Boiled Peanut Oral Immunotherapy for the Treatment of Peanut Allergic Pediatric Patients

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Boiled Peanut Oral Immunotherapy for the Treatment of Peanut Allergic Pediatric Patients (BPOIT)

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INVESTIGATOR'S SIGNATURE PAGE

Protocol Amendment: 3

Protocol Date: 12 February 2020

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

The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Pediatric Research Review Committee (PRRC) and Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Sponsor: Alton Melton, M.D.

Signed: _____ **Date:** _____

Investigator: Jaclyn Bjelac, M.D.

Signed: _____ **Date:** _____

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1. Protocol Summary

1.1 Study Synopsis

Title:	Boiled Peanut Oral Immunotherapy
Study Description:	Prospective Phase 1 clinical trial providing proof of concept data on boiled peanut oral immunotherapy (OIT) for the treatment of peanut allergy in children. We hypothesize that the proportion of subjects successfully desensitized with boiled peanut OIT is greater than the theoretical placebo rate of 20%.
Objectives:	• Determine the effect of boiled peanut immunotherapy on the immune response to peanut. • Compare the safety and tolerability of boiled peanut oral immunotherapy to published data on roasted peanut oral immunotherapy in pediatric subjects with confirmed IgE mediated peanut allergy.
Endpoints:	• Primary endpoint: Response to treatment defined as ability to successfully consume a single dose of 300 mg or greater of peanut protein with no dose limiting symptoms at exit double blind placebo controlled food challenge (DBPCFC). • Secondary endpoints: • Maximum dose achieved with no or minimal symptoms at exit DBPCFC. • Change in the maximum tolerated dose from screening to exit DBPCFC. • The rate of side effects of treatment defined as oral itching, rhinorrhea, conjunctivitis, urticaria, angioedema, abdominal upset, vomiting, diarrhea, cough, wheeze, or anaphylaxis. • Change in quality of life scores before and after treatment utilizing validated , age specific, food-related quality-of-life surveys before and after peanut oral immunotherapy (Supplement 1) • Peanut protein component panel, to determine the presence of high levels of sensitivity to peanut proteins known to be associated with severe systemic reactions (Arah 1,2,3) versus mild reactions (Arah8).

- Levels of peanut specific serum IgG4, with higher levels associated with increased tolerance to peanut protein.

Study Population:

Children ages 1-16 with peanut allergy suggested via history of reaction and objective evidence of IgE mediated hypersensitivity either via skin testing or in vitro testing (peanut specific IgE concentration) within the last 12 months.

Inclusion criteria:

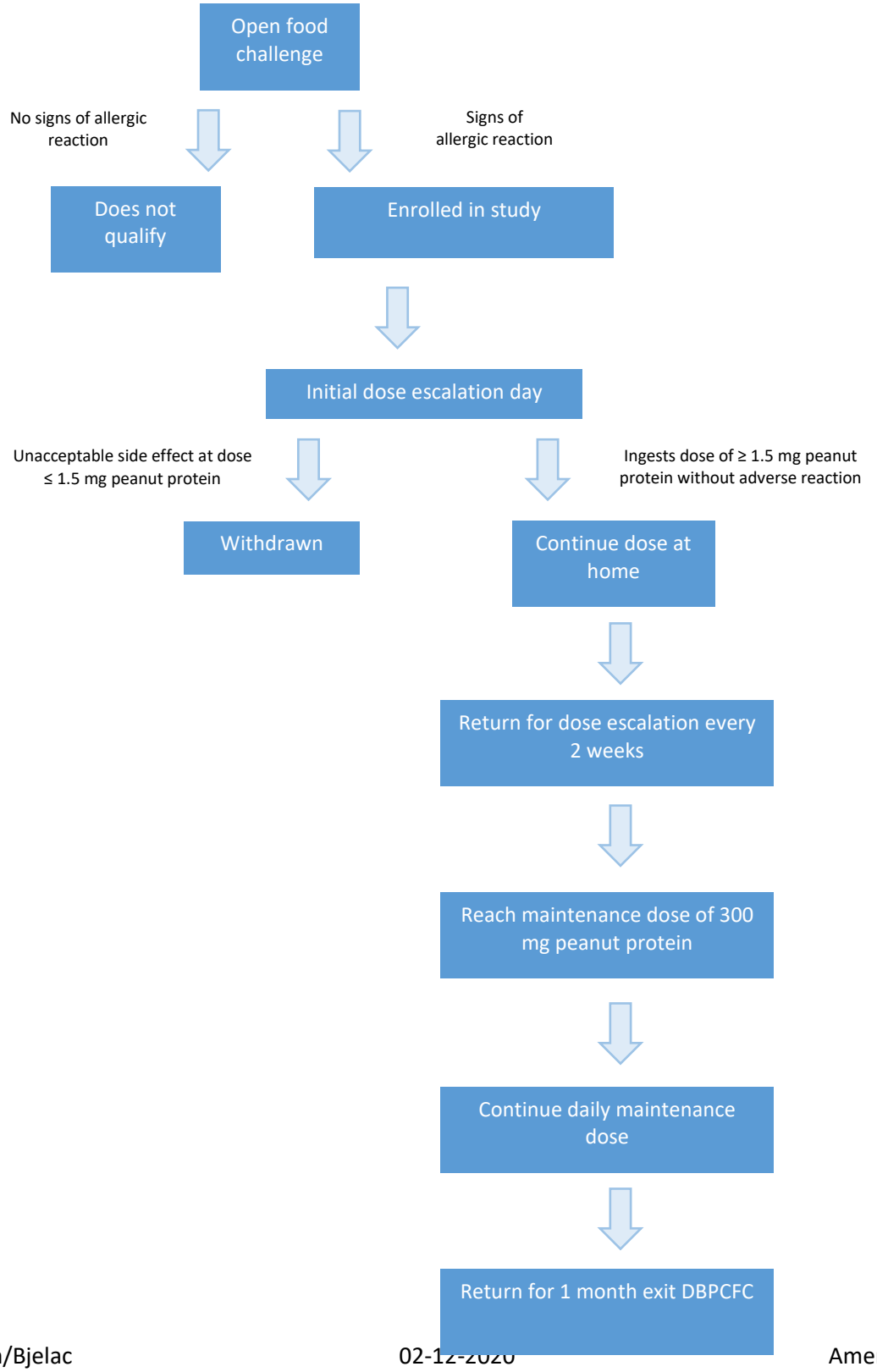
- Age 1-16 years
- History of immediate hypersensitivity reaction to peanut or a high level of suspicion based on testing at the discretion of the investigator
- Evidence of IgE mediated peanut hypersensitivity within a 12 month period of study enrollment including:
    - Skin prick test with wheal diameter of at least 3mm and/or
    - Peanut specific IgE >0.35 ku/L

Exclusion criteria:

- History of life threatening peanut anaphylaxis
- Asthma requiring more than medium dose inhaled corticosteroids for age per the National Heart, Lung, and Blood Institute Asthma Guidelines
- Cardiovascular disease
- Use of beta-blockers (oral), angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or calcium channel blockers
- Use of steroid medications in the following manners:
- Daily oral steroid dosing for greater than 1 month during the past year OR
- Burst or steroid course in the past 3 months before inclusion OR
- Greater than 2 burst oral steroid courses in the past year of at least 1 week duration
- Pregnancy or lactation
- Prior participation in food oral immunotherapy studies, including OIT, sublingual immunotherapy (SLIT), or epicutaenous immunotherapy (EPIT)
- Eosinophilic gastrointestinal disease
- Oat allergy, as oat flour is the vehicle with which study drug may be mixed for purposes of blinding and will be used as placebo for the exit DBPCFC

	• History of food protein-induced enterocolitis syndrome (FPIES) • History of developmental delay or speech delay that precludes age-appropriate communication, in the opinion of the investigator
Description of Sites and Facilities Enrolling Patients:	Screening will be performed at the Cleveland Clinic main campus and satellite outpatient clinic locations. Any patients identified as eligible will be referred to main campus for further evaluation and possible enrollment.
Description of Study Intervention:	Oral Immunotherapy will be administered utilizing a powder derived from boiled peanuts. Treatment will begin with an initial escalation day in which dosing is begun at 0.1 mg peanut protein and escalated to a final dose of 6 mg peanut protein. Doses are ingested orally. The subjects will continue daily oral ingestion of doses at home and return for updosing every 2 weeks to a final maintenance dose of 300 mg peanut protein. The subjects will continue daily oral ingestion of the peanut product for a minimum duration of 28 days before undergoing exit DBPCFC. At the conclusion of the study, patients will be offered continued maintenance therapy off study in line with current specialty standards.
Study Duration:	18 weeks
Participant Study Duration:	18 weeks

1.2 Study Schema



1.3 Schedule of Activities

Visit		Study Visit 1	Study Visit 2 Visit 1 +1-4 weeks	SV 3 Visit 2 +2 weeks	SV 4 Visit 2 +4 weeks	SV 5 Visit 2 +6 weeks	SV 6 Visit 2 +8 weeks	SV 7 Visit 2 +10 weeks	SV 8 Visit 2 +12 weeks	SV 9 Visit 2 +14 weeks	SV 10 Visit 1 +18 weeks
Procedures	Enrollment/Baseline visit	Oral Food Challenge	Initial dose escalation	Dose escalation visit 1	Dose Escalation Visit 2	Dose escalation visit 3	Dose escalation visit 4	Dose escalation visit 5	Dose escalation visit 6	Dose escalation visit 7	Oral Food Challenge
Informed Consent	**X**										
Demographics	**X**										
Vitals	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Spirometry*	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Blood Draw			**X**								**X**
Skin prick test			**X**								**X**
Oral food challenge		**X**									**X**
Urine Pregnancy	**X**										**X**
Study Drug Administration			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Study Drug Compliance				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
AE Review			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Conmed Assessment	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

FAQL Questionnaire	**X**										**X**

All dose escalation visits have a window of +/- 2 day
All follow up visits have a window of +/- 7 days
The enrollment/baseline visit, initial oral food challenge (SV 1), will take place at the Pediatric Allergy Clinic at the Cleveland Clinic main campus.

