. A total of 194 participants are anticipated to be included in the study. Enrollment is anticipated to be completed over a two-year time period. Because this clinical trial will compare two different diets, both of which have potential health benefits, no interim safety or effectiveness analyses are planned. However, analyses will be conducted to monitor recruitment, retention, and data quality.

5.2. Sample size

The study is designed to enroll 97 patients into each of the treatment arms. Specific aims 1 and 2 will be considered separately and no reduction in type 1 error will be applied for multiple testing. The anticipated remission rate in the group receiving the MSD is unlikely to exceed 40% given the historical remission rates in placebo arms of Crohn's disease trials[1] and assuming only a modest therapeutic benefit of this less restrictive of the two diets. Sample size calculations assume no loss to follow-up since all participants who are lost to follow-up will be categorized as non-responders in the analyses of both dichotomous primary outcomes (symptomatic remission and reduction in mucosal inflammation). Our PPRN Patient Governance Council met and determined that the minimum clinically important difference in remission rates is 20% as smaller differences are unlikely to justify the challenges of following a strict restriction diet such as the SCD. Thus, we used an anticipated remission rate of 40% with the MSD and 60% with the SCD to determine the sample size. With 97 participants per group, the study will have 80% power with a type 1 error of 5% to detect a difference of 40% vs 60% in effectiveness of the two diets using a chi2 test.

In reality, we anticipate that the remission rate in the MSD will be less than 40%. The power curve shown below depicts the power to detect a 20% difference based on the remission rate in the MSD arm of the trial where p1 represents the remission rate in the SCD arm (i.e., p1=0.3 represents power to detect a difference of 10% vs 30% across a sample size ranging from 60 to 120). With 97 participants per group, there is more than 90% power to detect a difference of 10% vs 30% and 80% power to detect a difference of 40% vs 60%.

Finally, all of the power estimates are likely slight under estimates. We expect even more power when the Cochran-Mantel-Haenszel (CMH) chi2 test is used since we expect that the odds ratios in different strata are in the same direction.



Viewed alternatively, with 97 participants per arm, there is 80% and 90% power to detect the following differences based on the effectiveness of the control diet (i.e. the MSD).

Proportion of MSD group achieving the outcome	80% power to detect an absolute difference (SCD - MSD) greater than or equal to	90% power to detect an absolute difference (SCD - MSD) greater than or equal to
10%	15%	18%
20%	18%	21%
30%	20%	22%
40%	20%	23%

Assumes 97 participants per group, type 1 error rate of 5%, and chi2 test

All power calculations were computed using PS Power and Sample Size Calculations Version 3.0, January 2009 (Copyright © 1997-2009 by William D. Dupont and Walton D. Plummer).

5.3. Analyses for recruitment, retention and data quality

Monthly recruitment statistics will be generated for the study as a whole and by clinical site. Run charts will plot cumulative recruitment and anticipated recruitment rates required to fully enroll the clinical trial according to the study timeline. Tabular data will be provided for the number of screen failures and the number of participants withdrawing from the study before week six and without reaching a study endpoint (i.e. lost to follow-up).

Tabular in distribution data will be generated to monitor data completeness and quality. Tables will describe the number of participants for whom eCRF data are incomplete, overall and stratified by study site. Baseline characteristics data and components of the sCDAI will be generated to identify outliers that may represent data entry errors. These data points will be confirmed or corrected by queries to the clinical site coordinators. Variables for which distributions will be generated will include: age, height, weight, body mass index, duration of Crohn's disease, and time since onset of the most recent flare of Crohn's disease. Additional data will be evaluated for illogical values or protocol violations including: baseline sCDAI score, current dose of prednisone, serum albumin, and body mass index.

