Challenging to Food With Escalating Thresholds for Reducing Food Allergy
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Immune Basis & Clinical Implications of Threshold-Based Phenotypes of Peanut Allergy

Study Title: ChAllenging to Food with Escalating ThrEsholds for ReducIng Food Allergy (CAFETERIA)

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INVESTIGATOR SIGNATURE PAGE	
Protocol: **Immune Basis & Clinical implications of Threshold-Based Phenotypes of Peanut Allergy**	**Version/Date: 3.0/ November 09, 2021**
Site Principal Investigator: Scott H Sicherer, MD	
Title: **C**h**A**llenging to **F**ood with **E**scalating **T**hr**E**sholds for **R**educ**I**ng Food **A**llergy, **CAFETERIA**	
Study Sponsor: The National Institute of Allergy and Infectious Diseases (NIAID)	
INSTRUCTIONS: *The Principal Investigator should print, sign, and date at the indicated location below. The original should be kept for your records and a copy of the signature page sent to DAIT RMC.*	

I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, and 312, and in the International Conference on Harmonization (ICH) document *Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance* dated April 1996. Further, I will conduct the study in keeping with local legal and regulatory requirements.

As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the IRB and NIAID.

_____

Site Principal Investigator (Print)

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Site Principal Investigator (Signature) **Date**

Protocol Synopsis

Title	CHALLENGING TO FOOD WITH ESCALATING THRESHOLDS FOR REDUCING FOOD ALLERGY
Short Title	CAFETERIA TRIAL
Clinical Phase	Phase II – Interventional
Number of Sites	Single (Icahn School of Medicine at Mount Sinai, New York, NY)
IND Sponsor/Number	18399
Study Objectives	The primary objective of this study is to determine whether allowing ingestion of sub-threshold amounts of peanut in those with a high threshold (tolerate at least 143 mg peanut protein on supervised double-blind, placebo-controlled oral food challenge [DBPCFC]) will be associated with attaining even higher thresholds over time in children with high threshold peanut allergy compared to those avoiding peanut. The secondary clinical objectives include assessing the development of sustained unresponsiveness (SU, a surrogate term for tolerance without daily ingestion), effects on quality of life, and safety compared to those avoiding peanut. Additionally, this study will phenotype the allergic response to peanut based on threshold and response to exposure. Mechanistic study objectives will determine the immune and molecular basis of the high threshold endotype, identify predictors of response to exposure, and determine mechanisms and biomarkers of remission.
Study Design	Prospective two-arm, parallel-group, randomized (1:1) controlled open trial of a diet allowing ingestion of tolerated, home-purchased, home-measurable quantities of peanut in children allergic to peanut in higher amounts.
Primary Endpoint(s)	The difference between the treatment and comparison (avoidance) groups in the percentage of children who by the endpoint DBPCFC tolerate a dose at least 2 steps higher than their baseline DBPCFC or 9043 mg of peanut protein.
Secondary Endpoint(s)	1. The percentage of children who achieve SU or natural tolerance during the study. 2. Safety parameters (acute allergic reactions, including anaphylaxis, gastrointestinal side effects). 3. Quality of life measures. 4. Changes in SPT mean wheal size. 5. Changes in Peanut-specific IgE and IgG4.

	6. Mechanistic endpoints including change in frequency of peanut-specific multi-Th2 cytokine effector cells and Tregs, basophil activation, peanut epitope binding, identification of a peripheral blood-based biomarker of desensitization potential, and identification of functional pathways underlying desensitization.
Accrual Objective	150-200 children undergoing DBPCFC to peanut to identify 72 with high threshold peanut allergy for trial randomization.
Study Duration	For each individual participant study participation may take up to 120 weeks.
Treatment Description	Approximately one hundred fifty children with possible peanut allergy will undergo DBPCFC challenge to peanut per modified PRACTALL guidelines. Those reactive to 143 mg or less, and those tolerant of 5043 mg or more, peanut protein will contribute biosamples for mechanistic studies but will not be randomized. Trial subjects, tolerating a cumulative DBPCFC dose of 143 mg but not 5043 mg peanut protein will be randomized to continue avoidance of peanut (comparison group, standard care) or to daily ingestion of a home measurable amount of peanut butter (intervention group) based upon their oral food challenge threshold. For initial home ingestion, store bought peanut butter will be used and measured with study-supplied kitchen measuring spoons. Depending upon reaction threshold, participants may begin with different starting amounts of peanut butter (e.g., 1/8 teaspoon [approximately 140 mg peanut protein], ¼ teaspoon, 3/8 teaspoon, 1 teaspoon). Depending on preference, when having exceeded 3/8 teaspoon of peanut butter, participants may substitute specific amounts of other peanut products (Bamba, peanut candy, etc.). Every 8 weeks, participants will return for attempting to ingest a higher amount of peanut along a ladder of 1/8 tsp, ¼ tsp, 3/8 tsp, ½ tsp, ¾ tsp, 1 tsp, 1.5 tsp, 2 tsp, 3 tsp. A repeat DBPCFC will be performed 8 weeks after reaching 1 tablespoon (or equivalent) in the intervention group, or at 72 weeks. A repeat DBPCFC will be performed in the control group at a time point determined by an algorithm matching controls to the intervention participants. Subjects tolerating the full challenge amount will add peanut to the diet for 16 weeks and then avoid peanut for 8 weeks, followed by a DBPCFC to assess for sustained unresponsiveness [SU] (remission during avoidance).
Inclusion Criteria	Subject and/or parent guardian must be able to understand and provide informed consent. Inclusion criteria for screening DBPCFC: Age 4-14 years, either sex, any race, any ethnicity who are enrolled while strictly avoiding peanut and have a history of sensitization (detectable peanut IgE >0.35 kUA/L). Inclusion criteria for randomization: On screening DBPCFC are able to ingest >= 143 mg peanut protein but < 5043 mg peanut protein.

	All children will have documented consent and assent as is appropriate for age.
Exclusion Criteria	Individuals who meet any of these criteria are not eligible for enrollment as study participants: 1. Inability or unwillingness of a participant to give written informed consent or comply with study protocol 2. Serum peanut-specific IgE antibody level > 50 kU_A/L 3. Recent (within the past 2 years) life-threatening (grade 3) anaphylactic reaction to peanut. 4. Any disorder in which epinephrine is contraindicated such as known hypertension or cardia rhythm disorders. 5. History of chronic disease requiring therapy (other than asthma, atopic dermatitis, rhinitis). 6. On a build-up phase of any allergen immunotherapy. 7. For those with a history of asthma, the following are assessed and any of the following is an exclusion (markers of current uncontrolled or moderate to severe asthma): A. FEV1 value <80% predicted (only for participants age 7 years or older and are able to perform spirometry)* B. ACT or cACT < 20 C. >Step 3 controller therapy as defined for children 0-4, 5-11 and >=12 years of age by EPR-3 tables D. Use of steroid medications in the following manners: a. history of daily oral steroid dosing for >1 month during the past year, b. having 1 burst or steroid course within the past 6 months, or c. having >1 burst oral steroid course within the past 12 months. E. Asthma requiring >1 hospitalization in the past year for asthma or >1 ED visit in the past 6 months for asthma, or any prior intubation/mechanical ventilation for asthma/wheezing. *When COVID related institutional restrictions on spirometry are in effect, spirometry will be not performed and peak flow will be used with 80% predicted as the cut-off. 8. Gastrointestinal eosinophilic disorders, esophagitis, gastroenteritis. 9. Use of short-acting antihistamines (diphenhydramine, etc.) more than one time within 3 days prior to DBPCFC or skin testing.*

	10. Use of medium-acting antihistamines (hydroxyzine, loratadine, etc.) more than one time within 7 days of DBPCFC or skin testing.* 11. Use of systemic steroid medications (IV, IM or oral) for indications other than asthma for > 3 weeks within the past 6 months 12. Use of beta-blockers (oral), (ACE) inhibitors, angiotensin-receptor blockers or calcium channel blockers. 13. Participation in any trials of therapeutic interventions for food allergy in the past year. 14. Therapy with anti-IgE or other biologics, including within 1 year of enrollment. 15. Use of investigational drugs within 52 weeks of participation. 16. Allergy to all of the following: oat, rice, corn, tapioca. 17. Pregnancy 18. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study. *Any subject meeting these criteria during the visits can be rescheduled for the oral food challenge or prick skin testing.
Study Stopping Rules	The study will be temporarily suspended pending DSMB review if any of the following occurs • Any death possibly related to study participation . • 2 subjects requiring more than 1 injection of epinephrine for at home study-allowed ingestion of peanut. • 3 subjects diagnosed with eosinophilic esophagitis
Participant Stopping Rules	Participants may be prematurely terminated from the study for the following reasons: • The participant elects to withdraw consent form all future study activities, including follow-up. • The participant is "lost to follow-up" (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed. • The participant dies. • The Investigator no longer believes participation is in the best interest of the participant. This includes subjects who refuse to come for the Desensitization DBPCFC visit.

	• Subjects who fail to adhere to the request to stop the study intervention per section 6.5 will be considered for premature termination. • Pregnancy • Diagnosis of eosinophilic esophagitis
Premature Discontinuation of Investigational Agent	Study therapy may be prematurely discontinued for any participant for any of the following reasons: • Severe (grade 3) anaphylaxis secondary to any DBPCFC or ingestion of the measured dose of peanut. • Significant worsening or persistent activation of atopic dermatitis, allergic rhinitis or asthma believed to be related to participation in the study. • Any subject deemed to have severe allergic and/or GI symptoms and receiving aggressive therapy. • Inability or unwillingness to comply with study procedures (re-education can be provided at the discretion of the PI/Co-I to allow continuation) as evidenced by o Excessive missed days i.e., > 7 consecutive days missed on 3 occasions. o failure to report if they have more than mild symptoms; o do not ingest the designated amount of peanut for over 10 consecutive days; o attempt to increase amounts without supervision; o or experience symptoms judged by the PI/Co-I to warrant withdrawal from ingestion Study therapy may also be prematurely discontinued for any participant if the investigator believes that the study treatment is no longer in the best interest of the participant.

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Glossary of Abbreviations

CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DAIT	Division of Allergy, Immunology, and Transplantation
DBPCFC	Double-blind, placebo-controlled oral food challenge
DSMB	Data Safety Monitoring Board
EoE	Eosinophilic esophagitis
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HT	High threshold peanut allergy
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
LT	Low threshold peanut allergy
MOP	Manual of Procedures
NIAID	National Institute of Allergy and Infectious Diseases
NPA	Not peanut allergic (tolerant)
OFC	Oral food challenge
PI	[Site] Principal Investigator
PBMC	Peripheral blood mononuclear cells
PST	Prick skin test
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SOP	Standard Operating Procedure
SU	Sustained unresponsiveness
SUSAR	Serious Unexpected Suspected Adverse Reaction

Study Definitions Page

1. Anaphylaxis	Anaphylaxis is a generalized allergic reaction that is rapid in onset and may progress to death.1
2. Criteria for anaphylaxis	Anaphylaxis is likely when any one of the three following sets of criteria are fulfilled: 1. Acute onset of an illness (minutes to hours) with involvement of: • Skin/mucosal tissue (e.g., generalized hives, itch or flush, swollen lips/tongue/uvula) AND • Airway compromise (e.g., dyspnea, stridor, wheeze/ bronchospasm, hypoxia, reduced PEF) AND/OR • Reduced BP or associated symptoms (e.g., hypotonia, syncope, incontinence) 2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to hours): • Skin/mucosal tissue (e.g., generalized hives, itch/flush, swollen lips/tongue/uvula) • Airway compromise (e.g., dyspnea, stridor wheeze/bronchospasm, hypoxia, reduced PEF) • Reduced BP or associated symptoms (e.g., hypotonia, syncope, incontinence) • Persistent GI symptoms (e.g., nausea, vomiting, crampy abdominal pain) 3. Reduced BP after exposure to known allergen for that patient (minutes to hours): • Infants and Children: low systolic BP (age-specific) or >30% drop in systolic BP* • Adults: systolic BP <90 mm Hg or >30% drop from their baseline * Low systolic BP for children is defined as <70 mmHg from 1 month to 1 year; less than (70 mmHg + [2 x age]) from 1-10 years; and <90 mmHg from age 11-17 years.

<table>
<tr><td>3. Anaphylaxis grading</td><td>Grading System of Severity of Anaphylaxis
<table><tr><th><u>Grade</u></th><th><u>Defined By</u></th></tr><tr><td>1. Mild (skin & subcutaneous tissues, GI, &/or mild respiratory)</td><td>Flushing, urticaria, periorbital or facial angioedema; mild dyspnea, wheeze or upper respiratory symptoms; mild abdominal pain and/or emesis</td></tr><tr><td>2. Moderate (mild symptoms + features suggesting moderate respiratory, cardiovascular or GI symptoms)</td><td>Marked dysphagia, hoarseness, and/or stridor; SOB, wheezing & retractions; crampy abdominal pain, recurrent vomiting and/or diarrhea; and/or mild dizziness</td></tr><tr><td>3. Severe (hypoxia, hypotension, or neurological compromise)</td><td>Cyanosis or SpO2 <u>≤</u> 92% at any stage, hypotension, confusion, collapse, loss of consciousness; or incontinence</td></tr><tr><td>4. Life-threatening</td><td>The above, and cardiac or respiratory arrest</td></tr><tr><td>5. Death</td><td></td></tr></table></td></tr>
<tr><td>Tolerant or tolerate</td><td>Ability to ingest an allergenic food without evidence of allergic symptoms; does not infer concomitant long-lasting change in the individual’s immunologic response to food; may reflect “desensitization” or “tolerance”</td></tr>
<tr><td>Tolerance</td><td>Long-lasting change in an individual’s immunologic response to a food allergen in conjunction with the ability of the individual to ingest the food without evidence of allergic symptoms. Induced tolerance refers to having an active intervention resulting in tolerance. Natural tolerance refers to attaining tolerance without an intervention (i.e., outgrowing an allergy).</td></tr>
<tr><td>Sponsor- Medical Monitor</td><td>A physician administratively independent of the Sponsor-Investigator who is familiar with clinical trials who will oversee the safety of the participants on behalf of the Sponsor-Investigator</td></tr>
</table>

1. Background and Rationale

1.1. Background and Scientific Rationale

Food allergy affects up to 5% of adults and 4-8% of young children in the US, an estimated 15 million Americans.[1,2] Food allergy carries a significant cost, and a negative impact on nutrition and quality of life.[3-6] Peanut allergy affects nearly 2% of children, is often severe, and life-long.[7] The current standard for food allergy management relies on strict avoidance of the offending food. Children are monitored for resolution of food allergy with periodic oral food challenges (OFC), which are performed when diagnostic tests and the medical history suggest a possibility that the allergy has resolved. An OFC involves gradually feeding increasing amounts of the food under medical supervision until a "meal-sized" portion is ingested, unless there are symptoms requiring cessation of dosing. These tests are performed by allergists for clinical diagnosis when they suspect resolution of peanut allergy or sensitization without reactivity, using office-measured foods such as peanut butter, peanut flour, or Bamba, in amounts measured by common kitchen materials such as spoons.[8] A child who reacts at any dose during an OFC, even at the top dose, even with mild symptoms, is considered allergic and advised to continue strict avoidance until the next OFC is performed, typically not less than a year later.[4,9-11]

However, the paradigm of strict avoidance of a food as therapy for food allergy is changing. Our research group fundamentally changed the paradigm for egg and milk allergy in children without exquisite sensitivity to these allergens. We showed that approximately 70% of children with milk or egg allergy tolerated extensively heated forms (bakery goods); allowing them to eat these forms facilitated allergy recovery (including evidence of immune modulation and, for some, eventual tolerance of unheated, full servings of these foods) and was safe.[12-20]

For those with low threshold food allergy, oral (OIT), sublingual (SLIT), and epicutaneous (EPIT) immunotherapy, as well as combination therapy using OIT and omalizumab have all shown some promise to improve treatment.[13,21-23] However, studies of these immunotherapies typically exclude persons with high thresholds of reactivity, those who react at doses higher than 100 or 300 mg of peanut protein. While this is understandable given the needs of those with severe allergies (low threshold, serious symptoms at low doses), a large proportion of the allergic community have a high threshold of reactivity and yet they are instructed to avoid the allergen. A large proportion of individuals are not exquisitely sensitive and exhibit a high threshold phenotype. Therefore, current immunotherapeutic treatment approaches are likely focusing on less than half of the affected population, potentially neglecting millions of people with food allergy. There is an unmet need to provide approaches for people with high threshold food allergy, the majority of the food-allergic population.

