Study Protocol Cover Page

Official Study Title: Using Single Subject (N-of-1) Designs to Answer Patient-Identified Reseach Questions – Aim 1
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USING SINGLE SUBJECT (N-OF-1) DESIGNS TO ANSWER PATIENT-IDENTIFIED RESEARCH QUESTIONS—AIM 1

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Sponsor: *Cincinnati Children's Hospital Medical Center*

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**Data and Site
Coordinating Center:**   *Cincinnati Children's Hospital Medical Center*

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Document History

Document	Date of Issue	Summary of Change
Original Protocol, V1.0	TBD	Not applicable
Protocol V2.0	TBD	Removal of Aims 2 and 3. The grant research plan was inclusive of Aims 1, 2 and 3; however, it was decided that, because of the nature of the condition being studied in Aims 2 and 3 (i.e., adult atrial fibrillation), it would be more appropriate to submit Aims 2 and 3 as separate proposals. This decision was made by the co-PIs, and supported by the advice of the reviewing IRB member. The Title of the protocol was amended to reflect this change. The estimate of the number of study sites was increased to reflect current site interest. The eligibility verification process was changed to have the site PI (not research coordinator) verify eligibility on page 17. Typographical errors were corrected in Figure 2 and on page 14 (completion of final treatment period is week 34 not week 32). A rationale is now provided (page 17) for the exclusion of non-English speakers.
Protocol v3.0	5/15/2017	Changed "liberal SCD" to "modified SCD" throughout the protocol, consents, and study materials/figures. Added and removed some study measures. Edited wording on some measures to improve clarity. Updated inclusion/exclusion criteria based on parent/patient and clinician stakeholder feedback to ensure study integrity and better account for participant safety. Process for diet staging is now specified in the protocol. Removed suggestions for timing of returning stools samples to enable more flexibility in the collection and shipping process. Altered the process for collecting and analyzing the food diaries to centralize the nutrient analysis and provide greater diet monitoring oversight from the study co-investigators with expertise in the SCD (Suskind/Braly). Added a variable for data collection to track Vitamin D status per recommendations of DSMB. Edited Figure 2 to reflect a change in study process that will allow for education on both the A and B diet at enrollment. Refined the analytic plan related to the washout period and run-in period associated with the diet staging. Added multiple study documents that will be used for recruitment and diet resources. Updated consent forms to verify participant willingness to allow de-identified use of data in future studies. Expanded appendix to add: Eureka technology platform privacy statement provided in the app prior to patient use, another version of the study flyer, phone script, and a study letter. Added multiple study staff. Removed information about adding a study-specific Facebook group as there are no longer plans of perusing a study-specific Facebook group for this study.
Protocol v4.0	6/29/2017	Protocol: Added a signature page for site PIs. Modified Figure 1 and added changes in the text in order to have more flexibility for study site staff in their timelines for collecting data from participants. Modified Figure 2 and added more specific language regarding how often participants need to be tracking data to continue in the study as well as more specific language about collection of stool samples and how that relates to continuation in the study. Made stipend remuneration consistent with expectations of data collection. Revised Appendix C language to be consistent with protocol and consents (i.e., using "modified" instead of "liberalized"). Added parent versions of relevant questionnaires under Appendix C, D, and H. Developed new diet diary for Appendix F, replacing previous version which

		is attached as a separate document. Added language throughout specifying that a participant can be seen by a physician or advanced care provider. Consents: Added language in the assent and consent forms to be consistent with expectations regarding tracking of diet and sending in stool sample. Added in Master Consent and Site Consent to footer for tracking purposes in both assent and consent. Added a line about no compensation from CCHMC or PCORI for injury in consent. Added language in consent regarding standard rates that may apply for data usage or text messaging related to the study. Added "provider" in addition to doctor throughout consent and assent to be consistent with the protocol that a participant can be seen by either a physician or advanced care provider throughout the study.
Protocol v4.1	9/12/2017	Minor clarifications to the modified SCD (removal of requirement for organic sweet potatoes, addition of a requirement for organic rice, addition of grade A maple syrup as an allowable food, and clarification of the minimum/maximum suggested serving amounts). Adjustment of the diet staging to be less restrictive and to advance more quickly. Modification of exclusion criteria to include those who are on another interventional study as the study procedures could affect the results of the individual N-of-1 study if a participant is exposed to an intervention at different times in the N-of-1 protocol. Addition of pregnancy and ≥7.5% weight loss as criteria for automatic withdrawal in order to ensure participant safety. Clarified adverse events procedures including specifying expected adverse events. Updated Appendix G with results review. Updated 1 question in Appendix C in the expectation of benefit questionnaires for both patient and parent. In Appendix D, we reordered the weekly questionnaires moving all the parent questionnaires together. We did not change the wording of any of the questions. Updated the DSMB charter (Appendix M). Updated Appendix I- added new study staff and reordered staff members. Removed a site that is no longer participating and added a new site that is. Other changes were cosmetic consistent with what is stated under Appendix I section below. Also added minor wording updates to Appendices J and B (SCD Summary and SCD Detailed Summary) to be consistent with the allowed foods in the protocol and the dates of the study. Make changes to Appendix B stages for the PRODUCE study to be consistent with the staging as it is described in the protocol. Assent: Added in "organic" rice, took out "organic" for sweet potatoes and added in "Grade A" for maple syrup. Consent: Added in "organic" rice, took out "organic" for sweet potatoes and added in "Grade A" for maple syrup. Changed description of fistula. Added interventional study exclusion.
Protocol v4.2	11/27/2017	Protocol: Added changes about the timing of the diet diary being sent to the study site and communication between the site and participant around the diet diary. Added verbiage that a less than 5% weight loss is expected in the study and greater than that will be reported as an AE. Clarified wording around SPDCAI and PUCAI regarding when score needs to be obtained related to study enrollment, and clarified what qualifies as mild to moderate disease activity. Added information regarding NiMBAL book being used as compensation for the study. Changed "Increase in corticosteroids within 4 weeks of screening…" to "within 4 weeks of enrollment". Added more specific language regarding cocoa and cacao that can be used by participants. Updated version number and dates where necessary. Clarified patient symptom tracking. Added information about a video we may make and included the video script as an Appendix B. Clarified screening visit timing. Clarified information regarding the statistical methods in the study. Appendix B Changed documents include: Brandlist PRODUCE, SCD

		Detailed Summary, SCD Summary, and Stages for the PRODUCE Study. Appendix B new documents include: 3 Week Meal Plan Ideas, Blurb for Clinic Newsletter, Family Tried and True Recipe Links, Making SCD Yogurt, Next Steps Figure, SCD Resources, and Script for PRODUCE Patient Video. Added changes to Appendix E-Stool Collection Instructions. Added changes to Appendix F-3-Day Diet Diary. Added changes to Appendix I-Trifold Flyer. Added changes to Appendix J-Introductory Flyer. Added changes to Appendix K- PRODUCE Recruitment Letter. Finally, added changes to Appendix L- Phonescript. All appendices are uploaded as separate documents.
Protocol v4.3	4/30/2018	Added the lab test lactoferrin as an option for establishing evidence of active inflammation for study inclusion. Added language in the Study Procedures section allowing dietitians to carry out standard of care activities during participant contact. Added language in the Participation Selection and Withdrawal section clarifying that GI care providers will determine if a patient and their family's treatment decisions may be informed by the results of this study. Updated screenshots of the Eureka app in Appendix A. Added in that dietitian phone follow-up visits can also be done in-person, in-clinic.
Protocol v4.4		Added the clarifier "nonintentional" to "≥ 7.5% weight loss" in section 3.5.4 Early Withdrawal of Participants to clarify that the ≥ 7.5% weight loss will only result in a participant's early withdrawal if the weight loss was unintentional. Changed exclusion criteria from a BMI in the 10th percentile to the 5th percentile. Change inclusion criteria from "Past or present history of intra-abdominal abscess, fistula, stricturing CD, or ostomy" to "Currently or within the past 9 months has had an intra-abdominal abscess, fistula, stricturing CD, or ostomy" and added the exclusion criteria "Ever had history of full colectomy".
Protocol v4.5	9/19/2018	Changed the inflammation criteria for the study: evidence of acute inflammation and/or elevated acute phase reactant as measured by Fecal calprotectin 1.5 (formerly 2) times the upper limit of normal, Lactoferrin 1.5 (formerly 2) times the upper limit of normal, CRP 1,15 (formerly 1.25) times the upper limit of normal, or ESR 1.15 (formerly 1.25) times the upper limit of normal (based on local reference ranges) obtained within 8 weeks of enrollment.
Protocol v4.6	10/24/2018	Added using social media as a way to disseminate flyers already approved by the IRB, as well as a newly created poster. Created a poster(s) to advertise study (Appendix O). Added a letter written by parent partners for study participants and potential participants (Appendix P). Changed the baseline period from a minimum of 2 weeks to a minimum of 1 week. Changed the inclusion/exclusion criteria to include patients that are already on the SCD or modified SCD but are not compliant with the diet per the site dietitian or primary GI physician. Made edits to the statistical analysis plan. Changed the wording surrounding the standard of care visits to make only the first SOC visit necessary, the others are only if/as needed.

Protocol v4.7	12/7/2018	Removed "Mild to moderate disease activity as measured by a short Pediatric Crohn's Disease Activity Index (SPCDAI) score of 15-45 or Pediatric Ulcerative Colitis Activity Index (PUCAI) score of 10-60 assessed within 3 weeks of enrollment" from inclusion criteria and added "Severe disease activity as measured by a short Pediatric Crohn's Disease Activity Index (SPCDAI) score of >45 or Pediatric Ulcerative Colitis Activity Index (PUCAI) score of >60 assessed within 3 weeks of enrollment" to the exclusion criteria. Changed inclusion criteria from 7-17 years to 7-18 years.
Protocol v4.8	2/18/19	Decreased the sample size from n=120 to n=50. Revised sample size calculation demonstrates adequate power at this smaller sample size. Edited the study timeline by adding more time to our enrollment period (enrollment now ends 10/31/19). Increased the number of participating study sites from 12 to 21. Changed the due date for diet diary entries from specifying submission 3-5 weeks after starting a new diet phase to allowing submission anytime during the diet phase. Changed the dietitian in-clinic visit to allow this visit to be able to take place by phone, video call or telemedicine. Changed the dietitian phone follow-ups to allow this visit to be completed either by the site dietitian or the site coordinating center dietitian.
Protocol v4.9	3/26/19	Changed the dietitian in-clinic visit and dietitian portion of the enrollment visit to allow these visits to be conducted via phone or video call by the site coordinating center dietitian, in the event that the site dietitian is absent or unavailable to conduct the visit. Changed the wording around subject disposition and withdrawal, allowing subjects who have completed at least one full treatment period of each diet to discontinue study participation and terminate the protocol early, rather than withdraw completely from the study. Subjects who discontinue study participation and terminate the protocol early will be able to review their final results with their site PI or study clinician and complete the final survey questionnaire about their N-of-1 experience.
Protocol v5.0	5/27/19	Removed the word "intra-abdominal" from the study exclusion criteria related to fistulas or abscesses in order to clarify that all abscesses and fistulas are study exclusion criteria.
Protocol v5.1	11/11/2019	Increased the sample size from 50 to 60. Removed the provider end of study survey in the study procedures section.

Protocol v5.2	1/29/2020	Edited the study procedures section (3.4) to include that we will obtain data using sources outside of what is listed in the outcome measures section if needed and added the option of conducting the final results review virtually.

Investigator Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

PRODUCE Study

Version 5.2, January 29, 2020

I agree to conduct the study in accordance with the relevant, current protocol and will not make changes to the protocol without permission, except when necessary to protect the safety, rights, or welfare of study participants.

I agree to personally conduct or supervise this study.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations.