5.4. Analysis of Baseline Data

The initial analyses will utilize descriptive statistics to define the characteristics of the study cohort. Continuous variables will be described as medians and interquartile ranges. Categorical variables will be defined as proportions. Formal statistical comparisons of these descriptive variables will be performed comparing the two arms of the study using the Wilcoxon rank sum test for continuous variables and the chi squared or Fisher's exact test for categorical variables [2]. Because any unbalance in the two groups is by definition a chance occurrence, these analyses will be used to highlight areas of substantial unbalance between the study arms.

5.5. Efficacy Analysis

Analysis of the primary outcome: The primary outcomes will be measured at 6 weeks after the start of the study diets. The primary analyses for the RCT will use 2-sided tests of statistical significance and will be performed using the intention-to-treat principle.[3] Thus, patients will be classified according to the study arm that they were assigned, regardless of the amount of food from the assigned diet consumed.

5.5.1. Outcome definitions

Clinical remission will be defined use the sCDAI which provides a composite measure of relevant patient reported outcomes (PROs). Symptomatic remission will be defined as a sCDAI <150[4] in the absence of the need for increasing corticosteroid dose or initiation of new therapies for CD during the study period. Participants who withdraw from the study prior to week 6 will be categorized as failing to achieve symptomatic remission and other related outcomes.

5.5.1.1. sCDAI

The sCDAI was derived from the Crohn's Disease Activity Index[5] , the standard disease activity index for CD clinical trials in adults for the last several decades[6]. The original index includes the number of liquid stools per day, abdominal pain, general wellbeing, extraintestinal complications of CD, use of Lomotil or opiates for diarrhea, anemia, weight loss, and the presence of an abdominal mass on physical exam. The CDAI has increasingly fallen out of favor as it combines PROs with physical exam, medication use, and laboratory data[7]. As such, investigators validated the sCDAI which patients can complete using a simple web-based survey tool without an office visit or blood draw[4,8]. The sCDAI uses the same scale as the full CDAI, such that scores <150 define remission, 150-219 mild activity, 220-450 moderate activity, >450 severe activity. The correlation between the full CDAI and sCDAI for baseline scores and score change was 0.90 and 0.96, respectively[4]. Our research team has subsequently demonstrated that the sCDAI can be accurately measured with less than 7 days of data, thereby reducing participant burden and allowing for use of data with missing values for selected days[8].

Computation is straightforward:

$$sCDAI = 44 + \left(2 * \sum_{n=1}^{7} L\right) + \left(5 * \sum_{n=1}^{7} A\right) + \left(7 * \sum_{n=1}^{7} W\right)$$

where *L* is the number of liquid stools, *A* is the rating of abdominal pain (0-3, none to severe), *W* is the rating of general wellbeing (0-4, generally well to terrible), and *n* is the day of follow-up.
Similarly, when computing the sCDAI scores for fewer than 7 days, the individual component scores from the available days can be weighted to take on the value as if there were 7 days of data and the available data are considered to be reflective of the missing data. The computation is to multiply the sum of the individual components by 7 and divided by the number of total days of data used (*d*) to adjust for the missing days:

$$sCDAI = 44 + \frac{7}{d} * \left(\left(2 * \sum_{n=1}^{d} L\right) + \left(5 * \sum_{n=1}^{d} A\right) + \left(7 * \sum_{n=1}^{d} W\right)\right)$$

5.5.1.2. Secondary Endpoints

5.5.1.3. Reduction in fecal calprotectin

We will compare the proportion of patients who achieve reduction in FCP to less than 250mcg/g and by greater than 50% from baseline. Fecal concentration of calprotectin, a calcium binding protein found in neutrophilic granulocytes, will be measured by LabCorp Diagnostics. FCP concentration is correlated with endoscopic findings of mucosal inflammation and decreases following initiation of medications in active CD[11,12]. There is no single standard to define mucosal healing with FCP[13-15]; a recent meta-analysis identified 250 µg/g as the optimal cut point for endoscopically defined inflammation among patient with IBD[16,17]. **Participants with a baseline FCP less than than 250mcg/g will be excluded from this analysis.**

5.5.1.3.1. Reduction in systemic inflammation

Reduction in systemic inflammation based on measurement of hsCRP will be defined as having a final hsCRP <5mg/L and >50% reduction from the baseline hsCRP concentration.

