PROTOCOL TITLE:
**A single-center open-label study to determine the effect of diet on microbiome signatures in Crohn's disease patients**

**NCT NCT04065048**

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**Indicate the origin of this protocol** (who conceived of and leads the development of the protocol regardless of funding):

☒ Investigator initiated *(Investigator(s) developed protocol, regardless of funding)*

☐ Industry *(Pharmaceutical, Device, etc.) (Industry developed protocol)*

☐ Federal *(NIH, DOD, etc.)*

☐ Cooperative Group *(SWOG, GOG, etc.)*

☐ Other -

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## Objectives

**Brief Summary:**

This protocol is designed to compare the effectiveness of a dietary intervention for 7 days, given to patients with Crohn's disease (CD) in remission: a soy-based diet, which has been demonstrated to have numerous health benefits. The protocol will also compare the effectiveness of the soy-based dietary intervention vs. an identical diet without soy for 7 days, given to subjects with Crohn's disease (CD) and to controls subjects without a diagnosis of Crohn's disease. The diet will be compared to participant 'baseline' (pre-diet) in terms of its ability to change the composition of gut bacteria.

**Primary outcome measure**

1. Maintaining the quiescent disease status or prevent worsening of disease activity of the patient with Crohn's disease (CD) after consuming the study diet.
   - Symptomatic remission assessed daily, using the short Crohn's Disease Activity Index[1] (sCDAI), in combination with the Crohn's Disease Activity Index[2] (CDAI) and the Harvey Bradshaw Index[3] (HBI). Fecal MPO will also be assessed.

**Secondary outcome measure**

1. Gut bacteria composition
   - Gut bacteria composition measured by 16S rRNA gene amplicon sequencing,
2. Gut bacteria metabolites

# Background

## Introduction

This study will be conducted in full accordance with all applicable University Hospital Cleveland Medical Center (UHCMC) Policies and Procedures and all applicable Federal and state laws and regulations. This protocol is designed to determine the effect of a short-term diet intervention on gut bacteria composition and dietary-induced changes to the metabolites the diet produces.

## Background and Relevant Literature

Crohn's disease (CD), a subtype of inflammatory bowel disease (IBD), affects more than 600,000 individuals in the US and several million worldwide. The majority of patients with CD will require at least one bowel resection over their disease course, with many patients requiring multiple resections.[4, 5] The most feared complication of repeated bowel resections is short gut syndrome, a condition with results in chronic diarrhea, nutrient malabsorption, malnutrition and often requires long term artificial nutrition. Other complications of CD include mouth 'extraintestinal' manifistations (complications outside of the intestines), affecting the eyes (e.g. uveitis and episcleritis), joints (arthritis and arthralgia), skin (erythema nodosum, pyoderma gangrenosum), or other organs (e.g., kidney stones, blood clots).

Despite substantial progress in our mechanistic understanding of chronic intestinal inflammation, including the integral role of gut bacteria in disease pathogenesis, the precise cause of the disease is still unknown, and available treatment modalities are not curative with the majority resulting in significant side effects. Numerous medications are used in the treatment of CD, nearly all of which suppress the immune system (reviewed in [6, 7]). 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, available medical therapies are effective in only a fraction of CD patients and, even with this approach remission rates are <60%[8] and substantially wane over time.[9, 10] In addition, chronic immunosuppression as a result of the medication is associated with numerous adverse effects including uncommon but potentially fatal adverse reactions, particularly lymphoma and serious infections.[11, 12, 13, 14]. Patients with CD, even those in remission or with residual active disease, have high rates of disability,[15, 16] reduced quality of life, [17, 18, 19, 20] and reduced life expectancy relative to the general population.[20] Concerns about these uncommon but life threatening adverse effects strongly influence patients' choice of medical therapies.[21, 22] Therefore, effective control of CD is a realistic goal, and an ideal therapy is one that can alter the natural history of the disease in preventing complications while featuring a safe side effect profile and acceptable methods of delivery.

Diet is considered the main driving force in shaping gut microbiota composition *and, in turn, the metabolites they produce.* Today, gut microbiota modulation by dietary intervention is a well-advocated strategy in the therapeutic management of Crohn's disease (CD). However, *no specific recommendations exist for CD patients*, and little is known regarding the microbiota-mediated effects of diet on host immune systems, particularly for patients with evidence of residual active CD or in context to intra-individual variability in microbial profiles.[23]

**Name and Description of the Investigational Diet**
**Soy-based diet**

Recent studies have uncovered that soy protein alleviates symptoms associated with IBD, such as loss of gut barrier function and colon inflammation in animal models of IBD.[24] Specifically, soy protein concentrate was found to have antioxidant and cytoprotective effects in cultured human bowel cells. Furthermore, in mice induced with IBD administered a diet substituted with 12% soy protein concentrate had reduced weight loss and attenuated inflammation. Many questions about the underlying mechanisms behind the anti-inflammatory effect remain, however soya-oligosaccharides have been proposed to increase bacterial diversity as well as selectively enrich Bifidobacterium species, a known producer of butyrate in the gut.[25, 26] However, evidence level is not enough to appreciate the potential efficacy of a plant-based diet in IBD.

## Inclusion and Exclusion Criteria

### Diet Intervention:

| | **Inclusion Criteria** |
|---|---|
| 1. | Age range: from 18 to 65 years |
| 2. | Male or female |
| 3. | Control subjects: no documented diagnosis of CD. |
| 4. | CD subjects: Documented diagnosis of Crohn's disease with a Harvey Bradshaw Index (HBI) score <4 ('CD remission'), or with HBI score >8 ('CD moderate disease') |
| 5. | Capable of providing consent to participate |
| 6 | Access to technology that permits the daily completion of study related activities |
| 7 | Able to receive and have an adult sign for food shipments delivered to a work or home environment. |
| 8 | Negative pregnancy test at screening visit in females of childbearing potential |
| 9 | Able to take oral nutrition and medication intake for 3 months prior to and at time of study enrolment. |
| 10. | 'CD remission' subjects: No change in 'IBD related' medications within 8 weeks prior to normally scheduled appointment with treating gastroenterologist (pre-screening): biologics, immunosuppressants, corticosteroids. |

| | **Exclusion Criteria** |
|---|---|
| 1. | Short bowel syndrome. |
| 2. | Hospitalized patients |
| 3. | Body mass Index <19 kg/m or ≥35. |
| 4. | Known clinically significant liver/gallbladder/pancreatic disease/dysfunction |
| 5 | Individuals who lack consent capacity, including the mentally ill, prisoners, cognitively impaired participants, dementia patients. |
| 6 | Uncontrolled Diabetes Type I type II |
| 7 | Known drug abuse. |
| 8 | Known parasitic disease of the digestive system. |
| 9 | symptomatic intestinal stricture. |
| 10 | Presence of an ostomy. |
| 11 | Known concurrent malignancy. |

| | |
|---|---|
| 12 | Other conditions that would be a contraindication to and of the study diets (e.g. Soy, peanut, wheat, gluten allergy.) or preclude the participant from completing the study |
| 13 | Start of new 'IBD related' medications within 8 weeks prior to enrollment: biologics, immunosuppressants, corticosteroids. |
| 14 | Documented C difficile colitis within four weeks of screening |
| 15 | Well-founded doubt about the patient's cooperation. |
| 18 | Existing pregnancy or lactation. |
| 19 | Current participation in another diet intervention, simultaneous participation in another clinical trial, or participation in any other dietary intervention trial within the last 30 days. |
| 20 | History of <3 natural bowel movements per week. |
| 21 | Unable to access to technology that permits the daily completion of study related activities. |
| 22 | Currently consuming a soy-based diet |
| 23 | |

## Number of Research Participants

For the diet intervention, we will enroll 30 subjects per group from the UHCMC Digestive Health Institute. The enrollment total could increase to a maximum of 40 per arm, if subjects agree to enroll in the study for a second time to complete the other diet intervention.

## Vulnerable Populations

- Indicate specifically if you will include each of the following special populations by checking the appropriate box:

☐ **Adults unable to consent**
☐ **Minors (infants, children, teenagers)**
  ☐ Wards of the state
  ☐ Foster Children
☐ **Pregnant Women**
☐ **Neonates**
☐ **Neonates of Uncertain Viability**
☒ **Employees of CWRU or UHHS**
☐ **Prisoners**
☐ **Illiterate Individuals**
☐ **Non-English Speaking**
☒ **University Students**
☐ **None**

- If excluding pregnant women, illiterate or non-English speaking individuals, provide a scientific rationale for the exclusion. Inconvenience or cost is not an acceptable rationale.

The study protocol involves a 12-hour fasting period that precedes the soy based dietary intervention. Because of this, both pregnant woman and individuals with diabetes will be excluded. In addition, because the dietary intervention will involve specific written instructions

to participants regarding the diet and respective 12-hr fasting period, and because participants will be required to complete daily online surveys, illiterate individuals will be excluded.

- If the research involves individuals that are included in a vulnerable population, describe the additional safeguards included to protect the rights and welfare of the individuals for each population indicated.

Students, Employees of CWRU or UHHS will be included because our study intends to include individuals from heterogeneous demographics who attend the Digestive Health Institute at UHHS. In this study, the safeguards described in this protocol to protect the rights and welfare of all potential study participants are adequate to protect the rights and welfare of the special requested populations.

## Recruitment Methods

3. Which of the following methods will be used to recruit research participants.
   - ☒ Email
   - ☒ Phone call
   - ☒ Letter
   - ☒ Advertisement (e.g., poster, flyer, etc.)
   - ☐ Social media
   - ☐ Other. *Please specify:* I will complete the UH Letter Recruitment Form. In addition, I intend to use the CRC referral lists from Redcap, ResearchMatch, and TriNetX.

