Study Application (Version 1.14) **NCT03339245**

1.0 General Information

***Please enter the full title of your study:**

Effects of dietary fructose on gut microbiota and fecal metabolites in obese men and postmenopausal women: A pilot study

***Please enter the study short title:**

Fructose study

Is this Study using Subject Management?

(•) Yes ( ) No

2.0 Add Lab/Dept(s)

2.1 List departments associated with this study:

Primary Dept?	Department Name
(•)	**RUH** - Laboratory of Biochemical Genetics and Metabolism (Breslow)
( )	**RUH** - Rockefeller University Hospital

3.0 Assign key study personnel(KSP) access to the study

3.1 *Please add a Principal Investigator for the study:

Holt, Peter R, MD

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

B) Research Support Staff

Brassil, Donna, MA, RN, CCRC
Facilitator
George-Alexander, Glenis A, B.S
Bionutritionist
Hutt, Richard, RN, BA, CCRC
Study Coordinator
O'Sullivan, Barbara, MD, MPH
Participating Clinician

Ronning, Andrea, M.A.
Bionutritionist
Vasquez, Dacia P., AS, DTR
Lab Manager
Walker, Jeanne Marie, DNP, ANP-BC
Participating Clinician

3.3 *Please add a Study Contact:

Brassil, Donna, MA, RN, CCRC
Holt, Peter R, MD
Hutt, Richard, RN, BA, CCRC
Walker, Jeanne Marie, DNP, ANP-BC

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

4.0 Rockefeller University Conflict of Interest

4.1 Investigator Financial Conflict of Interest All KSP must complete an annual certification of their Significant Financial Interest ("SFI") disclosures in the University's online Research Administration System at https://RAS.rockefeller.edu. Disclosures also must be updated in connection with new human subjects research protocols ("Research Certification"), and within 30 days of discovering or acquiring a new SFI. To avoid delays in the IRB review process, when prompted by an email from rascoi@rockefeller.edu requesting an updated Research Certification, KSP should click on the Research Certification link contained in that email notification, or go to https://RAS.rockefeller.edu, to (a) review and update his or her SFI disclosures or certify that he/she has no updates, as appropriate, and (b) indicate whether any of his/her SFI disclosures are reasonably related to the design, conduct, or reporting of the research protocol. If a KSP discloses a SFI that might constitute a conflict of interest with respect to the proposed protocol, he or she must e-mail a copy of the Lay Summary of the draft protocol to Teresa Solomon, Esq. (solomot@rockefeller.edu). Doing so will facilitate addressing COI issues in step with the development of the study protocol. Non-compliance or tardiness in making or updating COI disclosures will result in a delay in IRB review.
Institutional Conflict of Interest:

As early as possible the PI (or a designee) preparing a clinical research protocol must review a list of entities in which The Rockefeller University has an Institutional Financial Interest at https://icoi.rockefeller.edu/account/login.php. If the proposed study involves any entity on that list, the PI (or designee) must notify Teresa Solomon, staff to the FCOI Committee, by e-mail solomot@rockefeller.edu and Sarah Schlesinger, Chair of the IRB, by email: schless@rockefeller.edu, provide the name(s) of the entities and a copy of the Lay Summary. Doing so will facilitate addressing institutional COI issues in step with the development of the study protocol. Failure to take steps to review and address potential institutional conflicts of interest will delay the IRB review process.

5.0 External Personnel

5.1 List external personnel who will be working on the study:

Name	Institution	Telephone	E-mail	Role
David Montrose	WCMC	646-962-2894	dam2040@med.cornell.edu	Collaborator
Wendy Henderson	NIH	412-780-8471	hendersw@mail.nih.gov	Collaborator
Andrew J. Dannenberg	Weill Cornell Medical College	212-639-8802	ajdannen@med.cornell.edu	Collaborator

6.0 Delegation of Authority

6.1 Enter authorized activities for all Rockefeller University personnel named on the study.

Activity Codes:

1. Informed consent	12. Perform assays	23. Diet design and preparation
2. Inclusion / exclusion criteria	13. Specimen / sample analysis	24. Nutritional assessment and counseling
3. Medical / medication history	14. Lumbar puncture	25. Addition of PABA to food
4. Perform physical exam 4a. Write/Sign LIP orders	15. Femoral line placement	26. Data analysis
5. Skin assessments and photos	16. Central line placement	27. Data review
6. Study drug dispensing	17. Insulin clamp procedure	28. Data management
7. Study drug administration	18. Leukapheresis	29. Maintain regulatory documents / files
8. Study drug reconciliation	19. Sigmoidoscopy	30. Complete CRF's
9. Study drug compliance	20. Fat biopsy	
10. Administer study questionnaire(s)	21. Skin biopsy	
11. Participant recruitment	22. Conduct sleep study	

Add up to three additional authorized activities specific to this study (do NOT add activities that have previously designated codes):

31:	lab result review to maintain study blind
32:	randomization and dispensing of study supplement
33:	

Activity Codes Continued:
34. Behavioral Testing
35. Bod Pod
36. Bone Marrow Aspiration
37. Neuropsychological Testing
38. Conduct Focus Group
39. Conduct Smell Study
40. Genetic Counseling
41. Apply EEG Electrodes
42. Olfactometer Test
43. Study Participant Teaching
44. Resting Energy Expenditure
45. Source Document Review & Correction
46. Medical Photography
47. See 4a
48. Adverse Event Assessment
49. Clinical Trial Registration
50. Study Support Drug Dispensary

Enter delegation of authority for Rockefeller University Key Study Personnel:

Name	Title	Authorized Activities	Start Date	End Date

Holt, Peter R, MD	PI	1, 2, 3, 4, 11, 26, 27, 28, 47, 48	08/22/2017	
Walker, Jeanne Marie, DNP, ANP-BC	clinician	1, 2, 3, 4, 11, 27, 28, 29, 30, 47, 48	08/22/2017	
Brassil, Donna, MA, RN, CCRC	facilitator	1, 2, 29	08/22/2017	
Eylers, Ellen, MPH, MSN, RN, CCRC	coordinator	1, 2, 29	08/22/2017	03/23/2018
Ronning, Andrea, M.A.	bionutritionist	10, 23, 24, 26, 28, 35	08/22/2017	
George-Alexander, Glenis A, B.S	bionutritionist	10, 23, 24, 26, 28, 35	08/22/2017	
Ponda, Manish, MD	clinician	47, 4, 48	08/22/2017	04/18/2018
MacArthur, Robert B, PharmD MS	research pharma	32	09/13/2017	06/13/2019
Johnson, Amber, PharmD	research pharma	32	09/25/2017	06/13/2019
Vasquez, Dacia P., AS, DTR	lab manager	35	01/03/2018	
Hutt, Richard, RN, BA, CCRC	coordinator	1, 2, 29	03/28/2018	
O'Sullivan, Barbara, MD, MPH	Clinican	4.47.18	04/18/2018	

Enter delegation of authority for additional Rockefeller University Key Study Personnel:

Name	Title	Authorized Activities	Start Date	End Date
No records have been added				

Enter the authorized activities for External Personnel:

Name	Title	Authorized Activities	Start Date	End Date
No records have been added				

7.0 Study Description

7.1 * Lay Summary

Please provide a summary of your study in lay language. The summary should be no more than a half page (500 words or less) and should contain a clear statement of the rationale for the study.

Non- alcoholic fatty liver disease (NAFLD) occurs in 30% of the adult US population (Luther, J., et al., 2015). Eating large amounts of fructose (a dietary sugar) increases liver fat accumulation and worsens NAFLD. In addition, fructose consumption has been shown to greatly increase triglycerides(fat) in the blood after meals, increasing the risk of heart disease,(Stanhope,et al., 2009) insulin resistance and diabetes. Current theories on liver disease caused by consuming fructose focuses on changes in the breakdown of fat by the liver. In experimental animals, fructose feeding changes the bacteria population (microbiota) in the gut, causes NAFLD and fatty liver hepatitis (NASH), and increases leaking of toxins from the intestine (intestinal permeability) to the blood stream resulting in inflammation.

In humans, fructose consumption rapidly increases liver fat. However, changes in gut microbiota have not been studied. The proposed study will compare the addition of fructose or glucose to the study subjects' usual diet in a crossover design. The subjects will eat their usual diet with either fructose or glucose added, for 14 days while staying in the RU hospital. They will then be discharged home for 2 weeks without any sugar addition so that they will "wash out" the effects of the sugar. They will then be re-admitted for 14 more days of the other sugar added to the diet. They will not know which sugar they are receiving.

We plan to study five postmenopausal, moderately obese but healthy women, and five moderately obese but healthy men (age 45-70 years) to find out the effect of fructose verses glucose on the bacteria in their stool and inflammation in the bowel. We hypothesize that adding fructose to the participant's usual diet, compared to glucose, will change stool bacteria composition and the products that the bacteria produce, which may increase intestinal leakage, and increase markers of inflammation in the stool and blood due to this leakage. These changes may contribute to fructose -induced liver disease.

7.2

*** Public Health Impact Statement**

Provide a brief plain language statement (100 words or less) of the value of the research proposed and its potential impact on population health. Additional instructions located in Help.

Non alcoholic fatty liver disease (NAFLD) is the most common cause of abnormal liver function tests in the U.S. (Browning, et al., 2004), ranging from steatosis to end-stage liver disease. Fructose ingestion by the American public has steadily increased since the 1980's, and with it increases in NAFLD, NASH, diabetes, obesity, and cardiovascular disease. Foods and beverage in the U.S. are typically sweetened with sucrose (50% glucose and 50% fructose) or high fructose corn syrup (45-58% glucose and 42-55% fructose) (Stanhope, et al., 2009). Research into the role that added fructose plays in the emerging chronic health issues is necessary to affect public policy and provide the connection between fructose and the increasing incidence of these co-morbidities.

There is evidence that gut bacteria contribute to a range of human diseases including those of the liver and gastrointestinal tract. Dietary fructose has been suggested to play a role in the development of these diseases and has been shown to alter gut microbes in animals. If we find that dietary fructose alters bacteria in the human gut, this would suggest a potential targetable link between high fructose diet and disease.

7.3

Study Classification

Full Review

7.4

*** Submission Request Category**

Note: For each submission, please designate the level of review, or "Submission Request Category" you are requesting. When completing this field, please indicate the level of review you are requesting for the specific submission you are working on. For example, if you are submitting an Expedited Amendment request to change the Key Study Personnel on your existing Full Board study, you should select "Expedited Review" in both the Amendment Submission Form and Study Application. The IRB will confirm an Expedited review of the Amendment submission is appropriate, and the overall study will remain classified as a full Board review.

- ○ Exempt from Review
- ○ Expedited Review
- ◉ Full Review
- ○ Not Human Subjects
- ○ Exempt with Limited Review

8.0 Clinical Trial Registration

8.1

Clinical Trial Registration

The types of studies listed below must be registered at **www.ClinicalTrials.gov**

- ○ Study involves testing of FDA regulated drugs or biologics (See HELP)
- ○ Study is funded by the NIH, and meets the definition of a "clinical trial" (see HELP)
- ◉ Study meets the ICMJE definition of a "clinical trial" (See HELP)
- ○ None of the above

If you selected 1, 2, or 3, you must register your trial with ClinicalTrials.gov through the Rockefeller University institutional account. Please contact the Clinical Research Support Office x7408 for assistance.

9.0 Study Overview/Summary

9.1 * Who initiated this study?