We believe that the next logical step is a simple and cost-effective approach of allowing children with high threshold peanut allergy to ingest tolerated amounts of peanut. The approach is based in part on our prior success with allowing children to ingest milk and egg in tolerated forms, and the promise seen in OIT studies.

Currently, allergists perform OFCs in the office setting by feeding supermarket forms of peanut measured with simple kitchen materials often using foods brought in by the patient. We propose that allowing children with high threshold peanut allergy to ingest tolerated, sub-threshold amounts of peanut, using home-purchased, home-measured foods based on the results of an OFC, may be associated with benefits such as further increased threshold with time and potentially sustained unresponsiveness (SU, remission off daily ingestion), should be safe, and result in improved quality of life. This approach may become a prototype for studying additional foods. Additionally, we will undertake immunologic genomic, and transcriptomic characterization of a high threshold endotype of peanut allergy to inform identification of biomarkers and mechanisms of threshold, response to therapy, reaction severity, and SU/tolerance/remission.

1.2. Rationale for Selection of Investigational Product or Intervention

The intervention is to allow children with a threshold greater than or equal to 143 mg peanut protein but less than 5043 mg peanut protein to ingest, if tolerated, a daily home-purchased, home-measured amount of peanut. The rationale to this practical approach is that allowing ingestion of sub-threshold amounts of food allergens will induce changes in the immune response that will allow ingestion of larger amounts of the food over time (increased threshold). We anticipate that introduction and periodic increase of the sub-threshold amounts of peanut will induce desensitization and over time will lead to SU.

The background for the rationale and intervention has 3 themes: 1) moderate allergy is common (significant unmet need), 2) ingestion of tolerated amounts of allergen is generally safe and can be achieved using "regular food" at home (inexpensive, simple), and has been an acceptable approach, and 3) ingesting allergen may result in increasing desensitization and possibly, with time and increased quantities, maintaining a high threshold despite discontinued daily ingestion (sustained unresponsiveness, SU, a surrogate term for tolerance or remission) indicating a health benefit of this approach.

1) ***There is a large unmet need for those with high threshold food allergy.*** Prior studies suggest that overall, during oral food challenges approximately 75% of the reactions occur at doses over 100 mg of food protein, and 55% of reactions occur at cumulative doses over 250 mg, with over 30% at doses over ~1.5 grams,[24-31] as summarized in Table 1.

Table 1: Selected studies reporting threshold doses during diagnostic oral food challenges in food allergy practices

Study/Food/N of subjects	Median age	Cumulative threshold, mg food protein
Ballmer Weber JACI 2015[25] Peanut, Hazelnut Celeriac, Fish; N=224	Overall 24.2 years; peanut-10.4 years; fish-14.2 years	75% reacted at or above 100 mg
Taylor S et al, Food and Chemical Toxicology, 2010[26]; Peanut; N=286	7 years	75% reacted above 100 mg peanut
Osterballe et al, JACI, 2003[27]; Egg, N=56	2.2 years	Median threshold was 2.2 g whole egg
Moneret-Vautrin, 1998, Clin Exp Allergy[28] Peanut, egg; N=90	Children	Peanut: 75% reacted above 100 mg; 63% reacted at 100-1000 mg Egg: 70%-reacted above 100 mg; 30% reacted at 100-1000 mg
Sicherer et al, JACI 2000[24] Milk, egg, peanut, wheat, soy and fish N=196	5 years 9 mo	Overall 56% of the ofc were to the cumulative doses over 500 mg of food (protein is generally <25% of the whole food): egg-51%, milk-45%, peanut-74%, fish-83%, soy-72%, wheat-75%; 75% of children reacted to milk at >100 mg [starting dose]; 89% of children reacted to egg at >100 mg [starting dose].
Blumchen et al, JACI, 2014[30]; Peanut; N=63	5.5 years (3.2-17.8)	50% reacted above 100 mg
Allen KJ, et al, JACI 2013[31]; Peanut, milk; N=400	Children and adults	Peanut: 60% react above 100 mg Milk: 70% react above 100 mg
Zhu J, et al, Food and Chemical Toxicology, 2015[32]; Peanut, N=257; Milk, N=167	Children	Peanut: 55% reacted above 100 mg Milk: 75% reacted above 100 mg

2) ***Ingestion of tolerated amounts of food, below a threshold of reaction, is generally safe and for those with high threshold peanut allergy, can be achieved using foods measured at home.*** The notion that allergens must be strictly avoided has come under scrutiny. In a series of studies conducted at Mount Sinai, children allergic to milk or egg but tolerant of baked forms were permitted to ingest these forms. The approach was noted to be safe, improved outcomes and is now a worldwide accepted approach.[12,13,17,19,33,34] In these trials, children who incorporated baked milk had improved growth and caregiver-reported improvement in the quality of life compared to those who could have but did not incorporate the food, highlighting additional benefits of introducing tolerated amounts of food allergens to the diet. Indeed, there are other examples where persons with a food allergy are "permitted" to ingest a potential allergen with specific stipulations. OIT, currently under study in phase III trials, is another example of a change in approach where ingestion of a known allergen is permitted. OIT consists of introduction of the food allergen starting from minimal doses, usually in the subjects with exquisite allergy who react to a cumulative dose of 143 mg food protein or less (i.e., react at the single 100 mg dose given during a PRACTALL OFC).[35-43] Following an initial dose escalation day, the dose of food is ingested daily and the treated subjects return every 2 weeks for dose escalations followed by a prolonged period of maintenance dosing.[21,44] OIT, although often beneficial, carries a known adverse effect profile, with about 20% unable to progress.[45] However, severe systemic reactions occur infrequently during OIT clinical trials; estimated rates of anaphylaxis are about 0.01% of all doses across various studies on peanut and milk OIT. Both severe and mild adverse events are more common during the initial dose escalation and in the early stages of build-up phase when dosing is being escalated from milligram doses every 2 weeks.[46,47] Therefore, patients with high threshold food allergy as defined previously are anticipated to experience fewer reactions from being allowed to ingest sub-threshold amounts of the allergen, as we intend to study. In a study of 39 children with peanut allergy undergoing OIT aiming for a 4 gram maintenance dose, 26 who successfully attained this dose continued long term ingestion with few adverse events and no withdrawals. [48] Their higher threshold therefore appears to be stable.

The concept that an individual has a threshold of reaction that is generally stable (repeated oral food challenge performed yearly do not vary widely spontaneously) is central to all studies of food allergy therapy (the oral food challenge threshold is the relied-upon endpoint). Specifically, in interventional studies, DBPCFCs are repeated at intervals to determine if the intervention is having an effect. Although there is a "placebo" effect of treatment, studies suggest that control groups do not vary significantly (it is unusual to see control participants vary from low threshold to high threshold). [39,46-49] In a recent peanut OIT trial, no participants in the control group (entry reaction <143 mg peanut protein) tolerated 600 mg on re-challenge.[50] In a recent trial of peanut EPIT, only 3/25 children in the placebo group changed their threshold from <500 mg to > 500 mg.[51] In a trial that was unusual in performing DBPCFCs just a few months apart, the procedures reproducibility was noted.[52] In the current study, participants randomized to ingest peanut will have a medically supervised ingestion of the amount to be ingested at home (separate from the study DBPCFC) to be sure it is tolerated.

Regarding the use of home measured and home purchased foods, our approach is akin to our prior baked milk/baked egg studies, where a tolerated amount of the food is permitted for feeding. Oral food challenges are performed with store bought foods (peanut flour, peanut butter, Bamba™, etc.) measured by teaspoon measures (1/8 etc.) as routine clinical practice.[8] Importantly, OIT studies have allowed home measurement of food once larger amounts are safely attained (data not shown, NCT01980992)[39] Various store bought peanut foods (peanut butter, Bamba™, peanut flour) have also been recommended for oral food challenge testing and prevention therapies.[8,53] Allowing persons to eat a food despite having reactions to higher amounts or with exercise is also accepted practice with regard to food-associated, exercise-induced anaphylaxis.[54,55]

3) ***Ingesting allergen may result in increasing the threshold (desensitization, temporary hypo-responsiveness***

dependent upon regular ingestion) and possibly, with time and increased quantities, maintaining a high threshold despite discontinued daily ingestion, termed sustained unresponsiveness, SU (indicating a health benefit of this approach). The success of OIT for the majority treated has intrinsically dispelled the notion that strict avoidance is the only option, but has also informed potential benefits of the approach we will test. In OIT, approximately 75% of the actively treated subjects become desensitized and reach the daily maintenance dose.[35-37,39,42,48,50] The reported rates of SU following OIT treatment are significantly lower, but are highest for those able to ingest larger doses daily for long periods of time, like those we are targeting for study.[39,48] Lower pre-OIT serum peanut-specific IgE antibody levels, more in line with levels we will see in this study, are associated with SU following peanut (and egg) OIT.[48,56-58]

In summary, there are millions of children with high threshold food allergy who are strictly avoiding foods; currently emerging therapeutics are not targeting these children. These individuals may be able to safely ingest sub-threshold amounts of allergen. The amounts they could ingest are easily measurable as "real food" at home just like these foods are used during OFCs in physician offices or used at home for prevention. Based on OIT studies and our baked milk/egg studies, allowing these children to ingest the amount of food that does not trigger reactions, and performing intermittent OFCs to determine if increasingly more food can be ingested without reactions, has a high chance to induce increasing desensitization and possibly SU. This dietary approach uses "regular food" and no medical products, making it practical and inexpensive. This study will carefully assess this approach to inform safety and outcomes for potential utilization by allergists. Studying the proposed approach with peanut will provide a prototype for studies of additional foods.

1.3. Preclinical Experience

Not applicable.

1.4. Clinical Studies

The reader is referred to studies mentioned above (section 1.2) regarding the number of peanut allergic individuals with high threshold allergy, the safety of ingestion of home-prepared foods, and the immunotherapeutic potential of ingestion exposure. There are two small case series exploring the notion of allowing children to ingest tolerated amounts of a food based upon the results of OFC. Garvey et al[59] permitted children with mild reaction to high doses of peanut to ingest 1 peanut at home daily, increasing while still at home to an amount under their OFC reaction threshold. After 6 months, 9/10 tolerated the OFC and 8/10 showed SU. Yanagida et al[60] described their clinical experience in Japan in which children undergo egg, milk or wheat OFCs by trying single dose challenges of increasing amounts several months apart and are allowed to ingest up to the amount they tolerated at home at each step (3 steps). Although the study (n=760) did not evaluate the benefit of ingesting a tolerated amount with regard to outcomes, they demonstrated safety of allowing the ingestion of subthreshold amounts measured at home with natural foods. We recently offered to allow 6 children who failed peanut oral food challenges at higher amounts to undertake lower dose ingestion under supervision on an IRB-approved observational protocol. The children, 2 male, 4 female (ages 2, 2, 3, 10, 12, 14 yrs), had mild symptoms (urticaria, abdominal pain, pruritus) on doses from 5/8th to 3 teaspoons of peanut flour/butter during OFCs. With informed consent, repeat oral food challenges to a lower dose were performed (single starting dose 1/8 teaspoon for 3, ¼ teaspoon for 2, 3/8 teaspoon for 1) and was tolerated. Periodic visits with OFC for higher amounts resulted over a mean follow up of 10 months with 5 on 3 teaspoons and one on 2 teaspoons without symptoms.

2. Study Hypotheses/Objectives

2.1. Hypotheses

Clinical hypothesis and research question

The research question we will address: Is there a benefit to allowing children with high threshold peanut allergy to ingest home measured amounts of peanut below their threshold, as compared to standard care avoidance?

We hypothesize that for persons with high threshold peanut allergy, ingesting sub-threshold amounts of the allergen (amounts not causing symptoms) will result in an ability to ingest higher amounts with time (desensitization) and potentially sustained unresponsiveness (SU).

We also hypothesize that the approach will be safe and improve quality of life compared to avoidance.

We base these hypotheses in part on observations from studies of OIT in low threshold subjects as described in 1.2 above.

Mechanistic hypothesis

We hypothesize that ingestion of sub-threshold amounts of peanut protein will be associated with peanut-specific immunomodulation, consistent with the development of desensitization and sustained unresponsiveness. Specifically, we hypothesize that ingestion of peanut will be associated with changes in peanut-specific humoral immunity, with a decrease in anaphylaxis-promoting IgE antibodies and an increase in blocking antibodies, and a modulation of the peanut-specific T cell response consistent with immune tolerance. We anticipate that individuals' potential for desensitization via the ingestion of subthreshold amounts of peanut protein will be detectable as early IgE and IgG4 epitope-specific and transcriptional signatures in peripheral blood, and that data-driven selection of these signatures will yield a clinically useful biomarker of desensitization potential. Further, these transcriptional signatures will elucidate functional pathways underlying desensitization success.