4. Describe when, where, and how potential research participants will be recruited.

   We will send a recruitment letter (UH Letter Recruitment Form) via mail to potential research participants. The source of addresses of potential subjects will be patients under the care of Dr. Jeffry Katz and Dr. Vu Nguyen at the DHI Ahuja and DHI University Hospitals Cleveland Medical Center (UHCMC). Control subjects (individuals without CD diagnosis) will be recruited in the same manner, as well as via a flyer advertisement posted within the DHI outpatient waiting area, the Biomedical Reseach Building (bulletin board located on each floor of the elevator area) CWRU, as well as the 6th floor of Bolwell by the back elevators area. In addition, we will use the CRC referral lists from Redcap, ResearchMatch, and TriNetX. A prescreening survey in RedCap will be used to assist potential healthy control participant identification via ResearchMatch. We will also advertise the study using the IRB-approved flyer in the Department of Nutrition, CWRU, newsletter. Potential healthy control subjects will also be recruited from the following 1) Researchers affiliated with NIH National Institute Diabetes and Digestive and Kidney Diseases (NIDDK) Digestive Diseases Research Core Centers (DDRCC) Facilities, 2) Researchers registered with the Taconics Biosciencs, 'Gnotobiotics' and American Association for Laboratory Science (AALAS).

   We will send to a maximum of 1000 people to hit our target enrollment of 60 for the diet intervention study. We will stagger the sending of recruitment letters each month, so that only 60 go out at a time. Recruitment letters and introductory survey emails will be sent to all patients with scheduled appointments within the next 60-90 days. Monitoring of opt out requests will be performed daily by the study coordinator or alternatively the study site investigator when necessary.

   Diet intervention recruitment letters: Participants who do not opt out will be contacted within 14 days by the study coordinator via telephone (Telephone script). The study coordinator will attempt to contact the potential research participant a total of 4 times. A voicemail will be left

if there is no answer after the first attempt to contact the potential research participant. The study coordinator will leave one additional follow-up voicemail.

The treating gastroenterologist will determine eligibility during the normally scheduled appointment of the patient or at study visit 1. For the former scenario, the treating gastroenterologist will ask suitable patients whether they are interested in participating in the described dietary intervention study during the patient appointment. The gastroenterologist will obtain consent, but not participant's signature. Subjects will be given the opportunity to ask questions and will be provided a copy of the Study Consent Document by the treating gastroenterologist. Subjects will then be contacted by the study coordinator over the phone or in person after the clinic visit to schedule a screening visit (visit 1), and if study eligibility is confirmed, and informed consent provided, enrolled into the study.

No data collection or other study procedures will take place until the potential participant provides written informed consent to participate in the research study. Phone contact will be used for determining interest in the study (after recruitment letter sent) and scheduling of study visit 1 (eligible participants identified by treating gastroenterologist) by the study coordinator.

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

The study visit will be scheduled based on patient preference. Identical study procedures will be followed irrespective of the site chosen by the participant. The participant will have the opportunity to schedule study visits at either site throughout the study duration.

Participants who have completed the study will be offered the option to enroll/participate in the study a second time, to receive the other diet not originally assigned. Recruitement will occur via recruitment letter and telephone contact. For the latter, the study coordinator will attempt to contact the potential research participant a total of 4 times (voicemail script attached). A voicemail will be left if there is no answer after the first attempt to contact the potential research participant. The study coordinator will leave one additional follow-up voicemail. Participants may participate for a second time in the study at any point following completion of the study for the first time. Participation will in the study for a second time will require re-consent. Reconsent will occur in person at UHCMC.

5. Describe the source (e.g., from what department, EMR, etc.) of the research participants.

Subjects will be sourced from the gastroenterology outpatient clinic digestive health services of the Digestive Health Institute (DHI) located at University Hospitals Ahuja and DHI UHCMC. Outpatient appointments are held at either site weekly at the DHI. In addition, we will use the CRC referral lists from Redcap, ResearchMatch, and TriNetX. We will also advertise the study using the IRB-approved flyer in the Department of Nutrition, CWRU, newsletter. Potential healthy control subjects will also be recruited from the following 1) Researchers affiliated with NIH National Institute Diabetes and Digestive and Kidney Diseases (NIDDK) Digestive Diseases Research Core Centers (DDRCC) Facilities, 2) Researchers registered with the Taconics Biosciencs, 'Gnotobiotics' and American Association for Laboratory Science (AALAS).

6. Describe the methods that will be used to **identify** potential research participants.

Potential research participants will be identified by appointments lists scheduled within 90 days and patients seen within previous 180 days with treating

gastroenterologist Dr. Jeffry Katz and and Dr. Vu Nguyen at the DHI. Recruitment letters will be sent and followed by phone contact. Subjects will be pre-screened for eligibility during their normally scheduled appointment, or at study visit 1, with their treating gastroenterologist. A request for a waiver of HIPPA for pre-screening has been included in this application. In addition, we will use the CRC referral lists from Redcap, ResearchMatch, and TriNetX. A prescreening survey in RedCap will be used to assist potential participant identification via ResearchMatch. We will also advertise the study using the IRB-approved flyer in the Department of Nutrition, CWRU, newsletter. Potential healthy control subjects will also be recruited from the following 1) Researchers affiliated with NIH National Institute Diabetes and Digestive and Kidney Diseases (NIDDK) Digestive Diseases Research Core Centers (DDRCC) Facilities, 2) Researchers registered with the Taconics Biosciencs, 'Gnotobiotics' and American Association for Laboratory Science (AALAS).

7. Describe the feasibility of recruiting the required number of suitable research participants within the agreed recruitment period. For example, how many potential research participants do you have access to?
   The Digestive Disease Institute at Case Medical University Hospitals has a very large patient volume with more than 49,000 annual patient visits registered, of which include 986 annual CD outpatient visits per year. The majority of CD outpatients are seen at the two flagship sites of the Digestive Health Institute (DHI), Case Medical Center (530 CD outpatients per year) and Ahuja Medical Center (260 CD outpatients per year), both free standing hospitals located in Cleveland Ohio. Participant screening and enrollment will occur only at one site, UH Ahuja Medical Center. The Department of Gastroenterology has 44 full time gastroenterologists, of whom two treating gastroenterologists will be recruiting suitable participants for this study. On average, each doctor sees 40 outpatients per week, approximately 50% of which have CD. An estimated accrual rate of 1 eligible patient per month generates a conservative study accrual period of up to 12 months.

## Setting

**Physical location where identification and recruitment of all subjects, pre-screening, consent process, participant enrollment and all in-person visits will occur in a private patient room at the following sites:**

Digestive Health Institute (DHI)
UH Physician offices
11100 Euclid Avenue
CMC Bolwell 6th floor
Cleveland, Ohio, 44106

Dahms Clinical Research Unit (DCRU)
11100 Euclid Avenue
Lakeside Building, 6th floor
Cleveland, Ohio, 44106

**Physical location where all receipt and processing of stool samples will be conducted:**
Digestive Health Research Institute (DHRI)
Division of Gastroenterology and Liver Diseases
Case Western Reserve University
Biomedical Research Building, 5th floor (Cominelli Laboratory)
2019 Adelbert Road
Cleveland, OH, 44106.

## Consent Process

- **Indicate whether you will be obtaining consent:**

  ☒ Yes ☐ No

  *If yes, answer the following questions:*

  - Describe where the consent process will take place:

The formal consent process will occur in a private patient room in the Digestive Health Institute (DHI) UHCMC, or at the Dahms Clinical Research Unit (DCRU) at UHCMC. Study site visit location will be based on patient preference. Reconsent will occur in person at the same locations.

  - The time that will be devoted to the consent discussion:

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

  - Any waiting period available between informing the prospective subject and obtaining the consent:

Participants will be permitted to provide informed consent at the time of the consent discussion during study visit 1 or they may to come back to provide written informed consent if they choose to do so (would require a second scheduled study visit 1).

  - Steps that will be taken to ensure the research participants' understanding:

Potential participants will be given a copy of the consent form and the investigator/ study coordinator will read the consent form with the participant and answer any questions. In addition, the potential participant will be given ample time to review, or return a different day. The study coordinator will ask the potential participant to repeat or paraphrase understanding of different points of discussion, as well as ask open-ended questions or non-directive questions to ensure understanding.

  - Any process to ensure ongoing consent:

Informed consent will be obtained from each subject at entry into the study. No study activities will occur until Informed Consent occurs. For the 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 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 investigator obtaining consent will also sign and date the consent form and provide a copy to the participant. For potential

participant is identified as eligible by the treating gastroenterologist the potential participant then be contacted by the study coordinator to schedule visit 1. Participants who choose to participate in the study for a second time to receive the other diet not originally assigned, participation will require re-consent.

- The role of the individuals listed in the application as being involved in the consent process:

The treating gastroenterologist will determine eligibility during the normally scheduled appointment of the patient or at visit 1. For the former scenario, the treating gastroenterologist will ask suitable patients whether they are interested in participating in the described dietary intervention study during the patient appointment. Subjects will be given the opportunity to ask questions and will be provided a copy of the Study Consent Document (to serve, in this case, as a Participant Information Document) by the treating gastroenterologist. Subjects will then be contacted by telephone by the study coordinator to schedule a screening visit (visit 1) and if study eligibility is confirmed, and informed consent provided, enrolled into the study.

- Steps that will be taken to minimize the possibility of coercion or undue influence to the subjects:

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.

