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Supplementary information

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A fasting-mimicking diet in patients with mild-to-moderate Crohn's disease: a randomized controlled trial

In the format provided by the authors and unedited

Supplementary data

Variable	Adjusted odds ratio (95% CI)
Female sex	0.72 (0.26 to 2.03)
Black race	1.14 (0.04 to 31.1)
Other race	3.02 (0.65 to 22.3)
Non-Hispanic or Latino ethnicity	0.85 (0.15 to 4.84)
Past or current smoker	1.70 (0.65 to 4.75)
BMI with obesity	0.50 (0.18 to 1.35)
Use of advanced therapy at baseline	0.84 (0.33 to 2.07)
Use of corticosteroids at baseline	0.64 (0.22 to 1.78)

Supplementary Table 1. Regression analysis to adjust for residual confounding of variables with baseline imbalances post-randomization. Multivariable logistic regression (adjusted) was conducted in R, adjusted for all covariates that had mild or greater imbalance after randomization defined by SMD of ≥0.20. BMI, body mass index; FMD, fasting-mimicking diet.

Dietary adherence	FMD	Control
	n (%)	n (%)
During FMD cycles		
Adherent	50 (76.9)	NA
No changes to regular diet		
Adherent	63 (96.9)	28 (87.5)

Supplementary Table 2. Dietary adherence data. Criteria for adherence during FMD cycles was defined as completing all five days of each FMD cycle without consuming more than 400 additional calories beyond what was provided in the meal kit on any given day of an FMD cycle. If there were no changes in diet reported when participants were assigned to consume the baseline diet, participants met criteria for adherence to baseline diet. FMD, Fasting-mimicking diet.

Target	Forward (5'– 3')	Reverse (5'–3')
HPRT1	GACCAGTCAACAGGGGACAT	GCTTGCGACCTTGACCATCT
TNF	GTGCTTGTTCCTCAGCCTCT	CTACAGGCTTGTCACTCGGG
IL-1β	CTTAAAGCCCGCCTGACAGA	ACACTGCTACTTCTTGCCCC
IL-18	ATCGCTTCCTCTCGCAACAA	ACTGGTTCAGCAGCCATCTT
NF-κB	GCTTAGGAGGGAGAGCCCA	AGGACGTTGTGTTCCTTCCG
CCL20	TTGTCTGTGTGCGCAAATCC	CCAACCCCAGCAAGGTTCTT
CXCL10	CCTGCAAGCCAATTTTGTCCA	TGCATCGATTTTGCTCCCCT
NLRP3	GGCAACACTCTCGGAGACAA	GGAAAGATCCCAGCAGCAGT
IL-10	CCGTGGAGCAGGTGAAGAAT	TAGAGTCGCCACCCTGATGT

Supplementary Table 3. Primer sequences used for qPCR analysis. HPRT, Hypoxanthine phosphoribosyltransferase; TNF, Tumor necrosis factor; IL, interleukin; NF-κB, nuclear factor-kappa B; CCL, C-C motif chemokine ligand; CXCL, C-X-C motif chemokine ligand; NLRP, NOD-like receptor family, pyrin domain-

containing 3.

Characteristic	FMD	Control
	n (%), median (IQR)	n (%), median (IQR)
Withdrawal frequency	14 (21.5)	3 (9.4)
Scheduling/Loss of interest/COVID-19 pandemic	4 (6.2)	2 (6.3)
Dislike of diet and/or dietary protocol	10 (15.3)	1 (3.1)
Age at enrollment, *yrs*	47.0 (38.0–51.5)	54.0 (49.0–55.5)
Male sex	2 (14.3)	2 (66.7)
Race		
White	11 (78.6)	1 (33.3)
Black	0 (0.0)	1 (33.3)
Asian	1 (7.1)	1 (33.3)
Native Hawaiian or Pacific Islander	0 (0.0)	0 (0.0)
American Indian or Alaska Native	0 (0.0)	0 (0.0)
Other	1 (7.1)	0 (0.0)
Unknown	1 (7.1)	0 (0.0)
Ethnicity		
Hispanic or Latino	1 (7.1)	0 (0.0)
Not Hispanic or Latino	11 (78.6)	3 (100.0)
Unknown	2 (14.3)	0 (0.0)
BMI at inclusion, *kg/m²*	26.7 (22.6–35.0)	24.8 (24.6–28.7)
Normal (18.0–23.9)	5 (35.7)	0 (0.0)
Overweight (24.0–29.9)	4 (28.5)	2 (66.7)
With obesity (≥30.0)	5 (35.7)	1 (33.3)
CD phenotype (Montreal Classification)		
Age at CD onset, *yrs*	44.0 (34.8–48.5)	49.0 (46.5–51.5)
A1 (≤16 yrs)	1 (7.1)	0 (0.0)
A2 (17–39 yrs)	4 (28.6)	0 (0.0)
A3 (≥40 yrs)	9 (64.3)	2 (66.7)
CD disease distribution[a]		
Ileum alone (L1)	4 (28.6)	0 (0.0)
Colon alone (L2)	3 (21.4)	0 (0.0)
Ileocolon (L3)	6 (42.9)	2 (66.7)
Upper GI alone (L4)	0 (0.0)	0 (0.0)
CD behavior[b]		
Non-stricturing, non-penetrating (B1)	8 (57.1)	2 (66.7)
Stricturing (B2)	5 (35.7)	0 (0.0)
Penetrating (B3)	1 (7.1)	0 (0.0)
History of perianal disease (p)	4 (28.6)	1 (33.3)
CDAI at inclusion	190 (162–225)	195 (183–298)
Mild (151–220)	10 (71.4)	2 (66.7)
Moderate (221–450)	4 (28.6)	1 (33.3)
CD medications at inclusion		
Any biologic, immunomodulator, or small molecule	9 (64.3)	1 (33.3)

Supplementary Table 4. Demographic and clinical characteristics of participants who withdrew from the study. [a]L4 is added as a modifier to categories L1 to L3 when disease is found proximal and distal to the terminal ileum; if disease is only present proximal to the terminal ileum, L4 can be assigned as a mutually exclusive category. [b]Per Montreal classification guidelines, participants with <10 years of disease history without evidence

of stricturing or penetrating disease course were assigned to B1 category; participants who reported perianal fistulae and/or abscesses within 10 years of CD diagnosis were considered to have a history of perianal CD. Median and IQR, or counts and percentages. FMD, Fasting-mimicking diet; BMI, Body mass index; CDAI, Crohn's Disease Activity Index.

Inflammatory markers	*P* value	FDR-adjusted *P* value (q)
Calprotectin	0.03	0.03**
CRP	0.06	0.03**
ESR	0.87	0.29

Supplementary Table 5. *P* values for inflammatory markers adjusted for multiple comparisons. Analysis for both calprotectin, CRP, and ESR were pre-specified and registered on ClinicalTrials.gov (NCT04147585). Unadjusted *P* values are presented in the main body of the manuscript to remain consistent with this established practice in IBD clinical trials and to facilitate comparability across studies. CRP, C-reactive protein, ESR, Erythrocyte sedimentation rate. *P* values were FDR-adjusted using the two-stage Benjamini–Krieger–Yekutieli procedure across the fecal calprotectin/CRP/ESR panel. Significance was defined as FDR-adjusted $P \leq 0.10$ and is denoted by ** indicating $q \leq 0.05$.

Characteristic (Female Participants)	**FMD** (n = 52) n (%), median (IQR)	**Control** (n = 18) n (%), median (IQR)
Age at enrollment, *yrs*	45.5 (37.8–52.3)	39.5 (29.3–57.3)
Race		
White	39 (75.0%)	15 (83.3%)
Black	0 (0.0%)	1 (5.6%)
Asian	4 (7.7%)	1 (5.6%)
Native Hawaiian or Pacific Islander	0 (0.0%)	0 (0.0%)
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)
Other	2 (3.8%)	0 (0.0%)
Unknown	7 (13.5%)	1 (5.6%)
Ethnicity		
Hispanic or Latino	3 (5.8%)	2 (11.1%)
Not Hispanic or Latino	41 (78.9%)	15 (83.3%)
Unknown	8 (15.4%)	1 (5.6%)
BMI at inclusion, *kg/m²*	25.3 (21.5–28.7)	26.8 (23.9–31.0)
Normal (18.0–23.9)	24 (46.2%)	8 (44.4%)
Overweight (24.0–29.9)	18 (34.6%)	3 (16.7%)
With obesity (≥30.0)	10 (19.2%)	7 (38.8%)
Smoking status		
Never	29 (55.8%)	10 (55.6%)
Past	10 (19.2%)	3 (16.7%)
Current	2 (3.8%)	2 (11.1%)
Alcohol use at baseline		
Never	23 (44.2%)	6 (33.3%)
Light	25 (48.1%)	11 (61.1%)

Moderate	4 (7.7%)	1 (5.6%)
Heavy	0 (0.0%)	0 (0.0%)
CD phenotype[a]		
Age at CD onset, *yrs*	39.5 (28.0–47.0)	31.0 (25.3–50.0)
A1 (≤16 yrs)	6 (11.5%)	0 (0.0%)
A2 (17–39 yrs)	20 (38.5%)	11 (61.0%)
A3 (≥40 yrs)	26 (50.0%)	7 (39.0%)
CD distribution[b]		
Ileum alone (L1)	18 (34.6%)	6 (33.0%)
Colon alone (L2)	11 (21.2%)	8 (44.0%)
Ileocolon (L3)	21 (40.4%)	3 (16.7%)
Upper GI alone (L4)	1 (1.9%)	0 (0.0%)
CD behavior[c]		
Non-stricturing, non-penetrating (B1)	28 (53.8%)	15 (83.0%)
Stricturing (B2)	18 (34.6%)	2 (11.0%)
Penetrating (B3)	6 (11.5%)	1 (5.6%)
History of perianal disease (p)	16 (30.8%)	4 (22.2%)
CDAI score at baseline	193.0 (162.8–226.0)	197.8 (177.8–228.3)
Mild (151–220)	36 (69.2%)	12 (66.7%)
Moderate (221–450)	16 (30.8%)	6 (33.3%)
CD medications at baseline		
Any biologic, small molecule, or immunomodulator	29 (55.8%)	11 (61.1%)
Anti TNF	12 (23.1%)	7 (38.9%)
Anti IL-12, IL-23	11 (21.2%)	2 (11.1%)
Anti Integrin	6 (11.5%)	2 (11.1%)
Immunomodulator (6-mercaptopurine, azathioprine, methotrexate)	9 (17.3%)	3 (16.7%)
Small molecule (JAK inhibitor)	2 (3.8%)	0 (0;0%)
5-aminosalicylate	12 (23.1%)	2 (11.1%)
Corticosteroids	12 (23.1%)	1 (5.6%)
Antibiotics	3 (5.8%)	0 (0.0%)
CRP, *mg/L*	0.3 (0.1–0.63)	0.3 (0.2–0.72)
CRP >10 mg/L	14 (26.9%)	5 (27.8%)
ESR, *mm/h*	10.5 (4.8–24.8)	16.0 (6.0–19.0)
ESR elevated	10 (19.2%)	2 (11.1%)
Fecal calprotectin, *µg/g*	94.0 (28.0–203.5)	69.5 (48.0–186.5)
Fecal calprotectin >120 µg/g	22 (42.3%)	6 (33.3%)

Supplementary Table 6. Demographic and clinical characteristics of female participants. [a]L4 is added as a modifier to categories L1 to L3 when disease is found proximal and distal to the terminal ileum; if disease is only present proximal to the terminal ileum, L4 can be assigned as a mutually exclusive category. [b]Per Montreal classification guidelines, participants with <10 years of disease history without evidence of stricturing or penetrating disease course were assigned to B1 category; participants who reported perianal fistulae and/or abscesses within 10 years of CD diagnosis were considered to have a history of perianal CD. Median and IQR, or counts and percentages. FMD, Fasting-mimicking diet; BMI, Body mass index; CDAI, Crohn's Disease Activity Index; TNF, Tumor necrosis factor; IL, Interleukin; JAK, Janus kinase; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate.

