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Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

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ABSTRACT

BACKGROUND

The prevalence of peanut allergy among children in Western countries has doubled in the past 10 years, and peanut allergy is becoming apparent in Africa and Asia. We evaluated strategies of peanut consumption and avoidance to determine which strategy is most effective in preventing the development of peanut allergy in infants at high risk for the allergy.

METHODS

We randomly assigned 640 infants with severe eczema, egg allergy, or both to consume or avoid peanuts until 60 months of age. Participants, who were at least 4 months but younger than 11 months of age at randomization, were assigned to separate study cohorts on the basis of preexisting sensitivity to peanut extract, which was determined with the use of a skin-prick test — one consisting of participants with no measurable wheal after testing and the other consisting of those with a wheal measuring 1 to 4 mm in diameter. The primary outcome, which was assessed independently in each cohort, was the proportion of participants with peanut allergy at 60 months of age.

RESULTS

Among the 530 infants in the intention-to-treat population who initially had negative results on the skin-prick test, the prevalence of peanut allergy at 60 months of age was 13.7% in the avoidance group and 1.9% in the consumption group ($P<0.001$). Among the 98 participants in the intention-to-treat population who initially had positive test results, the prevalence of peanut allergy was 35.3% in the avoidance group and 10.6% in the consumption group ($P=0.004$). There was no significant between-group difference in the incidence of serious adverse events. Increases in levels of peanut-specific IgG4 antibody occurred predominantly in the consumption group; a greater percentage of participants in the avoidance group had elevated titers of peanut-specific IgE antibody. A larger wheal on the skin-prick test and a lower ratio of peanut-specific IgG4:IgE were associated with peanut allergy.

CONCLUSIONS

The early introduction of peanuts significantly decreased the frequency of the development of peanut allergy among children at high risk for this allergy and modulated immune responses to peanuts. (Funded by the National Institute of Allergy and Infectious Diseases and others; ClinicalTrials.gov number, NCT00329784.)

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THE PREVALENCE OF PEANUT ALLERGY among children in Western countries has doubled in the past 10 years, reaching rates of 1.4 to 3.0%,¹⁻³ and peanut allergy is becoming apparent in Africa and Asia.^{4,5} This allergy is the leading cause of anaphylaxis and death due to food allergy and imposes substantial psychosocial and economic burdens on patients and their families.⁶

Peanut allergy develops early in life and is rarely outgrown.⁷⁻⁹ Clinical practice guidelines from the United Kingdom in 1998⁹ and from the United States in 2000¹⁰ recommended the exclusion of allergenic foods from the diets of infants at high risk for allergy and from the diets of their mothers during pregnancy and lactation. However, studies in which food allergens have been eliminated from the diet have consistently failed to show that elimination from the diet prevented the development of IgE-mediated food allergy.¹¹ In 2008, recommendations for the avoidance of allergens were withdrawn. The question of whether early exposure or avoidance is the better strategy to prevent food allergies remains open.^{12,13}

Several years ago, we found that the risk of the development of peanut allergy was 10 times as high among Jewish children in the United Kingdom as it was in Israeli children of similar ancestry.¹⁴ This observation correlated with a striking difference in the time at which peanuts are introduced in the diet in these countries: in the United Kingdom infants typically do not consume peanut-based foods in the first year of life, whereas in Israel, peanut-based foods are usually introduced in the diet when infants are approximately 7 months of age, and their median monthly consumption of peanut protein is 7.1 g.¹⁴ This finding led us to hypothesize that the early introduction of peanuts to the diet may offer protection from the development of peanut allergy.

Oral tolerance is an incompletely understood immunologic phenomenon. In studies in animals, specific immune unresponsiveness has been achieved through the oral administration of antigens.¹⁵ In a single study in humans, researchers attempted to induce primary oral tolerance to egg in infants at high risk for allergy, but the study lacked the power to show efficacy.¹⁶ Several small studies have evaluated the use of oral immunotherapy with peanut and egg in older children with established food allergies; although the early results of these studies have been promising, the majority of children who initially showed a positive response to the therapy regained their allergic

reactivity a few months after discontinuing the therapy.¹⁷⁻²⁰

The primary prevention of allergy targets non-sensitized persons, whereas secondary prevention targets those who are known to be sensitized on the basis of test results for allergen-specific IgE or reactions on skin-prick testing. The Learning Early about Peanut Allergy (LEAP) trial was conceived to determine whether the early introduction of dietary peanut could serve as an effective primary and secondary strategy for the prevention of peanut allergy. Here we report the primary findings of the LEAP trial.

METHODS

STUDY DESIGN AND OVERSIGHT

The LEAP study was a randomized, open-label, controlled trial conducted at a single site in the United Kingdom. An open-label design was chosen because participants and their parents were necessarily aware of their assigned group. The trial was approved by the institutional review board (the National Research Ethics Service Committee London-Fulham) and was overseen by the allergy and asthma data and safety monitoring board of the National Institute of Allergy and Infectious Diseases. Informed written consent was obtained for all participants from their parent or guardian. No manufacturer of peanut products contributed to the design of the study, the accrual or analysis of the data, or the preparation of the manuscript. The peanut snack used in the study, called Bamba, was purchased from Osem at a discounted rate. The protocol for the LEAP study is available with the full text of this article at NEJM.org.

ENROLLMENT AND STUDY PROCEDURES

Study enrollment took place from December 2006 to May 6, 2009. To be eligible for enrollment, infants had to be least 4 months and less than 11 months of age and had to have severe eczema, egg allergy, or both.²¹ Participants were stratified into two study cohorts on the basis of the results of a skin-prick test for peanut allergy (no measurable wheal after testing versus a wheal measuring 1 to 4 mm in diameter); participants in each study cohort were then randomly assigned to a group in which dietary peanut would be consumed or a group in which its consumption would be avoided (Fig. 1). Infants randomly assigned to consumption underwent a baseline, open-label food



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challenge in which those who had had negative results on the skin-prick test were given 2 g of peanut protein in a single dose and those who had had positive test results were given incremental doses up to a total of 3.9 g. Participants who had a reaction to the baseline challenge were instructed to avoid peanuts. These participants were included in the intention-to-treat analysis but not in the per-protocol analysis.

Participants randomly assigned to consumption who did not have a reaction to the baseline challenge were fed at least 6 g of peanut protein per week, distributed in three or more meals per week, until they reached 60 months of age. The preferred peanut source was Bamba, a snack food manufactured from peanut butter and puffed maize; it was not possible to administer a placebo for Bamba because of financial and logistic constraints. Smooth peanut butter (the brands Sunpat or Duerr's) was provided to infants who did not like Bamba. Participants assigned to avoidance were to avoid the consumption of peanut protein until they reached 60 months of age. Adherence was assessed with the use of a validated food-frequency questionnaire,²² as detailed in the schedule of events in Table S1 in the Supplementary Appendix, available at NEJM.org. Some families agreed to have peanut protein levels measured in dust collected from the participant's bed 2 to 4 weeks before the final visit.^{23,24}

Clinical assessments were undertaken at baseline (when participants were between 4 months and 11 months of age) and at the ages of 12, 30, and 60 months; between-visit scheduled telephone consultations were conducted weekly until participants reached 12 months of age, every 2 weeks from 12 months to 30 months of age, and monthly thereafter. Additional clinic visits were scheduled to evaluate aversion to peanut or refusal to eat peanut (Bamba or peanut butter) or suspected peanut allergy.

OUTCOMES

The primary outcome was the proportion of participants with peanut allergy at 60 months of age and was determined in 617 participants by means of an oral food challenge. Participants in whom peanut allergy was unlikely (no wheal after a skin-prick test at months 30 and 60, no history of allergic symptoms after ingestion of peanut, no diagnosis or suspicion of allergies to sesame or tree nut, and no history of anaphylaxis in response to any food) received 5 g of peanut protein in a

single dose. A double-blind, placebo-controlled food challenge was conducted for other participants (with a total of 9.4 g of peanut protein administered in increments) in accordance with standard dose-escalation procedures²⁵ (see the study protocol). Among 11 study participants for whom data from the oral food challenge were either inconclusive or not available, a diagnostic algorithm based on clinical history, the results of a skin-prick test, and the values for peanut-specific IgE were used to determine whether or not a participant should be considered to have peanut allergy (Fig. S1 in the Supplementary Appendix).²¹

IMMUNE MARKERS

At baseline and at all study visits, skin-prick tests for peanut allergy were performed in duplicate with the use of a lyophilized peanut extract (manufactured by ALK-Abello), and the average of the diameter of the two widest wheals was recorded. Mean diameters were rounded off to the nearest millimeter, with the lowest positive value being 1 mm; positive values of 1 mm and 2 mm (which are associated with peanut-specific IgE production²¹) were considered to be indicative of early sensitization, even though these values are lower than the traditional cut-off of 3 mm. Serum levels of peanut-specific IgE, IgG, and IgG4 antibodies were measured at each visit, since these are known biomarkers of allergic responses, antigen exposure, and potential immune modulation, respectively.^{26,27} The peanut-specific IgG4:IgE ratio was calculated, since it has been reported that this ratio may additionally reflect immune modulation.²⁸ Immunoglobulin measurements were made with the use of the ImmunoCAP 100 and 250 assays (Thermo Fisher Scientific).

STATISTICAL ANALYSIS

Primary statistical analyses were performed in each cohort independently on an intention-to-treat basis with data from all participants who could be assessed for the primary outcome. The analyses compared the proportion of participants with peanut allergy in the peanut-avoidance group with the proportion with peanut allergy in the peanut-consumption group at month 60 with the use of a two-tailed chi-square test. Analyses of the data from the two cohorts were independently powered. In the cohort with negative results on the initial skin-prick test, the power to detect a difference in risk of 7 percentage points (9.0% in the avoidance group vs. 2.0% in the consumption group) was

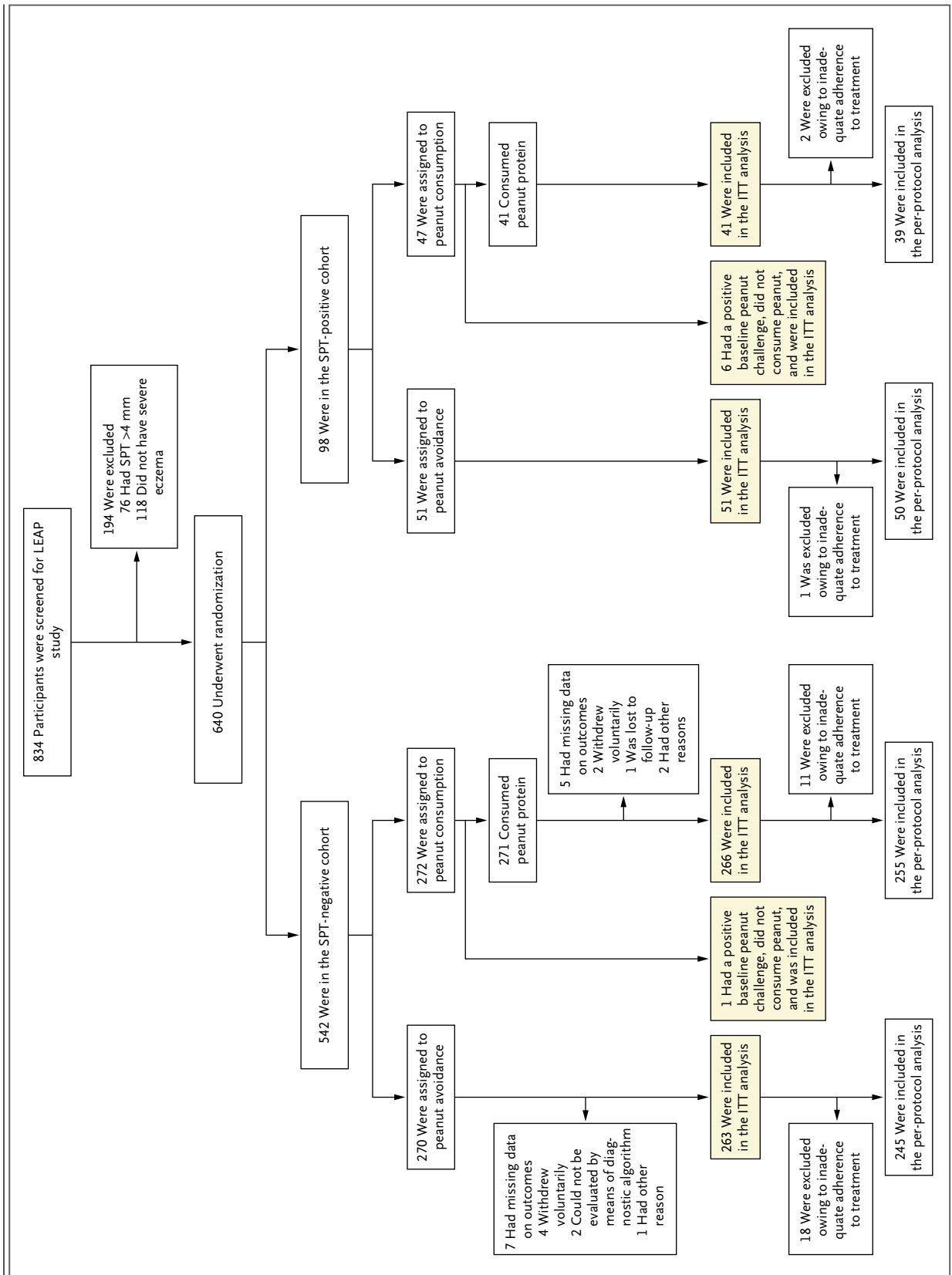


Figure 1 (facing page). Enrollment and Randomization.

Baseline visits occurred when participants were at least 4 months of age but younger than 11 months of age. Participants randomly assigned to peanut consumption who had a positive response to the oral food challenge administered at baseline were instructed not to eat peanuts but were included in the intention-to-treat analysis. Only participants who adequately adhered to treatment were included in the per-protocol analysis. Adequate adherence to treatment was defined in the peanut-avoidance group as consumption of less than 0.2 g of peanut protein (the equivalent of one peanut) on any occasion and less than 0.5 g over a single week in the first 2 years of life. In the peanut-consumption group, adequate adherence was defined as consumption of at least 2 g of peanut protein on at least one occasion in both the first and second years of life and of at least 3 g of peanut protein (25 g of Bamba [a snack food made from peanut butter and puffed maize] or 12 g of peanut butter) per week for at least 50% of the weeks during which data were recorded. SPT denotes skin-prick test.

89.0%. In the cohort with positive results on the initial skin-prick test, the power to detect a difference in risk of 30 percentage points (50.0% in the avoidance group vs. 20.0% in the consumption group) was 80.0%. Worst-case imputation analyses were performed (Fig. 2).

The per-protocol population included participants who adhered adequately to the assigned regimen (consumption or avoidance of peanuts) until 2 years of age (Fig. 1). Analyses of immune markers, including wheal size after skin-prick tests, were performed in the per-protocol population, with data pooled from participants who had negative results on the initial skin-prick test and those who had positive results. Datasets for both the intention-to-treat and per-protocol analyses are available through TrialShare, a public website managed by the Immune Tolerance Network (www.itntrialshare.org/LEAP.url).

RESULTS

STUDY POPULATION

At screening, the median age of participants was 7.8 months (interquartile range, 6.3 to 9.1); the mean ($\pm$ SD) age was 7.8 ± 1.7 months. More male infants were randomly assigned to avoidance than to consumption (64.8% of the avoidance group vs. 55.2% of the consumption group were male infants). The groups were otherwise evenly balanced. Additional information on the base-

line characteristics of the participants is presented in Table S2 in the Supplementary Appendix. The study had a 98.4% retention rate; 10 participants were withdrawn voluntarily by a parent or guardian or were lost to follow-up (Fig. 1).