All participants will 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. All participants will be given time to read over the study information and discuss it with their doctor, family, or friends, if they would like.

Participation is voluntary. Completion of online surveys (RedCap) and participation in other research studies is voluntary and not required for participation in the proposed open label diet intervention study. They can opt out of any questionnaire and can decline any research study. They can also withdraw at any time from the study.

- **Indicate if you will be asking for a waiver or alteration of consent process or documentation (consent will not be obtained, written consent will not be documented)**

  ☒ Yes ☐ No

  **If yes, indicate which part of the consent process you are requesting to be waiver or altered and the rationale for requesting the waiver or alteration.**

  ☒ I will obtain consent, but not participant's signature

  ☒ I will obtain consent, but request a waiver for pre-screening purposes

  ☐ I will obtain consent, but request a waiver of some of the elements of consent (e.g. use of deception)

  ☐ I will not obtain consent and I am requesting a full waiver of consent

1. Give the rationale for the request of a waiver or alteration of the consent process or documentation:

   Clinical appointment schedules are available to all gastroenterologists each week for outpatient clinic visits and include patient name, appointment time and patient diagnosis (e.g., Crohn's disease vs ulcerative colitis). The study coordinator will send recruitment letters and conduct follow up phone calls, as well as introductory emails for the online survey to patients on behalf of their treating gastroenterologist . A waiver of the consent process for the study coordinator to manage sending of recruitment letters, opt out requests and providing follow up phone contact is needed.
   Written informed consent must still be obtained at the in person screening visit. No study procedures will occur until written consent is obtained. E-Consent consent must be obtained for the online survey.

2. Explain how the research involves no more than minimal risk

   The PHI obtained includes patient name, address, email address, scheduled appointment time and diagnosis (e.g., Crohn's disease vs ulcerative colitis). This information is available to the treating gastroenterologist the DHI. Identifiable information will not be used or disclosed by anyone other than the research team.

3. Explain why the waiver or alteration of consent will not adversely affect the rights and welfare of the participants:

   Identification of potential participants via the treating gastroenterologist and use of recruitment letters with follow-up phone call (for those who do not opt out) to determine interest in participation, prior to the patient scheduled appointment is important to give subjects the opportunity to ask questions to the treating gastroenterologist at time of appointment. Written informed consent must still be obtained at the in person screening visit. Prior to obtaining written consent, subjects will be given the opportunity to ask questions and will be provided a copy of the Study Consent Document (to serve, in this case, as a Participant Information Document) by the treating gastroenterologist.

4. Explain why the research could not practicably be carried out without the waiver or alteration of consent.

   Patient appointment schedules are freely available and typically reviewed prior to patient clinic visits by the treating gastroenterologists and because appointment schedules provide information that would allow gastroenterologists to identify potential participants in the case of long-standing patients at the clinic, therefore it is ethically important to obtain a waiver of consent at this juncture. Contact of the participant to discuss the research (after sending recruitment letter) involving dietary intervention involves no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

5. If you will obtain consent, but not document consent in writing (e.g. over the phone, verbally, electronic survey, etc.), please describe and provide a rationale.

   ☐ N/A

Describe how you will be documenting that a research participant has consented:
Following the recruitment letter, contacting the subject by telephone to discuss the research study involving a dietary intervention involves no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Either before or at end of consent form discussion, participant will be provided with a copy of the Study Information Document. All information, including the Subject Authorization for Release of PHI for Research (HIPAA Form) will be reviewed and all questions answered. Once the individual verbally agrees, the consent form will be signed and dated. The HIPAA authorization is in the consent form. A copy of the consent form with HIPAA Authorization for Release of PHI for Research will be provided to the participant. The investigator will also keep a copy of: 1) the signed consent form with HIPAA authorization in the research medical records (stored in locked cabinet, DHI) and will be documented in the study data management system UH RedCap. Documentation of when consent process took place and who consented will be recorded, and that consent form with HIPAA authorization and Study information document were given to participant.

**Additional Considerations for Consent Process with Adults**
Non-English Speakers

☒ I am **not** enrolling non-English speaking individuals in this research study. The following is justification for why non-English speaking individuals cannot be enrolled:
Only English or non-native English speaking patients have been recorded to attend the outpatient services at the DHI.

☐ I will be targeting non-English speaking adults

- Describe the process to ensure that the oral and written information provided to those research participants will be in that language during initial consent as well as throughout the study.

- List the language(s) other than English that will be targeted:

☐ I am **not** targeting non-English speaking individuals. If a non-English speaking individual is eligible for the trial, we will use the following procedures to enroll:

- Describe the process to ensure that the oral and written information provided to those research participants will be in that language during initial consent as well as throughout the study.

- List the language(s) other than English that will be targeted:

Adults Unable to Consent

☒ I am **not** enrolling adults unable to consent in this research study.

☐ There is an anticipated direct benefit to the subject. Explain:

☐ There is NOT an anticipated direct benefit to the subject. Explain:

1. Describe the process to determine whether an individual is capable of consent.

2. List the individuals from whom permission will be obtained in order of priority (e.g. durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child).

3. For research conducted outside of the state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in the research.
   ☐ N/A

4. Describe the process for assent of the research participants. Indicate:

1. Which subjects that are unable to consent will be required to give assent? If not all, explain why.

*2.* Describe whether assent of the research participants will be documented and the process to document assent.

☐ The subject will be informed about the research to the extent compatible with the subject's understanding.
☐ Subjects will be closely monitored.
☐ The subject will be withdrawn if they appear unduly distressed.

**Research Participants Who Are Not Yet Adults (infants, children, teenagers)**

☒ I am not enrolling participants who are not yet adults in this research study.

1. Will parental permission be obtained from:

☐ One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child

☐ Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child

☐ Waiver of parental permission

2. Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals' authority to consent to each child's participation in research.
3. Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent.
4. When assent of children is obtained, describe how it will be documented.
5. For children who are pregnant, describe how assent and permission are obtained.
   ☐ N/A
6. Describe how the risk is justified by the anticipated benefit to the subjects.
7. Describe how the anticipated risk-to-benefit ratio is at least as favorable to the subjects as that presented by currently available alternative approaches.

## Sharing of Results with Research Participants

☒ Results will **not** be shared with research participants

☒ Results will **not** be shared with research participants' doctors

## Study Design

### General Design

**DIET INTERVENTION**

This is an open label, single-center study to compare the ability of a soy- based diet for 7 days to change the composition of gut bacteria (stool samples) in adult Crohn's disease patients and control subjects without a diagnosis of Crohn's disease. Participants will be pre-screened by the treating gastroenterologist for eligibility criteria during their normally scheduled appointment or at visit 1 at the Digestive Health Institute (DHI) UHCMC, or at the Dahms Clinical Research Unit at UHCMC. The treating gastroenterologist will ask suitable patients whether they are interested in participating in the described dietary intervention study during the patient appointment. Control subjects will be recruited in the same manner, as well as via a flyer advertisement posted/available to patients within the DHI outpatient waiting area, the Biomedical Reseach Building CWRU, as well as the 6th floor of Bolwell by the back elevators area. The gastroenterologist will obtain consent, but not participant's signature. Subjects will be given the opportunity to ask questions and will be provided a copy of the Study Consent Document (to serve, in this case, as a Participant Information Document) by the treating gastroenterologist. Subjects will then be contacted by the study coordinator to schedule a screening visit (visit 1) and if study eligibility is confirmed, and informed consent provided, enrolled into the study. Participants will follow either a soy-based diet or identical diet without soy to which they were randomized for 7 days. A block randomization approach[27] using pre-determined group

assignments will be used every 2 healthy controls and every 2 CD subjects, the latterbased on baseline HBI score (2 levels; score between 0-4 'low' vs. 8-16 'moderate') as this covariate has the potential to influence disease activity. Randomization will occur after eligibility is confirmed AND the baseline stool sample is received; the participants assigned diet will be documented in REDCap. The diets will be preceded by a 12-hr overnight fast and will be immediately followed participants returning to their usual eating habits.

Participants will provide at least 2 fresh stool samples, each collected before and after diet intervention. Two blood draws will be taken (visit 1, end of study visit; within 24hrs of completing diet) to calculate the CDAI and to measure C-reactive protein (CRP) to be used as a third biomarker to complement fecal calprotectin and myeloperoxidase activity (MPO) measured in stool samples.. Participants will complete questionnaires each day for the entire duration of the study on well-being (sCDAI;), as well as a diet satisfaction questionnaire (end of each dietary intervention) and a diet history questionnaire. A dietary recall will be conducted in-person at visit 1 and telephonically (at time of stool collection) at baseline. One month after the end of study visit, subjects will be sent a questionnaire asking about dietary choices (i.e. when study foods not provided). Changes to the composition of gut bacteria and differences in butyrate production will be analyzed in batch at the end of the study.

Participants will receive all of study meals and snacks at no cost shipped directly from the food vendor to the participant. Participants will receive one food delivery. To improve feasibility of stool sample collection, a medical courier same day service will be available at no cost to the participants.

Participants who have completed the study will be offered the option to participate in the study for a second time, to receive the other diet not originally assigned. Recruitement letters sent via mail and telephone contact will be used. Participation for a second time may occur at any point following completion of the study for the first time. Participation will require re-consent. All study procedures, as originally described in the protocol, remain unchanged.

# Study Procedures

## 2. STUDY PROCEDURES

### 2.1.2 DIET INTERVENTION:

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. A phone call reminder will be placed by the study coordinator or the study PI to participants at the start of each study phase and/or for upcoming food delivery.