Characteristic (Male participants)	**FMD** (n = 13) n (%), median (IQR)	**Control** (n = 14) n (%), median (IQR)
Age at enrollment, *yrs*	36.0 (28.0–56.0)	49.0 (43.0–56.0)
Race		
White	8 (61.5%)	9 (69.2%)
Black	0 (0.0%)	1 (7.1%)
Asian	3 (23.1%)	3 (21.4%)
Native Hawaiian or Pacific Islander	0 (0.0%)	0 (0.0%)
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)
Unknown	2 (15.4%)	1 (7.1%)
Ethnicity		
Hispanic or Latino	1 (7.7%)	0 (0.0%)
Not Hispanic or Latino	11 (84.6%)	13 (92.9%)
Unknown	1 (7.7%)	1 (7.1%)
BMI at inclusion, *kg/m²*	22.5 (22.0–23.8)	27.9 (23.8–29.2)
Normal (18.0–23.9)	10 (76.9%)	5 (35.7%)
Overweight (24.0–29.9)	3 (23.1%)	6 (42.9%)
With obesity (≥30.0)	0 (0.0%)	3 (21.4%)
Smoking status		
Never	11 (84.6%)	10 (71.4%)
Past	0 (0.0%)	1 (7.1%)
Current	2 (15.4%)	2 (14.2%)
Alcohol use at baseline		
Never	9 (69.2%)	8 (57.1%)
Light	4 (30.8%)	5 (35.7%)
Moderate	0 (0.0%)	1 (7.1%)
Heavy	0 (0.0%)	0 (0.0%)
CD phenotype[a]		
Age at CD onset, *yrs*		
A1 (≤16 yrs)	1 (7.7%)	2 (15.4%)
A2 (17–39 yrs)	7 (53.8%)	4 (30.8%)
A3 (≥40 yrs)	5 (38.5%)	7 (53.8%)
CD distribution[b]		
Ileum alone (L1)	0 (0.0%)	4 (28.6%)
Colon alone (L2)	6 (46.2%)	1 (7.1%)
Ileocolon (L3)	7 (53.8%)	7 (50.0%)
Upper GI alone (L4)	0 (0.0%)	0 (0.0%)
CD behavior[c]		
Non-stricturing, non-penetrating (B1)	11 (84.6%)	10 (71.4%)
Stricturing (B2)	2 (15.4%)	1 (7.1%)
Penetrating (B3)	0 (0.0%)	2 (14.3%)
History of perianal disease (p)	3 (23.1%)	3 (21.4%)
CDAI score at baseline	202.0 (176.0–293.0)	194.5 (176.0–228.8)
Mild (151–220)	7 (53.8%)	10 (71.4%)
Moderate (221–450)	6 (46.2%)	4 (28.6%)
CD medications at baseline		

Any biologic, small molecule, or immunomodulator	3 (23.1%)	11 (78.6%)
Anti TNF	1 (7.7%)	5 (35.7%)
Anti IL-12, IL-23	1 (7.7%)	3 (21.4%)
Anti Integrin	1 (7.7%)	2 (14.2%)
Immunomodulator (6-mercaptopurine, azathioprine, methotrexate)	0 (0.0%)	1 (7.1%)
Small molecule (JAK inhibitor)	0 (0.0%)	0 (0.0%)
5-aminosalicylate	5 (38.5%)	1 (7.1%)
Corticosteroids	2 (15.4%)	3 (21.4%)
Antibiotics	0 (0.0%)	0 (0.0%)
CRP, *mg/L*	0.5 (0.1–1.1)	0.3 (0.1–0.6)
CRP >10 mg/L	6 (46.2%)	5 (35.7%)
ESR, *mm/h*	7.0 (4.3–16.0)	8.5 (2.8–15.5)
ESR elevated	1 (7.7%)	2 (14.2%)
Fecal calprotectin, *µg/g*	215.0 (74.0–584.0)	176.0 (85.3–344.5)
Fecal calprotectin >120 µg/g	9 (69.2%)	9 (64.3%)

Supplementary Table 7. Demographic and clinical characteristics of male participants. [a]L4 is added as a modifier to categories L1 to L3 when disease is found proximal and distal to the terminal ileum; if disease is only present proximal to the terminal ileum, L4 can be assigned as a mutually exclusive category. [b]Per Montreal classification guidelines, participants with <10 years of disease history without evidence of stricturing or penetrating disease course were assigned to B1 category; participants who reported perianal fistulae and/or abscesses within 10 years of CD diagnosis were considered to have a history of perianal CD. Median and IQR, or counts and percentages. FMD, Fasting-mimicking diet; BMI, Body mass index; CDAI, Crohn's Disease Activity Index; TNF, Tumor necrosis factor; IL, Interleukin; JAK, Janus kinase; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate.

Section/topic	No	CONSORT 2025 checklist item description	Reported on page no.
Title and abstract			
Title and structured abstract	1a	Identification as a randomised trial	1–2
	1b	Structured summary of the trial design, methods, results, and conclusions	2
Open science			
Trial registration	2	Name of trial registry, identifying number (with URL) and date of registration	2, 23
Protocol and statistical analysis plan	3	Where the trial protocol and statistical analysis plan can be accessed	24
Data sharing	4	Where and how the individual de-identified participant data (including data dictionary), statistical code and any other materials can be accessed	31
Funding and conflicts of interest	5a	Sources of funding and other support (eg, supply of drugs), and role of funders in the design, conduct, analysis and reporting of the trial	12–13
	5b	Financial and other conflicts of interest of the manuscript authors	13
Introduction			
Background and rationale	6	Scientific background and rationale	3–4
Objectives	7	Specific objectives related to benefits and harms	4
Methods			
Patient and public involvement	8	Details of patient or public involvement in the design, conduct and reporting of the trial	23–24
Trial design	9	Description of trial design including type of trial (eg, parallel group, crossover), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	23–24
Changes to trial protocol	10	Important changes to the trial after it commenced including any outcomes or analyses that were not prespecified, with reason	26–27
Trial setting	11	Settings (eg, community, hospital) and locations (eg, countries, sites) where the trial was conducted	24
Eligibility criteria	12a	Eligibility criteria for participants	24–25
	12b	If applicable, eligibility criteria for sites and for individuals delivering the interventions (eg, surgeons, physiotherapists)	N/A
Intervention and comparator	13	Intervention and comparator with sufficient details to allow replication. If relevant, where additional materials describing the intervention and comparator (eg, intervention manual) can be accessed	25
Outcomes	14	Prespecified primary and secondary outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome	25–26
Harms	15	How harms were defined and assessed (eg, systematically, non-systematically)	27–28
Sample size	16a	How sample size was determined, including all assumptions supporting the sample size calculation	24
	16b	Explanation of any interim analyses and stopping guidelines	25–26
Randomisation:			
Sequence generation	17a	Who generated the random allocation sequence and the method used	24
	17b	Type of randomisation and details of any restriction (eg, stratification, blocking and block size)	24

			Reported on page no.
Allocation concealment mechanism	18	Mechanism used to implement the random allocation sequence (eg, central computer/telephone; **sequentially numbered**, opaque, sealed containers), describing any steps to conceal the sequence until interventions were assigned	24
Implementation	19	Whether the personnel who enrolled and those who assigned participants to the interventions had access to the random allocation sequence	12
Blinding	20a	Who was blinded after assignment to interventions (eg, participants, care providers, outcome assessors, data analysts)	7, 11–12
	20b	If blinded, how blinding was achieved and description of the similarity of interventions	N/A
Statistical methods	21a	Statistical methods used to compare groups for primary and secondary outcomes, including harms	28–29
	21b	Definition of who is included in each analysis (eg, all randomised participants), and in which group	28
	21c	How missing data were handled in the analysis	26, 30
	21d	Methods for any additional analyses (eg, subgroup and sensitivity analyses), distinguishing prespecified from post hoc	29–31
Results			
Participant flow, including flow diagram	22a	For each group, the numbers of participants who were randomly assigned, received intended intervention, and were analysed for the primary outcome	4
	22b	For each group, losses and exclusions after randomisation, together with reasons	4
Recruitment	23a	Dates defining the periods of recruitment and follow-up for outcomes of benefits and harms	4
	23b	If relevant, why the trial ended or was stopped	N/A
Intervention and comparator delivery	24a	Intervention and comparator as they were actually administered (eg, where appropriate, who delivered the intervention/comparator, how participants adhered, whether they were delivered as intended (fidelity))	4
	24b	Concomitant care received during the trial for each group	5
Baseline data	25	A table showing baseline demographic and clinical characteristics for each group	13–15
Numbers analysed, outcomes and estimation	26	For each primary and secondary outcome, by group: ● the number of participants included in the analysis ● the number of participants with available data at the outcome time point ● result for each group, and the estimated effect size and its precision (such as 95% confidence interval) ● for binary outcomes, presentation of both absolute and relative effect size	5–8, 13–16
Harms	27	All harms or unintended events in each group	8–9
Ancillary analyses	28	Any other analyses performed, including subgroup and sensitivity analyses, distinguishing pre-specified from post hoc	9
Discussion			
Interpretation	29	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	9–12
Limitations	30	Trial limitations, addressing sources of potential bias, imprecision, generalisability, and, if relevant, multiplicity of analyses	12

Citation: Hopewell S, Chan AW, Collins GS, Hróbjartsson A, Moher D, Schulz KF, et al. CONSORT 2025 Statement: updated guideline for reporting randomised trials. BMJ. 2025; 388:e081123. https://dx.doi.org/10.1136/bmj-2024-081123

Effects of an Intermittent Reduced Calorie Diet on Crohn's Disease

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Table of Contents

1. Protocol History

Protocol Amendments			
The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version:			
Amendment number	Date	Protocol version number	Summary of amendments
1	1/6/20	2.0	Addition of recruitment materials: study information sheet, email to IBD physicians. Corrected error in NCT#.
2	1/9/20	2.1	Minor wording changes to recruitment materials.
3	1/22/20	2.2	Minor wording change specifying endoscopy (an optional intervention) criteria.
4	2/25/20	2.3*	Minor personnel changes. To allow for additional patient flexibility, we broadened the window for obtaining labs to allow up to an additional +/-4 days at data collection points. Clarified timing of 3 phone calls during each diet cycle. Addition of printable symptom diary. *First patient recruited on 1/30/2020
5	3/24/20	3.0	Amended procedures for allowing patients impacted by COVID-19 to re-enroll after at least 3 month “washout”. Included detailed description of interim analysis (prespecified in the original sponsor proposal) to conduct sample size re-estimation (in light of COVID-19 pandemic and difficulty recruiting). Clarified exclusion of patients with relevant prior gastrointestinal surgery such as proctocolectomy.
6	8/24/20	3.1	Adjustments to format of study visits to reduce face-to-face interactions between study staff and patients during the COVID-19 pandemic.
7	2/2/21	4.0	Minor personnel changes. Study end date extended to adjust for slower recruitment during the COVID-19 pandemic.Included national social media advertising campaign. Expanded locations for laboratory testing to include common commercial laboratories (LabCorp, Quest Diagnostics).
8	4/28/21	4.1	Minor personnel changes. Minor change to screening procedure to allow email scheduling of phone calls with possible candidates. Minor edits to advertising materials.

9	5/5/21	4.2	Minor personnel changes. Study dietitian may provide recipes nutritionally consistent with the L-Nutra FMD diet if the participants have intolerance of FMD component.
10	4/7/22	4.3	Minor personnel changes.
11	8/4/22	4.4	Minor personnel changes.
12	11/22/22	4.5	Minor personnel changes.
13	5/5/23	4.6	Minor personnel changes.
14	6/21/23	4.7	Minor personnel changes.
15	10/24/23	5.0	Prior to exceeding the original recruitment goal of 75 patients approved by IRB (and based on results of our interim analysis in June 2022 and approval from Sponsor), recruitment goal was expanded to include up to 97 patients (80 completed study; 17 withdrawals).

2. Protocol Summary

The role of diet in managing Crohn's disease (CD) is one of the most common inquiries by patients yet our knowledge of how diet influences intestinal inflammation is severely limited[1–5]. There have been numerous diet studies in CD that have failed to show meaningful change in outcomes, suggesting that modifying individual components of a diet may be insufficient[6,7]. Although data is limited, fasting appears to be a promising dietary intervention to reduce inflammation and improve health outcomes in a variety of inflammatory diseases[8–11]. Though complete fasting can be difficult to maintain, an intermittent reduced calorie diet **(IRCD, also known as a fasting mimicking diet (FMD))** allows for some oral nutrition (with significantly reduced calorie intake for a few days followed typically by regular diet) and has shown promising results in inflammatory models, including colitis[12,13]. However, no randomized controlled clinical trials investigating such a diet in CD exist.

Clinical trials investigating the effects of IRCD/FMD on healthy subjects indicate several health benefits including decreased abdominal fat and blood pressure[14,15]. Notably, the IRCD significantly reduced elevated baseline C-reactive protein (CRP, a common marker of inflammation) in a subset of the "healthy" population[14]. Though research in this field is limited, results such as reduced inflammatory markers with IRCD provide a promising basis for therapeutic dietary applications, particularly for patients with CD where "bowel rest" (fasting) during flares has shown potential benefit[16–21].

In this proposed study, we posit that the use of a plant-based IRCD in patients with CD will improve patient outcomes including clinical response and clinically relevant inflammatory markers (CRP, erythrocyte sedimentation rate (ESR), and/or fecal calprotectin). The core of this study is clinical and aimed at providing an effective diet for patients with CD to mitigate disease. Since it is well known that patients respond to therapies (both pharmacologic and dietary) differently we will also collect samples for future analysis in order to describe changes or signatures in immune and microbial/metabolomic profiles that may predict a person's ability to respond to the diet[22].