Lead Site Investigator: _____
(Printed name, Title)

Signed:_____   Date: _____

Table of Contents

List of Abbreviations

ACRONYM	Long name
PCORI	Patient Centered Outcomes Research Institute
PPRN	Patient powered research network
ICN	ImproveCareNow
IBD	Inflammatory Bowel Disease
SCD	Specific Carbohydrate Diet
CD	Crohn's Disease
UC	Ulcerative Colitis
IC	Indeterminate Colitis
AWS	Amazon Web Services
PRO	Patient reported outcome
sCDAI	Short Crohn's Disease Activity Index
sPCDAI	Short Pediatric Crohn's Disease Activity Index
PUCAI	Pediatric Ulcerative Colitis Activity Index
CRP	C Reactive Protein
ESR	Erythrocyte Sedimentation Rate
MCMC	Markov chain Monte Carlo
HTE	Heterogeneity of Treatment Effects
DSMB	Data Safety Monitoring Board
UCSF	University of California San Francisco
RCT	Randomized Controlled Trial

1   Aim 1 Summary

Title	Personalized Research On Diet in Ulcerative Colitis and Crohn's Disease
Short Title	PRODUCE Study
Protocol Number	2017-0683
Methodology	Series of N-of-1 trials
Study Duration	4 years
Study Centers	Multi-center with estimated 21 centers
Objectives	Use a series of N-of-1 trials to determine the effectiveness of a specific carbohydrate diet (SCD) in reducing symptoms and inflammatory burden in patients with IBD versus a modified SCD at both the individual and population level.
Number of Participants	Up to 60 recruited across all sites
Diagnosis and Main Inclusion Criteria	Age 7-18 years; IBD; Stable medications
Statistical Methodology	Analysis of individual trial results using Bayesian models to estimate treatment differences; Meta-analysis of series of N-of-1 trials using multilevel mixed models

2   Overall Study Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (Food and Drug Administration Title 21 part 50, part 56 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

2.1   Overall Study Objectives

The overall study is designed to enable patients and clinicians to collaborate in using mobile heath (mHealth) technology supported N-of-1 trials to answer patient-generated research questions from two national patient powered research networks (PPRNs)—the ImproveCareNow (ICN) network of children with inflammatory bowel disease (IBD) and the Health eHeart (HeH) network of adults with cardiovascular disease. By using a common method to answer research questions from two very different PPRNs, this study will provide evidence in support of N - o f - 1 methods as an approach to advance personalized and patient-centered outcomes research. This protocol details the study being conducted in the ICN network only (Aim 1)

2.2   Overall Study Aims:

Aim 1: Use a series of N-of-1 trials to determine the effectiveness of a specific carbohydrate diet (SCD) in reducing symptoms and inflammatory burden in patients with IBD versus a modified SCD at both the individual and population level.

Aim 2: Test the comparative effectiveness of N-of-1 trials versus data tracking alone to identify and eliminate individual-level triggers and reduce atrial fibrillation (AF) frequency and severity.

Aim 3: Assess the feasibility, acceptability, and impact of using N-of-1 methodology across diverse populations (pediatric IBD and adult AF) to answer different types of patient-initiated questions and provide meaningful data for all   PPRN stakeholders.

This protocol details Aim 1 only (study being conducted in ICN). The activities of Aim 2 (study being conducted in HeH) and Aim 3 (N-of-1 Evaluation) are outlined in separate protocols.

3   Aim 1: PRODUCE Study

3.1   Background

3.1.1   Pediatric Inflammatory Bowel Disease (IBD)

Pediatric Inflammatory Bowel Disease (IBD) is a debilitating condition that negatively impacts the health of children. IBD includes Crohn's disease (CD) and ulcerative colitis (UC) and affects 1.4 million children and adults in the US, at an overall cost of more than $1.7 billion[1]. Childhood IBD is particularly aggressive, with significant impacts on both physical and psychosocial well-being that influence individuals over their entire lifespan[2,3]. Typical symptoms, such as abdominal pain

and bloody diarrhea result in significant morbidity, including hospitalization and surgery, missed school, and decreased quality of life[3,4]. While treatment options have improved, over 40% of patients still have frequent, troubling symptoms that negatively impact their health and daily functioning[5-7].

While IBD treatment has improved, evidence regarding the role of diet in managing IBD is lacking. The mainstays of IBD treatment have been anti-inflammatory, immunomodulators, and biologic medications, but specific types of nutritional therapy (formula based enteral nutrition)[8] are as effective in reducing symptoms and inducing remission as steroids for pediatric patients with CD[9,10]. Patient and family interest in examining the impact of diet on IBD symptoms is high. Between 36%-50% of pediatric IBD patients use complementary and alternative therapies[11]. Yet, studies of the efficacy of diet in treating and controlling IBD symptoms remain limited[9]. Preliminary data regarding the specific carbohydrate diet (SCD) suggests that it may result in clinical benefit and improvement in inflammatory biomarkers[10]. The diet eliminates grains, including but not limited to wheat, barley, corn and rice, sugars except honey, and limits milk products except fully fermented yogurt and aged cheeses (>30 days)[12]. Several small retrospective and prospective studies conducted by a study co-investigator (David Suskind) suggest improvement in clinical symptoms and inflammatory markers within 2-3 months of initiating the SCD[10,13]. Despite the promise of SCD, there is no evidence of its effectiveness compared to unrestricted diets from controlled, large scale, multi-center studies. There is also little evidence about the effectiveness of the SCD as compared to more liberalized, or modified, versions of the diet, which is important given the burden associated with the SCD. Therefore, determining the effectiveness of the SCD diet in reducing symptoms and improving inflammation in IBD in a large scale study will address an important gap in care. If an exclusionary diet can effectively induce and maintain remission, then patients will have another viable therapy.

3.1.2   A Critical Research Gap

The role of diet in managing IBD is important to ICN patients and families. To identify research questions important to the community, ICN used a formal research prioritization process that engaged all stakeholders. Participating clinicians, parents, and patients were identified through listservs, social media, community meetings, monthly newsletters, and emails from network leaders. Respondents (94 clinicians and 116 parents/patients) identified 210 research questions of interest. An expert stakeholder panel classified the questions using the taxonomy of the James Lind Alliance[14] and eliminated redundancies and topics with sufficient evidence[14].   Sixty-two network stakeholders, including parents, clinicians, and researchers, subsequently rated these learning objectives at ICN's biannual Community Conference. We identified the subset of questions amenable to N-of-1 study. Among these, the effectiveness of diets in reducing the symptoms of IBD was rated the highest.

3.1.3   Potential to improve health care and outcomes

By using an N-of-1 approach, we will generate individualized evidence about the effectiveness of diet in managing IBD. This methodology provides a direct benefit to patients by helping provide them a greater certainty about their treatment choices, including the relative benefits vs. burdens of maintaining an exclusively SCD diet. This has tremendous potential to improve their individual health in a way that is truly personalized and patient centered.

By examining diet in IBD, we will add to the body of knowledge about effective treatments, especially for children and parents who are either reluctant to use standard immunomodulators or who continue to have mild to moderate disease activity despite standardized therapy. A preliminary analysis of our ICN registry found that >2,000 (20%) patients on stable medication

regimens still had mild to moderate disease activity. These children and their families would benefit from additional treatment choices that would enable them to achieve remission and improved health outcomes.

3.1.4   Study Setting

Aim 1 will take place in the ImproveCareNow (ICN) Learning Network whose mission is to transform the health, care and costs for all children and adolescents with IBD by enabling patients, families, clinicians and researchers to work together to accelerate innovation, discovery and application of new knowledge[15]. ICN's organizational structure ensures that all stakeholders are engaged in its governance. A major advantage of conducting this trial within ICN is that infrastructure has been optimized to support all components of this study – screening, enrollment, follow-up, and data collection/management. The study will take advantage of the ICN registry that contains standardized, IBD-specific data from >15,000 patients who have consented for research. ICN represents an ideal setting for this diet trial because: (1) a collaborative network of highly engaged providers, researchers, patients, and caregivers has already been established; (2) the network is large and diverse, so results are likely to be generalizable; and (3) mechanisms of patient identification, follow-up, and data collection (including measurement of several study outcomes) are already built into routine clinical care.

3.2   Study Objective

Use a series of N-of-1 trials to determine the effectiveness of a specific carbohydrate diet (SCD) in reducing symptoms and inflammatory burden in patients with CD and UC versus a modified SCD at both the individual and population level.

3.3   Study Design

3.3.1   Basic PRODUCE Study Design:

This study will employ a series of individual N-of-1 trials that compare the SCD to a modified SCD using a collaborative approach between patients, parents, and their clinical team. Patients will enter the study on a usual (non-SCD) diet and will have a minimum 1-week run in period for diet planning and baseline data collection before beginning their assigned treatment. Treatment periods will be assigned in blocks of two (e.g., AB) with the goal of each patient completing two balanced treatment blocks (e.g., ABAB) where treatment 'A' represents SCD and treatment 'B' represents modified SCD. Patients will be randomized to either the SCD or modified SCD as their starting intervention and alternate between these two conditions for four 8-week treatment periods. The study design is summarized in Figure 1.

Figure 1

Data Collection
Daily: Stool Frequency, Stool Consistency
Weekly: PROMIS Pain, PROMIS GI symptoms, patient reported
disease activity measures, weight (optional)
Baseline + Each Period: Fecal calprotectin, Diet Adherence
Periodic (ICN Registry): Disease Activity (Clinician Report), Labs
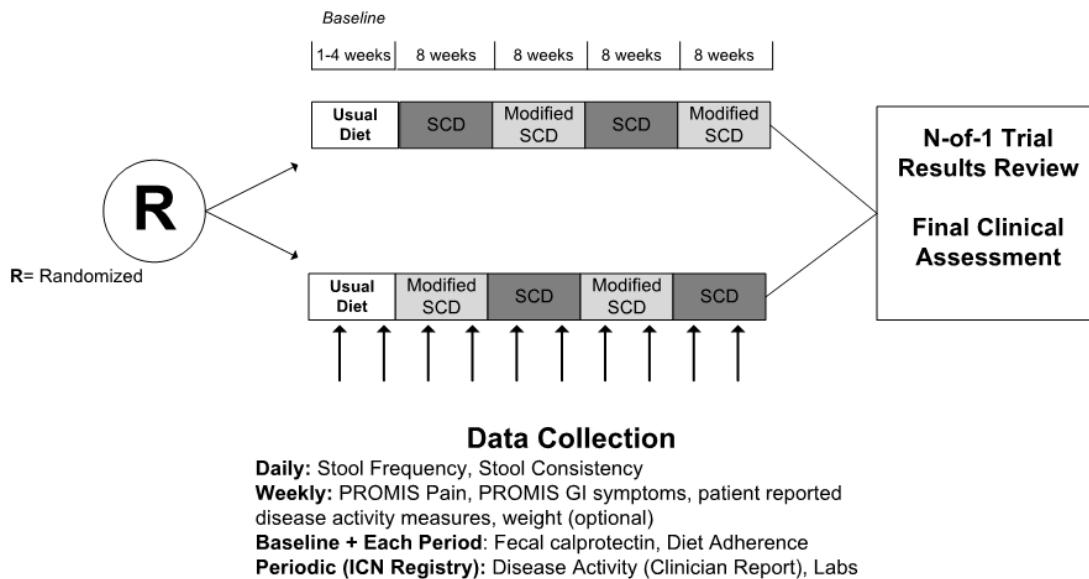
By completing an N-of-1 study, each individual will have a personalized answer regarding the comparative effectiveness between a highly restrictive diet (SCD) and a more broadly sustainable middle ground option (modified SCD) as compared to their baseline diet. In addition, we will aggregate the results of the completed N-of-1 trials across all patients to estimate the population level comparative effectiveness of these dietary treatments and the effectiveness of each compared to a typical, non-SCD, diet. As there is uncertainty regarding whether the sequencing of the intervention is important (e.g., whether patients must initiate a full SCD diet before modifying the diet to be less restrictive), we opted to randomize the initial treatment to be able to examine whether effects differ based on the initial diet type. Although using an ABAB/BABA design without randomization of treatment periods may result in patients anticipating their next intervention period, we do not believe this will result in increased dropout rates or failure to complete all treatment periods because patients and parent stakeholders expressed that they are interested in testing both diets—those who improve on SCD will be interested in determining whether they can maintain improvements on the modified SCD and those who improved on the liberal SCD will be interested in determining whether they can achieve greater improvements on a more strict SCD. The rationale for the duration of each treatment period (8-weeks) was based on the concern that patients would be unlikely to stay on a diet for more than 8 weeks if they did not observe a benefit and based on information from *Breaking the Vicious Cycle* and preliminary studies from research co-investigators indicating the symptoms improve within ~1 month and markers of inflammation by 2 months.