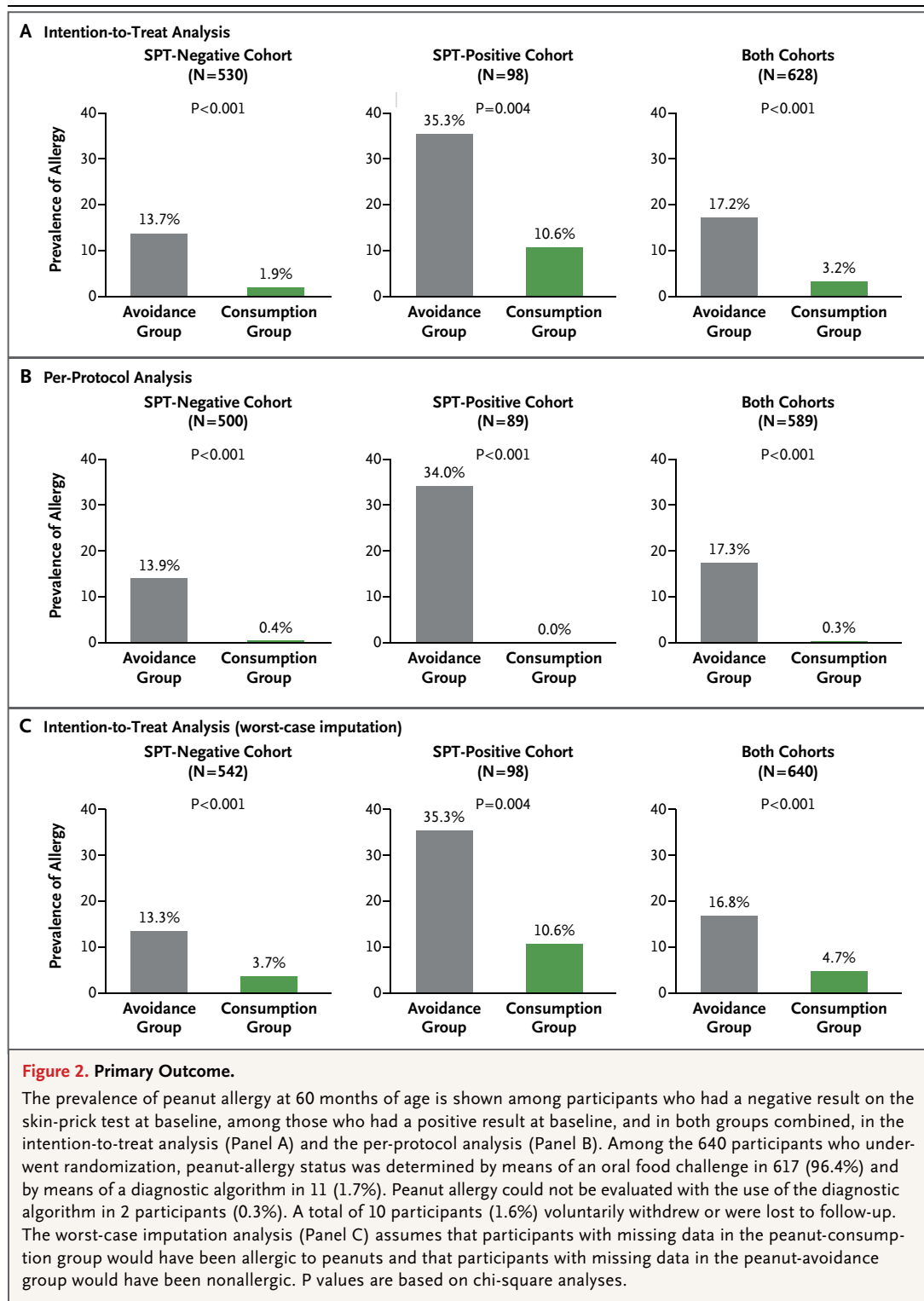
PEANUT CONSUMPTION AND ALLERGY IN HIGH-RISK CHILDREN

Among the 542 infants in the group with a negative result on the initial skin-prick test, 530 (97.8%) could be evaluated for the primary outcome and were included in the intention-to-treat analysis (Fig. 1). At 60 months of age, 13.7% of the avoidance group and 1.9% of the consumption group were allergic to peanuts; this absolute difference in risk of 11.8 percentage points (95% confidence interval [CI], 3.4 to 20.3; $P < 0.001$) represents an 86.1% relative reduction in the prevalence of peanut allergy (Fig. 2).

All 98 children in the group with positive results on the initial skin-prick test were evaluated and were included in the intention-to-treat analysis. At 60 months of age, 35.3% of the avoidance group and 10.6% of the consumption group were allergic to peanuts; the absolute difference in risk of 24.7 percentage points (95% CI, 4.9 to 43.3; $P = 0.004$) represents a 70.0% relative reduction in the prevalence of peanut allergy (Fig. 2).

The per-protocol analysis included 500 infants from the group with negative results on the initial skin-prick test (94.3% of the 530 who could be evaluated) and 89 infants from the group with positive results on the test (90.8% of the 98 who could be evaluated) (Fig. 1). The results in the per-protocol population were similar to those observed in the intention-to-treat population (Fig. 2). The results of a worst-case imputation analysis in the intention-to-treat population were also consistent with the results of the main intention-to-treat analysis (Fig. 2).

Primary prevention targets persons who are not sensitized to peanuts and secondary prevention targets those who are sensitized. In this study, the intervention was effective in reducing the prevalence of peanut allergy in terms of both primary prevention (prevalence of 6.0% in the avoidance group vs. 1.0% in the consumption group, $P = 0.008$) and secondary prevention (33.1% vs. 6.8%, $P < 0.001$) (Table S3 in the Supplementary Appendix). (Results of subgroup analyses according to race or ethnic group are provided in Table S12 in the Supplementary Appendix.)

**ADHERENCE**

The median weekly consumption of peanut protein in the first 2 years of life in the avoidance

group was 0 g, whereas the median in the consumption group was 7.7 g (interquartile range, 6.7 to 8.8). The results with respect to adher-

ence were used to define the per-protocol population (Fig. 1). Dust samples from participants' beds were obtained at month 60 from 423 of the 640 participants (66.1%) in the study population to provide an index of peanut exposure independent of parental reporting. The median level of peanut detected in the bed dust of participants in the avoidance group was 4.1 μg per gram of dust (interquartile range, 1.4 to 14.5), whereas the level in the consumption group was 91.1 μg per gram of dust (interquartile range, 27.2 to 362.0) (Fig. S2 in the Supplementary Appendix). For both measures of adherence, there were no significant differences between the cohort with negative results on the skin-prick test and the cohort with positive results (Tables S4 and S5 in the Supplementary Appendix).

SAFETY

No deaths occurred in the study. There were no significant differences in rates of hospitalization or serious adverse events between the avoidance group and the consumption group (Tables S6 and S7 in the Supplementary Appendix). Considering all adverse events, 99% of participants in each group reported at least one event, with more events recorded in the consumption group than in the avoidance group (4527 vs. 4287, $P=0.02$), according to a Poisson regression analysis (Table S8 in the Supplementary Appendix). With respect to adverse events for which frequencies differed between the two groups, we identified five categories of interest in which the frequencies were higher in the consumption group: upper respiratory tract infection, viral skin infection, gastroenteritis, urticaria, and conjunctivitis. Events in these categories were generally mild or moderate and did not differ significantly in severity between groups. The severity of the events was also similar in a comparison of participants with a peanut-specific IgE level below 0.1 kU per liter and those with a level of 0.1 kU per liter or higher (Table S9 in the Supplementary Appendix). (Additional data and discussion regarding adverse events are provided in the Results and Discussion sections in the Supplementary Appendix and in Table S9 and Fig. S3 in the Supplementary Appendix. All data on adverse events are also available in an interactive graphic at <http://graphics.rhoworld.com/studies/leap/aes/explorer/>.)

RESPONSE TO ORAL FOOD CHALLENGE

Seven participants who were randomly assigned to the consumption group had a positive response to the oral food challenge at baseline and did not consume peanuts. At month 60, four of these participants had a positive response to an oral food challenge and three had a negative response.

Nine participants who were randomly assigned to peanut consumption subsequently discontinued consumption (Table S10 and the Results section in the Supplementary Appendix). At month 60, six of these participants had a positive response to the oral food challenge and three had a negative response.

The 7 participants randomly assigned to consumption who had a positive response to the oral food challenge at baseline had symptoms that were predominantly cutaneous during the challenge. Six were treated with an antihistamine and 1 was treated with an oral glucocorticoid. Among the 57 participants (9 randomly assigned to consumption and 48 to avoidance) who had a positive response to the oral food challenge at 60 months, 14 had respiratory or cardiovascular signs and 9 received intramuscular epinephrine owing to concerns about the severity of the allergic reaction (Table S11 in the Supplementary Appendix).

IMMUNOLOGIC ASSESSMENTS

Peanut-specific immunoglobulins were measured in serum samples at baseline (at which time participants were between 4 months and 11 months of age) and when the children were 12, 30, and 60 months of age. Figure 3A shows wheal size and level of peanut-specific IgE in participants who met the per-protocol criteria. A significant increase from baseline in wheal size was seen only in the peanut-avoidance group. Participants who were allergic to peanuts at month 60 showed a more pronounced increase in wheal size over time. These participants also had higher peanut-specific IgE levels. Although peanut-specific IgE levels increased over time in both the peanut-avoidance and peanut-consumption groups, there were fewer participants in the consumption group with very high IgE levels at 12, 30, and 60 months (Fig. S4 in the Supplementary Appendix).

Figure 3B shows the levels of peanut-specific IgG and IgG4 and the IgG4:IgE ratio. The levels of peanut-specific IgG and IgG4 were higher in the consumption group than in the avoidance group. Peanut-specific IgG4 levels increased over

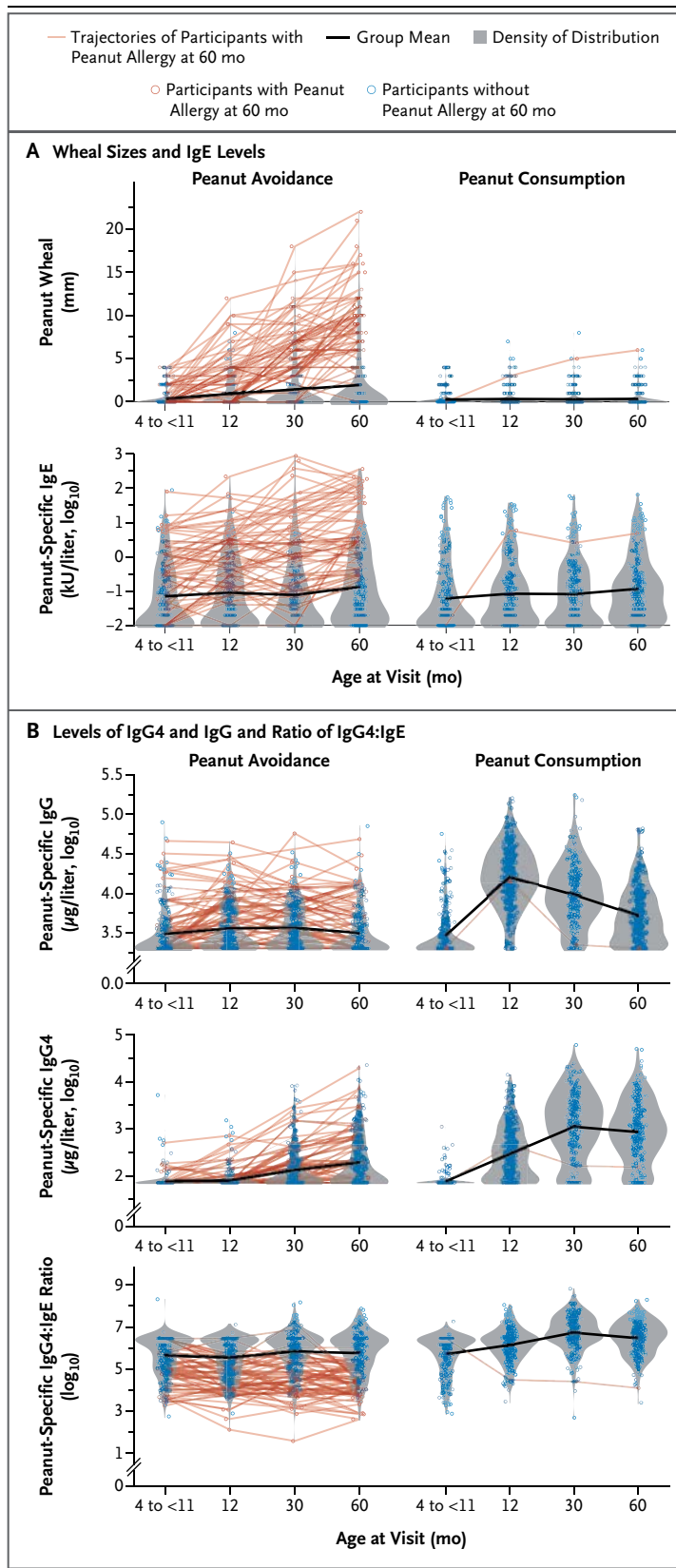


Figure 3. Immunologic Outcomes for the Peanut-Avoidance and Peanut-Consumption Groups at Baseline (4 to <11 Months of Age) and at 12, 30, and 60 Months of Age.

Panel A shows wheal sizes after the peanut-specific skin-prick test and the levels of peanut-specific IgE in participants in the avoidance and consumption groups who met the per-protocol criteria. The solid black lines show the group mean over the course of the study period; the mean wheal size after the peanut-specific skin-prick test differed significantly between the randomized groups at all time points after baseline ($P=0.002$ at 12 months and $P<0.001$ at 30 months and 60 months). The thin red lines represent the trajectory of the development of allergic responses among participants who were allergic at 60 months of age. Panel B shows the levels of peanut-specific IgG and IgG4 and the peanut-specific IgG4:IgE ratio over the course of the study period. The means of each of these measures differed significantly between the two study groups at all postbaseline time points ($P<0.001$). The log₁₀ of the ratio of peanut-specific IgG4:IgE was calculated after peanut-specific IgG4 levels were converted from milligrams per liter to nanograms per milliliter and the peanut-specific IgE levels were converted from kilo unit per liter to nanograms per milliliter with the use of the formula $(\text{IgG4} \times 1000) \div (\text{IgE} \times 2.4)$.

time in both groups, but these changes were significantly larger in the consumption group ($P<0.001$). The ratio of peanut-specific IgG4 to IgE increased up to 30 months of age in the consumption group but was relatively constant in the avoidance group. At month 60, the IgG4:IgE ratio in nearly all the participants with peanut allergy in the avoidance group fell below the mean ratio for the group.

Some participants in the per-protocol analysis who were allergic at month 60 had elevated levels of peanut-specific IgE as early as 12 months of age. At month 60, all the participants in the peanut-avoidance group who had peanut-specific IgE levels of more than 10.0 kU per liter were allergic to peanuts, regardless of their level of peanut-specific IgG4. All other allergic participants had levels of peanut-specific IgE between 0.1 and 10 kU per liter and levels of IgG4 that were less than 1000.0 μg per liter. (Fig. S5 in the Supplementary Appendix shows contour diagrams of the distribution of peanut-specific IgE in relation to peanut-specific IgG4 over time in participants who met the per-protocol criteria. Fig. S5 also shows that levels of peanut-specific IgE did not exceed 100.0 kU per liter in the peanut-consumption group. Peanut-specific IgG4 levels in this

group rose early and continued to increase through 60 months of age.)

DISCUSSION

Among infants with high-risk atopic disease, sustained peanut consumption beginning in the first 11 months of life, as compared with peanut avoidance, resulted in a significantly smaller proportion of children with peanut allergy at the age of 60 months. This intervention was safe, tolerated, and highly efficacious. In the intention-to-treat analysis, peanut consumption was associated with an 86% reduction in peanut allergy at 60 months of age among participants who had had negative results on a peanut-based skin-prick test at study entry and with a 70% reduction among those who had had positive test results at study entry.