3. Objectives

To assess the ability of an IRCD to induce clinical response in patients with mild to moderate CD. We also will evaluate the ability of IRCD to induce biochemical response in patients with mild to moderate CD.

Primary Endpoint:

- Clinical response - defined as reduction of the CDAI of at least 70 points or achieving a CDAI score ≤150 (assessed at Data Collection #4).

Secondary Endpoints:

- Clinical remission - defined as a CDAI score ≤150 (assessed at Data Collection #4).
- Clinical response - defined as reduction of the CDAI of at least 100 points or achieving a CDAI score ≤150 (assessed at Data Collection #4).

- Clinical response - defined as reduction of the CDAI of at least 70 points or achieving a CDAI score ≤150 (assessed at Data Collection #6).
- Change in the clinical inflammatory marker CRP (assessed at Data Collection #4).
- Change in the clinical inflammatory marker ESR (assessed at Data Collection #4).
- Change in the clinical inflammatory marker fecal calprotectin (assessed at Data Collection #4).
- Clinical remission as per Patient Reported Outcome (PRO) score with the average worst daily abdominal pain score of ≤1 (using a 4-point scale, 0–3) and a loose/watery stool (Bristol Type 6 or 7) frequency score of ≤3 (assessed at Data Collection #4).
- Patient global assessment: "Do you believe you are in remission from your CD symptoms?" (Yes/No) (assessed at Data Collection #4).
- Effect of IRCD on endoscopic outcomes: Changes in SES-CD (assessed at Data Collection #4).
- Effect of IRCD on patient quality of life: Changes in SIBDQ (assessed at Data Collection #4).

Changes are assessed relative to baseline measurements.

4. Background and Rationale

Fasting mimicking diets (FMDs) have proven to be an effective method in easing symptoms of other inflammatory diseases (e.g., rheumatoid arthritis) by lowering levels of CRP and improving ESR. Bowel rest is also commonly used to reduce inflammation in patients with CD. Though evidence is limited, there are studies investigating the role of fasting diets on patients with CD. Previous studies have found that nutrient scarcity acts as a suppressor of mTOR responsible for producing the inflammatory cytokines Th1 and Th17, and promotes differentiation of Treg cells. These FMDs, also known as intermittent reduced calorie diets (IRCDs), substantially reduce daily caloric consumption and have shown promising results similar to standard fasting. These successes open investigation to the efficacy of IRCD as a sustainable solution to ease symptoms of patients with mild to moderate CD. Several animal studies have shown reduced inflammation in IBD and other disease models with fasting and/or IRCDs.

Strategy: We have designed a randomized, controlled study to investigate the effects of a IRCD/FMD on CD.
Outcomes: Desired outcomes will include improved disease activity, as reflected in established disease scores, clinically relevant inflammatory markers, and improved quality of life. Successful completion of these studies will provide patients with a dietary means to better manage and treat disease. Utilizing the IRCD, we hope to provide patients an empowering means to manage their disease, which could potentially minimize conventional therapy failures, the need for escalation to often-toxic drugs, and avoid surgery.
Need/Problem: There are enormous unmet needs in providing care for patients with CD. Up to a third of patients never respond to our best therapies and most patients who take even our most potent biologics don't achieve complete long-term remission of disease and are at risk of

increased side effects[23]. Currently there are no non-exclusion/enteral, dietary interventions that clearly benefit adults with CD[24]. Additional, more effective, and safer solutions are needed to mitigate and potentially prevent the disease. The IRCD not only shows promise in preclinical studies, but also in healthy subjects and could provide an effective and safe method to reduce intestinal inflammation on its own and/or together with conventional therapies[13,14].

5. Study Design

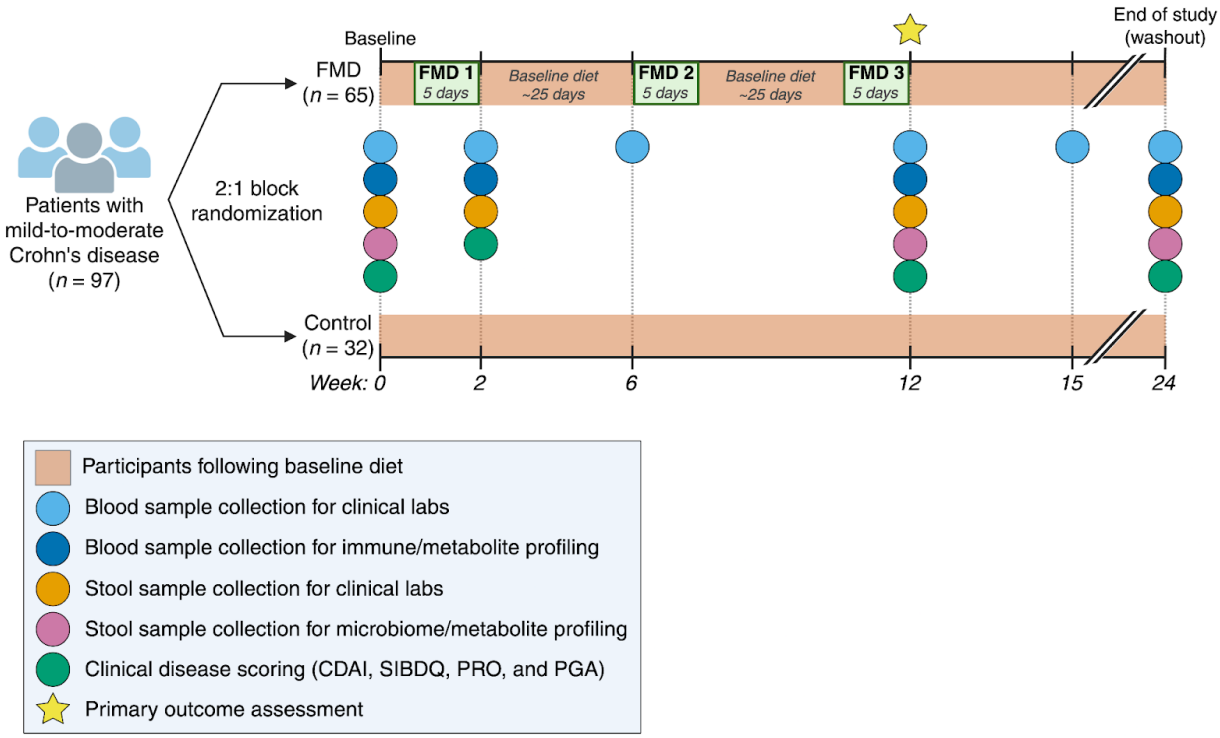
We have designed a randomized, controlled clinical trial to assess the effects of a plant-based IRCD on patients with CD. We will measure relevant clinical metrics such as the Crohn's Disease Activity Index (CDAI), common inflammatory markers (in serum and stool), and endoscopic disease activity measured by the Simplified Endoscopic Score for Crohn's Disease (SES-CD) to assess response. In addition, we will examine changes in quality of life in patients. Samples will be collected at specified time points as outlined.

Subjects will be randomized to an IRCD intervention or a control group in a 2:1 fashion using a Microsoft Excel generated block randomization list, and a block size of 6. The nature of this study does not allow blinding of participants as the control arm will consume their regular diet. However, all samples will be coded and analyzed in a blinded manner, and the endoscopist will be blinded as well.

Sample Collection for IRCD in CD Study

Study Visit	CRP	ESR	CBC	Fecal Calprotectin	Research Blood Sample*	Research Stool Sample*	Colonoscopy (optional)
Data Collection 1	X	X	X	X	X	X	X
Data Collection 2	X	X	X	X	X		
Data Collection 3	X	X	X				
Data Collection 4	X	X	X	X	X	X	X
Data Collection 5	X	X	X				
Data Collection 6	X	X	X	X	X	X	

*For future identification of potential response signatures to diet



6. Study Population

6.1 Recruitment

97 adult patients (ages 18–70) with mild to moderate CD (CDAI 151–450) at Stanford or Stanford-affiliated sites and clinics, or through self-referral will be recruited. Based on prespecified interim analysis and discussions with the study sponsor, our sample size was increased from the original proposal of 75 patients to 97 patients. All gender and ethnic backgrounds were included.

No potentially vulnerable subjects (including children, pregnant women, economically and educationally disadvantaged, decisionally impaired, homeless people, employees and students) will be recruited. Children will not be included due to possible interference of caloric restriction on normal growth and development. We will not be targeting recruitment of participants who are laboratory personnel, employees, and/or students.

Patients will be recruited by chart review from the Stanford hospitals and associated clinics, by referral from treating physician, and nationally by self-referral in accordance with the inclusion and exclusion criteria stated previously. For patients treated at Stanford: The study coordinator will inform the treating provider of our interest to discuss the study with the patient. We plan to either request the treating provider inform the patient of our study or (if no clinic visit is planned) we will request the treating provider contact the patient about our study prior to us seeking

recruitment. Patients will be asked whether they would be willing to participate in the study done by one of the study personnel/coordinators or a trained care provider. The study will be posted on campus and patient areas in the Stanford Hospital and Clinics, advertised by email to providers, and will be advertised online through a social media (Instagram and Facebook) national advertising campaign conducted by StudyPages. Interested patients can connect with the study team directly via the study website (also hosted by StudyPages) and will be enrolled in accordance with stated eligibility (inclusion and exclusion) criteria. In addition, to enhance recruitment we will advertise locally and will recruit from health systems outside of Stanford. Investigators will contact colleagues at regional health systems and inform them of our study. We will also provide information on the study to the provider who can offer it to any patient interested. We have already received about a dozen participation inquiries and have created a waitlist of patients to contact once the study commences.

6.1.1 Screening Procedures

Patients presenting to Stanford and affiliated clinics meeting our inclusion/exclusion criteria will be screened for participation based upon chart review. Patients connecting to the study team by self-referral or national recruitment campaign will be screened telephonically. Qualifying laboratory values will be obtained from standard diagnostic criteria including standard history, lab studies, imaging, previous endoscopic and surgery evaluation. Trained study coordinators will inform and consent patients into the study.

Participants will be asked about their participation in other studies and will be excluded from participation if the other studies are interventional. This will be reviewed by the PI.

6.2 Participant Discontinuation/Withdrawal

If subjects express desire to withdraw their participation, an optional final visit will be requested to collect the following blood and stool tests: CRP, ESR, CBC, blood samples for immune profiling, fecal calprotectin, and samples for microbiome/metabolite profiling, as well as the CDAI score and SIBDQ.

Subjects that withdraw because of unforeseeable circumstances/situations of *force majeur* such as a COVID-19 pandemic will be offered the option to re-enroll after a wash-out period of at least three months. However, re-enrollment is only possible for those that drop out before Data collection #4. In case of a re-enrollment, the data collected at the first enrollment will not be included into the analysis.

6.3 Inclusion Criteria

1. Patients with mild to moderate Crohn's disease (CDAI score 151-450)
2. Age between the ages of 18–70 (inclusive) at the start of the study

All recruited patients will be advised to discuss participation with their treating IBD physician.

6.4 Exclusion Criteria

Women who are pregnant, nursing or expect to be pregnant, individuals allergic to nuts, individuals with a body mass index (BMI) lower than 18, individuals diagnosed with a serious medical condition (unless approved in writing by a physician), individuals who have been severely weakened by a disease or medical procedure, individuals who are taking medication which may not be safely consumed with a calorie restricted diet, individuals with diabetes who are taking anti-diabetic drugs associated with risk of hypoglycemia, individuals with more than mild-moderate cardiovascular disease or life-threatening cancer (as determined by patient's physician) unless approved by a physician, individuals with history of severe cardiac disease (particularly uncompensated congestive heart failure NYHA grade 2 or more or LVEF <40%), individuals with a history of syncope, individuals with dietary needs incompatible with the IRCD meal plan, individuals with liver or kidney disorders that may be affected by very low glucose and protein content of the diet. Patients on a calorie restricted diet will also be excluded. Patients with relevant prior gastrointestinal surgery and consequences such as short bowel syndrome, ostomy of small or large intestine, total colectomy, proctocolectomy, ileoanal pouch will be excluded (not excluded are patients with resection of terminal ileum, resection of short strictures of the small intestine, hemicolectomy).

Subjects must be willing and able to adhere to all scheduled visits, treatment plan, laboratory tests, and other study procedures. All potential participants that plan to relocate or travel during the study period in a way that would interfere with their participation will not be included. If relocation becomes necessary unexpectedly, we—in discussion with the patient—will decide on a case-by-case basis if continued study participation is possible. Complications of disease (albeit less common in mild to moderate CD) such as penetrating or structuring phenotypes or extraintestinal manifestations (EIMs) are not automatically considered exclusion criteria. Appropriate medical treatment for CD and/or EIMs will not be withheld. Any adverse events will be solicited on regularly scheduled phone calls and patients will be clearly instructed to contact the investigators to report such events.

