FIBER SUPPLEMENTATION IN CHILDREN WITH PEANUT ALLERGY ON ORAL IMMUNOTHERAPY: A RANDOMIZED CONTROLLED PILOT STUDY

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Study Product: Fiber supplement (Resistant Potato Starch) (GRAS)

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List of Abbreviations

ACT	asthma control test
AE	adverse event
CBC	complete blood count
CRF	case report forms
DBPCFC	double blind placebo controlled food challenge
FS	fiber supplement
GALT	gut associated lymphoid tissue
GI	gastrointestinal
GRAS	generally regarded as safe
OIT	oral immunotherapy
PI	principal investigator
POIT	peanut oral immunotherapy
RPS	resistant potato starch
RMS	resistant maize starch
ACS	accessible corn starch
SAE	serious adverse event
SCFA	short chain fatty acids
UChicago	The University of Chicago

Study Summary

Title	Fiber Supplementation in Children with Peanut Allergy on Oral Immunotherapy: A Randomized Controlled Pilot Study.
Short Title	Pinpoint Study
Protocol Number	UCM001
Methodology	Double Blind, Placebo Controlled Pilot Study
Study Duration	July 2021-June 2026 (estimated)
Study Center(s)	UChicago Medicine Comer Children's Hospital UChicago Medicine Comer Children's Merrillville UChicago Medicine South Loop
Primary Endpoints	• To determine the proportion of subjects who tolerate at least 1043 mg cumulative of peanut protein with no more than mild symptoms at the 12-month DBPCFC
Secondary Endpoints	• To determine the proportion of subjects who experience dose related GI side effects during oral immunotherapy • To determine the proportion of subjects who experience hypersensitivity reactions (other than GI) during oral immunotherapy

Exploratory Endpoints	• To demonstrate the effect of resistant potato starch (RPS) on the fecal microbiome and metabolome
	• To determine if gnotobiotic mice colonized with the fecal microbiota of study participants models clinical response
	• To evaluate the immunological effects of fiber supplementation in children
	  ○ Change in peanut specific IgE and IgG4 levels
	  ○ Change in peanut skin prick test mean wheal diameter
	  ○ Change in peanut component levels

Number of Subjects	30 peanut allergic subjects will be randomized 1:1 of dietary supplementation of a fiber supplement (RPS) versus placebo

Diagnosis and Main Inclusion Criteria	• Age 4 to 17 (inclusive)
	• A convincing clinical history of peanut allergy
	• Immune markers consistent with peanut allergy
	  ○ Serum IgE to peanut of >0.35 kUA/L and a skin prick test to peanut >8mm greater than the negative saline control –or-
	  ○ Serum IgE to peanut of >5 kUA/L and a mean peanut wheal diameter on skin prick test 3 to 8mm greater than the negative saline control –or-
	  ○ Serum IgE to peanut of >14 kUA/L and mean peanut wheal diameter on skin prick test 3mm greater than the negative saline control
	• Experience dose-limiting symptoms at or before 100mg challenge dose of peanut protein on screening double blind placebo-controlled food challenge (DBPCFC)
	• Written informed consent from parent/guardian
	• Written assent from subjects above the ages 4-17

Exclusion criteria	• History of a chronic disease (other than asthma, allergic rhinitis, and atopic dermatitis) that is at significant risk of becoming unstable or requiring a change in chronic therapeutic regimen • History of mast cell disease • History of recurrent idiopathic or virally induced urticaria, angioedema or anaphylaxis • Any history or presence of autoimmune, cardiovascular disease, chronic lung disease (other than asthma), malignancy, psychiatric illness, or gastrointestinal inflammatory conditions, including celiac disease, inflammatory bowel disease, eosinophilic esophagitis or other eosinophilic gastrointestinal disease • Current participation in any other interventional study • Subject who has undergone any type of oral immunotherapy • Severe asthma or uncontrolled mild to moderate asthma • Uncontrolled atopic dermatitis • Current use of oral steroid medications • Use of >1 bursts of oral steroid medications in the past year • Inability to eat by mouth the fiber supplementation or placebo control and peanut flour for any reason • Use of any therapeutic antibody (biologic medication) or any immunomodulatory medication in the past 12 month (other than a short course of oral steroids) • Current use of any type of immunotherapy • Pregnancy or lactation • Allergy to potato, corn, oat or cow's milk • Unwillingness to carry an epinephrine autoinjector • Unwillingness to comply with activity restrictions during OIT or any other study procedure
Study Product and Planned Use	A prebiotic, resistant potato starch (RPS), will be given as a dietary supplement before and during oral immunotherapy to peanut
Reference therapy	Oral immunotherapy to peanut
Treatment Description	Subjects who meet inclusion criteria will be randomized 1:1 to receive either RPS or placebo. After 30 days of prebiotic therapy, subjects will start peanut oral immunotherapy (POIT) in addition to the prebiotic and continue through a prescribed course of POIT, approximately 180 days. After completion of POIT updosing, subjects will continue on maintenance POIT plus prebiotic therapy for an additional 180 days at which time they will undergo a DBPCFC. Subjects will then stop prebiotic therapy and continue on maintenance POIT in extended observation for approximately 4 years.

Schedule of Events	• Inclusion/exclusion criteria • Informed consent (and assent, as age appropriate) • Medical/allergy history • Concomitant medications • Physical examination, including height and weight • Vital signs • Quality of life assessment • Spirometry (if has asthma diagnosis as COVID allows) • eNO (if has asthma diagnosis as COVID allows) • Asthma control test (ACT; if has asthma diagnosis) • Blood draw (total IgE, peanut-specific IgE, peanut component testing, peanut-specific IgG4, complete blood counts (CBC), 25-hydroxyvitamin D (screening only), omega-3 index (screening only)) • Skin prick testing (screening and exit) • Stool collection • DBPCFC (screening and exit) • Randomization • Study product administration and dispensation for home dosing • Peanut oral immunotherapy (POIT) -in both placebo/control and investigational groups. • Dose compliance monitoring • Adverse event (AE) monitoring (including serious adverse event)
Statistical Methodology	Chi-square testing (or non-parametric equivalent) will be used to compare categorical variables. Student's *t*-test (or non-parametric equivalent) will be used to compare continuous variables. Microbial relationships between samples will be compared using principal coordinate analysis and average-neighbor hierarchical clustering. Welch's *t*-test will be used to determine significant abundance differences between OTUs.