The overall rate of adherence to the two assigned interventions was 92.0%. Among the 319 participants randomly assigned to consumption, 7 were instructed not to consume peanuts because they had a positive result at baseline to the oral food challenge, and 9 terminated consumption largely because they began to have allergic symptoms to peanuts. This indicates that peanut consumption may not be possible in some children who meet the LEAP eligibility criteria. In addition, the LEAP study design excluded 9.1% of the infants who were screened (76 of 834) because large wheals (greater than 4 mm in diameter) developed after the skin-prick test²¹ that were probably associated with peanut allergy; the safety and effectiveness of early peanut consumption in that population remain unknown.

Almost all the participants (98.4%) were available for assessment at 60 months of age, with 617 (96.4%) assessed by means of an oral food challenge, the most stringent determination of food allergy. Adherence was monitored with the use of food-frequency questionnaires during the study and was corroborated at the end of the study through the measurement of peanut in bed dust, an objective and previously validated surrogate for consumption.^{23,24}

The main weakness of the study was the lack of a placebo regimen, a problem that was partially mitigated by the use of objective peanut challenges as the primary outcome. In addition, the study did not include low-risk infants and those who had large wheals (>4 mm in diameter) after the

skin-prick test. A further limitation was the failure to collect dust samples to validate consumption at earlier time points in the study.

At 60 months, the mean diameter of wheals and the number of participants with markedly elevated levels of peanut-specific IgE titers were higher in the peanut-avoidance group than in the consumption group. In contrast, the peanut-consumption group showed a significantly greater and earlier increase in levels of peanut-specific IgG and IgG4 (Fig. 3B); this effect mirrors the immunologic changes seen in successful allergen immunotherapy.²⁹ Furthermore, in the avoidance group, unless peanut-specific IgE levels were very high, elevated IgG4 levels were associated with the absence of an allergic reaction to peanuts (Fig. S5 in the Supplementary Appendix). Both observations indicate that IgG4 is associated with a protective role against the development of allergy; although peanut-specific IgG4 has recently been shown to inhibit basophil activation *in vitro* in response to peanut,³⁰ our data do not establish causality at the clinical level.

In this study, very early sensitization was observed in infants with no history of peanut consumption. As we have proposed in our dual allergen hypothesis, early environmental exposure (through the skin) to peanut may account for early sensitization,³¹ whereas early oral exposure may lead to immune tolerance. The LEAP study showed that early oral introduction of peanuts could prevent allergy in high-risk, sensitized infants and in nonsensitized infants (Table S3 in the Supplementary Appendix).

The question of whether the participants who consumed peanut would continue to remain protected against the development of peanut allergy even after prolonged cessation of peanut consumption requires further study and is under investigation in the LEAP-On study (Persistence of Oral Tolerance to Peanut; ClinicalTrials.gov number, NCT01366846). Our findings showed that early, sustained consumption of peanut products was associated with a substantial and significant decrease in the development of peanut allergy in high-risk infants. Conversely, peanut avoidance was associated with a greater frequency of clinical peanut allergy than was peanut consumption, which raises questions about the usefulness of deliberate avoidance of peanuts as a strategy to prevent allergy.

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Dr. Brough reports receiving grant support from Action Medical Research and study materials from Stallergenes, Thermo Scientific, and Meridian Foods. Dr. Lack reports holding stock and stock options in DBV Technologies. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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SUPPLEMENTARY APPENDIX

Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

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1. SUPPLEMENT TO THE METHODS

Enrollment and Study Procedures: Definition of Severe Eczema

Severe eczema was defined in the protocol eligibility criteria and defined in one of three ways. The study definition for severe eczema is described in the Protocol under Study definitions Section 3.5. and is as follows:

- A rash that required the application of a topical creams and ointments containing corticosteroids or calcineurin inhibitors and if the participant is:
 - <6 months of age, lasted for at least 12 out of 30 days on two occasions, or
 - >6 months of age, lasted for at least 12 out of 30 days on two occasions in the last 6 months; or
- Has been described by the participant's parent or guardian in a pre-enrollment questionnaire as "a very bad rash in joints and creases" or "a very bad itchy, dry, oozing, or crusted rash"; or
- Is currently or was previously graded ≥ 40 using the modified SCORAD evaluation.

2. SUPPLEMENT TO THE RESULTS

Peanut Consumption Prevents Allergy in Children: Analysis of Primary and Secondary Prevention

The LEAP study was conceived as two independently powered studies to examine the effects of intervention in an SPT negative group who are presumed to be non peanut sensitized and a peanut sensitized SPT positive group. The SPT negative group is described in the manuscript as 'the cohort with negative results on the initial skin-prick test' and the SPT positive group as 'the cohort with positive results on the initial skin-prick test'. It emerged early in the study that a high percentage of children who were SPT negative already showed serological evidence of IgE sensitization to peanut. Thus there are two levels of sensitization; firstly sensitization with IgE production in the serum, and secondly SPT positive sensitization where IgE is bound to cutaneous mast cells.

Our primary endpoint analyses were conducted independently on the SPT-negative and SPT-positive strata as per our statistical analysis plan. However we performed further analyses to distinguish between primary and secondary effects. In order to examine primary prevention, we looked at the efficacy of intervention in infants who were both SPT negative and specific IgE negative ($<0.1\text{kU}_A/\text{L}$). The supplementary table (Table S3) shows how we are able to look at primary prevention vs secondary prevention in children with exclusively serological sensitization and secondary prevention in children with both serological and SPT positive sensitization.

Compliance and Safety: Participants Who Discontinued Peanut Consumption

At baseline, Oral Food Challenges (OFC) were undertaken for all participants randomized to the peanut group ($n=319$). All but 7 of these OFCs were negative; of the participants with a positive OFC, 6 were in the SPT-positive stratum and one in the SPT-negative stratum. The symptom presentation, and medication requirement, for these seven positive baseline OFCs are detailed in **Table S11**. There were no SAE's reported.

There were 9 participants with a negative baseline OFC who subsequently discontinued peanut consumption. Only one of these participants met the criteria for per-protocol peanut consumption. A peanut-induced SAE was reported for one of these 9 participants. **Table S10** provides the clinical details of these 9 participants including stratum, age of discontinuation of peanut ingestion, symptoms that influenced the decision to stop ingesting peanut, and month 60

outcome. As shown in the table, several of these participants had an unscheduled visit (USV) to evaluate more fully their symptoms.

There were 3 OFCs undertaken at USVs; no SAEs were reported.

There were 617 OFCs undertaken at V60 of which 57 were positive. The clinical symptoms and medication requirements for all positive OFCs are detailed in **Table S11**.

3. SUPPLEMENT TO THE DISCUSSION

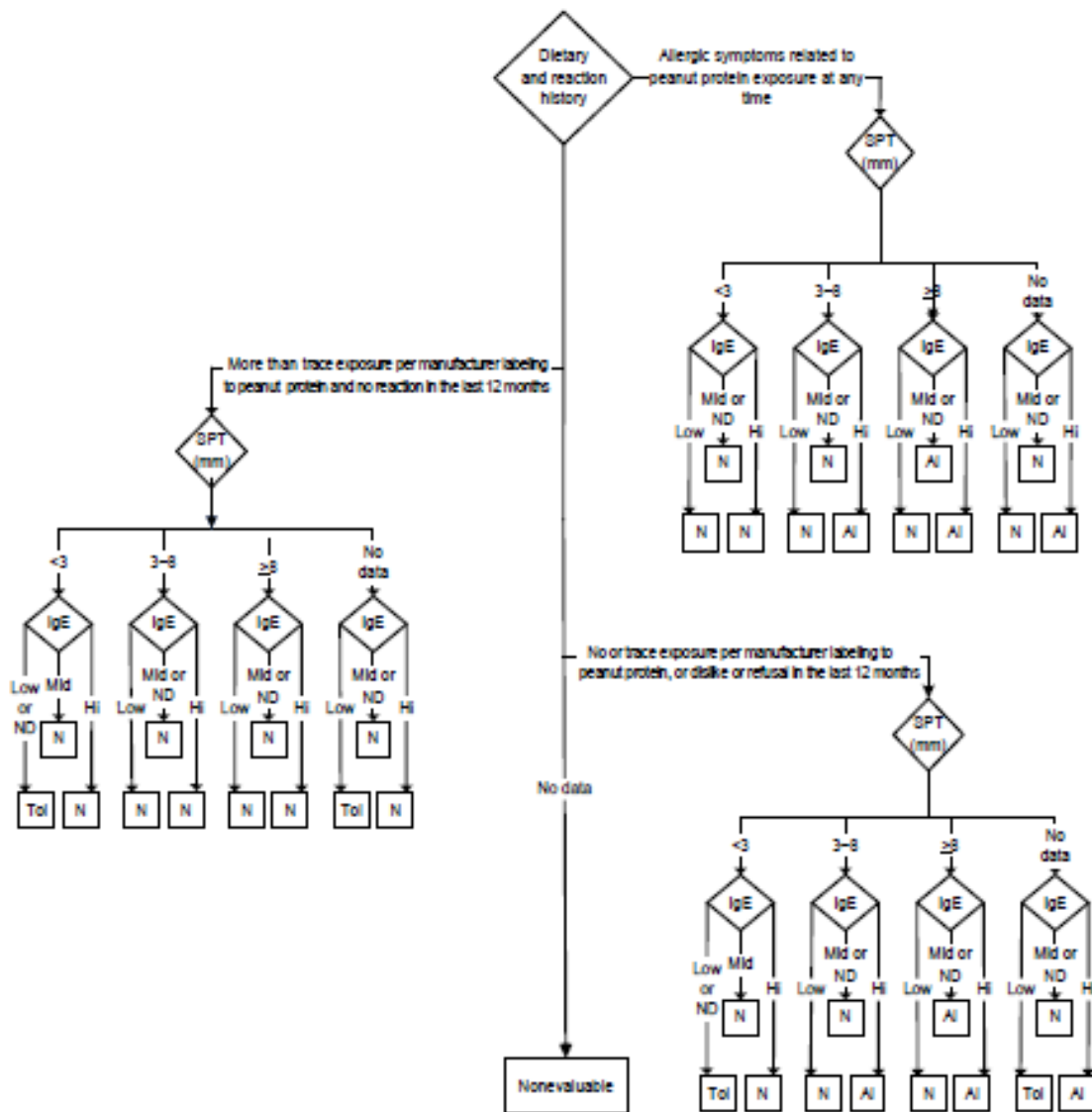
Compliance and Safety

Although there was no difference in the rate of serious adverse events between the two groups, we did note an increase in the total number of adverse events in the consumption group which cannot easily be accounted for. This could represent a real association with the intervention, or alternatively could reflect a reporting bias due to the unblinded study design. It is noteworthy that the reactions reported more frequently in the consumption group generally relate to symptoms that patients perceive to be a consequence of food allergy or food intolerance, such as rashes or gastrointestinal complaints. Given that this excess of reactions was not IgE-associated; this could reflect either non-IgE mediated immunological pathways or parental concern due to the nature of the intervention. It should be noted, however, that this excess of adverse events generally comprised mild and moderate symptoms and we believe is outweighed by the burden of peanut allergy in the population that did not undergo the intervention.

4. SUPPLEMENTARY FIGURES

Figure S1. Diagnostic Algorithm for Determination of Peanut Allergy in the Absence of Peanut-Challenge Results Using Dietary and Reaction History, SPT, and Peanut-Specific IgE.

An oral food challenge was used for the assessment of peanut allergy for 96% (617 of 640) of participants; this diagnostic algorithm was therefore required for 13 study participants whose outcomes were as follows: 7 were peanut allergic, 4 were peanut tolerant and 2 were non-evaluable.