Please specify one:

- ◉ Principal Investigator Initiated
- ○ Industry Initiated
- ○ Other

If other, please specify:

9.2 * This study in collaboration with:

- (•) Weill Cornell Medical College
- ( ) Memorial Sloan-Kettering Cancer Center
- ( ) Both Weill Cornell Medical College and Memorial Sloan-Kettering Cancer Center
- ( ) Neither Weill Cornell Medical College nor Memorial Sloan-Kettering Cancer Center

Please note: If any of the first three options is checked, you will be prompted to attach the **IRB of Record** forms later on in the submission. Links to these forms can be found in the Help link to the right.

9.3 *Are other institutions involved in the study?

- ( ) 1. No
- ( ) 2. Yes, and a federal, industry or private organization is administratively coordinating the study.
- (•) 3. Yes, however, a federal, industry or private organization is not administratively coordinating the study.

Please provide the following for each involved institution:

	Name of Other Institution	Date of Approval by Other Institution	Date of Pending Approval by Other Institution	Date of Expiration at Other Institution	Exempt	No End Date
	WCMC (Dannenberg)	11/27/2017				☐
	WCMC (Montrose)	11/27/2017				☐
	NIH	02/07/2018				☐

9.4 * Is this a multi-center trial?

( ) Yes (•) No

9.5 * Who (What) is to be studied?

- ☑ Human Subjects - including coded samples and/or data with links to Identifiers
- ☐ Deidentified Samples - unable to be linked to identifiers by receiver
- ☐ Data Only - unable to be linked to identifiers
- ☐ Identifiable samples or data for exemptions (per 104 (s)(4))

9.6 *Study Type:

- (•) Interventional
- ( ) Observational

9.7 The initial date of IRB approval was:

10/15/2017

9.8 * What is the expected duration of the study?

3 years

9.9 * Are any of the following agents to be used in the study?

Check all that apply:

- [ ] Drug FDA Approved
- [ ] Approved Drug for Off-Label Purpose (This might require an IND)
- [ ] Investigational New Drug
- [ ] Biologic Agents
- [x] Nutritional Supplements
- [ ] Placebo
- [ ] Vaccines
- [ ] No Agents

9.10 * Are investigational devices to be used in the study?

- ( ) Yes
- (•) No

9.16 Special Research Procedures

Does the study propose to directly involve participants in the following special research procedures?

- [ ] Recombinant DNA
- [ ] Gene Therapy
- [ ] Fetal Tissue
- [ ] Embryonic Stem Cells
- [ ] Induced Pluripotent Stem Cells
- [ ] CRISPR-Cas9

If any item is checked, please see Help for details.

9.17 * Radioactive Isotopes Involved

Will participants be exposed to any radiation other than routine x-rays solely for clinical care purposes?

- ( ) Yes
- (•) No

10.0 Interventional

10.1 *Interventional, please specify:

- ( ) Open Label
- ( ) Single Blind
- (•) Double Blind
- ( ) Other

If Other, specify:

11.0 Objectives and Rationale

11.1 * Overview

Briefly state the ***purpose of this study***. Give enough background and rationale to provide both scientists and lay members of the IRB and ACCTS with the basis for exposing human participants to the risks involved.

Dietary fructose consumption in the United States has risen markedly in the past four decades, led by added sugar consumption which is correlated with the presence of the metabolic syndrome (Rodriguez LA et al, 2016). In a similar time interval, non-alcoholic fatty liver disease (NAFLD) has increased, now occurring in over 30% of the adult US population (Luther, J. et al., 2015). NAFLD can lead to steatohepatitis (NASH), cirrhosis and liver cancer (Fuchs, M. & Sanyal, AJ, 2010). Fructose consumption itself results in hypertriglyceridemia and can induce or worsen NAFLD (Stanhope, K.L. et al., 2009). In mice (Le, K.A., et al., 2009) and zebrafish (Sapp, V. et al., 2014) fructose feeding induces fatty liver disease. In humans, a fructose bolus increases serum triglycerides and palmitate (Hudgins, L.C., et al, 2011) and two weeks of a high fructose diet increased hepatic fatty acid synthesis. (Hudgins, L.C., et al, 2000). Other studies showed that nine days of a diet including 25% of total calories as fructose increases hepatic fatty acid synthesis (Schwarz, J.M. et al., 2015) which was reversed by substitution of fructose by starch (Schwarz, J.M. et al., 2017). In monkeys, fructose supplementation leads to hepatic inflammation and hepatic fibrosis (Kavanaugh, K., et al, 2013). Much of this work has recently been summarized (Alwahsh, S.M. & Gebhardt, R. 2017). The current mechanistic hypothesis for these effects focuses on fructose-induced changes in hepatic lipid metabolism. Fructose undergoes first-pass metabolism in the liver (Havel, P.J. 2005). It is a substrate for de novo lipogenesis driving triglyceride accumulation (Stanhope, K.L. et al., 2009) increasing reactive oxygen formation and causing cellular injury (Nan Y., et al., 2014).

Small intestinal fructose absorption is limited when compared to glucose absorption. Many individuals cannot absorb more than about 25-50 grams of fructose when given as a bolus (Gibson, P.R., et al., 2007). Limited fructose absorption occurs because of the selective absorption mechanism for the small intestinal transport of fructose (Jones, H.F. et al, 2011). Unabsorbed fructose in the colon is fermented by gut bacteria into short chain fatty acids, hydrogen, carbon dioxide and occasionally methane (Gibson, P.R. et al., 2007).

At the same time, an increase in dietary fructose would be expected to alter colonic microbiota within 1 to 3 days (Wu, G.D., et al., 2011). Changes in the distribution (and function) of colonic microbiota would be expected simultaneously to change the microbial metabolite production. Fructose- induced changes in fecal microbiota have been described in mice by our collaborators (Appendix1). One of consequences of these fructose-induced changes in gut microbiota and metabolites, including bile acids, is an increase in intestinal permeability. In mice, fructose feeding alters intestinal tight junctions (Spruss, A., et al., 2012) (Kavanaugh, K., et al., 2013). Antibiotics in fructose fed obese mice (or transfer of feces from normal mice) altered gut microbial composition (particularly coprococcus and ruminococcus) and evidence of the metabolic syndrome (Di Luccia, B. et al., 2015).

Alterations in fecal microbiota also have been described in human fatty liver disease (Boursier J., et al, 2016). Increased intestinal permeability has been described in NASH (Luther, J. et al., 2015) as well as in experimental studies in the mouse (Miele, L., et al., 2009). Increased intestinal permeability has been accompanied by endotoxemia in human fatty liver disease (Miele, L., et al., 2009) and such endotoxemia is known to sensitize hepatic Kupfer cells to induce inflammation (Luther, J., et al., 2016). However, we have found no studies in the literature that focused on the effects of fructose feeding in humans on gut microbiota and

metabolites as examined in the feces nor on intestinal permeability. Better understanding of such changes in gut microbiota may permit therapeutic approaches other than requiring patients with fatty liver disease to lower their fructose consumption, advice that is often not followed.

11.2 * Engaging Stakeholders: Describe any plans to engage other stakeholders (Scientists, practitioners, patients, advocacy groups, etc.) for hypothesis generation, or feasibility purposes.

David Montrose (WCMC) did the initial studies of fructose in mice in which colon inflammation was induced with DSS. He has experience in the analysis of fecal metabolites in previous studies in mice.

Andrew Dannenberg (WCMC) has extensive background in designing experimental studies in mice and humans.

Wendy Henderson will perform analyses of urine sugar excretion following a standard multi sugar standardized drink perfected in her laboratory at the NIH.

11.3 * Hypothesis

Describe the ***research hypothesis*** in a single sentence.

Fructose, compared to glucose supplementation, alters gut microbiota and metabolites leading to enhanced intestinal permeability and endotoxemia, which can worsen non-alcoholic fatty-liver disease (NAFLD).

11.4 * Aim(s)

Indicate how you will ***address the hypothesis*** (e.g., to compare groups, to estimate a parameter, to ascertain feasibility). Since the sample size determination is usually based on the primary aim only, the primary aim should be sufficient to justify the study.

Primary Aim:
To determine the effect of fructose compared to glucose supplementation on the relative composition of gut microbiota as measured in the feces after approximately 14 days of study intervention.

Secondary Aims:
To determine the effects of fructose compared to glucose supplementation on:

1. the composition of gut metabolites as measured in the feces
2. intestinal permeability
3. fecal calprotectin concentrations
4. circulating lipids and liver function tests

11.5 * Primary Outcome(s)

Indicate which ***variable(s)*** will be assessed to judge the primary specific aim. Give measurement units, if applicable.

Difference in the distribution of fecal microbiota in each participant, between the fructose versus glucose supplemented diet arms of the study, as measured at the end of each intervention.

11.6 * Secondary Outcome(s)

Indicate which ***additional variable(s)*** will be assessed to judge the secondary outcome(s). Give measurement units, if applicable.

1. Change in composition of fecal metabolites between the fructose versus glucose supplemented arms.
2. Change in intestinal permeability in the fructose arm of the study.
3. Change in fecal calprotectin concentrations in the fructose arm of the study.
4. Stable circulating lipids and liver function tests

11.7 * Methods and Procedures

Please provide a description of the laboratory and clinical analyses and procedures that will be performed. Include the role of external collaborators and consultants when appropriate. Please refer to Help text for Guidance.

Men and post menopausal women who are obese (BMI 30-39), age 45 to 70 and without clinical or electrocardiographic evidence of cardiometabolic disease will be recruited to the RUH utilizing the CRSO Volunteer Repository, and advertising on Craigslist and newspapers if needed. Participants will undergo two screening visits in the Outpatient Research Center (OPRC) where they will meet with a member of the research team. This is a double blind crossover study with a 2 week wash out period.

Enroll up to 30 participants to yield 10 completers.

End Point Analyses

1. Fecal analysis. Duplicate samples will be taken from the middle (3X2 samples) of the stool and immediately frozen at -80ºC.

2. Fecal microbiota will be analyzed by 16S technology by MR DNA Co situated in Texas, US. This is a commercial laboratory run by an academic researcher that provides reliable information and initial analysis in a very timely manner. Our collaborator, Dr. Andrew Dannenberg, has used this laboratory in a satisfactory manner.

3. Fecal metabolites. Stool samples will be shipped to Metabolome for analysis. Our collaborator, Dr. Andrew Dannenberg, has used this laboratory in a satisfactory manner.

4. Fecal calprotectin concentrations are increased with gut inflammation. Samples will be analyzed by Elisa kits in the Breslow laboratory.

5. Intestinal permeability will be performed fasting using a 100 ml "5 sugar," absorption test, which is composed of sucralose, sucrose, mannitol, and lactulose, that will be prepared by the RUH research pharmacy. Only water is consumed for the next 5 hours Excreted urine sugars in the 5 hour urine will be expressed per m^2 of body surface area and analyzed by HPLC/ mass spectrometry in the laboratory of Dr. Wendy Henderson at the NIH. Dr. Henderson will add the raffinose during analysis as an internal standard. Duplicate 5 mL aliquots of the 5 hour urine collection (plastic containers) are frozen for batch submission to the NIH. Baseline urine will also be sent to Dr. Henderson pre-5 sugar urine collection for evaluation of gut permeability.

Potential Analysis:

1.Serum and plasma samples will be kept frozen at -80ºC for later research testing.

2. Potential testing may include soluble CD-14 analysis, intestinal fatty acid binding protein, LPS binding protein, TNF-alpha, IL-1, IL-6, and IL-8 determination.

3. Potential Metabolome/Metabolite testing
Duplicate 5 ml urine samples will be collected from the first void prior to gut permeability urine collection and frozen at -80ºC for studies of urine excretion of metabolites that reflect altered gut microbiota metabolism of the fructose versus glucose supplemented diets.