The initial escalation day, dose escalation visits, and final oral food challenge (SV 2-10) will take place in the Clinical Research Unit.

* Spirometry will be performed on all patients ages 5+ and/or at the physician's discretion at the initial study visit as well as the exit oral food challenge. Rather than full spirometry, peak flow will be performed at every updosing visit on all patients ages 4+ and/or if the physician feels that it is developmentally appropriate

2. Introduction

2.1 Study Rationale

Peanut allergy (PA) is a common and potentially life threatening condition for which the only current approved management involves strict dietary avoidance. Oral immunotherapy (OIT) is a promising investigational treatment option for this condition, and multiple published studies have demonstrated efficacy in achieving successful desensitization to peanut in children with peanut allergy.[8-16] However, the widespread clinical use of OIT has been limited by numerous factors. These include the high rate of adverse events (AEs), including anaphylaxis, which often leads to high subject drop-out rates in published studies (Table 1). These studies all used peanut products produced by roasting methods, including flour, peanut powder, or peanut butter. Published data have demonstrated that boiling peanut results in reduced allergenicity while preserving the immunogenicity necessary to produce tolerance.[19] In this pilot study, we plan to compare the use of boiled peanut OIT to published data on roasted peanut OIT in children with peanut allergy. Based on currently available data, we hypothesize that the subjects treated with this novel regimen of boiled peanut will demonstrate lower rates of adverse events while demonstrating similar immunologic markers of peanut desensitization and possible tolerance compared to published data on subjects treated with OIT utilizing a traditional roasted peanut product.

2.2 Background and Significance

Peanut allergy (PA) has a reported prevalence of 2% in children and 0.7% in adults.[1] The prevalence of PA also appears to be increasing, and in a registry of fatal food induced anaphylaxis, 63% of the 32 fatalities were caused by peanut.[2] The implications of PA extend beyond the patient and their family. This food allergy in particular has impacted the educational system as well as the food industry.[3] The effect on quality of life can be significant,[4,5] often leading to social isolation and even fear of death. Currently standard of care for PA consists of allergen avoidance, which is often ineffective, and administration of emergency medications on accidental exposure.[6] Given the prevalence of PA and its associated morbidities, safe and effective therapies are desperately needed.

Immunotherapy relies on the delivery of increasing doses of specific allergens over time with the goal of developing desensitization, which increases the dose of protein needed to elicit an allergic response.

Over the past century, immunotherapy has been successfully used to treat asthma, allergic rhinitis, and insect venom anaphylaxis through subcutaneous or sublingual administration. Although the exact mechanisms underlying allergen immunotherapy are still not fully understood, it is known to induce allergen-specific regulatory T cells, which suppress TH2 responses that promote IgE production. This response is coupled with increases in serum concentrations of allergen-specific IgG4 antibodies which compete with IgE on cell surfaces and result in reductions in mast cell and basophil activation and mediator release.[7] An increased IgG4 to IgE ratio is associated with clinical tolerance to a given food.

Though immunotherapy can be administered in a variety of methods, oral immunotherapy (OIT) has shown the most promise in the treatment of food allergy. Several recent trials have utilized the technique of oral immunotherapy for treatment of peanut and other food allergies. This therapy involves mixing the food allergen into a vehicle of choice and having the subject begin daily consumption while gradually increasing the dose. Several endpoints have been defined when evaluating the response to immunotherapy. Desensitization results in a higher threshold for an allergic reaction, typically above the amount that will be encountered in an accidental exposure. However, this does require ongoing dosing. The most desirable outcome of OIT is sustained unresponsiveness, or continued long term tolerance of the food without the need for daily maintenance therapy.

Although individual responses vary considerably, OIT will induce significant desensitization in most subjects who are able to tolerate the therapy. However, these studies are limited by frequent treatment related AEs and high rates of withdrawal due to these AEs. The reported AEs and dropout rates from representative studies are outlined in Table 1.[8-16]

There is a large amount of heterogeneity in the reporting of AEs. More specifically, AEs are at times reported in terms of the percent of subjects experiencing an adverse reaction. At other times, adverse reactions are reported in terms of the percent of doses that cause an AE. This method is often utilized to report AEs during maintenance dosing. This is in part due to the fact that over the course of all phases of an individual study and when including mild AEs in addition to more significant reactions, nearly 100% of patients have some form of AE during treatment. Thus it may be more meaningful to report the percent of doses causing symptoms at times.

Table 1: Prior OIT Trials

Author	N	Age	Design	Adverse Events	Drop outs	Additional Detail on Drop Outs
Jones et al 2009 [8]	39	1-16	Open label	92% of subjects on initial escalation day, 46% doses during build up, 3.7% doses during maintenance	10 (25%)	4 withdrew for allergic effects and 6 for personal reasons
Hofmann et al 2009 [10]	28	1-16	Open label	93% of subjects on initial escalation day, 46% doses during build up, 3.5% of doses during maintenance	5 (18%)	3 withdrew following initial escalation, 1 during build up, 1 during maintenance
Blumchen et al 2010 [9]	23	3-14	Randomized, open label	7.8% of doses during rush protocol, 2.9% of doses during maintenance	8 (35%)	1 during rush protocol, 7 during long term buildup of which 4 for allergic side effects
Varshney et al 2011 [11]	19	1-16	Double blind, placebo controlled	47% subjects with “clinically relevant” AEs during initial escalation day, 1.2% doses during build up	3 (16%)	2 withdrew during initial escalation day and 1 after first build up dose
Anagnostou et al	22	4-18	Open label	86% subjects during build up and maintenance	1 (5%)	Withdrew after the first up dose at home

2011 [12]						
Anagnostou et al 2014 [13]	99	7-16	Randomized, placebo controlled cross over	6.3 % of all doses	7 (7%)	5 withdrew for allergic reactions or persistent symptoms, 1 disliked taste, and 1 no specific reason
Vickery et al 2014 [14]	39	1-16	Open label	Previously reported in pilot study (Jones et al 2009)	15 (38%)	6 withdrew due to allergic side effect and 9 for personal reasons
Narisety et al 2014 [15]	21	7-13	Randomized, double blind, placebo controlled	43% doses during blinded phase (escalation and maintenance), 36.7% doses in OIT group during unblended phase	7 (33%)	1 withdrew after initial escalation, 1 during build up and 3 during maintenance. 1 drop out on SLIT with placebo OIT
Vickery et al 2016 [16]	37	9-36 months	Randomized, double blind, low and high dose	95% patients during entire study, 0.8% doses during study	5 (14%)	2 withdrew for nonadherence, 1 for recurrent emesis and 1 for EoE

Abbreviations: N, number of subjects, AEs, adverse events, SLIT, sublingual immunotherapy, OIT, oral immunotherapy, EoE, eosinophilic esophagitis

Given the high rate of these treatment related AEs such as oral itching, stomach upset and other GI complaints, and occasional serious systemic allergic reactions requiring the use of injectable epinephrine, OIT is still considered an experimental treatment. While some major medical centers and a number of private practice allergists offer peanut OIT to their patients, it is not yet FDA approved.

A commercially developed product, AR101 (Aimmune Therapeutics), an investigational oral biologic drug, was recently trialed in a phase 3 study evaluating efficacy. In the intervention group, 67.2% of patients ages 4–17 tolerated at least a 600-mg dose of peanut protein in the exit food challenge, compared to 4.0% of placebo patients ($p<0.00001$). In the trial's primary analysis group of ages 4-17, 496 patients from both arms (372 AR101 and 124 placebo) were evaluable for safety. In both arms, the incidence of serious adverse events (SAEs) was low. A total of 10 patients experienced SAEs, none of which were considered life-threatening: nine of these patients were in the AR101 arm (2.4%) and one was in the placebo arm (0.8%). Of the nine AR101 patients who experienced a SAE, five patients experienced mild or moderate SAEs. The other four AR101 patients experienced severe SAEs, which, for two of these patients, were not related to treatment (a concussion and a viral asthmatic exacerbation). Of the two patients who experienced severe SAEs related to treatment, both of whom had elevated baseline peanut-specific IgE levels greater than 100 kU/L, one experienced anaphylaxis, and the other experienced wheezing on the first day of treatment. Both of these patients discontinued from the study. In ages 4–17, 20.4% of AR101 patients and 6.5% of placebo patients discontinued the trial. In the AR101 arm, 12.4% of patients discontinued due to investigator-reported adverse events, including 6.7% due to gastrointestinal adverse events and 2.7% due to systemic allergic hypersensitivity reactions. In the placebo arm, 2.4% of patients discontinued due to investigator-reported adverse events (Table 2).[28]

Table 2: Discontinuations in the AR101 Group[28]