1 Introduction

1.1 Background and Rationale

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (International Conference on Harmonization ICHE6), the Code of Federal Regulations Title 21 parts 812, and other applicable government regulations and Institutional research policies and procedures.

After a 50% increase in prevalence between 1997 and 2011, food allergy has become one of the most common chronic diseases of childhood now affecting 8% of American children, or roughly 2 children in every classroom in the United States. In a similar time period, the prevalence of peanut allergy has more than tripled in American children.[1] Children with peanut allergy have been shown to have a worse quality of life then children with insulin dependent diabetes mellitus and feel limited in their ability to safely attend social events.[2] In fact more than 40% of children with peanut allergy have had a severe allergic reaction requiring emergency care at least once in their life, and 20% of children with peanut allergy have a reaction to peanut every year.[1] These reactions are potentially life threatening and lead to significant anxiety and a financial burden for families with peanut allergic children.[3] Unfortunately, children rarely grow out of peanut allergy naturally, and although it is a potentially fatal disease, currently, only one FDA approved treatment exists, oral immunotherapy (OIT) for peanut.[4]

Oral immunotherapy is a method of inducing desensitization to peanut in those with an IgE mediated peanut allergy to make them “bite-safe”, or unlikely to experience a severe reaction upon the accidental ingestion on peanut. When undergoing oral immunotherapy, a child is given slowly increasing doses of peanut that are below the threshold of reactivity that eventually induce an increasing threshold, so an even higher dose of peanut can be given safely. After approximately 6 months of up-dosing, children become tolerant to eating one peanut a date. After continuing to eat one peanut a day, desensitized children appear to undergo continued immunomodulation that raises their reactivity threshold to be tolerant of ingestion of 3 peanuts.[4-6]

Unfortunately, OIT is an imperfect therapy as >70% of children undergoing therapy experience gastrointestinal (GI) side effects, including eosinophilic esophagitis, which has led to a significant drop out rate in clinical trials. In addition, a high rate of systemic allergic reactions, that were treated with epinephrine, have been seen in study populations.[4] Finally, little evidence exists to support using OIT as a cure for or to induce remission of peanut allergy, nor does evidence exist that supports the ability of children to “free eat” peanut in their diet after completion of therapy. As a result, children must continue to take a daily dose of peanut protein for the rest of their lives in order to remain bite safe without expectation of any other benefit.[7]

One barrier to the development of a more effective therapy is the lack of understanding of the pathogenesis of this disease. The rate of increase in peanut allergy is too high to be explained by genetics alone. A theory that may, however, explain both the development and increasing prevalence of peanut allergy is the “microbiome hypothesis” which posits that commensal microbes or “good bacteria” in our gastrointestinal (GI) tract interact with our immune system through production of short chain fatty acids (SCFA), including butyrate, after digestion of dietary fibers. In turn, butyrate acts as a “postbiotic” that influences both the development and severity of chronic non-infectious inflammatory diseases such as food allergy.[8-10]

This hypothesis is supported by the vast changes in the modern lifestyle that may impact colonization of commensal microbes in our GI tract, including diet, antibiotic use, antiseptic use, food sterilization, smaller family sizes, and reduced exposure to farm animals. The American diet is largely devoid of fibrous fruits and vegetables that act as prebiotic “food” for our commensal bacterial and instead high in processed sugars which favor growth of non-SCFA producing bacterial species. Both antibiotics and external antiseptic use have been shown to influence the GI microbiome, including antibiotics fed to livestock later

sacrificed for meat. Finally, the colonization or recolonization of commensal bacteria has likely been affected by the lack of exposure to bacteria in our day to day life.[11]
As a result of this hypothesis, interest has been gained in manipulating the microbiome of the GI tract in order to control chronic, non-infectious inflammatory diseases, such as peanut allergy. Prebiotic, probiotic and postbiotic formulations may all hold therapeutic potential. In this trial, we propose using a prebiotic therapy (potato starch) previously shown to modulate the microbiome in adults in children with peanut allergy to determine if it has an effect on the commensal bacteria of the GI tract and subsequently influences the immune response.[12]

Murine model studies have demonstrated that both germ free mice and mice treated with a cocktail of antibiotics, beginning pre-weaning, are highly susceptible to allergic sensitization to food[10]. Studies involving selective colonization of gnotobiotic mice demonstrate that mucosa-associated Firmicutes in the Clostridia class protect against allergic sensitization by inducing IL-22 dependent barrier protective responses in the intestine that limit systemic access of allergenic food proteins[10,12]. Numerically, Firmicutes (which includes Clostridia) are a dominant component of the gut microbiota[13,14]. Many Clostridia are involved in the complex process of digesting fiber and resistant starches. This process involves sequential breakdown by particular bacterial taxa and ultimately results in the formation of short chain fatty acids (SCFAs). SCFAs have potent immunomodulatory effects correlated with host health[15,16] including induction of colonic regulatory T cells and improvement of allergy symptoms in a mouse model[17,18]. Butyrate, in particular, is an important energy source for colonic epithelial cells[19]. Butyrate drives oxygen consumption by colonocytes through b-oxidation, which maintains a locally hypoxic niche for butyrate-producing obligate anaerobes[20]. Induction of SCFA production may therefore be a key component of Clostridia's allergy-protective effect.

Initial translational studies established that the composition of the fecal microbiota is altered (and butyrate production is reduced) in infants with cow's milk allergy[21]. Feehley et al. demonstrated that there were numerous differentially abundant bacterial operational taxonomic units (OTUs) between healthy and CMA infants or GF mice colonized with the feces of these infants[22]. Analysis of differentially abundant OTUs that distinguished the CMA and healthy populations in both the human donors and colonized mice. Correlation of ileal taxa with differentially expressed genes in the ileum of healthy-colonized mice identified a Clostridial species, Anaerostipes caccae, that mimicked the effects of the healthy microbiota, supporting a causal role for a specific bacterial taxon in protection against food allergy. A. caccae is an extremely efficient butyrate producer commonly found in the infant gut but can be identified in adults as well[23,24].