3.3.2 Technology Platform Configuration

Study participants will use the Eureka N-of-1 platform (website and mobile app) to execute the research proposed in this study. The Eureka N-of-1 platform will enable participants and their clinicians to collect outcome data, track intervention/exposure status, and review collected data in real time. Upon trial completion, Eureka will present N-of-1 results to patients and providers with easy-to-understand graphics that include probabilistic assessments of the benefits of the

intervention. Eureka will configure a study-specific version of the platform to execute the research proposed in this study. Screen shots of the Eureka app are provided in Appendix A.

The Eureka Research Platform is a digital research platform developed at the University of California San Francisco as part of a cooperative agreement with the National Institutes of Health. The purpose of the platform is to facilitate mobile health research for any interested investigator. The Eureka platform includes a participant-facing "front end," with mobile app and web-based interfaces, an investigator portal, and a secure "back end" for data storage and analyses. The platform is designed as an all-inclusive, configurable, easily-scalable research platform, inclusive of all aspects of research—from participant enrollment, onboarding and consent, to multi-modal data collection, study administration/management, and data extraction. The platform's front end can be customized by individual investigators to implement their specific research project. Existing functionality includes the ability to obtain remote consent (although in-person consent can also be used), deploy participant surveys, message participants via push notifications, texts, or emails, integrate with external apps, sensors, and Bluetooth enabled devices, and capture data collected from smartphones (such as geolocation data or accelerometer/ activity data). The investigator portal provides a secure website wherein investigators, coordinators or other individuals with appropriate permissions can visualize relevant participants' data and study status. The back end of the Eureka platform is a multi-tenant system that enables data collection, management and storage derived from multiple sources and from studies of various forms. This architecture rests on a secure and HIPAA-compliant Amazon Web Services (AWS) cloud with the capacity to curate dense data from more than 1 million participants. In addition to providing data as needed to investigators, the infrastructure houses a de-identified data repository that is publicly available to help fulfill the general mission of advancing science and wellness.

As part of design sessions held prior to enrollment, members of the research team including patients, parents, and clinicians will provide input regarding the study-specific configurations of the Eureka platform. Study specific configurations will include: (1) trial specific onboarding page, (2) code to generate and perform analyses of trials based on a trial-specific template, (3) server workflow that automates execution of the personal trials, and (4) customization of the user interface for prompts, reminders, forms, surveys, and visualizations. Final configurations will depend on input from key stakeholders. Technology modifications will be done via iterative, rapid development and testing cycles

3.3.3 Interventions and Comparators

The diets are defined as follows:

1. Usual Diet (Baseline Condition): Patient eats a typical, non-SCD, diet. Diet may include some restrictions (which is common in IBD) such as seeds/nuts or gluten, but exclusions will not be as broad as with the SCD and Modified SCD (e.g., patient still eating grains and/or dairy). May include full or partial exclusive enteral nutrition as the currently available liquid supplements are not SCD compatible.

2. Specific Carbohydrate Diet (SCD): The dietary program will follow recommendations outlined in *Breaking the Vicious Cycle* by Elaine Gottschall[12]. Allowed foods include meat/fish/poultry, eggs, some legumes (e.g., lentils and split peas are permitted, chickpeas and soybeans are not), fully fermented yogurt, non-starchy vegetables, ripe fruit, nuts/seeds, honey and nut flours (e.g. almond flour or coconut flour). SCD compatible vitamins are allowed and will be recommended on as needed basis by study dietitians. Restricted foods include all grains, milk

products aside from 24-hour fermented SCD yogurt and cheeses aged greater than 30 days, starchy vegetables, processed foods with food additives and sweeteners other than honey.[16]

3. <u>Modified Specific Carbohydrate Diet (SCD):</u>   A more liberal, and thus, perhaps more sustainable version of the SCD. In addition to the foods in the SCD, allowed foods will expand to include organic rice, oats, sweet potatoes, Grade A maple syrup and 100% unsweetened cocoa powder (not Dutch processed) or 100% cacao powder, nibs, or butter (no sugar added) for this group.   For oats, organic rice, and sweet potatoes, patients will be instructed to consume a minimum of 3 servings and a maximum of 6 servings of any combination of these items per week.   On any given day, they should not have more than 2 servings of any combination of these items. A serving size is 1 cup. For maple syrup and 100% unsweetened cocoa powder (not Dutch processed) or 100% cacao powder, nibs, or butter (no sugar added), patients will be asked to consume a minimum of 2 Tablespoons of each item per week and a maximum of ½ cup of each per week. The reasons for the minimum amount of these food items each week is to distinguish the diet from the SCD enough to provide a useful comparison.   Gluten, corn products, milk products (except yogurt and aged cheeses), sweeteners (except honey), and process foods will still be restricted.

3.4   Study Procedures

<u>Baseline evaluation</u>: Study participants will complete a routine clinical assessment including disease activity measures and standard lab tests that assess inflammation and disease status (per center standard of care). Participants must have documented evidence of acute inflammation and/or elevated acute phase reactant as measured by Fecal calprotectin 1.5 times the upper limit of normal, Lactoferrin 1.5 times the upper limit of normal, CRP 1.15 times the upper limit of normal, or ESR 1.15 times the upper limit of normal (based on local reference ranges) within 8 weeks of enrollment. Potential participants who are close to meeting one of the acute inflammation and/or elevated acute phase reactant markers and who meet all other study criteria will be considered for study participation on a case by case basis by the investigative study team in consultation with the patient's primary gastroenterologist. A stool sample for fecal calprotectin and banking for microbiome analysis will be collected by the patient at home and sent in for analysis. A trained dietitian will provide 1:1 diet training and resources, including print and web-based materials (Appendix B). The dietitian will send the participant home with a 3-day diet recall to be returned to clinic (see process outlined in section on "Diet Monitoring"). In the event that the site dietitian is unavailable for the baseline training, it may be conducted by the site coordinating center dietitian via video call (i.e., Zoom, Skype) if permission is granted by the patient's primary GI physician or advanced care provider. Patients and parents will be trained in the use of the Eureka N-of-1 app. Participants will be randomized to either the SCD or modified SCD as their starting intervention with a 1:1 allocation ratio. We will utilize a centralized, stratified, block randomization approach. We will stratify within sites and by disease type (UC/IC or CD). Patients and parents will also complete psychological assessments and questions regarding their baseline expectation of benefit related to diet (see Table 1, Appendix C) via paper, tablet, website, or Eureka app at the baseline visit. Following the baseline evaluation, participants will spend a minimum of 1 week (maximum of 4 weeks) collecting baseline data and preparing to begin their first assigned diet treatment. They will be asked to not change their diet until they begin their first treatment period. The baseline period is defined as the period from enrollment to the start of the N-of-1 trial (1- to a maximum of 4 weeks).

<u>Diet Staging:</u> At the start of the initial diet treatment block (either SCD or modified SCD), participants will gradually transition from their usual diet to their initial diet intervention. For

patients randomized to the SCD, they will restrict their diet to the most easily digestible foods such as broths, fruit juice, ripe, peeled and cooked fruits, squash and carrots, and non-fried lean meat, fish, poultry and eggs for the first 2-3 days. After this initial step, participants will expand their diet to include all remaining SCD approved foods. For patients randomized to the modified SCD, for the first 2-3 days, they will restrict their diet in the same manner as those randomized to the SCD. Then, they will expand their diet to include all remaining SCD approved foods for another 2-3 days before adding the additional foods allowable on the modified SCD. Thus, by 5-7 days into the treatment, participants randomized to start with the modified SCD will have advanced to the full modified SCD diet.

Follow Up contact: Based on standard of care for initiating a new dietary treatment, patients will be evaluated by the dietitian and/or physician or advanced practice care provider (i.e., nurse practitioner or physician's assistant) at 2 ± 1 weeks after starting each new diet. This visit may be completed by phone call, video call or telemedicine visit, per the discretion of the primary GI physician or advanced care provider. If this appointment does not take place in-clinic, it is the site's research staff's responsibility to make sure that the patient's weight is obtained using the same scale at every weigh in and that the patient reports the measured weight to the study staff. Participants will also have a phone or in-person follow-up with either their site's dietitian or the site coordinating center dietitian in each treatment period. The dietitian will evaluate patient weight (on clinic scale at follow up visits and if available by home scale) and nutritional intake. S/he will prescribe SCD compatible nutritional supplements as needed based on review of the diet recall. In addition, at the clinic visits, follow up phone calls or visits, and during any other patient contact, the dietitian will carry out standard of care activities including, but not limited to, evaluating the participant's nutrition and overall health, assessing the participants nutritional and dietary needs, providing diet advice, sharing sample meal plans, developing new meal plans, and sharing recipes from books, online resources, or other personal sources. In the event that the site dietitian is unavailable for follow-up contact, these visits may be conducted by the site coordinating center dietitian via video call (i.e., Zoom, Skype) if permission is granted by the patient's primary GI physician or advanced care provider.

Symptom tracking: Participants will use the Eureka N-of-1 mobile app to execute the N-of-1 protocol, track treatment periods, and track daily and weekly symptoms and disease activity. Participants and their clinician will be able to visualize the tracked data in real-time via the Eureka N-of-1 app and on the web portal. Parents of participants will always track symptoms using the mobile app. Patients ≥14 to 18 years will have the option of tracking for themselves (in addition to their parent). Patients < 14 years will have parents track for them with child input. The questions to assess symptom and disease activity metrics are included in Appendix D. Participants will be asked to start tracking at the baseline visit. Patients will be asked to complete a minimum of 2 weeks of symptom tracking in the baseline period (14 daily measures, 3 weekly measures) and will be asked to continue with tracking once they initiate the N-of-1 Trial via the Eureka app.

Stool Collection: Participants will collect a home-based stool sample for fecal calprotectin analysis and biobanking for future analysis during the baseline period and the end of each treatment period. Stool specimens will be accepted as early as up to 2 weeks before the end of the treatment periods. Active participants will not be able to advance to their next treatment block until stool is collected and sent. If a patient elects to terminate a treatment condition early, they will be asked to submit a stool specimen at that time, prior to changing treatment conditions. Participants who discontinue the study after the first crossover (e.g., completion of baseline, Diet A1, and Diet B1) and terminate the protocol early may advance to the end of the study without additional stool collection. Patient instructions for stool collection are documented in Appendix E. Fecal

calprotectin results will be made available to the clinicians as the results are returned from the lab.

Clinical Evaluations: Participants will be seen for clinic visits as needed throughout the study. Based on standard of care for initiating a new dietary intervention and the fact that patients enrolled in this study have mild or moderate disease activity, close follow up is recommended. Participants will have a follow up visit 8 ± 2 weeks from initiation of the first diet period and then as needed over the remainder of the study, with timing based on each individual center's standard practice and patient need. This pragmatic design allows us to test the use of the N-of-1 methodology for diet intervention as it would be delivered in regular clinical care. Data collected at routine clinic visits is standardized and includes weight, height, current medications, laboratory assessment, and disease activity (PUCAI and SPCDAI). This data is entered in the ICN registry. Assessment of Vitamin D levels is performed per local site standard of care. This data is not collected in the ICN registry. The date and results of all Vitamin D levels collected at regular clinical evaluations will be entered in the REDCap database by the research coordinator or dietician at each site.

Diet Monitoring: Patients will complete a 3-day diet diary at baseline and during each diet period, ideally around the mid-point of that period (approximately 3-5 weeks after transitioning to the new diet). The questions that will be used in the 3-day diet diary are included in Appendix F. The participant will return their completed diet diary to the local center dietitian or research coordinator via email/scan/text/mail. Once received from the patient and verified for completeness, the center dietitian or research coordinator will email the patient's completed 3-day diet diary to the study's central email at CCHMC and it will be triaged to approved research staff at Seattle Children's Hospital all using a secure and IRB-approved email system. The research staff member at Seattle Children's Hospital will enter the data from the 3-day diet diary into a nutrient composition program. Output from the nutrition composition program (e.g., total calories, percent calories from fat, percent calories from carbohydrates, percent calories from protein, micronutrient composition) will be communicated back to the patient's site dietitian (using IRB-approved communication channels) and will be entered into a REDCap database by the research staff at Seattle Children's Hospital or exported electronically and sent to CCHMC. The site dietitian or site coordinating center dietitian (if local dietitian is unavailable) will follow up with the patient via telephone or in-clinic to discuss any issues with the diet, discuss nutritional adequacy of diet, and recommend any adjustment in dietary intake or vitamin supplements. The dietitian will continue to attempt contact until the participant is reached.