Justification for Measuring Fecal Metabolites
When a dietary intervention alters gut microbial composition this may directly affect gut epithelial and immune cells and activate gut receptors. Alternatively, the altered microbial community may produce bacterial metabolites which then can act on epithelial and immune cells to increase gut permeability for example. We have found no data in the literature describing bacterial metabolites that are formed accompanying the passage of fructose into the colon in humans.
In the mouse, high fructose feeding profoundly changes fecal bile acid composition (personal communication Dr. A. Dannenberg). A remarkable increase in conjugated and primary unconjugated bile acids suggests a major reduction in bile acid deconjugase with fructose feeding. Since secondary bile acids are important agonists for gut FXR and TGR3 receptors these changes may impact upon hepatic carbohydrate and lipid metabolism.
Thus, measurements of the effects of fructose feeding upon gut metabolites including bile acids as measured in the feces are important end points in our proposed study.

Future Fecal Testing
For particpants who give permission we would like to keep a small portion (about 50mg) of the fecal collection performed before and after the two fructose and glucose added arms of the study for analysis of other end points that may become important in the future (for example fungal community studies)

Participant Management:

Screening Visit 1: 120 minutes

- Informed consent process
- History and physical
- Measurement of waist and hip circumference
- Measurement of height and weight, determination of BMI
- HIV consent and rapid HIV testing
- EKG
- Bionutrition consult to complete VioScreen* and 3 day food diary
- Fructose drink tasting for participant to select their preferred mix, 1) water, 2) water and lemon, 3) tea.

*VioScreen is a web-based interactive and graphical food frequency questionnaire, to determine usual nutritional intake. In consultation with the bionutritionist, participants will complete a 3 day food diary by incorporating the results generated by the VioScreen. This will be documented on the 3 day food diary study document. They will be advised to continue their usual diet, and to use the diary as a guide. The information will be used to prepare meals during the inpatient phase and maintain each participant's usual consistent diet. This will eliminate any variable that dietary change may introduce to the fecal microbiome.

Screening Visit 2: 90 minutes

The participant will return to the OPRC after a 10 hour overnight fast

- Screening labs: CBC, ESR, CMP, Lipid panel, TSH, Hepatitis C Antibody, HgbA1c, Uric Acid, (two lavender EDTA tubes 3 ml each, two gold tubes 3.5 ml each, total 10ml)

- If not done on Screening Visit 1, VioScreen and 3 day food diary will be completed with bionutritionist.
- If not done on Screening Visit 1, after fasting bloods are drawn, fructose drink tasting for participant to select their preferred mix, 1) water, 2) water and lemon, 3) tea.

Optional Screening Visit 3

- To complete / repeat any necessary screening procedures.

The timeframe from screening visit #1 to the first inpatient admission will be within 8 weeks.

Enrolled participants who meet inclusion / exclusion criteria will be admitted to the RU inpatient unit for 16 to 18 days for the first arm of the crossover study.

The total blood draw for the entire study (both arms) is about 199 ml.

Arm 1

Day 0

- Admission to RUH after 5pm.
- Usual diet for dinner
- NPO after 9pm

Days 1-16 (+2 days)

- Pedometer to be worn daily, put on upon awakening, removed at bedtime. Steps will be recorded by the nursing staff at bedtime to monitor activity.
- Daily measurement of weight and vital signs by nursing staff.

Meals will be consumed on a regular schedule when not testing, unless the participant has a schedule conflict. All food eaten by the participant by midnight on any given inpatient study day will be considered compliant with the daily diet protocol.

- Breakfast: 7AM-9AM
- Lunch: 11:30AM-1:30PM
- Dinner: 5:30PM-7:30PM

Day 1

- Fasting labs MSKCC (one gold top 3.5 ml, one lavender top 3 ml, total 6.5 ml)
    - CBC
    - ESR
    - CRP
    - Lipid panel
    - CMP
    - Uric Acid
- Research blood (total 39 ml)
- 2X 10 ml serum red top
- 1X 9 ml plasma (EDTA) purple top
- 1X 10 ml (heparin) green top
- BodPod to determine body composition

Day 1 (+1 day)
Gut permeability testing cannot commence until baseline stool is obtained.

- Stool samples for microbiome, metabolites and calprotectin will be collected.

Day 2 (+1 day)
After stool sample collected and 10 hour overnight fast,
Gut permeability testing:

- Subject will be requested to empty bladder prior to 0 timepoint and research samples will be collected from this first void for possible metabolome/microbiome research analysis.
- Drink Pre-prepared, "Five Sugar test solution," while observed by the nursing staff, followed by at least 250 ml water over 2 hrs.
- May drink water ad lib during the testing period
- All urine will be collected until 5 hour timepoint.
- From the 5 hour urine collect two 6ml samples, one for random creatinine level, and one for frozen research storage.

Day 3 (+1 day)

- Start study diet (Usual diet with fructose or glucose substituted for some dietary 75 grams carbohydrate).

Days 3 to16 (+2 days)

- Participants will remain inpatient, consuming their study diet as prepared by the bionutrition department.
- Daily measurement of weight and vital signs by nursing staff.
- Calories will be adjusted to maintain weight within 2% of baseline.
- Participants will be allowed to go out on pass, but must consume breakfast and dinner in-house. They may take packed lunch out with them during the day.

Day 9 (+1 day)

Fasting Safety Labs

- Liver function tests (HFP) and serum triglycerides will be drawn to monitor effect of fructose/glucose on hepatic function, 7 days after starting intervention (one gold top tube, total 3.5 ml).

- Lab results will be followed by Jeanne Walker or Manish Ponda.

Day 14 (-1/+2 days)

Stool samples for microbiome, metabolites and calprotectin will be collected.
After stool sample is collected and 10 hour overnight fast

- Fasting labs: MSKCC (one gold top 3.5 ml, one lavender top 3 ml, total 6.5 ml)
    - CBC
    - ESR
    - CRP
    - Lipids
    - LFTs (HFP)
    - Uric Acid
- Research blood (total 39 ml)
    - 2X 10 ml red top serum
    - 1X 9 ml plasma (EDTA) purple top
    - 1X 10 ml (heparin) green top

Gut permeability testing:

- Subject will be requested to empty bladder prior to 0 timepoint and research samples will be collected from this first void for possible metabolome/microbiome research analysis.

- Drink Pre-prepared, "Five Sugar test solution," while observed by the nursing staff, followed by at least 250 ml water over 2 hrs.
- May drink water ad lib during the testing period
- All urine will be collected until 5 hour timepoint.
- From the 5 hour urine collect two 6ml urine samples, one for random creatinine level, and one for frozen research storage.
- Discharge home after breakfast to begin 2 week wash out period. Participants to remain on their usual diet.

Two to three week washout period:

- Participant will maintain usual, stable diet at home.
- If participant experiences an illness during wash out period requiring treatment that would interfere with the study, as determined by the investigator, they will not be re-admitted for Arm 2 until they have been stable for 2 weeks.
- A study team member will maintain phone contact weekly with the participant during the wash out period to reinforce maintenance of usual diet, as well as follow health status.
- Participant will have contact information to get in touch with study team as needed.

Arm 2: Re-Admission

Day 0

- Admission to RUH after 5pm.
- Usual diet for dinner
- NPO after 9pm

Days 1-16 (+2 days)

- Pedometer to be worn daily, put on upon awakening, removed at bedtime. Steps will be recorded by the nursing staff at bedtime to monitor activity.
- Daily measurement of weight and vital signs by nursing staff.

Meals will be consumed on a regular schedule when not testing, unless the participant has a schedule conflict: we are talking about the day of the sugar tests when the "5 sugar solution," will be administered fasting. The diet will be modified to provide a meal (breakfast/lunch) total nutrients will be maintained constant on these days. All food eaten by the participant by midnight on any given inpatient study day will be considered compliant with the daily diet protocol.

- Breakfast: 7AM-9AM
- Lunch: 11:30AM-1:30PM
- Dinner: 5:30PM-7:30PM

Day 1

Fasting labs

- Fasting labs MSKCC (one gold top 3.5 ml, one lavender top 3 ml, total 6.5 ml)
    - CBC
    - ESR
    - CRP
    - Lipids
    - CMP
    - Uric Acid
- Research blood (total 39 ml)
    - 2X 10 ml serum red top
    - 1X 9 ml plasma (EDTA) purple top

- 1X 10 ml (heparin) green top

Day 1 (+1 day)

Bionutrition consult
Stool samples for microbiome, metabolites and calprotectin will be collected.

Day 2 (+1 day):
After stool sample collected and 10 hour overnight fast
Gut permeability testing:

- Subject will be requested to empty bladder prior to 0 timepoint and research samples will be collected from this first void for possible metabolome/microbiome research analysis.
- Drink Pre-prepared, "Five Sugar test solution," while observed by the nursing staff, followed by at least 250ml water over 2hrs.
- May drink water ad lib during testing.
- All urine will be collected until 5 hour timepoint.
- From the 5 hour urine collect two 6ml urine samples, one for random creatinine level, and one for frozen research storage.

Day 3

Start study diet (Usual diet with fructose or glucose substituted for some dietary carbohydrate).

Days 3 -16 (+2 days)

- Participants will remain inpatient, consuming their usual diet as prepared by the bionutrition department.
- Daily measurement of weight and vital signs by nursing staff.
- Calories will be adjusted to maintain weight within 2% of baseline.
- Participants will be allowed to go out on pass, but must consume breakfast and dinner in-house.
- They may take packed lunch out with them during the day.

Day 9 (+1 day)

Fasting Safety Labs

- Liver function tests (HFP) and serum triglycerides will be drawn to monitor effect of fructose / glucose on hepatic function, 7 days after starting intervention (one gold top tube, total 3.5 ml).

Day 14 (-1/+2 days)

- Stool samples for microbiome, metabolites and calprotectin will be collected.

Day 16 (+2 days)
After 10 hour overnight fast

- Fasting labs: MSKCC (one gold top 3.5 ml, one lavender top 3 ml, total 6.5 ml)
  - CBC
  - ESR
  - CRP
  - Lipids
  - LFTs (HFP)
  - Uric Acid
- Research blood (total 39 ml)
  - 2X 10 ml serum red top

- 1X 9 ml plasma (EDTA) purple top
- 1X 10 ml (heparin) green top

Gut permeability testing:
After a stool sample is collected and a 10 hour overnight fast

- Subject will be requested to empty bladder prior to 0 timepoint and research samples will be collected from this first void for possible metabolome/microbiome research analysis.
- Drink Pre-prepared, "Five Sugar test solution," while observed by the nursing staff, followed by at least 250 ml water over 2 hrs.
- May drink water ad lib during testing
- All urine will be collected until 5 hour timepoint.
- From the 5 hour urine collect two 6ml urine samples, one for random creatinine level, and one for frozen research storage.
- Discharge home after breakfast.
- Study completed.

Research Sample Processing

Stool samples: Collect and immediately aliquot into 2 sets of 3X 10ml sarstedt tubes (total 6 sarstedt tubes). Label with study #, subject #, STOOL, and date. Place ½ of the samples in a box labeled **PHO-0956 STOOL**, and ½ of the samples in a box labeled **PHO-0956 STOOL Back-up** Freeze at -80°C.

First Void urine**:**
Obtain prior to starting 5-hour urine for gut permeability urine collection.
Aliquot 2ml into 8 Wheaton tubes (total 16 ml), **Label tubes with PHO-0956, study ID #, date** and "**1st void urine"**.
Store in boxes labeled **PHO-0956**"**1st void urine and Back-up** at -80°C. (1/2 in each box)
Collect 2ml into 6 Wheaton tubes (total 12ml). Label tubes with **PHO-0956, study ID#, date,** and **urine for metabolites**.
Place 3 tubes in Box labeled **PHO-0956 Urine for metabolites** and 3 tubes in Back Up box. Freeze at -80°C.