More recently, evidence expands this observation beyond infants. Identification of differentially abundant OTUs in healthy and allergic twins revealed that 84% were in the Clostridia class[25]. These bacterial OTUs were then correlated with fecal metabolites from nonbiased metabolomic profiling, which identified another potentially protective Clostridial species in healthy twins: R. bromii. R. bromii is measurable in the feces of many (but not all) adults and is recognized as a keystone species for the degradation of type III resistant starches, like resistant potato starch (RPS)[26]. R. bromii abundance in feces significantly increases upon dietary intervention with RPS[27,28]. Individuals that do not have detectable R. bromii in the feces before beginning a RPS-supplemented diet consume about 40% less total starch than individuals colonized with R. bromii, demonstrating that this species alone is responsible for much of the total starch digestion in the colon[27]. R. bromii performs the initial phases of resistant starch digestion, producing intermediate metabolites such as acetate which can then be consumed by butyrate producing bacteria. While R. bromii is not capable of producing butyrate itself, a recent report demonstrated that two weeks of RPS consumption by young adults was sufficient to induce detectable increases of butyrate in feces[29]. This increase in butyrate concentration was greater in individuals who also demonstrated increased fecal abundance of R. bromii compared to those with no change. Butyrate concentration was also significantly correlated with changes in the abundance of Eubacteriium rectale, a well characterized butyrate producing Clostridia[29]. Interestingly E. rectale is one of the few bacterial species detectable in the microbiomes of most healthy individuals worldwide[30]. Taken together the data suggest that R. bromii is a tractable biomarker, associated with a healthy microbiota and increased butyrate production, and responsive to dietary intervention. Interestingly, and in agreement with our hypothesis, the Canadian

Healthy Infant Longitudinal Development birth cohort study reported that depletion of R. bromii early in life (3 and 12 months of age) is associated with the development of atopy and reduced genetic potential to produce butyrate[31].

Due to the existing limitations of OIT, multiple strategies of combination therapy to reduce symptoms associated with treatment and induce remission or prolonged non-responsiveness have been trialed, but each have significant limitations thus far. Combining the IgE-blocking antibody omalizumab with peanut OIT reduces adverse reactions initially, but these adverse events return after stopping omalizumab treatment and to date the cost associated with omalizumab has limited its utility in the clinical setting[32]. Microbial therapies have also recently been studied in combination with OIT in both preclinical and clinical settings[33]. Both prebiotics (bacteriaaccessible carbohydrates) and probiotics (live bacteria themselves) can improve allergic responses to food in mouse models[16,33,34]. Further, the combination therapy of OIT plus Lactobacillus rhamnosus GG (LGG), a bacterial species that when supplemented in infant formula increases the abundance of butyrate-producing bacteria in feces, demonstrated improved efficacy of OIT compared to previous studies and showed potential for inducing remission at 2-5 weeks and up to four years after discontinuing treatment[21,35,36]. However, this study lacked appropriate controls preventing adoption of the approach.

In a series of publications, the beneficial effects of both the Clostridia class (as a whole) as well as individual species (A. caccae and R. bromii) has been shown in protection against food allergy in humans and gnotobiotic mice. The candidate species that we have identified may work together in the process of fiber digestion to produce butyrate. As mentioned above, others have shown that a significant expansion of R. bromii upon dietary supplementation with RPS correlates with increased concentrations of fecal butyrate[28,29]. We now seek to extend these findings by using RPS as an additive therapy for peanut allergic children undergoing POIT. We predict that the high incidence of GI symptoms and systemic allergic reactions during POIT may be due, in part, to the fact that POIT is administered without any strategy to address intestinal barrier dysfunction in allergic subjects. We predict that administering RPS prior to and during POIT will expand populations of protective bacteria, elicit a bacteria-induced barrier protective response, and improve clinical outcomes of POIT.

1.2 Investigational Food

The following foods will be used:

- Resistant potato starch (RPS)
- Corn starch (as placebo)

1.3 Preclinical Data

Murine models have shown that the GI microbiota affect allergic sensitization. When mice are raised in a germ-free environment, gut associated lymphoid tissue are poorly developed and have lower levels of IgA and IL-10 secreting T regulatory cells, important for oral tolerance. In fact, these mice raised in a germ-free environment are unable to be tolerized to oral antigens. However, when certain bacteria or bacterial components are introduced into germ-free mice, these observations are reversed. Introduction of B fragilis or LPS into germ-free mice can redevelop GALT and induce oral tolerance. In addition, introduction of certain butyrate-producing Clostridium species can increase T regulatory cells and protects against peanut allergic sensitization.[10] Finally, transfer of gut microbiota from food allergic mice into germ-free mice increases the germ-free mice's susceptibility to food allergy; while, transfer of stool from healthy infants, but not milk-allergic infants, protects against anaphylactic responses to cow's milk.[22]

One study has looked at the effect of high fiber diet on oral tolerance and the development of food allergy in mice. In this study, mice were fed a high fiber diet containing cellulose and guar gum. The diet reshaped the gut microbial ecology and increased the release of SCFAs, including butyrate. This, in turn, enhanced oral tolerance and protected against food allergy.[18]

1.4 Clinical Data to Date

One recent single center study compared the dynamics of the gut microbiota and SCFA in response to 2-week dietary interventions with three fibers, resistant starch from potato (RPS), resistant starch from maize (RMS), inulin from chicory root with an accessible corn starch (ACS) used as a control. This study found that RPS resulted in the increase in total SCFAs, including butyrate. In addition, RPS caused an increase in relative abundance of bifidobacteria and the butyrate producing *Ruminococcus bromii* and *Clostridium chartatabidum*.[29] The benefits of RPS have similarly been shown in several other chronic, non-infectious inflammatory diseases, including obesity, diabetes and inflammatory bowel disease.[37-39]