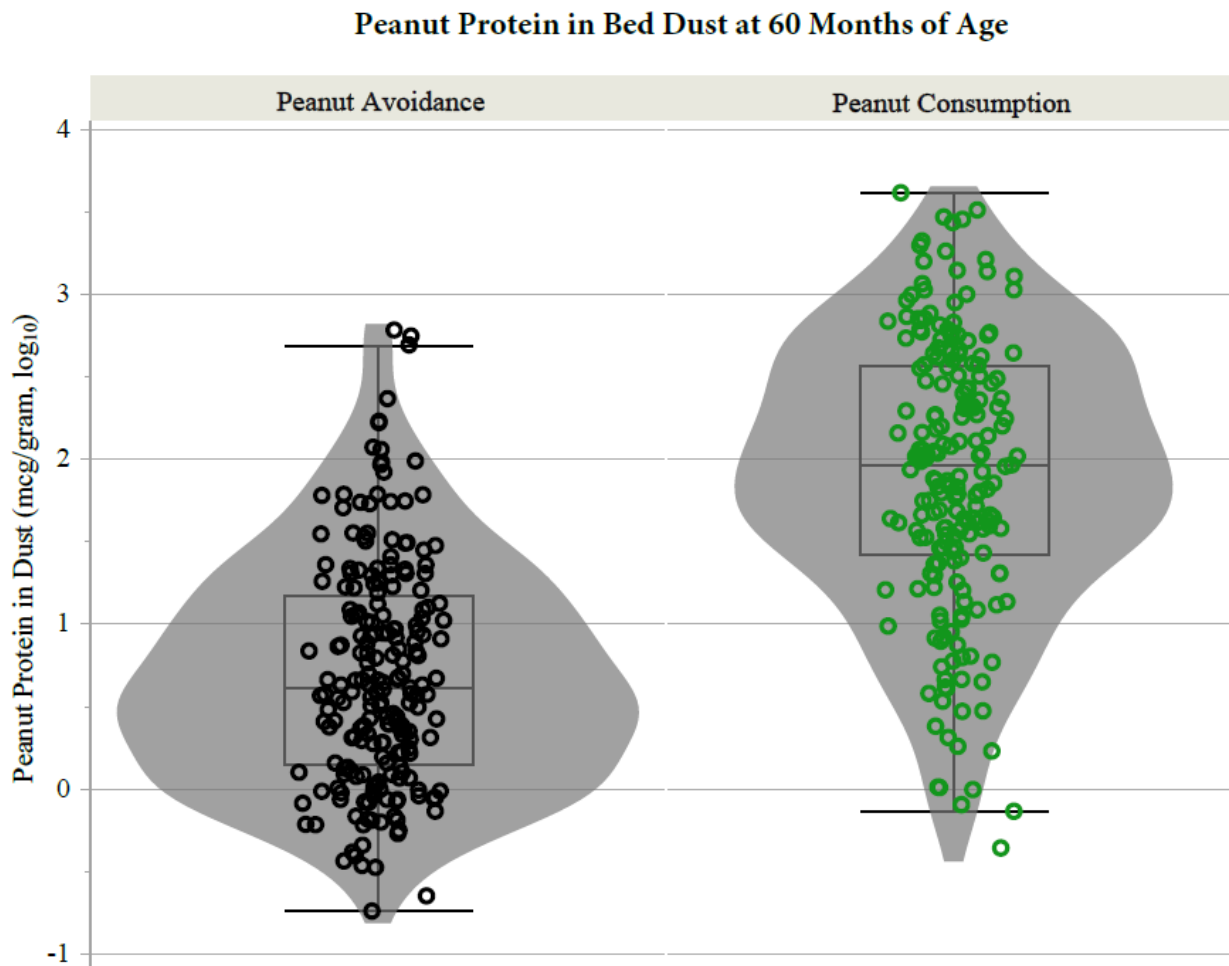


LEGEND

IgE Levels in kU_A/L
 Low: < 0.35
 Mid: ≥ 0.35 and < 15
 Hi: ≥ 15
 ND: No data

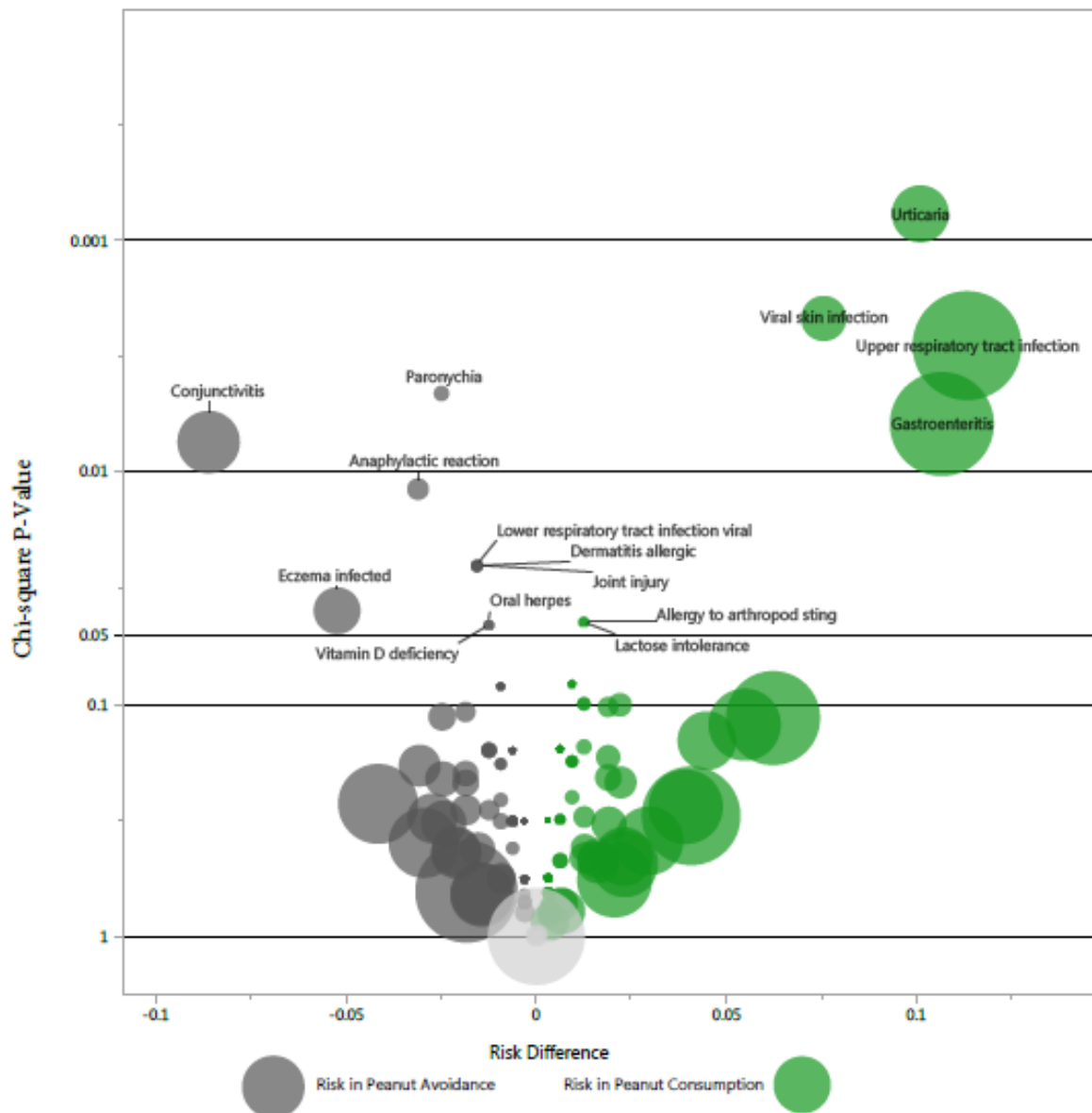
Tol: tolerant
 Al: allergic
 N: nonevaluable

Figure S2. Peanut Protein in Bed Dust at 60 Months of Age



Peanut protein levels (mcg/g, log₁₀ transformed units) are shown from dust collected from individual participant's bed sheets who provided samples at 60 months. These represent data from subjects in the peanut avoidance group (N=218), in black, and the peanut consumption group (N=205), shown in green. The box in the box and whisker plots represents the median and IQR. The whiskers represent the furthest point within 1.5 times the IQR from the box.

Figure S3. Adverse Event Volcano Plot



These analyses are performed on the preferred term categorization, which is a coded version of the verbatim term using the Medical Dictionary for Regulatory Activities (MedDRA). The sizes of the bubbles are proportional to the number of subjects having the preferred term. The risk difference is displayed on the x-axis and is calculated by subtracting the incidence of the preferred term between the randomized groups. The y-axis displays chi-square p-values.

All AE and SAE data are also available in an interactive explorer at
<http://graphics.rhoworld.com/studies/leap/aes/explorer/>.

Figure S4. Proportion Density Plot

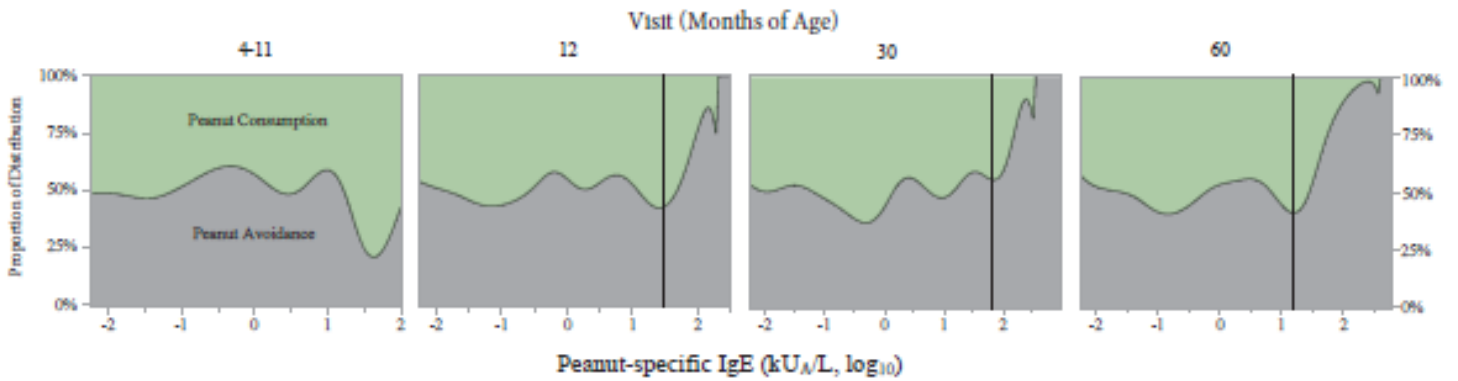
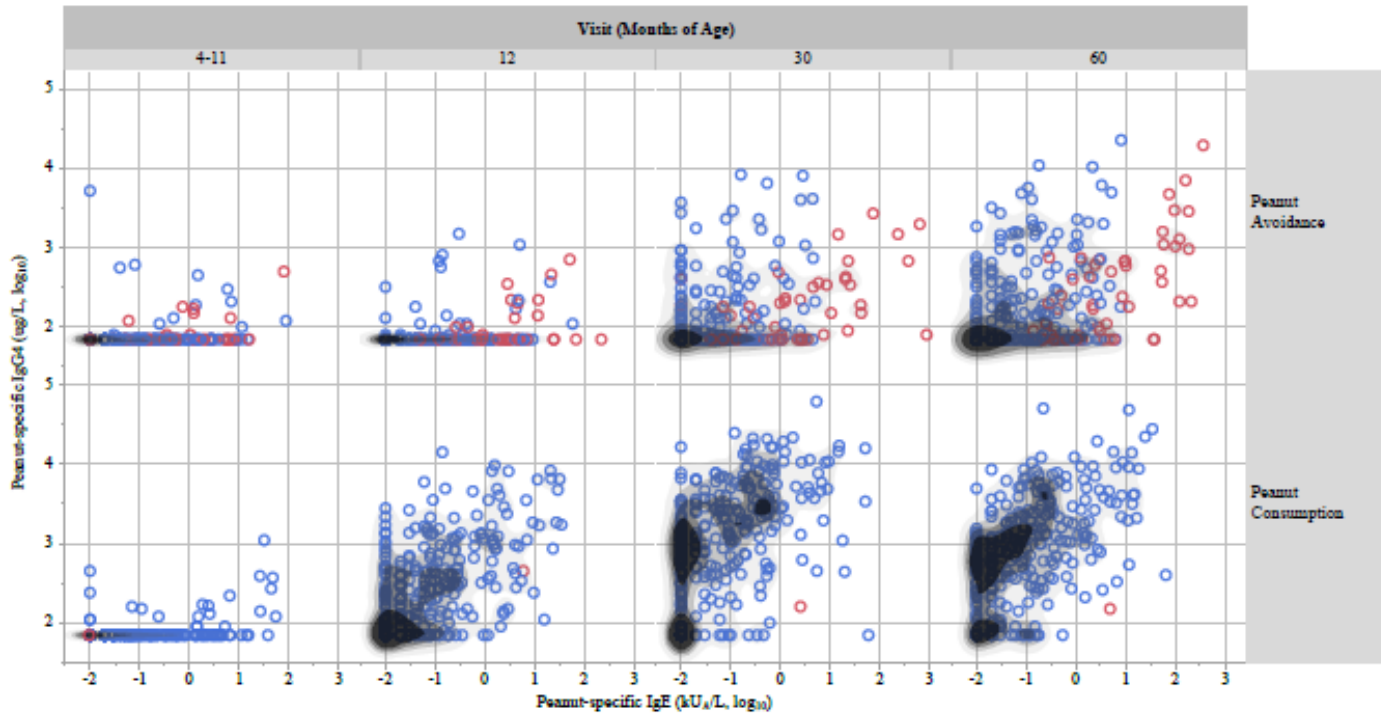


Figure S4 shows the relative distribution of peanut-specific IgE between the peanut consumption (shown in green) and avoidance (shown in gray) arms. The vertical reference lines indicate where the higher end of the distribution begins to significantly differ ($p < 0.05$) between the randomized arms using bootstrap sampling of 1000 replicates of the upper percentiles. The progressive divergence in the distribution over time demonstrates that very high peanut-specific IgE values are disproportionally represented in the avoidance arm compared to the consumption arm.

Figure S5. Contour Scatter Plots of Peanut-specific IgG4 versus Peanut-specific IgE at 4-11, 12, 30 and 60 Months of Age



Peanut-specific IgG4 is plotted against peanut-specific IgE for individual participants in the peanut avoidance group (top) and the consumption group (bottom). The dark gray to light gray shading represents the density of participants in each part of this distribution. Participants with peanut allergy at 60 months are colored red; non-allergic participants are colored blue.

5. SUPPLEMENTARY TABLES

Table S1. Leap Study Schedule of Events

Age in months	4–10	4–10	4–11	12	13–29	30	31–59	60	
Visit	–1	0	0.01–0.36	12	12.01–12.39	30	30.01–30.30 ¹	60	Unscheduled 99
			Weekly phone dietary consultation ²		Biweekly phone dietary consultation		Monthly phone dietary consultation		USV ³
Informed consent	X								
Randomization		X							
Dietary education		X	X	X	X	X	X	X	X
General Assessments									
Physical examination	X	X		X		X		X	X
Medical history	X								
Adverse events		X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Dietary history		X	X ⁴	X	X ³	X		X	X
Food reaction history			X	X	X	X	X	X	X
Eczema evaluation	X			X		X		X	
Rhinitis evaluation						X		X	
Asthma evaluation						X		X	
Laboratory Assessments									
Hematology	X							X	
Serum chemistries	X							X	
Skin and nasal swab culture		X		X		X		X	
Allergy Assessments									
SPT for ingested allergens	X			X		X		X	X
SPT for tree nuts								X	
IgE for ingested allergens	X			X		X		X	X
IgE for inhalant allergens						X		X	
Oral food challenges								X	X
Peanut challenges		X						X	X
Peanut Consumption									
Maternal peanut protein consumption history		X							
Participant peanut protein consumption monitoring	X	X	X	X	X	X	X	X	X
Household peanut protein consumption monitoring		X	X ³	X	X ³	X		X	X
Immunologic Assessments									
PBMC T-cell assay	X			X		X		X	
Serum allergen-specific immunoglobulins	X			X		X		X	
Serum total IgE	X					X		X	
Plasma allergen archive	X			X		X		X	
Whole blood DNA-HLA genotypes	X			X					

¹ Additional monthly phone dietary consultation visits (30.31 – 30.36) were allowed during the protocol window for V60 i.e. ± 6 months

² In addition to telephone dietary consultations, an in-home dietary consultation was performed at 9 months of age for participants enrolled younger than 6 months of age and at 21 months of age for all participants.

³ An unscheduled clinic visit was conducted when necessary for aversion to peanut, refusal of peanut, or both, or for suspected peanut allergy.

⁴ Performed only at the in-home dietary consultation.

The Baseline visit occurred between ≥ 4 to < 11 months of age, the V12 visit at 12 months, the V30 visit at 30 months of age and the V60 at 60 months of age; these were face-to-face visits. Visit windows are detailed in Section 6.1 of the Study Protocol (Supplementary Material). Dietary consultations were conducted by telephone and at the above face-to-face visits.

Table S2. Baseline Characteristics

	Negative Stratum (N=542)		Positive Stratum (N=98)		Overall (N=640)	
	Avoidance Group (N=270)	Consumption Group (N=272)	Avoidance Group (N=51)	Consumption Group (N=47)	Avoidance Group (N=321)	Consumption Group (N=319)
Age at screening (mo), mean (SD)	7.7 (1.71)	7.7 (1.77)	8.4 (1.66)	7.9 (1.56)	7.8 (1.72)	7.8 (1.74)
Male sex, no. (%) [*]	174 (64.4%)	148 (54.4%)	34 (66.7%)	28 (59.6%)	208 (64.8%)	176 (55.2%)
Race, no. (%)						
White	207 (76.7%)	196 (72.1%)	37 (72.5%)	30 (63.8%)	244 (76.0%)	226 (70.8%)
Black	21 (7.8%)	21 (7.7%)	5 (9.8%)	1 (2.1%)	26 (8.1%)	22 (6.9%)
Other						
Mixed	34 (12.6%)	40 (14.7%)	6 (11.8%)	9 (19.1%)	40 (12.5%)	49 (15.4%)
Asian [†]	6 (2.2%)	10 (3.7%)	3 (5.9%)	5 (10.6%)	9 (2.8%)	15 (4.7%)
Chinese, Middle Eastern or other	2 (0.7%)	4 (1.5%)	0 (0%)	2 (4.3%)	2 (0.6%)	6 (1.9%)
Severe eczema, no. (%)	236 (87.4%)	246 (90.4%)	48 (94.1%)	41 (87.2%)	284 (88.5%)	287 (90.0%)
Age at onset of eczema (mo), mean (SD)	2.2 (1.65)	2.3 (1.61)	2.1 (1.60)	2.4 (1.47)	2.2 (1.64)	2.3 (1.59)
SCORAD, mean (SD)	35.0 (19.87)	33.3 (18.35)	33.7 (16.16)	37.8 (18.64)	34.8 (19.31)	34.0 (18.43)
Total IgE (kU _L /L), mean (SD)	95.1 (321.80)	76.4 (181.39)	125.7 (174.83)	306.4 (666.51)	100.0 (303.24)	109.7 (312.98)
Peanut-specific IgE (kU _A /L), median (IQR)	0.0 (0,0)	0.0 (0,0)	0.4 (0,3)	1.3 (0,5)	0.0 (0,0)	0.0 (0,0)

* P-value <0.05 in the overall and in the Negative Stratum comparisons; based on a Fisher's exact test comparing the percentage of subjects in the Avoidance Group to the Consumption Group.

† Participants with origins in the Indian subcontinent.