Urine for gut permeability**:**
Collect urine after subject drinks**" 5 sugar solution**" for 5 hours. Keep urine refrigerated.
After the test is completed, measure total volume and record in chart. Gently mix the container.
Aliquot 2 X 6ml urine into 15ml falcon tubes. Send one sample to MSKCC along with the total volume, for urine for **random urine creatinine** as per MSKCC standard practice.
Label the other tube with **PHO-0956, study #, urine for creatinine and date**. Freeze -80°C for back up in box labeled PHO-0956 **Urine creatinine.**
Aliquot 12 X 4ml urine into 15ml falcon tubes, labeled with **PHO-0956**, study ID#, date**, Urine for gut perm**.
Place 6 tubes in Box labeled PHO-0956 Urine for gut perm and 6 tubes in Back Up box. Fr eeze at -80°C.

Serum samples: 2X 10 ml red top tubes. Clot fully at room temperature for 30-60 minutes. Spin at 2500rpm, 15 minutes at 4°C. Immediately after spinning, aliquot serum in 0.25 ml increments into Sarstedt tubes, label tubes with study #, subject #, SERUM, and date. Place ½ of the samples in box labeled **PHO-0956 Serum** and ½ of the samples in box labeled **PHO-0956 Serum Back-up**. Freeze at -80°C.

Plasma samples: 1X 9ml plasma (EDTA) purple top tube. Gently invert tube 5 times. Place on ice 30-60 minutes. Spin at 2500rpm X 15 minutes at 4°C. Immediately after spinning and using

pipette, aliquot plasma in 0.25ml increments into Sarstedt tubes. Label tubes with study#, subject #, EDTA, and date. Place ½ of the samples in box labeled **PHO-0956 EDTA Plasma,** an d ½ of the samples in box labeled **PHO-0956 EDTA Plasma Back-up**. Freeze at -80°C.

Plasma samples: 1 X 10ml plasma (Heparin) green top tube. Gently invert tube 5 times. Place on ice 30-60 minutes. Spin at 2500rpm X 15 minutes at 4°C. Immediately after spinning and using pipette, aliquot plasma in 0.25ml increments into Sarstedt tubes. Label tubes with study#, subject #, HEPARIN, and date. Place ½ of the samples in box labeled **PHO-0956 HEPARIN Plasma,** and ½ of the samples in box labeled **PHO-0956 HEPARIN Plasma Back-up**. Freeze at -80°C.

Diet Management
The bionutritionist will interview each subject at the first screening visit and complete a food frequency questionnaire using the VioScreen electronic computer software program. The bionutritionist will then instruct the subject to complete a detailed 3 day recent diet recall. The results of the VioScreen analysis and the 3 day diet recall analysis will be reviewed with the subject at the second screening visit and used to determine the study participant's average 3 month fructose (from natural sources e.g. fruit), added sugar (from food processing sources e. g. high-fructose corn syrup), and average total carbohydrate and calorie intake. The 3 day diet recall will be used to mimic a typical diet that the subject had consumed prior to the study. The bionutritionist will then mimic this diet for each individual subject which will be provided during the inpatient 2 to 3 day testing period. The nutritionist will also construct a 3 day rotating diet in which 75 grams of carbohydrate (from the complex carbohydrate, bread, milk, and vegetable portions) will be reduced for each subject aiming for a 75 gram reduction in carbohydrate daily (which is equivalent to 1 slice of bread and 1 medium piece of fruit). In addition, a drink will be prepared containing 75 grams of either fructose or glucose mixed in 16 oz. of water, water with lemon or tea. Half of the drink, 37.5 grams fructose or glucose will be served in two doses daily, 8 ounces with breakfast and 8 ounces with dinner, to substitute for the reduced carbohydrate during the inpatient sugar test periods. Both the glucose and fructose solutions will be obtained from Now Foods. This pure fructose / glucose drink will be consumed during breakfast and dinner by all the study subjects, for a total daily amount of 75 grams of glucose or fructose. The Nursing staff will observe the subjects ingesting the initial glucose and fructose solutions but will not witness the entire solution being ingested.

In summary, each individual subject will consume a diet that mimics their usual pre-study diet for the initial 2 to 3 day testing period and their diet modified to reduce the carbohydrate portion by about 75 grams plus a drink containing either 37.5 grams of glucose or 37.5 grams of fructose, twice daily with breakfast and dinner, for a total of 75 grams a day during the 14 day study period. Each subject's diet is unique and is maintained to keep their fecal microbiota as constant as possible while examining the effect of the substituted fructose or glucose.

In addition, the baseline diet and the fructose supplemented and glucose supplemented diet for each subject will be homogenized and a portion kept for subsequent analysis of calories and composition of macronutrients.

Bionutrition previously has constructed an inpatient diet mimicking the subjects' prestudy diet for PHO 807.

Blinding:

Blinding of fructose/glucose will continue throughout the study until the last subject has completed the protocol, unless there is a safety issue.

Jeanne Walker or Manish Ponda (as back-up clinician) will monitor safety labs and determine if the blind must be broken prematurely. They will monitor lab results within 24 hours of posting.

The Principal Investigator will maintain the blind by not looking at the lab result section of the medical record.

The research pharmacy staff will be unblinded and will conduct the randomization of subjects and dispense the study supplement in a blinded fashion, to be administered by the nursing personnel of the hospital.

External Personnel:

Andrew Dannenberg: Data analysis of fecal microbiota and metabolites

David Montrose: Data analysis of fecal metabolites

Wendy Henderson:

1. Analysis of urine for sugar concentration to determine intestinal permeability.
2. Analysis of soluble CD-14 I-FABP intestinal fatty acid binding protein, and LPS binding protein, LBP (lipopolysaccharide binding protein), TNFa. IL1B, IL6, IL8 to evaluate inflammation.

No samples or data will be transferred to collaborators before IRB approval has been obtained.

All samples will be de-identified and will not be traceable back to the participant. The samples will contain only the study number, subject ID and date.

Data will be sent using ELF secure email and returned using a similar secure email system.

11.8 * Data Analysis

Describe method(s) of data analysis. Include the role of external collaborators as appropriate.

The primary statistical analysis compares the changes in fecal microbiota distribution between the fructose and glucose supplemented diets. A cross-over experiment will submit each subject to both diets in a randomized order.

11.9 * Explain the rationale for the choice of statistical measures and the number of participants proposed for the study, including the power calculations when applicable.

Statistical Analysis and Sample Size Justification

The statistical analysis for the primary aim of the study:

- Compares the changes in fecal microbiota distribution between the fructose or glucose supplemented diets. A cross-over experiment submits subjects to both diets in a randomized order.
- A sample size of 10 subjects will allow 80% power to detect minimum differences as 1.10 standard deviations in the fecal microbiota distribution at 5% significance with the use of Wilcoxon non-parametric tests.

This power analysis is based on a variability that is 20% inflated when compared to the average coefficient of variation (~40%) reported by Di Luccia et al.(2015) when comparing microbiota distribution between two groups of six different rats each.

Secondary aims:

- Changes in fecal metabolites will be assessed using both significantly differing individual metabolites and metabolite pathways between the glucose and fructose study in the 10 subjects by both t-test and Wilcoxon test for paired samples.
- For differences in intestinal permeability, mass spectrometry data of urine sugars is converted to sucrose or sucralose urine output and the fractional excretion (FE) of lactulose (L) and mannitol (M). L/M ratios=FE L/FE M.
- Paired t-test and Wilcoxon will be used to compare data for the 10 subjects.
- Fecal calprotectin concentrations will be compared using Wilcoxon and paired t-tests.

In addition to the two-sided hypotheses tests to be applied in primary and secondary outcomes, we will run generalized linear mixed-effects models that will include the order in which the diet is given as a fixed factor. This approach enables an estimate of any effect in the sequence of interventions as well as modeling data distributions in the outcomes that are different from the Gaussian.

All calculations were performed with G* power software version 3.1.

11.10 * Will samples be coded?

(•) Yes ( ) No

If Yes, Please describe coding scheme consistent with GCP. If samples will not be coded, please provide justification for this proposed departure from GCP practice.

ARM 1: Pre: PHO-0956-1001A, 1002A, 1003A etc.
Post: PHO-0956-1001B, 1002B, 1003B, etc.

ARM 2: Pre: PHO-0956- 1001C, 1002C, 1003C, etc.
Post: PHO-0956-1001D, 1002D, 1003D, etc.

If available, upload the Data and Sample Sharing Management Plan approved by RU IT.

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
No Document(s) have been attached to this form.						

12.0 Participants of Study

12.1 Specify age range of participants:

* Minimum Age:

45

* Maximum Age:

70

Please note: If the age of participants indicated is less than 18 years old, you will be prompted to attach a Pediatric Assent form later on in the submission process. A link to the Pediatric Assent form can be found in the Help link to the right, or this form can be downloaded later on in the submission process.

12.2 * Indicate the gender(s) of the participants:

- [x] Female
- [x] Male
- [ ] Unknown
- [ ] Not Reported

12.3 * Indicate projected enrollment by race and ethnicity. See Help for disease/volunteer population demographics.

Ethnic Category	Sex/Gender			
	Females	Males	Unknown or Not Reported	Total
Hispanic or Latino	2	2	0	4
Not Hispanic or Latino	3	3	0	6
Unknown (individuals not reporting ethnicity)	0	0	0	0
Ethnic Category: Total of All Subjects*	5	5	0	10
Racial Categories				
American Indian/Alaska Native	0	0	0	0
Asian	1	1	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	1	1	0	2
White	3	3	0	6
More Than One Race	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of All Subjects*	5	5	0	10

12.4 * Will participants of a specific racial/ethnic group be excluded from participation?

- ○ Yes
- ◉ No

If Yes, please specify:

- [ ] Caucasian
- [ ] African-American
- [ ] Hispanic
- [ ] Asian
- [ ] Other

Reason for the exclusion:

- ○ The condition being studied does not occur in the selected group(s)
- ○ Other

If Other, please specify:

12.5 Gender/Minority Exclusion Justification

All research involving human participants should be designed and conducted to include members of both genders and members of minority groups, unless a rationale and justification is provided. Please provide such justification below:

12.6 Vulnerable Populations

Indicate whether any of the following populations will be included in the study:

- [ ] Children
- [ ] Pregnant Women
- [ ] Cognitively Impaired Persons
- [x] RU Employees
- [ ] RU Students
- [ ] Other:

If you checked any of the above, give a brief explanation of the need to use these particular individuals:

Special precautions will be used in recruiting employees of the Rockefeller University to minimize the possibility of undue influence. Rockefeller University employees will be made aware of the study through flyers rather than directed presentation to selected groups. Subjects will be reassured that refusal to participate in the study will not affect their studies or employment in any way.

If the participant is a Rockefeller University employee, does she/he work within the Laboratory of the Principal Investigator or Co-Investigator(s)?

- ○ Yes
- ◉ No
- ○ N/A

If the participant is a Rockefeller University student, does she/he work within the Laboratory of the Principal Investigator or Co-Investigator(s)?

- ○ Yes
- ○ No
- ◉ N/A

12.7 *What is the total number of evaluable participants you plan to enroll at Rockefeller University Hospital over the course of the entire study?

10

12.8 * What is the total number of participants who will need to sign consent *at Rockefeller University Hospital over the course of the entire study* to result in the desired number of evaluable participants?