7. Intervention Description

7.1 IRCD (FMD) Intervention

Patients in the intervention arm will follow the plant-based IRCD for five consecutive days once per month for three months (see above study schematic). The IRCD (produced in a licensed commercial facility and commercially available) will be purchased. The IRCD provides all the nutritional requirements for those five-day diet periods each month. Patients in the control arm will follow their regular diet. A weekly questionnaire including dietary intake during periods of regular diet for both the IRCD and control arm will be provided. Regular phone calls and a daily online questionnaire will be administered to patients randomized to the IRCD during their cycles as described further below. Patients agreeing to colonoscopy will have this done at baseline (up to six weeks before Data Collection #1) and after the third cycle (Data Collection #4 or up to four weeks after the end of the third cycle). To learn more about possible long-term effects and durability of effects induced by an IRCD we will collect data on participants three months after

the last IRCD cycle (Data Collection #6). The current version of this research protocol has been approved by the Stanford IRB (#53161). All food to be consumed during each five-day IRCD cycle will be purchased from L-Nutra and be given directly to the patient (Table 1 and 2).

Vegetable Soup Mix
Ingredients: Rice Flour, Dried Onion, Inulin (Chicory Fiber), Dried Tomato, Dried Carrot, Salt, Dried Red Pepper, Dried Leek, Potato Starch, Olive Oil, Freeze Dried Basil, Spinach Powder, Dried Parsley, Natural Flavor

Tomato Soup Mix
Ingredients: Rice Flour, Dried Tomato Powder, Dried Onion, Inulin (Chicory Fiber), Potato Starch, Dried Tomato Pieces, Olive Oil, Salt, Yeast Extract, Dried Basil, Dried Parsley, Natural Flavor

Mushroom Soup Mix
Ingredients: Rice Flour, Carrot Powder, Dried Onion, Champignon Mushroom Powder, Inulin (Chicory Fiber), Dried Champignon Mushroom, Salt, Yeast Extract, Potato Starch, Olive Oil, Dried Parsley, Natural Flavor

Energy Drink Mix
Ingredients: Purified Water, Natural Vegetable Glycerin, Polylysine (Natural Preservative).

Energy Bar
Ingredients: Almond Meal, Macadamia Nut Butter, Honey, Pecan, Coconut, Flaxseed Meal, Coconut Oil, Vanilla, Sea Salt.

Chip Snack
Ingredients: Kale, Red Bell Peppers, Cashews, Sunflower Seeds, Nutritional Yeast, Lemon Juice, Cayenne Pepper, Sea Salt

Vegetable Powder with Vitamins and Minerals Supplements
(provides equivalent of a multivitamin; please see Supplementary Information – uploaded)

Table 1. Composition of IRCD/FMD

	Day 1	Days 2-5
Kcals	1090	725
Protein (gr/%)	29/10	18/9
Fat (gr/%)	67/56 20-30g MUFA 6-10 gr PUFA 12 gr SFA	35/44 10-15 gr MUFA 3-5 gr PUFA 6 gr SFA
Carbohydrates (gr/%)	92/34 Sugar 29gr Fiber 22 gr	85/47 Sugar 17.6 gr Fiber 14 gr

Table 2. Caloric Content of IRCD/FMD

The precise diet is sold commercially as a Fasting Mimicking Diet and has been used in clinical trials[14]. L-Nutra is a vendor in this study and will not receive any other benefit from this grant. This diet does not contain probiotics or other supplements apart from the equivalent of a multivitamin. For organizational reasons all meals for 5 days will be delivered on one day. The IRCD food comes in 5 small boxes, one box for each day, in order to avoid accidental consumption of the food for the following day. Participants will receive the IRCD foods at the beginning of each cycle and will be counseled and provided with written instructions.

7.2 Study Duration

We anticipated that the duration of the entire study will be thirty-two months. Screening will take about 20 minutes per participant. Regarding active participation by participant in the study: Subjects will have 15 days of active participation on the actual diet (over the course of three months) and additional days for sample collection, endoscopy (optional), and questionnaires; active participation is up to a maximum of 30 days over the course of six months. The completion of the online questionnaires will take about 15–30 minutes each. Data analysis is anticipated to be completed within 14 months of the end of data collection.

8. Outcome Measures

The forms of assessment in this aim include changes in CDAI and serum/stool markers of inflammation described below[25,26]. In addition to measures of disease activity, we will also evaluate the quality of life of patients using the validated SIBDQ, which we have licensed from McMaster University[27].

Primary Endpoint:

- Clinical response - defined as reduction of the CDAI of at least 70 points or achieving a CDAI score ≤150 (assessed at Data Collection #4)*.

Secondary Endpoints:

- Clinical remission - defined as a CDAI score ≤150*.
- Clinical response - defined as reduction of the CDAI of at least 100 points or achieving a CDAI score ≤150*.

- Clinical response - defined as reduction of the CDAI of at least 70 points or achieving a CDAI score ≤150 (assessed at Data Collection #6)*.
- Change in the clinical inflammatory marker CRP (assessed at Data Collection #4).*
- Change in the clinical inflammatory marker ESR (assessed at Data Collection #4).*
- Change in the clinical inflammatory marker fecal calprotectin (assessed at Data Collection #4).*
- Clinical remission as per Patient Reported Outcome (PRO) score with the average worst daily abdominal pain score of <=1 (using a 4-point scale, 0-3) and a loose/watery stool (Bristol Type 6 or 7) frequency score of <=3 (assessed at Data Collection #4).*
- Patient global assessment (PGA): "Do you believe you are in remission from your CD symptoms?" (Yes/No)* (assessed at Data Collection #4).
- Effect of IRCD on endoscopic outcomes: Changes in SES-CD* (assessed at Data Collection #4).
- Effect of IRCD on patient quality of life: Changes in SIBDQ* (assessed at Data Collection #4).

Exploratory Outcomes:

- Clinical remission – defined as CDAI score ≤150 at Data Collection #6.
- Clinical response – defined as reduction of the CDAI of at least 100 points or achieving a CDAI score ≤150 at Data Collection #6.
- Changes in clinical inflammatory markers at baseline versus at Data Collection #6
- Changes in SIBDQ at baseline versus at Data Collection #6.
- Changes in clinical markers of disease activity at baseline versus at Data Collection #2.
- Changes in gut metabolites (including short-chain fatty acids, bile acids) and microbiome (using 16s rRNA and shotgun metagenomics)*.

* Baseline values (Data Collection #1) will be compared to those from Data Collection #4.

9. Data Management

The proposed research will include data from 97 patients with CD recruited from the outpatient clinics of the Stanford Hospital and through a national recruitment campaign. The final data set will include clinical data from the patient's medical record, self-reported data about consumed diet and quality of life from questionnaires (collected using the REDCap electronic data capture tools), laboratory data from blood, tissue and stool works including metabolomic, microbiome, flow cytometry/CyTOF, and endoscopic data. The data will be generated by the study coordinator, the postdoc, the lab technician, the dietitian and the bioinformatician, under the supervision of PI and Co-Investigators. All study personnel will be trained in HIPAA protocols and are responsible for collecting, storing, and assuring that the data is stored appropriately on the group's servers. Backups are done in real-time using enterprise software implemented by Stanford University. Dr. Sinha will be responsible for implementing the data sharing and management plans and for monitoring regular adherence to the proposed plan.

All data that we will be collecting will be coded prior to storage, analysis, and release for sharing in order to protect the identity and privacy of the study subjects. All electronic data will be stored

on encrypted and password protected servers (Stanford Medicine Box and REDCap) that are able to handle protected health information and have the option to limit permissions to individuals. Clinical data will be digitally logged into a spreadsheet. Any sequencing data will be stored as the original raw data files containing reads and quality scores on the laboratory computer and on encrypted and password protected servers in accordance with the Stanford University Privacy Office. De-identified raw data will also be stored on the instrument computer as well as on the group servers mentioned above. Laboratory notebooks will be generated and maintained by researchers conducting experimentation and stored securely in the laboratory/office.

We aim for a timely release and sharing of our research for use by other researchers to expedite the translation of our results into knowledge and subsequent trials, and to make our work accessible to non-scientists. Our findings will be published and presented at scientific meetings to make it publicly accessible and usable. All data provided for journal articles will be maintained online by the publisher or in accordance with mentioned policies. The above-mentioned servers will be used for long term data preservation and access. Stored samples and auxiliary data will be made available upon request made to the PI.

Tissue and stool samples will be stored at -80°C in the PI's and/or Co-Investigator's laboratory. To ensure confidentiality, subjects' names and all personal identifying information will be removed. Each biobank sample will be given a code number. The samples will be utilized for the aims as outlined and for additional follow-on investigations.

10. Human Subjects Protection

10.1 Human Subjects Involvement and Risk Assessment

This study will recruit adult participants aged 18–70 (inclusive) years with mild to moderate CD as defined previously. The study design is a prospective, randomized, controlled, interventional diet trial. Subjects will be recruited from the Stanford IBD group, nationally through national recruitment campaigns, and by self-referral. This study does not impact standard medical care for any of the participants. Stanford IRB deemed this dietary intervention to be low risk and therefore not require a Data Safety Monitoring Board. Adverse events will be reported to the study PI and, as per IRB protocol, to the IRB as needed.

10.2 Purpose of Research

The purpose of this study is to test the efficacy of an IRCD to lower disease activity in individuals and/or improve quality of life with mild to moderate CD. Fasting has already been shown to reduce inflammation in animal models and bowel rest (fasting) is commonly used to treat intestinal inflammation clinically. An IRCD has clinical evidence of reduction of inflammatory markers such as CRP and TNF-alpha levels in human and animal models. Currently, there are no diets clearly associated with reducing symptoms in patients with CD. In this study, we will investigate if IRCD will reduce disease activity (assessed with disease activity score CDAI) and/or improve quality of life in patients with mild to moderate CD. Furthermore, we will

characterize gut-infiltrating immune cells, allowing us to identify alterations in immune profiles that may be influenced by the IRCD. In parallel, microbial/metabolomic changes in CD mediated by IRCD will be investigated. Immune and microbial changes will be correlated to participant genetics to determine if certain genetic variations are more susceptible to the dietary intervention. There is a paucity of research and an enormous need for better understanding of diet and intestinal inflammation.

10.3 Study Procedures, Materials, and Potential Risks

10.3.1 Screening and Consent

Patients will be screened based upon chart review to fit exclusion and inclusion criteria at Stanford-affiliated GI clinics or by direct self-referral or referral from care providers at non-Stanford GI clinics. Trained care providers and/or research coordinator(s) will recruit patients. Participants will be assigned ID numbers. All clinical data will be linked to the ID number, and the dataset linking patient names with ID numbers will be kept separately.

10.3.2 Study Procedures

Patients with mild to moderate CD who meet the inclusion and exclusion criteria will be enrolled. Upon enrollment, subjects will be randomized to either receive the IRCD intervention or to the control arm where they pursue their regular diet.

Labs will be performed at Stanford Clinical Laboratory or at common commercial labs (LabCorp and Quest). Research procedures will involve collecting stool and blood. The total amount of blood drawn at the data collection timepoints is anticipated to be less than 5 tablespoons. Patients can choose to have their lab work done at Stanford or at common commercial labs such as LabCorp or Quest Diagnostics. Subjects may elect to undergo colonoscopy as part of the research study at two timepoints ((1) up to 6 weeks before the baseline visit and (2) up to 4 weeks after the last day of the third diet cycle or at a corresponding time for the control group) with results scored using the SES-CD. All data and specimens collected will be de-identified to protect privacy.

All participants will complete a weekly online questionnaire about their diet and body weight throughout the study.

At the baseline visit (Data Collection #1), all patients will have blood and stool collected for clinical labs and research samples; SIBDQ, CDAI, PRO, and PGA scores will also be computed.

Subjects randomized to the intervention arm will start the first cycle of IRCD within 14 days after the baseline visit. All patients in the intervention arm will either receive a commercially available diet purchased by the research team from L-Nutra prior to each IRCD cycle. If participants have a strong preference against or intolerance for any foods provided in the commercially available diet, we will substitute using recipes developed by our dietitian that are consistent with the L-Nutra IRCD in terms of nutrients. During each IRCD cycle, participants will receive a daily

online questionnaire, and up to 3 phone calls by a study coordinator or dietitian to assess for adherence and adverse events. There will be two additional phone calls during non-IRCD days for all participants.

Within 7 days after completion of the first IRCD cycle, blood and stool samples will be collected for clinical labs and for research; SIBDQ, CDAI, PRO, and PGA scores will also be computed (Data Collection #2).

Up to 7 days before the start of IRCD cycle 2, blood samples will be collected for clinical labs (Data Collection #3).

Within 7 days after completion of IRCD cycle 3, blood and stool samples will be collected for clinical labs and as research samples; SIBDQ, CDAI, PRO, and PGA scores will also be computed (Data Collection #4).