1.5 Risks/Benefits

Risks Associated with RPS and placebo (corn starch)
RPS is a food product and generally regarded as safe (GRAS) by the following. Under sections 201(S) and 409 of the Federal Food, Drug, and Cosmetic Act, "any substance that is intentionally added to food is a food additive, that is subject to premarket review and approval by FDA, unless the substance is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use, or unless the use of the substance is otherwise excepted from the definition of food additive. Under sections 201(s) and 409 and FDA's implementing regulations in 21 CFR 170.3 and 21 CFR 170.30, the use of a food substance may be GRAS either through scientific procedures or, for a substance used in food before 1958, through experience based on common use in food Under 21 CFR 170.30(b), general recognition of safety through scientific procedures requires the same quantity and quality of scientific evidence as is required to obtain approval of the substance as a food additive. General recognition of safety through scientific procedures is based upon the application of generally available and accepted scientific data, information, or methods, which ordinarily are published, as well as the application of scientific principles, and may be corroborated, by the application of unpublished scientific data, information, or methods." GRAS notice 310 claims exemption from the requirement of premarket approval for potato fiber and was closed on 12-24-2009 with no questions from the FDA. In addition, under 21 CFR 170.30(c) and 170.3(f), general recognition of safety through experience based on common use in foods requires a substantial history of consumption for food use by a significant number of consumers. Potatoes have been commonly consumed throughout history by numerous populations.

In this study, we are enrolling subjects between the ages of 4 and 17, inclusive with peanut allergy and asking them to consume either a RPS or a control starch (corn starch). This consumption of either product may increase the overall caloric intake of subjects which may lead to weight gain. Subjects in the RPS group will be asked to consume 1 tablespoon (12 grams) of a fiber supplement daily which contains 40 calories/tablespoon. Subjects in the control group will be asked to consume 1 tablespoon (8 grams) of ACS daily which contains 30 calories/tablespoon. In addition, an increase in fiber consumption may lead to bloating, gas and/or constipation.

Risks Associated with DBPCFC

In this study DBPCFCs will be conducted in accordance with the recommended PRACTALL guidelines. The screening DBPCFC is utilized as the standard of care to confirm peanut allergy and does not confer higher then minimal risk then a open label food challenge used clinically to confirm peanut allergy priori to POIT. The screening DBPCFC will also establish a threshold for reactivity for comparison with the exit DBPCFC. The exit DBPCFC will be used to establish efficacy of POIT and confirm safety of accidental ingestion of peanut. The exit DBPCFC also does not confer more than minimal risk above a standard of care open label food challenge used during POIT to confirm tolerance of peanut ingestion. DBPCFC are expected to induce allergic reactions. Reactions range from mild (nausea, few hives) to severe (wheezing, diffuse urticaria, rhinitis/conjunctivitis, vomiting/diarrhea, impending doom) to potentially life threatening (low blood pressure, difficulty breathing, neurologic changes). Administered in a controlled setting under the supervision of experienced staff, food challenges are considered safe and are the

current gold standard for the diagnosis of peanut allergy. As soon as symptoms consistent with an allergic reaction are witnessed, interventions to stop the reaction are begun (H1 antihistamines and epinephrine).

Risks Associated with POIT
The most common side effect associated with POIT is GI symptoms, including stomach pain and mouth itching. These are expected to occur in nearly 2/3 of individuals. These symptoms tend to be transient in nature and typically occur in the first few days after up-dosing POIT and for the first hour after taking the dose. GI symptoms are mitigated by eating large meal with each dose and staying well hydrated. Symptoms will be controlled with H1-antihistamines as needed. Systemic allergic reactions/anaphylaxis is also a side effect of POIT. This risk is mitigated by restricting physical activity, hot showers, and NSAID use for 3 hours after daily dosing of POIT. Should symptoms occur, they will be treated with epinephrine. All participants will be required to carry an epinephrine autoinjector. POIT may also be associated with eosinophilic esophagitis. The reported incident is <1% and typically resolves with removal of peanut protein exposure.

Risks Associated with Blood Draw
All subjects enrolled in the study will be asked to undergo a blood draw. The risks involved in drawing blood from a vein may include, but are not limited to, momentary discomfort at the site of the blood draw, possible bruising, redness, and swelling round the site, bleeding at the site, feeling of lightheadedness when the blood is drawn, and rarely, an infection at the site of the blood draw. In order to minimize these risks, blood draws will be done under hygienic conditions by experienced personnel.

Potential benefits of Prebiotic Fiber
The potential benefits of consuming a fiber supplement include reducing constipation, maintaining a healthy weight, lower blood sugar and cholesterol levels. The theoretic benefit to consuming a fiber supplement is that it may improve tolerance of oral immunotherapy to peanut and/or improve immunologic markers associated with peanut allergy. No additional benefit is hypothesized from the control fiber.

Benefits of Oral Immunotherapy (OIT)
The benefit of undergoing peanut OIT is that subjects become “bite-safe” in case of an accidental ingestion of peanut protecting them from a severe, systemic allergic reaction.

2 Study Objectives

2.1 Primary Objective

The primary objective of this study is to determine if prebiotic therapy improves outcomes and reduces side effects associated with POIT.

2.2 Secondary Objective(s)

The secondary objectives of this study are:

- To determine if prebiotic therapy influences the gut microbiome/metabolome
- To determine if prebiotic therapy influences immunological markers associated with peanut allergy

3 Study Design

3.1 General Design

This study is a randomized, double-blind, placebo controlled, single center clinical trial. Subjects are anticipated to be in this study for 1 year with extended, active monitoring for an additional 4 years. After enrollment, screening and randomization, patients will be assigned to consume either RPS or placebo for

30 days. At the end of the 30 days, patients will begin the standard of care treatment for peanut allergy, peanut oral immunotherapy. Initial dose escalation and up-dosing of POIT plus prebiotic will take approximately 180 days to complete.At the end of the maintenance phase, subjects will undergo a DBPCFC to determine efficacy of treatment. Finally, patients will be monitored for approximately 4 year following completion of the active drug dosing (off prebiotic) therapy during the continued immunomodulation/extended maintenance phase of POIT.