	AR101 (n= 372)	
	%	n
Total discontinuations regardless of causality	20.4%	76
Discontinuations not related to adverse events	8.0%	30
Discontinuations related to adverse events	12.4%	46
• Gastrointestinal[2]	6.7%	25
• Systemic hypersensitivity reactions[3]	2.7%	10
• Respiratory system	1.1%	4
• Cutaneous	0.8%	3
• Other	1.1%	4

We seek to identify a means of accomplishing peanut desensitization while decreasing the rate of treatment related AEs. It has been shown that standard roasting methods of peanut preparation can play a significant role in increasing the undesirable allergenic properties of peanuts.[17] It has also been demonstrated that peanut antigen stimulation of peripheral blood T lymphocytes is unaffected by various heating methods, which is necessary for induction of tolerance.[18] An additional study confirms the findings of extended boiling resulting in reduction of peanut allergenicity while preserving the effect on T cell reactivity.[19] A group recently reported a series of 4 subjects with peanut allergy who were treated with daily doses of boiled peanut, one of which subsequently transitioned to raw peanut. All subjects demonstrated lower IgE reactivity to boiled peanut compared to control suggesting that in vivo findings correlate with the prior in vitro data.[20]

While OIT is a promising therapy, we hypothesize that by treating peanut allergic subjects with a peanut product of reduced allergenicity but preserved T cell reactivity, we will be able to desensitize these subjects to a target maintenance dose of peanut protein with reduced rates of allergen associated AEs, while preserving immunologic effects that will promote tolerance. This will confirm that the immunologic changes produced by roasted peanut OIT can be replicated more safely using boiled peanut. If successful, such a therapy will decrease the number of subjects that must discontinue this treatment due to related AEs, and offer a potentially important therapy for this life threatening condition. Improved safety of this intervention may also allow for higher treatment doses to be used, may allow inclusion of more severely allergic subjects excluded from previous trials, and possibly increase the likelihood for attainment of permanent tolerance with sustained unresponsiveness, rather than perpetuating the need for continual daily dosing. This will likely result in the eventual inclusion of BPOIT in general Allergy/Immunology practice as a treatment for peanut allergy. We suspect this therapy will improve quality of life as measured by validated questionnaires as well as, or better than, roasted peanut oral immunotherapy.[28]

2.3 Risk/Benefit Assessment

2.3.1 Known potential risks

There is a significant rate of adverse reactions with peanut oral immunotherapy in clinical trials to date. Mild adverse reactions such as oral itching or nausea are reported in up to 10-15% of all doses. Over the course of an individual study, this reaches nearly 100% of all subjects. The rate of these adverse events are outlined in representative studies in Table 1.

More severe reactions requiring treatment with epinephrine or inhaled beta-agonists are less frequent but can occur. In a large review of multiple centers performing peanut OIT, Wasserman et al noted a total of 95 adverse reactions requiring epinephrine in 352 patients that collectively received more than 240,000 doses of peanut.[25] The results of the largest peanut OIT trial to date, a phase 2 clinical trial utilizing product AR101 were published in March of 2018.[21] In this study, 9 (14%) of 63 subjects received a single injection of epinephrine during initial double blind placebo controlled food challenge (DBPCFC) at screening: 4 were randomized to AR101, 4 to placebo, and 1 was not enrolled. For the duration of maintenance therapy, one treatment subject received a single epinephrine injection for moderate anaphylaxis at home. Finally, during the exit DBPCFC, 11 of 26 placebo subjects (42%) were administered epinephrine and 2 of 23 AR101 subjects (9%) received a single injection of epinephrine.

Across the various peanut OIT trials, there has been no specific statistical analysis examining adverse reaction rate or withdrawal rate at various ages. Presumably this is due to the fact that no specific age related pattern has emerged and that anaphylaxis and subject withdrawal has occurred in subjects of all ages.

There is also a risk for development of Eosinophilic Esophagitis (EoE). A recent review estimated the prevalence across the OIT clinical trials as 3-4% and in the study conducted by Bird et al, EoE occurred in only 1 subject (<5%) from the treatment group.[21] Once OIT is discontinued in these patients, the EoE typically resolves.

There is also a risk of causing anxiety or stress in the subject or the family. The impact of oral immunotherapy on quality of life has been examined with a variety of foods. Quality of life in patients with food allergy improves in some but declines in others while undergoing OIT, and in particular tends to decline in those rating a higher quality of life prior to initiation of the treatment.[26]

2.3.1 Known Benefits

The primary benefit of peanut oral immunotherapy is increasing the threshold of peanut which will result in an allergic reaction. This increased threshold is typically above the amount encountered upon accidental ingestion. This can reduce the risk of a subject experiencing a severe or life-threatening allergic reaction due to an accidental ingestion. Importantly, this can also ease anxiety in both the subject and family that is often associated with the diagnosis of a food allergy.

The question of whether oral immunotherapy will induce sustained unresponsiveness, or ongoing tolerance of peanut following cessation of the daily maintenance doses, is yet to be fully elucidated.

Results have varied among initial clinical trials. If this can be obtained, this would allow full incorporation of peanut into the diet of previously allergic subjects.

2.3.3 Assessment of the potential risks and benefits
We believe that given the low rate of serious adverse reactions along with the hypothesis that subjects receiving the boiled peanut will experience a lower rate of these adverse reactions, that the potential benefit to induce desensitization to peanut outweighs these risks. In addition to personal benefit, this study has the potential to further the future treatment options for peanut allergic children.

3. Objectives and Endpoints

Objective	Endpoints	Justification
Primary		
Determine the effect of boiled peanut immunotherapy on the immune response to peanut and demonstrate that the proportion of subjects successfully desensitized with boiled peanut OIT is not appreciably lower than the proportion of subjects successfully desensitized with roasted peanut OIT in published data.	Primary Endpoint: Response to treatment defined as ability to successfully consume a single dose of 300 mg or greater of peanut protein with no dose limiting symptoms at exit double blind placebo controlled food challenge (DBPCFC). The highest dose of roasted peanut protein tolerated by the subject at exit DBPCFC will also be compared to the highest dose tolerated at baseline. The effect of boiled peanut immunotherapy on the immune response to peanut will be evaluated via specific serum markers of sensitization and tolerance to peanut. • Levels of serum specific peanut IgE, with higher levels associated with greater likelihood of clinical reaction on exposure to peanut protein. • Peanut protein component panel, to determine the presence of high levels of sensitivity to peanut proteins known to be	Previous in vitro data has demonstrated that boiling peanuts can result in reduction of peanut allergenicity while preserving the effect on T cell reactivity.

	associated with severe systemic reactions (Arah 1,2, 3) versus mild reactions (Arah8) • Levels of peanut specific serum IgG4, with higher levels associated with increased tolerance to peanut protein • These markers will be evaluated at baseline and the conclusion of the study.	
Secondary		
Compare the rate of adverse effects of boiled peanut oral immunotherapy to published data on roasted peanut oral immunotherapy.	The rate of adverse events in the subjects receiving boiled peanut oral immunotherapy. Possible adverse events include: side effects of treatment defined as oral itching, rhinorrhea, conjunctivitis, urticaria, angioedema, abdominal upset, vomiting, diarrhea, cough, wheeze, or anaphylaxis • Adverse events will be recorded in terms of the percentage of subjects with adverse events on initial escalation day and at dose escalation visits by CRU staff. • Adverse events will also be recorded in terms of overall percentage of home doses that result in adverse reaction, with data compiled from home logs **(Supplement 2).** The adverse reactions will be graded in severity and the treatment required will be recorded. Validated, age-specific, food-related quality-of-life surveys before and after peanut oral immunotherapy will be completed	As described above, the rate of adverse events with roasted peanut oral immunotherapy is high. Thus treatment options with less adverse effects are highly desirable. In vitro data has demonstrated that boiled peanut has reduced allergenicity compared to roasted peanut and similar immunogenicity. As such, we anticipate a lower rate of adverse reactions in our subjects compared to published data on roasted peanut OIT.

	by all patients/families[27] **(Supplement 1).**	

4. Study Design

4.1 Overall Design

We will perform a phase 1 clinical trial utilizing oral immunotherapy with powder derived from boiled peanut. Our hypothesis is that the subjects treated with this novel regimen of boiled peanut will demonstrate lower rates of adverse effects while demonstrating similar immunologic markers of peanut desensitization and possible tolerance in comparison to published data on subjects treated with OIT utilizing roasted peanut product.

4.2 Scientific Rationale

Oral immunotherapy has not yet been approved by the FDA for the treatment of food allergy. However, multiple clinical trials in recent years have shown significant promise in utilizing oral immunotherapy for peanut allergy. It is expected that oral immunotherapy will be more widely available in the near future, and options with a more favorable side effect profile are highly desirable.

The phases of our clinical trial were modeled after the previous high quality studies utilizing roasted peanut OIT and are comparable in methodology and duration.

4.3 Justification for Dose

The maintenance dose for oral immunotherapy with peanut has varied across previous clinical trials. Doses have ranged from 300 mg up to a maximum of 4000 mg.[8-16] Only one study has compared the efficacy of different maintenance doses. In this study, Vickery et al found that a maintenance dose of 300 mg was as efficacious as a 3000 mg dose at inducing sustained unresponsiveness. This is also likely to be above the dose encountered in an accidental ingestion, as 1 whole peanut contains roughly 250 mg of peanut protein.[22]

4.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA.