**2.1.2.1 Randomization.** A block randomization approach[27] using pre-determined group assignments will be used every 2 healthy controls, and every 2 CD subjects, the latter based on baseline HBI score (2 levels; score between 0-4 'low' vs. 8-16 'moderate') as this covariate has the potential to influence disease activity. Randomization will occur after eligibility is confirmed AND the baseline stool sample is received; the participants assigned diet will be documented in REDCap. If participants choose to participate in the study for a second time, no randomization will occur as the participant will receive the other diet, originally not assigned.

**Visit 1**

At Visit 1 the Investigator must collect the following:

- Informed Consent (if not done so already)
- Medical History
- Urine Pregnancy
- Diet History Questionnaire; DHQ
- 24-hour dietary recall
- Medications, supplements/vitamins
- Vitals
- Height and weight (calculation of BMI)
- Short Crohn's Disease Activity Index (sCDAI)
- Blood draw for hematocrit (calculate CDAI) and C-reactive protein (CRP)
- Stool Collection
- Provide study instructions and stool collection kits

## 2.2 Participant Assessment Visit 1

### 2.2.1 RedCap Questionnaires

We will use RedCap for all participant data collection including repeat surveys sent via email to participants and for data collection purposed during the in-person visits. The project has been created and tested (see data collection instrument details).

### 2.2.2 24-hour dietary recall

A 24-hr dietary recall will be completed at visit 1 and at time of baselie stool collection. The baseline and post study diet, diet recalls will be performed by telephone contact. Diet recall will involve asking/quantifying the participant what they ate the day before. A registered dietitian from the CTSC Bionutrition will complete this.

### 2.2.3 Diet History Questionnaire (DHQIII):

The participant will complete a DHQ via the web-based system (https://www.dhq3.org) constructed by the Epidemiology and Genomics Research Program, Division of Cancer Control and Population Sciences National Cancer Institute (NCI). The research tool is developed as a computerized tool and the database is intended for researchers to develop study projects that allow assignment of unique alphanumeric username tag to records within a study project developed by a researcher allowing absence of identifying information in data collection. Participants will complete the online DHQ at home immediately following the screening visit 1. 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 investigator will assign the participant their unique userID and passcode where they will be able to login and access the questionnaire.

### 2.2.4 sCDAI

Patient symptoms will be monitored using the sCDAI[1] over the duration of the study. A minimum of 5 and maximum of 7 days of patient reported symptoms will be required to compute the sCDAI during study diet to compare to baseline CDAI and HBI. (Note: symptoms are

assessed/calculated for the previous day). The participant will accomplish this via daily online surveys (RedCap) sent via email to the participant after informed consent is obtained at visit 1. 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.

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

### 2.2.5 Medical History

Self-reported medical history will be obtained during visit 1 in combination with physician notes and medical chart review.

### 2.2.6 Medication History

Self-reported medication history including vitamin and supplement use will be obtained during visit 1 in combination with physician notes and medical chart review.

## 2.3 Sample Collection

### 2.3.1 Fresh stool sample

Fresh stool sample must be provided by the participant within 14 days prior to receiving the study food (Phase II). Alternatively, participants can also provide a stool sample to visit 1. Fecal collection kits will be provided at visit 1; kits provided will be pre-labelled with participant unique study code ID. A medical courier service will be available for home pick up of stool specimens. Stool samples will be received and signed for by the principal investigator at the Division of Gastroenterology Laboratory located in the Biomedical Research Building, 5$^{th}$ Floor. The principal investigator will anaerobically process stool samples into 3 aliquots measure: *i)* to measure fecal calprotectin and fecal myeloperoxidase activity, *ii)* batch analysis for mass spectrometry analysis, and *iii)* batch analysis for 16S rRNA gene sequencing. After receipt of the baseline stool sample study food items (Phase II) and stool collection kits will be shipped to participants.

If a participant is unable to have a bowel movement over the 7 day period of the diet, the study coordinator can approve an extension of the period until a bowel movement occurs (up to 7 days). After a 7 day extension participant will be removed from study.

### 2.3.2 Blood draw:

One to two tubes of blood will be drawn by a DHI research nurse to determine hematocrit (calculate CDAI) and for measurement of C-reactive protein (CRP). CRP levels will serve as a third biomarker to supplement the fecal calprotectin and myeloperoxidase activity measured in stool. An additional blood tube may be drawn. Blood tubes labelled with the participant unique study identifier, and other collection materials will be provided. After blood is drawn, the tube

will be sent to the UH Laboratory services for determination of hematocrit and CRP levels. The additional tube will be spun and plasma extracted. Extracted plasma will be placed in a separate sterile tube, labelled with the participant unique study identifier code and stored in a secure locked -80C freezer in the BRB 5th floor.

**2.3.3 Urine:**
Female participants of childbearing age will be asked to take a urine pregnancy test.

**3. STUDY INTERVENTION**
Participants will follow either a soy-based diet or identical diet without soy to which they were randomized for 7 days. Randomization will occur after eligibility is confirmed AND the baseline stool sample is received. The diet will be preceded by a 12-hr overnight fast and will be immediately followed by participant returning to their usual eating habits.

Participants will receive all of their meals shipped directly from the food vendor to the participant. 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 at visit 1. The 7-day diet will be provided in one delivery. For accurate monitoring of diet adherence participants will be given a food log to record any foods other than those provided for the study. Participants will receive the delivery of study foods after the study coordinator has confirmed receipt of the baseline or relevant post diet stool sample. A phone call reminder will be placed by the study coordinator or the study PI to participants at the start of each study phase and/or for upcoming food delivery.

Participants will receive daily online surveys sent from UH RedCap server via email to complete during the study diet. Dietary adherence will be evaluated by a food log as described above.

Participants must collect a minimum of one stool sample any time between day 5-7 during study diet (see below). A satisfaction survey about the study diet will also be sent via email (UH RedCap) following completion of each diet.

**1.1 Study Intervention Protocol**
A phone call reminder will be placed by the study coordinator or the study PI to participants at the start of each study phase and/or for the upcoming food delivery.

**Phase I: baseline 'pre-diet' study period**

- Participants continue to consume their usual foods.
- Completion of DHQ (if participant did not complete at visit 1)
- Dietary Recall – telephone contact with participant (Dhams Bionutrition)
- complete sCDAI
- Stool collection: participants must collect one stool sample A medical courier service will be available for home pick up of stool specimens. Once stool sample is received participant is eligible to receive study diet.
- Signed delivery of study food items

- Ensure end of study visit is scheduled

**Phase II: Twelve-hour overnight fast (8:00pm-8:00am)**

- A 12-hr fast will precede the assigned study diet. Participants will be instructed to consume their last meal no later than 8:00pm the evening prior to commencement of their study diet. Plain water will be permitted.
- Stool collection (optional): participants may collect one stool sample in the morning at the end of the 12-hr fast (prior to starting the diet, see below). A medical courier service will be available for home pick up of stool specimens

**Phase III-diet: Soy-based diet intervention (7 days):**

The assigned study diet will commence in the morning following the 12-hour overnight fast (see Phase II), and will continue for 7 consecutive days. The diet will be based on the detailed descriptions according to the American Heart Association, US Food and Drug Administration (FDA), and the Soyfoods Association of North America Website, which all promote soy products as having beneficial nutrient profiles with a daily consumption of 25 grams or more of soy protein (average serving = 6.25 grams), upper limit of 50g. Carbohydrates will be restricted to simple carbohydrates. The only carbohydrates that will be included in meals will be monosaccharides: glucose, fructose, and galactose. No grains will be included in the soy-based diet. Saccharin and honey will be included in addition to moderate use of sorbitol and xylitol. Canned fruits and vegetables will be included. Soymilk will be included in the diet without limitation. Animal based food products, eggs, dairy (yogurt, cheeses, milk etc.), fish, unprocessed meats, processed, canned, and smoked meats will not be included or permitted during the diet intervention.

- sCDAI questionnaire
- Stool collection: participants must collect at least one stool sample. Sample collection should occur any time between days 5-7 on study diet. A medical courier service will be available for home pick up of stool specimens End of diet: Online diet satisfaction/adverse events questionnaire

**Phase IV: End of Study Visit and Resume usual eating habits (minimum of 7 days)**

Following the completion of the 7 day plant-based diet the participant will be instructed to resume their usual eating habits.

- Attend end of study visit within 24 hours of diet completion.
- Online diet satisfaction questionnaire
- sCDAI

**End of Study visit**

The end of study visit will take place following no more than 24 hours following the end of the diet intervention, after the participant has resumed a usual diet, or at the visit where the participant withdraws or is withdrawn from the study. One stool sample may be collected. This visit includes a physical exam by their treating gastroenterologist for end of study HBI score (CD

patients only). As a secondary clinical outcome, we will measure the CDAI. The CDAI includes measurement of hematocrit with 5 days of patient symptoms (sCDAI). Blood sample will be drawn by treating gastroenterologist or DHI research nurse to determine hematocrit (calculate CDAI). Participants will be asked to complete a 24-hour dietary recall, and provide information about adverse events, medications, supplement use. Participants will also be weighed.

The following will be conducted at the end of study visit:

- Blood draw
- Stool collection
- Weight
- Instructions to resume usual eating habits
- Adverse Events
- Physical exam by gastroenterologist (CD patients only).

**Blood draw:** One tube of blood will be drawn by a DHI research nurse to determine hematocrit (calculate CDAI). An additional blood tube will be drawn for evaluation of plasma metabolites. Blood tubes labelled with the participant unique study identifier, and other collection materials will be provided. After blood is drawn, the tube will be sent to the Core Laboratory services at CWRU for determination of hematocrit levels. The second tube will be processed in the same manner as in Visit 1.