Description of DBPCFC

DBPCFC will be conducted in accordance with PRACTALL guidelines and utilize either peanut flour (Anthony's Organic Peanut Flour) or placebo (Oat Flour; Bob's Red Mill) as previously described. Food challenges will be conducted on two separate days no more than 7 days apart and no more than 30 days prior to initial dose escalation day (for the screening food challenge). Prior to the food challenges, patients will be instructed to stop all antihistamines for 5 days prior to each challenge. All subjects will be free from asthma or atopic dermatitis flare. Asthma will be assessed by auscultation for active wheeze prior to start of the challenge and a peak expiratory flow of greater than or equal to 80% of personal best value. Atopic dermatitis flare will be assessed by investigator examination. Subjects will be admitted to the University of Chicago special procedure unit for initial dose escalation where walls are transparent glass for continuous observation by trained nursing staff. The special procedure area is located immediately above a pediatric dedicated emergency department. Subjects will be monitored on a continuous heart rate and oxygen saturation monitor throughout the procedure. Intramuscular epinephrine and oral antihistamines will be in the room with the patient prior to initiation of any doses. The patient's temperature and blood pressure will be checked before each dose. A resuscitation cart will be available within the area. A resuscitation team will be available within the hospital. Peanut flour and placebo will be mixed in either chocolate pudding and peppermint extract or applesauce and cinnamon to mask flavor and nose clips (as tolerated by the child) will be utilized during consumption to mask flavor. A second bite of vehicle will be given that does not contain challenge material followed by a sip of water prior to removal of nose clips (if nose clips can be utilized). Doses will be given every 15-20 minutes at the following doses: 1mg, 3mg, 10mg, 30mg, 100mg, 300mg (exit only), 600mg (exit only), 1000mg (exit only) peanut protein. Peanut protein constitutes half the peanut flour by weight, thus both peanut and oat flour will be administered in the following weights: 2mg, 6mg, 20mg, 60mg, 200mg, 600mg (exit only), 1200mg (exit only), 2000mg (exit only). Subjects will be monitored for at least 2 hours beyond resolution of symptoms but this period may be extended at the discretion of the investigator.

Reactions will be determined in the following way. Symptoms will be considered consistent with a reaction and the food challenge stopped if the subject experiences any moderate or severe symptoms outlined below. The food challenge will be stopped if the subject experiences two of more mild, symptoms. If the subject experiences one mild subjective symptom, the dose will be repeated before escalation.

Mild Symptoms:
Skin: limited (few) or localized hives, mild swelling, mild skin flushing or mild pruritus (only occasional scratching)
Respiratory: rhinorrhea, nasal congestion, occasional cough, throat discomfort
Gastrointestinal: mild nausea abdominal discomfort, a single minor vomiting episode and/or a single episode of diarrhea

Moderate symptoms:
Skin: systemic hives, significant swelling, pruritus causing protracted scratching, more than a few areas of erythema or pronounced erythema
Respiratory: throat tightness without hoarseness, persistent cough, wheezing without dyspnea
GI: persistent moderate abdominal pain/cramping/nausea, more than a single episode of vomiting and/or diarrhea

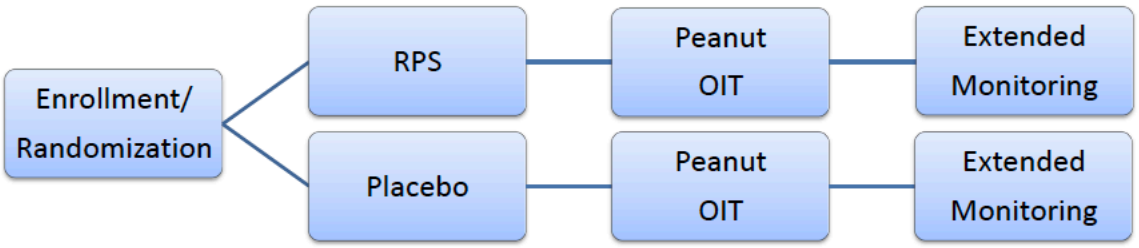
Severe symptoms:
Skin: severe generalized urticaria/angioedema/erythema
Respiratory: laryngeal edema, throat tightness with hoarseness, wheezing with dyspnea, stridor

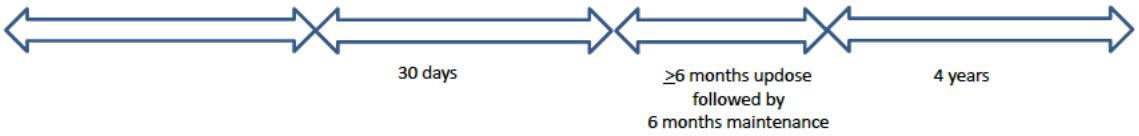
GI: severe abdominal pain/cramping/repetitive vomiting and/or diarrhea
Neurological: change in mental status
Circulatory: clinically significant hypotension

Description of POIT

Anthony's Organic Peanut Flour will be utilized for POIT, and doses will be prepared by the study PI or by trained study staff under direct supervision of the PI. Peanut flour will be mixed into water to form a slurry and delivered via a medication syringe to optimize at home dosing until doses are sufficiently high to be measured with standard kitchen utensils (i.e. 1/8 teaspoon). Throughout the course of POIT, patients will be instructed to eat a large meal before every dose and will also be instructed to abstain for any activity that will increase his/her heartrate for 3 hours following each dose, including physical activity (other than light walking) and hot showers. No sleep will be allowed during this observation period. Patients will be asked to avoid use of nonsteroidal anti-inflammatory medications throughout the course of oral immunotherapy (acetaminophen will be allowed). No updosing will occur in menstruating women during menses. If a patient develops a fever (T > 100°F), asthma flare, or gastrointestinal illness during the course of POIT, dosing will be help for up to two days and restarted upon fever resolution at home. If a fever lasts longer than two days, patients will return to clinic to restart. If more than 2 consecutive days of doses (but less than 7 days) are missed at any time during POIT for any reason (including fever), patients will be restarted at 50% of their current dose under supervision of the investigator but allowed to return to current dosing at home at the discretion of the investigator in 2-4 days. If 7 or more consecutive days of doses are missed, POIT will be restarted under supervision of the investigator at less than 50% of the current dose with a modified updosing schedule.