Table S3. Primary and Secondary Prevention for Different Levels of Sensitization

	Peanut Avoidance (N=313)	Peanut Consumption (N=312)	Total (N=625)	p value
Primary Prevention Group				0.0079 ¹
Not Allergic	172 (94.0%)	193 (99.0%)	365 (96.6%)	
Allergic	11 (6.0%)	2 (1.0%)	13 (3.4%)	
Secondary Prevention Group				<0.0001 ¹
Not Allergic	87 (66.9%)	109 (93.2%)	196 (79.4%)	
Allergic	43 (33.1%)	8 (6.8%)	51 (20.6%)	
SPT-Negative & IgE Positive				<0.0001 ¹
Not Allergic	54 (68.4%)	67 (95.7%)	121 (81.2%)	
Allergic	25 (31.6%)	3 (4.3%)	28 (18.8%)	
SPT-Positive & IgE Positive				0.0061 ¹
Not Allergic	22 (59.5%)	34 (87.2%)	56 (73.7%)	
Allergic	15 (40.5%)	5 (12.8%)	20 (26.3%)	
SPT-Positive & IgE Negative				0.1589 ¹
Not Allergic	11 (78.6%)	8 (100.0%)	19 (86.4%)	
Allergic	3 (21.4%)	0 (0.0%)	3 (13.6%)	

¹Chi-Square

The primary prevention group comprised those participants who were both peanut SPT-negative AND specific IgE negative (<0.1 kU_A/L) at baseline, as shown in Table 1. The overall secondary prevention group comprised participants who were either SPT-positive, peanut-specific IgE positive (IgE ≥0.1 kU_A/L), or both at baseline. Table S3 shows the results for the sensitization permutations within the secondary prevention group; these three groups include participants with baseline sensitization results that are SPT Negative AND IgE Positive, SPT Positive AND IgE Positive, and SPT Positive AND IgE Negative. The results demonstrate that the intervention was highly effective in all groups; however, the SPT-Positive AND IgE Negative group included only 22 participants and was not sufficiently powered to detect a statistically significant difference in the prevalence of peanut allergy (21.4% versus 0%, p=0.1589). The sample size for this analysis is 625 (not 628) because of 3 missing peanut specific-IgE values at baseline.

Table S4. Peanut Protein Consumption (grams) by Randomized Group and Stratum

	SPT-negative Stratum		SPT-positive Stratum			
	Peanut Avoidance (N=270)	Peanut Consumption (N=272)	Peanut Avoidance (N=51)	Peanut Consumption (N=47)	Total (N=640)	p value
Average Weekly Consumption First Year of Life						<0.01 ¹
Mean (SD)	0.00 (0.00)	6.25 (2.56)	0.00 (0.00)	5.15 (2.65)	3.03 (3.55)	
Median	0.00	6.38	0.00	6.00	0.00	
Range	(0.00-0.04)	(0.00-14.29)	(0.00-0.00)	(0.00-8.84)	(0.00-14.29)	
Average Weekly Consumption Second Year of Life²						<0.01 ¹
Mean (SD)	0.02 (0.18)	8.44 (2.81)	0.00 (0.01)	7.20 (3.69)	4.13 (4.63)	
Median	0.00	8.37	0.00	8.23	0.01	
Range	(0.00-2.75)	(0.00-18.09)	(0.00-0.07)	(0.00-13.69)	(0.00-18.09)	
Average Weekly Consumption First and Second Years of Life						<0.01 ¹
Mean (SD)	0.01 (0.10)	7.76 (2.30)	0.00 (0.01)	6.58 (3.30)	3.79 (4.18)	
Median	0.00	7.69	0.00	7.45	0.02	
Range	(0.00-1.55)	(0.00-15.17)	(0.00-0.04)	(0.00-11.64)	(0.00-15.17)	

¹Kruskal Wallis

²Three participants in the SPT-negative Stratum (2 in avoidance and 1 in consumption) were missing weekly consumption data during the second year of life.

Peanut protein consumption (in grams) in the first two years of life as measured by a validated food frequency questionnaire administered during telephone and clinic visits.

Table S5. Peanut Protein in Bed Dust at 60 Months of Age by Stratum

Peanut Protein in Dust by Stratum				
	SPT-negative Stratum (N=355)	SPT-positive Stratum (N=68)	Total (N=423)	p value
Peanut Protein in Dust (mcg/gram dust)				0.70 ¹
N	350	67	417	
Median	18.0	18.3	18.1	
Range	(0.2-4140.6)	(0.2-1165.2)	(0.2-4140.6)	
¹ Wilcoxon				

Table S6. All Cause Hospitalizations and Mortality

All Cause Hospitalizations and Mortality				
	Peanut Avoidance (N=321)	Peanut Consumption (N=319)	Total (N=640)	p value
Number of Hospitalizations				0.83 ¹
0	269 (83.8%)	269 (84.3%)	538 (84.1%)	
1	37 (11.5%)	36 (11.3%)	73 (11.4%)	
2	10 (3.1%)	11 (3.4%)	21 (3.3%)	
3	3 (0.9%)	2 (0.6%)	5 (0.8%)	
4	2 (0.6%)	0 (0.0%)	2 (0.3%)	
5	0 (0.0%)	1 (0.3%)	1 (0.2%)	
Was Subject Ever Hospitalized?				0.86 ²
No	269 (83.8%)	269 (84.3%)	538 (84.1%)	
Yes	52 (16.2%)	50 (15.7%)	102 (15.9%)	
Did Subject Die?				
No	321 (100.0%)	319 (100.0%)	640 (100.0%)	
¹ Fisher Exact ² Chi-Square				

Table S7. Serious Adverse Events

	Negative Stratum (N=542)		Positive Stratum (N=98)		Overall (N=640)		P-value [1] SPT-Neg	P-value [2] SPT-Pos	P-value [3] Overall
	Avoidance Group (N=270)	Consumption Group (N=272)	Avoidance Group (N=51)	Consumption Group (N=47)	Avoidance Group (N=321)	Consumption Group (N=319)			
Number of Events	78	65	23	24	101	89			
Number of Participants with at Least One Event	55(20.4)	47(17.3)	15(29.4)	14(29.8)	70(21.8)	61(19.1)	0.380	>0.999	0.434
Respiratory, thoracic and mediastinal disorders	19(7.0)	24(8.8)	8(15.7)	9(19.1)	27(8.4)	33(10.3)	0.526	0.791	0.419
Wheezing	17(6.3)	18(6.6)	6(11.8)	6(12.8)	23(7.2)	24(7.5)	>0.999	>0.999	0.881
Asthma	4(1.5)	9(3.3)	2(3.9)	2(4.3)	6(1.9)	11(3.4)	0.261	>0.999	0.230
Lung consolidation	0(0)	0(0)	0(0)	1(2.1)	0(0)	1(0.3)		0.480	0.498
Respiratory failure	0(0)	0(0)	0(0)	1(2.1)	0(0)	1(0.3)		0.480	0.498
Infections and infestations	24(8.9)	15(5.5)	2(3.9)	4(8.5)	26(8.1)	19(6.0)	0.138	0.423	0.354
Gastroenteritis	4(1.5)	3(1.1)	1(2.0)	1(2.1)	5(1.6)	4(1.3)	0.724	>0.999	>0.999
Pneumonia	3(1.1)	2(0.7)	0(0)	0(0)	3(0.9)	2(0.6)	0.685		>0.999
Gastroenteritis viral	1(0.4)	3(1.1)	0(0)	0(0)	1(0.3)	3(0.9)	0.624		0.372
Viral infection	4(1.5)	0(0)	0(0)	0(0)	4(1.2)	0(0)	0.061		0.124
Eczema herpeticum	0(0)	1(0.4)	1(2.0)	1(2.1)	1(0.3)	2(0.6)	>0.999	>0.999	0.623
Eczema infected	1(0.4)	2(0.7)	0(0)	0(0)	1(0.3)	2(0.6)	>0.999		0.623
Cellulitis	2(0.7)	0(0)	0(0)	0(0)	2(0.6)	0(0)	0.248		0.499
Lower respiratory tract infection	1(0.4)	0(0)	0(0)	1(2.1)	1(0.3)	1(0.3)	0.498	0.480	>0.999
Tonsillitis	1(0.4)	1(0.4)	0(0)	0(0)	1(0.3)	1(0.3)	>0.999		>0.999
Upper respiratory tract infection	2(0.7)	0(0)	0(0)	0(0)	2(0.6)	0(0)	0.248		0.499
Urinary tract infection	1(0.4)	1(0.4)	0(0)	0(0)	1(0.3)	1(0.3)	>0.999		>0.999
Arthritis bacterial	0(0)	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	>0.999		0.498

Note: At each level of summarization, a participant is counted once if the participant reported one or more events. Events are coded according to MedDRA V11.1.

[1] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group within the SPT-negative stratum.

[2] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group within the SPT-positive stratum.

[3] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group across both the SPT-negative and SPT-positive strata.

All AE and SAE data are also available in an interactive explorer at <http://graphics.rhoworld.com/studies/leap/aes/explorer/>.

	Negative Stratum (N=542)		Positive Stratum (N=98)		Overall (N=640)		P-value [1] SPT-Neg	P-value [2] SPT-Pos	P-value [3] Overall
	Avoidance Group (N=270)	Consumption Group (N=272)	Avoidance Group (N=51)	Consumption Group (N=47)	Avoidance Group (N=321)	Consumption Group (N=319)			
Infections and infestations									
Bronchiolitis	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Febrile infection	0(0)	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	>0.999		0.498
Measles	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Meningitis viral	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Meningococcal sepsis	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Paronychia	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Sepsis	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Urinary tract infection pseudomonal	0(0)	0(0)	0(0)	1(2.1)	0(0)	1(0.3)		0.480	0.498
Varicella	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Viral tonsillitis	0(0)	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	>0.999		0.498
Immune system disorders									
Anaphylactic reaction	5(1.9)	0(0)	7(13.7)	4(8.5)	14(4.4)	6(1.9)	0.105	0.528	0.110
Food allergy	0(0)	2(0.7)	0(0)	2(4.3)	0(0)	4(1.3)	0.030	0.322	0.033
Allergy to animal	0(0)	0(0)	1(2.0)	0(0)	1(0.3)	0(0)		>0.999	0.061
Hypersensitivity	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.499		>0.999
Milk allergy	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Injury, poisoning and procedural complications									
Head injury	5(1.9)	4(1.5)	1(2.0)	1(2.1)	6(1.9)	5(1.6)	0.751	>0.999	>0.999
Forearm fracture	2(0.7)	2(0.7)	0(0)	0(0)	2(0.6)	2(0.6)	>0.999		>0.999
Foreign body trauma	0(0)	1(0.4)	0(0)	1(2.1)	0(0)	2(0.6)	>0.999	0.480	0.248
Post procedural haemorrhage	1(0.4)	0(0)	1(2.0)	0(0)	2(0.6)	0(0)	0.498	>0.999	0.499
	2(0.7)	0(0)	0(0)	0(0)	2(0.6)	0(0)	0.248		0.499

Note: At each level of summarization, a participant is counted once if the participant reported one or more events. Events are coded according to MedDRA V11.1.

[1] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group within the SPT-negative stratum.

[2] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group within the SPT-positive stratum.

[3] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group across both the SPT-negative and SPT-positive strata.

	Negative Stratum (N=542)		Positive Stratum (N=98)		Overall (N=640)		P-value [1] SPT-Neg	P-value [2] SPT-Pos	P-value [3] Overall
	Avoidance Group (N=270)	Consumption Group (N=272)	Avoidance Group (N=51)	Consumption Group (N=47)	Avoidance Group (N=321)	Consumption Group (N=319)			
Injury, poisoning and procedural complications									
Clavicle fracture	0(0)	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	>0.999		0.498
Nervous system disorders	2(0.7)	4(1.5)	0(0)	0(0)	2(0.6)	4(1.3)	0.686		0.450
Febrile convulsion	2(0.7)	4(1.5)	0(0)	0(0)	2(0.6)	4(1.3)	0.686		0.450
Gastrointestinal disorders	1(0.4)	1(0.4)	0(0)	0(0)	1(0.3)	1(0.3)	>0.999		>0.999
Inguinal hernia strangulated	0(0)	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	>0.999		0.498
Intussusception	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Skin and subcutaneous tissue disorders	0(0)	2(0.7)	0(0)	0(0)	0(0)	2(0.6)	0.499		0.248
Swelling face	0(0)	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	>0.999		0.498
Urticaria	0(0)	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	>0.999		0.498
General disorders and administration site conditions	0(0)	0(0)	1(2.0)	0(0)	1(0.3)	0(0)		>0.999	>0.999
Pyrexia	0(0)	0(0)	1(2.0)	0(0)	1(0.3)	0(0)		>0.999	>0.999
Hepatobiliary disorders	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Hepatitis	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Metabolism and nutrition disorders	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Diabetes mellitus	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Diabetic ketoacidosis	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999

Note: At each level of summarization, a participant is counted once if the participant reported one or more events. Events are coded according to MedDRA V11.1.

[1] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group within the SPT-negative stratum.

[2] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group within the SPT-positive stratum.

[3] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group across both the SPT-negative and SPT-positive strata.

	Negative Stratum (N=542)		Positive Stratum (N=98)		Overall (N=640)		P-value [1] SPT-Neg	P-value [2] SPT-Pos	P-value [3] Overall
	Avoidance Group (N=270)	Consumption Group (N=272)	Avoidance Group (N=51)	Consumption Group (N=47)	Avoidance Group (N=321)	Consumption Group (N=319)			
Musculoskeletal and connective tissue disorders	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Arthritis reactive	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999

Note: At each level of summarization, a participant is counted once if the participant reported one or more events. Events are coded according to MedDRA V11.1.

- [1] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group within the SPT-negative stratum.
- [2] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group within the SPT-positive stratum.
- [3] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group across both the SPT-negative and SPT-positive strata.

Table S8. Adverse Events - Poisson Analysis

System Organ Class Preferred Term	Peanut Avoidance (N=321)				Peanut Consumption (N=319)				Rel. Risk [3]	Subject Level p-value [1]	Rate Ratio [3]	Event Level p-value [2]
	No. Pts with >=1 AE	Pct. Pts	No. Events	Event Rate	No. Pts with >=1 AE	Pct. Pts	No. Events	Event Rate				
Any AE	319	(99.4%)	4287	3.022	318	(99.7%)	4527	3.179	0.997	0.446	0.950	0.017
Infections and infestations	318	(99.1%)	2128	1.500	317	(99.4%)	2358	1.656	0.997	0.490	0.906	<.001
Upper respiratory tract infection	187	(58.3%)	337	0.238	222	(69.6%)	470	0.330	0.837	0.005	0.720	<.001
Gastroenteritis	170	(53.0%)	276	0.195	203	(63.6%)	349	0.245	0.832	0.010	0.794	0.004
Rhinitis	184	(57.3%)	206	0.145	177	(55.5%)	204	0.143	1.033	0.543	1.013	0.892
Varicella	143	(44.5%)	146	0.103	162	(50.8%)	170	0.119	0.877	0.145	0.862	0.187
Lower respiratory tract infection	117	(36.4%)	198	0.140	103	(32.3%)	165	0.116	1.129	0.231	1.204	0.077
Ear infection	94	(29.3%)	157	0.111	100	(31.3%)	158	0.111	0.934	0.628	0.997	0.981
Nasopharyngitis	89	(27.7%)	107	0.075	101	(31.7%)	132	0.093	0.876	0.314	0.814	0.112
Viral infection	52	(16.2%)	60	0.042	66	(20.7%)	81	0.057	0.783	0.159	0.743	0.080
Tonsillitis	55	(17.1%)	79	0.056	62	(19.4%)	99	0.070	0.882	0.488	0.801	0.140
Eczema infected	46	(14.3%)	63	0.044	29	(9.1%)	48	0.034	1.576	0.035	1.317	0.148
Otitis media	39	(12.1%)	47	0.033	31	(9.7%)	34	0.024	1.250	0.304	1.387	0.143
Viral skin infection	23	(7.2%)	24	0.017	47	(14.7%)	50	0.035	0.486	0.002	0.482	0.002
Viral upper respiratory tract infection	34	(10.6%)	39	0.027	36	(11.3%)	41	0.029	0.939	0.812	0.955	0.836
Croup infectious	35	(10.9%)	39	0.027	25	(7.8%)	32	0.022	1.391	0.171	1.223	0.397
Respiratory tract infection	24	(7.5%)	27	0.019	29	(9.1%)	32	0.022	0.822	0.481	0.847	0.524
Molluscum contagiosum	24	(7.5%)	26	0.018	25	(7.8%)	27	0.019	0.954	0.892	0.966	0.901
Pharyngitis	25	(7.8%)	30	0.021	17	(5.3%)	19	0.013	1.461	0.197	1.585	0.112
Urinary tract infection	22	(6.9%)	27	0.019	17	(5.3%)	28	0.020	1.286	0.402	0.968	0.903
Impetigo	18	(5.6%)	33	0.023	20	(6.3%)	26	0.018	0.894	0.747	1.274	0.354
Influenza	14	(4.4%)	15	0.011	21	(6.6%)	22	0.015	0.663	0.228	0.684	0.253
Eye infection	19	(5.9%)	21	0.015	13	(4.1%)	15	0.011	1.452	0.272	1.405	0.311
Hand-foot-and-mouth disease	11	(3.4%)	11	0.008	15	(4.7%)	17	0.012	0.729	0.429	0.649	0.259
Bronchiolitis	9	(2.8%)	10	0.007	15	(4.7%)	18	0.013	0.596	0.215	0.558	0.130
Skin infection	15	(4.7%)	16	0.011	9	(2.8%)	9	0.006	1.656	0.209	1.784	0.156

[1] The subject-level p-value comes from a ln-Poisson regression model as described in Zou (J Epidemiol 2004; 159;702-6). The comparison is adjusted for the ln follow-up time contributed by each subject.