40

12.9 * What is the total number of participants you plan to sign consent *at Rockefeller University Hospital in the next year?*

40

12.10

*** What will be the total number of evaluable participants *at all sites over the course of the entire study?***

10

12.11 Inclusion Criteria

Please list participant inclusion criteria:

Order Number	Criteria
1	Post menopausal female, last menstrual period at least 24 months ago OR male
2	Age 45-70
3	Willing to consume usual diet with either fructose or glucose added during (2) 16-18 day inpatient stays
4	Willing to consume usual diet during 2 week wash-out period at home
5	BMI 30.0-39.9
6	Willingness not to travel long distances while on study, including wash-out period
7	Willingness not to be exposed to new pets while on study including wash-out period

12.12 Exclusion Criteria

Please list participant exclusion criteria:

Order Number	Criteria
1	Fasting serum triglycerides >200mg/dl
2	Fasting blood glucose >126mg/dl
3	Renal function tests >2x ULN
4	LFTs (HFP) > 1.5x ULN
5	Currently on statins
6	Daily use of a cathartic
7	Broad spectrum antibiotic use within the past 45 days
8	Currently on proton pump inhibitor
9	Currently on insulin or oral hypoglycemic agents

10	Active viral Hepatitis
11	Chronic constipation
12	Inflammatory bowel disease
13	Chronic diarrhea
14	GI resection
15	Any evidence of cardiovascular disease on EKG
16	History of cardiovascular disease such as coronary artery disease, CABG, valve replacement, MI, stroke / TIA.
17	History of macronutrient malabsorption
18	Current smoker. Stopped < 3 months ago.
19	Daily alcohol intake equal to 1.5 oz of 40 proof alcohol.
20	HIV positive
21	Any medical, psychological or social condition that, in the opinion of the Investigator, would jeopardize the health or well-being of the participant during any study procedures or the integrity of the data
22	Persons taking probiotics
23	Hgb A1c > 6.5%
24	Serum uric acid of > 9mg/dL

13.0 Study Plan

13.1 * Describe the study plan:

*** What is the total number of outpatient visits for all participants projected for the next year?**

60

*** What is the average length of each outpatient visit (in hours)?**

1

*** What is the total number of Day Patient visits for all participants projected for the next year?**

0

*** What is the average length of each Day Patient visit (in hours)?**

0

*** What is the total number of inpatient days for all participants projected for the next year?**

360

13.2 *Number of Patients per arm

Study Arm	Number of Patients
Fructose	10
Glucose	10

14.0 Investigational and Support Medications

14.1 List all the investigational medications

See Help for link to Rockefeller University Research Pharmacy web page for additional information.

View Details	Drug Name	FDA Approved	IND Number
⊟	**Trade Drug Name:** Fructose Solution **Generic Drug Name:** **Investigational Drug Name:**	No	

Trade Drug Name:	Fructose Solution
Generic Drug Name:	
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Now Foods
Is the Drug FDA Approved:	No
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	> 99.5% pure fructose < 0.5% potentially other sugars
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Dose(s):	75 Grams
Dosing Frequency:	

View Details	Drug Name	FDA Approved	IND Number
⊟	**Trade Drug Name:** Dextrose **Generic Drug Name:** D-glucose **Investigational Drug Name:**	No	

Trade Drug Name:	Dextrose

Generic Drug Name:	D-glucose
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Now Foods
Is the Drug FDA Approved:	No
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	> 99.5% pure D glucose < 0.5% potentially other sugars
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Dose(s):	75 grams
Dosing Frequency:	

⊟	**Trade Drug Name:** 5 sugar test solution **Generic Drug Name:** **Investigational Drug Name:**	No	

Trade Drug Name:	5 sugar test solution
Generic Drug Name:	
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	RUH research pharmacy
Is the Drug FDA Approved:	No
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	The 4 ingested ingredients are sucralose, sucrose, mannitol and lactulose. Raffinose is added later to the sample for analysis, as an internal standard.
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Dose(s):	
Dosing Frequency:	

14.2 * Will the study involve the use of a placebo?

○ Yes ◉ No

If yes, complete A and B.

A. Is there a proven effective therapy for the condition under study?

○ Yes ◉ No

If Yes, please specify:

B. Please give a justification for the use of the placebo.

14.3 Study support medications are medications that will support the conduct of the study. Please list all support medications to be used in the study (include all prescription drugs, over the counter drugs herbs, and supplements).

15.0 Consent Procedure

15.1 * This study will use the following types of informed consent:

- [x] Informed Consent Form Standard - a standard consent form with instructions for adapting it to your study
- [ ] Consent Form Genetic- a consent form designed for a study where genetic testing (as defined by NYS law) is to be done in the CURRENT study
- [ ] Consent for studies including genome wide sequencing
- [ ] Pediatric Assent Form (To be used in addition to Consent) for Pediatric patients
- [ ] Other (e.g., waivers)

Links to the **Standard Consent, Genetic Testing Consent** and the **Pediatric Assent** forms can be found in the Help link to the right, or these forms can be downloaded later on in the submission process.

15.2 * Indicate the consent process to be used. (See Help for CCTS SOP)

Describe how the required information is being presented to participants (consent form, orally, information sheet, etc.). Attach a copy of what is being presented to participants (usually the ICF and Assent forms).

Prior to the initiation of any study related procedures, the potential subjects will be given a copy of the most recent IRB stamped and approved informed consent to read. Additionally, the PI or study staff member who has been designated to consent will discuss the specifics of the study including but not limited to the purpose of the research, procedures, time commitment, required tasks, test article or device, alternative treatments, benefits, risks, confidentiality etc. in a comprehensible (non-scientific) manner, using language readily understandable by the subject. Subjects will be told that participation is voluntary and that, if they do not consent, they will not be penalized. The person consenting will assure the voluntariness of the subject.

Describe the circumstances under which consent will be obtained, where the process will take place and any waiting period between informing the prospective participant and obtaining consent.

A private, confidential setting will be provided for the potential subject to read and discuss the informed consent free from coercion, undue influence or constraints of time. All subjects will be given a chance to ask questions and express concerns. They will be given the option to take the consent home and discuss it with family, friends, and /or health care providers. After a subject and the person conducting the consenting signs and dates the consent, the subject will be given a copy of the signed informed consent form.
An enrollment note will be written in the source document as to who obtained consent, how, when, were questions asked and answered, and that a copy of the informed consent was given to the subject.

Describe the experience of the investigators designated for this task in the DOA in obtaining consent from participants.

P.Holt, MD, J.Walker, NP, D. Brassil, RN, and R Hutt, RN have extensive experience consenting human subjects for participation in research studies.

How will it be determined that the participants or the participants' authorized representatives understand the information presented?

The "Teach Back" method will be used in the clinical research setting to ask research participants to repeat or “teach back” the information, concepts and directions that the staff member has attempted to convey to the subject. This method is used to assess comprehension and retention of protocol requirements, adverse event information, risks and benefits, and the subject's rights described in the Informed Consent process.

If English is not the participants' native language, how will written and/or verbal translation be provided?

For unexpected or isolated subjects who are candidates for this study, but for whom English is not a primary language, a translator provided through Pacific Interpreters will be used to facilitate the explanation of the study.

Will any participants be cognitively impaired so that they may not have the capacity to give consent?

○ Yes ◉ No

If yes, Describe the procedures to be used to determine the individual participant's capacity to provide consent.

For participants where it has been determined that they lack the capacity to give consent, describe the provisions for obtaining consent from the participants' legally authorized representative.

15.3 * Based on the demographics, will this study's participant population require foreign language consent form?

○ Yes ◉ No

If Yes, please list the language(s):

15.4 * This study's consent procedure will require the following waivers: (See Help for additional information.)

○ Waiver of one or more elements of informed consent, 45CFR46.116(d)
○ Waiver of documentation of informed consent, 45CFR46.117(c)
◉ No waiver is requested

If a waiver is requested, please explain:

15.5 * Does this study include video/audio recording, photography or other electronic recording of human participants?

○ Yes ◉ No

15.7 Describe what will be done:

16.0 Recruitment and Advertising

For assistance consult CRSO to create a robust Recruitment Plan see Help.

16.1 * What is the plan for recruitment?

Overview: The CRROSS estimates prescreening 150 healthy volunteers to identify 25 volunteers who will enroll for screening to achieve the ultimate enrollment goal of 10 evaluable participants.

Feasibility and Assessment:
Incentives: 1) Altruism; 2) Compensation for efforts; 3) Interest in the topic
Challenges: 1) Extended study duration: Total 7+ week participation including screening– 2 x 18 day inpatient stays and 2-week washout period; 2) Retention challenges: Some participants may withdraw after the first and before the second inpatient stay of the study which yields no usable data; 3) The level of compensation for the inpatient stays is low compared to other inpatient studies.

Issues relevant to rapid accrual: Positive: 1) There are volunteers in the Research Volunteer Database who participated in previous PHO and JWA studies and may qualify for participation in this study. 2) Participants can leave the hospital on pass during the day to work, shop, socialize, as long as they stick to the diet; **Negative:** 1) The 36-day inpatient stay may be very inconvenient for some candidates and may conflict with the ability to enroll. We anticipate that it will be the major barrier to enrollment. 2) The PI would like individual's enrollment period to avoid the major holidays (Christmas/Chanukah/Kwanzaa/New Year's) that usually involve changes in diet. Also, participants will not want to be in-house during Thanksgiving (though they can be in the washout period over Thanksgiving). So these constraints mean there is a narrow window between study approval and the start of November, limited by Nov 4th, when participants can be screened, have their diets prepared and enroll in the study and be ready for washout by November 20th. Otherwise, enrollment will be deferred to restart in January 2018.

Projected Time to Accrual Completion (PTAC):
Due to the likelihood of no-shows with healthy volunteer studies, the research team should anticipate the scheduling of 3-4 per week to screen 2 participants per week. Furthermore, the PTAC will be significantly impacted by the 36-day inpatient stay and the 2017 holiday season, we expect to complete enrollment within 12 months. The PI would like to enroll 2 participants in 2017 (the feasibility of this will be evaluated after IRB approval and screening has started); 4 in the early new year and Spring of 2018, and 4 more in the late Spring/early summer. We anticipate full accrual will take about 9-12 months from the start of recruitment.

Factors Affecting Predicted Time to Accrual Completion	Weeks
Research team plans to screen 5 participants per week; 48 weeks to complete accrual	48
Anticipated start up, add 1 2 weeks	2
Add any vacation time when screen/visit capacity will be reduced	0
Recruitment to occur across Dec January time frame	2
Known anticipated maternity leave, other LOA of key staff	0
Staff or KSP changes	0
Staff travel for major conferences	0
Institutional interruptions (graduation, symposium days, etc.)	0
Projected Time to Accrual Completion (PTAC)	52 weeks

Recruitment Implementation:
Advertising- CRROSS will place ads with local newspapers (i.e. Metro), as well as internet outlets (i.e. Craigslist, Clinicaltrials.gov, centerwatch.com, etc.)

Research Volunteer Repository Database - The investigator has agreed to associate protocol PHO-0956 with RKO-0648, the Research Volunteer Repository Protocol, enabling the CRSO to query the existing volunteer database to identify a list of potential volunteers who have agreed to be contacted for future studies and who meet basic eligibility criteria. The CRROSS will contact potential volunteer as allowed to determine interest and will refer eligible and interested volunteers to the study coordinator/investigator. In parallel, the research team will seek and document the granting or denial of permission to contact volunteers about future studies.
Centralized Call Management – CRROSS will work with the research team to develop a protocol-specific pre-screening script based on IRB approved protocol eligibility criteria to prescreen volunteers who call 1800RUCARES. Potentially eligible candidates will be scheduled for the study team for further screening. CRROSS staff will also call volunteers based on Repository queries described above. Research teams are responsible to provide timely updates on pre/screening outcomes (through iRIS, etc.) to keep CRSO strategies on target.

16.2 *From the date of final IRB approval, how long will it take to complete enrollment of the study?