For initial dose escalation, patients will be instructed to eat a large meal prior to arrival in clinic then eat snacks throughout the morning. Patients will be admitted to the University of Chicago special procedure unit for initial dose escalation where walls are transparent glass for continuous observation by trained nursing staff. Patients will be monitored on a continuous heart rate and oxygen saturation monitor throughout the procedure. Intramuscular epinephrine and oral antihistamines will be in the room with the patient prior to initiation of any doses. The patient's temperature and blood pressure will be checked before each dose. A resuscitation cart will be available within the area. Patients will be dosed every 20 to 30 minutes. Doses given on initial dose escalation day are as follows: 0.5mg, 1mg, 1.5mg, 3mg, 6mg of peanut protein. If patients tolerate at least 3mg on initial dose escalation, they will return the following day for their first monitored dose of 3mg. If the patient tolerates, the 3mg the will continue this dose daily for two weeks then return for updosing. The updosing schedule will be as follows: 3mg, 6mg, 12mg, 20mg, 40mg, 80mg, 100mg, 125 mg, 150 mg, 250 mg, 300 mg. If the patient is experiencing gastrointestinal side effects that do not subside prior to updoing in 2 weeks, updosing may be delayed from 1 week to indefinitely until side effects improve and at the discretion of the investigator. If POIT is discontinued for any reason, patients will continue to be observed on study but not undergo the final DBPCFC (unless the patient withdraws from the study). Patients will continue on 300mg dosing until the end of study at which time they may choose to consent to an extended maintenance study or follow up with their allergist for continued standard of care monitoring and dosing.





SCHEDULE OF PROCEDURES									
Phase of Study	*SCREENI NG*			*INITIAL ESCALATION*		*UPDOSING*	*MAINTENANCE*	*EXIT DBPCFC*	
Visit Number	V1	V2	V3	V4	V5	V6 - V14	V15	V16	V17
Visit Day/Month	(D-55)	(D-37)	(D-30)	*D1*	*D2*	*D16 - M8*	*M11*	*M14*	*M14*
Time Window		*Within 4 weeks of V1*	*Within 1 Week of V2*	*30 Days After V3*	*1 Day After V4*	*Every 2-4 weeks*	*3 months post V14*	*3 months after V15*	*Within 1 Week of V16*
Informed Consent/Assent	X								
Medical/Allergy History	X								
Interval Medical History				X		X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X	X	X	X
QoL Assessment	X								
Spirometry	X	X	X	X				X	X
eNO	X								
ACT Score	X								
Skin Prick Test	X			X				X	
Blood Draw	X			X				X	
Stool Sample Collection		X		X		X (monthly)	X	X	
DBPCFC Randomization		X						X	
DBPCFC Administration		X	X					X	X
Study Arm Randomization			X						
Prebiotic Dispensing/Placebo 7.15 grams			X						
Dosing/AE Log Collection				X		X	X		
SOC Consent for POIT				X					
POIT Initial Escalation				X					
OIT Administration					X	X			

3.2 Primary Study Endpoints

The primary endpoint is the proportion of subjects who tolerate at least 1043 mg cumulative of peanut protein with no more than mild symptoms at the 12 month DBPCFC

3.3 Secondary Study Endpoints

The secondary endpoints are as follows:

- To determine the proportion of subjects who experience dose related GI side effects during oral immunotherapy

- To determine the proportion of subjects who experience hypersensitivity reactions (other than GI) during oral immunotherapy

The exploratory endpoints are as follows:

- To demonstrate the effect of resistant potato starch (RPS) on the fecal microbiome and metabolome
- To determine if gnotobiotic mice colonized with the fecal microbiota of study participants models clinical response
- To evaluate the immunological effects of fiber supplementation in children
    - Change in peanut specific IgE and IgG4 levels
    - Change in peanut skin prick test mean wheal diameter
    - Change in peanut component levels

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

The following criteria are used to determine eligibility for the trial:

- Age 4 to 17 (inclusive)
- A convincing clinical history of peanut allergy
- Immune markers consistent with peanut allergy
    - Serum IgE to peanut of >0.35 kUA/L and a skin prick test to peanut >8mm greater than the negative saline control –or-
    - Serum IgE to peanut of >5 kUA/L and a mean peanut wheal diameter on skin prick test 3 to 8mm greater than the negative saline control –or-
    - Serum IgE to peanut of >14 kUA/L and mean peanut wheal diameter on skin prick test 3mm greater than the negative saline control
- Experience dose-limiting symptoms at or before 100mg challenge dose of peanut protein on screening double blind placebo-controlled food challenge (DBPCFC)
- Written informed consent from parent/guardian
- Written assent from subjects above the age of 7
- Fully vaccinated against COVID-19

4.2 Exclusion Criteria

The following are criteria used to determine eligibility for the trial:

- History of a chronic disease (other than asthma, allergic rhinitis, and atopic dermatitis) that is at significant risk of becoming unstable or requiring a change in chronic therapeutic regimen
- History of mast cell disease
- History of recurrent idiopathic or virally induced urticaria, angioedema or anaphylaxis
- Any history or presence of autoimmune, cardiovascular disease, chronic lung disease (other than asthma), malignancy, psychiatric illness, or gastrointestinal inflammatory conditions, including celiac disease, inflammatory bowel disease, eosinophilic esophagitis or other eosinophilic gastrointestinal disease
- Current participation in any other interventional study
- Subject who has undergone any type of oral immunotherapy
- Severe asthma or uncontrolled mild to moderate asthma
- Uncontrolled atopic dermatitis
- Current use of oral steroid medications
- Use of >1 bursts of oral steroid medications in the past year
- Inability to eat by mouth the fiber supplementation or placebo control and peanut flour for any reason
- Use of any therapeutic antibody (biologic medication) or any immunomodulatory medication in the past 12 month (other than a short course of oral steroids)
- Current use of any type of immunotherapy

- Pregnancy or lactation
- Allergy to potato or corn
- Unwillingness to carry an epinephrine autoinjector
- Unwillingness to comply with activity restrictions during OIT or any other study procedure