Study Completion and N-of-1 Results Review: Following the final treatment period, participants will return to clinic within 4 weeks to complete a standard physical exam including weight, height, medications, and clinical measure of disease activity. They will review the results of their trial via the Eureka N-of-1 platform with their clinician (Appendix G) and will complete a final questionnaire regarding their experience with the N-of-1 trial via tablet, website, Eureka app, or paper. If the final results review is unable to be conducted in person with the study physician, the results can be provided via phone call, video call or telemedicine visit, per the discretion of the primary GI physician or advanced care provider. If the results are provided virtually, the site is still required to schedule an in-person clinician visit to complete a standard physical exam with the participant.

The overall study procedure timeline is summarized in Figure 2.

Figure 2*
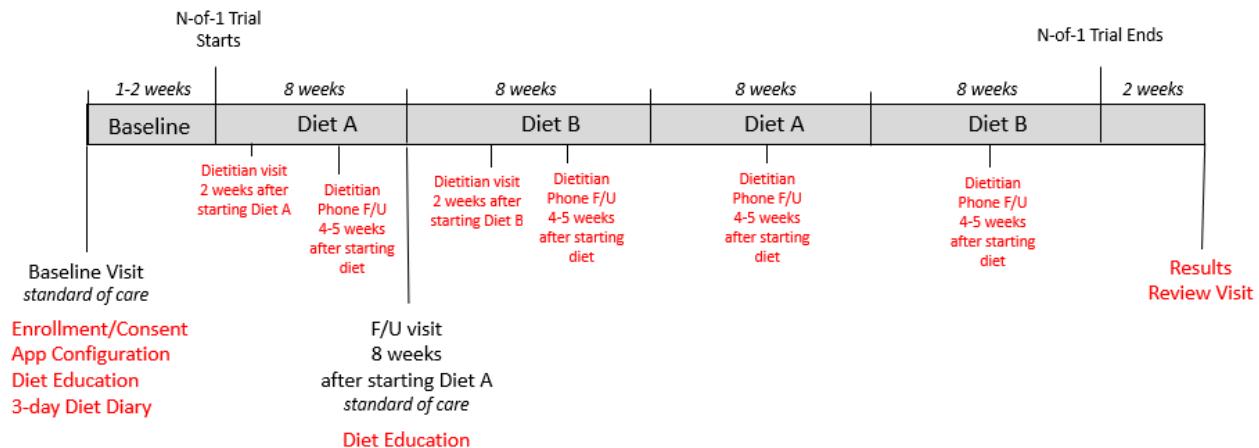
*This figure is an approximate representation of the typical time it would take for a participant to finish the study.

Patients will be supported in their adherence to the diet through a variety of means. Dietitian/physician or advanced practice provider involvement and follow-up (as described above) is a key component to providing supportive coaching for patients and families. In addition, resources, including print and web-based materials (Appendix B), will be made available for patients to support them in learning about the diet, provide ideas for meal planning, offer approaches for teaching other family members and friends about the SCD, handling family gatherings and special occasions, etc.[16]

Outcome Measures

Study outcomes and mediating factors are detailed in Table 1. *Primary outcomes* across all patients will include patient reported outcomes (PROs) of stool frequency, stool consistency, pain interference and GI symptom severity (see Appendix D), and fecal calprotectin. *Secondary outcomes* will include patient-reported disease activity scores as measured by the   Pediatric Ulcerative Colitis Activity Index (PUCAI)[17,18] and Short Crohn's Disease Activity Index (SCDAI)[19], clinically-evaluated disease activity scores contained in ICN   registry (PUCAI and sPCDAI), growth, laboratory markers of inflammation and disease status [C Reactive Protein (CRP), Hematocrit, Erythrocyte Sedimentation Rate (ESR), Albumin]. Fecal calprotectin was selected as the central marker of intestinal inflammation because it correlates well with both clinical and histologic remission, is noninvasive and objective, and has been shown to be a useful tool to monitor response to therapy[20,21]. *Safety Outcomes:* The major safety concerns for patients with IBD participating in a diet intervention include weight loss and inadequate nutrition. Weight loss typically occurs within the first few weeks of starting the diet. Weight will be assessed at all clinic visits and at the dietitian follow up visits (weeks 4 and 12) and by weekly weights entered in the Eureka app if there is a home scale available. If a home scale is available, patients will be instructed to obtain an initial weight on their home scale at the beginning of the baseline period and use the same home weighing scale throughout the study period. Nutrition intake will be monitored by the dietitian regularly for all enrolled patients and will be assessed via 3-day diet diaries conducted at specified intervals (baseline and in weeks 3-5 of each treatment period) and weekly weight tracking (if available). In addition, we will collect results of any serum Vitamin D level monitoring conducted as part of routine care and will report these results to the DSMB. *Mediating factors:* We will collect demographic data from the ICN registry including age, gender,

race, ethnicity, family education level, disease type, disease location, medications, and disease characteristics at baseline. Dietitians will use data from 3-day diet diaries to assess deviation from the prescribed diet (Appendix F). We will also measure the patient and parent psychological well-being and expectations regarding benefit of diet as a treatment strategy as these may mediate adherence to the diets.

If a measure is missing in any of the sources listed below, we will obtain the data using other sources which could include secured email correspondence with the site and/or screening and eligibility verification case report forms. The screening and eligibility verification case report form is a non-patient facing tool currently used by the site coordinator to verify participant eligibility. This form is uploaded to OneDrive so that the site coordinating center can confirm eligibility; thus, it is data the site coordinating center already routinely receives.

Table 1: Outcome Measures

Construct	Measure(s)	Timing	Source
OUTCOMES			
Stool Frequency	Single integer count	Daily	N-of-1 App
Stool Consistency	Bristol Stool Scale[20]	Daily	N-of-1 App
Pain Interference	PROMIS® Pain Interference[22]	Weekly	N-of-1 App
IBD Severity	PROMIS® Gastrointestinal (GI) Symptoms*	Weekly	N-of-1 App
Growth	Weight[+]	Weekly	N-of-1 App
Self-Report Disease Activity	Pediatric Ulcerative Colitis Activity Index (PUCAI)[17,18] Short Crohn's Disease Activity Index (sCDAI)[19]	Weekly	N-of-1 App
Intestinal Inflammation	FecalCalprotectin	Baseline and at the end of each treatment period	Lab
Disease Activity	sPCDAI[23], PUCAI[18]	Sporadic, Clinic Visits	Registry
MEDIATORS			
Psychological Well-being (Parent)	PROMIS® Anxiety PROMIS® Depression	Baseline	Web-survey or N-of-1 App
Psychological Well-being(Child)	PROMIS® Anxiety PROMIS® Depression	Baseline	Web-survey or N-of-1 App
Expectations of Benefit	Treatment expectations and preferences (adapted from published study)[24,25]	Baseline	Web-survey or N-of-1 App

*Measure was validated in a sample of 1,007 children and youth in ICN ages 8-24. The scale exhibits acceptable internal consistency with a with a Cronbach's alpha of 0.74. The measure is highly responsive to differences in clinical status as assessed by both the patient and their physician/advanced practice care provider using validated measures and produces reliable estimates of GI symptom T-Scores ranging from 45 to 80.
[+]Optional, only if home scale available

3.5   Participant Selection and Withdrawal

From ICN, we will recruit up to 60 patients with IBD and their families (primary caregivers) whose treatment decisions may be informed by the results of this study as determined by their GI care team. We will not exclude patients based on sex or race/ethnicity. We intend to enroll evenly across ICN centers, but will allow for fewer or more participants per site based on numbers of eligible patients and success with recruitment.

3.5.1   Inclusion Criteria

- Diagnosis of CD or UC or Indeterminate colitis (IC)
- Age 7-18 years
- Enrolled in the ImproveCareNow ICN2 registry; and

- Evidence of acute inflammation and/or elevated acute phase reactant as measured by Fecal calprotectin 1.5 times the upper limit of normal, Lactoferrin 1.5 times the upper limit of normal, CRP 1.15 times the upper limit of normal, or ESR 1.15 times the upper limit of normal (based on local reference ranges) obtained within 8 weeks of enrollment.
    - Potential participants who are close to meeting one of the acute inflammation and/or elevated acute phase reactant markers and who meet all other study criteria will be considered for study participation on a case by case basis by the investigative study team in consultation with the patient's primary gastroenterologist.

3.5.2 Exclusion Criteria

Complex and Unstable IBD:
- Currently or within the past 9 months has had an abscess, fistula, stricturing CD, or ostomy
- Ever had history of full colectomy
- Severe disease activity as measured by a short Pediatric Crohn's Disease Activity Index (SPCDAI) score of >45 or Pediatric Ulcerative Colitis Activity Index (PUCAI) score of >60 assessed within 3 weeks of enrollment
- Hospitalization or surgery planned within 3 months
- Ongoing active gastrointestinal infection
- Severe Malnutrition (BMI less than 5th percentile)
- Recent medication changes including:
    - Thiopurines, natalizumab, or methotrexate started within 8 weeks prior to enrollment
    - Anti TNF (infliximab, adalimumab) started within 8 weeks prior to enrollment
    - Vedolizumab started within 16 weeks prior to enrollment
    - Increase in corticosteroids within 4 weeks of enrollment or have dose >20 mg prednisone or equivalent

Evidence of Other Complicating Medical Issues:
- Other serious medical conditions, such as neurological, liver, kidney, or systemic disease
- Serious psychological or psychiatric conditions such as eating disorders or self-harm
- Pregnancy
- Tobacco, alcohol, or illicit drug abuse

Inability to Complete the Protocol
- Non-English speaking participants will be excluded because the mobile app only supports English speakers. The study timeline and funding prohibits development of a bi-lingual app.
- On SCD or modified SCD anytime within 8 weeks of enrollment
    - If an otherwise eligible patient is on SCD or modified SCD within 8 weeks of enrollment but they are noncompliant per the determination of the patient's dietitian/primary gastroenterologist, then this patient is eligible to participant in the study.

- Participants on a vegan diet will be excluded as the added restrictions of the SCD (on top of a vegan diet) would not provide these participants with the essential nutrients needed for a healthy diet
- Lack of smart phone and data plan for participating caregiver
- Participating in another interventional study

3.5.3 Participant Pre-screening and Recruitment

We will recruit patients from participating ICN clinical sites. To introduce the study and provide information about dietary management for IBD/SCD, participating ICN clinics will mail a study flyer (Appendix J) to clinic patients prior to their upcoming appointment, call them by phone, and/or approach them at their clinic visit. Additionally, the study flyer will be available on various social media platforms. There will also be a study poster available for participating ICN clinics for use in advertising the study to potential participants (Appendix O). For those families who may be interested in a parent perspective of the SCD diet, a letter from our parent partners will be available (see Appendix P). Potential participants will also be informed about the study opportunity via several established channels within the ICN network, including monthly newsletters and blogs. In addition, we hope to make a short, animated video that will be used to recruit patients. The script for the video is attached as an Appendix B. As with our other patient-facing materials, since the study is pragmatic and minimal risk, we request to use this script as a template. It may have minor edits to the script which would not require IRB approval. Eligible participants will be identified through the standardized ICN pre-visit planning process. The site principal investigator will verify eligibility at the clinic visit. Study participants will enroll in the trial with their clinical team at a regularly scheduled clinic visit or at another visit within 2 weeks of a regularly scheduled visit if more convenient for the participant. Local clinic research coordinators will maintain a screening log in REDCap to track those that are screened, those who are excluded (and for what reasons), those that decline, and those who have enrolled. Most ICN clinic sites have obtained HIPAA waivers that allow study coordinators to identify potential study participants, evaluate patients for study eligibility at pre-visit planning meetings, and discuss participation in studies prior to consent being signed. For those who decide to participate, informed consent (and assent where applicable) will be obtained prior to initiation of study procedures.