One month after the start of IRCD cycle 3, blood samples will be collected for clinical labs (Data Collection #5).

Three months after the start of IRCD cycle 3, blood and stool samples will be collected for clinical labs and as research samples; SIBDQ, CDAI, PRO, and PGA scores will also be computed (Data Collection #6).

Subjects randomized to the control arm will make no changes to their diet during the study, but will have a collection of blood and stool samples (for clinical labs and research) as well as computation of SIBDQ and disease scores at the same time points. At the end of the study (off-protocol), participants in the control arm will receive three cycles of IRCD at no cost to increase motivation for study participation.

If subjects decide to withdraw their participation, a final visit will be requested to collect blood and stool samples (for clinical labs and research) as well as the SIBDQ, CDAI, PRO, and PGA scores.

Subjects that withdraw because of unforeseeable circumstances/situations of *force majeur* such as a SARS-CoV-2 pandemic will be offered the option to re-enroll after an appropriate wash-out period of at least three months. However, re-enrollment is only possible for those that drop out before Data collection #4. In case of a re-enrollment, the data collected at the first enrollment will not be included into the analysis.

10.3.3 Analysis of Collected Specimens

Blood and stool specimens collected for clinical lab tests (blood and stool) will be sent to Stanford Clinical Lab or will be collected at common commercial labs (e.g., LabCorp and Quest) for determination of ESR, CRP, CBC, calprotectin levels. Additional flow cytometry, Cytof, or other immunological/microbiome studies may be conducted on stored samples. Blood samples for research will only be collected at Stanford.

In the case that a participant experiences a serious medical event (excluding an IBD flare or symptom exacerbation) within ~4 weeks of a Data Collection, such data will be excluded from analysis. Examples of such events will include infections treated with antimicrobials or antivirals (e.g., C. diff, COVID-19, major surgery) or a medical event deemed serious in nature by the participant's treating physician (e.g., non-IBD hospitalization).

10.3.4 Steps Taken to Minimize Risk

Blood and stool will be collected from patients who have volunteered to be part of the study and have provided informed consent. Risks of blood draws are minimal. Optional colonoscopies will be performed in a subgroup of participants who provide consent to that (estimated to be up to 10 subjects in each arm). Colonoscopies are low-risk interventions. The risk associated with the study is low.

No standard treatment will be withheld from patients who consent to participate in the study. All patients will continue to take their recommended treatment for Crohn's disease as directed by their physician. This study does not affect standard medical care for any participants.

The most common potential risks include discomfort from the reduced calorie diet, blood draws, colonoscopy, and privacy concerns regarding the handling of identifiable data, of which we are taking all requisite steps to ensure proper handling. Physical risks are minimal and limited to standard and low-risk procedures such as venipuncture, colonoscopy, and sample collection. Psychological and social risks are also minimal, given the nature of the research and the steps taken to ensure privacy and confidentiality. We believe the risk level to be low. Further details are outlined below.

10.3.5 Study Endpoints

Primary Endpoint

- Clinical response, defined as reduction of the baseline (up to 14 days before IRCD cycle 1, or equivalent time point for control) CDAI by at least 70 points or achieving a CDAI score ≤150 at Data Collection #4 (within 7 days of completing IRCD cycle 3, or equivalent time point for control)

Key Secondary Endpoints

- Clinical remission (CDAI ≤150) at Data Collection #4
- Clinical response, defined as reduction of the baseline CDAI by at least 100 points or achieving a CDAI score ≤150 at Data Collection #4
- Clinical response, defined as reduction of the baseline CDAI by at least 70 points or achieving a CDAI score ≤150 at Data Collection #6 (three months after start of IRCD cycle 3, or equivalent time point for control)
- Change in clinical inflammatory markers (CRP, ESR, fecal calprotectin) at Data Collection #4

- Clinical remission as per Patient Reported Outcome (PRO) score with the average worst daily abdominal pain score of ≤1 (using a 4-point scale, 0–3) and loose stool (Bristol Type 6 or 7) frequency score of ≤3 at Data Collection #4
- *Patient global assessment (PGA), or response to "Do you believe you are in remission from your CD symptoms?" (Yes/No) at Data Collection #4
- Change in SES-CD from baseline at Data Collection #4
- Change in SIBDQ score at baseline versus at Data Collection #4

Additional Secondary Endpoints

- Clinical remission (CDAI ≤150) at Data Collection #6
- Clinical response, defined as reduction of the baseline CDAI by at least 100 points or achieving a CDAI score ≤150 at Data Collection #6
- Changes in clinical inflammatory markers (CRP, ESR, fecal calprotectin) at baseline versus at Data Collection #6
- Change in SIBDQ score at baseline versus at Data Collection #6
- Changes in clinical markers of disease activity at baseline versus at Data Collection #2 (within 7 days of completing IRCD cycle 1, or equivalent time point for control)
- Changes in cytokines/chemokines and immune cell profiles (as mentioned above) using flow cytometry and mass cytometry (CyTOF) at Data Collection #4 compared to baseline
- Changes in gut metabolites (including short-chain fatty acid and bile acid profiles) and microbiome profiles (using 16S rRNA/shotgun metagenomics) at baseline versus at Data Collection #4 and #6

10.4 Benefits

The benefits which may reasonably be expected to result from this study are an improvement of symptoms relating to CD, as reflected by a reduced disease activity score CDAI. Future patients may benefit upon integration of the IRCD into their lifestyle for a consistent relief of symptoms.
In addition, further analyses of blood and stool samples (immune profiling, microbial or metabolomic changes in CD mediated by IRCD) help to elucidate the mechanism by which IRCD reduces intestinal inflammation, and also help identify subgroups of patients that my differentially respond to diet based on personalized signatures.

The potential benefits of this research include a deeper understanding of diet in CD, which could lead to personalized treatment strategies and improved clinical outcomes for participants and others. While direct benefits to participants are not anticipated, the risk level is low, and the potential for significant contributions to the field of CD and IBD justifies the study.

10.4.1 Importance of the Knowledge to be Gained

The knowledge to be gained from this research is critical to advancing our understanding of IBD and its underlying mechanisms. By investigating the role of diet in CD response, this study could lead to significant improvements in personalized medicine and therapeutic strategies for IBD. The anticipated benefits of this research far outweigh the minimal risks, making it a valuable contribution to the field of gastroenterology and beyond.

10.5 Compensation and Incentives

Compensation for participating in the study will be paid to the subjects to partially offset patient costs to participate in the study such as parking/travel-related expenses, the need for time off work for lab visits and colonoscopies, and inconvenience. Study participants will receive compensation of $200 for complete study participation (less than $35 per visit) and those completing the optional two colonoscopies will receive an additional $100 per colonoscopy.

All subjects will require 6 study visits. Patient participation lasts approximately 5 months and will be reimbursed $200 in total to cover parking, travel, and inconvenience. Those subjects who agree to colonoscopies will have 8 study visits in total and will be reimbursed additional $100 per colonoscopy ($400 in total: $200 for study participation + $200 for two colonoscopies). Colonoscopies impose additional burden on the participant, likely including some amount of discomfort and additional study visits as well as time off from work. The compensation offered reflects this burden.

For logistical reasons we will provide payment when the subject ends their participation in the study or completes the study. The payments are provided to compensate for the inconvenience/personal cost of participating in a study that requires multiple visits. Therefore, if a patient completes several visits, we will prorate their compensation. Participants who complete only 1–3 visits will not receive compensation. No costs will be charged to the participant.

10.6 Risks

Risks of the IRCD include those associated with reduced caloric intake such as mild fatigue, dizziness, weakness, and headaches. The risks of blood draws include pain, a bruise at the point where the blood is taken, redness and swelling of the vein and infection, and a rare risk of fainting. The risks of colonoscopy include pain, bloating, bleeding, infection, perforation, and adverse reaction to anesthetics.

10.6.1 Overall Evaluation of Risk

Low - innocuous procedures such as phlebotomy, urine or stool collection, no therapeutic agent, or safe therapeutic agent such as the use of an FDA approved drug or device.

10.6.2 Procedures for Minimizing all Potential Risks

For colonoscopies: Patients will be in a monitored setting with an MD during the procedure. Data will be maintained electronically on encrypted USB that is password protected or on encrypted and password protected laptops or servers. The online questionnaires will be stored in REDCap. No other hazards are anticipated.

10.6.3 Termination of Experiment

Experiment will terminate upon completion of follow-up evaluations (lab and stool sample collection, SIBDQ and disease score evaluation) three months after cycle three. Patients can also choose to withdraw from the study at any time. An MD will always be present in case of

adverse effects to the participants by email or in the clinic. Data collection is expected to terminate by June 14, 2025.

10.7 Adequacy of Protection Against Risks

10.7.1 Informed Consent and Assent

Informed consent will be obtained from all participants prior to their involvement in the study as further outlined above. This process will occur in a private setting, either in person or remotely, where the study team will explain the study, its risks, and benefits, and answer any questions. Participants will be given sufficient time to consider participation and ask any questions before signing the consent form. The consent process will be documented on PHI-compliant REDCap, and all necessary steps will be taken to ensure that participants fully understand the study's scope and their rights as participants, including the right to stop participation at any time.

10.7.2 Protections Against Risk

Each employee or investigator involved with this study is required to participate in human subjects and HIPAA training. To protect against potential risks, all specimens and data will be de-identified, removing all HIPAA identifiers before analysis. The data will be stored on secure, PHI-compliant servers (e.g., Stanford's Nero cluster). Only authorized study personnel will have access to the data, and all data will be encrypted. Participants' privacy will be rigorously protected.

10.7.3 Privacy and Confidentiality

Privacy Protections: All interaction with potential and active participants will occur in standard exam/clinical areas, or through phone or video calls. Participants may be consented via REDCap. Only the participant, investigator(s), coordinators, and standard clinical personnel (e.g. MD, RN, and/or nursing assistant) will be present. Others may be present in the GI clinic if the participant wishes. There will not be follow-up interactions with the patient after the completion of the study. Specimens will be labeled with a numbered coding system if any analysis that is not part of the standard of care is used. Specimens used in this study will not contain PHI data. A numbered coding system will be used to label the specimens. The patient's coded disease-related data will be available only to investigators associated with the study. All the research staff are clinical care providers and scholars affiliated with Stanford and are aware of the HIPAA regulations and are CITI trained.

Confidentiality Protections: We will be working with the following types of data in support of recruitment activities: full name, telephone numbers, email addresses, medical record numbers, demographics (age, sex, etc.), lab or pathology test results, diagnosis or procedure codes, clinical narratives or reports, and prescriptions or medications. We will be using these types of data internally at Stanford. Furthermore, since we will be working with free text narratives we may be incidentally exposed to the following: Names, Telephone numbers, Address, Dates more precise than year only, Email addresses, Medical record numbers, as well as any other unique identifying number, characteristic, or code.

Data will be maintained electronically on encrypted USB that is password-protected or on encrypted and password protected laptops or servers. The online questionnaires will be stored in REDCap. Electronic data will be stored on encrypted and password-protected USB, laptops or servers. The research team will have access to the data. All investigators handling such data will be CITI trained and qualified to handle HIPAA information. Patients will be assigned a coded study ID number upon enrollment. Specimen labels will only include the coded "number" as well as description of the tissue and the date of collection. The investigator collecting the data and samples will be responsible for coding them using a numbered coding system. The coding system will be stored on an encrypted USB (password-protected and stored in a locked office that only the study personnel will have access to) or on encrypted and password-protected laptops or servers.

Data will be shared using encrypted USB or servers on password-protected computers. Any shared PHI data will be done with encryption. All of the research staff are clinical care providers and/or scholars, or clinical research professionals affiliated with Stanford; they are aware of/trained in the HIPAA regulations and are CITI certified as applicable.

De-identified samples and data sets for patients who have agreed to sample collection will be analyzed by lab members trained in the protection of human subject data on PHI-compliant, secure servers at Stanford.

10.7.4 Protections for Vulnerable Populations

We do not intend to specifically study populations that are vulnerable to coercion or undue influence and pregnant women, fetuses, and neonates as part of this study. This study involves only adult participants due to the inherent differences of pediatric and adult IBD disease course and treatments and risk for introduction of biases, as previously described. We do not intend to recruit for vulnerable populations such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons or others who may be considered vulnerable populations. Pregnant women are excluded.

10.8 Data and Safety Monitoring Plan

Not applicable to this application as it does not include conduct of a clinical trial and is low risk.

10.8.1 Approach to Data Safety and Monitoring

The following data and events will be reviewed: adverse events (AEs), serious adverse events (SAEs), suspected unexpected serious adverse reactions (SUSARs), participant consent forms, protocol deviations, and case report forms.

The study PI (Dr. Sidhartha Sinha) will be responsible for implementing the data sharing and management plans and for monitoring regular adherence to the proposed plan. Any SAEs and SUSARs will be reported within 24 hours of learning, and unanticipated problems (UPs) within 5 days of learning to the IRB.