4.3 Subject Recruitment and Screening

Subjects will be recruited for this trial in several ways

1. A letter and attached flier will be sent to those enrolled in the University of Chicago Allergy and Asthma Research Registry
2. A short description will be posted in social media
3. Patients will be approached during clinic visits to the Allergy/Immunology clinic at the University of Chicago
4. Fliers will be sent to outside allergists

Subjects who respond to advertisement will first undergo a prescreen to confirm inclusion and exclusion criteria. Those who meet criteria will be invited in for a screening visit where skin testing, spirometry, blood draw, and questionnaire will be administered. Those who meet criteria after the screening visit will be randomized and enrolled.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects may be withdrawn from this study at any time. Subjects may be withdrawn from the study prior to the completion of the study by the subject for safety reasons, failure of the subject to protocol requirements, subject consent withdrawal. Abrupt withdrawal from this study poses no additional risk to the subject.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Even if subjects withdraw or are withdrawn prematurely from the study, data from the electronic medical record may continue to be used and patients may continue to be contacted, periodically by phone to determine if the patient has suffered any adverse events from withdrawal from the study if subjects allow contact to continue.

5 Study Food

5.1 Description

The following foods will be used:

- Fiber supplement: resistant potato starch
- Placebo: corn starch

5.2 Treatment Regimen

Subjects will be asked to take 1 tablespoon of fiber supplement (or placebo daily) mixed with a liquid or semi-solid food, such as pudding, applesauce or guacamole. If the supplementation causes abdominal distress, the participants will be asked to cut the dose in half for one week then increase back to the full tablespoon dose.

5.3 Method for Assigning Subjects to Treatment Groups

Subjects will be randomly assigned to either the treatment or placebo. Randomization will be conducted by IDS pharmacy . Study staff will be blinded throughout the course of the study. Subject compliance will

be monitored by subject/parent self-report in paper diary provided to the subject at the start of the study as well weight of returned investigational product.

5.4 Prior and Concomitant Therapy

Subject will be asked to discontinue any daily antihistamine use. However, subjects will be allowed to use oral antihistamines on an as needed basis. A record of all current medications will be kept from the start to the completion of the study. A record of medications taken to manage POIT related side effects will be monitored in a daily diary. All study participants will be required to have an epinephrine autoinjector throughout the duration of the study. If the study participant is unable to obtain a new epinephrine autoinjector after the expiration, use or loss of a current epinephrine autoinjector, every effort will be made by the Principal Investigator to obtain one for the subject; however, if one cannot be obtained, the subject may be withdrawn from the study.

Please see exclusion criteria for medications not allowed during this study.

5.5 Packaging

The study food will be transferred from the original packaging into a sealed plastic container appropriately labeled.

5.6 Blinding of Study

Neither the study participant nor the study team will be aware of the contents of the sealed plastic container provided to the study participant2

Only the study pharmacist will have access to the form which links each study participant to their respective groups. The investigational product and placebo will be stored at the University of Chicago IDS pharmacy at:
5835 South Cottage Grove
CCD Room 2-520, MC 0010
Chicago IL, 60611

5.7 Storage, Dispensing and Return

5.7.1 Storage

The study food may be stored at room temperature but should not be subject to extreme hot or cold. The study food should remain in the provided contained throughout the duration of the study. If the contents of the contained spill or become contaminated, the investigators will provide a new container of study food to the participant.

5.7.2 Return or Destruction of Study Device

At the completion of the study, any remaining study food will be returned to the investigator, and there will be a final reconciliation of the study food by weighing the container and its contents. All remaining study food will be destroyed by the IDS pharmacy.

6 Study Procedures

6.1 Visit 1

- Informed consent/assent
- Medical/allergy history
- Concomitant medications
- Vital signs
- Physical examination, including height and weight

- Quality of life assessment
- Spirometry (if has asthma diagnosis; as COVID allows)
- eNO (if has asthma diagnosis; as COVID allows)
- ACT score (if has asthma diagnosis; as COVID allows)
- Skin prick testing
- Blood draw
- Stool sample kit given

6.2 Visits 2 and 3 (within 4 weeks of visit 1)

- Stool sample collection (visit 2 only)
- Vital signs
- Physical examination, including height and weight
- Spirometry (if has asthma diagnosis; as COVID allows)
- DBPCFC
- Randomization
- Prebiotic dispense

6.3 Visit 4 (30 days after visit 3)

- Interval medical history
- Vital signs
- Physical examination, including height and weight
- Spirometry (if has asthma diagnosis as COVID allows)
- Skin prick testing
- Blood draw
- Stool sample collection
- Collection of dose and symptom logs
- Standard of care consent for POIT
- POIT initial dose escalation day

6.4 Visits 5 (day after visit 4)

- Vital signs
- Physical examination, including height and weight
- POIT 3mg dose start

6.5 Visits 6-14 (every 2-4 weeks)

- Interval medical history
- Vital signs
- Physical examination, including height and weight
- Stool sampling (monthly)
- Collection of logs

6.6 Visit 15 (3 months after visit 14)

- Interval medical history
- Vital signs
- Physical examination, including height and weight
- Stool sample collection
- Collection of logs

Visit 15 (3 months after visit 14; virtual)

- Interval medical history

- Height and weight
- Stool sample collection
- Collection of logs

6.7 Visits 16 and 17 (3 months after visit 15)

- Interval medical history (visit 16 only)
- Vital signs
- Physical examination, including height and weight
- Stool sample collection (visit 16 only)
- Skin prick test (visit 16 only)
- Blood draw (visit 16 only)
- Spirometry (if has asthma diagnosis; as COVID allows)
- DBPCFC

7 Statistical Plan

7.1 Sample Size Determination

As this study is an exploratory, pilot study we will enroll 30 subjects.

7.2 Statistical Methods

Chi-square testing (or non-parametric equivalent) will be used to compare categorical variables. Student's t-test (or non-parametric equivalent) will be used to compare continuous variables. Microbial relationships between samples will be compared using principal coordinate analysis and average-neighbor hierarchical clustering. Welch's t-test will be used to determine significant abundance differences between OTUs.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Unanticipated Serious Adverse Event
An Unanticipated Effect is any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with the study food, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a study food that relates to the rights, safety, or welfare of subjects.