3.5.4 Early Withdrawal of Participants

If a patient experiences symptom flare, leading to either the diet intervention being stopped, medication being changed, or the need for surgical intervention, their participation in the N-of-1 protocol will be discontinued. In addition, patients who become pregnant during the study will be automatically withdrawn, as will patients that have ≥ 7.5% nonintentional weight loss. Patients may also withdraw if they feel that they are unable or unwilling to continue the assigned diet or data collection. Participants will be dropped from the study if they have a symptom tracking response rate of <50% in the baseline period that does not improve after reasonable attempts by research coordinators (as outlined in the study SOPs) to assist participants in improving data collection. Because completion of stool fecal calprotectin is required to advance from one treatment period to another, a participant who never collects and sends in a stool specimen will be dropped at that point in the study. All data from such participants will be retained and analyzed. Patients who wish to terminate a treatment period early (and switch to the next assigned treatment) will not be considered withdrawals. Participants who wish to end their study participation early, but have completed at least two full diet treatment periods (i.e., A1 and B1), will have the option to discontinue participation and terminate the protocol early. Participants who choose to discontinue from the study in these instances will schedule a time to come into clinic to

receive their final study results and complete the end of survey questionnaire regarding their N-of-1 experience. These participants will not be considered withdrawals.

3.5.5   Duration of Participation

Full participation in the study will last a minimum of 34 weeks from the baseline visit to the completion of the N-of-1 trial. Participation may last more than 34 weeks if a family experiences delays at any phase of the study.

3.6   Statistical Plan

3.6.1   Sample Size Determination

The primary goal of Aim 1 is to determine effectiveness of the SCD vs. modified SCD vs. usual diet for an *individual* patient. Because the focus is on the immediate decision of which treatment to select, or if the treatments were different than the patient's usual diet, it is not necessary to protect against a false-positive decision as in standard hypothesis tests used in clinical trials; thus sample size calculations are not recommended for individual N-of-1 trials[26]. For obtaining an estimate of the population average effects of the SCD vs. modified SCD on improving symptoms, a total of up to 60 patients will participate in the two- treatment crossover study. Using the weekly PROMIS pain interference T-score measure (standardized mean of 50 and standard deviation of 10) and incorporating aspects of the design related to the number of planned crossovers, washout periods, and autocorrelation from repeated measures, we will have 90% power with a two-sided 5% alpha to detect a mean difference of 3 points between groups which corresponds to the minimally important difference on the PROMIS measures, except in the case when $\sigma_t = 5$ and $\rho > 0.5$ when the minimal detectable difference is above 3 to obtain 90% (but not 80% power).

3.6.2   Statistical Methods

An overview of the statistical analysis can be found below. A formal data and statistical analysis plan will be prepared as a separate document

Analysis of Individual N-of-1 Trials: For the first treatment period only, there will be a 1-week run-in period as the participant gradually transitions from their usual diet to the intervention diet. A gradual transition is not needed beyond the first treatment period. For the first period, we will discard the first 7 days of data including the first weekly measurement. Based on clinical experience we expect that diet effects on symptoms wash out by 1 week. Thus, for all subsequent treatment periods we will discard the first 7 days of data including the first weekly measure during each treatment period. At the end of each person's N-of-1 trial, statistical analysis will be performed to compare results on the two treatments. Each N-of-1 trial requires a separate analysis which is automated to run in the background once each trial is completed. The analysis consists of running Bayesian models that compare the average response on each of the two treatments and baseline diet. Models will incorporate the appropriate scales for the outcomes (e.g. normal distributions for continuous variables, multinomial distributions for categorical variables) and the appropriate representation of the function linking the expected outcome to the predictors (e.g., cumulative logit link for ordinal outcomes).

Results will be reported for all study measures (stool frequency, stool consistency, PROMIS Pain interference, PROMIS GI Symptoms, fecal calprotectin) to enable patients to weigh symptoms that are most important to them. For each outcome, each patient will be provided with an estimate

of the (1) difference in efficacy between the two diets; and (2) probability that each treatment is better than the other; as well as the (3) difference in efficacy between each diet and the baseline level; and (4) probability that each treatment is better than the baseline. Results will be portrayed numerically and graphically. We will develop educational materials to aid patients and clinicians in interpretation (Appendix B). Posterior probabilities of outcomes will be calculated using an interface that incorporates open-source R software interfacing through Rjags with open-source JAGS software.[27] The R code creates the Bayesian model, loads the stored data and chooses intelligent starting values that are then fed into JAGS to return the Markov chain Monte Carlo (MCMC) simulations of the joint posterior distribution. The R package will accept input from the Eureka platform to construct models and return results back to Eureka for display.

Statistical analyses will be completed and patients will be given results of their individual N-of-1 studies if they complete at least one paired treatment period and there is enough data in both treatment periods to perform valid statistical analysis.

Meta-Analysis of N-of-1 Trials: The collection of individual N-of-1 trials can be thought of as a set of studies whose results can be combined as in a meta-analysis. The data can be considered as a multilevel structure in which a set of patients is studied with each patient having a set of measurements. Standard multilevel mixed model methods will be used to estimate the average effect and variance within and across patients. Across patient values estimate the average effect in the population of patients studied, while the within-patient estimates describe an improved estimate of each patient's true effect assuming exchangeability across patients. We will fit these models using a Bayesian multilevel model with non-informative priors in order to obtain posterior distributions of the within and between effect sizes. We will then compare the multilevel patient estimates with those from the patient's data alone in order to determine how much the effects change and how much additional precision these estimates gain. We will also include between-patient covariates to account for variability and to test for heterogeneity of treatment effects (HTE). We hypothesize that HTE may exist based on age, sex, disease (CD or UC/IC), disease activity (mild or moderate), maintenance medication use, disease location, and disease type (inflammatory or penetrating). The model will include the baseline levels of the outcomes which will enable estimates of the effect of the study diets relative to the unrestricted diet. We will also fit models that adjust for trends over time and account for correlation and carryover. Analyses will use the appropriate probability distribution and link function for the outcome variable type (e.g. normal distributions for continuous outcomes and ordinal logistic regression with a cumulative logit link for scales).

Missing data: Based on our experience, the overall completion rates of daily symptom trackers and weekly surveys by ICN patients and parents is >80%, we have found that when participants are working on a specific test or personal experiment with their physician, adherence increases to >90%. In cases of missing outcome data, we will ignore the missing values in the analysis of individual N-of-1 trials which is equivalent to treating them as being missed at random since the analysis is not adjusted for covariates. In the meta-analysis, we will explore the association of missingness with observed variables and condition analyses on these variables as appropriate. We will also explore treating the missing observations as latent parameters and estimate them as part of the Bayesian model assuming them to be missing at random. If patients decide to stop a treatment before 8 weeks, we will analyze the data available. Since effect modifiers in the meta-analysis are collected at the patient level, we expect them to be completely collected (e.g., there will not be a need for a statistical approach to address missing data for these variables). In the meta-analysis, we will perform the following sensitivity analyses for different types of missing data:

(1) analysis of all available data; (2) analysis excluding patients who withdrew early from the trial; (3) analysis of patients who completed the entire protocol, i.e. excluding those who withdrew early and those who terminated any treatment periods early.

3.7   Safety and Adverse Events (AE)

3.7.1   AEs

Clinical adverse events (AEs) will be monitored throughout the study. Since the study procedures are not greater than minimal risk, significant AEs are not expected. Potential AE's could include allergic reaction to a component of the diet, significant intolerance of the diet other than as an allergic reaction, and/or unintentional weight loss of ≥ 5%.

Expected adverse events include:
- Mild to moderate increase in abdominal pain, diarrhea, gas/bloating within the first 3-4 weeks of starting the new diet
- Weight loss of less than 5% in the first 3-4 weeks of starting the new diet
- Worsening of IBD due to failure of the diet to improve the disease. This could be manifested as new onset or worsened, bloody stools, diarrhea, abdominal pain, fistula, abscess, or bowel obstruction
- Hospitalization or surgery due to failure of the diet to improve the disease

Serious adverse events are not expected. However, if an SAE occurs and is determined to be possibly or definitely related to study treatment, it will be reported in accordance with CCHMC's IRB SOPs (as described in Section 3.7.2).

3.7.2   Adverse Event Reporting

As the study is being conducted with the engagement of the participant's clinical team/gastroenterologist, the medical team will seek information on AE's as a part of regular contact with the participant (any patient or clinician initiated phone call or email, or at scheduled clinical visits). The Investigator is responsible for recording and reporting anticipated and unanticipated problems related to research that occur during and after study treatment. All AE's will be reported to the data coordinating center at CCHMC, including relationship of the AE to the study procedures (definitely related, possibly related, unlikely related, or not related). AE's that are unexpected (not included in list of expected adverse events in Section 3.7.1) and are deemed by the site PI as either possibly or definitely related to the intervention will be summarized in narrative or other format and submitted to the IRB at the time of continuing review. All SAEs (CCHMC or relying sites) deemed possibly or definitely related to the intervention will be reported to the IRB in accordance with CCHMC IRB policies. Since the study procedures are not greater than minimal risk, SAEs are not expected. If any unanticipated problems related to the research, involving risks to participants or others, happen during this study (including SAEs), these will be reported to the IRB in accordance with CCHMC IRB SOPs

3.7.3   Investigator reporting

Investigators are responsible for safety reporting to the central and/ or local IRBs. Investigators are responsible for complying with the central and/or local IRB's reporting requirements, though must submit the required reports no later than 10 working days. Copies of each report and documentation of IRB notification and receipt will be kept in the investigator's study file.

3.7.4 Sponsor reporting

The study sponsor will notify all participating investigators, as well as the central IRB, of relevant DSMB safety reports as described in section 6.2.3.

3.7.5 Data and Safety Monitoring Plan

A DSMB will regularly review interim data to monitor safety. The DSMB has overall responsibility for interpreting data on adverse events. Committee members are independent experts chosen on the basis of their expertise and scientific rigor. The Committee has the responsibility to review the research protocol and to evaluate the progress of the trial overall and at each participating clinical center. This includes accrual, data quality and completeness, episodes of hospitalization, and protocol violations. Serious unexpected events will be disclosed to the committee between meetings. The Committee will begin its work on this trial by identifying key data points that will be monitored at each of the interim meetings. The DSMB will work closely with the investigators and biostatistician. Following each meeting, its chair will prepare a report on the questions raised by Committee members and monitoring recommendations. This report will be distributed confidentially to meeting participants. The Committee also will prepare a redacted summary of this report, focusing on safety issues, for distribution to clinical site co-investigators and their IRBs. Finally, the DSMB will make recommendations to the ICN study leadership team regarding actions to ensure that participants are not exposed to undue risks. The DSMB Charter is provided in Appendix M.

3.8 Data Handling and Record Keeping

3.8.1 Confidentiality

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

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

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

3.8.2 ICN Registry

In 2007, ICN established a standardized, web-based clinical registry that enabled collection of standardized, IBD-specific data about processes and outcomes of care (e.g., disease characteristics, patient well-being, laboratory results, and medications). In 2010, with AHRQ funding, ICN developed a modular, open-source, registry that can be linked to an electronic health record (EHR) to minimize the burden of manual data entry. This allows for a significant portion of registry data to be transferred electronically via a secure web portal to the registry, and stored for re-use in QI, chronic care delivery, and comparative effectiveness research.

Data captured through EHR-linkage or web-based forms consist of discrete elements that conform to a standardized data model. As previously described, this study will use data on demographics, baseline characteristics, and changes to disease activity/inflammation and medications as collected from the ICN Registry.

3.8.3   Study REDCap Database

The study will utilize a REDCap database for data collection. The REDCap database will be designed and housed at CCHMC on a secure server. Access to the database will be limited to members of the research team at each site. Each team member will have an individual login ID and password. Data on screening and enrollment (including patient name linked to study ID), nutritional assessments (including Vitamin D levels obtained as part of routine care), and AE reporting will be collected at the ICN site by the local study coordinator, dietitian, and/or central research coordinator at Seattle Children's Hospital (for nutritional assessments only) and will be entered into the REDCap database.

3.8.4   Source Documents

Source data is all information, original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the research. Source data are contained in source documents. Examples of these original documents and data records include: Eureka N-of-1 app and database, the ImproveCareNow registry, clinical and office charts, memoranda, participants' diaries (including 3-day food diary), output from the nutrition analysis program, recorded data from automated instruments, patient reported data recorded in the N-of-1 app, electronic case report forms, and records kept at laboratories and at medico-technical departments involved in the study.