5. Study Population

We will recruit 10 children ages 1 to 16 years with peanut allergy suggested via history and objective evidence of IgE mediated hypersensitivity to peanut either via skin testing or in vitro testing (peanut specific IgE concentration) within the last 12 months. Skin prick testing will be performed with standard peanut extract (1:20 w/v, Greer) and peanut specific IgE concentration will be performed using ImmunoCap. We will use standard criteria to indicate sensitization.

5.1 Inclusion Criteria

Inclusion Criteria
Age 1-16 years
History of immediate hypersensitivity reaction to peanut or a high level of suspicion based on testing at the discretion of the investigator
Evidence of IgE mediated peanut hypersensitivity within a 12 month period of study enrollment **SPT with wheal/flare of at least 3 x 6 mm** **and/or** **Peanut specific IgE >0.35 kU/L**

Abbreviations: SPT, skin prick test

In addition, the individual's parent or guardian must provide signed and dated informed consent and the individual must provide signed and dated assent when appropriate. The individual and parent or guardian must agree to comply with all study procedures and the individual must have the ability to take oral medication.

5.2 Exclusion Criteria

Exclusion Criteria
History of life threatening peanut anaphylaxis
Asthma requiring more than medium dose ICS
Prior participation in OIT, SLIT or EPIT
Oat allergy
Cardiovascular Disease
Use of beta-blockers (oral), angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or calcium channel blockers
Use of steroid medications in the following manners: **Daily oral steroid dosing for greater than 1 month during the past year OR** **Burst or steroid course in the past 3 month before inclusion OR** **Greater than 2 bursts oral steroid courses in the past year of at least 1 week duration**
Pregnancy or lactation
Eosinophilic Gastrointestinal Disease
History of food protein-induced enterocolitis (FPIES)
History of developmental delay or speech delay that precludes age-appropriate communication, **in the opinion of the investigator**

Abbreviations: ICS, inhaled corticosteroid, OIT, oral immunotherapy, SLIT, sublingual immunotherapy, EPIT, epicutaneous immunotherapy

A history of life-threatening anaphylaxis is defined as a reaction involving respiratory failure, hypotension or neurologic compromise. Medium dose ICS is defined by the National Heart, Lung, and Blood Institute asthma guidelines. Patients with oat allergy, while rare, are to be excluded as this will serve as the placebo for our exit food challenge (SV10).

5.3 Lifestyle Considerations

With the exception of the oral immunotherapy treatment, subjects will be instructed to continue strictly avoiding peanut in their diet. Prior oral immunotherapy studies have sought to determine predictors of adverse reactions to treatment and co-factors are often noted in subjects that do experience adverse reactions. This can include illness, exercise, or allergen exposure in subjects with allergic rhinitis.[23] Subjects will be instructed to refrain from exercising for 60 minutes following ingestion of the study drug. Subjects and their families will also be instructed to contact the physician investigators if an illness or significant rhinitis symptoms occur, as a temporary adjustment to the daily dose may be necessary.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because there are no objective signs of an IgE mediated reaction during initial food challenge may not be rescreened. These individuals are not peanut allergic and thus not candidates for the treatment of peanut allergy.

5.5 Strategies for Recruitment and Retention

Individuals will be screened for possible study eligibility at the Cleveland Clinic Allergy Clinic locations. The recruiting physicians will include the Pediatric Allergy clinic staff as well the Respiratory Institute Allergy staff. All Allergy physicians will be made aware of the study and details of recruitment at a Quarterly Allergy and Immunology staff meeting which is attended by both Pediatric Institute and Respiratory Institute allergy physicians.

Once potential participants are identified, a study investigator will reach out to the parent/guardian of the patient via an introductory letters and telephone to inquire about study interest. Should the family express a desire to participate, they will be invited to the main campus for Enrollment/Baseline visit. This visit will take place with one of the physician investigators and will involve extensive discussion of the study including protocol, risks and benefits. If the individual and their parent or guardian opt to participate in the study, informed consent, and assent when appropriate, will be obtained at this time and the individual will be enrolled.

There has been a significant amount of media and online attention to these evolving treatment options for food allergy including OIT. As such, frequent and unsolicited inquiries regarding OIT are made by patients/families encountered in the Allergy clinics. This fact accompanied by the prevalence of peanut allergy in the pediatric population leads us to believe the accrual rate of participants will be fairly rapid.

6. Study Intervention

6.1 Study Interventions Administration

6.1.1 Study Intervention Description
Commercially available whole canned boiled peanuts (Peanut Patch, McCall Farms) will be purchased from online retailers. This commercially available product, regulated by the Food and Drug Administration, is regularly consumed by humans.

Although additives are typically contained in commercially available products, this is not expected to be clinically relevant. The prevalence of allergy to food additives has been reported as high as 0.23% based on self-report. However, the reported cases in medical literature are typically either anecdotal or diagnosed based on poorly-controlled challenge procedures. Thus expert consensus is that relatively few food additives have been convincingly demonstrated to true hypersensitivity reactions.[6]

Peanut Patch

Information from the Manufacturer's Website:

Nutrition Facts

Serving Size 1/4 cup (about 34g)

Amount Per Serving

Calories 100	Calories from Fat 70
	% Daily Value*
Total Fat 8g	**12%**
Saturated Fat 1.5g	**8%**
Trans Fat 0g	
Cholesterol 0mg	**0%**
Sodium 320mg	**13%**
Total Carbohydrate 3g	**1%**
Dietary Fiber 2g	**8%**
Sugars 0g	
Protein 4g	

Vitamin A 0%	Vitamin C 0%
Calcium 0%	Iron 2%

* Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

Calories per gram:

Fat 9 • Carbohydrate 4 • Protein 4

The boiled peanuts will be processed into powder. All processing will take place in the University Hospitals Dahms Clinical Research Unit kitchen. The Dahms Clinical Research Unit kitchen is a Class III Non-Commercial Food Service establishment and is inspected on a routine basis through the Cleveland Health Department. The peanut processing will be supervised by the CRU Bionutrition director who is certified in food protection through the Ohio Department of Health.

Boiled peanuts will be shelled and placed evenly on individual trays of a food dehydrator purchased for use of this process only (Nesco FD-75a Food Dehydrator). The dehydrator was purchased specifically for this study and no other food items will come into contact with or be used on this device. Peanuts will be dehydrated at a temperature of 105 degrees F (41 degrees C) for 17 hours (1,020 minutes). Immediately upon removal, peanuts will be ground to a fine powder in a food processor.

Peanut powder will be placed in Pactiv/Newspring plastic deli containers with lids. These will be sealed, labeled, and shipped via courier from the Case Western Clinical Research Unit directly to the investigational drug pharmacy for storage in a refrigerator.

We will characterize the processed boiled peanut and determine the concentration of peanut protein. This will be necessary to calculate the doses for subjects in the boiled peanut immunotherapy arm. To further characterize this product, the specific component proteins including Ara h 1, 2, 3, 8 and 9 will also be quantified. These specific proteins are known to be associated with either higher risk for anaphylaxis (Ara h 1, 2, and 3) versus more mild reactions (Ara h 8).24 This assay will be performed as an ELISA within the Cleveland Clinic Proteomics lab.

A representative sample from each batch of prepared boiled peanut powder will be sent to JLA laboratories, a USDA certified lab, in order to test for aflatoxin levels and to quantify a total bacterial count and total mold count. This lab is approved by the USDA-AMS for Aflatoxin in Peanuts and ISO 17025 accredited by ANAB for aflatoxin and microbiological testing. Aflatoxin testing is performed by HLPC method in accordance with AOAC 991.31 and AOAC 2005.08. The total bacterial count will be obtained using AOAC-RI 051702/MB073.6 and the mold count using AOAC- RI 051702/MB074.03.

The doses will be measured and allotted into individual medicine cups by the Investigational Drug Service Department as outlined in Section 6.2. The subjects will mix the powder with a vehicle of the subject/family's choice (applesauce, pudding, or hot cereal) just prior to oral ingestion.

6.1.2 Dosing and Administration

Oral Food Challenge

After informed consent is obtained (and assent when relevant), eligible subjects will undergo an open roasted peanut graded food challenge to 4000 mg of peanut protein to confirm peanut allergy and to determine the amount of peanut protein required to induce an allergic reaction at baseline. An oral food challenge is the gold standard for diagnosis of food allergy. PB2 peanut powder (PB2 Foods, Tifton, GA) will be used exclusively for this challenge, mixed in a vehicle of the family's choice (such as applesauce, pudding, etc).

Subjects will be instructed to hold medications with strong antihistamine properties for five days prior to the challenge (diphenhydramine, loratadine, desloratadine, cetirizine, levocetirizine, fexofenadine, azelastine). The challenge will not be performed in the setting of acute illness, including febrile illness, asthma exacerbations, and significant flares of atopic dermatitis.

The oral food challenge protocol is outlined in Table 3. The initial oral food challenge will take place under the supervision of a trained Allergy/Immunology investigator and trained Allergy/Immunology nurse at Cleveland Clinic Children's main campus Allergy Clinic, where similar food challenges are routinely conducted. The physician investigator available will be trained in recognition and treatment of IgE mediated food reactions, will be available for immediate evaluation of any signs or symptoms of reaction.