5.5.1.3.2. Crohn's Disease Activity Index (CDAI)

As a secondary clinical outcome, we will measure the CDAI at baseline, 6 weeks and 12 weeks. Computation of the CDAI is the sum of the following components over the course of 7 days and multiplied by the weighting factor:

Variable	Weighting factor
Number of liquid or soft stools each day for seven days	x 2
Abdominal pain (graded from 0-3 on severity) each day for seven days	x 5
General well being, subjectively assessed from 0 (well) to 4 (terrible) each day for seven days	x 7
Presence of complications*	x 20
Taking Lomotil or opiates for diarrhea	x 30
Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite)	x 10
Hematocrit below normal of 0.47 in men and 0.42 in women	x 6
Percentage deviation from standard weight^	x 1

*One point each is added for each set of complications:

- the presence of joint pains (arthralgia) or frank arthritis
- inflammation of the iris or uveitis
- presence of erythema nodosum, pyoderma gangrenosum, or aphthous ulcers
- anal fissures, fistulae or abscesses
- other fistulae
- fever during the previous week.

^ Standard weight is derived from the patients sex and height

CDAI remission will be defined as a CDAI<150 in the absence of the need for increasing corticosteroid dose or initiation of new therapies for CD during the study period

5.5.1.3.3. PRO2 and PRO3

The same data elements included in the sCDAI have been combined into two item (stool frequency and abdominal pain) and three item patient reported outcome measures using the original weights derived from the full CDAI. PRO2 includes only stool frequency and abdominal pain while PRO3 includes stool frequency, abdominal pain and general well-being. These outcome measures are calculated as the sum of the mean of the daily value for each domain.
PRO2 = mean daily soft or loose stool frequency + mean abdominal pain score
PRO3 = mean daily soft or loose stool frequency + mean abdominal pain score + mean general wellbeing score
In one validation study of the PRO2 and PRO3, optimum cut-points for CDAI remission were mean daily stool frequency ≤1.5, abdominal pain ≤1, and general well-being score of ≤1 (areas under the ROC curve 0.79, 0.91 and 0.89, respectively).PRO2 and PRO3 values corresponding to CDAI scores of 150, 220, and 450 points were 8, 14, and 34 and 13, 22, and 53 respectively, and the corresponding values for CDAI changes of 50, 70, and 100 points, were 2, 5, and 8 and 5, 9, and 14, respectively[18]. We will examine the individual components of these PROs to determine the proportion of each group that met the optimum cutpoint for remission that met the PRO2 definition of remission. Finally, we will determine the proportion of each group with a reduction in the PR02 and PRO3 that corresponds to 100 point reduction in the CDAI.

5.5.1.4. Combined PRO and FCP outcome

As a secondary outcome, we will assess the proportion of patients achieving combined clinical remission based on the sCDAI and reduction in FCP using the same criteria described above.

5.5.1.5. PROMIS measures

The Patient Reported Outcome Measurement System (PROMIS) questionnaire contains several measures previously show to correlate with disease activity and to have construct validity in CD. These include measures of fatigue, pain interference, and sleep[19]. PROMIS items are calibrated using a T score such that 50 is the mean for the general US population with a standard deviation of 10. Higher scores reflect greater level of the domain.

5.5.1.6. Physical function and joint pain

Physical function and joint pain will be assessed with a subset of core variables found in the Multi-dimensional Health Assessment Questionnaire (MD-HAQ)[20,21]. We will screen for inflammatory back pain using the criteria developed by Sieper et al.[22] and assess symptom severity with the Bath AS Functional Index in those who screen positive[23].