3.8.5   Patient Surveys and Questionnaires

Surveys and questionnaires to collect patient reported outcomes data (as described in Table 1) will be administered through the Eureka N-of-1 app, weblink, or paper/pencil as previously described. Symptom tracker and PRO questions that will be administered through the Eureka app are documented in Appendix D. The surveys to assess experience with the N-of-1 app are provided in Appendix H. The questions to assess baseline expectations are provided in Appendix C.

3.8.6   Records Retention

The investigator must retain all study records and source documents for the maximum period required by their institution or as required by local and national governing regulations, whichever is longer. Study records include consent forms and source documentation. The investigator must contact the sponsor prior to destroying any records associated with the study.

3.9   Data Security for Eureka Technology Platform

Data on patient symptoms and PRO's will be collected via the Eureka platform. The Eureka mHealth Research Platform Resource is a mobilized cohort and infrastructure used to carry out clinical research studies using mobile and digital technology. Patients will submit their data via SMS text messages, via mobile applications, via secure websites, or will upload their data from other services they may authorize. Simple, non-PHI carrying messages are sent by the system, and typically unidentifiable numeric responses are returned. The only PHI involved in the

transaction is the phone number or unique ID used to identify the patient's phone. This data is then stored on the study platform as previously described.

Eureka will support a registration procedure that will allow registration with identifying information that will generally include name, date of birth, and mobile phone number or email address. Eureka also provides investigators with the option of requiring confirmation of mobile phone numbers and email addresses.   In registering for our study, the Eureka Privacy Policy and Data Security Measures will be presented to participants (Appendix N).

3.9.1   Eureka Risks:

The risk of loss of privacy in our study hosted by the Eureka Research Platform will be present for all persons participating. Loss of privacy could occur by compromise of the Eureka technical system or if Eureka is required by law to disclose data to authorities, e.g. to prevent serious harm to the participant or others. This is the primary reason for the Eureka Privacy Policy and Data Security Measures (attached document).

3.9.2   Eureka Efforts to Minimize Risk:

To minimize risk of loss of privacy, Eureka takes the following steps:

Technical system security: Information will be transmitted and stored using state-of-the-art security systems similar to those that protect websites used by banks and electronic health record systems. Specifically, the Eureka Platform is hosted on Amazon Web Services (AWS), a cloud-based server system and computing services that are HIPAA compliant, and Eureka follows security guidelines of the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). Specifically, all research data are stored behind a secure firewall, guarded by intrusion detection software, and encrypted at rest and in transit in our Amazon Virtual Private Cloud.

Inform patients: As described above, we will include the Eureka Privacy Policy and Data Security Measures that will be referenced in study onboarding and viewable at any time. The statement will inform patients of the risks of loss of privacy, including via technical compromise or legal requirements. We will also make them aware that they are responsible for keeping their login credentials secure.

3.9.3   Confidentiality Measures:

Identifying information (name and email address) will be stored in separate (but linked) data tables so that health-related data can be viewed by approved staff as needed without inadvertent association with identifiers when such linkage is not required.

In the event of a data break, the Eureka Research Platform Team will notify all Study Teams and Study Participants in accordance with UCSF guidelines.

3.9.4   Data Storage & Security:

Data is stored on Amazon Web Services (AWS or Amazon Cloud). AWS is FEDRAMP compliant and has an Authorization to Operate from the Department of Health and Human Services. The security controls in place meet or exceed HIPAA compliance. Data are coded; data key is kept

separately and securely. Electronic data are protected with a password. Data are stored on a secure network

3.10 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 50, part 56 and ICH guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a centralized, properly constituted independent Ethics Committee (EC) or IRB, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The sponsor and investigator will maintain a list of the central EC/IRB members and their affiliates in their files.

All participants (and/or the participant's legally authorized representative) for this study will be provided a consent form describing this study and providing sufficient information for participants (and/or their legally authorized representative) to make an informed decision about their participation in this study. The sponsor will provide the investigator with appropriate sample informed consent forms. These consent forms will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a participant (and/or the participant's legally authorized representative), using the EC/IRB-approved consent form, must be obtained before that participant undergoes any study procedure. The consent form must be signed by the participant (and/or the legally authorized representative), and the investigator-designated research professional obtaining the consent.

All participants enrolled as children and who turn 18 during the study will be consented as adults at the earliest opportunity (but no later than 6 months after reaching age of consent). The same process will be followed if parents/patients need to be re-consented during the study for any other reason (i.e. new information becomes available).
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3.10.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned study specific conflict management plan that has been reviewed and approved by the IRB providing oversight for that investigator prior to participation in this study. This information shall also be made available to the study sponsor upon request or as required under any separately executed agreement between the sponsor and study site.

3.10.2 Participant Stipends or Payments

Patients participating in the study will be given incentives for continued participation. They will receive a $25 gift card when they have returned their stool samples at the end of the first three diet treatment phases and when they return to review results with their provider following the fourth and final diet treatment phase. If a participant completes the entire study s/he will have received a total incentive of $100. In addition, participants will receive a *Nutrition in Immune*

Balance (NiMBAL) Therapy: Using Diet to Treat Inflammatory Bowel Disease book at the start of the study as a resource to help them with the diet.

5   Study Finances

5.1   Funding Source

This research study is partially funded through a Patient- Centered Outcomes Research Institute (PCORI) Award (PCS-1406-18643). The Patient-Centered Outcomes Research Institute (PCORI) is an independent, nonprofit organization authorized by Congress in 2010. Its mission is to fund research that will provide patients, their caregivers, and clinicians with the evidence-based information needed to make better-informed healthcare decisions. PCORI is committed to continually seeking input from a broad range of stakeholders to guide its work.

6   Publication Plan

Dissemination of study results is an essential component of this research project. Regardless of the outcome of the trial, we submit study findings to high-impact, peer-reviewed journals and present results in the form of abstracts at scientific meetings. We will also make our research findings publically available on the ICN and PCORI websites, including lay summaries of relevant findings.

7   References

1.   Prevention CfDCa. Inflammatory bowel disease (IBD). http://www.cdc.gov/ibd/. Accessed February 28, 2013.
2.   Kappelman MD, Rifas-Shiman SL, Kleinman K, et al. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. *Clin Gastroenterol Hepatol.* 2007;5(12):1424-1429.
3.   Mackner LM, Sisson DP, Crandall WV. Review: psychosocial issues in pediatric inflammatory bowel disease. *J Pediatr Psychol.* 2004;29(4):243-257.
4.   Debruyn JC, Soon IS, Hubbard J, Wrobel I, Panaccione R, Kaplan GG. Nationwide temporal trends in incidence of hospitalization and surgical intestinal resection in pediatric inflammatory bowel diseases in the United States from 1997 to 2009. *Inflamm Bowel Dis.* 2013;19(11):2423-2432.
5.   Marcus SB, Strople JA, Neighbors K, et al. Fatigue and health-related quality of life in pediatric inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2009;7(5):554-561.
6.   Minderhoud IM, Oldenburg B, van Dam PS, van Berge Henegouwen GP. High prevalence of fatigue in quiescent inflammatory bowel disease is not related to adrenocortical insufficiency. *Am J Gastroenterol.* 2003;98(5):1088-1093.
7.   Wolters FL, Russel MG, Stockbrugger RW. Systematic review: has disease outcome in Crohn's disease changed during the last four decades? *Aliment Pharmacol Ther.* 2004;20(5):483-496.
8.   Mallon DP, Suskind DL. Nutrition in pediatric inflammatory bowel disease. *Nutr Clin Pract.* 2010;25(4):335-339.
9.   Lee D, Albenberg L, Compher C, et al. Diet in the pathogenesis and treatment of inflammatory bowel diseases. *Gastroenterology.* 2015;148(6):1087-1106.
10.   Suskind DL, Wahbeh G, Gregory N, Vendettuoli H, Christie D. Nutritional therapy in pediatric Crohn disease: the specific carbohydrate diet. *J Pediatr Gastroenterol Nutr.* 2014;58(1):87-91.
11.   Wong AP, Clark AL, Garnett EA, et al. Use of complementary medicine in pediatric patients with inflammatory bowel disease: results from a multicenter survey. *J Pediatr Gastroenterol Nutr.* 2009;48(1):55-60.

12.   Breaking the Vicious Cycle: Intestinal Health Through Diet with the Specific Carbhydrate DietTM. http://www.breakingtheviciouscycle.info. Accessed July 10, 2015.

13.   Cohen SA, Gold BD, Oliva S, et al. Clinical and mucosal improvement with specific carbohydrate diet in pediatric Crohn disease. *J Pediatr Gastroenterol Nutr.* 2014;59(4):516-521.

14.   Alliance JL. The James Lind Alliance Guidebook. http://www.jlaguidebook.org. Accessed July 17, 2015.

15.   Crandall W, Kappelman MD, Colletti RB, et al. ImproveCareNow: The development of a pediatric inflammatory bowel disease improvement network. *Inflamm Bowel Dis.* 2011;17(1):450-457.

16.   Nutrition in Immune Balance (NIMBAL): Using Diet to Treat Inflammatory Bowel Disease. https://www.nimbal.org/. Accessed January 9, 2017. Accessed 01/09/2017.

17.   Lee JJ, Colman RJ, Mitchell PD, Atmadja ML, Bousvaros A, Lightdale JR. Agreement between patient- and physician-completed Pediatric Ulcerative Colitis Activity Index scores. *J Pediatr Gastroenterol Nutr.* 2011;52(6):708-713.

18.   Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. *Gastroenterology.* 2007;133(2):423-432.

19.   Thia K, Faubion WA, Jr., Loftus EV, Jr., Persson T, Persson A, Sandborn WJ. Short CDAI: development and validation of a shortened and simplified Crohn's disease activity index. *Inflamm Bowel Dis.* 2011;17(1):105-111.

20.   Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol.* 1997;32(9):920-924.

21.   Wright EK, Kamm MA, De Cruz P, et al. Measurement of fecal calprotectin improves monitoring and detection of recurrence of Crohn's disease after surgery. *Gastroenterology.* 2015;148(5):938-947 e931.

22.   PROMIS. PROMIS: Dynamic tools to measure health outcomes from the patient perspective. http://www.nihpromis.org/default. Accessed November 14, 2011.

23.   Kappelman MD, Crandall WV, Colletti RB, et al. Short pediatric Crohn's disease activity index for quality improvement and observational research. *Inflamm Bowel Dis.* 2011;17(1):112-117.

24.   Kalauokalani D, Cherkin DC, Sherman KJ, Koepsell TD, Deyo RA. Lessons from a trial of acupuncture and massage for low back pain: patient expectations and treatment effects. *Spine (Phila Pa 1976).* 2001;26(13):1418-1424.

25.   Sherman KJ, Cherkin DC, Ichikawa L, et al. Treatment expectations and preferences as predictors of outcome of acupuncture for chronic back pain. *Spine (Phila Pa 1976).* 2010;35(15):1471-1477.

26.   Kravitz RL, Duan N, eds. *and the DEcIDE Methods Center N-of-1 Guidance Panel (Duan N, Eslick I, Gabler NB, Kaplan HC, Kravitz RL, Larson EB, Pace WD, Schmid CH, Sim I, Vohra S). Design and Implementation of N-of-1 Trials: A User's Guide. AHRQ Publication No. 13(14)-EHC122-EF. www.effectivehealthcare.ahrq.gov/N-of-1-Trials.cfm.* Rockville, MD: Agency for Healthcare Research and Quality; 2014.

27.   Plummer M. JAGS: a program for analysis of Bayesian graphical models using Gibbs sampling. *Proceedings of the 3rd International Workshop on Distributed Statistical Computing (DSC 2003) March 20-22, Vienna, Austria ISSN 1609–395X.* 2003.