- ○ 6 Months
- ○ 12 Months
- ○ 18 Months
- ◉ 24 Months
- ○ More than 2 years (specify in years)

16.3 This Study

- ◉ Involves an intervention or comparison and a defined enrollment target
- ○ Is a natural history study with expected annual enrollment over many years
- ○ Is an exploratory mechanistic study
- ○ Other

16.4 This Study will enroll:

- ◉ Healthy volunteers
- ○ Individuals affected with a specific disease/disorder
- ○ Both

16.5 * Do you plan on using the Research Participant Repository (RKO-0648) ?

◉ Yes ○ No

16.6 * Are you screening or recruiting from or through a record review of an existing patient database of a healthcare provider?

○ Yes ◉ No

16.7 * Please describe how the Recruitment Plan addresses recruitment of the volunteers consistent with the demographics of the condition under study:

The demographics of the RKO-0648 repository have been consistently similar (2009-20173) to the demographics reported in the NYC 2010 census. Through our plan to utilize our call management service and query the RKO-648 repository, we anticipate being able to enroll participants who match the demographics projected in the application.

16.8 * Do you plan to advertise directly to potential volunteers? (As opposed to relying on practitioner referrals or flyers to practitioners)

(•) Yes ( ) No

16.9 * Do you plan to use the free, web-based volunteer registry, ResearchMatch.org, as a recruitment tool?

(•) Yes ( ) No

17.0 Research Participant Repository (RKO-0648)

17.1 This protocol, will be linked with the Research Volunteer Screening/Recruitment Data Repository run by the Recruitment staff and the Clinical Research Support Office (protocol RKO-0648-1008). In order to participate in the generation of the Repository the PI will enter into a Collector /Collaborator agreement regarding the Repository. The role of Collector/Collaborator is to contribute to the Repository the name, contact and demographic information, recruitment referral information, and screening outcome information, as well as appropriate protocol specific screening information, of volunteers who are screened by telephone or in person for entry into the protocol regardless of the screening outcome. In addition to screening volunteers for the PI's current study, verbal consent will be obtained from the volunteers regarding their willingness to be contacted in the future about possible additional research studies. This permission may be obtained by the Recruitment office staff through the central Call Center. If the PI receives calls directly from participants for initial prescreening, then the PI is responsible for collecting the required information and conveying it to the Recruitment staff for data entry. The consent or withholding of permission will be recorded in the Repository as will the name of the person who obtained the permission. A volunteer's permission or declination will not affect their eligibility for my current protocol, or future protocols. The Recruitment staff of the Clinical Research Support Office may gather the Repository information and request the verbal consent of the volunteer for re-contacting on my behalf as part of our recruitment plan. In order to benefit from the Repository, the PI will enter into a Recipient /Collaborator agreement with the Repository. The Recipient/Collaborator may receive from the Repository pre-screened lists of potentially eligible participants for his/her study as a means to facilitate recruitment. The Recruitment staff will prepare the Repository queries according to the protocol eligibility requirements and available Repository information, and may re-affirm permission to re-contact volunteers as necessary. The PI may use the information and names in the list from the Repository only for the current study and may not save the list to use for a future study of his/her own, nor may he/she share the list with colleagues for other studies."

18.0 Utilization of ResearchMatch.org

18.1 Utilization of ResearchMatch.org for Recruitment

Basic information regarding this tool:

- **ResearchMatch.org is a national electronic, web-based recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University. There is no cost for researchers at participating institutions in the ResearchMatch.org Network to use ResearchMatch.org. The Vanderbilt IRB provides oversight for ResearchMatch.org as a recruitment tool and this has been documented within the ResearchMatch.org IRB Letter of Understanding which was executed by Dr. Gotschlich in October, 2009. However, individual requests to use ResearchMatch.org as a recruitment tool must be submitted to this institutions' IRB.**

Registration:

- **This recruitment tool may be utilized once the PI or research staff registers for recruitment access through ResearchMatch.org and the Institutional Liaison provides approval.**
- **The ResearchMatch.org Institutional Liaison will review the study information and evidence of IRB approval. He/she will set the researcher's expiration date to mirror that of the study's IRB approval.**

Search Capability:

- **After being granted recruitment access, the researcher can search for appropriate matches amongst the non-identifiable ResearchMatch.org Volunteer profiles in the system. He/she can enter study inclusion/exclusion criteria in the ResearchMatch.org Search Builder which will yield a list of potential matches to the study's criteria.**

Contacting ResearchMatch.org Volunteers:

- **Once yielding a list of potential matches (ResearchMatch.org Volunteers), the researcher will send out IRB-approved content that will be the initial recruitment message that these volunteers receive about the study through ResearchMatch.org. The study's recruitment message will be inserted into the standard ResearchMatch.org electronic notification that informs possible matched Volunteers that he/she has been identified as a potential match for the study. The secure ResearchMatch.org clearinghouse will route this standard ResearchMatch.org email notification. These potential matching volunteers will have the option of replying yes, no, or not respond through a set of quick links available in this notification to the study announcement. THE CONTACT MESSAGE WILL NOT INCLUDE THE STUDY'S DIRECT CONTACT INFORMATION (e.g. EMAIL, PHONE). By responding yes, the Volunteer has authorized ResearchMatch.org to release his/her contact information to the researcher. The researcher will be responsible for managing this contact information as called for by this IRB-approved study protocol.**

Study Management in ResearchMatch.org:

- **Researchers (and the Liaison) can view information regarding his/her study's status in ResearchMatch.org (e.g. number of volunteers contacted for the study via ResearchMatch.org to date, response rate of volunteers, etc.). ResearchMatch.org will also be collecting aggregate data regarding the status of ResearchMatch.org volunteers within the study. Volunteers consent to this within the ResearchMatch.org Volunteer Agreement. This information will allow the researcher to indicate where the Volunteer currently stands within the recruitment process and thus will help the researcher monitor the utility and effectiveness of using this resource (e.g. Did not contact, Not eligible, Enrolled, Completed, etc.).**

19.0 Potential Benefits to Participants

19.1 * Will participation in this study provide direct benefits to the participant?

○ Yes ◉ No

19.2 If Yes, describe the potential direct benefits:

20.0 Potential Risks to Participants

20.1

*** Describe any potential risks: physical, psychological, social, legal or other and assess their likelihood and seriousness. Indicate risks both to the participants and to the embryo or fetus if the participant is or may become pregnant. Please provide the potential risks below:**

Risk from venipuncture: Potential risks from venipuncture include discomfort or pain, ecchymosis, bleeding, phlebitis and infection at the needle insertion site. Additional risks include lightheadedness and a vasovagal response.

Privacy Risk: There is the risk that there could be computer security breaches which could reveal your identity. There may be the risk that data about you may become public, and could be used by employers or law enforcement agencies.

Risk from glucose ingestion: Potential risk includes mild nausea after drinking sweet drink, possible loose stool or diarrhea due to concentrated glucose load.

Risk from fructose ingestion: Potential risk of mild nausea after drinking sweet drink, possible loose stool or diarrhea due to concentrated fructose load, potential elevation of serum triglycerides due to metabolism of fructose by the liver. Rare cases of acute pancreatitis can occur with extremely high serum triglyceride levels (>2000mg/dl). Potential elevation of liver function tests.

Risk from BodPod: Potential risk of feeling claustrophobic while in the bod pod.

Risk from stool collection: Potential risk from stool collection is embarrassment and discomfort while collecting stool.

Risk from permeability test: Potential GI distress from drinking 5 sugar mixture on fasting stomach. Inconvenience of collecting urine for 5 hours and remaining NPO except water and in house during the test period.

Risk from fructose enhanced diet: Increased serum triglycerides, increased liver enzymes.

21.0 Procedures to Minimize Risks

21.1 * Describe the procedures for protecting against or minimizing any potential risks, and include an assessment of their likely effectiveness. Include a discussion of confidentiality safeguards, where relevant, and arrangements for providing medical treatment, if needed.

Venipuncture: Only skilled nurses and phlebolotomists will perform this procedure.

GI symptoms from sugar drinks: Participants will be informed of potential side effects and closely monitored. Drinks will be given in small doses with meals. If unable to tolerate, testing and study participation will be ended and symptoms will be treated.

Urine and Stool collection: Participants will be provided privacy and support by staff to make collection as comfortable as possible.

Potential elevation of liver function tests (AST, ALT): Only participants who are cardiometabolically healthy with AST/ALT < 2XULN will be enrolled. Safety labs will be monitored after 7 days on fructose/glucose. Stopping rules: AST/ALT> 2XULN or 1.5 X baseline value, whichever is greater.

Potential for elevated serum triglyceride levels: Triglycerides will be monitored pre and post intervention. Stopping rules: Serum triglycerides > 500 mg /dl.

Privacy Risk:
Risk of invasion of subject privacy is reduced by secure computers maintained by the IT department with up-to-date monitoring and firewalls requiring pass-phrases to access patient information, secure e-mails and locked file cabinets and offices.

22.0 Alternative Methods or Treatments

22.1 * Describe alternative methods or treatments for the disease(s) under study, if any, that were considered and why they will not be used:

There are no alternative methods to understand the effect of fructose on the stool microbiome and metabolome at this time.

23.0 Data and Safety Monitoring

This section describes the Data and Safety Monitoring Plan (DSMP) required of each protocol undertaken at the CCTS according to HRPP and NIH policies Notice 98 -084 and Notice 00-038, as cited in Help Sections below. Depending on the level or risk and trial phase, some protocols will need Data and Safety Monitoring Boards.

23.1 * Overall Risk Classification

An estimate of risk is necessary to evaluate the adequacy of the planned monitoring. The HELP section provides guidance in making the risk assessment.

Read the risk definitions and examples of risk in the HELP section and select the risk category that best describes the current study.

If your assessment differs from the definitions the HELP section, describe any factors that modify your judgment of the overall risk in the text box after the risk designation.

- ○ MINIMAL RISK
- ○ LOW RISK
- ◉ MODERATE RISK
- ○ SIGNIFICANT RISK

Please provide any optional description(s):

23.2 Protocols Involving Minors

The chance of direct benefit to the child, or to understanding a disorder not otherwise understood, may be major factors in justifying more than minimal risk in research involving children.

Based on the above definitions, please specify your study's risk classification below:

- ○ NOT GREATER THAN MINIMAL RISK (the risk of daily life to a healthy child living in a safe environment) 45 CFR 46.404
- ○ GREATER THAN MINIMAL RISK WITH DIRECT BENEFIT TO PARTICIPANT; 45 CFR 46.405
- ○ GREATER THAN MINIMAL RISK, NO DIRECT BENEFIT, BUT BENEFIT TO UNDERSTANDING OF PARTICPANT'S DISORDER; 45 CFR 46.406
- ○ RESEARCH NOT OTHERWISE APPROVED PRESENTING OPPORTUNITY TO UNDERSTAND, PREVENT OR ALLEVIATE SERIOUS PROBLEM AFFECTING CHILDREN 45 CFR 46.407 (cannot be approved by IRB; requires public comment)

23.3 DSMB

1. The NIH requires that all SIGNIFICANT RISK protocols have a **Data and Safety Monitoring Board** and provide information about the expertise and independence of that Board
2. Phase III trials require a Data and Safety Monitoring Board,

3. A DSMB may be appropriate for some Phase I and II protocols. (See Help for examples.)
4. It is the investigator's responsibility to report to the IRB, the findings and recommendations of the DSMB as they become available.

Please specify:

- ○ A DSMB is required for this study
- ◉ A DSMB is not required for this study
- ○ Unsure

If a DSMB is required, please indicate why:

- ☐ Significant Risk
- ☐ Study Design - Phase III
- ☐ Study Design - Placebo Controlled
- ☐ Study Design - Multicenter Trial
- ☐ Study Design - Other Factor

If other factor, please specify:

If a DSMB is required, select one:

- ○ An independent DSMB has been constituted; the members, mission charter, schedule for meetings, and a listing of the data to be reviewed by the DSMB will be attached.
- ○ A DSMB has not yet been constituted; the PI will consult the IRB and/or CRSO for assistance in assembling a DSMB.