Serious Adverse Event
Any injury or illness that is any one of the following:

- death
- life-threatening (at the opinion of the investigator an immediate risk of death occurred)
- results in permanent impairment of a body function or permanent damage to body structure

- necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

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

- results in study withdrawal
- is associated with a serious adverse event
- leads to additional treatment other than epinephrine, antihistamines and corticosteroids or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Adverse Event Severity
The investigator will assign severity grades to adverse events. Adverse events will be graded using the CoFAR grading system as follows:

Grade 1 (mild): transient or mild discomforts (<48 hours); no or minimal medical intervention/therapy required. For allergic reactions, these symptoms may include pruritus, swelling, or rash, abdominal discomfort or other transient symptoms.

Grade 2 (moderate): symptoms that produce mild to moderate limitation in activity that may require some assistance; no or minimal intervention/therapy is required; hospitalization is possible. For allergic reactions, these symptoms may include persistent hives, wheezing without dyspnea, abdominal discomfort/increased vomiting or other symptoms

Grade 3 (severe): marked limitation in activity that usually requires some assistance usually; medical intervention/therapy required; hospitalization is possible. For allergic reactions, symptoms may include bronchospasm with dyspnea, severe abdominal pain, throat tightness with hoarseness, transient hypotension among others. Parenteral medications are usually indicated.

Grade 4 (life-threatening): extreme limitation in activity that requires significant assistance; significant medical/therapy or intervention is required; hospitalization is probable. Symptoms may include persistent hypotension and/or hypoxia with resultant decreased level of consciousness associated with collapse and/or incontinence or other life threatening symptoms.

Grade 5 (death): death

8.2 Recording of Adverse Effects

At each contact with the subject, the investigator will seek information on adverse effects of the fiber supplementation by specific questioning and, as appropriate, by examination. Information on all adverse effects will be recorded immediately in the source document, and also in the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse device effects that occur after the study period will be recorded and reported promptly (see section 8.3 below).

The minimum initial information that will be captured in the subject's source document concerning the adverse event includes:

- Study identifier
- Subject number
- A description of the event
- Date of onset
- Investigator assessment of the association between the event and study treatment
- Current status
- Whether study treatment was discontinued
- Whether the event is serious and reason for classification as serious

8.3 Reporting of Adverse Events and Unanticipated Problems

Researchers will submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

Any adverse event that occurs any time during or after the research study, which in the opinion of the principal investigator is:

- **Unexpected** (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

  AND

- **Related** to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

The above will be completed regardless of whether the event is serious or non-serious, on-site or off-site

Protocol Deviations
Any protocol deviations initiated without the The University of Chicago IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, will be reported to the IRB as soon as a possible, but no later than 5 working days of the protocol deviation.

8.4 Medical Monitoring

The Principal Investigator will oversee the safety of the study at the site. This safety monitoring will include careful assessment and appropriate reporting of adverse events.

8.4.1 Data Monitoring Board

A Data Safety Monitoring Board (DSMB) will monitor the safety of the study. The DSMB will continually review safety data and halt the study for any substantial imbalance in adverse events. Full details are provided in the DSMB charter.

8.4.2 Overall Stopping Rules

This study will be suspended at any time if a study related death occurs in a subject on active therapy or upon the hospitalization of the second of two study related hospitalizations. If the study is suspended, screening, enrollment and POIT increases will immediately stop but active subjects will continue on current dosing unless otherwise directed by the FDA. The study and POIT dose escalation will not resume until discussed with the DSMB and FDA.

8.4.3 Individual Stopping Rules

Individuals may stop participation at any time for any reason, including inability to tolerate study related side effects. If individuals discontinue either study drug treatment or POIT treatment at their discretion or because they meet an individual stopping rule, they will continue to be monitored for the length of

the study unless the subject withdraws consent. Subjects will not undergo a DBPCFC at exit unless the subject reaches POIT maintenance dosing of 300mg peanut protein for 6 months.

Specific individual stopping rules are as follows:

1. A subject misses 5 or more consecutive days of POIT or study drug dosing due to non-compliance (but not illness)

2. The subject misses 14 consecutive days of POIT or study drug dosing for any reason

3. Administration of three or more doses of epinephrine as a result of an allergic reaction caused by a single POIT dose

4. Meeting any exclusion criteria during the course of the study

5. Development of eosinophilic esophagitis (biopsy proven)

6. Any reason at the discretion of the investigator that continued participation in this study places the subject at unacceptable risk or for any reason prevents safe conduct of the study.

In this study, if a subject fails to tolerate an updose after 3 or more attempts but do not meet the aforementioned stopping criteria, the subject will continue maintenance dosing at the last tolerated dose indefinitely. Failure to tolerate an updose after 3 or more attempts is not an individual stopping rule for purposes of this study.

9 Data Handling and Record Keeping

9.1 Confidentiality

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

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

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

9.2 Source Documents

Source documents for this study will include (but is not limited to) hospital records (EPIC), case report forms, subject diaries as well as questionnaires.

9.3 Case Report Forms

All data requested on the case report form (CRF) will be recorded, and all missing data will be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked,

"N/D" will be written. If the item is not applicable to the individual case, "N/A" will be written. All entries will be printed legibly in black ink. If any entry error has been made, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data will be written above it. All such changes will be initialed and dated.

9.4 Records Retention

All essential documents will be retained for at least 2 years after completion of the study.

10 Ethical Considerations

This study will be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the legally acceptable guardian and the principal investigator.

11 Study Finances

11.1 Funding Source

This study will be funded through the Duchossois Family Institute Multidisciplinary Grant; the Comer Development Board; and through a generous donation by Paul and Mary Yovovich.

11.2 Conflict of Interest

All University of Chicago investigators will follow the applicable University conflict of interest policy(ies).

11.3 Subject Stipends or Payments

Subjects will not receive reimbursement for their participation in this trial other than vouchers to pay for parking at the University.

12 Publication Plan

The results of this study will be reported in manuscripts by the co-investigators and submitted to relevant journals.

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