8   Appendices

Appendix A: Eureka Screenshots
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Appendix A: Sample Eureka Screenshots
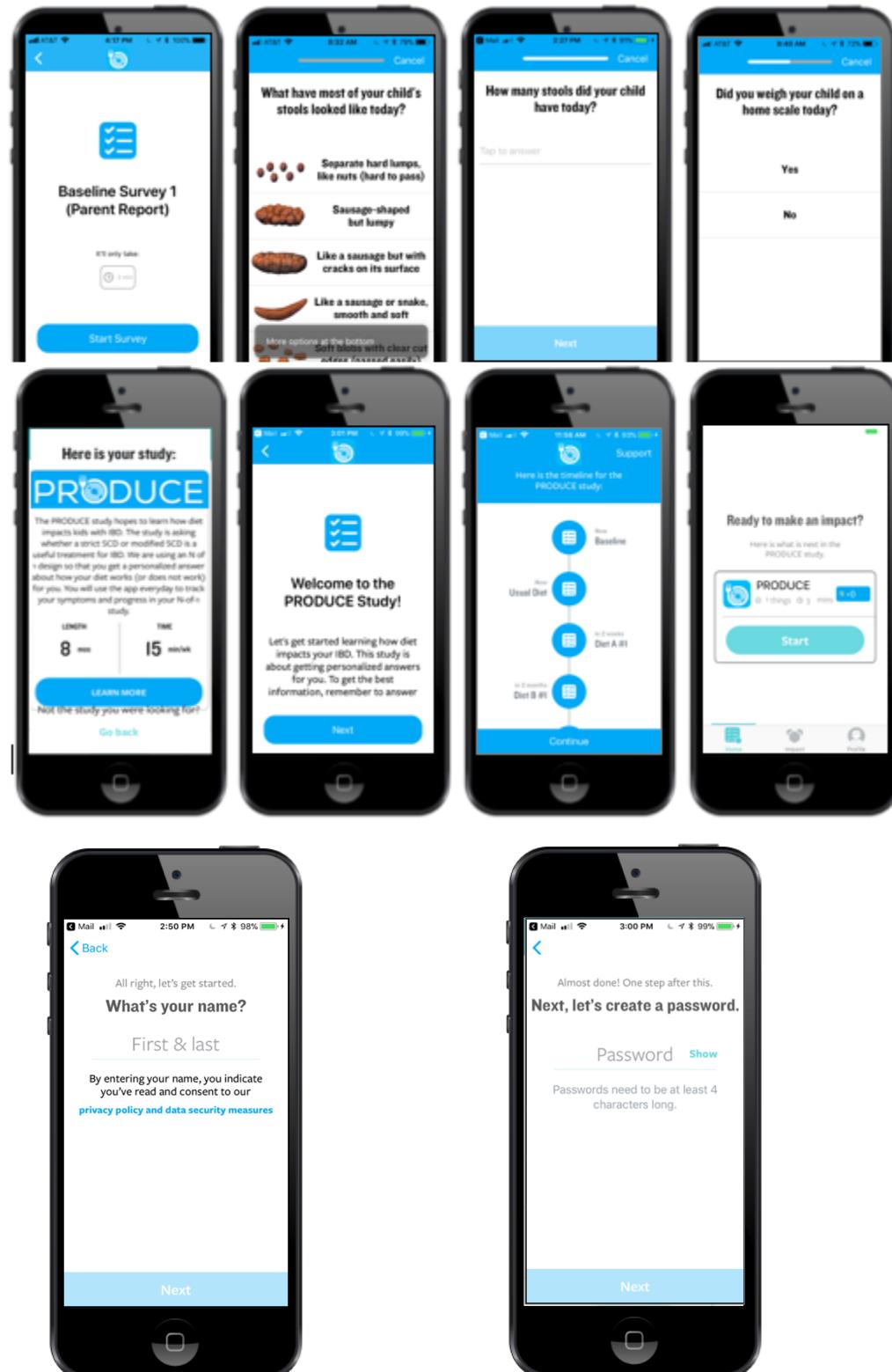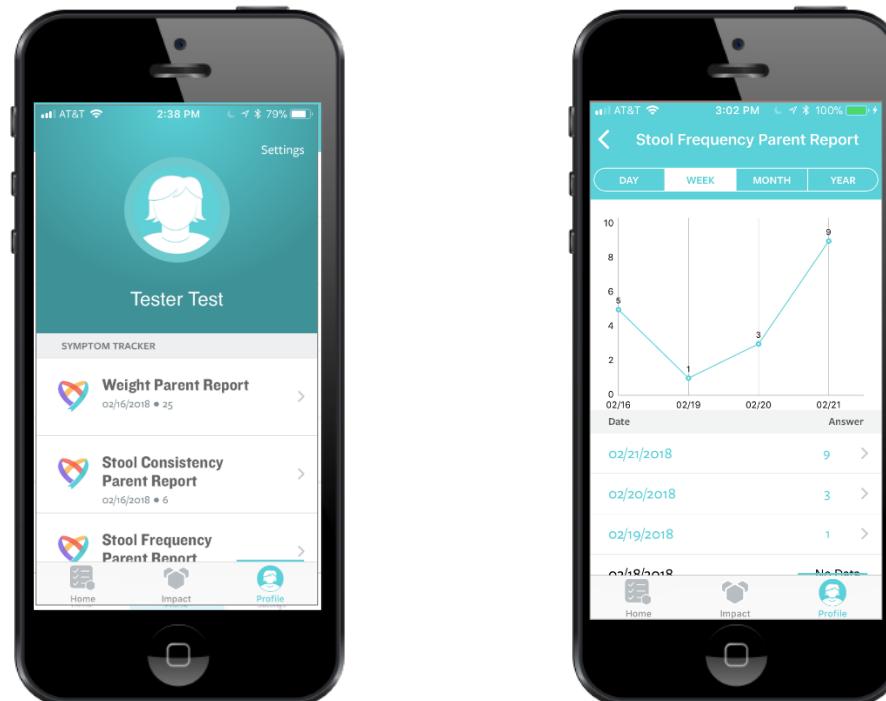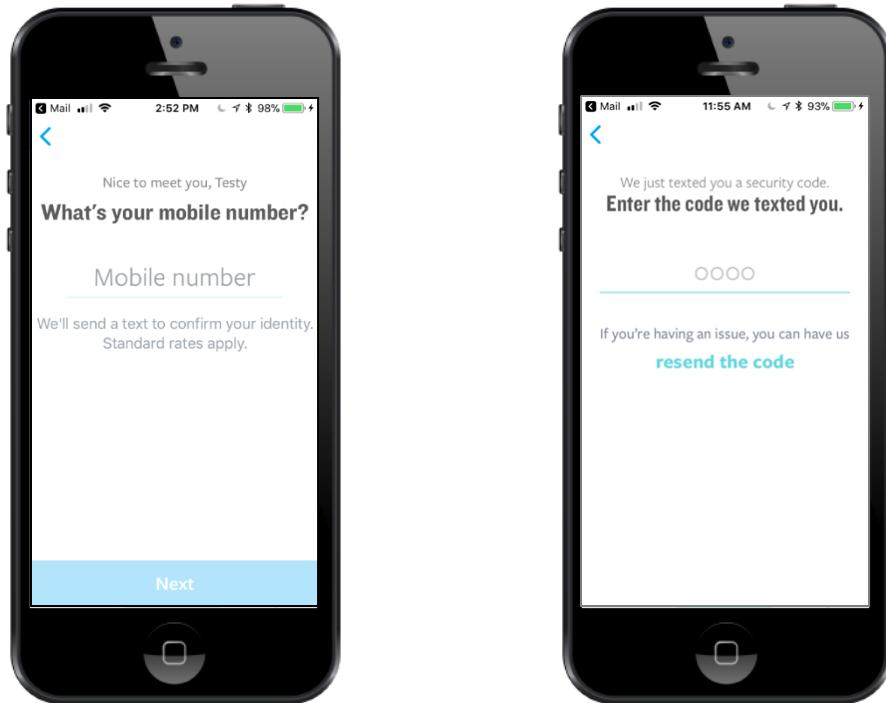
Appendix B: Patient Facing Materials*

See Separate documents

*All patient materials will be publicly hosted on the general NiMBAL website (www.nimbal.org) and on a study-specific section of the website (www.nimbal.org/education/produce-study). Educational materials of broader interest are housed on the general NiMBAL website (e.g., recipes, cookbook resources, educational lectures about the SCD, etc.). Materials directly relevant to the study will be hosted on the study-specific section of the website (e.g., study flyer, study information, lists of approved food for the study SCD and modified SCD diets, etc.). We are also hoping to make a video to recruit the patients. A script for the video is attached as an Appendix as well.

As this study is pragmatic and minimal risk, we request to use these patient-facing materials as templates. These materials may have minor edits to the layout/design and content (e.g., addition/removal of food brands due to changes in ingredients that no longer fit the diet regimen), which would not require IRB approval.

Appendix C: Baseline Questionnaires

PROMIS Depression (Child ≥ 14 years)

In the past 7 days…	Never	Almost Never	Sometimes	Often	Almost Always
I could not stop feeling sad	1	2	3	4	5
I felt alone	1	2	3	4	5
I felt everything in my life went wrong	1	2	3	4	5
I felt like I couldn't do anything right	1	2	3	4	5
I felt lonely	1	2	3	4	5
I felt sad	1	2	3	4	5
I felt unhappy	1	2	3	4	5
It was hard for me to have fun	1	2	3	4	5

PROMIS Anxiety (Child ≥ 14 years)

In the past 7 days…	Never	Almost Never	Sometimes	Often	Almost Always
I felt like something awful might happen	1	2	3	4	5
I felt nervous	1	2	3	4	5
I felt scared	1	2	3	4	5
I felt worried	1	2	3	4	5
I worried when I was at home	1	2	3	4	5
I got scared really easy	1	2	3	4	5
I worried about what could happen to me	1	2	3	4	5
I worried when I went to bed at night	1	2	3	4	5

Parent PROMIS Anxiety

In the past 7 days...

	Never	Rarely	Sometimes	Often	Always
I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt nervous	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt like I needed help for my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt anxious	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt tense	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Parent PROMIS Depression

In the past 7 days....

		Never	Rarely	Sometimes	Often	Always
EDDEP04	I felt worthless....................	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt that I had nothing to look forward to....................	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless....................	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP17	I felt sad....................	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP22	I felt like a failure....................	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed....................	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP36	I felt unhappy....................	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless....................	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Expectation of benefit (Baseline) – Patient Version

1. How **helpful** do you think the specific carbohydrate diet (SCD) will be for you as part of your treatment for IBD? If you are not sure, please take your best guess. Remember we are only interested in your opinion.

Not at all helpful	Not very helpful	Somewhat helpful	Very helpful	Extremely helpful
☐	☐	☐	☐	☐
1	2	3	4	5

2. How **helpful** do you think the modified version of the specific carbohydrate diet (SCD) will be for you as part of your treatment for IBD? If you are not sure, please take your best guess. Remember we are only interested in your opinion.

Not at all helpful	Not very helpful	Somewhat helpful	Very helpful	Extremely helpful
☐	☐	☐	☐	☐
1	2	3	4	5

3. If you had to choose between the specific carbohydrate diet (SCD) or the modified version right now, which one would you select?

☐	Specific Carbohydrate Diet (SCD)
☐	Modified Specific Carbohydrate Diet (SCD)
☐	Not sure

4. Which symptom(s) are you hoping improves the most with this diet? Check all that apply:

☐	Consistency of Stools
☐	Frequency of Stools
☐	Stomach Pain
☐	Bloody Stools
☐	Rushing to the Bathroom

Expectation of benefit (Baseline) - Parent Version

1. How helpful do you think the specific carbohydrate diet (SCD) will be for your child as part of his/her treatment for IBD? If you are not sure, please take your best guess. Remember we are only interested in your opinion.

Not at all helpful	Not very helpful	Somewhat helpful	Very helpful	Extremely helpful
☐	☐	☐	☐	☐
1	2	3	4	5

. How helpful do you think the modified version of the specific carbohydrate diet (SCD) will be for your child as part of his/her treatment for IBD? If you are not sure, please take your best guess. Remember we are only interested in your opinion.

Not at all helpful	Not very helpful	Somewhat helpful	Very helpful	Extremely helpful
☐	☐	☐	☐	☐
1	2	3	4	5

. If you had to choose between the specific carbohydrate diet (SCD) or the modified version right now, which one would you select?