If a DSMB is not required, but is being constituted for other reasons, please explain:

23.4 * Safety Review

Select one:

- ○ Safety Review is conducted as follows: Laboratory results for research volunteers will be reviewed in a timely manner, usually within 24 hours of receipt by a licensed practitioner. The potential clinical significance of any abnormal finding will be documented in the medical and research record(s), and an appropriate plan or referral developed. The PI's review of safety issues at research team rounds will be documented in the meeting minutes.
- ◉ Protocol Specific

If Protocol Specific, please describe safety review for protocol tests and procedures that require other than routine review. For example, an EKG taken to detect emerging conduction problems might require immediate safety review.

Jeannie Walker will review the safety labs within 24 hours of receipt and will follow the stopping rules of the protocol to maintain clinical safety of participants.

23.5 Monitoring

Monitoring Personnel: See Help Bubble to the right.

Internal Monitoring

The PI or his/her designee shall conduct internal monitoring to assure the safe and proper conduct of the protocol and all the elements list above in monitoring, following the general principles of quality management. The intensity and frequency of internal monitoring will depend on the protocol risk to

participants, the experience of the PI and research team, rate of enrollment, and specific details of the protocol.

Internal monitoring of informed consent and eligibility documentation will be conducted by the research team shortly after enrollment begins. Internal monitoring activities will be documented by logs, meeting minutes or other systematic means.

Specify the research team members who will conduct the internal monitoring of the study (see Help for who may monitor):

Peter Holt MD
Jeanne Walker NP
Richard Hutt RN

For new investigators: Internal monitoring should be conducted at least monthly by new investigators until there are essentially no findings to correct at each review.

External Monitoring

* Is external monitoring planned for this protocol?

- ○ Yes
- ◉ No
- ○ Unsure

If external monitoring is planned, please specify (see Help for who may monitor):

- ○ (Significant Risk) External monitoring will occur at least every six weeks unless there is no enrollment
- ○ (Moderate Risk) External monitoring will occur at least quarterly
- ○ (Low or Minimal Risk) External monitoring will occur at least annually

If external monitoring is planned, please specify the name of the monitor:

☑ Note that copies of external monitoring reports must be supplied to the IRB and the CRSO as soon as they are made available

Additionally, audits of the research records of minimal, moderate or significant-risk protocols may be performed by the CRSO staff on a random basis or as part of a prospectively identified auditing plan.

23.6 Adverse Event Classification

Adverse events are classified by definition, severity, and association with the investigational trial.

Definition of an Adverse Event
Any unfavorable or unintended sign (including abnormal lab findings), symptom or disease temporally associated with the use of a medical treatment or procedure, or protocol, regardless of whether it is considered related to the medical treatment or procedure or protocol.

Definition of a Serious Adverse Event
Any unanticipated event that involves the following:
- o results in death
- o is life-threatening
- o requires hospitalization or prolongs existing hospitalization
- o results in persistent or significant disability/incapacity
- o is any medical event which requires treatment to prevent one of the outcomes listed above

Other events can be classified as "serious adverse events" at the discretion of the PI.

Definition of Anticipated/Expected Adverse Event

Any adverse event, which has been reported in the Investigator's Brochure, package insert, safety reports, clinical protocol, consent form or listed in the NCI agent-specific Expected Adverse Event List[3], is

classified as an expected adverse event. The investigator must provide the available data of known adverse events and toxicities that have been associated with the study drug, device, intervention, or procedures. This information helps to define the level of risk of the trial and enables safety monitoring. A minimal risk trial may not have any defined risks and a statement to that effect is sufficient to meet the DSMP requirements.

Definition of an Unanticipated/Unexpected Adverse Event
Any adverse event that is not consistent with the known, predicted possible effects of the research protocol. An unexpected adverse event varies in nature, intensity or frequency from information on the investigational product provided in the Investigator's Brochure, package insert, safety reports, clinical protocol, or listed in the consent form.

Definition of an Unanticipated Problem (UaP)
A UaP is an event or circumstance that meets all the following three criteria: [1] the nature, severity, frequency of the event(s) or information was not expected in the descriptions in the study documents or the characteristics of the participant population being studied; [2] there is a reasonable possibility that the procedures involved in the research caused or are linked in a significant way to the problem; [3]the event or information suggests that the research places particpants or others at a greater risk of harm than was previously known or recognized (including physical, psychological, economic, or social harm.

Grade and Relatedness of Adverse Events:

Adverse Events are graded for severity and scored for relatedness to the protocol, according to a published scale. Several standardized AE Reporting scales are available. (See Help for links to these scales.)

* Please indicate the scale you intend to use:

- ○ CTC v2.0 (http://ctep.info.nih.gov/reporting/ctc.html)
- ○ CTCAE v3.0 (http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf)
- ◉ CTCAE v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf)
- ○ CTCAE v5.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf)
- ○ AIDS Clinical Trials Group (http://aactg.s-3.com/)
- ○ Other

If Other, please specify:

23.7 Reporting Adverse Events

All AEs will be reported to the IRB at least annually.

Reporting Serious AEs

- ☑ Serious Adverse Events, (SAEs) will be reported to the IRB according to policy, within two working days of identification of the SAE.

Select all that apply:

- ☐ SAEs will be reported to the Sponsor and or ESCROW

SAEs will be reported to the sponsor within how many days of the event?

2

- ☐ SAEs will be reported directly to the FDA, per 21 CFR 312

SAEs must be reported directly to the FDA within 7 days of the event by the investigator/sponsor.

☐ SAEs will be reported to another entity

Describe:

Reporting Unanticipated AEs:

Select all that apply:

☑ UAEs will be reported to the IRB

UAEs that are related and greater than moderate severity must be reported to the IRB according to policy, within two working days of identification of the UAE.

☐ UAEs will be reported to the Sponsor

UAE will be reported to the sponsor within how many days of the event?

☐ UAEs will be reported to the FDA, per 21 CRF 312

UAEs will be reported to the FDA, per 21 CRF 312, within 15 days.

☐ UAEs will be reported to another entity

Describe:

23.8 Reporting Unanticipated Problems

☑ Unanticipated problems involving risks to participants or others will be reported to the IRB and the CRSO within five working days.

23.9 CLIA/CLEP

Only laboratory and research tests that are CLIA/CLEP certified or waived may be used to determine eligibility, shared with research volunteers, and used in clinical decision making.

Select if applicable:

☑ This study includes tests that are not CLIA/CLEP certified; the results of such tests will not be used in clinical decision making, or to determine eligibility, or shared with participants or their health care providers.

23.10 Tissue Repository

Human Tissue and Data Repositories collect, store, and distribute human tissue materials and or data for research purposes. Repository activities involve three components: (i) the collectors of tissue samples\data; (ii) the repository storage and data management center; and (iii) the recipient investigators.

* Select one:

◉ I DO NOT intend to collect, store, and distribute human tissue materials for research purposes

○ I DO intend to collect, store, and distribute human tissue materials for research purposes, therefore this protocol entails the Operation of a Tissue Repository. The IRB requires that the protocol specify the conditions under which data and specimens may be accepted and shared, and ensuring adequate provisions to protect the privacy of participants and maintain the confidentiality of data.

If you do intend to collect, store, and distribute human tissue materials, you will be asked to upload the following documents later on in the submission:

- A Sample collection protocol (for tissue collector collaborators to follow) and informed consent document for distribution to tissue collectors and their local IRBs.
- A Certificate of Confidentiality (to protect confidentiality of repository specimens and data).
- A Recipients Agreement describing the commitment of the recipient to preserve the anonymity of the samples shared.

24.0 Toxicity Management and Stopping Rules

24.1 * Describe any drug toxicity or other conditions under which the participation of a participant or the conduct of the study would be stopped in order to maximize safety (e.g., toxicity management and stopping rules):

Serum triglycerides > 500 mg/dl
Inability to tolerate glucose or fructose dose.
Serum uric acid > 10mg/dL

*** Indicate withdrawal criteria and procedures below:**

Intolerance of fructose/glucose addition to diet
Serum triglycerides > 500 mg/dl
AST/ALT > 2X ULN or 1.5X baseline value, whichever is greater
The participant may withdraw at any time.
The investigator may withdraw the participant at any time if (s)he is not tolerating the study.

25.0 Compensation/Costs

25.1 *Will any compensation be offered to participants in return for their participation, e.g., direct payment, medical care, tests, etc.?

- ○ No
- ◉ Yes (Please describe)

Arm 1:
$25 per inpatient day X16 days = $400
$50 per testing day X 4= $200
Total: $ 600

Arm 2
$25 per inpatient day X 16 days = $400
$50 per testing day X 4 = $200
Total $600 for Arm 2

Completion bonus $100
Total compensation for entire study: $1300
Additional $25/day if study arm requires > 16 days per arm.

25.2 * Will there be any costs to participants associated with their participation in research?

- ○ Yes
- ◉ No

If so, please explain:

26.0 Bibliography

26.1 * Enter your bibliography below:

References

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27.0 Appendices

27.1 Enter your appendices below:

28.0 Funding

28.1 * Do you have sufficient financial resources to support your study?

(•) Yes ( ) No

If No, explain:

28.2 If this study is/was a pilot funded, please specify dates of funding:

From date:

To date:

28.3 Specify funding by Rockefeller University, industry sponsor and/or grant:

	Sponsor	Funding
Rockefeller University	Breslow Laboratory	■
Industry		
Grant		
Pilot Award		

28.4 List grants in which this study is named:

	PHS or Non-PHS	Program	Grant Number	Grant Name	From Date	To Date
No records have been added						

29.0 Clinical Services

29.1

- [x] Well/Minimally Ill
- [ ] Moderately Ill
- [ ] Severely Ill

☐ Other
☐ Not Applicable

If other than Well/Minimally Ill, please describe:

29.2 * Does your study group have special care needs?

○ Yes ◉ No

If Yes, specify:

☐ Assistance with ambulation
☐ Wound care
☐ Assistance with ADL
☐ Other

If Other, please describe:

29.3 * Does your study have special equipment needs?

○ Yes ◉ No

If Yes, please describe:

29.4 * Will you require storage space on the clinical units for supplies to conduct this study?

◉ Yes ○ No

If Yes, please describe:

Temporary -80C freezer storage

29.5 * Is special training of hospital staff required?

◉ Yes ○ No

If Yes, please describe:

"Five sugar," permeablility testing
Stool collection and freezing procedure

30.0 Pharmacy Services

30.1 * Does the study require Pharmacy Services?

◉ Yes ○ No

If Yes, please proceed to next section.