The study will be terminated prematurely if, in the opinion of the study PI, an unfavorable risk-benefit ratio develops or if continuation of the study no longer appears to be reasonably justified (due to scientific, organizational, financial, or other reasons). The final decision regarding the premature termination of the study will be made by the study PI. The study PI will disseminate the outcome of the reviews to the IRB. The Protocol Director (study PI) will be the only monitoring entity for this study.

11. Monitoring and Quality Assurance

Scheduled “check-ins” and surveys will also be utilized to assess/improve adherence with the IRCD and to collect additional information pertinent to potential subgroup analysis. First, participants will be asked to complete a daily online questionnaire regarding their experience on the IRCD. This questionnaire will include details on any possible IRCD foods that were not consumed and if there were any protocol deviations. Given the reduced calories of the IRCD, we anticipate the vast majority of participants will be eager to consume the entire diet. Furthermore, participants will be called by the study coordinator or the dietitian up to three times during the IRCD cycles (e.g. on the first, third, and fifth day) to assess adherence and address concerns. In addition, all participants will be asked to complete a weekly online questionnaire that includes assessment of the contents of their regular diet. In order to obtain key information and reduce the burden on patients that could impact recruitment, we ask mainly closed questions. We will send weekly reminders as text or email to improve the participant’s compliance in completing the survey. All participants will undergo two phone calls by our dietitian to obtain an assessment of food intake on non-diet days. We recognize the limitations of a self-reported diet assessment. A somewhat unique aspect of our study, however, is that while we would ideally like to have a more rigorous measure of food consumption on each day, our intervention is only five days per month, and the main adherence goal is to ensure participants in the IRCD arm take IRCD as instructed. Hence, phone calls and succinct online questionnaires appear to be an appropriate assessment method for this study (versus other means such as food photographs/mobile application entry). Study participants will also be educated on the importance of accuracy for the results of the study to be useful. From our personal experience treating patients with CD and the available literature, we believe this study population is very eager to explore dietary interventions for their disease and will be motivated to adhere to the study protocol[3,4].

STATISTICAL ANALYSIS PLAN

Effects of an intermittent reduced calorie diet on Crohn's disease

Registration: NCT04147585
Experimental Treatment: Intermittent reduced calorie diet/fasting-mimicking diet
Principal Investigator: Sidhartha Sinha, MD
Control Treatment: baseline diet
Indication: mild-to-moderate Crohn's disease
Statistical analysis plan version: 3.0

List of Abbreviations

Abbreviation	Full Term
5-ASA	5-aminosalicylic acid
anti-TNF	Anti-tumor necrosis factor
BMI	Body mass index
CD	Crohn's disease
CDAI	Crohn's disease activity index
CRP	C-reactive protein
CTCAE	Common terminology criteria for adverse events
ESR	Erythrocyte sedimentation rate
IBD	Inflammatory bowel disease
ICE	Intercurrent events
IQR	Interquartile range
IRCD	Intermittent reduced calorie diet
ITT	Intention-to-treat
SES-CD	Simple Endoscopic Score for Crohn's Disease

1. Statistical Overview

1.1 Study Objectives

The primary objective of the study is to compare the ability of IRCD versus control diet to induce clinical response in patients with mild-to-moderate CD. Clinical response is defined as a reduction in CDAI by at least 70 points (relative to baseline) or achieving a CDAI score ≤150 at Data Collection #4.

The secondary objectives of the study are to:

- To determine the ability of IRCD versus control diet to induce clinical remission in patients with mild-to-moderate CD.
- To assess the ability of IRCD to reduce clinical biomarkers of inflammation relative to control diet.

- To understand the impact of IRCD on quality of life in patients.
- To evaluate the safety of IRCD in patients with mild-to-moderate CD.
- To determine the impact of IRCD of endoscopic disease activity, as determined by SES-CD.

1.2 Study Design

1.2.1 Overall Design

This is a randomized, controlled, national study in which 97 patients with mild-to-moderate (defined by CDAI at screening) Crohn's disease will be enrolled. Eligible patients will be block randomized in a 2:1 ratio to the IRCD group and control group.

Patients in the experimental group will consume one 5-day cycle of IRCD per month for 3 consecutive months. Patients in the control group will continue their baseline diet throughout the study period.

1.2.2 Determination of sample size

This study is powered to detect a significant change in our primary endpoint of reduction of the CDAI of at least 70 points or achieving a CDAI score ≤150, given an alpha of 0.05 and a power of 90%. The expected difference in CDAI between groups is assumed to be proportional to the difference observed in Wei *et al.* between IRCD and control for CRP[14]. Given these parameters, approximately 75 patients would need to be recruited, allowing for a dropout rate slightly above 30%, congruent to what is seen in diet trials. Furthermore, the use of immune profiling (and comparison with known profiles in CD during flare and remission that we have recently published) will allow us to detect even subtle changes/trends that may be missed in conventional measures used in diet studies[28]. The study was not powered to detect significance in all outcomes, partially because of the lack of comparable studies and the scope of this investigation.

Additionally, we will perform an interim analysis after half of the subjects have completed the study in order to do a sample size re-estimation.

1.2.3 Randomization

The patients will be randomized using block randomization in a 2:1 ratio to the IRCD group or control group. The block size will be six.

2. Estimands

We will set both estimands for the primary and secondary endpoints for this study, with due consideration of intercurrent events. Definitions for intercurrent events (ICE) are below and are followed by definitions for estimands.

2.1 Definition of intercurrent events

ICE1: premature discontinuation due to patient preference, intolerability or safety event.
ICE2: major protocol deviation affecting efficacy evaluation.

2.2 Primary estimand

Clinical response - defined as reduction of the CDAI of at least 70 points or achieving a CDAI score ≤150 (assessed at Data Collection #4).

Population: Adult patients (age 18–70) with mild-to-moderate Crohn's disease (CDAI 150–450)
Treatment:

- Treatment group: IRCD for 5 consecutive days per month for a total of 3 months. Consume baseline diet for all remaining days in the 3-month period.
- Control group: continue baseline diet for 3 months.
- All participants continued standard-of-care treatment for their Crohn's disease. Medication changes (e.g. vedolizumab to infliximab), dose changes (infliximab 5 mg/kg to 10 mg/kg) and steroid prescription were allowed for all participants.

Variable: reduction of the CDAI of at least 70 points (assessed at Data Collection #4 relative to baseline CDAI) or achieving a CDAI score ≤150.
Intercurrent events and strategies:

1. ICE1: premature discontinuation due to patient preference, intolerability or safety event
    a. Strategies: data after premature discontinuation will be included in the analysis regardless of the occurrence of ICE1; all collected data will be analyzed.
    b. Considerations: data after occurrence of ICE1 will be analyzed, given this will provide the most accurate reflection of real-world efficacy IRCD
2. ICE2: major protocol deviation affecting efficacy evaluation
    a. Strategies: data after major protocol deviation will be handled by carrying forward using the last observation prior to the onset of the intercurrent event.

Population Level Summary: difference between groups

2.3 Secondary estimands

Secondary estimands are summarized below:

2.3.1 Clinical remission - defined as a CDAI score ≤150.

Population: Adult patients (age 18–70) with mild-to-moderate Crohn's disease (CDAI 150–450)
Treatment:

- Treatment group: IRCD for 5 consecutive days per month for a total of 3 months. Consume baseline diet for all remaining days in the 3-month period.
- Control group: continue baseline diet for 3 months.
- All participants continued standard-of-care treatment for their Crohn's disease. Medication changes (e.g. vedolizumab to infliximab), dose changes (infliximab 5 mg/kg to 10 mg/kg) and steroid prescription were allowed for all participants.

Variable: Achieving a CDAI score ≤150.
Intercurrent events and strategies:

3. ICE1: premature discontinuation due to patient preference, intolerability or safety event
    a. Strategies: data after premature discontinuation will be included in the analysis regardless of the occurrence of ICE1; all collected data will be analyzed.
    b. Considerations: data after occurrence of ICE1 will be analyzed, given this will provide the most accurate reflection of real-world efficacy IRCD
4. ICE2: major protocol deviation affecting efficacy evaluation
    a. Strategies: data after major protocol deviation will be handled by carrying forward using the last observation prior to the onset of the intercurrent event.

Population Level Summary: difference between groups

2.3.2 Clinical response - defined as reduction of the CDAI of at least 100 points or achieving a CDAI score ≤150

Population: Adult patients (age 18–70) with mild-to-moderate Crohn's disease (CDAI 150–450)
Treatment:

- Treatment group: IRCD for 5 consecutive days per month for a total of 3 months. Consume baseline diet for all remaining days in the 3-month period.
- Control group: continue baseline diet for 3 months.
- All participants continued standard-of-care treatment for their Crohn's disease. Medication changes (e.g. vedolizumab to infliximab), dose changes (infliximab 5 mg/kg to 10 mg/kg) and steroid prescription were allowed for all participants.

Variable: defined as reduction of the CDAI of at least 100 points (relative to baseline) or achieving a CDAI score ≤150.
Intercurrent events and strategies:

5. ICE1: premature discontinuation due to patient preference, intolerability or safety event
    a. Strategies: data after premature discontinuation will be included in the analysis regardless of the occurrence of ICE1; all collected data will be analyzed.
    b. Considerations: data after occurrence of ICE1 will be analyzed, given this will provide the most accurate reflection of real-world efficacy IRCD
6. ICE2: major protocol deviation affecting efficacy evaluation
    a. Strategies: data after major protocol deviation will be handled by carrying forward using the last observation prior to the onset of the intercurrent event.

Population Level Summary: difference between groups

2.3.3 Clinical response - defined as reduction of the CDAI of at least 70 points or achieving a CDAI score ≤150 (assessed at Data Collection #6)

Population: Adult patients (age 18–70) with mild-to-moderate Crohn's disease (CDAI 150–450)
Treatment:

- Treatment group: IRCD for 5 consecutive days per month for a total of 3 months. Consume baseline diet for all remaining days in the 3-month period.
- Control group: continue baseline diet for 3 months.
- All participants continued standard-of-care treatment for their Crohn's disease. Medication changes (e.g. vedolizumab to infliximab), dose changes (infliximab 5 mg/kg to 10 mg/kg) and steroid prescription were allowed for all participants.

Variable: defined as reduction of the CDAI of at least 70 points at Data Collection #6 relative to baseline or achieving a CDAI score ≤150 at Data Collection #6.
Intercurrent events and strategies:

7. ICE1: premature discontinuation due to patient preference, intolerability or safety event
    a. Strategies: data after premature discontinuation will be included in the analysis regardless of the occurrence of ICE1; all collected data will be analyzed.
    b. Considerations: data after occurrence of ICE1 will be analyzed, given this will provide the most accurate reflection of real-world efficacy IRCD
8. ICE2: major protocol deviation affecting efficacy evaluation
    a. Strategies: data after major protocol deviation will be handled by carrying forward using the last observation prior to the onset of the intercurrent event.

Population Level Summary: difference between groups

2.3.4 Change in the clinical inflammatory marker CRP

Population: Adult patients (age 18–70) with mild-to-moderate Crohn's disease (CDAI 150–450)
Treatment:

- Treatment group: IRCD for 5 consecutive days per month for a total of 3 months. Consume baseline diet for all remaining days in the 3-month period.
- Control group: continue baseline diet for 3 months.
- All participants continued standard-of-care treatment for their Crohn's disease. Medication changes (e.g. vedolizumab to infliximab), dose changes (infliximab 5 mg/kg to 10 mg/kg) and steroid prescription were allowed for all participants.

Variable: defined as the change in CRP at Data Collection #4 relative to baseline.
Intercurrent events and strategies:

9. ICE1: premature discontinuation due to patient preference, intolerability or safety event
    a. Strategies: data after premature discontinuation will be included in the analysis regardless of the occurrence of ICE1; all collected data will be analyzed.
    b. Considerations: data after occurrence of ICE1 will be analyzed, given this will provide the most accurate reflection of real-world efficacy IRCD
10. ICE2: major protocol deviation affecting efficacy evaluation
    a. Strategies: data after major protocol deviation will be handled by carrying forward using the last observation prior to the onset of the intercurrent event.

Population Level Summary: difference between groups

2.3.5 Change in the clinical inflammatory marker calprotectin

Population: Adult patients (age 18–70) with mild-to-moderate Crohn's disease (CDAI 150–450)
Treatment:

- Treatment group: IRCD for 5 consecutive days per month for a total of 3 months. Consume baseline diet for all remaining days in the 3-month period.
- Control group: continue baseline diet for 3 months.
- All participants continued standard-of-care treatment for their Crohn's disease. Medication changes (e.g. vedolizumab to infliximab), dose changes (infliximab 5 mg/kg to 10 mg/kg) and steroid prescription were allowed for all participants.