2.2. Primary Objective(s)

Primary clinical objective

The primary objective of this study is to determine whether allowing ingestion of sub-threshold amounts of peanut in subjects with a high threshold (those who tolerate at least 143 mg peanut protein on supervised double-blind, placebo-controlled oral food challenge [DBPCFC]) will be associated with attaining even higher thresholds over time compared to those avoiding peanut. Primary mechanistic objectives

The primary mechanistic objectives are to elucidate immune mechanisms induced by daily ingestion of sub-threshold amounts of peanut, and to identify biomarkers of and functional pathways underlying desensitization potential. We will test if peanut ingestion is associated with the following immune and transcriptomic processes:

- Suppression of serum peanut-specific IgE
- Increase in serum peanut-specific IgG and IgG4
- Change in peanut IgE and IgG4 epitope binding scores
- Decrease in basophil activation tests
- Decrease in peanut-specific multifunctional Th2 cells
- Increase in peanut-specific regulatory T cells
- Change in peripheral blood transcriptional signatures
- Up and downregulation of distinct gene ontology pathways

2.3. Secondary Objective(s)

Secondary clinical objectives

The secondary clinical objectives of this study are to determine whether ingesting sub-threshold amounts of peanut in children with high threshold peanut allergy, compared to avoidance, will:

A) Result in increased rates of sustained unresponsiveness.
B) Have positive effects on quality of life.
C) Be a safe approach.

Secondary mechanistic objectives
Secondary mechanistic objectives are to:

A) Determine if immune and transcriptomic measures obtained early in the course of ingestion exposure can predict development of desensitization or sustained unresponsiveness.
B) Identify immune and genomic biomarkers of the high threshold phenotype.
C) Identify early-appearing functional pathways underlying a successful desensitization course (exploratory).

3. Study Design

3.1. Description of Study Design

This is a prospective, two-arm parallel-group, randomized (1:1; 36 per group), controlled, open label trial of peanut ingestion and dose escalation (versus avoidance) in children age 4 to less than 15 years at enrollment who have high threshold peanut allergy (tolerate ≥143 mg but not 5043 mg cumulative peanut protein) based on DBPCFC. It is anticipated that approximately 150-200 subjects undergoing DBPCFCs will be needed to identify 72 participants for randomization.

3.1.1 Screening DBPCFC to determine threshold and identify subjects for randomization

Subject fulfilling inclusion/exclusion criteria will undergo an initial DBPCFC according to modified PRACTALL guidelines.[61] Dosing is 3 mg, 10 mg, 30 mg, 100 mg, 300 mg, 600 mg, 1000 mg, 3000 mg, 4000 mg peanut protein. The dosing interval is 20-30 minutes except the final dose, 4000 mg, will be given 60 minutes after the 3000 mg dose. This baseline DBPCFC will phenotype participants as having LT peanut allergy, HT peanut allergy or no peanut allergy (Figure 1). Blood samples will be obtained in association with screening DBPCFC for mechanistic studies associated with peanut allergy endotypes. Those tolerating 9043 mg (approximately 8 teaspoons of peanut butter or equivalent)will be permitted to add peanut to the diet.

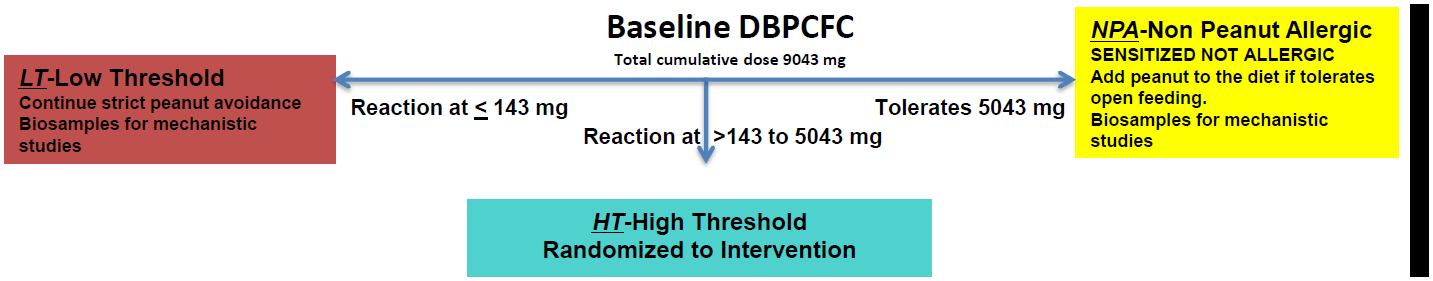

Figure 1. Initial screening DBPCFC to phenotype threshold, obtain biosamples, and identify those qualified for randomization.

3.1.2. Overview of trial scheme

Children with HT peanut allergy will be randomized to continue avoidance (control) or to ingest a home measured amount of peanut daily (intervention) based on their threshold. Subjects in the intervention group return to the research unit for re-challenge to increased amounts of peanut at 8 week intervals and are instructed to ingest the larger amount if tolerated. A repeat DBPCFC will be performed 8 weeks after reaching 1 tablespoon (or equivalent) in the intervention group, or at 72 weeks. A repeat DBPCFC will be performed in the control group at a time calculated according to a surveillance algorithm to ensure similar lengths between initial and desensitization DPBCFC between the two groups (see Section 13.3). Subjects in the intervention arm tolerating the full challenge amount will add peanut to the diet for 16 weeks and then avoid peanut for 8 weeks, followed by a DBPCFC to assess for sustained unresponsiveness [SU] (ability to consume without reaction after a period of avoidance). The study scheme is shown in Figure 2.

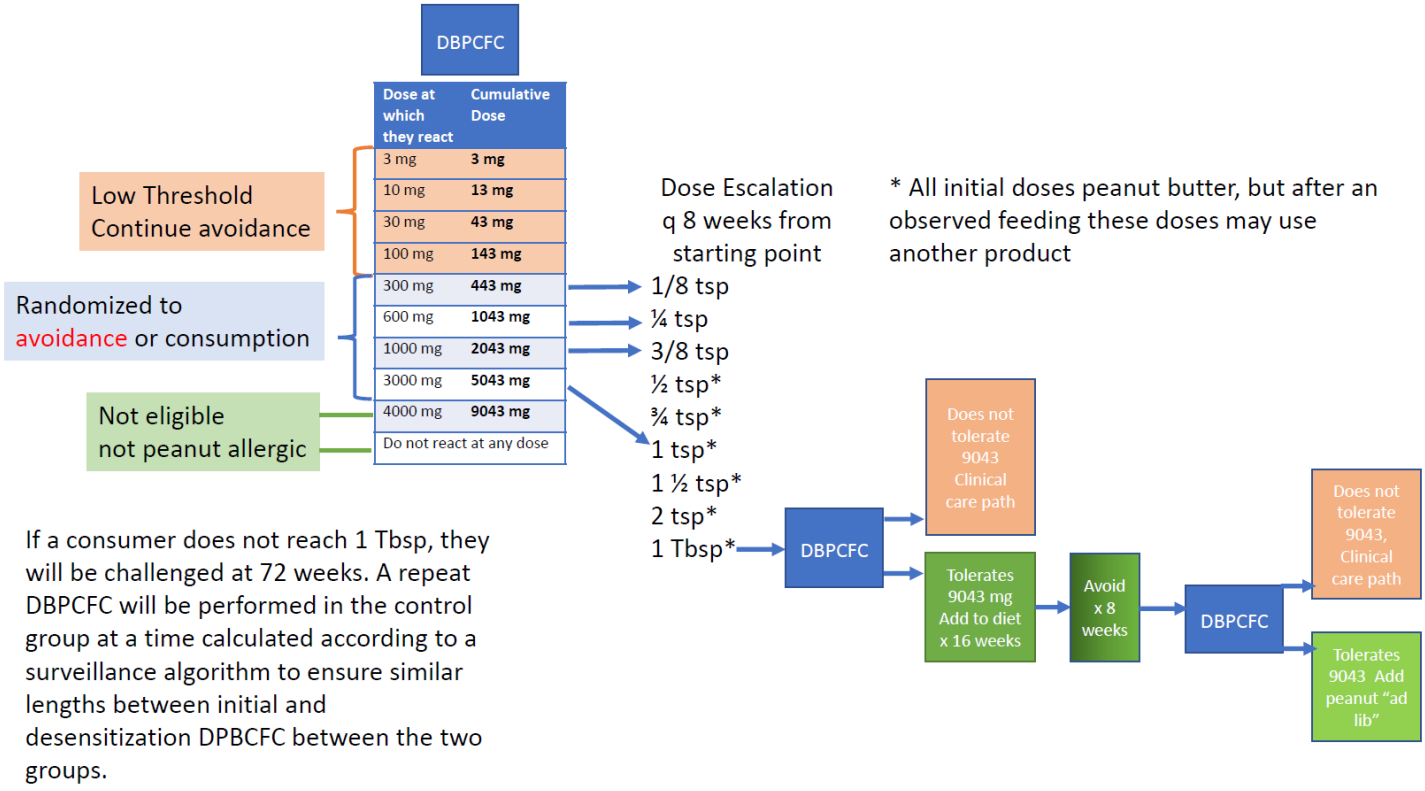

Figure 2. Randomized Intervention Study scheme

3.1.3 Intervention Arm Procedures

Children randomized to the active arm will return for an observed administration of the highest amount of peanut they should tolerate with no or minimal (oral) symptoms based on their baseline DBPCFC. The starting amount of peanut butter will be 1/8th teaspoon [approximately 140 mg peanut protein] if they reacted at 443 mg cumulative dose on DBPCFC, ¼ teaspoon [approximately 280 mg peanut protein], if they reacted at 1043 mg cumulative dose on DBPCFC, 3/8 teaspoon [approximately 430 mg peanut protein] for a reaction at 2043 mg cumulative dose) or 1 teaspoon [approximately 1140 mg] for a reaction at 5043 mg cumulative dose. To continue on daily peanut, the 1/8th teaspoon supervised feeding post food challenge must be tolerated. Study participants/families will be given detailed instructions

specifying the types and amounts of the commercial foods allowed for home ingestion. They also will be required to strictly avoid the food allergen other than the amount under the study. They will return every 8 weeks to attempt a supervised feeding of the next higher amount, as shown in **Figure 2**. If successfully consumed, they will continue the one step higher amount daily. When participants have exceeded 3/8 teaspoon of peanut butter, alternative forms (Bamba™, candies)[62,63] can be substituted but such substitutions will be performed as observed feedings. (Table available in the MOP.) If subjects have symptoms at 1/8 teaspoon peanut butter during the study, they will be permitted to trial 1/16th teaspoon under observed feeding, but this will be the lowest amount allowed in the study.

3.1.4 Control Arm Procedures

Children randomized to the control arm will follow standard care of strict avoidance of peanut. They will have a repeat DBPCFC to peanut at a time determined by a surveillance algorithm as described in Section 13.3, to match the distribution of DBPCFC to those of the intervention group. Based on the outcome of the DBPCFC, they will either be considered no longer allergic (naturally tolerant, NT) if they tolerate the full dose of the challenge (9043 mg) or will continue strict avoidance under clinical care off of the study.

3.1.5 Desensitization DBPCFC in intervention arm

(a) Children in the active arm who react at or below the full dose of 9043 mg peanut protein on the second DBPCFC will be considered not fully desensitized and will pursue clinical care off of the study.

(b) Children in the active arm, who are able to ingest the full dose of the DBPCFC (9043 mg) will be considered fully desensitized and will go to a more open diet, with no upper limit to the amount they may eat, but they must eat at least one serving (equivalent of approximately 2 tablespoons or approximately 6800 mg) of peanut per week for 16 weeks.

3.1.6 Sustained unresponsiveness (SU) DBPCFC (Intervention group)

To determine SU, children in the active arm after 16 weeks of the open diet described in 3.1.5, will strictly avoid peanut for 8 weeks followed by the repeated SU DBPCFC to the full dose of peanut. Those who tolerated the full dose of peanut (9043 mg) after the 8 weeks of strict avoidance will be considered to have achieved SU (**TS-SU**) and will add peanut to their diet without restrictions other than the recommendation that they continue to have at least one serving every week and will pursue clinical care off of the study. Those who react at the SU OFC following the 8-week avoidance period will be considered desensitized but not achieving SU (**TS-D**) and will be followed clinically off study.

3.1.7 Study timelines

Participation for individual subjects is up to 120 weeks.

3.2. Primary Endpoint(s)/Outcome(s)

3.2.1 Primary Clinical Endpoints

The difference between the treatment and comparison (avoidance) groups in the percentage of children who by the desensitization endpoint DBPCFC tolerate a dose at least 2 steps higher than their baseline DBPCFC or the full dose (9043 mg) of peanut protein.

3.2.2 Primary Mechanistic Endpoints

1. Change in peanut and Ara h 2-specific IgE from baseline as measured by ImmunoCAP assay
2. Change in peanut and Ara h 2-specific IgG4 from baseline as measured by ImmunoCAP assay
3. Change in peanut epitope-specific IgE and IgG4 binding score from baseline
4. Change in basophil activation from baseline, as measured by %CD63+ basophil by flow cytometry/mass cytometry
5. Change in frequency of peanut-specific Th2 cells, as measured by CD154 and cytokine co-expression after in vitro stimulation with peanut.
6. Change in frequency of peanut-specific T cells expressing CD137 and regulatory markers or producing IL-10 after in vitro stimulation with peanut.
7. Change in peripheral blood transcriptional signature.

3.3. Secondary Endpoint(s)/Outcome(s)

3.3.1 Secondary Clinical Endpoints

1. The percentage of children who achieve SU or natural tolerance during the study.

2. Safety parameters (acute allergic reactions, including anaphylaxis, gastrointestinal side effects).

3. Quality of life (QOL) measures (the QOL instrument will not administered to participants who do not speak English because it is not validated in languages other than English).

4. SPT mean wheal size changes.

3.3.2 Secondary Mechanistic Endpoints

1. Immune and transcriptomic measures obtained early in the course of ingestion exposure that predict development of desensitization or sustained unresponsiveness.

2. Immune and genomic biomarkers of the high threshold phenotype.
3. (**Exploratory**) Early-appearing functional pathways underlying a successful desensitization course.

3.4.1. **Additional samples for future/ancillary studies**.

Saliva and stool samples will be collected at specified visits (see Table 2) and stored for anticipated microbiome studies.

3.4. Stratification, Randomization, and Blinding/Masking

This is a prospective two-arm parallel-group, randomized (1:1) controlled open trial. The data and statistical coordinating center (DSCC) will maintain control of stratification and randomization, described in Section 13.3.

Neither the children nor the investigators will be blinded to randomization assignment. The study staff conducting the DBPCFCs, however, will be blinded to the participant randomization status.

3.4.1. Procedure for Unblinding/Unmasking

Not applicable.