☐	Specific Carbohydrate Diet (SCD)
☐	Modified Specific Carbohydrate Diet (SCD)
☐	Not sure

. Which symptom(s) are you hoping improves the most with this diet? Check all that apply:
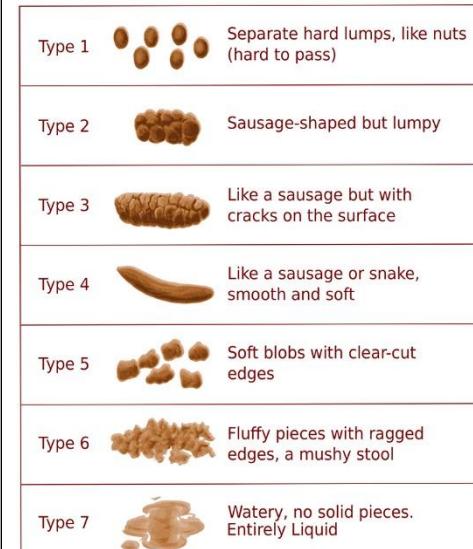
☐	Consistency of Stools
☐	Frequency of Stools
☐	Stomach Pain
☐	Bloody Stools
☐	Rushing to the Bathroom

Appendix D: Symptom Trackers

Daily Symptom Trackers – Patient Version

Stool Consistency	What have most of your stools looked like today?
	Bristol Stool Chart
	Type 1 — Separate hard lumps, like nuts (hard to pass)
	Type 2 — Sausage-shaped but lumpy
	Type 3 — Like a sausage but with cracks on the surface
	Type 4 — Like a sausage or snake, smooth and soft
	Type 5 — Soft blobs with clear-cut edges
	Type 6 — Fluffy pieces with ragged edges, a mushy stool
	Type 7 — Watery, no solid pieces. Entirely Liquid
Stool Frequency	How many stools did you have today? [Enter Integer]

Daily Symptom Trackers - Parent Version

Stool Consistency	What have most of your child's stools looked like today?
	Bristol Stool Chart
	Type 1 — Separate hard lumps, like nuts (hard to pass)
	Type 2 — Sausage-shaped but lumpy
	Type 3 — Like a sausage but with cracks on the surface
	Type 4 — Like a sausage or snake, smooth and soft
	Type 5 — Soft blobs with clear-cut edges
	Type 6 — Fluffy pieces with ragged edges, a mushy stool
	Type 7 — Watery, no solid pieces. Entirely Liquid

Stool Frequency - Parent Version	How many stools did your child have today? [Enter Integer]

Weekly Symptom Trackers – Patient Version

Weight (optional)	What is your current weight taken on your home scale **in pounds**? [Number]
PROMIS Pain Interference (patient ≥ 14 years)	
PROMIS GI Symptoms (patient ≥ 14 years)	In the past 7 days... My poop was loose or watery I rushed to the bathroom to avoid an accident I had blood in my poop I had a stomachache Each of the four items is scored as 1 (Never), 2 (Rarely), 3 (Sometimes), 4 (Often), and 5 (Always)
Pediatric Ulcerative Colitis Activity Index (PUCAI) – **Patient Version**	*"These are questions about how your child has been feeling over the past 24 hours"* *Question 1.* How much has your stomach been hurting in the past 24 hours? ☐ Not at all ☐ Hurting somewhat, but I can ignore it ☐ Hurting very much; it is always on my mind

	Question 2. Did you have stools containing blood over the past 24 hours? □ Not at all □ A small amount only, in less than half of stools □ Small amount with most stools □ Large amount, in more than half of stools *Question 3.* Which of the following best describes your stool over the past 24 hours? □ Solid □ Soft (passes easily) □ Watery *Question 4.* Number of stools per 24 hours (from yesterday this time until now). Please remember that if you are having small frequent stools one after another without having left the bathroom, it counts as one stool. □ 0-2 □ 3-5 □ 6-8 □ More than 8 *Question 5.* Did you wake up overnight because you needed to move your bowels? □ No □ Yes *Question 6.* How has your activity level been over the past 24 hours? □ I have been able to do my usual activities without a problem □ Sometimes I have had to stop what I wanted to do because I was not feeling well □ I have not been able to do my usual activities at all
Short Crohn's Disease Activity Index (SCDAI) – **Patient Version**	These questions refer to the time period from when you awoke yesterday to when you awoke today. 1. Please indicate the number of liquid or soft stools that you have had (answer: open ended frequency)

	2. Please indicate your abdominal pain level (answer choice: 0=none; 1=mild; 2=moderate; 3=severe) 3. Please rate your general well-being (answer choice: 0=generally well; 1= slightly under par; 2=poor; 3=very poor; 4=terrible)

Weekly Symptom Trackers - Parent Version

Weight (optional)	What is your child's current weight taken on your home scale **in pounds**? [Number]
PROMIS Pain Interference Parent Proxy	
PROMIS GI Symptoms Parent Proxy	In the past 7 days... My child's poop was loose or watery My child rushed to the bathroom to avoid an accident My child had blood in his/her poop My child had a stomachache Each of the four items is scored as 1 (Never), 2 (Rarely), 3 (Sometimes), 4 (Often), and 5 (Always)
Pediatric Ulcerative Colitis Activity Index (PUCAI)	*"These are questions about how your child has been feeling over the past 24 hours"* *Question 1.* How much has your child's stomach been hurting in the past 24 hours? • Not at all • Hurting somewhat, but my child can ignore it • Hurting very much; it is always on my child's mind

	Question 2. Did your child have stools containing blood over the past 24 hours? • Not at all • A small amount only, in less than half of stools • Small amount with most stools • Large amount, in more than half of stools *Question 3.* Which of the following best describes your child's stool over the past 24 hours? • Solid • Soft (passes easily) • Watery *Question 4.* Number of stools per 24 hours (from yesterday this time until now). Please remember that if your child is having small frequent stools one after another without having left the bathroom, it counts as one stool. • 0-2 • 3-5 • 6-8 • More than 8 *Question 5.* Did your child wake up overnight because s/he needed to move his/her bowels? • No • Yes *Question 6.* How has your child's activity level been over the past 24 hours? • My child has been able to do his/her usual activities without a problem • Sometimes my child has had to stop what s/he wanted to do because s/he was not feeling well • My child has not been able to do his/her usual activities at all
Short Crohn's Disease Activity Index (SCDAI)	These questions refer to the time period from when your child awoke yesterday to when s/he awoke today. 1. Please indicate the number of liquid or soft stools that your child has had (answer: open ended frequency)

|	
	2. Please indicate your child's abdominal pain level (answer choice: 0=none; 1=mild; 2=moderate; 3=severe) 3. Please rate your child's general well-being (answer choice: 0=generally well; 1= slightly under par; 2=poor; 3=very poor; 4=terrible)

Appendix E: Patient Handout Instructions for Stool Collection

See Separate Document

Appendix F: 3-day Diet Recall Questions
See Attached

Appendix G: N-of-1 Trial Results Display

Phrasing	Percent
Certain	≥95%
Very Likely	75-94%
Likely	60-74%
Possible	20-59%
Unlikely	<20%
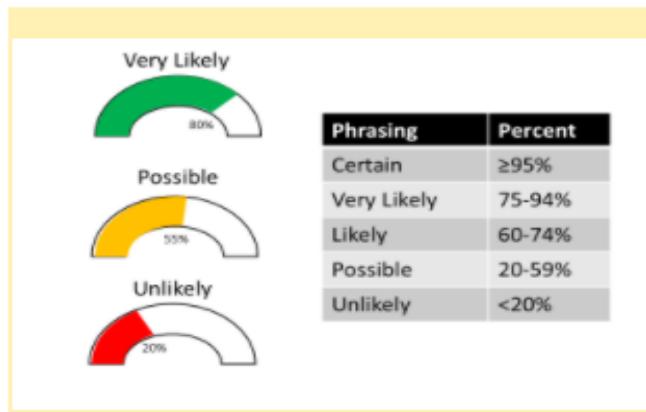
iii. Text with each gauge
    c. Chance that SCD is Better than your Usual Diet
        a. Text: You have a [X]% chance that you showed improvement in your stool frequency and a [X]% chance your stool frequency got worse.
    d. Chance that the Modified SCD is Better than your Usual Diet
        a. Text: You have a [X]% chance that you showed improvement in your stool frequency and a [X]% chance your stool frequency got worse.
    2. Chance that the SCD is Better than the Modified SCD
        a. Text: There is a [X]% chance that your stool frequency was better on the SCD and a [X]% chance that it was better on the Modified SCD.

Appendix H: Questionnaire about N-of-1 Experience – Patient Version

Patient Experiences:

1. Now that you have completed your N-of-1 trial, how **helpful** do you think the Specific Carbohydrate Diet (SCD) was for you (your child) as part of your (your child's) treatment for IBD? If you are not sure, please take your best guess. Remember we are only interested in your opinion.

Not at all helpful	Not very helpful	Somewhat helpful	Very helpful	Extremely helpful
☐	☐	☐	☐	☐
1	2	3	4	5

2. How **helpful** do you think the modified version of the Specific Carbohydrate Diet (SCD) was for you (your child) as part of your (your child's) treatment for IBD? If you are not sure, please take your best guess. Remember we are only interested in your opinion

Not at all helpful	Not very helpful	Somewhat helpful	Very helpful	Extremely helpful
☐	☐	☐	☐	☐
1	2	3	4	5

3. Which treatment would you prefer to use going forward into the future?	☐	Specific Carbohydrate Diet
	☐	Modified Version of the SCD
	☐	Neither
	☐	Not sure

4. What is your main reason for selecting that treatment?

_____

_____

How helpful was the your N-of-1 trial in	Not at all helpful	Not very helpful	Somewhat helpful	Very helpful	Extremely helpful
5. …. helping you understand the impact of diet on your (your child's) IBD symptoms?	☐	☐	☐	☐	☐
6. …..helping you keep track of your (your child's) IBD symptoms?	☐	☐	☐	☐	☐
7. …helping you work more closely with your (your child's) clinician to achieve your (your child's) treatment goals?	☐	☐	☐	☐	☐
8. …helping you notice things that make your (your child's) IBD symptoms feel better?	☐	☐	☐	☐	☐
9. **…**helping you have more confidence in the treatment approach you (your child) will follow going forward?	☐	☐	☐	☐	☐

Questionnaire about N-of-1 Experience - Parent Version

. Now that your child has completed his/her N-of-1 trial, how **helpful** do you think the Specific Carbohydrate Diet (SCD) was for your child as part of his/her treatment for IBD? If you are not sure, please take your best guess. Remember we are only interested in your opinion.

Not at all helpful	Not very helpful	Somewhat helpful	Very helpful	Extremely helpful
☐	☐	☐	☐	☐
1	2	3	4	5

. How **helpful** do you think the modified version of the Specific Carbohydrate Diet (SCD) was for your child as part of his/her treatment for IBD? If you are not sure, please take your best guess. Remember we are only interested in your opinion

Not at all helpful	Not very helpful	Somewhat helpful	Very helpful	Extremely helpful
☐	☐	☐	☐	☐
1	2	3	4	5

Which treatment would you prefer to use for your child going forward into the future?	☐	Specific Carbohydrate Diet
	☐	Modified Version of the SCD
	☐	Neither
	☐	Not sure

4. What is your main reason for selecting that treatment?

_____

_____

How helpful was **your child's** N-of-1 trial in	Not at all helpful	Not very helpful	Somewhat helpful	Very helpful	Extremely helpful
…. helping you understand the impact of diet on his/her IBD symptoms?	☐	☐	☐	☐	☐
….helping you keep track of his/her IBD symptoms?	☐	☐	☐	☐	☐
..helping you work more closely with your child's clinician to achieve his/her treatment goals?	☐	☐	☐	☐	☐
…helping you notice things that make his/her IBD symptoms feel better?	☐	☐	☐	☐	☐
..helping you have more confidence in the treatment approach s/he will follow going forward?	☐	☐	☐	☐	☐

Appendix I: Study Introduction Flyer: Trifold*

See Separate Document

*The Study Introduction Flyer (trifold) may have cosmetic (i.e., design) edits to the layout and format of document, which would not require IRB approval. No wording/verbiage changes will be made without official IRB approval.

Appendix J: Study Introduction Flyer: Single-Sided

See Separate Document

*The Study Introduction Flyer (single-sided) may have cosmetic (i.e., design) edits to the layout and format of document, which would not require IRB approval. No wording/verbiage changes will be made without official IRB approval.

Appendix K: Study Letter

See Separate Document

Appendix L: Phone Script

See Separate Document

Appendix M: DSMB Charter

See Separate Document

Appendix N: Eureka Mobile App Patient Facing Privacy Policy

See Separate Document

Appendix O: Study Poster

See separate document

Appendix O: Parent Letter

See separate document