30.2 Types of pharmacy services required:

☑ Dispensing
☑ Randomization
☐ Compounding

☐ Other

If Other, please specify:

For the randomization code, there will be 10 treatment slots (subjects).
The study is a 2X crossover, so there are two possible sequences.
There will be 5 males and 5 females enrolled, and the groups will be stratified such that within each sequence there will be balance with gender, as follows:

	Treatment Sequence	n of N	Gender balance
Sequence 1	Glucose then Fructose	for 5 of 10 enrolled	3 males, 2 females
Sequence 2	Fructose then Glucose	for 5 of 10 enrolled	2 males, 3 females

30.3 Dispensing:

☐ Sponsor supplied drugs
☐ Pharmacy supplied drugs
☑ Other

If Other, please describe:

Investigator supplied study supplement: glucose or fructose

30.4 Type of medication(s):

☐ Injectable
☐ Ophthalmic
☐ Inhalational
☐ Topical
☐ Suppository
☐ Other

If Other, please specify:

If Injectable, please specify:

☐ Monday-Friday 8:30AM-5PM
☐ Off-hours [all other days/times]

30.5 Compounding: (including mixing medications)

☐ Oral Capsule
☑ Oral Liquid
☐ Topical, ointment/cream/gel
☐ Injection, Intramuscular
☐ Injection, Subcutaneous
☐ Injection, Intradermal
☐ Injection, Intravenous
☐ Other

If Other, please specify:

31.0 Bionutrition

31.1 * **Will study require patient meals?**

(•) Yes ( ) No

If Yes, please specify:

Type of Diet	In/Outpatient	Pack Meal
Standard	☐ Inpatient ☐ Outpatient	○ Pack Meal
Therapeutic	☐ Inpatient ☐ Outpatient	○ Pack Meal
Research Diet	☑ Inpatient ☐ Outpatient	○ Pack Meal
Formula Diet	☐ Inpatient ☐ Outpatient	○ Pack Meal

Nutrient(s) to be controlled (specify):

Diets will be prepared to reflect participant's usual dietary intake with a total substitution of 75 gms of glucose or fructose provided in two divided drinks of 37.5 gm each, for 75 gms of carbohydrate in usual diet of participant. The diet will include either glucose or fructose depending on the arm the participant is in.

31.2 Will meal times be altered?

(•) Yes ( ) No

If Yes, please explain:

On testing days, if participant must be NPO for the test, breakfast will be served after testing is completed.

31.3 Does the protocol require any of the following activities?

☐ Food Frequency Questionnaire
☐ Bod Pod/ Anthropometric Measurements
☐ Diet History/ Food Records
☐ Diet/ Nutrition Education

31.4 Will food be provided to caregiver, parent or significant other?

( ) Yes (•) No

31.5 For metabolic diets, is diet homogenization required for nutrient analysis by independent lab?

(•) Yes
( ) No
( ) N/A

32.0 Clinical and Translational Research Facilitation Office

32.1 Indicate navigation assistance requested and/or received in the development of the study:

	Requested	Received
Protocol Development	☑	☑
Protocol Implementation	☐	☐
Protocol Conduct	☐	☐
ACCTS/IRB Submission	☑	☑

32.2 Indicate additional education assistance requested and/or received in the development of the study:

	Requested	Received
IND	☐	☐
IDE	☐	☐
Team Science Education	☑	☑
Study Progress Meeting	☑	☑
Investigator Responsibilities	☐	☐
Regulatory Binder/Folder	☑	☑
Source Documentation	☑	☑
Participant Involvement in Research	☐	☐

33.0 Clinical Research Support Office Resources (CRSO)

33.1 Indicate regulatory input assistance requested and/or received in the development of the study:

Regulatory Support/Design	Requested	Received
General, Vulnerable Populations, Minors, Group Harms	☐	☐
IND/IDE advice, assistance, and referral	☐	☐
Informed Consent/Assent	☐	☐

Data Safety Monitoring Plan	☐	☐
Clinical Trial Registration	☐	☐
Plan For Return of Research Results	☐	☐
Audit/Monitoring Service, Referrals, SOPs	☐	☐

33.2 Indicate recruitment assistance requested and/or received in the development of the study:

Recruitment of Participants	Requested	Received
Recruitment Planning and/or written Plan	☑	☑
Advertising Strategy, Content, Placement	☑	☑
Repository/Research Match Queries	☑	☑
Call Center/Prescreening /Scheduling	☑	☑
Cost Sharing for Advertising	☐	☐

33.3 Indicate community engagging assistance requested and/or received in the development of the study:

Community Engagement	Requested	Received
PHI Statement/Engaging Stakeholders Section	☐	☐
CEnR Navigation – fostering pt /community partnership	☐	☐
Outreach to community/partner /advocacy group/CE Studio	☐	☐

33.4 Indicate other assistance requested and/or received in the development of the study:

Other	Requested	Received
Survey design, fielding, validation	☐	☐
	☐	☐

Data transfer and security planning		

34.0 BERD: Biostatistics, Epidemiology and Research Design Resource

34.1 Indicate Biostatistic assistance requested and/or received in the development of this study:

	Requested	Received
Development of experimental design	☐	☐
Power analysis/Sample size determination (# of subjects)	☑	☑
Navigation (Did Statistician participate in a navigation meeting)	☑	☑
Randomization schedule	☐	☐
Data analysis	☐	☐
Development of new statistical techniques for data analysis (Statistical research)	☐	☐
Protocol implementation	☐	☐
Other	☐	☐

If other, specify:

34.2 If you are/will be using data analysis specify:

- ☑ Exploratory
- ☐ Descriptive
- ☐ Hypothesis testing
- ☐ Statistical modeling
- ☐ Other

If other, specify:

34.3 If you are/will be assisted with protocol implementation, specify:

- ☐ Publication
- ☐ Conference

- [ ] Other (type of dissemination)
- [ ] Grant(s)

If other, specify:

34.4 Please select the Biostatistician on this Protocol:

- [x] Roger Vaughan, DrPH
- [x] Caroline Jiang, MS
- [ ] Sandra Garcet, PhD
- [ ] Neha Singh, MS
- [ ] Other

If other please specify:

35.0 Biomedical Informatics Resources

35.1 Indicate Bioinformatics assistance requested and/or received in the development of this study:

	Requested	Received
Microarray analysis	☐	☐
Pathway analysis	☐	☐
RNA-seq analysis	☐	☐
Bioinformatics training and consultation	☐	☐
Bioinformatics experimental design	☐	☐
HPC computing	☐	☐
Other	☐	☐

If other, explain:

35.2 If you are/will be using microarray analysis software, specify:

- [ ] Genespring
- [ ] Other

If Other, specify:

35.3 If you are/will be using pathway analysis software, specify:

- [ ] Ingenuity IPA
- [ ] David

- [ ] GSEA
- [ ] Other

If Other, specify:

35.4 If you are/will be using RNAseq analysis software, specify:

- [ ] Tophat
- [ ] Cufflinks
- [ ] Cuffdiff
- [ ] CummRbund
- [ ] STAR
- [ ] featureCounts
- [ ] DESeq2
- [ ] VOOM
- [ ] RNA-SeQC

If other, specify:

35.5 Indicate Medical Informatics assistance requested and/or received in the development of this study:

	Requested	Received
Data storage inside of iRIS	☐	☐
Redcap Database	☐	☐
Custom or Ad Hoc reports	☐	☐
Study plan creation	☐	☐
Specialize database or custom software	☐	☐
Other	☐	☐

If Other, explain:

36.0 HIPAA Form

36.1 A study's specific HIPAA form signed by the volunteer is required for institutions that are HIPAA covered entities so that they may communicate Private Health Information (PHI) to the Investigator.

Below, Memorial Sloan Kettering Cancer Center, New York-Presbyterian Hospital and Weill Medical College of Cornell University are listed so that that they may report laboratory results and X-ray readings respectively. If you foresee that any other entity may need to provide PHI then add them to the field highlighted in green.

36.2 Name of Study:

Effects of dietary fructose on gut microbiota and fecal metabolites in obese men and postmenopausal women: A pilot study

36.3 Principal Investigator:

Peter R Holt, MD

36.4 Industry Sponsor:

none

If the funding source is industry please type in the sponsor here

Who may obtain, use, and/or disclose your health information?

The following persons and organizations may obtain, use, or disclose health information about you.

- The Principal Investigator(s) listed at the top of this form, and persons who assist the Investigator (s) in carrying out the research
- Each research site for this study, including The Rockefeller University, and the research management and support staff and the medical staff at each site
- Health care providers who have provided in the past, or currently provide, health care services to you
- Laboratories and other persons and organizations that will analyze your health information and/or biological samples as part of this study, including Memorial Sloan Kettering Cancer Center, New York-Presbyterian Hospital and Weill Medical College of Cornell University

Other entities that may need to provide PHI:

NIH

- Members and staff of the Institutional Review Board and other boards and committees that watch over research at The Rockefeller University
- Members and staff of The Rockefeller University's Office of Sponsored Research
- The sponsor(s) of the research, named above, and persons who watch over the research for the sponsor(s)
- The United States Food and Drug Administration, other government agencies, regulatory entities and Rockefeller University consultants that watch over the safety, effectiveness, and quality of research and/or fund The Rockefeller University Hospital
- Others (as described here):

What information will be obtained, used, or disclosed?

The persons and organizations listed above may obtain, use, and disclose:

- Information about you that is created or collected during the research study (but not including any HIV-related information)
- Health information in your medical records that is relevant to the research study (but not including any HIV-related information)
- **And**, if checked below:

___ HIV-related information (this includes any information indicating that you have had an HIV-related test or have HIV infection, HIV-related illness, or AIDS, as well as information that could indicate you may have been exposed to HIV)

___ Other information (as described here):

_____

_____

_____

_____

- Other information (as described here):

By signing this form, you give permission to the persons and organizations listed above to obtain, use and disclose your health information noted above.

How will your health information be used?

The health information noted above, as well as information shown by the boxes checked above (if any), may be obtained, used, and disclosed:

- to conduct the research study explained to you during the informed consent process; and
- to assure the quality, safety, and effectiveness of the research study

Please note that the persons and organizations listed above may re-use or further disclose your information if they are permitted by law to do so.

What are your rights?

It is your right to refuse to sign this authorization form. If you do not sign this form, you will not be able to participate in the research study. Your health care outside the study will not be affected. The payment for your health care and your health care benefits will not be affected.
If you sign this authorization form, you will have the right to withdraw it at any time except to the extent that the persons and organizations listed above:

- have already taken action based upon your authorization;
- need the previously collected information to complete analysis and reports of data for this research; or
- will continue to use and disclose previously collected information as permitted by the informed consent form signed by you (except as to HIV-related information, for which disclosure to new persons or organizations will not occur unless permitted by federal or state law).

If you withdraw the authorization, you will not be permitted to continue taking part in the research study. This authorization form will not expire unless you withdraw it. If you want to withdraw this authorization, please write to the above named investigators.
You have a right to see and copy your health information described in this authorization form in accordance with The Rockefeller University's policies; in certain circumstances where the integrity of the study will be affected, you will not be able to obtain your health records in this study until the study has been completed.
You will receive a copy of this form after you have signed it.

Notice Concerning HIV-Related Information

If you are authorizing the release of HIV-related information, you should be aware that such information may not be shared without your approval unless permitted by federal or state law. You also have a right to request a list of people who may receive or use your HIV-related information without authorization. If you experience discrimination because of the release or disclosure of HIV-related information, you may contact the New York State Division of Human Rights at (212) 480-2493 or the New York City Commission of Human Rights at (212) 306-7450. These agencies are responsible for protecting your rights.

Your signature

I have read this form, and all of my questions have been answered. By signing below, I acknowledge that I have read and accept all of the information above.

_____	_____
Signature of participant or participant's legal representative	Date

Printed name of participant

Printed name of legal representative (if applicable)

Representative's relationship to participant

THE STUDY PARTICIPANT OR HIS OR HER PERSONAL REPRESENTATIVE MUST BE PROVIDED WITH A COPY OF THIS FORM AFTER IT HAS BEEN SIGNED.

37.0 End of Application Form

37.1 The study application form is complete. The next step in the submission process is to gather attachments before proceeding to the submission form.

The following submission reports are generated in the Lab/Dept Reports menu, Submission Reports section:

- **Delegation of Authority** (if applicable, and if not previously generated)
- **HIPAA form** (if applicable)
- **CCTS Utilization Report** (required for all submissions)
- **Study Progress Report** (if the study has been managed in iRIS for a minimum of one year, generate the Progress Report from the report menu in iRIS. if the study has not been managed in iRIS for one year, complete the Progress Report located on the IRB website.)

All other required forms can be downloaded from the corresponding sections' help links above or from the IRB website.