4. Selection of Participants and Clinical Sites/Laboratories

4.1. Rationale for Study Population

The screening eligibility for the study population are those age 4-14 years strictly avoiding peanut and having a history of sensitization (detectable peanut IgE >0.35 kUA/L). These children must also be generally healthy and able to undergo study procedures (see Section 4.3).

Children with peanut IgE levels over 50 kU_A/L are excluded because it is unlikely they will be high threshold.[64] The study inclusion criteria are those with high threshold peanut allergy who are likely to safely ingest sub-threshold amounts of peanut and may benefit by doing so as described in Section 1 of this Protocol. Those with high threshold peanut allergy have no current therapeutic or standard of care options other than avoidance and allowing ingestion of subthreshold amounts of peanut for this population has not been studied and equipoise exists.

The age range of 4 through age 14 years was chosen because there is less chance of spontaneous resolution compared to younger peanut-allergic children[65-67], the home-measured amounts and foods would not be significantly varied on a per kg basis compared to including infants or older teenagers, subjective side effects would be easier to monitor with verbal participants (itchy mouth), and adherence may be maximized compared to including older adolescents or adults.[41,68]

4.2. Inclusion Criteria

Individuals who meet all of the following criteria are eligible for enrollment as study participants:

1. Subject and/or parent guardian must be able to understand and provide informed consent.
2. Inclusion criteria for screening DBPCFC: Age 4-14 years, either sex, any race, any ethnicity who are enrolled while strictly avoiding peanut and have a history of sensitization (detectable peanut IgE >0.35 kUA/L).
3. Inclusion criteria for randomization (post screening): On screening DBPCFC are able to ingest >=143 mg peanut protein but <5043 mg peanut protein.

4.3. Exclusion Criteria

Individuals who meet any of these criteria are not eligible for enrollment as study participants: *[Suggested line items are included in italics; modify, add or remove as needed; line items #1, 10 and 11 should be included without modification]*

1. Inability or unwillingness of a participant to give written informed consent or comply with study protocol
2. Serum peanut-specific IgE antibody level > 50 kUA/L
3. Recent (within the past 2 years) life-threatening (grade 3) anaphylactic reaction to peanut.
4. Any disorder in which epinephrine is contraindicated such as known hypertension or cardia rhythm disorders.
5. History of chronic disease requiring therapy (other than asthma, atopic dermatitis, rhinitis).
6. On a build-up phase of any allergen immunotherapy.

7. For those with a history of asthma, the following are assessed and any of the following is an exclusion (markers of current uncontrolled or moderate to severe asthma):

   A. FEV1 value <80% predicted (only for participants age 7 years or older and are able to perform spirometry*).
   B. ACT or cACT < 20
   C. >Step 3 controller therapy as defined for children 0-4, 5-11 and >=12 years of age by EPR-3 tables
   D. Use of steroid medications in the following manners:
      a. history of daily oral steroid dosing for >1 month during the past year,
      b. having 1 burst or steroid course within the past 6 months, or
      c. having >1 burst oral steroid course within the past 12 months.
   E. Asthma requiring >1 hospitalization in the past year for asthma or >1 ED visit in the past 6 months for asthma, or any prior intubation/mechanical ventilation for asthma/wheezing.
   F. *When COVID related institutional restrictions on spirometry are in effect, spirometry will be not performed and peak flow will be used with 80% predicted as the cut-off.

8. Gastrointestinal eosinophilic disorders, esophagitis, gastroenteritis.
9. Use of short-acting antihistamines (diphenhydramine, etc.) more than one time within 3 days prior to DBPCFC or skin testing.*
10. Use of medium-acting antihistamines (hydroxyzine, loratadine, etc.) more than one time within 7 days of DBPCFC or skin testing.*
11. Use of systemic steroid medications (IV, IM or oral) for indications other than asthma for > 3 weeks within the past 6 months
12. Use of beta-blockers (oral), (ACE) inhibitors, angiotensin-receptor blockers or calcium channel blockers.
13. Participation in any trials of therapeutic interventions for food allergy in the past year.
14. Therapy with anti-IgE or other biologics, including within 1 year of enrollment.
15. Use of investigational drugs within 52 weeks of participation.
16. Allergy to all of the following: oat, rice, corn, tapioca.
17. Pregnancy
18. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.

*Any subject meeting these criteria during the visits can be rescheduled for the oral food challenge or prick skin testing.

4.4. Selection of Clinical Sites/Labs

The study will be performed at the Icahn School of Medicine, Mount Sinai, NY, NY. Based on our clinical experience with patient inquiries regarding threshold food challenges (to determine the degree of allergy) and overall high level of interest in approaches enhancing desensitization and tolerance, we anticipate that the proposed approach will be extremely attractive to the food-allergic children and their caregivers. This study offers all potential participants an insight into their degree of sensitivity to peanut, thereby providing a uniform benefit. The enrollment criteria may represent the majority of children presenting to allergy practices with peanut allergy, and at Mount Sinai we evaluate over 6500 children with food allergies each year, about half with peanut allergy. We also have >4000 families registered for our research newsletter, demonstrating the large base of interested, potential participants. We assume this study,

like many of our others, will require a lottery system to choose potential participants because of the attractiveness of the study. We are not aware of any other trials with a similar approach that would compete. Regarding retention, with our experienced, multi-disciplinary staff, we are able to establish trusting relationships with our subjects and their family members and ensure open lines of communication at every stage. In addition, we have developed a variety of other novel approaches to further enhance retention in our clinical trials, including newsletters, periodic "rewards" (e.g. stickers, birthday cards, or milestone achievement awards), and involving child life services to make study visits a positive experience for our pediatric subjects. The timing of the tests is not intrusive, and the various controls would likely be having allergy tests yearly for clinical purposes. We already have protocols for food challenges and have successfully undertaken the general aspects needed for this study (sample acquisition and processing, monitoring, study procedure forms, dosing, etc.) in many other studies.

5 Known and Potential Risks and Benefits to Participants

5.1 Risks of Investigational Product or Intervention as cited in Investigator Brochure or Package Insert

The investigational product is a food commercially available at retail stores so there is no package insert. Because the protocol will be conducted at one site there is no investigator's brochure (see also Section 6.1).

5.2 Risks of Investigational Product or Intervention cited in Medical Literature

For several foods, allowing ingestion of tolerated amounts that could trigger reactions in circumstances of higher ingestion amounts or different forms is already accepted practice (e.g., baked milk in milk allergy, baked egg in egg allergy, heated cheese in milk allergy, wheat in tolerated quantities or without exercise in wheat allergy/food-associated exercise induced anaphylaxis, various foods causing food-associated exercise-induced anaphylaxis).[13,54,55] Recent studies suggest the safety of this approach (children permitted to ingest subthreshold amounts based on OFC).[59,60]

The risk of ingestion of allergen (DBPCFC and home ingestion). The potential risks are those associated with allergen ingestion, including those observed in food challenges[8,69] Oral food challenges (gradual feeding of the allergic food, or providing an amount somewhat higher than previously tolerated) are performed to determine if the food allergy exists or has resolved and to determine the threshold dose at which symptoms of an immediate allergic reaction appear. Symptoms can include itchy skin rash (urticaria, flare of atopic dermatitis, angioedema), nausea, stomach pain, vomiting, and/or diarrhea, rhinitis (stuffy "runny" nose and sneezing) and/or wheezing. The major risks involved include severe breathing difficulties and rarely a drop in blood pressure. There is a single reported fatality. To date, the investigators have performed more than 30,000 oral food challenges without a serious life-threatening anaphylactic reaction. The procedure is performed under direct medical supervision according to guidelines and dosing is stopped for persistent subjective or objective symptoms.[61] The procedure is performed with full treatment available, as per guidelines.[70] Details of the DBPCFC procedure (preparation, dosing, stopping, observations times, etc.), are detailed in the Manual of Procedures.

Home ingestion of an allergenic food that has been ingested safely under supervision during food challenges could cause an allergic response, although it is standard of care to permit ingestion of a food after an observed "negative" OFC.[69] Allowing ingestion of a tolerated amount that is below a known threshold is the novel aspect of this intervention (although there are examples of doing so as stated above). Extrapolating potential risks from studies of peanut oral immunotherapy to the current intervention may not be applicable for the following reasons: 1) peanut OIT studies target low threshold peanut allergic children who may be more reactive than the current study population; 2) OIT

regimens induce desensitization purposefully in an escalation phase rather than providing ingestion amounts known to be tolerated at presentation, and 3) permit dosing despite chronic symptoms. If extrapolation is accepted nonetheless, then the intervention (allowance of home ingestion of a tolerated amount) could be considered similar to the "maintenance phase" of peanut OIT. Most reactions to peanut OIT occur in the "escalation" or "build-up" phases.[46,47] However, anaphylaxis rates are 0.01% across studies.[46,47] In a representative study,[71] the risk of dosing symptoms to peanut was 93% during the escalation day, 46% during build-up, but only 3.5% for final home dosing. Most of those symptoms were upper respiratory (1.2%), skin (1.1%) and abdominal (0.9%) with 0.3% affecting the chest (mild in 0.2%, moderate in 0.06%, none severe). These observations speak to the stability of a threshold even for those with a low peanut allergy threshold.

Having food allergy is a risk for eosinophilic esophagitis (EoE)[72] and ingestion of ostensibly tolerated foods (i.e., no acute reaction) can be a trigger (most common triggers are milk and wheat). The risk that OIT can trigger EoE has been estimated at up to 2.7%.[73] This risk will also be communicated to potential participants. Participants will be monitored for new onset of persistent gastrointestinal symptoms and or weight loss and if EoE is suspected they will be instructed to discuss this with their allergist or pediatrician for potential referral to a pediatric gastroenterologist for evaluation outside of the study, if necessary. Therapy will be stopped in case of new onset EoE; pre-existing EoE is an exclusion criterion.

To minimize risk of allergic reaction to home ingested peanut, specific instructions are provided, e.g., eating the measured amount of peanut at the same time of the day following or with a full meal, avoidance of exercise for 2 hours following ingestion and temporary suspension of eating peanut during febrile illness, gastroenteritis or asthma exacerbation, which are known factors that may precipitate reactions to previously tolerated amounts.[74] Guidance is also provided regarding products and their measurement (details in the MOP). Participants will be advised on purchasing any of a number of commercially available peanut butters; these have remarkably similar peanut protein characteristics.[62] Participants will receive close monitoring regarding any allergic reactions (telephone follow-up and monitoring of any symptoms). We do not anticipate severe symptoms to suddenly appear without warning. Written emergency plans will be provided which include instructions on initial emergency treatment and calling 911 in the event of an acute allergic reaction. Subjects will be prescribed epinephrine autoinjectors and trained in their use.

5.3 Risks of Other Protocol Specified Medications

Not applicable.

5.4 Risks of Study Procedures

Blood draw: Blood drawing may aggravate a pre-existing anemic condition, but this risk is negligible since blood is drawn per NIH guidelines (not to exceed 5cc/kg on a single day or 9.5ml/kg over any eight-week period). Other risks are those attendant to any needle puncture, including slight bruising, local infection, or the possibility of the subject fainting. The discomfort involved is minimal.

Prick skin test: Skin prick tests will be performed utilizing the bifurcated nedle; this will cause minimal discomfort (the sensation of a prick and a pruritic, transient hive may result). Such tests could theoretically induce a systemic allergic reaction, but this is exceedingly rare (<.01%).[75]

Questionnaires: Parents will complete demographic surveys, diaries, diet questionnaires, and quality of life questionnaire (FAQOL-PB[76]). There should be no significant risk. Privacy wil be guarded through locking paper files and having password protected databases with protection of personal health information.

Collection of saliva and stool: These samples will be collected and stored (see Table 2) for anticipated ancillary microbiome studies. No risks are anticipated.

5.5 Potential Benefits

There may be no benefit to participating. The typical instructions are allergen avoidance, which should pose no added risk of a reaction to the control group. There may be a benefit to society to understand if children with peanut allergy, able to tolerate home-measured, home-purchased amounts of peanut below an amount that causes symptoms, are better for doing so compared to those following avoidance.

The benefits of undergoing a DBPCFC to peanut can include understanding the threshold of reactivity, determining that there is low threshold allergy which may allow referral for emerging/available treatment options, or identification of tolerance to peanut with allowing dietary inclusion of peanut.

The benefits of the intervention may include: 1) Increased threshold of ingestion (able to eat a larger amount without symptoms than before) after a time eating a tolerated amount of the food, 2) ability to eat full servings of peanut even after not having a daily amount for a period of 2 months, 3) better quality of life.

Mechanistic (laboratory) studies associated with this clinical trial will provide information on:

1. Mechanisms of (A) high threshold reactions; (B) development of desensitization in response to sub-threshold peanut ingestion; (C) development of sustained unresponsiveness in response to sub-threshold peanut ingestion;
2. Predictive biomarkers of response to dietary treatment.

These mechanistic outcomes will allow for personalized treatment approaches and will identify novel pathways for refinement of treatment strategies.

6 Investigational Agent /Device/Intervention

6.1 Investigational Agents/Devices/Interventions

The intervention allows ingestion of home-purchased, home-measured amounts of peanut (initially in the form of peanut butter). The instructions and measurements (e.g., 1/8 teaspoon peanut butter, 8 pieces of Bamba™, etc.) are similar to guidelines used for office-based food challenges and parental instructions for home feeding of peanut for prevention of peanut allergy, even for infants.[8,53]

Although there is no formal standardization of the peanut products that children will eat at home, several strategies have been employed to address this issue:

1. Parents will be provided with informational sheets describing the amounts to give and the foods they could purchase, including pictures.
2. For teaspoon measurements, parents will be given a set of spoons and will be instructed and observed (teaching) in their use for proper measurement.
3. Peanut butter, which is easily obtainable, measured, and can be mixed easily into foods the child enjoys will be a preferred product and used at least until the 1/2 teaspoon of peanut butter is the amount given. Transition to alternative products (peanut, Bamba, various candies) will be done under a supervised feeding.
4. Although there is some variation in home measured amounts (this also applies to office-based oral food challenges that use a variety of peanut products), the observed feeding of the amount and product that will be

given at home will use the highest amount measured by an analytical scale as tested during piloting the use of kitchen spoons (result of 10 measures each).

6.1.1 Investigational Agent #1

Not applicable, see 6.1.

6.1.1.1 Formulation, Packaging, and Labeling

NA

6.1.1.2 Dosage, Preparation, and Administration

NA

6.1.2 Investigational Agent #2

NA

6.1.2.1 Formulation, Packaging, and Labeling

6.1.2.2 Dosage, Preparation, and Administration

6.2 Drug Accountability

Not applicable

6.3 Assessment of Participant Compliance with Investigational Agent

All participants will be instructed to avoid peanut, except for the subthreshold amount allowed for ingestion by those randomized to the intervention. Symptom diaries will be monitored and all allergic reactions reported. Serum peanut-specific IgG will be measured as a potential marker of exposure which will be queried further if noted in the avoidance arm (i.e., drop-in to intervention).