**End of Study Follow Up Survey (1 and 6 months after end of study visit)**

1. Complete online Diet History Questionnaire (DHQ)
2. Follow up diet questionnaire

### 3.2 Intervention Regime

Participants will be provided with fully prepared meals, including beverages and snacks from CTSC Research Bionutrition (Dhams, Rainbow Babies, University Hospitals) totaling a minimum of 2500 calories. Participants do not have to eat all of the food provided. Participants will receive these meals for both of the diet (soy, plant) interventions. Some of the meals will require heating. Some of the beverages will require the addition of water for reconstitution. Plain water will be allowed ad libidum. Participants will be provided with detailed instructions and recipes for preparing their food. If participants require additional food to that provided (i.e. the 2500 kcal) additional food delivery will be provided at no cost to the participant.

#### 3.2.1 Receipt of Food & Storage

Participants will receive two shipments of food to their home (or another location, if desired) for the diet intervention (i.e. 2 shipments total for study period); one shipment prior to the start of the diet intervention providing 3 days' worth of study meals, and a second shipment on day 3 of the diet intervention, providing the remaining study meals for that diet. Alternatively,

participants will have the option to pick up the food items. These shipments will contain breakfast, lunch, dinner and two snacks and additional food items for each day of the diet intervention. Food items/meals will be delivered fresh or frozen as appropriate with sufficient ice packs to remain unrefrigerated 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. Proper preparation with regard to reheating will also be included on a label on each meal/snack. Each meal or snack will be labeled with the storage requirements for that meal (freeze, refrigerate, keep at room temperature). Additionally, each shipment will contain contact information for customer service representatives from CTSC bionutriton. The representatives can be contacted for any questions about the food, its ingredients, preparation instructions etc.

### 3.2.2 Preparation, Packaging & Delivery

All of the study meals including snacks for this study will be prepared by CTSC bionutriton in a single kitchen. All participants will receive their meals from CTSC bionutriton directly to their homes (or another location, if desired) via tracked courier. Food will arrive in a cooler box / cardboard box with the food inside surrounded by freezer packs. The box will have a label reading "Perishable." CTSC bionutriton will provide a report detailing all of the food deliveries including the date and time they were delivered and to whom; an adult must be present to sign for the delivery. Participants will return the empty food delivery coolbox at the end of study visit.

### 3.2.3 Fasting Instructions

A 12-hr fast will precede the assigned diet intervention.Participants will be instructed to not to eat or drink anything (except plain water) during the 12 hours prior to starting the diet. No juice, tea, coffee, diet soda or other beverage will be allowed. Participants will continue to take prescription medications unless physician informs them otherwise. No exercise will be permitted during the fasting period. For convenience, participants will be instructed to stop eating and drinking after 8:00pm and to start eating the proposed diet no later than 8:00am the following morning.

### 3.2.4 Resume ususal eating habits

Following the completion of the study diet the participant will be instructed to resume their usual eating habits (i.e. prior to study).

## 4. STUDY EVALUATIONS AND MEASUREMENTS

### 4.1 Study Evaluations

### 4.1.1 Medical History

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

- Medical and surgical history
- Crohn's disease history
- Medication use
- Smoking

- Hospitalizations
- Laboratory test results – albumin, C. difficile colitis, vitamin D, B-vitamin panel

### 4.1.2 Demographic Information

Gender, date of birth, race, email address will be collected from each participant. Medication and over-the-counter supplement and vitamin use will be collected at each visit. A suitable address of the participant address (e.g., home or work) will be required for scheduled delivery of study food items.

### 4.1.3 Current Symptoms

Participants' current symptoms, both Crohn's disease-related and otherwise, will be collected by the treating gastroenterologist during the normally scheduled appointment to obtain the HBI for identification of suitable potential participants. Crohn's symptoms will also be collected through daily online surveys.

### 4.1.4 Concomitant Medication

Medication use and over-the-counter supplements, herbal and vitamin use will be collected at each visit.

## 4.2 Study Measurements

### 4.2.1 Vitals

Participants will be weighed on a scale in the Digestive Health Institute clinic or Dahms Clinical Research Unit at each study visit. Participant's height will be measured at Visit 1 using a stadiometer. Participants' seated blood pressure will be measured at Visit 1 and at the end of study visit.

### 4.2.2 Laboratory Evaluations

Fecal Calprotectin (FCP) and fecal myeloperoxidase activity (MPO) – These biomarkers are 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. In addition, fecal MPO can change rapidly in response to inflammation. We will use these biomarkers as a surrogate for long-term disease remission status (in conjunction with the HBI and sCDAI) in patients FCP assays will be completed by the principal investigator (Human stool ELISA kit) at baseline and end of study. C-reactive protein (CRP) to be used as a third biomarker to complement fecal calprotectin and myeloperoxidase activity measured in stool samples.

All samples will be de-identified and tracked using study ID codes not derived from participants' personal identifiers.

### 4.2.3 Plasma Collection

One to two tubes (4 tsp) of blood will be drawn and centrifuged at visit 1 and at end of study visit for plasma separation and collection. The plasma samples will be banked stored long-term for future research use related to this study. Possible use of the plasma samples include testing for serological markers or other relevant metabolites.

### 4.2.4 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. Pregnancy tests will be read by the study coordinator.

### 4.2.5 Stool Sample Collection

Stool samples will be collected on the days described above. Stool sample collection kits, Styrofoam cold boxes and cold packs will be prepared at the Division of Gastroenterology, Biomedical Research Building and provided to participants. Participants will collect their samples at home, using Covidien commode specimen collectors, and place the collected specimen into the sealable bag. To improve feasibility of fecal collection, this study will employ a medical courier service. Participants should collect a stool sample prior to start of study diet and one stool sample any time between day 5-7 on study diet. Additional, optional stool collection may occur on the morning following the 12-hr fast and following the study diet when participants have resumed their usual eating habits.

A simply designed plastic container called Fisherbrand™ Commode Specimen Collection System has been extensively used in Human Microbiome Project and will be used in this study. This collection system includes a plastic frame to fit the container securely under the toilet to avoid contamination by urine and toilet water. Based on similar concept, a DIY stool collection option will be shown to participants in the event that their Commode is not available. In the condition of 4 °C preservation, the allowable same day courier shipment time from participant to laboratory staff handling can be <24hr without significant microbial composition alteration.

### 4.3 Medical Courier Service

A 24hour, 7-week day medical courier service for collection (e.g., home or work) of stool samples will be available to participants via same day telephone scheduling/request. This study will use American Expediting®, a medical courier service that meets all regulatory requirements. Drivers utilize medical transport bags that meet OSHA and US DOT 49CFR 173.6 criteria for shipping diagnostic specimens and biological products by ground courier transport. Drivers also carry biohazard spill kits and are certified (HAZMAT) and biohazard specialists. The service ensures that a HIPAA secure chain-of-custody procedure is followed and that patient confidentiality is protected at all times. In addition, the service will maintain samples specimen temperatures and carries dry ice at all times. The service (courier transport of diagnostic and infectious medical specimens, blood products, on site specimen pack and shipping and routine 24hr pick-up and delivery service) is available 24/7 for 365 days a year. Service delivery time range from: Express (1 hour), Rush (1.5 hours), Regular (2.5 hours), Standard (3.5 hours), STAT Medical (priority delivery time).

All stool kits will be pre-labelled with participant unique study ID code not derived from participants' personal identifiers.

### 4.4 Stool sample preparation and processing

Upon delivery of the stool sample by the courier to the Biomedical Research Building, the investigator will process the sample. All samples will be processed anaerobically, separated into 3 aliquots, to measure: *i)* fecal calprotectin and fecal MPO, *ii)* stored at -80C, then sent in batch to Metabolomics Core, CWRU for evaluation and quantification of metabolites (short chain fatty acids, i.e. butyrate) using LC-MS or GC-MS methodologies, and *iii)* storage at -80C until batch extraction of fecal genomic DNA using QIAmp DNA mini Kit and analysed in batch for 16s rRNA gene sequencing of the V3-V4 region bacterial DNA using Illumina protocols by the Genomics Core, CWRU. The remaining stool will be stored in sterile 15ml conicle tubes as 6g feces + (12mL phosphate buffer solution + (7% dimethyl sulfoxide)). Samples from this study will be stored and banked for future research use related to this study.

All samples will be de-identified and tracked using study ID codes not derived from participants' personal identifiers.

### 4.5 Blood Sample preparation and processing

One to two tubes of blood will be collected at visit 1 and at end of study visit (calculate CDAI). Hematocrit and C-Reactive protein levels will be measured at enrollment and at end of study visit. In all cases, tubes will be centrifuged and plasma will be aliquoted and frozen within one hour of collection in a locked -80°C freezer dedicated to Biorepository samples in the Cominelli laboratory located on the 5$^{th}$ floor of the BRB, CWRU. Samples will be analyzed in batch by core UH facilities.

All samples will be de-identified and tracked using study ID codes not derived from participants' personal identifiers.

### 4.7 Other Evaluations, Measures

#### 4.7.1 Diet Evaluations

24-hour dietary recalls will be used at visit 1 and at time of baseline stool collection. A trained dietitian will administer the dietary recall to determine what participants have eaten on the previous day. In addition, a dietary recall will be performed telephonically at baseline.