Variable: defined as the change in calprotectin at Data Collection #4 relative to baseline

Intercurrent events and strategies:

11. ICE1: premature discontinuation due to patient preference, intolerability or safety event
    a. Strategies: data after premature discontinuation will be included in the analysis regardless of the occurrence of ICE1; all collected data will be analyzed.
    b. Considerations: data after occurrence of ICE1 will be analyzed, given this will provide the most accurate reflection of real-world efficacy IRCD
12. ICE2: major protocol deviation affecting efficacy evaluation
    a. Strategies: data after major protocol deviation will be handled by carrying forward using the last observation prior to the onset of the intercurrent event.

Population Level Summary: difference between groups

2.3.6 Clinical remission as per Patient Reported Outcome (PRO) score

Population: Adult patients (age 18–70) with mild-to-moderate Crohn's disease (CDAI 150–450)
Treatment:

- Treatment group: IRCD for 5 consecutive days per month for a total of 3 months. Consume baseline diet for all remaining days in the 3-month period.
- Control group: continue baseline diet for 3 months.
- All participants continued standard-of-care treatment for their Crohn's disease. Medication changes (e.g. vedolizumab to infliximab), dose changes (infliximab 5 mg/kg to 10 mg/kg) and steroid prescription were allowed for all participants.

Variable: defined as the average worst daily abdominal pain score of <=1 (using a 4-point scale, 0-3) and a loose/watery stool (Bristol Type 6 or 7) frequency score of <=3. PRO score at Data Collection #4 was compared to baseline PRO.
Intercurrent events and strategies:

13. ICE1: premature discontinuation due to patient preference, intolerability or safety event
    a. Strategies: data after premature discontinuation will be included in the analysis regardless of the occurrence of ICE1; all collected data will be analyzed.
    b. Considerations: data after occurrence of ICE1 will be analyzed, given this will provide the most accurate reflection of real-world efficacy IRCD
14. ICE2: major protocol deviation affecting efficacy evaluation
    a. Strategies: data after major protocol deviation will be handled by carrying forward using the last observation prior to the onset of the intercurrent event.

Population Level Summary: difference between groups

2.3.7 Patient Global Assessment

Population: Adult patients (age 18–70) with mild-to-moderate Crohn's disease (CDAI 150–450)
Treatment:

- Treatment group: IRCD for 5 consecutive days per month for a total of 3 months. Consume baseline diet for all remaining days in the 3-month period.
- Control group: continue baseline diet for 3 months.
- All participants continued standard-of-care treatment for their Crohn's disease. Medication changes (e.g. vedolizumab to infliximab), dose changes (infliximab 5 mg/kg to 10 mg/kg) and steroid prescription were allowed for all participants.

Variable: Percentage of patients responding “yes” to this question at Data Collection #4: “Do you believe you are in remission from your CD symptoms?” (Yes/No).
Intercurrent events and strategies:

15. ICE1: premature discontinuation due to patient preference, intolerability or safety event
    a. Strategies: data after premature discontinuation will be included in the analysis regardless of the occurrence of ICE1; all collected data will be analyzed.
    b. Considerations: data after occurrence of ICE1 will be analyzed, given this will provide the most accurate reflection of real-world efficacy IRCD
16. ICE2: major protocol deviation affecting efficacy evaluation
    a. Strategies: data after major protocol deviation will be handled by carrying forward using the last observation prior to the onset of the intercurrent event.

Population Level Summary: difference between groups

2.3.8 Short IBD Questionnaire

Population: Adult patients (age 18–70) with mild-to-moderate Crohn’s disease (CDAI 150–450)
Treatment:

- Treatment group: IRCD for 5 consecutive days per month for a total of 3 months. Consume baseline diet for all remaining days in the 3-month period.
- Control group: continue baseline diet for 3 months.
- All participants continued standard-of-care treatment for their Crohn’s disease. Medication changes (e.g. vedolizumab to infliximab), dose changes (infliximab 5 mg/kg to 10 mg/kg) and steroid prescription were allowed for all participants.

Variable: the proportion of patients at Data Collection #4 with a good IBD-related quality of life, defined as an SIBDQ score of greater than or equal to 50.
Intercurrent events and strategies:

17. ICE1: premature discontinuation due to patient preference, intolerability or safety event
    a. Strategies: data after premature discontinuation will be included in the analysis regardless of the occurrence of ICE1; all collected data will be analyzed.
    b. Considerations: data after occurrence of ICE1 will be analyzed, given this will provide the most accurate reflection of real-world efficacy IRCD
18. ICE2: major protocol deviation affecting efficacy evaluation
    a. Strategies: data after major protocol deviation will be handled by carrying forward using the last observation prior to the onset of the intercurrent event.

Population Level Summary: difference between groups

2.3.9 Change in SES-CD

Population: Adult patients (age 18–70) with mild-to-moderate Crohn’s disease (CDAI 150–450)
Treatment:

- Treatment group: IRCD for 5 consecutive days per month for a total of 3 months. Consume baseline diet for all remaining days in the 3-month period.
- Control group: continue baseline diet for 3 months.
- All participants continued standard-of-care treatment for their Crohn’s disease. Medication changes (e.g. vedolizumab to infliximab), dose changes (infliximab 5 mg/kg to 10 mg/kg) and steroid prescription were allowed for all participants.

Variable: the proportion of patients achieving an SES-CD of less than 4 (as scored by a blinded endoscopist) at Data Collection #4
Intercurrent events and strategies:

19. ICE1: premature discontinuation due to patient preference, intolerability or safety event
    a. Strategies: data after premature discontinuation will be included in the analysis regardless of the occurrence of ICE1; all collected data will be analyzed.
    b. Considerations: data after occurrence of ICE1 will be analyzed, given this will provide the most accurate reflection of real-world efficacy IRCD
20. ICE2: major protocol deviation affecting efficacy evaluation
    a. Strategies: data after major protocol deviation will be handled by carrying forward using the last observation prior to the onset of the intercurrent event.

Population Level Summary: difference between groups

3. General Specifications for Statistical Analysis

3.1 General Considerations

All statistical analyses will be conducted using R. Data will be summarized using descriptive methods following typical principles unless otherwise specified. Continuous data will be described using median and IQR. Categorical data will be described using counts and percentages. One decimal place will be kept and the second rounded, e.g. 60.17 is presented as 60.2.

Between-group comparisons for continuous variables will be calculated using two-tailed, equal variance t tests. Chi-square test or Fisher's exact test will be used to compare dichotomous end points (i.e. clinical response based on CDAI change as defined above) as appropriate. For all tests, we will use a significance level of 0.05.

Primary analysis of all data will be done by intention-to-treat (ITT); however, we will also compare ITT to per protocol analysis to provide a better understanding of the possible effects in participants who complete the study as planned.

3.2 Multicenter study

Data from all centers will be fully integrated and analyzed together for analysis

3.3 Subgroup Analyses

Subgroup analyses will be conducted in the following sub-groups of patients:

- Mild (CDAI 150-219) and moderate (CDAI 220-450) CD
- Location of CD (L1 - terminal ileum, L2 - colon, L3 - ileocolonic)
- With and without concomitant IBD therapy

4. Data Handling Rules

4.1. Baseline and Change from Baseline

The baseline is defined at the last non-missing measurement before the data of the first day of dietary therapy but no more than 14 days prior to the start of the study. Changes are calculated at all subsequent time points relative to baseline.

4.2 Study Time Points

Study time point is defined as relative to the reference point. The reference point is baseline data collection. All timepoints beyond the baseline are for the assessment of clinical efficacy, biomarkers, and safety. The timepoints are as follows:

1) Data collection 1 (baseline): up to 14 days prior to start of the 1st cycle of IRCD
2) Data collection 2: starting immediately after completion of the 1st cycle of IRCD, days 1-7 post completion.
3) Data collection 3: up to 7 days before start of IRCD cycle 2
4) Data collection 4: starting immediately after completion of the 3rd cycle of IRCD, days 1-7 post completion.
5) Data collection 5: 1 month after completion of the 3rd cycle of IRCD.
6) Data collection 6: 3 months after completion of the 3rd cycle of IRCD.

4.3 Baseline Characteristics

The classifications for a diagnosis of Crohn's disease, assessment of clinical disease activity, disease phenotype, and concurrent treatment are below:

- Confirmation of original diagnosis of Crohn's disease: established by each patient's gastroenterologist based on usual clinical, radiographic, endoscopic, and histologic criteria. The participants are required to provide these records at enrollment, and the diagnosis will be confirmed by the principal investigator.
- Assessment of clinical disease activity: clinical activity was assessed by CDAI. All patients at screening are required to have either mild (CDAI 150-219) or moderate (CDAI 250-450) activity.
- Disease phenotype: disease behavior is characterized by the Montreal classification. A1 is defined as less than or equal to 16 years at diagnosis, A2 is defined as 17-40 years at diagnosis and A3 is defined as greater than 40 years at diagnosis. L1 is defined as ileal disease, L2 is defined as colonic disease, and L3 is defined as ileocolonic disease; L4 is used as a modifier or as a stand-alone designation for upper GI disease. B1 is defined as inflammatory disease, B2 is defined as stricturing disease, and B3 is defined as penetrating disease; +p is used as a modifier or as a stand-alone designation for perianal disease.
- Concurrent treatment: concurrent treatment is defined as use of any 5-ASA, thiopurines, methotrexate, steroids (prednisone, budesonide), anti-TNF (infliximab, adalimumab, certolizumab), vedolizumab, ustekinumab, or tofacitinib. Any emerging therapies that are

available after the writing of this protocol will also be allowed per the discretion of the treating physician.

4.4 Missing Data

For dichotomous outcomes, a participant who withdraws prior to time of assessment or is lost to follow-up will be categorized as a treatment failure. For continuous outcomes, missing data will be imputed by carrying forward the first observation.

4.5 Visit Window

All analyses will be conducted per schedule visits regardless of deviation from the visit window.

5. Statistical Analysis Methods

5.1 Study Subjects

The study subject disposition, and handling of protocol deviations, demographic and baseline characteristics is detailed below.

5.1.1 Subject Disposition

All subjects who are randomized will be included in the analysis (intention-to-treat).

The number of subjects who were screened (noting number who are excluded) and recruited (noting number who withdrew prior to randomization) will be summarized. After randomization, the number and patients who received the allocated intervention will be noted along with the number who were randomized but withdrew prior to starting the study period. During follow-up, the number of patients who withdrew from the study will be noted, and the reasons for withdrawal will be tabulated.

5.1.2 Protocol Deviation

Protocol deviation will be characterized as a minor or major deviation. The impact of the protocol deviation will be assessed and agreed upon by the investigators. Any major protocol deviations will be summarized by the treatment group.

5.1.3 Demographic and Baseline Characteristics

We will collect and tabulate the following demographic data and baseline characteristics by treatment group: age, sex, race, ethnicity, BMI, smoking status (never, past, current), alcohol use (never, light, moderate, heavy), CD phenotype by Montreal Classification, baseline CDAI score, CD medication at baseline, baseline CRP, baseline ESR, and baseline fecal calprotectin.

5.2 Efficacy Analysis

All efficacy analyses will be conducted by intention-to-treat analyses, according to the estimands that have been pre-specified.

5.2.1 Primary Estimand and Analysis

The primary endpoint of the trial is proportion of patients who achieve a reduction in CDAI by at least 70 points (relative to baseline) or achieving a CDAI score ≤150 at Data Collection #4. The null hypothesis is the proportion of patients who achieve clinical response is the same between IRCD and control groups.

Between-group comparisons for difference in proportion for the primary endpoint will be assessed by chi-square test using a significance level of 0.05.

5.2.2 Secondary Estimands

The study has multiple secondary endpoints as noted above. For all categorical secondary endpoints, between-group comparisons for difference in proportion for the primary endpoint will be assessed by chi-square test. For all continuous secondary endpoints, between-group comparisons will be made using a two-sided T-test.

5.2.3 Subgroup Analyses

The subgroup analyses will be performed similarly to the primary and secondary analyses. In subgroups where the number of patients is small, instead of a chi-square test, Fisher's exact test may be used as appropriate. The subgroups are detailed in 9.3.3.

5.3. Safety Analysis

All adverse events will be graded according to CTCAE criteria and tabulated by the assigned group.

Treatment-related adverse events are defined as CTCAE-tracked symptoms that are self-reported by the study participant, starting from the day of study initiation until the end of the study period. All adverse events will be considered to be related to the study treatment, unless otherwise determined by the study investigators. Serious adverse events will be monitored and noted. A serious adverse event is defined as any event that results in death, disability, requires hospitalization or requires an intervention to prevent significant harm. The investigators are required to be notified of any serious adverse events.

Analysis of adverse events will be part of the prespecified interim analysis as well as on study completion.