6.4 Toxicity Prevention and Management

Not applicable

6.5 Premature Discontinuation of Investigational Agent

Study therapy may be prematurely discontinued for any participant for any of the following reasons:

- Severe (grade 3) anaphylaxis secondary to any DBPCFC or ingestion of the measured dose of peanut.
- Significant worsening or persistent activation of atopic dermatitis, allergic rhinitis or asthma believed to be related to participation in the study.
- Any subject deemed to have severe allergic and/or GI symptoms and receiving aggressive therapy.
- Inability or unwillingness to comply with study procedures (re-education can be provided at the discretion of the PI/Co-I to allow continuation) as evidenced by subject:
    - Excessively missed days of PB ingestion; i.e., > 7 consecutive days missed on 3 occasions.
    - fails to report if they have more than mild symptoms;
    - does not ingest the designated amount of peanut for over 10 consecutive days;
    - attempts to increase amounts without supervision; or
    - experiences symptoms that the PI/Co-I considers warrant withdrawal from ingestion

Study therapy may also be prematurely discontinued for any participant if the investigator believes that the study treatment is no longer in the best interest of the participant.

Those discontinuing peanut for the above reasons will continue with other study procedures (e.g., monthly calls, AE monitoring, SU DBPCFC).

7 Other Medications

7.1 Concomitant Medications

All subjects may continue their usual medications, including those taken for asthma, allergic rhinitis and atopic dermatitis, during the study. They must, however, be able to discontinue antihistamines prior to skin testing and OFCs. Regular topical steroids use is permitted at the time of skin testing.

7.1.1 Protocol-mandated concomitant medications

Participants must have been prescribed epinephrine autoinjectors, see 7.4.

7.1.2 Other permitted concomitant medications

Not applicable.

7.2 Prophylactic Medications

Participants may receive routine vaccines during the study.

7.3 Prohibited Medications

Treatment with biologic therapies will not be allowed during the participation in this study. Other therapeutic interventions for food allergy (e.g. desensitization protocols) will not be allowed. Medications that interfere with treatment of allergic reactions are not allowed (see Exclusion Criteria).

7.4 Rescue Medications

Treatment of individual allergic reactions should be with either an H1 and/or H2 antihistamine and/or epinephrine, along with IV fluids, albuterol and steroids as indicated. Subjects and parents will be trained in proper use of an epinephrine autoinjector and will be able to demonstrate proper technique.

8 Study Procedures

8.1 Enrollment

The research study will be explained in lay terms to each potential research participant. The potential participant will sign an informed consent form before undergoing any study procedures. Once the consent form is signed, the participant will be considered enrolled and will be assigned a unique participant number.

8.2 Screening/Baseline Visit

The purpose of the screening period is to confirm eligibility to continue in the study. The procedures involved in the screening/baseline visit will determine if the participant can be randomized to the study intervention or will be characterized as low threshold (LT) peanut allergy or not peanut allergic (NPA). Those who are LT or NPA will participate for mechanistic studies but will not continue to the randomized trial.

The following procedures, assessments, and laboratory measures (windows for sample collection are detailed in the MOP as applicable) will be conducted, some of which to determine participant eligibility for the randomized trial:

- Physical exam, vital signs, complete medical history
- Spirometry (or peak flow under age 7 or if spirometry not allowed per COVID protocols)
- DBPCFC to peanut per modified PRACTALL (and associated examinations)
- Skin prick test to peanut
- Blood samples (before DBPCFC commences and 2 and 4 hours after starting; not to exceed 5cc/kg on a single day or 9.5ml/kg over any eight-week period per NIH guidelines). A saline lock may be placed to facilitate blood sampling at this and other visits where periodic samples are obtained.
- Quality of life survey, diet questionnaire, demographics
- Urine pregnancy if child bearing potential
- Saliva and stool collection

Screening takes place over 3 days (with one DBPCFC per day for 2 days). Each day is 4-8 hours.

If a participant reacts during the placebo arm of a DBPCFC, the DBPCFC may be repeated once. If a determination of reaction cannot be made due to unwillingness to repeat the DBPCFC or repeated placebo reactions, participation will end and any associated data will not be included in the analyses.

8.3 Study Visits or Study Assessments

Intervention Arm

For those with high threshold peanut allergy randomized to ingestion.

Participants in the intervention arm will receive monthly telephone follow up (unless they have a visit on that month) and reporting of any allergic reactions, including reporting accidental exposure to peanut, and will keep a diary. The diary will be accessed for the following issues: missed dose, ate peanut outside of the study dose, and any reaction, symptoms or illnesses. These will be confirmed/reviewed monthly by telephone, email (printout as source) or in person visit to evaluate that the entries match what the experience is. This will be documented on an eCRF (or email print out) and the clinical team will add any diary entries if needed.

Visit 1. Initial feeding challenge with subthreshold amount of peanut (visit length 2-3 hours)

- Physical exam, vital signs, medical history
- Spirometry (or peak flow under age 7, or if spirometry not allowed per COVID protocols)
- Open oral food challenge to amount determined by DBPCFC (Section 3.1.3) to confirm tolerance of threshold (if failed, can return for repeated Visit 1 with next lower dose if not already at 1/8 teaspoon).
- Training on measuring amounts for home use
- Provision of diaries and contact instructions

Escalation Visits (3-8 visits depending upon starting point and progress)

Visits 2 (week 8), 3 (week 16), 4 (week 24), 5 (week 32), 6 (week 40), 7(week 48), 8 (week 56), 9 (week 64) for increasing amounts of peanut (visit length 2-3 hours). These visits stop at week 64 or when 1 Tablespoon (equivalent) is reached.

Attempt to increase daily ingestion by open oral food challenge to next amount higher. Maximum amount is 3 teaspoons/equivalent.

- Physical exam, vital signs, medical history
- Blood samples, Visit 3, week 16 (before feeding challenge commences; not to exceed 5cc/kg on a single day or 9.5ml/kg over any eight-week period per NIH guidelines)
- Spirometry or peak flow (optional under age 7)
- Open oral food challenge to amount determined by DBPCFC (Section 3.1.3) unless at top amount
- Training/review on measuring amounts for home use
- Collection/Provision of diaries and contact instructions
- Saliva and stool collection (visit 3)
- Quality of life survey, diet questionnaire (visit 3)

Desensitization DBPCFC visit, (week 72 or 8 weeks after reaching 1 Tablespoon or equivalent. Visit length 4-8 hours each of 2 days.

- Physical exam, vital signs, medical history
- Blood samples (before feeding challenge commences and 2 and 4 hours after starting; not to exceed 5cc/kg on a single day or 9.5ml/kg over any eight-week period per NIH guidelines)
- Spirometry or peak flow (optional under age 7)
- DBPCFC to peanut per modified PRACTALL (and associated examinations)
- Skin prick test to peanut
- Quality of life survey, diet questionnaire
- Urine pregnancy if child bearing potential
- Saliva and stool collection

This is the end of study visit for those not tolerating the DBPCFC and they will transfer to clinical management off of the study. Those tolerating the DBPCFC will proceed to the SU visit.

Additional visits for evaluation of Sustained Unresponsiveness in Intervention Arm

Sustained unresponsiveness visit for DBPCFC following 16 weeks of "ad lib" peanut (no upper limit but at least 2 Tablespoons peanut butter or equivalent per week) and then 8 weeks peanut avoidance following the desensitization DBPCFC (visit length 4-8 hours each of 2 days).

If the desensitization DBPCFC is passed , the subject will be instructed to incorporate peanut into the diet for 16 weeks. If this is tolerated, peanut will then be avoided for 8 weeks at which time the following procedure will be performed:

- Physical exam, vital signs, medical history
- Blood samples (before feeding challenge commences and 2 and 4 hours after starting ; not to exceed 5cc/kg on a single day or 9.5ml/kg over any eight-week period per NIH guidelines)
- Spirometry (or peak flow under age 7, or if spirometry not allowed per COVID protocols)
- DBPCFC to peanut per modified PRACTALL (and associated examinations)
- Skin Prick Test to peanut
- Saliva and stool collection
- Urine pregnancy if child bearing potential
- Diet questionnaire, Quality of life survey

If this DBPCFC is tolerated, the subject will eat peanut "ad lib" but with at least one weekly serving recommended (serving is about 2 Tablespoons peanut butter or equivalent). If this DBPCFC is not tolerated, the subject will undertake clinical management off of the study.

Control Arm

Participants in the control arm will receive monthly telephone follow up and reporting of any allergic reactions, including reporting accidental exposure to peanut, and will keep a diary. The diary will be accessed for the following issues: ate peanut, and any reaction, symptoms or illnesses. These will be confirmed/reviewed monthly by telephone, email (printout as source) or in person visit to evaluate that the entries match what the experience is. This will be documented on an eCRF (or email print out) and the clinical team will add any diary entries if needed. They will have a visit 16 weeks following the initial DBPCFC for review of avoidance instructions and collection of a blood sample, saliva and stool for mechanistic studies, and QoL and diet questionnaires. The control arm subjects will undergo a DBPCFC and procedures listed under desensitization DBPCFC (above) are performed at a time determined by a surveillance algorithm (see Section 13.3). Control arm participants do not require follow up for SU. Those unable to tolerate the DBPCFC will pursue clinical management off of the study, those who tolerate the full feeding may add peanut to the diet "ad lib" but with at least one weekly serving recommended and pursue clinical care off of the study.

8.4 Unscheduled Visits

If disease activity increases or other concerns arise between regularly scheduled visits, participants will be instructed to contact study personnel and may be asked to return to the study site for an "unscheduled" visit. If the participant becomes/is unable to ingest at least 1/8 teaspoon of peanut butter, they will undergo a supervised feeding of $1/16^{th}$ teaspoon, which is the lowest amount permitted and may become the daily amount if tolerated. If the participant cannot ingest $1/16^{th}$ teaspoon of peanut butter they will be considered a treatment failure and will stop any daily ingestion, but will undergo the endpoint DBPCFCs at 72 weeks.

The following circumstances may lead to unscheduled visits (active arm):

1. Concern regarding peanut ingestion triggering increased chronic symptoms (e.g., increased eczema, gastrointestinal symptoms).

Procedures (1-8 hour visit):

- Physical exam, vital signs, medical history
- Spirometry (or peak flow under age 7, or if spirometry not allowed per COVID protocols)
- DBPCFC to the amount being ingested on a daily basis, or supervised open feeding of the amount ingested on a daily basis, or supervised feeding of a lower amount, as deemed necessary for full evaluation

The PI/Investigator and family will determine whether to continue daily ingestion, reduce the daily amount, or follow off intervention, and/or refer for additional medical evaluation (i.e., endoscopy).

2. Concern regarding acute symptoms from home ingestion.

Participants will be instructed to contact the PI/Investigator/study team for acute allergic symptoms (with the exception of oral pruritus, mild transient abdominal discomfort, or perioral redness/hives). The investigator will determine the best course of action, with possible actions being the following:

1. Continue with daily home dosing
2. Return for an observed ingestion of the same amount
3. Return for an observed ingestion of a step lower amount.
4. Discontinuation of ingestion

The following process algorithm will be applied regarding symptoms associated with the daily ingestion.

If the subject only experiences oral/pharyngeal pruritus, or perioral redness/hives, or mild transient abdominal discomfort, the daily ingestion may continue. Instructions about eating peanut with meals will be reviewed. If the symptoms are bothersome or persistent, procedures per #1 above (chronic symptoms) will be followed.

If the subject experiences *mild symptoms*, defined as:

- Skin – non-perioral hives/swelling, skin flushing or pruritus
- Respiratory – rhinorrhea/sneezing, nasal congestion, occasional cough, throat discomfort
- GI – abdominal pain that is more than mild transient/minor episode of vomit

The action should be either to repeat the daily amount at home, or a reduced amount, or to have the subject return to the site for a repeat of the ingested amount or to trial a step lower amount (at the physician's discretion). If the amount is tolerated, then the subject will continue on that amount until the next scheduled visit. If the ingestion again causes mild symptoms, then the subject may return to the site to trial a lower amount, as possible.

If the subject experiences *moderate symptoms*, defined as:

- Skin – systemic hives/swelling
- Respiratory – throat tightness without hoarseness, persistent cough, wheezing without dyspnea
- GI – persistent moderate abdominal pain/cramping/nausea, increased vomiting

The action should be to have the subject return to trial a lower amount, as possible and with physician discretion. If this amount is tolerated, it will be continued as the daily home ingestion amount until the next scheduled visit. If the amount is not tolerated, then a discussion with the Study PI or Co-PI will ensue to make a decision about whether to continue the subject on active ingestion in the study.

If the subject experiences *severe symptoms*, defined as:

- Respiratory – laryngeal edema, throat tightness with hoarseness, wheezing with dyspnea
- GI – significant severe abdominal pain/cramping/repetitive vomiting
- Neurological – change in mental status
- Circulatory – hypotension

The action should be to treat the subject, and at the physician's discretion either 1) have them return to the site for trial of a 2 step lower (at least) amount under observation or 2) discontinue them from the active arm. If the subject tolerates the reduction, then they will remain on that amount until the next scheduled visit. A discussion with the Study PI or Co-PI may ensue to make a decision about whether to continue the subject on active treatment in the study.

For a completed ingestion visit with no symptoms, subjects should be observed for 30 minutes. For mild symptoms, subjects should have a 1-2 hours post ingestion observation period. For moderate to severe

symptoms, the observation period should be at least 4 hours and up to 24 hours based on symptoms and treatment regimen needed to stabilize.

3. Excessive days without ingestion of peanut.

Participants will be instructed to skip days ingesting peanut for illness. However, if more than 5 consecutive days are missed, at the discretion of the PI, a visit for observed feeding may be undertaken versus allowing continuation at home.

4. Early withdrawal.

If the PI/Co-I or participant wishes to discontinue participation in the study, they will be asked to attend an early withdrawal visit for review of their diet, collection of diaries, blood, stool and saliva for mechanistic studies and completion of a QOL survey and diet questionnaire.

8.5 Visit Windows

Study visits should take place within the time limits specified as follows:

The visit window between the screening DBPCFC and Visit 1 is 14 days. The visit window for Visits 1-9 and SU visit is -7 to +14 days. The visit window for the Desensitization DBPCFC visit is -7 days to 6 months. Due to the uncertainty of the COVID-19 pandemic and the challenges with in-person visits, a large window is necessary to provide sufficient opportunity for subjects to return for the primary endpoint visit. For participants who pass this 6 month window by the time this version of the protocol has been approved, an extension of the window will be applied. If a visit window is missed for visits 2-9, the escalation will be skipped and addressed at the next scheduled escalation visit. An exception is for visits 2-9 that cannot be undertaken for study pause for COVID or similar reasons in which case the visit window is not considered and the study visits resume when possible in the planned sequence. When face to face visits resume after a pause, the visit window period to resume an in-person visit from approval to restart is extended to 8 weeks to allow safe scheduling and ramp-up study restart. After the 8 week period, windows resume.