Diet History Questionnaire (DHQ) will be completed confidentially, online by the participant either Patients will complete the online questionnaire at home immediately prior to or immediately following visit 1. Alternatively participants may be able to complete the questionnaire at the DHI clinic during visit 1 if a computer with internet access is available. We will use the National Cancer Institute's DHQ III 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 DHQ will be used to determine differences in eating habits between participants. Using a secure UH server, the study coordinatory will download the Excel file containing study participants' questionnaire responses from a secure https website. https://www.dhq3.org

Study diet satisfaction surveys will be administered via a UH RedCap survey following the study diet. 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.

### 4.7.2 Symptoms

We will assess symptomatic remission using the sCDAI survey administered via daily RedCap survey sent via email.

### 4.7.3 Harvey Bradshaw Index (HBI):

The HBI[3] is a valid tool for assessment of disease activity in Crohn's disease. The HBI consists of only of clinical parameters, with the first three items scored for the previous day. The HBI is computed to include; general well-being (0-4), abdominal pain (0-3), number of liquid stools per day, abdominal mass (required physical exam; pre-screening, end of study ), and complications (e.g., arthralgia). Patients who score 4 or less on the HBI are very likely to be in remission according to the Crohn's Disease Activity Index. Patients with a score of 9 or higher are considered to have severe disease. Because the clinical parameters of the HBI inherently overlap with those assessed in all patients during a routine visit to their treating gastroenterologist, the HBI will be used in this study to identify suitable participants (i.e. CD patients in remission vs active disease). An abbreviated format (excludes abdominal mass evaluation) will be used for evaluation (online) of patient symptoms.

### 4.7.4 Crohn's Disease Activity Index (CDAI)

As a secondary clinical outcome, we will measure the CDAI at end of study visit. Computation of the CDAI is the sum of the following components over the course of 7 days (sCDAI) and multiplied by the weighting factor:

| Variable | Weighting factor |
|---|---|
| Number of liquid or soft each day for seven days | x 2 |
| Abdominal (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

### 4.7.5 Combined CDAI, HBI and MPO outcome

As a primary outcome endpoint, we will use sCDAI, CDAI and MPO to assess overall maintenance of symptomatic remission.

**[see study time line on next page]**

## Study Timeline

| | Normally scheduled appointment | Visit 1 | Baseline (pre-diet) | Study Diet | End of Study Visit | 1 month and 6 months after end of study |
|---|---|---|---|---|---|---|
| Estimated time requirement of visit | 30min* | 90-180min | 30min | 7-days | 120-180min | 10-min |
| Finger Prick (blood glucose) | | X | | | | |
| Pregnancy Testing | | X | | | | |
| Vitals | | X | | | | |
| Height | | X | | | | |
| Weight | | X | | | | |
| Online Diet History Questionnaire (DHQ) | | | X | | | X |
| Usual eating habits | | | x | | x | |
| Harvey Bradshaw Index (HBI) | X | | | | X | |
| Crohn's Disease Activity Index (CDAI) | | X | | | X | |
| Dietary Recall | | X | X | | | |
| Blood Draw (Hemoglobin) | | X | | | X | |
| Demographics & Medical History | | X | | | | |
| Medication History | | X | | | X | |
| Online sCDAI (daily) | | | X | X | | |
| Stool Collection | | | X | X | | |
| Diet Satisfaction Survey | | | | X | | |
| Adverse Events | | | | | X | |
| Follow up diet questionnaire | | | | | | X |

## Radiation and Radioactive Substances

- Does the research involve the use of radiation or radioactive substances?

☐ Yes ☒ No

## ClinicalTrials.gov Information

The study protocol has been registered in ClinicalTrials.gov under NCT number: NCT04065048

## List of Data to be Collected

Note: If using REDCap, all selected identifiers below must be indicated as PHI.

1. Indicate what identifiers you will collect
   - ☒ Name
   - ☒ Address *(e.g., Zip code, other geographical designation, etc.)*
   - ☒ Dates related to an individual *(e.g., Date of admission, birth, surgery, etc.)*
   - ☒ Telephone number
   - ☐ Fax number
   - ☒ Email address
   - ☐ Social security number
   - ☒ Medical record number
   - ☐ Health plan beneficiary number
   - ☐ Account number
   - ☐ Certificate/license number
   - ☐ Any vehicle or other device serial
   - ☐ Device identifiers or serial numbers
   - ☐ Web URL
   - ☐ Internet protocol (IP) address
   - ☐ Finger or voice prints
   - ☐ Photographic images
   - ☐ Other:

2. List all other data to be collected for the research study *(e.g. laboratory values, physician notes, length of stay, etc.)*
   Other data to be collected in this study include: Laboratory values, physician notes, medication history, demographic information (gender, ethnicity, marital status, place of birth, employment), diet history, smoking history, alcohol use, stool & blood specimens, vitals.

   Perceptons' on the role of diet and food safety on digestive symptoms, as well as individuals perceived willingness to change dietary practices.

## Data Analysis Plan

This study is straightforward in principle; recruitment, provision of diet and a daily survey (sCDAI) form to complete online at home for 7 days, a fecal sample on day 1, and a fecal sample on day 7. The primary analysis will compare the absolute difference (before/after) using the paired t-test (or the non-parametric test) for ANOVA. Only patients that contribute to the two fecal samples before and after diet will be used for analysis. Attention will be placed on examining the reasons if patients drop out and do not complete the diet for both groups to ensure the cause of drop out is not due to diet (chi-square stats and interviews to assess 'safety of diet'). Continuous outcome measures, such as sCDAI, will compare before/after values using the Wilcoxon sign rank test (nonparametric paired test) and categorical variables using the chi-squared test. These analyses will be conducted separately for each treatment group. The identification of potential biomarkers will be examined using multivariable multinomial logistic ('no effect', 'moderate effect', 'prominent effect'), linear, and linear mixed random effect models (% of reduction in primary outcomes, *e.g.,* CDAI, with and without controlling for clustered and repeated measures data) as it has been published recently by the PI and/or the mentors.[28, 29, 30, 31, 32, 33] Interim analyses of efficacy data will be performed every 6 participants per arm o assess criteria for possible stopping is clearly defined. Because this study will compare two identical 7-day diets that differ only in the presence of soy, and both of which have potential health benefits, no interim safety is indicated. However, analyses will be conducted to monitor efficacy/study power (see section above) and data quality.

### Baseline Data

We will utilize descriptive statistics to define the characteristics of the study participants. 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 pre-(baseline) and post study diet data using the Wilcoxon rank sum test for continuous variables and the chi squared or Fisher's exact test for categorical variables. Analysis will be performed using SAS, STATA, GraphPad and R. All results will be reviewed by an experienced biostatistician (Alexander Rodriguez-Palacious, Asst. Professor, Division Gastroenterology).

## Confidentiality of Specimens and Banking

Are you storing the specimen(s) for future use for other research projects?

- ☐ I am **not** collecting specimens in this research project
- ☐ I am **not** storing specimens in this research project
- ☒ Yes
- ☐ No

If yes, describe:

1. The source of the specimens: Collecting directly from subjects.
2. Where the specimens will be stored: All specimens will be stored in the Division of Gastroenterology in a locked -80C freezer, located on the 5th floor Biomedical Research Building (BRB), CWRU.
3. How long the specimens will be stored: Samples will be stored no longer than 10 years.

4. How the specimens will be labeled: This study will use a unique study identifier (not derived from the participants' personal identifiers) to code individuals' data and study specimens, and the ID log will be stored separately from the study data.
   Data will be secured by appropriate methods including:
   - The key code ID log will be kept separately and securely
   - Data are kept in a locked file cabinet, office, or suite in the Biomedical Research Building, 5th floor, CWRU
   - Electronic data are password-protected stored on UH RedCap.

5. How the specimens will be accessed: Control access to and use of specimens stored under the supervision of the study coordinator.
6. Who will have access to the specimens: Only the study investigators will have access to the research study samples. The laboratory study team will not have access to the master list and no attempt will be made to re-identify the subjects/specimens. The linking sheet will be destroyed once the sample collection has been completed. Personnel such as regulatory authorities and members of the University Hospitals Cleveland Medical Center Institutional Review Board may inspect the subject's medical records and the database for verification of the accuracy of data. Medical records and data will be handled by professional standards and existing federal, state, and local laws.
7. When and how will the specimens be destroyed: Disposition at the completion of the study: All samples will be stored in the Division of Gastroenterology in a locked -80C freezer, located on the 5th floor BRB, CWRU. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking. Samples will be incinerated.
8. How will the specimens be transported? (Please note if transporting specimens, a Material Transfer Agreement (MTA) is required) The de-identified, archived data will be transmitted to and stored in Division of Gastroenterology of the DDRCC in a locked -80C freezer, located on the 5th floor BRB, CWRU., Permission to transmit data to the DDRCC freezer space will be included in the informed consent.

9. The procedures to release specimens including:
   - The process to request a release: we will not be sharing samples
   - Approvals required for a release:
   - Who can obtain specimens:
   - The data to be provided with specimens, including if the data will be identifiable to others:

   Specimens will de-identified and sent in batch for analysis and tracked using unique study ID code not derived from participants personal identifiers.

☐ For genomic data, please check the box to attest there is no master list and no attempt will be made to re-identify the specimens.