5.5.2.Statistical analysis for primary and secondary outcome measures

The primary analysis will compare the proportion of patients who achieve a symptomatic remission (aim 1) and reduction of inflammation (aim 2) at week 6 using the Cochran-Mantel-Haenszel (CMH) chisq test, which is equivalent to the score test derived from the conditional logistic regression with treatment

strata as the conditioning factor.2 All patients who are withdrawn or lost to follow-up prior to week 6 will be considered treatment failures. The MSD will be considered the reference group for all analyses. Although randomization should minimize unbalance between the groups, it is still possible that unbalance may occur. As such, we will use stratified analyses and conditional logistic regression analysis to adjust for potential unbalance between the two groups as observed in the descriptive analyses.[24] Age, sex, smoking status, duration of CD, presence of disease involving the colon and/or rectum, use of corticosteroids during the trial, current use of biologic therapy, and current use of immunomodulator therapy will be examined individually for potential confounding of the main outcome using logistic regression analysis. All variables that affect the crude estimate of the relative risk of effectiveness by 10% or greater will be included in the final model[25].

Stratified analyses will be used to assess for treatment effect heterogeneity based on the following variables: duration of CD (as EEN appears to work better in newly diagnosed patients), presence of colonic and/or rectal disease (EEN has been hypothesized to work better in patients with only small bowel disease), and use of corticosteroids during the trial (these patients may have more severe disease). We will use the logistic regression models to look for evidence of treatment-covariate interactions. Although pre-specified, we have not powered the study for these subgroup analyses and as such they will be considered hypothesis generating. Therefore, we will report the overall results as well as results for each subgroup. We note that the strongest a priori hypothesis for treatment effect heterogeneity is with the presence or absence of inflammation. We hypothesize that the SCD may appear relatively more effective among those patients without active inflammation than among those with confirmed active inflammation at baseline.

Analysis of secondary outcomes (Secondary Aim 1): hsCRP data will be analyzed in the same manner as FCP data.

Analysis of secondary outcomes (Secondary Aim 2): The secondary outcomes of clinical remission as assessed by the CDAI, PRO2, PRO3 and combined clinical remission and resolution of inflammation will be analyzed using the same methods described for the primary outcomes. We will compare PROMIS scores at baseline and at the end of the trial using a t-test. If there are meaningful differences in baseline scores between the treatment arms, comparison of the PROMIS measures at the end of follow-up will be adjusted for the baseline value using linear regression.

Analysis of data from the Extension Phase (Secondary Aim 2): After week 6, participants will need to provide for the meals on their own if they choose to remain on the diet. This provides an opportunity to further assess the combined feasibility of the diets in the real world and patients' satisfaction with following the diet. Utilizing results from 24-hour dietary recalls, we will determine the proportion of patients assigned to each arm who elect to remain on the diet through week 12. We will also determine the proportion of patients who were able to discontinue steroid use by week 12 among the subgroup who were taking steroids in weeks 1-6. Finally, we will assess reasons for discontinuation of the diet among those who did not continue. Comparisons will be made using Fisher's exact test following the principle of intention to treat. The analysis will be repeated among the subgroup of participants who achieved remission by week 6. These results will be qualitatively compared to the free text data on satisfaction and personal experience with the diets.

Change from baseline stratified by treatment arm: For continuous outcome measures, such as sCDAI, PRO2, PRO3, and FCP, we will compare the week 6 and week 12 values to the baseline value using the Wilcoxon sign rank test, a nonparametric paired test. These analyses will be conducted separately for each treatment group. Imputation of missing data for this analysis will assume that the worst case scenario that the outcome measure was worse during follow-up than at baseline. (Note that approach to missing data for other analyses are described below).