Table 2. Table of Events (does not include unscheduled visits)

Procedures	**Screening /Baseline DBPCFC** **week 0, 3 days**	**Visit #1. Initial feeding with sub-threshold amount, week 1**	**Visit 2-9, evaluate to increase threshold, week** **8,16, 24, 32, 40, 48, 56, 64 (all visits may not be needed depending upon escalation progress)**	**DBPCFC for desensitization (active) or follow up (controls) Week 32, 56, 64 or 72**	**SU DBPCFC (24 weeks after desensitization DBPCFC for those on active peanut**
Informed consent, screening, complete	All				

Procedures	Screening /Baseline DBPCFC week 0, 3 days	Visit #1. Initial feeding with sub-threshold amount, week 1	Visit 2-9, evaluate to increase threshold, week 8,16, 24, 32, 40, 48, 56, 64 (all visits may not be needed depending upon escalation progress)	DBPCFC for desensitization (active) or follow up (controls) Week 32, 56, 64 or 72	SU DBPCFC (24 weeks after desensitization DBPCFC for those on active peanut
medical history, demographic questions					
Physical assessment, vital signs, spirometry, interval medical assessment	All	Intervention group	Intervention group	All	Intervention group passing desensitization
Pregnancy test (urine) for females of child bearing potential	All			All	Intervention group passing desensitization
DBPCFC as per PRACTALL protocol, up to cumulative dose 9043	All			All	Intervention group passing desensitization
Open peanut feeding for threshold		Intervention group	Intervention group		
Skin prick testing	All			All	Intervention group passing desensitization
Blood sample , stool and saliva collection	All		All, week 16	All	Intervention group passing desensitization
Quality of life questionnaire, diet survey	All		All week 16	All	Intervention group passing desensitization
Review adverse events and home food administration diary, report all			All (including monthly call [monthly review call not	All	Intervention group passing desensitization

Procedures	Screening /Baseline DBPCFC week 0, 3 days	Visit #1. Initial feeding with sub-threshold amount, week 1	Visit 2-9, evaluate to increase threshold, week 8,16, 24, 32, 40, 48, 56, 64 (all visits may not be needed depending upon escalation progress)	DBPCFC for desensitization (active) or follow up (controls) Week 32, 56, 64 or 72	SU DBPCFC (24 weeks after desensitization DBPCFC for those on active peanut
food allergic reactions (both randomized groups)			performed if an in-person visit occurs; monthly calls continue until last study visit]).		

9 Mechanistic Assays

Peripheral blood will be collected in sodium heparin tubes to obtain whole blood, plasma, and cells. A whole blood aliquot will be stored at -80C, tubes will then be centrifuged to obtained plasma, and the remaining cellular fraction used for basophil activation and T cell assays. For biomarker identification, additional blood will be obtained in Tempus tubes for RNA isolation. This will be followed by library preparation and RNA sequencing. DNA may be isolated from selected whole blood aliquots for genotype determination by array.

Plasma will be aliquoted and stored in cryovials at -80 C until use. An aliquot of blood (1 ml) will be used fresh for basophil activation tests. Briefly, whole blood will be stimulated with peanut extract or anti-IgE or fMLP as positive controls. Blood will be stained, fixed, and acquired by flow cytometry. Additional blood will be stimulated and cryopreserved for mass cytometry.

The remaining cellular fraction will undergo ficoll separation for purification of PBMCs, which will be cryopreserved until use in batched stimulations.

To assess T cell frequency and phenotype, PBMCs will be thawed, rested overnight, and stimulated with peanut antigen in the presence of Brefeldin A. After 6h, cells will be harvested. Peanut-responsive cells will be identified by upregulation of CD154 and CD137. Intracellular cytokines and surface markers will be used to identify T cell subsets.

10 Biospecimen Storage

Whole blood aliquots, plasma and Tempus tubes will be stored at -80 until use. Freezers are on emergency backup power and monitored by alarm system that alerts lab staff by phone call.

Cryopreserved PBMCs will be stored in alarm-monitored liquid nitrogen tank.

11 Criteria for Participant and Study Completion and Premature Study Termination

11.1 Participant Completion

Participants will be considered to have completed the protocol if they completed the desensitization DBPCFC visit, or if they were in the active arm and tolerated peanut at desensitization DBPCFC and underwent evaluation for SU at final study visit .

The statistical analysis plan allows for inclusion of non-completers (Section 13).

11.2 Participant Stopping Rules

Participants may be prematurely terminated from the study for the following reasons:

1. The participant elects to withdraw consent from all future study activities, including follow-up.
2. The participant is "lost to follow-up" (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).
3. The participant dies.
4. The Investigator no longer believes participation is in the best interest of the participant. This includes subjecs who refuse to come for the Desensitization DBPCFC visit.
5. Pregnancy
6. Subjects who fail to adhere to the request to stop the study intervention per section 6.5 will be considered for premature termination. Development of eosinophilic esophagitis

11.3 Participant Replacement

Participants who withdraw or are withdrawn will not be replaced and will be part of the ITT analysis.

11.4 Follow-up after Early Study Withdrawal

See section 8.4.

11.5. Study Stopping Rules

There are no pre-specified study stopping rules, but study procedures and dosing will be temporarily suspended pending DSMB review (see 12.8.2.2.1) for the following reasons:

- Any death possibly related to study participation.
- 2 subjects requiring more than 1 injection of epinephrine during at-home, ingestion of study-allowed peanut.
- 3 subjects diagnosed with eosinophilic esophagitis

12 Safety Monitoring and Reporting

12.1 Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events that are classified as serious according to the definition of health authorities must be reported promptly (per Section 12.5, *Reporting of Serious Adverse Events and Adverse Events*) to the Sponsor-investigator, NIAID medical monitor, and Sponsor medical monitor. Appropriate notifications will also be made to site principal investigators, Institutional Review Boards (IRBs), and health authorities.

Information in this section complies with *ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice*, 21CFR Parts 312 and 320, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 : http://ctep.cancer.gov/reporting/ctc.html.

12.2 Definitions

12.2.1 Adverse Event (AE)

Any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)" http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2)

For this study, any adverse event will be assessed for relationship during the following times frames with:

- **Study therapy regimen**: Ingestion of sub-threshold amounts of home-measured, home-purchased peanut. AEs will be collected until study completion or withdrawal.
- **Study mandated procedures**: AEs associated with DBPCFC, blood draw, observed feedings, skin prick tests will be monitored for 24 hours after the procedure.

12.2.1.1 Suspected Adverse Reaction (SAR)

Any adverse event for which there is a reasonable possibility that the investigational drug [or investigational study therapy regimen] caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

12.2.2 Unexpected Adverse Event

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the protocol, or Informed Consent Forms or is not listed at the specificity, severity or rate of occurrence that has been observed; or, is not consistent with the risk information described in the general investigational plan or elsewhere.

12.2.3 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Sponsor-Investigator, it results in any of the following outcomes (21 CFR 312.32(a)):

1. Death.
2. A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the investigator or Sponsor-Investigator its occurrence places the subject at immediate risk of death. It does not include an AE or SAR that had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly or birth defect.
6. 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 subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

12.3 Grading and Attribution of Adverse Events

12.3.1 Grading Criteria

The study site will grade the severity of adverse events experienced by the study subjects according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE, 5.0), with the exception of anaphylaxis which will be graded according to the scale included in the definition section This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. The NCI-CTCAE has been reviewed by the PI/Co-I and has been deemed appropriate for the subject population to be studied in this protocol.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = mild adverse event.

Grade 2 = moderate adverse event.

Grade 3 = severe and undesirable adverse event.

Grade 4 = life-threatening or disabling adverse event.

Grade 5 = death.

Only events grade 2 or higher and SAEs will be recorded on the appropriate AE case report form for this study.

For grading an abnormal value or result of a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, an electrocardiogram etc.), a treatment-emergent adverse event is defined as an increase in grade from baseline or from the last post-baseline value that doesn't meet grading criteria. Changes in grade from screening to baseline will also be recorded as adverse events, but are not treatment-emergent. If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an adverse event if changes in study therapy or monitoring are implemented as a result of the event. For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site: http://ctep.cancer.gov/reporting/ctc.html.

12.3.2 Attribution Definitions

The relationship, or attribution, of an adverse event to the study therapy regimen or study procedure(s) will initially be determined by the site investigator or Sponsor-investigator and recorded on the appropriate AE eCRF. Final determination of attribution for safety reporting will be determined by the Sponsor-Investigator. The relationship of an adverse event to study therapy regimen or procedures will be determined using the descriptors and definitions provided in Table 12.3.2.

Table 12.3.2 Attribution of Adverse Events

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy or study procedure)
UNRELATED CATEGORY		
1	Unrelated	The adverse event is clearly not related: there is insufficient evidence to suggest a causal relationship.
RELATED CATEGORIES		
2	Possible	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Definite	The adverse event is clearly related.

12.4 Collection and Recording of Adverse Events

12.4.1 Collection Period

Adverse events will be collected from the time of the onset of the event until a subject completes study participation or until 30 days after he/she prematurely discontinues (without withdrawing consent) or is withdrawn from the study by the investigator.

12.4.2 Collecting Adverse Events

Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the subject.
- Interviewing the subject [e.g., using a checklist, structured questioning, diary, etc.] .
- Receiving an unsolicited complaint from the subject.
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 12.3, *Grading and Attribution of Adverse Events.*

12.4.3 Recording Adverse Events

Throughout the study, the investigator will record adverse events and serious adverse events as described previously (Section 12.2, Definitions) on the AE/SAE eCRF regardless of the relationship to study therapy regimen or study procedure.

The investigator will treat subjects experiencing AEs appropriately and observes them at suitable intervals until their symptoms resolve or stabilize. Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the subject prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.

12.5 Reporting of Serious Adverse Events and Adverse Events

12.5.1 Reporting of Serious Adverse Events

This section describes the responsibilities of the Sponsor- investigator to report serious adverse events. Timely reporting of adverse events is required by 21 CFR and ICH E6 guidelines.

Site investigators will report all serious adverse events to the Sponsor-Investigator (see Section 12.2.3, *Serious Adverse Event)*, regardless of relationship or expectedness within 24 hours of discovering the event. The Sponsor investigator will inform the DAIT NIAID Medical Monitor and Sponsor Medical Monitor in real time

For serious adverse events, all requested information on the AE/SAE CRF will be provided. However, unavailable details of the event will not delay submission of the known information. As additional details become available, the AE/SAE CRF will be updated and reported.

12.5.2 Reporting to Health Authority

The Sponsor-Investigator of the IND has the responsibility of reporting all AEs and SAEs to the FDA within the reporting time limits set forth by the FDA. It is the Sponsor-investigator's responsibility to report any serious adverse event to the Sponsor Medical Monitor at his site and to the NIAID Medical Monitor within 24 hours of becoming aware of the event.

After an adverse event requiring 24-hour reporting (per Section 12.5.1, *Reporting of Serious Adverse Events to Sponsor*) is reported by the site investigator and assessed by Sponsor-Investigator, there are two options for reporting the adverse event to the FDA:

12.5.2.1 Annual Reporting

The Sponsor-Investigator will report in the annual study report to FDA all adverse events classified as:

- Serious, expected, suspected adverse reactions (see Section 12.2.1.1, *Suspected Adverse Reaction,* and Section 12.2.2, *Unexpected Adverse Event*).
- Serious , and not a suspected adverse reaction (see Section 12.2.1.1, *Suspected Adverse Reaction*).
- Pregnancies.

Note that all adverse events (not just those requiring 24-hour reporting) will be reported in the Annual IND Report.

12.5.2.2 Expedited Safety Reporting

This option, with 2 possible categories, applies if the adverse event is classified as one of the following:

Category 1: **Serious, unexpected and suspected adverse reaction** [**SUSAR]** (see Section 12.2.1.1, *Suspected Adverse Reaction* and Section 12.2, *Unexpected Adverse Event*).

The sponsor shall report any suspected adverse reaction that is both serious and unexpected. The sponsor shall report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study drug and the adverse event, such as:

1. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, or Stevens-Johnson Syndrome);
2. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);

3. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Category 2: **Any findings from studies that suggests a significant human risk**

The sponsor shall report any findings from other epidemiological studies, analyses of adverse events within the current study or pooled analysis across clinical studies or animal or *in vitro* testing (e.g. mutagenicity, teratogenicity, carcinogenicity) that suggest a significant risk in humans exposed to the drug that would result in a safety-related change in the protocol, informed consent, investigator brochure or package insert or other aspects of the overall conduct of the study.

The IND Sponsor-Investigator shall notify the appropriate FDA and all participating sub investigators of expedited safety reports within 15 calendar days; unexpected fatal or immediately life-threatening suspected adverse reaction(s) shall be reported as soon as possible or within 7 calendar days.

12.5.3 Reporting of Adverse Events to IRBs/IECs

All investigators shall report adverse events, including expedited reports, in a timely fashion to their respective IRBs/IECs in accordance with applicable regulations and guidelines. All reports shall be distributed by DAIT/NIAID or designee to all participating institutions for site IRB/IEC submission.

12.6 Pregnancy Reporting

The females in this study will largely be pre-menarche. If a participant reports the onset of menarche, they will be counseled to use birth control if participating in sexual activity. The investigator shall be informed immediately of any pregnancy in a study subject. *A* pregnant subject shall be instructed to stop taking study intervention. The investigator shall counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant subject shall continue until the conclusion of the pregnancy. There are no reasons to think there would be an adverse effect on the pregnancy of a female partner of a male participant, and therefore, these pregnancies will not be followed.

The investigator or Sponsor-investigator shall report to the DAIT/NIAID Medical Monitor and the Sponsor Medical Monitor all participant pregnancies within 1 business day of becoming aware of the event using the Pregnancy eCRF. All participant pregnancies identified during the study shall be followed to conclusion and the outcome of each must be reported. The Pregnancy eCRF shall be updated and submitted to the SACCC and DAIT/NIAID when details about the outcome are available.

Information requested about the delivery shall include:

- Gestational age at delivery
- Birth weight, length, and head circumference
- Gender
- Appearance, pulse, grimace, activity, and respiration (APGAR) score at 1 minute, 5 minutes, and 24 hours after birth, if available

- Any abnormalities.