[2] The event level p-value comes from a poisson regression comparing the person-year adjusted event rates between the two treatment groups.

[3] Relative risks (and Rate Ratios) are calculated as Peanut Avoidance (Rate) divided by Peanut Consumption (Rate).

Preferred terms highlighted in gray are those with a p-value < .01 using either method. Relative Risks and Incidence Ratios cannot be computed for preferred terms where the event count is zero in either treatment group.

Only preferred terms with 5 or more events are included in the table.

System Organ Class Preferred Term	Peanut Avoidance (N=321)				Peanut Consumption (N=319)				Rel. Risk [3]	Subject Level p-value [1]	Rate Ratio [3]	Event Level p-value [2]
	No. Pts with >=1 AE	Pct. Pts	No. Events	Event Rate	No. Pts with >=1 AE	Pct. Pts	No. Events	Event Rate				
Infections and infestations												
Herpes zoster	7	(2.2%)	7	0.005	13	(4.1%)	13	0.009	0.535	0.175	0.540	0.179
Gastroenteritis viral	7	(2.2%)	7	0.005	8	(2.5%)	9	0.006	0.870	0.799	0.781	0.622
Candidiasis	4	(1.2%)	4	0.003	5	(1.6%)	5	0.004	0.795	0.741	0.803	0.743
Cellulitis	6	(1.9%)	7	0.005	2	(0.6%)	2	0.001	2.981	0.153	3.513	0.085
Fungal infection	3	(0.9%)	3	0.002	5	(1.6%)	6	0.004	0.596	0.480	0.502	0.315
Oral candidiasis	6	(1.9%)	6	0.004	2	(0.6%)	2	0.001	2.981	0.154	3.011	0.147
Paronychia	8	(2.5%)	9	0.006	0	(0)	0			0.004		<.001
Tinea infection	6	(1.9%)	8	0.006	2	(0.6%)	2	0.001	2.981	0.154	4.014	0.049
Measles	5	(1.6%)	5	0.004	2	(0.6%)	2	0.001	2.484	0.252	2.509	0.247
Pneumonia	4	(1.2%)	6	0.004	3	(0.9%)	3	0.002	1.325	0.700	2.007	0.310
Scarlet fever	4	(1.2%)	4	0.003	3	(0.9%)	3	0.002	1.325	0.701	1.338	0.701
Erythema infectiosum	1	(0.3%)	1	0.001	5	(1.6%)	5	0.004	0.199	0.101	0.201	0.089
Fungal skin infection	2	(0.6%)	2	0.001	3	(0.9%)	4	0.003	0.663	0.656	0.502	0.412
Lower respiratory tract infection viral	5	(1.6%)	5	0.004	0	(0)	0			0.025		0.008
Genital infection	3	(0.9%)	3	0.002	1	(0.3%)	2	0.001	2.981	0.315	1.505	0.651
Helminthic infection	2	(0.6%)	2	0.001	2	(0.6%)	3	0.002	0.994	0.997	0.669	0.657
Skin and subcutaneous tissue disorders	211	(65.7%)	480	0.338	234	(73.4%)	517	0.363	0.896	0.060	0.932	0.265
Eczema	162	(50.5%)	293	0.207	174	(54.5%)	300	0.211	0.925	0.370	0.980	0.808
Urticaria	40	(12.5%)	66	0.047	72	(22.6%)	102	0.072	0.552	<.001	0.649	0.006
Rash	45	(14.0%)	54	0.038	38	(11.9%)	46	0.032	1.177	0.400	1.178	0.413
Dermatitis diaper	17	(5.3%)	17	0.012	9	(2.8%)	10	0.007	1.877	0.107	1.706	0.173
Angioedema	6	(1.9%)	6	0.004	13	(4.1%)	18	0.013	0.459	0.105	0.335	0.013
Dermatitis contact	8	(2.5%)	10	0.007	8	(2.5%)	10	0.007	0.994	0.994	1.004	0.994
Keratosis pilaris	6	(1.9%)	7	0.005	3	(0.9%)	3	0.002	1.988	0.312	2.342	0.198
Rash maculo-papular	3	(0.9%)	3	0.002	3	(0.9%)	3	0.002	0.994	0.996	1.004	0.996
Dermatitis allergic	5	(1.6%)	5	0.004	0	(0)	0			0.025		0.008

[1] The subject-level p-value comes from a ln-Poisson regression model as described in Zou (J Epidemiol 2004; 159;702-6). The comparison is adjusted for the ln follow-up time contributed by each subject.

[2] The event level p-value comes from a poisson regression comparing the person-year adjusted event rates between the two treatment groups.

[3] Relative risks (and Rate Ratios) are calculated as Peanut Avoidance (Rate) divided by Peanut Consumption (Rate).

Preferred terms highlighted in gray are those with a p-value < .01 using either method. Relative Risks and Incidence Ratios cannot be computed for preferred terms where the event count is zero in either treatment group.

Only preferred terms with 5 or more events are included in the table.

System Organ Class Preferred Term	Peanut Avoidance (N=321)				Peanut Consumption (N=319)				Rel. Risk [3]	Subject Level p-value [1]	Rate Ratio [3]	Event Level p-value [2]
	No. Pts with >=1 AE	Pct. Pts	No. Events	Event Rate	No. Pts with >=1 AE	Pct. Pts	No. Events	Event Rate				
Skin and subcutaneous tissue disorders												
Rash macular	1	(0.3%)	1	0.001	4	(1.3%)	4	0.003	0.248	0.179	0.251	0.166
Immune system disorders	201	(62.6%)	635	0.448	199	(62.4%)	584	0.410	1.004	0.824	1.091	0.128
Food allergy	163	(50.8%)	397	0.280	162	(50.8%)	386	0.271	1.000	0.900	1.032	0.657
Seasonal allergy	47	(14.6%)	58	0.041	40	(12.5%)	48	0.034	1.168	0.409	1.213	0.322
Milk allergy	47	(14.6%)	93	0.066	38	(11.9%)	68	0.048	1.229	0.287	1.373	0.046
Hypersensitivity	18	(5.6%)	22	0.016	24	(7.5%)	26	0.018	0.745	0.344	0.849	0.572
Allergy to animal	14	(4.4%)	16	0.011	18	(5.6%)	21	0.015	0.773	0.474	0.765	0.417
Drug hypersensitivity	14	(4.4%)	15	0.011	11	(3.4%)	11	0.008	1.265	0.535	1.369	0.426
Anaphylactic reaction	13	(4.0%)	15	0.011	3	(0.9%)	5	0.004	4.306	0.011	3.011	0.022
Allergy to vaccine	10	(3.1%)	10	0.007	4	(1.3%)	4	0.003	2.484	0.104	2.509	0.102
Oral allergy syndrome	2	(0.6%)	3	0.002	2	(0.6%)	2	0.001	0.994	0.997	1.505	0.651
House dust allergy	1	(0.3%)	1	0.001	2	(0.6%)	4	0.003	0.497	0.565	0.251	0.166
Respiratory, thoracic and mediastinal disorders	159	(49.5%)	401	0.283	152	(47.6%)	439	0.308	1.040	0.550	0.917	0.208
Wheezing	89	(27.7%)	187	0.132	79	(24.8%)	173	0.121	1.120	0.355	1.085	0.440
Asthma	76	(23.7%)	113	0.080	85	(26.6%)	163	0.114	0.889	0.427	0.696	0.003
Cough	68	(21.2%)	83	0.059	63	(19.7%)	77	0.054	1.073	0.609	1.082	0.619
Rhinitis seasonal	4	(1.2%)	4	0.003	10	(3.1%)	12	0.008	0.398	0.106	0.335	0.041
Epistaxis	2	(0.6%)	2	0.001	6	(1.9%)	6	0.004	0.331	0.156	0.335	0.149
Gastrointestinal disorders	149	(46.4%)	238	0.168	156	(48.9%)	267	0.188	0.949	0.609	0.895	0.211
Vomiting	72	(22.4%)	92	0.065	79	(24.8%)	109	0.077	0.906	0.531	0.847	0.240
Diarrhoea	72	(22.4%)	78	0.055	67	(21.0%)	89	0.063	1.068	0.614	0.880	0.408
Constipation	27	(8.4%)	35	0.025	32	(10.0%)	38	0.027	0.838	0.503	0.924	0.737
Abdominal pain	6	(1.9%)	6	0.004	10	(3.1%)	12	0.008	0.596	0.314	0.502	0.156

[1] The subject-level p-value comes from a ln-Poisson regression model as described in Zou (J Epidemiol 2004; 159;702-6). The comparison is adjusted for the ln follow-up time contributed by each subject.

[2] The event level p-value comes from a poisson regression comparing the person-year adjusted event rates between the two treatment groups.

[3] Relative risks (and Rate Ratios) are calculated as Peanut Avoidance (Rate) divided by Peanut Consumption (Rate).

Preferred terms highlighted in gray are those with a p-value < .01 using either method. Relative Risks and Incidence Ratios cannot be computed for preferred terms where the event count is zero in either treatment group.

Only preferred terms with 5 or more events are included in the table.

System Organ Class Preferred Term	Peanut Avoidance (N=321)				Peanut Consumption (N=319)				Rel. Risk [3]	Subject Level p-value [1]	Rate Ratio [3]	Event Level p-value [2]
	No. Pts with >=1 AE	Pct. Pts	No. Events	Event Rate	No. Pts with >=1 AE	Pct. Pts	No. Events	Event Rate				
Gastrointestinal disorders												
Gastroesophageal reflux disease	9	(2.8%)	10	0.007	5	(1.6%)	6	0.004	1.789	0.277	1.673	0.311
General disorders and administration site conditions	93	(29.0%)	129	0.091	108	(33.9%)	138	0.097	0.856	0.211	0.938	0.602
Pyrexia	81	(25.2%)	111	0.078	98	(30.7%)	122	0.086	0.821	0.141	0.913	0.488
Influenza like illness	9	(2.8%)	9	0.006	10	(3.1%)	10	0.007	0.894	0.822	0.903	0.825
Eye disorders	94	(29.3%)	111	0.078	73	(22.9%)	80	0.056	1.280	0.055	1.393	0.023
Conjunctivitis	81	(25.2%)	97	0.068	53	(16.6%)	56	0.039	1.519	0.006	1.738	<.001
Conjunctivitis allergic	1	(0.3%)	1	0.001	5	(1.6%)	5	0.004	0.199	0.101	0.201	0.089
Astigmatism	3	(0.9%)	3	0.002	2	(0.6%)	2	0.001	1.491	0.651	1.505	0.651
Myopia	1	(0.3%)	1	0.001	4	(1.3%)	4	0.003	0.248	0.179	0.251	0.166
Injury, poisoning and procedural complications	52	(16.2%)	64	0.045	50	(15.7%)	61	0.043	1.034	0.813	1.053	0.773
Head injury	15	(4.7%)	17	0.012	12	(3.8%)	13	0.009	1.242	0.549	1.312	0.459
Limb injury	6	(1.9%)	6	0.004	6	(1.9%)	6	0.004	0.994	0.995	1.004	0.995
Thermal burn	2	(0.6%)	2	0.001	5	(1.6%)	5	0.004	0.398	0.256	0.401	0.251
Clavicle fracture	1	(0.3%)	1	0.001	4	(1.3%)	4	0.003	0.248	0.179	0.251	0.166
Joint injury	5	(1.6%)	6	0.004	0	(0)	0		0.025	0.025		0.004
Mouth injury	2	(0.6%)	2	0.001	3	(0.9%)	3	0.002	0.663	0.656	0.669	0.657
Metabolism and nutrition disorders	30	(9.3%)	34	0.024	22	(6.9%)	23	0.016	1.355	0.241	1.484	0.140
Obesity	14	(4.4%)	14	0.010	8	(2.5%)	8	0.006	1.739	0.190	1.756	0.195
Failure to thrive	7	(2.2%)	7	0.005	6	(1.9%)	6	0.004	1.159	0.774	1.171	0.776

[1] The subject-level p-value comes from a ln-Poisson regression model as described in Zou (J Epidemiol 2004; 159;702-6). The comparison is adjusted for the ln follow-up time contributed by each subject.

[2] The event level p-value comes from a poisson regression comparing the person-year adjusted event rates between the two treatment groups.

[3] Relative risks (and Rate Ratios) are calculated as Peanut Avoidance (Rate) divided by Peanut Consumption (Rate).

Preferred terms highlighted in gray are those with a p-value < .01 using either method. Relative Risks and Incidence Ratios cannot be computed for preferred terms where the event count is zero in either treatment group.

Only preferred terms with 5 or more events are included in the table.

System Organ Class Preferred Term	Peanut Avoidance (N=321)				Peanut Consumption (N=319)				Rel. Risk [3]	Subject Level p-value [1]	Rate Ratio [3]	Event Level p-value [2]
	No. Pts with >=1 AE	Pct. Pts	No. Events	Event Rate	No. Pts with >=1 AE	Pct. Pts	No. Events	Event Rate				
Nervous system disorders	9	(2.8%)	11	0.008	13	(4.1%)	16	0.011	0.688	0.390	0.690	0.339
Febrile convulsion	3	(0.9%)	4	0.003	5	(1.6%)	7	0.005	0.596	0.480	0.573	0.366
Musculoskeletal and connective tissue disorders	13	(4.0%)	15	0.011	7	(2.2%)	7	0.005	1.846	0.171	2.151	0.083
Ear and labyrinth disorders	12	(3.7%)	12	0.008	5	(1.6%)	5	0.004	2.385	0.084	2.409	0.084
Ear pain	4	(1.2%)	4	0.003	1	(0.3%)	1	0.001	3.975	0.177	4.014	0.164
Tympanic membrane perforation	4	(1.2%)	4	0.003	1	(0.3%)	1	0.001	3.975	0.177	4.014	0.164
Blood and lymphatic system disorders	8	(2.5%)	10	0.007	8	(2.5%)	9	0.006	0.994	0.994	1.115	0.812
Anaemia	3	(0.9%)	3	0.002	3	(0.9%)	3	0.002	0.994	0.996	1.004	0.996
Lymphadenitis	4	(1.2%)	5	0.004	2	(0.6%)	2	0.001	1.988	0.410	2.509	0.247
Lymphadenopathy	2	(0.6%)	2	0.001	3	(0.9%)	3	0.002	0.663	0.656	0.669	0.657
Congenital, familial and genetic disorders	6	(1.9%)	6	0.004	5	(1.6%)	5	0.004	1.193	0.757	1.204	0.758
Psychiatric disorders	6	(1.9%)	6	0.004	5	(1.6%)	5	0.004	1.193	0.757	1.204	0.758

[1] The subject-level p-value comes from a ln-Poisson regression model as described in Zou (J Epidemiol 2004; 159;702-6). The comparison is adjusted for the ln follow-up time contributed by each subject.

[2] The event level p-value comes from a poisson regression comparing the person-year adjusted event rates between the two treatment groups.

[3] Relative risks (and Rate Ratios) are calculated as Peanut Avoidance (Rate) divided by Peanut Consumption (Rate).

Preferred terms highlighted in gray are those with a p-value < .01 using either method. Relative Risks and Incidence Ratios cannot be computed for preferred terms where the event count is zero in either treatment group.