Approach to missing data: It is possible that missing follow-up data will be more common among participants who did not have reduced symptoms, particularly those whose symptoms worsened. There are several approaches to missing data in clinical trials. Complete case analysis violates the principle of intention to treat and as such will not be employed. For continuous measures, last observation carried forward (LOCF) is the most commonly used, but it is not necessarily the most conservative[26]. Baseline observation carried forward (BOCF) may be more appropriate, particularly in circumstances where the outcome would be expected to return to the baseline level if the treatment is discontinued[26]. The European Medicines Agency recommends picking the most conservative approach depending on the individual trial, favoring a responder analysis (i.e. converting continuous variables to dichotomous variables) and categorizing all dropouts as treatment failures[26]. We will use this approach in analyses for aims 1 and 2. For the continuous variables in the secondary outcomes, we will use BOCF as the most conservative

approach. Sensitivity analyses will compare results of our BOCF analysis with that obtained using LOCF or multiple imputation methods. All results will be interpreted and reported after taking into account the results of the sensitivity analyses, applying the principle put forth by the EMA to not favor the "experimental" arm, which in this RCT would be the SCD.

5.5.3. Analysis of PROMIS and arthritis measures

PROMIS measures will be compared at baseline, week 6 and week 8 using a t-test or with adjusted linear regression if there is evidence of confounding despite randomization. Additional analyses will compare change in PROMIS measures from baseline to week 6 and week 12 between groups. The RADAI arthritis screen, RAPID3, and BAS-FI will be treated as a continuous measures and compared between groups similar to the approach for PROMIS.

5.5.4. Safety analysis

All adverse events will be graded according to the NCI's Common Toxicity Criteria. A serious adverse event (SAE) will be defined as any of the following outcomes: death, life threatening adverse event, inpatient hospitalization or prolongation of stay, persistent or significant disability, congenital anomaly or birth defect, or other medically significant event as deemed such by the investigator.
The proportion of patients in each treatment arm who experience the following safety outcomes will be compared using the Fisher's exact test.[2]

Any adverse event
Any serious adverse event
Any adverse event occurring in at least 5% of either arm of the trial

5.6. Ancillary biomarker discovery studies:

Stool samples will be banked as part of this study for future research aimed at identifying biomarkers that can predict which patients will respond to dietary interventions and to help understand the mechanisms by which diet influences the course of Crohn's disease. The University of Pennsylvania Intestinal Microbiome Project Group is well positioned to analyze fecal samples from this study in search of new biomarkers. This group consists of a dozen PIs with expertise in microbiology, high throughput DNA sequencing, bioinformatics, computational biology, metabolomics, animal modeling, and human subject research. Together, we have published 20 primary manuscripts over the past four years in journals such as *Science*, *Nature Medicine*, *PNAS*, *Cell Host & Microbe*, and *Immunity*. These publications focus not only on the bacterial microbiota but also on fungi, Archaea, and viruses as well as the metabolome. Importantly, we also have expertise in the development of computational tools needed for the analysis of complex multidimensional datasets such as those needed for biomarker discovery research [27-32]. Note that requested funds are solely to bank the stool samples. Separate funding is being sought for the analysis of these samples.
Our approach to the analysis of the samples will depend both on the results of the clinical trial and, given the rapid developments in this field, the state of the art in translational science at the time the samples are analyzed. The following is a provisional plan to address these questions. First, we will characterize the gut microbiome by DNA sequencing of fecal samples. Samples will be analyzed by metagenomic sequencing. For DNA isolation, the MoBio Power Soil Kit will be used, implemented in 96-well format. Isolated DNA will be quantified using the Picogreen system. Primers will be barcoded to label each sample as described previously[33]. PCR reactions will be carried out in triplicate using Accuprime polymerase (Invitrogen, Carlsbad, CA, USA). Each reaction will contain 50 nanograms of DNA and 10 pM of each primer. To characterize bacterial populations, we will use 16S rRNA gene tags, as described in our previous work[27-31,34-47]. Primers annealing to the V1V2 region of the 16S bacterial gene will be used, as described previously[48]. Amplified 16S rDNA will be purified using a 1:1 volume of Agencourt AmPure XP beads (Beckman-Colter, Brea, CA, USA). The purified products from the stool samples will be pooled in equal amounts and analyzed by DNA sequencing using the Bushman Lab Illumina MiSeq. Negative controls (mock purification of DNA-free water) and positive controls (standard fecal and synthetic community samples) will be included in each run. Most liquid handling steps will be carried out using EpMotion (Eppendorf) automation. Sequence data will be processed using QIIME[49], augmented by the in-house R

package QIIMER. Taxonomy will be assigned to the sequences using Ribosomal Database Project (RDP) for 16S[50], augmented by BLAST. The 16S tag sequences will be collected into operational taxonomic units (OTUs) with 97% sequence identity and samples summarized as vectors of proportions.