Table 3: Oral food challenge to peanut for enrollment (Study Visit 1)

Time	Dose	Clinician Intervention *
0	5mg	Obtain weight, temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation level. Peak flow will be done on patients 4+ or deemed developmentally appropriate. Full physical examination of ears, oropharynx and nose, lungs, and skin prior to administration of dose
+15 minutes	10mg	Examination of skin and auscultation of lungs prior to dose
+30 minutes	25mg	Examination of skin and auscultation of lungs prior to dose
+45 minutes	50mg	Examination of skin and auscultation of lungs prior to dose
+60 minutes	100mg	Examination of skin and auscultation of lungs prior to dose
+75 minutes	500mg	Examination of skin and auscultation of lungs prior to dose
+90 minutes	1000mg	Examination of skin and auscultation of lungs prior to dose
+105 minutes	4000mg	Examination of skin and auscultation of lungs prior to dose Full physical examination of ears, oropharynx and nose, lungs, and skin after completion of final dose.

*Vital signs including heart rate, blood pressure, respiratory rate and oxygen saturation level to be obtained with any change in physical exam or clinical status

If objective signs of an allergic reaction occur, then the challenge will be stopped, and the subject treated based on the presenting symptoms and clinical judgment of the supervising investigator (Table 4). If no objective signs occur within 2 hours after the last dose is consumed, then the child will be considered not peanut allergic and will not qualify for the study.

Table 4: Oral food challenge stopping criteria

A positive food challenge will be defined by the presence of either of the following: • One or more major criteria • Two or more minor criteria An indeterminate food challenge will be defined by the presence of one minor criterion. A negative food challenge will be defined by the absence of major or minor criteria. All symptoms should be of new onset and not due to ongoing disease. Symptoms must occur no later than 2 hours after the last dose.
Major Criteria
• Confluent erythematous pruritic rash • Respiratory signs (at least one of the following): Wheezing Inability to speak Stridor Dysphonia Aphonia • >/= 3 noncontact urticarial lesions lasting for more than 3 minutes • >/= 1 site of angioedema • Hypotension for age not associated with vasovagal episode • Evidence of severe abdominal pain (such as abnormal stillness or doubling over) that persists for more than 3 minutes
Minor Criteria
• Vomiting (persistent symptoms would elevate to major criterion) • Diarrhea • Persistent rubbing of nose or eyes that lasts for >/= 3 minutes • Persistent rhinorrhea that lasts for >/= 3 minutes • Persistent scratching that lasts for >/= 3 minutes

The subjects with objective signs of an IgE mediated reaction to peanut using standard criteria (Table 4) will be eligible for enrollment.

If patient is found to be study eligible, then a urine pregnancy test will be done on females who have reached the age of child birthing potential.

Initial Dose Escalation

Upon enrollment, demographic data will be collected including age, sex, race, history of asthma/atopic dermatitis/allergic rhinitis. The enrolled subjects will present to the Clinical Research Unit for a one day dose escalation. The intent of the initial escalation is to begin and remain at subthreshold levels and identify a safe starting dose for home administration. Any subjects unable to tolerate at least 1.5 mg peanut protein will be discharged.

Active illness or asthma exacerbation will prompt rescheduling of the initial dose escalation. Patients are encouraged to eat foods brought from home before and during dose escalation.

Prior to the first dose, patients will receive the following interventions:

- Blood obtained by venipuncture for baseline laboratory evaluation
    - Peanut specific IgE concentration
    - Peanut component testing (peanut specific IgE concentration for Ara h 1, 2, 3, 8 and 9)
    - Peanut specific IgG4 concentration.
    - Serum samples will be sent to the Cleveland Clinic Main Campus laboratory with the exception of the peanut IgG4 level which will be sent out to the Mayo Clinic.
- Skin prick test to peanut with extracts routinely used for this purpose in clinical practice
    - Negative control (50% glycerin/50%Cocas)
    - Positive control (Histamine base 6mg/mL)
    - Peanut extract 1:20 (Hollister Stier)
    - Apply one drop of each solution to upper back (infants and young children) or forearm (children over the age of 6 able to avoid scratching the extract), and prick through with sterile bifurcated needle to disrupt the top layer of the epidermis. The location used for the skin prick test will remain consistent for each patient throughout the study.
    - The test will be read by the clinician 15 minutes following application. The wheal (raised center) and flare (flat erythematous patch) will be measured horizontally and vertically with an average of these 2 measurements recorded as the diameter.

Table 5: Initial dose escalation (Study Visit 2)

Time	Dose	Clinician Intervention *
0	0.5 mg peanut protein	Obtain weight, temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation level (i.e. vital signs). Peak flow will be measure on patient 4+ or deemed developmentally appropriate. Full physical examination of ears, oropharynx and nose, lungs, and skin prior to administration of dose
+30 minutes	1 mg	Repeat vital signs. Examination of skin and auscultation of lungs prior to dose
+60 minutes	2 mg	Repeat vital signs. Examination of skin and auscultation of lungs prior to dose
+90 minutes	4 mg	Repeat vital signs. Examination of skin and auscultation of lungs prior to dose
+120 minutes	6 mg	Repeat vital signs. Examination of skin and auscultation of lungs prior to dose

*Vital signs including heart rate, blood pressure, respiratory rate and oxygen saturation level to be obtained with any change in physical exam or clinical status

Dose escalation will begin with 0.5 mg of peanut protein and increase to a maximum of 6 mg (Table 5). The doses will be administered at 30 minute intervals following a set of vital signs and limited physical examination. At any objective sign of reaction (Table 4) the escalation will stopped, and the patient will be treated based on the presenting symptoms and clinical judgment of the supervising investigator. Subjects will be monitored for 2 hours after resolution of any signs of reaction and/or after completion of the final dose.

Subjects will then be instructed to consume the highest tolerated dose of peanut protein daily until their return for dose escalation.

Build-Up

For the next phase, participants will undergo incremental dose escalations every two weeks. These dose escalations with take place under the supervision of a trained Allergy/Immunology physician investigator within the Clinical Research Unit. The subject will be given an increased dose of the peanut and observed for at least 2 hours. Subjects will then continue to take daily doses of an identical amount of peanut protein at home. We will increase to a target maintenance dose of 300 mg of peanut protein, which should be accomplished in approximately 6 dose increases, or 12 weeks' time.

If a patient is unable to tolerate the maximum dose during the initial dose escalation visit, they will be given double the maximum dose tolerated during the dose escalation visits until they are back on the dose escalation schedule defined in Table 6.

If a subject does not tolerate a dose increase, then the patient will be administered a dose reduced by 25%, with increase to the originally intended dose at the subsequent visit. If the patient still does not tolerate the dose, then the decision on how to proceed will be determined at the investigator's discretion. This may involve temporarily decreasing the subject's dose, making a smaller increase, or prolonging the duration of a given dose. If any subject is unable to reach the goal maintenance dose, then the investigator may decide to continue the subject on a lower maintenance dose for the duration of the study.

Table 6: Dose Escalation Schedule

Dose of Peanut Protein	Week of Protocol
6 mg	**0**
12 mg	**2**
25 mg	**4**
50 mg	**6**
75 mg	**8**
150 mg	**10**
300 mg	**12**

Home Dosing

All subjects will be offered the opportunity to continue once daily consumption of the maintenance dose after the end of their study participation. This ongoing maintenance therapy is optional and will not be paid for by the study. The subjects will be instructed to otherwise continue a peanut free diet.

Follow Up
The subject will also undergo a final oral food challenge at the final visit (SV10). This food challenge will be double blind and placebo controlled. A double blind placebo controlled food challenge (DBPCFC) is the gold standard for diagnosis of food allergy and is the standard utilized for most oral immunotherapy trials at exit.

Roasted peanut powder will be utilized for the challenge, with oat flour as placebo. An individual will undergo a standard challenge described below (Table 7) with either the roasted peanut or the placebo, blinded to both subject and investigators. The same individual will then undergo a second challenge with the opposite (either peanut or placebo) either later that day or by returning to clinic the following day. Each challenge will be performed by increasing doses up to a final dose of 1000 mg of peanut protein. The individual doses will be 25, 100, 200, 300, 600, and 1000 mg of peanut protein. The highest tolerated dose will be recorded. If a patient reacted to a dose lower than 25 mg of peanut powder during the initial Oral Food Challenge then they will be started at the dose lower than where the reaction occurred for the DBOFC.

A urine pregnancy test will be repeated on all females of child bearing potential before the DBOFC.

Table 7: Double blind oral food challenge to peanut or control oat (SV 10)

Time	Dose	Clinician Intervention *
0	25 mg peanut protein	Obtain weight, temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation level. Peak flow in children ages 4+ or as developmentally appropriate. Full physical examination of ears, oropharynx and nose, lungs, and skin prior to administration of dose
+15 minutes	100 mg	Examination of skin and auscultation of lungs prior to dose
+30 minutes	200 mg	Examination of skin and auscultation of lungs prior to dose
+45 minutes	300 mg	Examination of skin and auscultation of lungs prior to dose
+60 minutes	600 mg	Examination of skin and auscultation of lungs prior to dose
+75 minutes	1000 mg	Examination of skin and auscultation of lungs prior to dose Full physical examination of ears, oropharynx and nose, lungs, and skin after completion of final dose.

*Vital signs including heart rate, blood pressure, respiratory rate and oxygen saturation level to be obtained with any change in physical exam or clinical status

If objective signs of an allergic reaction occur, then the challenge will be stopped, and the subject treated based on the presenting symptoms and clinical judgment of the supervising investigator (Table 4). If no objective signs occur within 2 hours after the last dose is consumed, then the challenge will be considered negative.