All pregnancy complications that result in a congenital abnormality, birth defect, miscarriage, and medically indicated abortion - an SAE shall be submitted to the SACCC and DAIT/NIAID using the SAE reporting procedures described above.

12.7 Reporting of Other Safety Information

An investigator or Sponsor-investigator shall promptly notify the site IRB as well as DAIT/NIAID Medical Monitor and the Sponsor Medical Monitor by telephone or email when an "unanticipated problem involving risks to subjects or others" is identified, which is not otherwise reportable as an adverse event.

12.8 Review of Safety Information

12.8.1 Medical Monitor Review

The Sponsor Medical Monitor and the DAIT/NIAID Medical Monitor shall receive monthly line listing reports from the site compiling new and accumulating information on AEs, SAEs, and pregnancies recorded by the study site on appropriate eCRFs.

In addition, the DAIT/NIAID Medical Monitor shall review and recommend on the disposition of SAE and pregnancy reports received by the Sponsor-Investigator (See Sections 12.5.1, *Reporting of Serious Adverse Events to Sponsor*, and 12.6, *Pregnancy Reporting*).

12.8.2 DSMB Review

12.8.2.1 Planned DSMB Reviews

The Data and Safety Monitoring Board (DSMB) shall review safety data at least yearly during planned DSMB Data Review Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs.

The DSMB will be informed of an Expedited Safety Report in a timely manner.

12.8.2.2 *Ad hoc* DSMB Reviews

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for *ad hoc* reviews. The DSMB will review any event that potentially impacts safety at the request of the protocol chair or DAIT/NIAID. In addition, the following events will trigger an *ad hoc* comprehensive DSMB Safety Review: Meeting study stopping rules (Section 11.5)

After review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

12.8.2.2.1 Temporary Suspension of enrollment, dosing and study procedures (skin tests, DBPCFC) for *ad hoc* DSMB Safety Review

A temporary halt in enrollment, DBPCFC, SPT and daily ingestion will be implemented if an ad hoc NIAID DSMB safety review is required.

A safety related suspension of enrollment will occur, pending expedited review of all pertinent data by the institutional review board (IRB), the National Institute of Allergy and Infectious

Diseases (NIAID) Medical Monitor, and the NIAID Data Safety Monitoring Board (DSMB) based on the following:

- Any death possibly related to study participation
- 2 subjects requiring more than 1 injection of epinephrine during for at-home, study-allowed ingestion of study-allowed peanut.
- 3 subjects diagnosed with eosinophilic esophagitis.

13 Statistical Considerations and Analytical Plan

13.1 Overview

The primary objective of this study is to test a simple peanut feeding protocol in children with a high threshold form of peanut allergy, allowing them to ingest a tolerated amount of peanut and to periodically try larger amounts under medical supervision, to determine whether allowing ingestion of sub-threshold amounts of peanut will be associated with increasing their threshold with time. The secondary clinical objectives include assessing for the development of sustained unresponsiveness (SU, a surrogate term for tolerance without daily ingestion), effects on quality of life, and safety. Additionally, this study will result in phenotyping the allergic response to peanut based on threshold and response to exposure. Mechanistic study objectives will determine immune characteristics of the high threshold endotype and predict response to exposure and determine mechanisms of remission. Mechanistic studies/biomarker studies will also identify genes that are differentially expressed in the resting state of peanut allergic subjects with high and low threshold reactivity, those associated with severity, and response to exposure.

This is a randomized, two-arm parallel-group, controlled open trial. The study randomizes (1:1) children age 4-14 years with high threshold peanut allergy to ingest a sub-threshold amount of peanut daily or to follow avoidance.

13.2 Endpoints

The clinical endpoints are:

Primary endpoint**:** The difference in the percentage of children who by the desensitization DBPCFC tolerate a dose at least 2 steps higher than their baseline DBPCFC or the full dose (9043 mg) of peanut protein in the two HT groups.

Secondary endpoints: The following secondary clinical endpoints will be compared between subjects in the intervention and control arm

1. The percentage of children who achieve SU or natural tolerance during the study.

2. Safety parameters (acute allergic reactions, including anaphylaxis, gastrointestinal side effects).

3. Quality of life measures.

4. SPT mean wheal size changes.

The mechanistic endpoints are:

1.Peanut and Ara h 2-specific IgE.

2. Peanut and Ara h 2-specific IgG4

3. Epitope binding score for IgE and IgG4.

4. Basophil activation measured by flow cytometry after peanut activation

5. Frequency of peanut-specific Th2 cells

6. Frequency of peanut-specific Tregs

7.Data-driven identification of functional pathways (derived from transcriptional data) underlying successful desensitization.

Secondary mechanistic endpoints:

1. Baseline mechanistic measures 1-7 from primary endpoints will be used to test prediction of desensitization or sustained unresponsiveness.
2. Baseline mechanistic measures 1-7 from primary endpoints will be used to test prediction of the high threshold phenotype.
3. (**Exploratory**) Early-appearing functional pathways (derived from transcriptional data) underlying a successful desensitization course.

13.3 Measures to Minimize Bias

Although this is an open trial, DBPCFCs will be performed by staff blinded to randomization assignment. Randomization will be stratified by age (4-<10 years vs. 10-14 years) and reaction dose at the initial DBPCFC, balanced by blocks of 4 and 6. This will guarantee that both treatment arms have similar distribution of those covariates without pre-specifying a number of patients per strata, which will limit enrollment. Clinical samples for mechanistic studies will be received by the laboratory personnel in coded fashion without indication of intervention allocation.

Defining the timing for the DBPCFC *in the control group:* Time from randomization to the DBPCFC will be dictated by the achievement of 1 tbsp threshold in children in the intervention group. In order to ensure that the two trial arms will have the same time to DBPCFC on average, we will develop an adaptive algorithm to assign a time to DBPCFC in avoiders that matches that of the consumers. After the baseline DBPCFC, patients in the avoider group will be assigned a 'time to the second DBPCFC' as a value randomly selected from the distribution of the consumer patients with the same baseline reactive dose. Initial distributions for time to DBPCFC will be assumed to follow a uniform distribution centered on the treatment expectations anticipated by the clinicians based on initial DBPCFC (i.e. ~32 weeks for those who fail at 3000 mg, ~72 weeks for those who fail at 300 mg) plus minus

3 weeks. After the recruitment of every 10 patients, the time to OFC distribution for each baseline reactive dose will be updated as a uniform distribution derived from the time to OFC of consumer patients if 2 or more observations are available, otherwise we will keep the initial uniform distribution for that baseline reactive dose. The statistician will receive an email from RedCap alerting them that 10 new patients had been accrued; and will update the timing distributions. Once a patient is randomized to the Avoider group, the unblinded statistician will send the timing of the second DBPCFC to the study coordinator, who will enter the assigned time into RedCap. For monitoring and data checking purposes, the unblinded statistician will maintain their own records. Inconsistencies will be identified and resolved in a timely manner within the monitoring process when producing data inconsistencies and data completeness reports.

13.4 Analysis Plan

13.4.1 Analysis Populations.

An intention-to-treat (ITT) analysis will be performed for the primary analysis and for selected secondary analyses. All hypothesis tests will be two-sided and performed at the 5% significance level. Baseline characteristics will be summarized for all of the patients in the ITT population.

13.4.2 Primary Analysis of Primary Endpoint(s)/Outcome(s)

The primary endpoint of this study is the ability to tolerate a dose at least 2 steps higher than the one tolerated at baseline or 9043 mg of peanut protein by the desensitization DBPCFC. The proportion of subjects in the intervention and the control group meeting the primary outcome will be compared using a continuity corrected chi-squared test at the 0.05 significance level. As the intent-to-treat principle includes all randomized subjects in the primary analysis, patients who are missing the trial's primary endpoint will have their outcome imputed using multiple imputation techniques. Missing data in the primary endpoint will be assumed to depend only on the observed values, i.e., data are missing at random (MAR). Data imputation under this assumption will be performed using the proposed multiple imputation method by Rubin.[77] Covariates in the imputation model will include treatment assignment, gender, age and baseline reactive dose strata, clinical severity during DBPCFC as well as peanut-specific IgE levels at baseline and week 16.

13.4.3 Supportive Analyses of the Primary Endpoint(s)/Outcome(s)

Sensitivity analyses will be performed to assess the sensitivity of the primary analysis results to choice of statistical test and missing imputation procedure as well as departures of the MAR assumption and to treatment cross-overs.

Sensitivity analysis include:

a) Stratified Chi-square test (by baseline reactive dose and age strata)

b) Fisher's exact test under 5 ad-hoc imputation strategies: i) all are failures, ii) are all failures except the highest dose at baseline which are successes, iii) all are failures except highest two doses at baseline, iv) all are successes except lowest dose at baseline, and v) all are successes. That is, the first and last of the five are the least conservative, respectively, and the others are in between but use the baseline dose as a means of an intermediate approach, which also incorporates a possible difference in distribution of baseline doses between the groups.

c) If the MAR assumption is not tenable, statistical methods that assume missing not at random (MNAR) such as pattern mixture models for non-ignorable missing data will be considered.

d) When cross-over rates are high, the ITT effect of being assigned to treatment may differ from the effect of actually receiving treatment. As a sensitivity analysis, we will perform an instrumental variable (IV) analysis to obtain an unbiased estimate of the treatment effect, using randomization assignment as the instrument.

e) Given the potential impact of COVID-19 pandemic on subject's return for the Desensitization DBPCFC visit, we will perform a sensitivity analysis that examines the effect of intervention on primary endpoint success adjusting for time from randomization to Desensitization DBPCFC visit and whether patients were randomized prior to study pause in March 2020 using logistic regression modelling.

13.4.4 Analyses of Secondary and Other Endpoint(s)/Outcome(s)

Sustained unresponsiveness or natural tolerance: The proportion of children who experience SU in the active arm of the HT group will be compared to the proportion of children who achieve natural tolerance in the control arm in an intent-to-treat analysis using a continuity corrected chi-squared test, similar to the plan detailed for the primary endpoint.

Immunological parameters: Changes in skin prick test mean wheal diameter will be compared between randomization groups using linear mixed effects models for data collected at baseline and desensitization DBPCFC. The linear mixed effects model has the advantage that the estimation of the model parameters will be unbiased even in the presence of missing outcomes, assuming that the missing values depend only on the observed values (MAR). If the MAR assumption is not plausible, pattern-mixture modeling (which stratifies subjects by their pattern of missing data) will be used.

Quality of life: Changes in quality of life over the study as measured by The Food Allergy Quality of Life-Parental Burden[76] will be compared between randomization groups and analyzed using linear mixed effects models as described previously (Immunological parameters, above).

Adverse Events: Adverse events (AEs) will be coded using the CTCAE, Common Terminology Criteria for AE, V4.0. Individual adverse events will be summarized as the number (%) of events and number (%) of patients with the event in each group. Adverse events will be modelled using Poisson regression and the rate of individual adverse events will compared between randomization arms over the study period. **Long-term adverse events** will be evaluated with data up to 96 weeks for those in the active group who are tested for SU following a desensitization DBPCFC.

13.4.5 Analyses of Exploratory Endpoint(s)/Outcome(s)

Not applicable.

13.4.6 Descriptive Analyses

Descriptive analysis will be used to describe patient variables such as age, sex, race/ethnicity, atopic conditions, use of medications, allergic reactions, and study completion.

13.5 Interim Analyses

Not applicable.

13.5.1 Interim Analysis of Efficacy Data-NA

13.5.2 Interim Analysis of Safety Data-NA

13.5.3 Futility Analysis-NA

13.6 Statistical Hypotheses

We hypothesize that for persons with high threshold peanut allergy, ingesting sub-threshold amounts of the allergen (amounts not causing symptoms) will result in an ability to ingest higher amounts with time (desensitization) and potentially sustained unresponsiveness (SU). We also hypothesize that the approach will be safe and improve quality of life compared to avoidance.

Section 13.7 describes the statistical considerations for these differences.

13.7 Sample Size Considerations

The primary objective of this study is to compare the proportion of children who at the desensitization DBPCFC tolerate an amount at least 2 steps higher than the baseline amount or who tolerate the full dose (9043 mg) of peanut protein between the active and the control arm in the HT group. Secondary clinical outcomes of this study include sustained unresponsiveness, skin prick test mean wheal diameters, quality of life, and adverse events. For sample size calculations, we assume a conservative estimate for the proportion of spontaneous tolerance in the control group of 10%. We believe that an additional absolute increase of 45 percentage points under the intervention is feasible and clinically meaningful (55% vs. 10%). We also assume a drop-in rate (avoiders to consumers) and drop-out rate (consumers discontinuing study treatment) of 5%and 20%, respectively. This results in an attenuated effect size of 33.75% percentage points (46% vs. 12.25%. A total of 72 children randomized with equal probability to the active or control arm (36per group) provides approximately 85% power to detect a difference of 33.75% (46% versus 12.25%) in the proportion of children who tolerate at least 2 steps higher amount from baseline or the full amount of peanut protein by the desensitization DBPCFC, based on a 0.05 level continuity corrected chi-squared test. We believe the drop-in rate will be kept at a minimum since parents and children will likely not attempt dose escalation on their own. The drop-out rate is conservative, based on our prior experience, which reported a drop-out rate of 15%.

We do not anticipate many families becoming “drop-in” doing this because those randomized to avoidance will not have their tolerance of a specific measured amount confirmed under supervision and there is generally a concern of allergic reactions from ingestion. More importantly, we believe this concern will be easily addressed because there are true issues of equipoise. It may be that those randomized to ingestion will have more allergic reactions than controls,[45] or develop side effects such as eosinophilic esophagitis,[73] or not be able to progress on the large steps outlined in the PRACTALL modified dosing. If families on avoidance are non-adherent, we can detect this. We will monitor peanut-specific IgG levels in all participants and those with rising peanut-specific IgG from ingestion could be identified. The statistical analysis plan includes a sensitivity analysis that uses instrumental variable methods to obtain an unbiased estimate of the treatment effect in the presence of cross-overs.

14 Identification and Access to Source Data

14.1 Source Data

Source documents and source data are considered to be the original documentation where subject information, visits consultations, examinations and other information are recorded. Documentation of source data is necessary for the reconstruction, evaluation and validation of clinical findings, observations and other activities during a clinical trial.

14.2 Access to Source Data

The site investigators and site staff will make all source data available to the DAIT/NIAID staff, as well as to relevant health authorities. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals.

15 Protocol Deviations

15.1 Protocol Deviation Definitions

Protocol Deviation – The investigators and site staff will conduct the study in accordance to the protocol; no deviations from the protocol are permitted. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. As a result of any deviation, corrective actions will be developed by the site and implemented promptly.

Major Protocol Deviation (Protocol Violation) - A Protocol Violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, protocol violations include willful or knowing breaches of human subject protection regulations, or policies, any action that is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles, and a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures.