6. Pre-specified Analysis

6.1 Interim Analysis

Interim analysis is planned once half of the target recruitment is complete. Analysis will be done for our primary outcome and for adverse events by ITT. Given the inherent uncertainty during initial power calculations regarding effect size (given there are no prior studies of IRCD in CD), sample size re-estimation will be done.

6.2 Final Analysis

The final analysis for the primary outcome, all secondary and exploratory outcomes specified above will be done after final target recruitment has been reached. Analyses will be done by ITT for all of the outcomes noted above. For the primary outcome and all secondary outcomes, we will complete per-protocol analysis as part of additional supplementary analysis.

7. References

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STANFORD CONSENT FORM
For MINIMAL RISK Medical Human Subject Research

Are you participating in any other research studies? _____ Yes _____No

FOR QUESTIONS ABOUT THE STUDY, CONTACT: Dr. Sidhartha Sinha, 300 Pasteur Drive Alway M211, Palo Alto, CA 94304, (650)-736-5555

DESCRIPTION: You are invited to participate in a research study on how a diet that mimics fasting affects inflammation in patients with mild to moderate Crohn's disease (CD). The diet may allow users to receive the benefits of fasting while also being able to enjoy food (the ingredients of which are GRAS (generally recognized as safe) by the Food and Drug Administration (FDA)). The diet is a commercially available diet provided by L-Nutra which is a plant-based diet, or an alternative intermittent reduced calorie diet (IRCD)/fasting mimicking diet (FMD) produced in a licensed commercial kitchen. The diet will be provided to you at no cost. Research on dietary interventions and CD are very limited. IRCDs/FMDs have been studied with support of the National Institute of Health and published in leading journals.

This research study is looking for up to 75 patients with mild to moderate Crohn's Disease. Stanford University expects to enroll up to 75 research study participants. This research investigates whether markers of inflammation decrease and/or quality of life increases after taking the fasting mimicking diet. If you agree to participate in the full study, you will be randomly assigned to the study group receiving the IRCD diet intervention or to the control group where you pursue your regular diet. The randomization is designed in a way that will give you a higher probability (2:1) to get into the diet intervention group. If you are selected into the intervention group, you will take three 5-day IRCD cycles over 3 months (one cycle per month) followed by regular diet for two months. If you are selected into the control group, you will consume your regular diet during the study duration. However, you will be offered by the end of the study 3 cycles of the IRCD at no cost that you can use outside of this study.

All participants will be asked to provide an initial blood and stool sample and fill out a short inflammatory bowel disease questionnaire (SIBDQ) on your quality of life. Up to 14 days prior to the start of the study, your disease will be evaluated using the Crohn's Disease Activity Index (CDAI), and if you agree it will also be evaluated endoscopically with a colonoscopy that is part of the research study. Following the first cycle of the 5-day IRCD (or regular diet), a follow-up evaluation with the disease score and SIBDQ will be performed, in addition to a second blood and stool sample being taken. Further data collections will occur before Cycle 2 (Labs), right after Cycle 3 (Labs/SIBDQ/Disease Score/Colonoscopy),

one month after Cycle 3 (Labs), and three months after Cycle 3 (Labs/Stool/SIBDQ/Disease score). In light of the ongoing COVID-19 pandemic, some of these interactions may happen via phone or video call such as the assessment of your symptoms using the CDAI and your quality of life using the SIBDQ.

The total amount of blood drawn at the data collection timepoints is anticipated to be less than 5 tablespoons.

You can choose to have the lab work done at Stanford clinical labs or at a common commercial lab such as LabCorp and Quest. If the latter is selected no blood samples will be collected for research and for genotyping. You are free to choose different locations of the lab work for different study visits (e.g., have the initial lab work and the one after the 3rd diet cycle done at Stanford and follow-on lab works done at LabCorp or Quest).

During the study you will be asked to complete an online-questionnaire once a week about your regular diet and your current body weight. If you are in the IRCD group you will additionally receive a daily online-questionnaire during the 5 days of each IRCD cycle, and up to three phone calls by the study coordinator or our dietitian. All participants will receive 2 phone calls on non-IRCD days. The completion of the weekly questionnaires will take about 15 to 30 minutes per week, and about 10 minutes to complete the daily online-questionnaires during the IRCD days. If you agree we will send you a weekly email and/or text as a reminder.

The study participation includes also the examination of your genetic information (genotyping) and might include whole genome sequencing. The above-mentioned blood draws will be used for that.

Genetic research is research that studies genes, including gene characteristics and gene versions that are transmitted by parents to children. Genetic research may include looking at information, such as personal appearance and biochemistry, gene sequences, genetic landmarks, individual and family medical histories, reactions to medications and responses to treatment. In this study, your DNA will be analyzed to look for genetic changes that might contribute to the development of Crohn's disease, and to potential response/non-response to the dietary intervention.

Genetic research raises certain questions about informing you of any results. Possible risks of knowing results include: anxiety; other psychological distress; and the possibility of insurance and job discrimination. A possible risk of not knowing includes being unaware of the need for treatment. These risks can change depending on the results of the research and whether there is a treatment or cure for a particular disease.

Sometimes patients have been required to furnish information from genetic testing for health insurance, life insurance, and/or a job. A Federal law, the Genetic Information

Nondiscrimination Act of 2008 (GINA), generally makes it illegal for health insurance companies, group health plans, and employers with 15 or more employees to discriminate against you based on your genetic information.

We will only give you results about specific abnormal gene variants that we think are important to your health, and that have been confirmed in a clinical laboratory. In this case, we will contact you by mail or phone to find out if you are interested in learning about your results. Overall, we expect that this will be a very rare occurrence.

If you are re-contacted and want to know what the investigators have learned about your specimens, you should understand the following:

- The information may be too limited to give you particular details or consequences;
- You may be determined to carry a gene for a particular disease that can be treated;
- You may be determined to carry a gene for a particular disease for which there is no current treatment;
- You carry a gene for a disease and might consider informing relatives that they, too, might carry the gene.

Genetic Information

Information from analyses of your coded specimens and your coded information will be put into one of the National Institutes of Health (NIH) databases along with information from the other research participants and will be used for future research. These databases will be accessible by the Internet. Only anonymous information from the analyses will be put in a completely public database, available to anyone on the Internet.

No traditionally-used identifying information about you, such as your name, address, telephone number, or social security number, will be put into the public database. While the public database will not contain information that is traditionally used to identify you, people may develop ways in the future that would allow someone to link your genetic information in our databases back to you. For example, someone could compare information in our databases with information from you (or a blood relative) in another database and be able to identify you (or your blood relative). It also is possible that there could be violations to the security of the computer systems used to store the codes linking your genetic information to you.

However, your privacy is very important to us and we will use safety measures to protect it. Despite all of the safety measures that we will use, we cannot guarantee that your identity will never become known.

Blood Sampling for Research

Research using blood samples is an important way to try to understand human disease. You have been given this information because the investigators want to include your samples in

a research project and because they want to save the samples for future research. There are several things you should know before allowing your blood samples to be studied.

Your blood, tissue and stool samples will be stored after they are de-identified and coded. Data collected upon analysis of your samples after completion of the study will be stored on an encrypted USB, laptop or server and will be labeled with the coding number.

Because your samples will not be linked to your name after they are stored, you cannot withdraw your consent to the use of the samples after they are taken.

Portions of your coded samples, genomic data, and health information will be stored for an unlimited period of time to be used in future research.

Identifiers might be removed from identifiable private information and/or identifiable specimens and, after such removal, the information and/or specimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you.

RISKS AND BENEFITS: The risks associated with this study are minimal, but may include slight pain and bruising during blood draw. Effects of the IRCD diet may include dizziness or light-headedness due to low-caloric intake, or other risks that are unforeseeable at this time.
The risks of a colonoscopy include pain, bloating, bleeding, infection, perforation, and adverse reaction to anesthetics.

The benefits which may reasonably be expected to result from this study are an improvement of symptoms relating to CD, as reflected by reduced inflammatory markers. We cannot and do not guarantee or promise that you will receive any benefits from this study.

Your decision whether or not to participate in this study will not affect your employment/medical care.

TIME INVOLVEMENT: This research study is expected to take 5 months. If you are selected into the diet group, your active participation in this experiment will be 5 days of IRCD per cycle, and you will have 6 clinic visits in 5 months. If you are selected into the control group, you will have 6 clinic visits in 5 months. It will take you about 15 to 30 minutes to complete the online-questionnaire once a week, and about 10 minutes to complete the daily online-questionnaires during the IRCD days. If you agree to have two colonoscopies done during the study period, you will have two additional clinic visits.

COSTS: There is no cost to you for participating in this study, other than basic expenses like transportation and the personal time it will take to come to all of the study visits.

PAYMENTS/REIMBURSEMENTS: You will receive reimbursement for your participation to offset the time and parking related expenses, and inconvenience. You will receive $200 for the study participation. If you agree to two colonoscopies, you will receive additional $200, and so a total of $400.

Payments may only be made to U.S. citizens, legal resident aliens, and those who have a work eligible visa. You may need to provide your social security number to receive payment. For logistical reasons we will provide payment when you end your participation in the study or complete the study. The payments are provided to compensate for the inconvenience/personal cost of participating in a study that requires multiple visits. Therefore, if you complete several visits, we will pro-rate your compensation. Participants who complete 3 cycles of the diet will get 50% of the compensation. If you complete less there will be no compensation.

PARTICIPANT'S RIGHTS: If you have read this form and have decided to participate in this project, please understand your participation is voluntary and you have the right to withdraw your consent or discontinue participation at any time without penalty or loss of benefits to which you are otherwise entitled.

You have the right to refuse to answer particular questions.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

The results of this research study may be presented at scientific or professional meetings or published in scientific journals. However, your identity will not be disclosed**.**

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time. Your de-identified information will be sent to the FDA, and possibly be published in articles that appear in medical journals.

Any of your specimens which are used in research may result in new products, tests or discoveries. In some instances, these may have potential commercial value and may be developed and owned by the Investigators, Stanford University and/or others. However, donors of specimens do not retain any property rights to the materials. Therefore, you would not share in any financial benefits from these products, tests or discoveries.

WITHDRAWAL FROM STUDY

The Protocol Director may also withdraw you from the study without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff.
- The Protocol Director decides that continuing your participation could be harmful to you.
- Pregnancy
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. You will be responsible for any associated co-payments or deductibles as required by your insurance.

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

Authorization to Use Your Health Information For Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?

The purpose of this study is to see how a diet that mimics fasting effects inflammation in patients with mild to moderate CD. The diet may allow users to receive the benefits of fasting while also being able to enjoy food (the ingredients of which are GRAS (generally recognized as safe) by the Food and Drug Administration (FDA). Research on dietary interventions and CD are very limited. Intermittent Reduced Calorie Diets (IRCD)/Fasting mimicking diets (FMD) have been studied with support of the National Institute of Health and published in leading journals. This research investigates whether markers of inflammation decrease and/or quality of life increases after pursuing an IRCD, and may provide rationale for its use to treat CD. Your information will be used to measure changes in these clinical markers of inflammation before and after the first and third cycle of the diet to determine whether an IRCD reduces intestinal inflammation.

Do I have to sign this authorization form?

You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?

If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your

health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must write to: Dr. Sidhartha Sinha, 300 Pasteur Drive Alway M211, Palo Alto, CA 94304, (650)-736-5555

What Personal Information Will Be Obtained, Used or Disclosed?
Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to:

- Full Name
- Telephone numbers
- E-mail addresses
- Medical record numbers
- Demographics (age, sex, etc.)
- Body weight
- Lab or pathology test results
- Diagnosis or procedure codes
- Clinical narratives or reports
- Prescriptions or medications
- Genomic data

Who May Use or Disclose the Information?
The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director Dr. Sidhartha Sinha
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff

Who May Receive or Use the Information?
The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services

- The Food and Drug Administration
- Future Researchers

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?
Your authorization for the use and/or disclosure of your health information will end on December 31st 2040 or when the research project ends, whichever is earlier.

Will access to my medical record be limited during the study?
To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

CONTACT INFORMATION:

If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should contact Protocol Director Dr. Sidhartha Sinha at (650)-736-5555. You should also contact him at any time if you feel you have been hurt by being a part of this study.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

Appointment Contact: If you need to change your appointment, please contact Protocol Director Dr. Sidhartha Sinha at (650)-736-5555.

EXPERIMENTAL SUBJECTS BILL OF RIGHTS: As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

An initial indicates that you give your permission to receive a weekly reminder about the completion of the online-questionnaire by email and/or text:

____ I agree to receive an email reminder to the following email address:

_____

____ I agree to receive a text reminder to the following phone number:

_____

May we contact you about future studies that may be of interest to you? ☐ Yes ☐ No

An initial indicates that you give your permission to colonoscopies:

____ I agree to have colonoscopies performed.

Signing your name means you agree to be in this study and that you will receive a copy of this signed and dated consent form.

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

_____ _____
Signature of Person Obtaining Consent Date

_____
Print Name of Person Obtaining Consent