## Confidentiality of Data

10. To maintain the confidentiality of the data:

☒ I will use a unique study identifier (not derived from the participants' personal identifiers) to code individuals' data and I will store this ID log separate from study data.
☐ Other

11. How are you storing your electronic data?
☒ UH Redcap
☐ CWRU Redcap
☐ CWRU's SRE (Secure Research Environment)
☐ CWRU Box
☐ OnCore
☐ UH Secure Network Drive
☐ CWRU Secure Network Drive
☐ Other -

12. ☒ I acknowledge that paper research data and documents will be stored in a double-locked secure environment in the following location:

**Location:** ☐ N/A

Paper research data and documents will be stored in a double-locked secure environment in the Biomedical Research Building, 5th Floor, CWRU. The laboratory study team will not have access to the master list and no attempt will be made to re-identify the subjects/specimens. The linking sheet will be destroyed once the sample collection has been completed. Personnel such as regulatory authorities and members of the University Hospitals Cleveland Medical Center Institutional Review Board may inspect the subject's medical records and the database for verification of the accuracy of data. Medical records and data will be handled by professional standards and existing federal, state, and local laws.

13. Will data be shared?
☐ N/A
☒ No
☐ Yes

- List the exact data elements that will be shared:
- Describe how data will be sent:

## HIPAA Authorization

If you are going to be accessing PHI (Protected Health Information), indicate how HIPAA authorization will be obtained (check all that apply):

☒ HIPAA authorization is in the consent form
☒ Requesting a full or partial waiver of HIPAA for prescreening
☐ Requesting a full or partial waiver of HIPAA

1. Describe why the study cannot be completed without the specified identifiable information.
   Study investigators will have access to participants' PHI and data for identification of suitable study participants (physician notes), and to facilitate participants' receipt of study food (name, telephone number, delivery address) to evaluate daily QOL and gastrointestinal symptoms) and problem solving.(email address – questionnaires sent via RedCap).

2. If the identifiable information will be used or disclosed by anyone other than the research team, please state who those individuals/entities are and provide justification for the disclosure.
   - ☐ Identifiable information will **not** be used or disclosed by anyone other than the research team
   - ☐ Identifiable information will be used or disclosed to:

3. Describe how long identifiers will be kept for in relation to study length and data collection and analysis.
   Research records to be retained for at least 3 years after the completion of the research (45 CFR 46) and data will be kept for at least 5 years.

☒ I assure that protected health information collected for purposes of this research study will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use of disclosure of protected health information for which an authorization or opportunity to agree or object is not required by 45 CFR 164.512

## Risks to Research Participants

1. List the reasonably foreseeable risks such as breach of confidentiality, discomforts, hazards, or inconveniences to the research participants related to their participation in the research. Include a description of the probability, magnitude, duration, and reversibility of the risks. Include the physical psychological, social, legal, and economic risks.

**5.0 Risks to Research Participants**
**5.1 Risks**
**Diet**
The intervention in this study poses little risk to participants. The prescribed diets are consistent with many dietary recommendations to minimize consumption of "processed" foods. Nevertheless, it is possible that some participants may feel inconvenienced by the diet or experience abdominal discomfort, particularly if the study diet contains a higher fiber content to that of their usual eating habits (increased flatulence). However, we expect this to be minimal, especially in context to the short duration of the diet intervention. In addition, there is a theoretical risk of delaying a change in the patient's medication regimen while trying the study diets, however we have taken this into consideration in the design of both our inclusion and exclusion criteria.

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.

**Medical record review**

Efforts will be made to keep the personal information in the subject's research record private and confidential, but absolute confidentiality cannot be guaranteed.

**Emotional and psychological risks:**

Participants may feel uncomfortable about answering questions pertaining to symptoms or diet history, or for the online survey, their perceptions on diet and food safety . If participants do not wish to answer a question, they may skip it and go to the next question.

**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 (e.g. UH IRB), 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 UH Data Coordinating Center (RedCap) before commencement of the study. Continuing review will be required through the UH Institutional Review Board or other local reviewing entities at the DHI recruiting center.

## 5.2 SAFETY AND ADVERSE EVENTS

### 5.2 Definitions

### 5.2.1 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.

### 5.2.2 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**.

### 5.2.3 Expected Adverse Events

As a short term study of a soy-based diet, there are few expected risks of the diet intervention. 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, or other complication such as bowel obstruction due to intestinal narrowing or intestinal fistula due to penetrating disease/ulcer. In addition, presence of or worsening of pre-existing extraintestinal manifestations of Crohn's disease is possible, such as joint pain (arthralgia), mouth sores, skin (e.g., erythema nodosum) or ocular manifestations (e.g., 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 sustain symptomatic 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.

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

### 5.2.3 Recording of Adverse Event (AE)

At each contact with the subject from the screening visit to the end of study visit, the primary Investigator will seek information on adverse events by specific questioning and, as appropriate, by examination by a gastroenterologist. 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.

### 5.2.4 Relationship of AE to Study

The relationship of each adverse event to the study procedures should be characterized by the Primary 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.

### 5.3 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 (Case Western Reserve University) 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, 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 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 (DHI)
- 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 treating gastroenterologist, the sponsor, and the relying IRB immediately.

#### 5.3.1 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 investigator is responsible for ensuring that all SAEs are followed until either resolved or stable.

#### 5.3.2 Investigator reporting: notifying the study sponsor

DHI investigators should report serious adverse events and unanticipated problems meeting the 3-day reporting requirement (as defined in section 5.2) to the DDRCC, DHI UH sponsor by phone

and via RedCap. Phone notification should be within 24 hours of the investigator becoming aware of the serious adverse event.

A specific AE documentation form will be provided to the investigators. In case of an SAE, this should be completed by the physician/gastroenterologist as an initial report, and sent (via fax) to the principal investigator. The report must contain a detailed description of the symptoms observed and the concomitant treatment administered. Furthermore, the investigator must comment on a possible causative relationship between the AE and study diet. Each SAE must be followed until it is resolved or can be explained satisfactorily. The general procedure for the observation, collection and analysis of risks (regulatory affairs) in conformity with the appropriate national Drug Law shall apply without qualification. In accordance with drug safety and national requirements, the study PI will inform the Data and Safety Managing Board (DSMB) of the study and will make sure that the involved persons will obtain adequate information. Also the principal investigator will inform the Ethics Committee at UH. Only those SAE will be notified which might affect the safety of the study subjects or the overall conduct of the study.

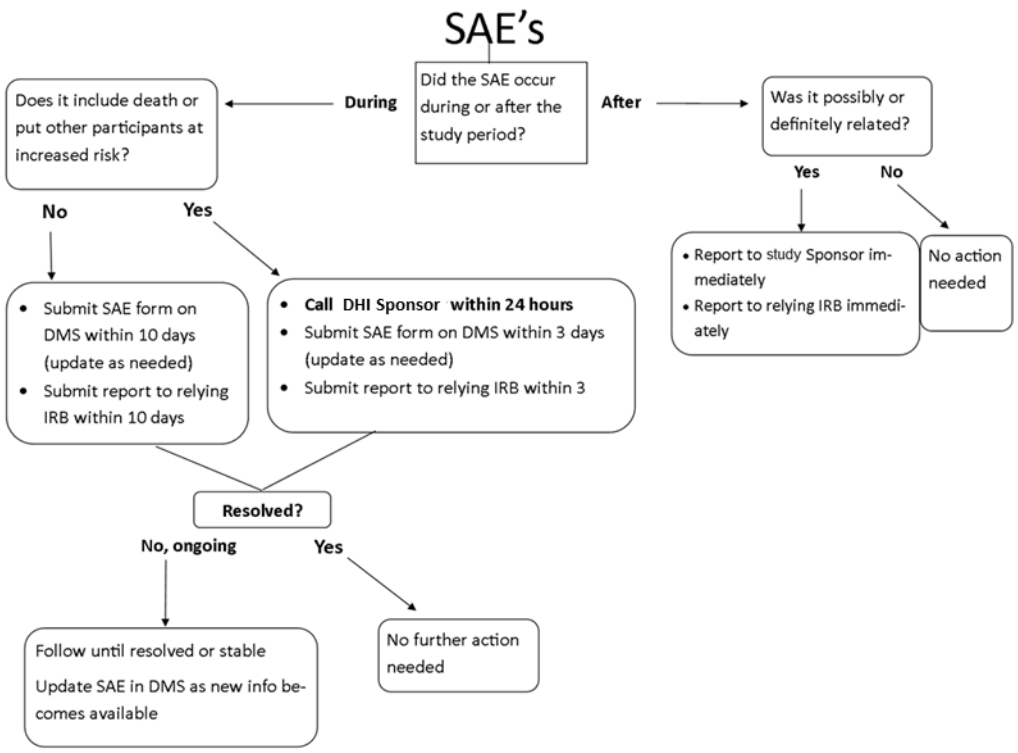
The following instructions must be heeded:
In the case of an intolerable SAE, the patient must, at the decision of the investigator, be withdrawn from the study, and symptomatic treatment must be administered. The measures taken must be recorded on the CRF. In accordance with local legislation, the investigators will submit copies of the final SAE-report to the Regulatory Authorities concerned, if necessary. 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.

**Online survey (perceptions on diet/food safety on digestive symptoms):** N/A

| **Address:** | **UH Site Investigator** | Phone/fax No: |
|---|---|---|
| Digestive Health Institute<br>University Hospitals<br>Cleveland Medical Center<br>Cleveland, OH | Fabio Cominelli, MD | 216-844-5951 |

OR

| **Address:** | **Research investigator** | Phone/fax No: |
|---|---|---|
| Dep. of Gastroenterology<br>Biomedical Research Bldg., 501<br>2109 Adelbert Road,<br>Cleveland, OH | Abigail Basson, PhD, RD, LD | 856 220 3445<br><br>Fax: 216-368-0647 |




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

2. If applicable, indicate which experimental procedures may have risks to the research participants that are currently unforeseeable.
   ☒ N/A
3. If applicable, describe the risks to others who are not research participants.
   ☒ N/A
4. Describe the availability of medical or psychological resources that research participants might need.
   ☒ N/A

**Additional Considerations for Pregnant Women:**

5. Indicate which procedures may have risks to an embryo or fetus should the research participant or their partner be or become pregnant.
   ☒ N/A

   ☐ Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.
   ☐ No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
   ☐ Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
   ☐ Individuals engaged in the research will have no part in determining the viability of a neonate.