Non-Major Protocol Deviation - A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

15.2 Reporting and Managing Protocol Deviations

The study site principal investigator has the responsibility to identify, document and report protocol deviations as directed by the study Sponsor. However, protocol deviations may also be identified during site monitoring visits or during other forms of study conduct review. Upon determination that a protocol deviation has occurred, the staff will a) notify the Principal Investigator, b) notify the NIAID Project Manager and c) will begin completing the Protocol Deviation CRF. The PI will be responsible for providing NIAID with listings of all protocol deviations periodically. NIAID may request discussion with the Principal Investigator and the Independent Medical Monitor to determine the effect of the protocol deviation on the study.

16 Ethical Considerations and Compliance with Good Clinical Practice

16.1 Statement of Compliance

This clinical study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance*, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the *[select: IRB, Ethics Committee]*. Any amendments to the protocol or to the consent materials will also be approved by the *[select: IRB, Ethics Committee]* before they are implemented.

16.2 Informed Consent Process

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The principal investigator or designee listed on the Investigator of

Record form will review the consent and answer questions. Study staff approved by the Investigator and IRB as qualified may also obtain consent. The prospective participant/parent will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants (or their legally acceptable representative) will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in participants' primary language. A copy of the signed consent form will be given to the participant.

The consent process will be ongoing with verbal review of the nature of the study at least yearly. The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

16.3 Privacy and Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers rather than names will be used to collect, store, and report participant information. Site personnel will not transmit documents containing personal health identifiers (PHI) to the study sponsor or their representatives.

17 Publication Policy

The *NIH* policy on the publication of study results will apply to this trial.

18 References

1. Sicherer SH, Sampson HA. Food allergy: recent advances in pathophysiology and treatment. AnnuRevMed 2009;60:261-77.
2. Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics 2011;128:e9-17.
3. Lieberman JA, Sicherer SH. Quality of life in food allergy. Curr Opin Allergy Clin Immunol 2011;11:236-42.
4. Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update-2014. J Allergy Clin Immunol 2014;134:1016-25 e43.
5. Mehta H, Ramesh M, Feuille E, Groetch M, Wang J. Growth comparison in children with and without food allergies in 2 different demographic populations. J Pediatr 2014;165:842-8.
6. Nowak-Wegrzyn A, Groetch M. Nutritional aspects and diets in food allergy. Chem Immunol Allergy 2015;101:209-20.
7. Sicherer SH, Sampson HA. Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J Allergy Clin Immunol 2018;141:41-58.
8. Bird JA, Groetch M, Allen KJ, et al. Conducting an Oral Food Challenge to Peanut in an Infant. J Allergy Clin Immunol Pract 2017;5:301-11 e1.
9. Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report. J Allergy Clin Immunol 2010;126:1105-18.
10. Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy 2014;69:1008-25.
11. Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, et al. Work Group report: oral food challenge testing. J Allergy Clin Immunol 2009;123:S365-83.
12. Leonard SA, Sampson HA, Sicherer SH, et al. Dietary baked egg accelerates resolution of egg allergy in children. J Allergy Clin Immunol 2012;130:473-80 e1.
13. Leonard SA, Caubet JC, Kim JS, Groetch M, Nowak-Wegrzyn A. Baked milk- and egg-containing diet in the management of milk and egg allergy. J Allergy Clin Immunol Pract 2015;3:13-23; quiz 4.

14. Nowak-Wegrzyn A, Bloom KA, Sicherer SH, et al. Tolerance to extensively heated milk in children with cow's milk allergy. The Journal of Allergy and Clinical Immunology 2008;122:342-7, 7.
15. Shreffler WG, Wanich N, Moloney M, Nowak-Wegrzyn A, Sampson HA. Association of allergen-specific regulatory T cells with the onset of clinical tolerance to milk protein. J Allergy Clin Immunol 2009;123:43-52 e7.
16. Wang J, Lin J, Bardina L, et al. Correlation of IgE/IgG4 milk epitopes and affinity of milk-specific IgE antibodies with different phenotypes of clinical milk allergy. J Allergy Clin Immunol 2010;125:695-702, e1- e6.
17. Kim JS, Nowak-Wegrzyn A, Sicherer SH, Noone S, Moshier EL, Sampson HA. Dietary baked milk accelerates the resolution of cow's milk allergy in children. J Allergy Clin Immunol 2011;128:125-31.
18. Caubet JC, Nowak-Wegrzyn A, Moshier E, Godbold J, Wang J, Sampson HA. Utility of casein-specific IgE levels in predicting reactivity to baked milk. The Journal of Allergy and Clinical Immunology 2012.
19. Ford LS, Bloom KA, Nowak-Wegrzyn AH, Shreffler WG, Masilamani M, Sampson HA. Basophil reactivity, wheal size, and immunoglobulin levels distinguish degrees of cow's milk tolerance. J Allergy Clin Immunol 2013;131:180-6 e1-3.
20. Caubet JC, Nowak-Wegrzyn A, Moshier E, Godbold J, Wang J, Sampson HA. Utility of casein-specific IgE levels in predicting reactivity to baked milk. The Journal of Allergy and Clinical Immunology 2013;131:222-4.
21. Albin S, Nowak-Wegrzyn A. Potential treatments for food allergy. Immunol Allergy Clin North Am 2015;35:77-100.
22. Jones SM, Burks AW, Dupont C. State of the art on food allergen immunotherapy: oral, sublingual, and epicutaneous. J Allergy Clin Immunol 2014;133:318-23.
23. Wood RA. Food allergen immunotherapy: Current status and prospects for the future. J Allergy Clin Immunol 2016;137:973-82.
24. Sicherer SH, Morrow EH, Sampson HA. Dose-response in double-blind, placebo-controlled oral food challenges in children with atopic dermatitis. J Allergy Clin Immunol 2000;105:582-6.
25. Ballmer-Weber BK, Fernandez-Rivas M, Beyer K, et al. How much is too much? Threshold dose distributions for 5 food allergens. J Allergy Clin Immunol 2015;135:964-71.
26. Taylor SL, Moneret-Vautrin DA, Crevel RW, et al. Threshold dose for peanut: Risk characterization based upon diagnostic oral challenge of a series of 286 peanut-allergic individuals. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association 2010;48:814-9.
27. Osterballe M, Bindslev-Jensen C. Threshold levels in food challenge and specific IgE in patients with egg allergy: is there a relationship? J Allergy Clin Immunol 2003;112:196-201.
28. Moneret-Vautrin DA, Rance F, Kanny G, et al. Food allergy to peanuts in France--evaluation of 142 observations 4. Clin ExpAllergy 1998;28:1113-9.
29. Glaumann S, Nopp A, Johansson SG, Borres MP, Nilsson C. Oral peanut challenge identifies an allergy but the peanut allergen threshold sensitivity is not reproducible. PloS one 2013;8:e53465.
30. Blumchen K, Beder A, Beschorner J, et al. Modified oral food challenge used with sensitization biomarkers provides more real-life clinical thresholds for peanut allergy. J Allergy Clin Immunol 2014;134:390-8.
31. Allen KJ, Remington BC, Baumert JL, et al. Allergen reference doses for precautionary labeling (VITAL 2.0): clinical implications. J Allergy Clin Immunol 2014;133:156-64.
32. Zhu J, Pouillot R, Kwegyir-Afful EK, Luccioli S, Gendel SM. A retrospective analysis of allergic reaction severities and minimal eliciting doses for peanut, milk, egg, and soy oral food challenges. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association 2015;80:92-100.
33. Nowak-Wegrzyn A, Bloom KA, Sicherer SH, et al. Tolerance to extensively heated milk in children with cow's milk allergy. J Allergy Clin Immunol 2008;122:342-7, 7.
34. Lemon-Mule H, Sampson HA, Sicherer SH, Shreffler WG, Noone S, Nowak-Wegrzyn A. Immunologic changes in children with egg allergy ingesting extensively heated egg. J Allergy Clin Immunol 2008;122:977-83.
35. Blumchen K, Ulbricht H, Staden U, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. J Allergy Clin Immunol 2010;126:83-91.
36. Skripak JM, Nash SD, Rowley H, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol 2008;122:1154-60.
37. Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, et al. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. J Allergy Clin Immunol 2012;129:448-55, 55 e1-5.

38. Wood RA, Kim JS, Lindblad R, et al. A randomized, double-blind, placebo-controlled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. J Allergy Clin Immunol 2015.
39. Burks AW, Jones SM, Wood RA, et al. Oral immunotherapy for treatment of egg allergy in children. N Engl J Med 2012;367:233-43.
40. Anagnostou K, Islam S, King Y, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. Lancet 2014;383:1297-304.
41. Fleischer DM, Burks AW, Vickery BP, et al. Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. J Allergy Clin Immunol 2013;131:119-27 e1-7.
42. Jones SM, Pons L, Roberts JL, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. J Allergy Clin Immunol 2009;124:292-300, e1-97.
43. Sato S, Utsunomiya T, Imai T, et al. Wheat oral immunotherapy for wheat-induced anaphylaxis. J Allergy Clin Immunol 2015;136:1131-3 e7.
44. Nowak-Wegrzyn A, Sampson HA. Future therapies for food allergies. J Allergy Clin Immunol 2011.
45. Nurmatov U, Devereux G, Worth A, Healy L, Sheikh A. Effectiveness and safety of orally administered immunotherapy for food allergies: a systematic review and meta-analysis. Br J Nutr 2014;111:12-22.
46. Virkud YV, Burks AW, Steele PH, et al. Novel baseline predictors of adverse events during oral immunotherapy in children with peanut allergy. J Allergy Clin Immunol 2017;139:882-8 e5.
47. Vickery BP, Berglund JP, Burk CM, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. J Allergy Clin Immunol 2017;139:173-81 e8.
48. Vickery BP, Scurlock AM, Kulis M, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. J Allergy Clin Immunol 2014;133:468-75.
49. Sampson HA, Leung DYM, Burks AW, et al. A phase II, randomized, double-blind, parallel group, placebo-controlled oral fod challenge trial of Xolair (omalizumab) in peanut allergy. J Allergy Clin Immun 2007;119:S117.
50. Bird JA, Spergel JM, Jones SM, et al. Efficacy and Safety of AR101 in Oral Immunotherapy for Peanut Allergy: Results of ARC001, a Randomized, Double-Blind, Placebo-Controlled Phase 2 Clinical Trial. J Allergy Clin Immunol Pract 2018;6:476-85 e3.
51. Jones SM, Sicherer SH, Burks AW, et al. Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. J Allergy Clin Immunol 2017;139:1242-52 e9.
52. Burks AW, Sampson HA. Double-blind placebo-controlled trial of oral cromolyn in children with atopic dermatitis and documented food hypersensitivity. J Allergy Clin Immunol 1988;81:417-23.
53. Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States: Report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel. J Allergy Clin Immunol 2017;139:29-44.
54. Christensen MJ, Eller E, Mortz CG, Brockow K, Bindslev-Jensen C. Exercise Lowers Threshold and Increases Severity, but Wheat-Dependent, Exercise-Induced Anaphylaxis Can Be Elicited at Rest. J Allergy Clin Immunol Pract 2018;6:514-20.
55. Feldweg AM. Food-Dependent, Exercise-Induced Anaphylaxis: Diagnosis and Management in the Outpatient Setting. J Allergy Clin Immunol Pract 2017;5:283-8.
56. Vickery BP, Lin J, Kulis M, et al. Peanut oral immunotherapy modifies IgE and IgG4 responses to major peanut allergens. J Allergy Clin Immunol 2013;131:128-34 e1-3.
57. Wright BL, Kulis M, Orgel KA, et al. Component-resolved analysis of IgA, IgE, and IgG4 during egg OIT identifies markers associated with sustained unresponsiveness. Allergy 2016.
58. Jones SM, Burks AW, Keet C, et al. Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy. J Allergy Clin Immunol 2016.
59. Garvey AA, O'Sullivan D, Hourihane JO. Home-based induction of sustained unresponsiveness in children with mild reactions to high doses of peanut. J Allergy Clin Immunol Pract 2017;5:1757-9.
60. Yanagida N, Minoura T, Kitaoka S, Ebisawa M. A three-level stepwise oral food challenge for egg, milk, and wheat allergy. J Allergy Clin Immunol Pract 2018;6:658-60 e10.

61. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol 2012;130:1260-74.
62. Filep S, Block DS, Smith BRE, et al. Specific allergen profiles of peanut foods and diagnostic or therapeutic allergenic products. J Allergy Clin Immunol 2018;141:626-31 e7.
63. Hindley JP, Filep S, Block DS, King EM, Chapman MD. Dose of allergens in a peanut snack (Bamba) associated with prevention of peanut allergy. J Allergy Clin Immunol 2018;141:780-2.
64. Sicherer SH, Wood RA. Advances in diagnosing peanut allergy. J Allergy Clin Immunol Pract 2013;1:1-13; quiz 4.
65. Fleischer DM, Conover-Walker MK, Christie L, Burks AW, Wood RA. The natural progression of peanut allergy: Resolution and the possibility of recurrence. JAllergy ClinImmunol 2003;112:183-9.
66. Savage J, Sicherer S, Wood R. The Natural History of Food Allergy. J Allergy Clin Immunol Pract 2016;4:196-203; quiz 4.
67. Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks W, Wood RA. The natural history of peanut allergy. The Journal of Allergy and Clinical Immunology 2001;107:367-74.
68. Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. JAllergy ClinImmunol 2007;119:1016-8.
69. Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS. Work Group report: oral food challenge testing. J Allergy Clin Immunol 2009;123:S365-S83.
70. Kowalski ML, Ansotegui I, Aberer W, et al. Risk and safety requirements for diagnostic and therapeutic procedures in allergology: World Allergy Organization Statement. World Allergy Organ J 2016;9:33.
71. Hofmann AM, Scurlock AM, Jones SM, et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy. The Journal of Allergy and Clinical Immunology 2009;124:286-91, 91.
72. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol 2011;128:3-20 e6; quiz 1-2.
73. Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. Ann Allergy Asthma Immunol 2014;113:624-9.
74. Niggemann B, Beyer K. Factors augmenting allergic reactions. Allergy 2014;69:1582-7.
75. Codreanu F, Moneret-Vautrin DA, Morisset M, et al. The risk of systemic reactions to skin prick-tests using food allergens: CICBAA data and literature review. AllergImmunol (Paris) 2006;38:52-4.
76. Cohen BL, Noone S, Munoz-Furlong A, Sicherer SH. Development of a questionnaire to measure quality of life in families with a child with food allergy. J Allergy Clin Immunol 2004;114:1159-63.
77. D.B. R. Multiple imputation for nonresponse in suveys: Wiley & Sons, Inc., New York; 1987.

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