Quality of Life Questionnaire
At enrollment and after completion of the study, patients or caregivers will be asked to complete previously validated, age specific food allergy quality of life questionnaires[27]**(Supplement 1)**

6.2 Preparation/Handling/Storage/Accountability

The Investigational Drug Service (IDS) will provide secure storage, temperature monitoring, drug accountability, and dispensing of Investigational Product (IP) to comply with the protocol and applicable state and federal regulations related to clinical research.

IP Management

Upon the receipt of the IP, IDS will electronically document lot numbers, expiration dates, and quantity. The supply of roasted peanut powder and boiled peanut powder will be tracked and stored separately.

IP dispensing

IDS will dispense the IP to eligible subjects upon receipt of a valid prescription. The prescription will be scanned to ids@ccf.org or faxed to 216 445-5554, Monday through Friday, 0700-1600. After reviewing the prescription, the pharmacist will:

1. Weigh the prescribed dose
2. Transfer the prescribed dose into a plastic jar
3. Dispense the quantity of doses prescribed
4. Update drug accountability log**
5. File the prescription in the subjects' tab in the study binder

** Associate the dose, quantity, lot of IP dispensed with subject number and date

IP disposition

Returned or expired IP will be accounted for and then destroyed per department policy.

6.3 Measures to Minimize Bias

This study utilizes a prospective trial design in order to minimize recall bias. In addition, the double blind placebo controlled exit challenge will help minimize bias.

6.4 Study Intervention Compliance

The subjects will have periodically scheduled trips to return the empty medicine cups for monitoring of adherence. In addition, the subjects or their families will complete a log at home recording administration of doses as well as any adverse effects.

6.5 Concomitant Therapy

Data regarding the subjects' concomitant medications will be recorded at each study visit to the Pediatric Allergy Clinic or the Clinical Research Unit. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported include concomitant prescription medications, over-the-counter medications such as oral antihistamines, and supplements.

The concomitant use of antihistamines could directly affect the primary endpoint. The use of antihistamines could mask or prevent some symptoms of an allergic reaction such as urticaria or pruritus. Upon enrollment, the treating physician investigator will evaluate the specific indication for antihistamine use and will make a determination regarding continued use or discontinuation. This will be documented within the electronic medical record.

6.5.1 Rescue Medication

All subjects will be prescribed an epinephrine auto-injector to have available for rescue at home. All subjects will also be prescribed an oral antihistamine, cetirizine, to have available for rescue at home. It will be confirmed that all subjects with an underlying diagnosis of asthma have a prescription for a short acting beta-agonist (albuterol or levalbuterol) available for rescue at home. Any subjects with a diagnosis of asthma that do not have a short acting beta-agonist will have one prescribed.

The study sites (Pediatric Allergy office and Clinical Research Unit) will have rescue medications available at the time of each study visit. The following rescue medications may be used:

Treatment	Adult Dose	Route	Dosing Interval	Special Considerations	Pediatric Dose
EPINEPHRINE IM/SQ	1:1000 concentration 0.3mg (range 0.3-0.5mg, maximum 1mg per dose)	IM vastus lateralis (lateral thigh) is recommended site for quickest absorption. Can also be given SQ or IM in deltoid.	Every 5 to 10 minutes prn or sooner if clinician deems appropriate	• Give as soon as diagnosis of anaphylaxis is suspected	1:1000 concentration 0.01mg/kg OR 0.15mg pediatric autoinjectable (maximum 0.5mg/mg per dose)
PATIENT POSITION				• Place patient in supine position and elevate lower extremities when there is concern for hemodynamic compromise.	
OXYGEN	Consider 8-10 L/min initially, may titrate using pulse oximetry as guide	Appropriate to patient condition – i.e. nasal canula or mask		• Especially appropriate for prolonged and severe reactions	Titrated using pulse oximetry as guide
INTRAVENOUS FLUIDS	Crystalloid Solution, preferably normal saline (NS) 1 to 2 liters bolus	Intravenous	5-10 ml/kg in the first 5 minutes. Colloid solution: 500 ml rapidly, followed by slow infusion.	• Caution for volume overload advised for patients with history of CHF • Intraosseous access infusion can be used if IV access is unsuccessful (must use infusion pump, pressure bag, or manual pressure to overcome venous resistance)	20-30 ml/kg in the first hour
INHALED β2 ADRENERGIC AGONISTS	Albuterol sulfate 2.5 mg/3ml unit dose or Xopenex (levalbuterol HCL) 1.25 mg/3ml unit dose	Per Nebulizer via mouth-piece or mask as tolerated.	Delivered over 5-15 minutes and continued as necessary for bronchospasm	• Used when bronchospasm does not respond to epinephrine	0.15 mg/kg (minimum dose 2.5 mg) every 20 minutes for 3 doses then 0.15-0.3 mg/kg (not to exceed 10 mg) every 1-4 hours as needed or 0.5 mg/kg/hour by continuous nebulization
GLUCAGON	1 to 5 mg IV over 5 minutes	Intravenous (Glucagon administered as IV push should be reconstituted with 1 ml sterile water for injection or sterile water for reconstitution)	If no response following IVP consider IV infusion, 0.05-0.1 mg/kg/h OR 1 – 5 mg/hr titrated to clinical response	• Used if epinephrine is not effective in patients taking β-blockers (may reverse refractory bronchospasm and hypotension) • Isotonic volume expansion may also be necessary (in some cases up to 7 L) • Protection of the airway is important since glucagon can cause vomiting and risk aspiration (place in lateral recumbent position to protect airway)	20-30 µg/kg IV x1 (maximum 1 mg)
EPINEPHRINE IV	1:100,000 solution (0.1 mg [1 ml of 1:1000] in 100 ml saline)	Intravenous	Initial rate of 30-100 ml/hr (5-15 µg/min) per infusion pump, titrate for hemodynamic response	• Used in patients with poor response to IM/SQ Epinephrine • Used only in profoundly hypotensive patients not responding to IV volume replacement. • Every minute VS and EKG monitoring should be considered	0.1 µg/kg/min [0.6 X body weight (in kg) = # of mg diluted to total 100 ml saline; then 1 ml/h delivers 0.1 µg/kg/min]
VASOPRESSOR	Dopamine (400 mg in 500 ml of 5% Dextrose)	Intravenous	2-20 µg/kg/min, titrated to maintain systolic > 90 mm Hg	• Used if epinephrine and volume expansion fail to alleviate hypotension. • Transfer to hospital ASAP	2-20 µg/kg/min [6 X body weight (in kg) = # of mg diluted to total 100 ml saline; then 1 ml/h delivers 1 µg/kg/min]

Cetirizine 10 mg	Oral				2.5-10 mg

		hypotension)			
H2 ANTIHISTAMINE	Famotidine (Pepcid) 20 mg or ranitidine 1mg/kg (max 50mg)	Intravenous (10 mg/ml, undiluted)	Administer each 20 mg or fraction thereof over at least 2 minutes IV push	• Side effects: headache, dizziness, constipation, diarrhea. • Confusion increased in patients > 50 years old; thought to be associated with renal or hepatic impairment	0.25 - 0.5 mg/kg (maximum dose 40 mg/day)
CORTICO-STEROID	Methylprednisolone sodium succinate (solumedrol) IV – 40-125mg q 4-6 hours; Status asthmaticus – 0.5-1mg/kg q6 hours	IV push Oral can be considered for risk of biphasic reaction, data inconclusive, doses vary	IV push doses administered over 2 to 3 minutes	• Not effective for acute treatment of anaphylaxis, but may prevent protracted anaphylaxis • No conclusive evidence for prevention of biphasic response	Children <12 years 0.5 – 1.7 mg/kg/day divided q6 – 12h. Status asthmaticus – 0.5-1mg/kg q6 hours

7. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Criteria for discontinuing oral immunotherapy in a subject will include:

- Subject nonadherence to OIT, specifically defined by 12 (approximately 10%) nonconsecutive missed doses.
- A life-threatening adverse reaction to OIT, specifically a grade 4 reaction as defined by the Consortium of Food Allergy Research (CoFAR) criteria. See table in Section 8.3.3.1.
- Symptoms suggestive of Eosinophilic Esophagitis of (EoE) – i.e. difficulty swallowing, chest pain, persistent heart burn, upper abdominal pain, and/or no response to gastroesophageal reflux disease (GERD) medication

Symptoms suggestive of Eosinophilic Esophagitis (EoE) will prompt discontinuation of oral immunotherapy and begin once weekly symptom monitoring phone calls with study staff. If symptoms fail to resolve after 1 month off therapy, consultation with Gastroenterology will be considered for further evaluation and management.

Discontinuation from oral immunotherapy does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Skin prick test to peanut
- Peanut sIgE, peanut component panel, and peanut IgG4

7.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request. Subjects may withdraw from the study for the following anticipated reasons

- Adverse events related to OIT
    - Chronic or recurrent GI symptoms
    - Acute hypersensitivity reactions
    - Chronic or recurrent cutaneous symptoms
- Social reasons: time constraints, transport
- Principal Investigator temporarily suspends or prematurely discontinues study participation. The date and reason for discontinuation must be documented (e.g. non-compliance). Every effort should be made to complete the appropriate assessments.
- Pregnancy during the course of the study for a child-bearing participant
- The investigator considers it, for safety reasons, to be in the best interest of the subject.
- Disease progression
    - Worsening asthma that requires increasing therapy such that exclusion criteria are met

The reason for subject discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are enrolled but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are enrolled and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 1 week for an updosing visit or within 1 month for a follow up visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8. Study Assessments and Procedures

8.1 Efficacy Assessments

Procedures

Skin tests: Skin testing to peanut will be performed at the visits specified in the SoA (section 1.3). Skin testing will include skin prick with peanut exact (1:20 w/v, Greer), negative control (saline) and positive control (histamine).