## Provisions to Protect the Privacy Interests of Research Participants

To protect the research participant's privacy interests, the consent process will occur in a quiet, private exam room in a private area of the Digestive Health Institute (DHI), UHCMC, or at the Dahms Clinical Research Unit at UHCMC. All additional study visits will also occur in a private exam room. This will allow for subjects to feel comfortable about asking and responding to questions.

## Potential Benefit to Research Participants

☐ There is potential benefit to research participants.

1. Describe the potential benefits that individual research participants may experience from taking part in the research. Include the probability, magnitude, and duration of the potential benefits.

☒ There is **no** direct benefit to research participants.

2. If no direct benefit, state the potential benefit to society or others.

Participants may benefit from participation in this study if the proposed dietary intervention reduces their symptoms of CD and the related inflammation. In healthy controls, it is possible that the dietary intervention promotes a feeling of individual well-being and/or gut health (e.g., improved shape or texture of stool). If the study diet is demonstrated to be superior to the participants usual eating habits, it is anticipated that many patients with CD or healthy individuals without CD would elect to follow a similar diet.

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 the study diets is demonstrated to be superior, then we can confidently recommend that diet to patients with active CD. If the study diet is found to be superior, the default recommendation will be to follow a "healthy" and well-rounded diet such as the soy-based diet, or that originally followed by the patient prior to the intervention if the patient found this diet beneficial for their individual disease symptoms. This is a low risk study, so the risks to subjects are reasonable in the context of the information to be gained.

## Withdrawal of Research Participants

☐ N/A

Participants may withdraw from the study at any time.
Participants may be withdrawn at the discretion of the investigator prior to initiation of diet intervention for the following reasons:

- **Failure to provide stool samples****
- **Failure to complete questionnaires**

**We have considered that participants may not have a natural bowel movement as anticipated during day 5-7 of the study diet. We have considered this in our inclusion/exclusion criteria. Nevertheless, if failure to provide stool sample is a result of absence of natural bowel movement at any time during day 5-7 of a study diet, provision of study meals may be extended and approval will be granted by study coordinator if criteria for daily diet intake and relevant questionnaires has been met for respective 7-day diet.

Participants will be withdrawn from the study if they experience worsening symptoms requiring a change in their Crohn's disease treatment.

Participants who have been enrolled in the study and completed or partially initiated any part of the diet intervention including fasting, and withdraw early from the study should complete an end of study visit and provide a stool sample at the time of withdrawal.

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. This will be the end of study visit.

**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 Withdrawal of Research Participants.

### Unscheduled Visits

Diet intervention; Unscheduled visits could potentially occur if a participant experiences an Adverse Event that requires medical evaluation. Refer to Section 5.2 Safety and Adverse Events in protocol.

## Alternatives to Participation

☒ The alternative is for research subjects not to participate.

## Costs to Research Participants

☒ There are **no** costs to research participants or their insurance companies (there are no clinical visits or billable procedures).

## Research Participant Compensation

☐ There is **no** compensation or reimbursement for research participants.
☒ There is compensation for research participants.
☐ There will be reimbursement for research participants.

At completion of study visit 1 and at completion of the end of study visit, participants who provide proof of parking will be given a date stamped parking voucher (3 hours visitor parking) to off-set any cost to subjects for participation in this study.

To off-set any cost to participants for participation in this study related to transportation expenses, storage, reheating and preparation of study meals, participants will be compensated a total of $100 given in the form of a gift card for their participation in this study. Given the short

duration of the diet study only one payment will be made. The one-time payment will be given to the participant at the End of Study Visit, after completion of the study. To receive payment participants must consent to complete a W-9 form.

## Compensation for Research Related Injury

Describe who will pay for the costs of medical treatment and/or compensation in the event of a research related injury:

- ☐ Funding agency is providing some/all payment for injury
- ☒ Funding agency is providing no payment for injury
- ☐ N/A

All minimal risk research involves a chance of research related injury to the participant. This may include the risk of personal injury or illness that is not the result of a pre-existing condition or the normal progression of the participants' disease. In spite of all safety measures, a participant might develop a reaction or injury from being in this diet study. If such problems occur, the University Hospitals Cleveland Medical Center (UHCMC) principal investigator will help participants get medical care at UHCMC or elsewhere; however, the study sponsor has not set aside funds to provide payment for research related injury and UHCMC has no plans to provide free care or compensation for lost wages; any costs for the medical care will be billed to the participant and/or the participants insurance company.

## Provisions to Monitor the Data to Ensure the Safety of Research Participants

1. Describe how often the data will be monitored for completeness, accuracy and adherence to the protocol.

**Diet Intervention:**

**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. Contact includes monitoring of completed daily questionnaires and in-person visits. 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 Case Western Reserve University, Cleveland, OH and University Hospitals Cleveland Medical Center. Additionally, we will employ a Data Safety and Monitoring Board (DSMB).

**Study Monitoring Plan**

Most of the data to be collected in this study will be collected directly from participants using repeat surveys sent via email under our UH RedCap project. For specific aim 1, the primary outcome of maintenance of symptomatic remission is derived from participant completed surveys. We will monitor 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 investigator at the DHI prints, redacts if needed, and

uploads into RedCap source documents that demonstrate the eligibility of the participants, as appropriate. All documents will be available for remote review for compliance with the study protocol. Any findings that demonstrate a protocol deviation will be reported to the UH IRB. Similar methods will be employed for reviewing the DHI study sites regulatory binder.

The DHI will provide an area where the study regulatory documents can be stored and then reviewed by the investigators. Data quality monitoring will be implemented after the second patient is enrolled at the DHI. Eligibility criteria and consent process will be monitored for all participants. If deemed necessary, on site monitoring will be employed.

Clinical data and baseline characteristics of the participants and follow-up data on adverse events and physician derived components of the CDAI will be collected by the site investigators and recorded in RedCap. All data analysis for secondary outcomes for specific aim 1 (changes to fecal bacteria composition and butyrate) will be performed blinded by an experienced biostatistician.

**Auditing and Inspecting**

The principal 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.

*2.* Indicate if there will be a Data and Safety Monitoring Board or Committee:

☐ There will **not** be a formal Data and Safety Monitoring Board/Committee.

☒ There will be a formal Data and Safety Monitoring Board/Committee.

**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 statistician, 2 experienced clinical investigators with knowledge of Crohn's disease. 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 after half 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 study as is, continue the study with modifications, suspend the study 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 UH IRB.

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

## Drugs or Devices

☒ This is **not** a drug or device study. The protocol is considered non-therapeutic (non-therapeutic is defined as research not intended to diagnose, prevent, cure, mitigate, treat, etc. a disease or condition) by the FDA. –

OR

☐ This is a drug or device study. The protocol is considered therapeutic (research intended to diagnose, prevent, cure, mitigate, treat a disease or condition) by the FDA.

1. Is there an active IND (Investigational New Drug) or IDE (Investigational Device Exemption) for the proposed clinical research study?
   - ☐ Yes, provide an official letter of support or proof of approval which identifies the IND/IDE holder and IND/IDE number.
   - ☒ No,

2. Is the drug IND exempt *OR* is the device (and its use) a non-significant risk device for the proposed study design?
   - ☐ Yes
   - ☐ No
   - ☒ N/A

## Additional Information
## Community-Based Participatory Research

☒ This is **not** a community-based participatory research project

☐ This is a community-based participatory research project

Note: Community based research is research that is conducted as an equal partnership between academic investigators and members of a community. In Community Based Participatory Research (CBPR) protects, the community participates fully in all aspects of the research process.

## International information

☒ This is **not** an international study

## MULTI-SITE RESEARCH (when UH or CWRU is the IRB of Record)

**Does this project have multiple sites?**

☐ **Yes**

☒ **No**

**Non-Local Site Information for Multi-Site Studies**
*If this is a multi-site study where you are the **lead investigator,** list the following information for each relying site:*

1. Name of site:
2. PI of relying site:
3. Name of IRB contact:
4. Phone number of IRB contact:
5. Email address of IRB contact:

**Non-Local Recruitment Methods for Multi-Site Studies**
*If this is a multi-site study and research participants will be recruited by methods **not under the control of the local site** (e.g. call centers, national advertisements) describe those methods. Local recruitment methods are described above.*

1. *Describe when, where, and how potential research participants will be recruited.*

1. *Describe the methods that will be used to identify potential research participants.*

2. *Describe the materials that will be used to recruit research participants.*

**Multi-Site Research Communication Plan (when you are the lead investigator)**
*If this is a multi-site study where you are the **lead investigator**, describe the processes to ensure communication among sites including:*

☐ *All sites will have the most current version of the protocol, consent document, and HIPAA authorization*
☐ *All required approvals (initial, continuing review and modifications) have been obtained at each site (including approval by the site's IRB of record)*
☐ *All modifications have been communicated to sites, and approved (including approval of the site's IRB of record) before the modification is implemented*
☐ *All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies*
☐ *All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies*
☐ *All local site investigators conduct the study in accordance with applicable federal regulations and local laws*
☐ *All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy*

*If this is a multi-site study where you are the **lead investigator,** describe the method for communicating to engaged participant sites the following:*

1. *Problems:*
2. *Interim results:*
3. *The closure of the study:*

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## Please reference the Investigator Manual for local institutional requirements.

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