Only preferred terms with 5 or more events are included in the table.

Table S9. Adverse Events of Interest

Table S9a. Adverse Events of Interest - Upper Respiratory Tract Infection

	Peanut Avoidance (N=321)	Peanut Consumption (N=319)	Total (N=640)	p-value
Severity of Upper Respiratory Tract Infection Events				0.416 ¹
Mild	139(43.3%)	157(49.2%)	296(46.3%)	
Moderate	48(15.0%)	65(20.4%)	113(17.7%)	
Baseline Peanut-specific IgE Category²				0.517 ¹
Above 0.1	68(21.2%)	74(23.2%)	142(22.2%)	
Below 0.1	118(36.8%)	147(46.1%)	265(41.4%)	
Stratum				0.986 ¹
SPT-negative Stratum	161(50.2%)	191(59.9%)	352(55.0%)	
SPT-positive Stratum	26(8.1%)	31(9.7%)	57(8.9%)	
Total Number of Upper Respiratory Tract Infection Events				<0.001 ³
0	134(41.7%)	97(30.4%)	231(36.1%)	
1	96(29.9%)	99(31.0%)	195(30.5%)	
2	54(16.8%)	55(17.2%)	109(17.0%)	
3	23(7.2%)	40(12.5%)	63(9.8%)	
4	7(2.2%)	13(4.1%)	20(3.1%)	
5	6(1.9%)	7(2.2%)	13(2.0%)	
6	1(0.3%)	5(1.6%)	6(0.9%)	
7	0(0%)	2(0.6%)	2(0.3%)	
10	0(0%)	1(0.3%)	1(0.2%)	

¹Chi-Square

²At baseline, one participant in each group was missing IgE data.

³Wilcoxon Rank Sum

Table S9b. Adverse Events of Interest - Viral Skin Infection

	Peanut Avoidance (N=321)	Peanut Consumption (N=319)	Total (N=640)	p-value
Severity of Viral Skin Infection Events				0.007 ¹
Mild	17(5.3%)	45(14.1%)	62(9.7%)	
Moderate	6(1.9%)	2(0.6%)	8(1.3%)	
Baseline Peanut-specific IgE Category²				>0.999 ¹
Above 0.1	6(1.9%)	12(3.8%)	18(2.8%)	
Below 0.1	17(5.3%)	34(10.7%)	51(8.0%)	
Stratum				0.615 ¹
SPT-negative Stratum	21(6.5%)	41(12.9%)	62(9.7%)	
SPT-positive Stratum	2(0.6%)	6(1.9%)	8(1.3%)	
Total Number of Viral Skin Infection Events				0.002 ³
0	298(92.8%)	272(85.3%)	570(89.1%)	
1	22(6.9%)	44(13.8%)	66(10.3%)	
2	1(0.3%)	3(0.9%)	4(0.6%)	

¹Chi-Square

²At baseline, one participant in each group was missing IgE data.

³Wilcoxon Rank Sum

Table S9c. Adverse Events of Interest - Asthma

	Peanut Avoidance (N=321)	Peanut Consumption (N=319)	Total (N=640)	p-value
Severity of Asthma Events				0.839 ¹
Mild	1(0.3%)	2(0.6%)	3(0.5%)	
Moderate	73(22.7%)	80(25.1%)	153(23.9%)	
Severe	2(0.6%)	3(0.9%)	5(0.8%)	
Baseline Peanut-specific IgE Category²				0.544 ¹
Above 0.1	34(10.6%)	34(10.7%)	68(10.6%)	
Below 0.1	42(13.1%)	51(16.0%)	93(14.5%)	
Stratum				0.869 ¹
SPT-negative Stratum	60(18.7%)	68(21.3%)	128(20.0%)	
SPT-positive Stratum	16(5.0%)	17(5.3%)	33(5.2%)	
Total Number of Asthma Events				0.292 ³
0	245(76.3%)	234(73.4%)	479(74.8%)	
1	51(15.9%)	50(15.7%)	101(15.8%)	
2	19(5.9%)	20(6.3%)	39(6.1%)	
3	1(0.3%)	6(1.9%)	7(1.1%)	
4	4(1.2%)	4(1.3%)	8(1.3%)	
5	1(0.3%)	0(0%)	1(0.2%)	
7	0(0%)	2(0.6%)	2(0.3%)	
8	0(0%)	2(0.6%)	2(0.3%)	
9	0(0%)	1(0.3%)	1(0.2%)	

¹Chi-Square

²At baseline, one participant in each group was missing IgE data.

³Wilcoxon Rank Sum

Table S9d. Adverse Events of Interest - Gastroenteritis

	Peanut Avoidance (N=321)	Peanut Consumption (N=319)	Total (N=640)	p-value
Severity of Gastroenteritis Events				0.401 ¹
Mild	134(41.7%)	171(53.6%)	305(47.7%)	
Moderate	35(10.9%)	31(9.7%)	66(10.3%)	
Severe	1(0.3%)	1(0.3%)	2(0.3%)	
Baseline Peanut-specific IgE Category²				0.096 ¹
Above 0.1	67(20.9%)	63(19.7%)	130(20.3%)	
Below 0.1	102(31.8%)	138(43.3%)	240(37.5%)	
Stratum				0.306 ¹
SPT-negative Stratum	140(43.6%)	175(54.9%)	315(49.2%)	
SPT-positive Stratum	30(9.3%)	28(8.8%)	58(9.1%)	
Total Number of Gastroenteritis Events				0.007 ³
0	151(47.0%)	116(36.4%)	267(41.7%)	
1	100(31.2%)	118(37.0%)	218(34.1%)	
2	44(13.7%)	43(13.5%)	87(13.6%)	
3	18(5.6%)	27(8.5%)	45(7.0%)	
4	6(1.9%)	11(3.4%)	17(2.7%)	
5	2(0.6%)	4(1.3%)	6(0.9%)	

¹Chi-Square

²At baseline, one participant in each group was missing IgE data.

³Wilcoxon Rank Sum

Table S9e. Adverse Events of Interest - Urticaria

	Peanut Avoidance (N=321)	Peanut Consumption (N=319)	Total (N=640)	p-value
Severity of Urticaria Events				0.222 ¹
Mild	12(3.7%)	30(9.4%)	42(6.6%)	
Moderate	28(8.7%)	42(13.2%)	70(10.9%)	
Baseline Peanut-specific IgE Category²				0.298 ¹
Above 0.1	21(6.5%)	30(9.4%)	51(8.0%)	
Below 0.1	19(5.9%)	41(12.9%)	60(9.4%)	
Stratum				0.894 ¹
SPT-negative Stratum	31(9.7%)	55(17.2%)	86(13.4%)	
SPT-positive Stratum	9(2.8%)	17(5.3%)	26(4.1%)	
Total Number of Urticaria Events				0.001 ³
0	281(87.5%)	247(77.4%)	528(82.5%)	
1	22(6.9%)	50(15.7%)	72(11.3%)	
2	14(4.4%)	16(5.0%)	30(4.7%)	
3	1(0.3%)	4(1.3%)	5(0.8%)	
4	2(0.6%)	2(0.6%)	4(0.6%)	
5	1(0.3%)	0(0%)	1(0.2%)	

¹Chi-Square

²At baseline, one participant in each group was missing IgE data.

³Wilcoxon Rank Sum

Table S9f. Adverse Events of Interest - Conjunctivitis

	Peanut Avoidance (N=321)	Peanut Consumption (N=319)	Total (N=640)	p-value
Severity of Conjunctivitis Events				0.613 ¹
Mild	50(15.6%)	35(11.0%)	85(13.3%)	
Moderate	31(9.7%)	18(5.6%)	49(7.7%)	
Baseline Peanut-specific IgE Category²				0.787 ¹
Above 0.1	29(9.0%)	18(5.6%)	47(7.3%)	
Below 0.1	51(15.9%)	35(11.0%)	86(13.4%)	
Stratum				0.806 ¹
SPT-negative Stratum	70(21.8%)	45(14.1%)	115(18.0%)	
SPT-positive Stratum	11(3.4%)	8(2.5%)	19(3.0%)	
Total Number of Conjunctivitis Events				0.004 ³
0	240(74.8%)	266(83.4%)	506(79.1%)	
1	65(20.2%)	51(16.0%)	116(18.1%)	
2	16(5.0%)	1(0.3%)	17(2.7%)	
3	0(0%)	1(0.3%)	1(0.2%)	

¹Chi-Square

²At baseline, one participant in each group was missing IgE data.

³Wilcoxon Rank Sum

Table S10. Participants Who Discontinued Peanut Consumption

Stratum¹	Age of peanut discontinuation	Sequence of medical events, prior to discontinuation.	Peanut-induced allergic symptoms as reason for discontinuation	V60 peanut OFC² outcome
1. SPT-Negative Stratum i.e. SPT to peanut 0 mm at baseline.	19 months	Parental caution to feed peanut as per study protocol. Participant developed active dislike of peanut, and then stopped eating peanut. SPT at most recent visit (12 months of age) was 0 mm.	No	Positive
2.SPT-Negative Stratum	39 months (Participant met per-protocol definition)	Peanut-induced facial hives; peanut had been eaten prior to that event. Peanut ingestion stopped. SPT at most recent visit (30 months of age) was 5 mm. Baseline OFC had resulted in a single hive but repeat baseline challenge was negative.	Yes	Positive
3. SPT-Negative Stratum	28 months	Peanut-induced pruritus and flare of eczema. Peanut intermittently eaten then stopped because of recurrence of these symptoms. SPT at next visit (30 months of age) was 9mm	Yes	Positive
4. SPT-Negative Stratum	15 months	Peanut-induced irritability and rash; peanut then intermittently eaten. USV ³ performed, SPT 11 mm, OFC not performed. Peanut ingestion stopped.	Yes	Positive
5. SPT Positive Stratum - Baseline SPT 3 mm	11 months	Peanut-induced peri-oral rash. Peanut ingestion stopped. USV performed, SPT 7mm, OFC positive.	Yes	Positive
6. SPT-Negative Stratum	6 months	Peanut-induced SAE (wheezing and angioedema, requiring intramuscular epinephrine). Peanut ingestion stopped. USV performed, initial SPT 1mm, repeat USV SPT 3mm, OFC's not performed. Participant had tolerated peanut on a few occasions prior to SAE.	Yes	Positive
7. SPT-Negative Stratum	10 months	Peanut-induced eczema flares, low and intermittent ingestion reported prior to peanut-induced urticaria and angioedema. Peanut ingestion stopped. SPT at next visit (V12) was 6mm.	Yes	Negative
8. SPT-Negative Stratum	37 months	Peanut-induced pruritus and flare of eczema. SPT at next visit (V30) was 2mm. USV performed, SPT 4mm, OFC positive. Peanut ingestion stopped.	Yes	Negative

9. SPT Positive Stratum - Baseline SPT 1 mm	8 months	Peanut-induced food protein induced enterocolitis syndrome diagnosed by OFC at USV, SPT 1mm (USV was performed because of uncertainty of consumption history). Peanut ingestion stopped.	Yes	Negative
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¹ Stratum was determined by a skin prick test to peanut performed as per the study protocol

² Oral Food Challenges described are to peanut and performed as per the study protocol

³ Unscheduled Visit

Table S11. Clinical Symptoms and Medication Requirements Associated with Positive Oral Food Challenges

	Negative Stratum (N=542)		Positive Stratum (N=98)		Overall (N=640)	
	Avoidance Group (N=270)	Consumption Group (N=272)	Avoidance Group (N=51)	Consumption Group (N=47)	Avoidance Group (N=321)	Consumption Group (N=319)
Positive Peanut-Induced Allergic Reactions						
Baseline Challenge (Consumption Group Only)	0 (0)	1 (0.4%)	0 (0)	6 (12.8%)	0 (0)	7 (2.2%)
Diagnostic Criteria at Baseline						
<u>Major Criteria</u>						
Confluent Erythematous Pruritic Rash	0 (0)	1 (100%)	0 (0)	2 (33.3%)	0 (0)	3 (42.9%)
Wheeze, Inability to Speak, Stridor, Dysphonia, and/or Aphonia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
≥3 Urticarial Lesions	0 (0)	1	0 (0)	5 (83.3%)	0 (0)	6 (85.7%)
≥1 Site of Angioedema	0 (0)	0 (0)	0 (0)	1 (16.7%)	0 (0)	1 (14.3%)
Hypotension for Age not Associated with Vasovagal Episode	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Evidence of Severe Abdominal Pain that Persists for ≥3 Hours	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
<u>Minor Criteria</u>						
Vomiting	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	0 (0)	0 (0)	0 (0)	1 (16.7%)	0 (0)	1 (14.3%)
Persistent Rubbing of Nose or Eyes that Lasts for ≥3 Minutes	0 (0)	0 (0)	0 (0)	2 (33.3%)	0 (0)	2 (28.6%)
Persistent Rhinorrhea that Lasts for ≥3 Minutes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Persistent Scratching that Lasts for ≥3 Minutes	0 (0)	1 (100%)	0 (0)	1 (16.7%)	0 (0)	2 (28.6%)
Medication Requirement at Baseline						
Antihistamine	0 (0)	1 (100%)	0 (0)	6 (100%)	0 (0)	7 (100%)
Salbutamol	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ranitidine	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Corticosteroid	0 (0)	0 (0)	0 (0)	1 (16.7%)	0 (0)	1 (14.3%)
Adrenaline x1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Adrenaline x2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Adrenaline x3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other Adrenaline	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Patient Requirement at Baseline						
Hospitalization	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Prolonged Hospitalization	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

	Negative Stratum (N=542)		Positive Stratum (N=98)		Overall (N=640)	
	Avoidance Group (N=270)	Consumption Group (N=272)	Avoidance Group (N=51)	Consumption Group (N=47)	Avoidance Group (N=321)	Consumption Group (N=319)
Positive Peanut-Induced Allergic Reactions						
Visit 60 Challenge	32 (11.9%)	4 (1.5%)	16 (31.4%)	5 (10.6%)	48 (15.0%)	9 (2.8%)
Diagnostic Criteria at Visit 60						
<u>Major Criteria</u>						
Confluent Erythematous Pruritic Rash	4 (12.5%)	0 (0)	3 (18.8%)	1 (20.0%)	7 (14.6%)	1 (11.1%)
Wheeze, Inability to Speak, Stridor, Dysphonia, and/or Aphonia	7 (21.9%)	0 (0)	3 (18.8%)	2 (40.0%)	10 (20.8%)	2 (22.2%)
≥3 Urticarial Lesions	13 (40.6%)	3 (75.0%)	4 (25.0%)	1 (20.0%)	17 (35.4%)	4 (44.4%)
≥1 Site of Angioedema	12 (37.5%)	0 (0)	6 (37.5%)	1 (20.0%)	18 (37.5%)	1 (11.1%)
Hypotension for Age not Associated with Vasovagal Episode	2 (6.3%)	0 (0)	0 (0)	0 (0)	2 (4.2%)	0 (0)
Evidence of Severe Abdominal Pain that Persists for ≥3 Hours	8 (25.0%)	1 (25.0%)	5 (31.3%)	1 (20.0%)	13 (27.1%)	2 (22.2%)
<u>Minor Criteria</u>						
Vomiting	6 (18.8%)	0 (0)	5 (31.3%)	2 (40.0%)	11 (22.9%)	2 (22.2%)
Diarrhea	1 (3.1%)	0 (0)	0 (0)	0 (0)	1 (2.1%)	0 (0)
Persistent Rubbing of Nose or Eyes that Lasts for ≥3 Minutes	12 (37.5%)	2 (50.0%)	8 (50.0%)	2 (40.0%)	20 (41.7%)	4 (44.4%)
Persistent Rhinorrhea that Lasts for ≥3 Minutes	11 (34.4%)	1 (25.0%)	6 (37.5%)	1 (20.0%)	17 (35.4%)	2 (22.2%)
Persistent Scratching that Lasts for ≥3 Minutes	9 (28.1%)	0 (0)	8 (50.0%)	1 (20.0%)	17 (35.4%)	1 (11.1%)
Medication Requirement at Visit 60						
Antihistamine	31 (96.9%)	4 (100%)	16 (100%)	5 (100%)	47 (97.9%)	9 (100%)
Salbutamol	12 (37.5%)	1 (25.0%)	5 (31.3%)	2 (40.0%)	17 (35.4%)	3 (33.3%)
Ranitidine	17 (53.1%)	2 (50.0%)	6 (37.5%)	2 (40.0%)	23 (47.9%)	4 (44.4%)
Corticosteroid	20 (62.5%)	2 (50.0%)	11 (68.8%)	4 (80.0%)	31 (64.6%)	6 (66.7%)
Adrenaline x1	2 (6.3%)	0 (0)	3 (18.8%)	1 (20.0%)	5 (10.4%)	1 (11.1%)
Adrenaline x2	1 (3.1%)	0 (0)	0 (0)	1 (20.0%)	1 (2.1%)	1 (11.1%)
Adrenaline x3	0 (0)	0 (0)	1 (6.3%)	0 (0)	1 (2.1%)	0 (0)
Other Adrenaline	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Patient Requirement at Visit 60						
Hospitalization	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Prolonged Hospitalization	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Table S12. Primary Outcome by Race