Laboratory tests: Blood samples will be collected at the visits specified in the SoA. Blood work will include peanut specific IgE concentration, peanut component testing (peanut specific IgE concentration for Ara h 1, 2, 3, 8 and 9), and peanut specific IgG4 concentration. The peanut sIgE and peanut component panel will be sent to the Cleveland Clinic main laboratory. The peanut specific IgG4 will be sent to Mayo Clinic laboratories. The laboratories used will supply a list of reference ranges and units of the laboratory parameters.

Volume of blood to be collected:

Peanut specific IgE concentration	0.5 mL
Peanut component panel	0.6 mL
Peanut IgG4 concentration	0.5 mL
Total	1.6 mL

8.2 Safety and Other Assessments

Screening to ensure all subjects meet the inclusion criteria and do not meet any exclusion criteria will be performed within 1 month of the initial oral food challenge visit. At Visit 1, the physician and participant will review and update the patient's Food Allergy & Anaphylaxis Emergency Care Plan. This plan will outline the recommended treatment in case of an allergic reaction occurs during their enrollment in the study. This plan is signed by a physician, and includes emergency contact information. In addition, each study visit will include obtaining a brief interim history to ensure that no potential augmenting factors, such as viral illness, are present at the time of study drug or control drug administration. Vital signs, a targeted physical exam and conmed review will be performed prior to any study drug administration for the same purposes.

Study visit evaluation:
Brief interim history
Discussion of any interim AEs
Vital signs: Temperature, Heart Rate, Respiratory Rate
Physical Exam: Targeted assessment of General Appearance, HEENT, Cardiac, Respiratory, Abdominal, and Skin

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of Adverse Event

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

The CoFAR (the consortium of Food Allergy research) scale will be referenced to assess SAEs/AEs related or possibly related to an allergic reaction. CTCAE (Common Terminology Criteria for Adverse Events) version 5.0 will be referenced for SAEs/AEs that are not related to allergic reactions and are therefore not listed in the CoFAR scale.

8.3.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home or hypotension not responsive to treatment with epinephrine.

8.3.3 Classification of an Adverse Event

8.3.3.1 Severity of an Event

All adverse events will be graded in severity utilizing criteria specifically developed by the Consortium of Food Allergy Research.[27] These criteria are widely accepted and applied to OIT clinical trials.

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life threatening	Grade 5 Death
Transient or mild discomforts (< 48 hours), no or minimal medical intervention/therapy required. These symptoms may include pruritus, swelling or rash, abdominal discomfort or other transient symptoms.	Symptoms that produce mild-to-moderate limitation in activity, some assistance may be needed; no or minimal intervention/therapy is required. Hospitalization is possible. These symptoms may include persistent hives, wheezing without dyspnea, abdominal discomfort/increased vomiting or other symptoms.	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible. Symptoms may include bronchospasm with dyspnea, severe abdominal pain, throat tightness with hoarseness, and transient hypotension among others. Parenteral medication(s) are usually indicated.	Extreme limitation in activity, significant assistance required; significant medical/therapy. 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	Death

8.3.3.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment.

The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician

8.3.3.3 Expectedness

An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 Time Period and Frequency for Event Assessment and Follow-up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

All reportable events will be recorded with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 Adverse Event Reporting

An independent Data Safety Monitoring Board (DSMB) will be utilized during the study. The DSMB will consist of 2 Board Certified Allergy/Immunology physicians who are not participating in the study and do not have any conflicts of interest as well as 1 pediatric physician of another specialty. The DSMB will meet prior to initiation of the study, following the enrollment of the 6th subject, and then quarterly during the course of the study.

8.3.6 Serious Adverse Event Reporting

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

The study sponsor is responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting

8.3.7 Reporting Events to Participants

All anticipated AEs will involve overt symptoms and thus be readily apparent to the subjects and their families. When an AE occurs during a study visit, the nature and severity of the AE as well as the implications for ongoing treatment will be discussed by a physician investigator with the subject and parents/guardians. This discussion will take place after any potential treatment is administered and the subject is deemed medically stable but prior to end of the study visit.

When an AE occurs at home, the nature and severity of the AE as well as the implications for ongoing treatment will be discussed by a physician investigator with the subject and parents/guardians via phone. If a study visit is deemed appropriate to further manage the AE or for further discussion of the AE, then additional discussion will take place at this time.

8.3.8 Events of Special Interest
This is not applicable to our study.

8.3.9 Reporting of Pregnancy
If a pregnancy were to occur during the course of the study, the subject would be withdrawn from the study. The pregnancy would be reported the PRRC and IRB at the Cleveland Clinic. The subject would be referred to an appropriate physician (OB/Gyn) for further management.

8.4 Unanticipated Problems

8.4.1 Definition of Unanticipated Problems (UP)
The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("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); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 Unanticipated Problem Reporting
The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that have serious impact or require a change to the protocol will be reported to the IRB and to the study sponsor within 10 days of the investigator becoming aware of the event.

- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP). The reporting timeline for UPs that do not have serious impact or require a change to the protocol will be the time of continuing renewal with the IRB.

8.4.3 Reporting Unanticipated Problems to Participants
Should unanticipated problems arise that have serious impact to the protocol or to the safety of participants, participants will be notified based on the opinion of the IRB once the UP has been reviewed.

9. Statistical Considerations

9.1 Statistical Hypothesis

We will obtain observation data on patients receiving boiled peanut oral immunotherapy which has not yet been well described in human trials. We will compare with proportion of patients successfully desensitized as defined by meeting the primary endpoint with the expected placebo rate. The null hypothesis is that the proportion of patients successfully desensitized by boiled peanut oral immunotherapy will not be greater than the expected 20% that has been previously published as the proportion of patients successfully meeting the primary endpoint in OIT studies (which aligns with the expected 20% that would naturally "outgrow" a peanut allergy). If we reject this null hypothesis, we will be able to conclude that the proportion of successfully desensitized by boiled peanut therapy is greater than placebo. For the safety aspect of the study we will be comparing the historical SAEs/AEs of patients who received OIT with roasted peanuts and compare them with the patients enrolled in this study for the rate of occurrence and severity of the SAEs/AEs observed.

9.2 Sample Size Determination

The sample of 10 patients will provide >90% power to determine the expected success rate (80%) is greater than a theoretical placebo rate (20%).

9.3 Populations for Analysis

Both an Intentional-to-Treat (ITT) and per-protocol analysis will be performed.

9.4 Statistical Analysis

Descriptive statistics will be used to summarize the data. Categorical variables will be presented as number and percentage of total patients. Continuous variables will be summarized using mean, standard deviation, median and [Q1, Q3]. The proportion of patients with successful consumption of peanut protein without symptoms (primary endpoint), will be tested to determine whether the proportion differs from 0.2 (20%) (the expected success rate in a theoretical placebo group).

10. Supporting Documentation and Operational Considerations

10.1 Regulatory, Ethical and Study Oversight Considerations

10.1.1 Informed Consent Process

10.1.1.1 Consent/Assent and Other Informational Documents Provided to Participants
Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol:

- Informed Consent
- Informed Assent

10.1.1.2 Consent Procedures and Documentation
Informed consent is a process that is initiated prior to the individual and parent/guardian's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Pediatric ResearchReview Committee (PRRC) and Institutional Review Board (IRB)-approved and the participant and/or parent/guardian will be asked to read and review the document. The investigator will explain the research study to the participant and parent/guardian and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant and parent/guardian's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants and parents/guardians will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants and parents/guardians should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant's parent/guardian will sign the informed consent document prior to any procedures being done specifically for the study. Participants and parents/guardians must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participant's parent/guardian for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study

10.1.2 Study Discontinuation and Closure
This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to <study participants, investigator, funding agency, the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor and regulatory authorities>. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 Confidentiality and Privacy
Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at within RedCap Cloud. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by CRU research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived within RedCap Cloud.

10.1.4 Future Use of Stored Specimens and Data
Data will be maintained on RedCap Cloud per institute policy. Stored specimens will be discarded after analysis per Cleveland Clinic Laboratory policy.