Fungal communities will be characterized by ITS gene tag sequencing as described in our published work[35,37,39,40,43]. Extensive characterization of positive control specimens will document the organisms queried with this approach[40]. Taxonomy will be assigned using the in house software program BROCC [40], which mitigates extreme problems with fungal databases and underlying taxonomy by implementing a voting-based analytical strategy taking advantage of multiple top-scoring alignments.

We will conduct targeted fecal metabolomics of bile acids and their conjugates/metabolites, short chain fatty acids (SCFAs), and amino acids.

Fecal Bile acids: Weighed stool and small intestinal fluid samples will be suspended in 15 l/mg methanol. Following vortex for 1 minute (for 96-well plates we will use adapter SI-0510 two-tier microplate foam insert), samples will be centrifuged at 13,000g for 5 minutes. Supernatant will be transferred to new tube/plate. Plates will be covered and stored at -20^{o}C until high performance liquid chromatography (HPLC) is performed. Each plate will be on HPLC with the following settings: Acquity UPLC I-Class/Fixed Loop with QDa mass detection, ESI Negative mode**,** Scan and Single Ion Monitoring modes**.** UPLC will be performed using a Cortecs UPLC C-18+ 1.6 m 2.1 x 50 mm column.

Fecal short chain fatty acids (SCFAs): Weighed fecal samples will be suspended in phosphate buffered saline (PBS), vortexed, and centrifuged to remove particulate matter. The supernatant will be vacuum filtered in a 96-well plate and transferred to an autosampler for injection into a HPLC for a run under the following conditions: Mobile phase: 0.01 N H_2SO_4, Flow rate: 0.6 mL/minute, Initial column temperature: 50^{o}C, Run time: 30-50 minutes (depending on complexity of the samples), System pressure: 900-1000 psi, Injection volume: 10 uL, Standards range: 0.1-20 mM.

Fecal Amino Acids: Fecal amino acids will be quantified using the Amino Acid AccQTag Analysis Kit (Waters Corporation, Milford, MA). Briefly, fecal samples will be homogenized in PBS (10 uL/mg) and centrifuged at 13,000g for 5 minutes. Supernatant will be derivatized with AccQTag reagents, and stored at -80C until analysis. Samples will be analyzed on a Waters uPLC with an AccqTag Amino Acid Column using eluents and standards provided in the Amino Acid Analysis Kit. Concentration of samples will be calculated against dilutions of the Amino Acid Hydrolysate Standard (Waters Corporation).

Our analytic approach will be tailored to the specific research question. The following is a general overview of our approach to identifying biomarkers that predict patients who will respond to the dietary intervention. We anticipate implementing analyses using a traditional case-control design nested within the cohort of patients receiving the specific carbohydrate diet (SCD) where case subjects are those who responded to therapy and controls are the remaining subjects. As we have done in our prior work[27,32,51], the microbiome composition will then be compared among cases and controls using principle coordinate and random forest analyses and by relative abundance of unique taxa after accounting for multiple comparisons using false discovery rate methodology. Prediction models will be developed using logistic regression. Internal validation methods such as bootstrapping techniques will be used to assess for overfitting[52]. Similar approaches will be used to analyze fecal metabolites. Subsequently predictors identified from different analytic methods can be combined and the incremental predictive accuracy from adding biomarkers can be assessed using methods such as net reclassification improvement[52].

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