10.1.5 Key Roles and Study Governance
Principal Investigator
Jaclyn Bjelac, MD
Staff, Pediatric Allergy and Immunology
Cleveland Clinic
9500 Euclid Ave/A120
Cleveland, OH 44195

Medical Monitor
Clinical Research Unit

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12.Supplements

12.1 Food Allergy Quality of Life Questionnaire for Parents (1-12 years old)

Supplement 1 A

Food Allergy Quality of Life Questionnaire for Parents (children 1-12 years old)

Instructions: The questions below are about the influence of food allergy on your child's quality of life. If is important that all questions be completed. Answer every question by putting an 'x' in the proper box. You may choose from the following answers:

	1 Not	2 Barely	3 A little	4 Fairly	5 Quite	6 Very	7 Extremely
Because of food allergy, my child feels…							
1. Different from other children	☐	☐	☐	☐	☐	☐	☐
Because of food allergy, my child has been negatively affected by…							
2. Receiving more attention than other children of his/her age	☐	☐	☐	☐	☐	☐	☐
3. Having to grow up more quickly than other children of his/her age	☐	☐	☐	☐	☐	☐	☐
4. His/her environment being more restricted than other children of his/her age	☐	☐	☐	☐	☐	☐	☐
Because of food allergy, my child…							
5. Experiences physical distress	☐	☐	☐	☐	☐	☐	☐
6. Experiences emotional distress	☐	☐	☐	☐	☐	☐	☐
7. Is more anxious in general than other children of his/her age	☐	☐	☐	☐	☐	☐	☐
8. Is more cautious in general than other children of his/her age	☐	☐	☐	☐	☐	☐	☐
9. Is not as confident as other children of his/her age in social situations	☐	☐	☐	☐	☐	☐	☐
10. Wishes his/her food allergy would go away	☐	☐	☐	☐	☐	☐	☐
11. Has a lack of variety in his/her diet	☐	☐	☐	☐	☐	☐	☐
Because of food allergy, my child feels…							
13. Anxious about food	☐	☐	☐	☐	☐	☐	☐
13. Afraid to try unfamiliar foods	☐	☐	☐	☐	☐	☐	☐
14. Concerned that I am worried that he/she will have a reaction to food	☐	☐	☐	☐	☐	☐	☐
15. Frustrated by dietary restrictions	☐	☐	☐	☐	☐	☐	☐
16. Left out of activities involving food	☐	☐	☐	☐	☐	☐	☐
Because of food allergy, my child's ability to take part has been limited…							
17. By anxiety when going to new places	☐	☐	☐	☐	☐	☐	☐
18. By concern that he/she must always be cautious about food	☐	☐	☐	☐	☐	☐	☐
19. By anxiety when eating with unfamiliar adults/children	☐	☐	☐	☐	☐	☐	☐
20. In social activities in other people's houses (sleepovers, parties, playtime)	☐	☐	☐	☐	☐	☐	☐
21. In preschool/school events involving food (class parties/treats/lunchtime)	☐	☐	☐	☐	☐	☐	☐
22. Being upset that family social outings have been limited by food allergy	☐	☐	☐	☐	☐	☐	☐
23. By frustration from social restrictions	☐	☐	☐	☐	☐	☐	☐
24. Restaurants we can safely go to as a family	☐	☐	☐	☐	☐	☐	☐
25. Holiday destinations we can safely go to as a family	☐	☐	☐	☐	☐	☐	☐
How troublesome did you find side effects of oral immunotherapy (OIT)?	☐	☐	☐	☐	☐	☐	☐

12.2 Food Allergy Quality of Life Questionnaire for Parents (13-16 years old)

Supplement 1B

Food Allergy Quality of Life Questionnaire for Adolescents (13-16 years old)

Instructions: The questions below are about the influence of food allergy on your quality of life. If is important that all questions be completed. Answer every question by putting an 'x' in the proper box. You may choose from the following answers:

	1 Not	2 Barely	3 A little	4 Fairly	5 Quite	6 Very	7 Extremely
How *troublesome* do you find it, because of your food allergy, that you…							
1. Must always be alert as to what you are eating?	☐	☐	☐	☐	☐	☐	☐
2. Are able to eat fewer products	☐	☐	☐	☐	☐	☐	☐
3. Are limited by the products you can buy	☐	☐	☐	☐	☐	☐	☐
4. Must read labels	☐	☐	☐	☐	☐	☐	☐
5. Are less easily able to spontaneously accept an invitation to stay for a meal?	☐	☐	☐	☐	☐	☐	☐
6. Are les able to taste or try various products when eating out?	☐	☐	☐	☐	☐	☐	☐
7. Must check yourself whether you can eat something when eating out?	☐	☐	☐	☐	☐	☐	☐
8. Hesitate eating a product when you have doubts about it?	☐	☐	☐	☐	☐	☐	☐
9. Must refuse treats at school or work?	☐	☐	☐	☐	☐	☐	☐
10. That you have to explain to people around you that you have a food allergy?	☐	☐	☐	☐	☐	☐	☐
11. Have the feeling that you have less control of what you eat when eating out?	☐	☐	☐	☐	☐	☐	☐
12. Must carry an epinephrine auto injector?	☐	☐	☐	☐	☐	☐	☐
13. Must be careful about touching certain foods	☐	☐	☐	☐	☐	☐	☐
14. That the ingredients of a product change?	☐	☐	☐	☐	☐	☐	☐
15. That the label states, "may contain traces of peanut?"	☐	☐	☐	☐	☐	☐	☐
16. That the labeling of the bulk packaging (for example box or bag) is different than the individual packages?	☐	☐	☐	☐	☐	☐	☐
17. That during social activities others can eat the food to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
18. That during social activities your food allergy is not taken into account enough?	☐	☐	☐	☐	☐	☐	☐
How *frightened* are you, because of your food allergy…							
19. Of an allergic reaction?	☐	☐	☐	☐	☐	☐	☐
20. Of unintentionally eating the wrong food?							
21. To eat something you have never before?							
Please answer the following questions:	☐	☐	☐	☐	☐	☐	☐
22. How *discouraged* do you feel during an allergic reaction?	☐	☐	☐	☐	☐	☐	☐
After completion of study only:							
23. How *troublesome* did you find side effects of oral immunotherapy (OIT)?	☐	☐	☐	☐	☐	☐	☐

12.3 Dosing/Adverse Events Recording Sheet

Supplement 2

Dosing/Adverse Events Recording Sheet

Patient Name:
Number:

Date _____	Dose _____		Time of Dose _____			
Any Reaction?	☐ Yes	☐ No				
If yes…						
Symptoms of Reaction? (check all that apply)	☐ Rash/hives	☐ Lip/Mouth Itching	☐ Nausea/Upset Stomach	☐ Vomiting	☐ Cough/ Wheeze	☐ Other: Please comment
Treatment Required?	☐ No	☐ Yes	If yes, what?	☐ Antihistamines	☐ Albuterol	☐ Epinephrine
How soon after dose did symptoms begin?	☐ Within 5-10 minutes	☐ 10-60 minutes	☐ 60-120 minutes	☐ >120 minutes		
Location of rash, if present (check all that apply)	☐ Face	☐ Neck/Chest	☐ Arms and/or legs	☐ Stomach and/or back		
How long were symptoms present before treatment was given?	☐ < 10 minutes	☐ 10-30 minutes	☐ 30-60 minutes	☐ > 60 minutes		
How many doses of treatment were given?	☐ 1	☐ 2	☐ 3 or more			
How long did symptoms last?	☐ <10 minutes	☐ 10-60 minutes	☐ 60-120 minutes	☐ >120 minutes		
Any other comments?						

SUMMARY OF CHANGES

Please provide a list of changes from the previous approved version of the protocol starting at IRB approval. This table will remain blank until initial IRB approval. The list shall be a brief overview. When appropriate, a brief justification for the change should be included. This is a running list for the life of the study.

Protocol Date	Section	Change
04.02.2019	Footer and PSP	Changed Version number and version date to 4.0 and 4-2-19 respectively
	6. Study Intervention	All references to "UH Lerner Tower Kitchen" were replaced with "UH Dahms Clinical Research Unit"
	6. Study Intervention	The onging post study OIT maintenance period was changed to being optional for study participants and is not paid for by the study.
	8.2 Study Assessments and Procedures	At Visit 1, the physician and participant will review and update the patient's Food Allergy & Anaphylaxis Emergency Care Plan. Conmed review also added before each dose escalation
	PSP and section 8.3.9	Changed PIRC (Pediatric Institute Review Committee) to PRRC (Pediatric Research Review Committee)
	Inclusion criteria	Added the additional language "within a 12 month period of study enrollment" in the inclusion criteria requiring Evidence of IgE mediated peanut hypersensitivity
	1.3 Schedule of activities and section 6.1	Added Urine Pregnancy
	6.2 IP dispensing	Remove randomize to treat and place a blinded label on jar from.
	Section 7.2	Added additional reasons for discontinuation
	1.3 Schedule of activities	Changed Adverse event review to AE review, added Study drug compliance and conmed assessment lines

Protocol Date	Section	Change
	8.3.1	The CoFAR and CTCAE are mentioned as the scales that will be used to assess SAEs/AEs
	8.4.2 and 8.4.3	Rewording of reporting requirements and timelines
05.28.2019	PSP and footer	Updated amendment # and version date
	Schedule of events, table #4 and table #5	Added spirometry and peak flow measure to study visits
	9.1 Statistical Hypothesis	Added language in regards to safety hypothesis
10.01.2019	PSP and footer	Updated amendment # and version date
	Schedule of Events section 1.3 and section 6.1	Added additional urine pregnancy at visit 10
	Schedule of Events section 1.3	Added language on spirometry being done at investigators discretion at enrollment as well visit 10
	Section 6.1	Clarified that the location of the skin prick test must be the same throughout the study
	Section 6.1 and table 7	Added a 25 mg dose in DBOFC as well as clarification that additional smaller doses may be necessary on a patient by patient basis depending on the results of the initial OFC
	Section 6.1	In build-up phase a dose double the size of the highest tolerated dose in the initial escalation may be used before the patient can be entered into the build-up phase schedule
02.12.2020	Footer	Updated protocol version date and amendment number
	PSP	Added signature line for sponsor
	Inclusion criteria	Added verbiage to inclusion criteria #2 "or a high level of suspicion based on testing at the discretion of the investigator."

Protocol Date	Section	Change
	Initial dose escalation (Table 5)	Removed the first 2 doses in the initial dose escalation (0.1 and 0.2 milligrams of peanut protein). Added a 4mg dose to be given at +90 minutes. Adjusted time for 6mg dose to +120 minutes