Primary Outcome Analysis Stratified by Race				
	Peanut Avoidance (N=321)	Peanut Consumption (N=319)	Total (N=640)	p value
Asian				0.012 ¹
Not Allergic	5 (55.6%)	15 (100.0%)	20 (83.3%)	
Allergic	4 (44.4%)	0 (0.0%)	4 (16.7%)	
Black				0.025 ¹
Not Allergic	20 (76.9%)	22 (100.0%)	42 (87.5%)	
Allergic	6 (23.1%)	0 (0.0%)	6 (12.5%)	
Chinese, Middle Eastern, or Other				0.464 ¹
Not Allergic	1 (50.0%)	5 (83.3%)	6 (75.0%)	
Allergic	1 (50.0%)	1 (16.7%)	2 (25.0%)	
Mixed				<0.001 ¹
Missing Primary Outcome	1	1	2	
Not Allergic	27 (69.2%)	47 (97.9%)	74 (85.1%)	
Allergic	12 (30.8%)	1 (2.1%)	13 (14.9%)	
White				<0.001 ¹
Missing Primary Outcome	6	4	10	
Not Allergic	207 (87.0%)	215 (96.8%)	422 (91.7%)	
Allergic	31 (13.0%)	7 (3.2%)	38 (8.3%)	
Missing Race				
Allergic	0 (0.0%)	1 (100.0%)	1 (100.0%)	
¹ Fisher Exact Test				

Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;372:803-13. DOI: 10.1056/NEJMoa1414850

This supplement contains the following items:

1. Original protocol, final protocol (version 7.0), summary of changes.
2. Original statistical analysis plan, final statistical analysis plan (version 3.0), summary of changes

LEAP Study Protocol (ITN032AD) – summary of changes

The LEAP Study Protocol Version 1.0 resulted from a comprehensive development and review process in 2005-2006, with many early working drafts. Dr Lack and the site team worked with the Immune Tolerance Network (ITN, USA), the National Institute of Allergy and Infectious Diseases (NIAID, USA) and several other ITN and NIAID committees, to add detail to and refine these working drafts.

At the time of study start and enrolment of first participants in December 2006, Version 1.0 (29 September 2006) was in operation, following approval by the UK NRES Committee London – Fulham, formerly West London REC2 (REC Ref. 04/Q0403/13).

From study opening until completion of Last Patient Last Visit (LPLV) in May 2014 the LEAP Study Protocol underwent a series of updates, as follows:

Version 1.0, 29 September 2006 (original)

Version 2.0, 17 April 2007

Version 3.0, 25 April 2008

Version 4.0, 15 September 2008

Version 5.0, 10 May 2010

Version 6.0, 4 March 2011

Version 7.0, 18 July 2011 (final)

The major elements and rationale for these updates is described below in this document.

Summary of changes from Version 1.0 (29 September 2006) to Version 2.0 (17 April 2007)

A major change was made to the study design (refer to Version 7.0 Study Design section in Synopsis and Section 1.4.1 Population and Stratification).

In this study, participants were stratified based on skin prick test (SPT) results to assess the effect of peanut consumption in those with minimal or no skin-test reactivity and those with moderate skin-test reactivity. They were stratified into a two-minus stratum, including children with a SPT wheal diameter of 0, 1 or 2 mm; and a three-plus stratum, including children with a SPT wheal diameter of 3 or 4 mm.

New information obtained early after study opening, however, indicated that even children with wheal sizes of 1 or 2 mm may have a risk of peanut allergy much higher than average. This was based on recent clinical observations and the fact that one child in the two-minus stratum had a positive baseline challenge.

In version 2.0, the strata were therefore redefined into a SPT-negative stratum including only children with a SPT wheal diameter of 0 mm, and a SPT-positive stratum including children with a SPT wheal diameter of 1, 2, 3, or 4 mm. This redefinition led to three participants' reallocation to a different stratum after enrolment.

The NRES Committee gave ethics approval for this change on 23 April 2007.

Summary of changes from Version 2.0 (17 April 2007) to Version 3.0 (25 April 2008)

The study sample size was increased from 480 to 640 participants (440 to 542 in SPT-negative stratum, 40 to 98 in SPT-positive stratum), based on new information regarding the distribution of SPT

wheel sizes assessed prior to random assignment. The rationale for the sample size increase is described in Version 7.0, Section 9.3 Sample Size.

Briefly, the increase was recommended because of new data that had emerged.

1. Firstly it was found many children were excluded from the SPT-negative stratum because of positive skin prick tests to peanut.
2. Secondly it was found in the SPT-negative stratum that the age of screening was skewed towards older infants (greater than 6 months of age) whereas rates and levels of peanut specific IgE were significantly higher in infants less than 6 months of age.

Together these observations could have had the consequence that infants enrolled in the control (avoidance) arm of the study would be at lower risk of developing peanut allergy than originally predicted, resulting in reduced power of the study to detect a difference in peanut allergy between the two groups.

On that basis it was decided to:

1. Increase the SPT-negative stratum to 542 participants
2. Take measures to ensure an age mix with at least 25% of screened infants under 6 months of age so that the study group would not be skewed towards older infants.
3. Increase the SPT-positive stratum to 98 infants as this was a clinically important group in which to evaluate the efficacy of the intervention
4. To increase the enrolment period and total study duration by a further 6 months in view of the increased number of participants. New study duration was therefore 84 months.

Several other minor protocol changes were made in this version change, including:

- amendment of exclusion criteria (refer to Version 7.0 Section 4.2 Exclusion Criteria – raised AST removed, low polymorphonuclear cell count replaced by investigator-suspected immunocompromise)
- reassessment (refer to Version 7.0 Section 4.3 Reassessment for Eligibility) – change made it explicit that children can only be reassessed once
- blood pressure not routinely done as part of screening, as not reliably measured in young children, therefore removed from general assessments (refer to Version 7.0 Section 6.2 General Assessments)
- Total IgE was removed. It was mistakenly included at the 12 month visit in previous versions of the protocol (refer to Version 7.0 Schedule of Events)

The NRES Committee gave ethics approval for this change on 13 June 2008.

Summary of changes from Version 3.0 (25 April 2008) to Version 4.0 (15 September 2008)

In 2008, NIAID contracted with a new contract research organisation (CRO) to support Immune Tolerance Network for all statistical and data management aspects of their research studies.

The purpose of this protocol version change was therefore to address the CRO transition from Pharmaceutical Products Development Inc. (PPD) to Rho Federal Systems Division, Inc. (Rho Fed). Sections 6.2, 8.5.1, 11.1, and the Glossary of Abbreviations of the protocol were revised to reflect the change in CRO.

The NRES Committee gave ethics approval for this change on 30 October 2008.

Summary of changes from Version 4.0 (15 September 2008) to Version 5.0 (10 May 2010)

The main purpose of this protocol change was to include amendments made to the oral peanut challenge protocol for V60 visits (which were due to start in early 2011). Based on the team's clinical experience the version 4.0 oral peanut challenge regimen would have posed some logistical difficulty – therefore procedures were amended slightly to reduce the overall volume and number of feeds. These amendments to the oral peanut challenge protocols occur mainly in Section 6.5 Peanut Challenges.

The NRES Committee gave ethics approval for this change on 21 June 2010.

Summary of changes from Version 5.0 (10 May 2010) to Version 6.0 (4 March 2011)

The main purpose of this protocol change was to include amendments to Section 5.2 “Assessment of Compliance with Study Intervention” and Section 6.4.2 “Skin Prick Testing: Procedures and Interpretation”.

Section 5.2 “Assessment of Compliance with Study Intervention”:

New text was added to state that at their final visit (V60) LEAP participants will be invited to participate in a separate additional study of dietary compliance. The title of this separate study is “Environmental peanut protein exposure and allergic outcomes in children enrolled in the LEAP study” (REC Reference number 08/H0804/162, approval on 16th December 2008). This study was intended to measure peanut protein levels in household dust.

Section 6.4.2 “Skin Prick Testing: Procedures and Interpretation”:

New text was added to detail the clinical interpretation of peanut Skin Prick Testing (SPT) where large SPT results were returned. It stipulates that when both SPT results are above 4 mm, the average of the two SPTs will be recorded without necessitating a third SPT even if the difference between the two SPTs is higher than 2 mm. This approach reflects routine clinical practice and is recommended for the following reasons: the third SPT would have a) been large and uncomfortable for the child b) provided little additional management information as a large SPT is still recorded and c) been associated with a slight risk of inducing an allergic reaction.

The NRES Committee gave ethics approval for this change on 7 April 2011.

Summary of changes from Version 6.0 (4 March 2011) to Version 7.0 (18 July 2011)

The main purpose of this protocol change was to include more specific criteria for the use of cannulation during food challenges, as described in Section 6.5.4.1. Protocol versions 1 through 6 specified that children with suspected peanut allergy and children with a history of anaphylaxis to foods should be cannulated, that is, have intravenous access established, prior to peanut challenge. Beginning with version 7.0 in 2011 when additional information and experience became available, this specification was modified to include only children with both suspected peanut allergy as defined and other specific risk factors for a severe reaction described in the protocol. Version 7.0 also supplied a definition of suspected peanut allergy.

The full justification for changing the cannulation criteria can be found in Section 1.6.3. of Protocol Version 7.0, where relevant new text was added. The cannulation criteria change also required amendments to the “Criteria for open challenge” text box in Figure 3 (Section 3.4) and the addition of a new “Suspected peanut allergy” definition in Section 3.5.

The NRES Committee gave ethics approval for this change on 30 August 2011.



Protocol ITN032AD

Induction of Tolerance through Early Introduction of Peanut in High-Risk Children

Short Title: Tolerance to Peanut in High-Risk Children

Version 1.0 (September 29, 2006)

This clinical study is supported and conducted by the Immune Tolerance Network, which is sponsored by the National Institute of Allergy and Infectious Diseases.

Protocol Approval

Protocol ITN032AD	Version 1.0 (September 29, 2006)
	Protocol Chair: Gideon Lack, MD
Short Title: <i>Tolerance to Peanut in High-Risk Children</i>	
I have read protocol ITN032AD and I approve it. As the principal investigator, I agree to conduct this protocol using good clinical practices, as delineated in <i>ICH Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance</i> (April 1996), and according to the criteria specified in the protocol.	
Principal Investigator (Print)	
Principal Investigator (Signature)	Date

Synopsis

Title	Induction of Tolerance Through Early Introduction of Peanut in High-Risk Children
Short Title	Tolerance to Peanut in High-Risk Children
Sponsored by	National Institute of Allergy and Infectious Diseases
Conducted by	Immune Tolerance Network
Protocol Chair	Gideon Lack, MD
Participating Site(s)	Evelina Children's Hospital, Guys and St. Thomas' NHS Foundation Trust, King's College, London, UK
Accrual Objective	480 participants
Study Design	This is a randomized controlled trial in which children at high risk for peanut allergy, as demonstrated by eczema, egg allergy, or both, are enrolled. Participants are stratified based on skin prick test (SPT) results for peanut into those with a wheal diameter of 0, 1, or 2 mm (SPT two-minus stratum), and those with a wheal diameter of 3 or 4 mm (SPT three-plus stratum). Participants in each stratum are randomly assigned to receive a peanut-containing snack or to avoid peanut. The group assigned to receive a peanut-containing snack will eat at least 2 g of peanut protein three times per week until 60 months of age. The prevalence of peanut allergy at that time is compared between the peanut consumption and the avoidance groups.
Pace of Enrollment and Study Duration	78 months
Primary Endpoint	The proportion of participants with peanut allergy at 60 months of age.
Secondary Endpoints	At 30 and 60 months of age: the proportion of participants with allergic sensitization to selected ingested and inhaled allergens, and with seasonal rhinoconjunctivitis, perennial rhinoconjunctivitis, and asthma. At 60 months of age: the proportion of participants with type-1 immediate onset food allergy to selected ingested allergens. Incidence of adverse events and laboratory abnormalities; nutritional evaluations. Results of cellular and humoral assessments of immune response related to the development of allergy or tolerance to specific allergens.

Inclusion Criteria

1. Children ≥ 4 to < 11 months old who have had solids successfully introduced into their diet.
2. Egg allergy, severe eczema, or both.
3. Informed consent obtained from parent or guardian.

Exclusion Criteria

1. Clinically significant chronic illness, except for eczema or recurrent wheeze.
2. Positive skin prick test for peanut allergen with a wheal diameter > 4 mm in the presence of a negative saline control.
3. Previous or current consumption of peanut protein that exceeds 0.2 g of peanut protein on at least one occasion or 0.5 g over a single week
4. Investigator-suspected allergy to peanut protein.
5. Investigator-suspected allergy to peanut protein in care provider or current household member.
6. Diagnosis of persistent asthma.
7. AST (SGOT), ALT (SGPT), or bilirubin > 2 times the upper limit of age-related normal value.
8. BUN or creatinine > 1.25 times the upper limit of age-related normal value.
9. WBC $< 3.5 \times 10^3/\text{mL}$, polymorphonuclear cell count $< 1500/\text{mL}$, platelet count $< 100,000/\text{mL}$, or hemoglobin $< 9 \text{ g/dL}$.
10. Unwillingness or inability to comply with study requirements and procedures.

Study Intervention

Participants assigned to the peanut consumption group will be fed at least 2 g of peanut protein 3 times per week. The preferred peanut source will be Bamba, although peanut butter may be substituted. Participants assigned to the peanut avoidance group will avoid exposure to peanut protein during study participation.

Glossary of Abbreviations

BMI	body mass index
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 food challenge
DSMB	data safety monitoring board
FAP	facilitated antigen presentation
GCP	good clinical practice
ICH	International Conference on Harmonization
IND	investigational new drug
IRB	institutional review board
ITN	Immune Tolerance Network
KLH	keyhole limpet hemocyanin
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Diseases
PEFR	peak expiratory flow rate
PPDI	Pharmaceutical Products Development, Inc.
SAE	serious adverse event
SAEC	safety adverse event coordinator
SAP	statistical analysis plan
SPT	skin-prick test
UCSF	University of California, San Francisco
UK	United Kingdom

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1. BACKGROUND

1.1 SUMMARY AND RATIONALE FOR TRIAL

Peanut allergy is an increasingly prevalent cause of serious allergic reactions and is a recognized public health concern. Dietary avoidance of peanut in early life has been recommended in many countries. In the United Kingdom (UK), for example, infants identified as at risk are advised to avoid peanut for the first 3 years of life.¹ However, there is evidence that the prevalence of peanut allergy is decreased in countries where children are fed peanut beginning at an early age. This raises the possibility that avoidance guidelines may promote the development of peanut allergy by preventing the induction of oral tolerance in infants exposed to high levels of environmental peanut. This trial proposes to compare the two approaches in a population of high-risk children. In addition, it will allow the mechanisms that underpin antigen-specific oral tolerance induction to be addressed.

1.2 CLINICAL ASPECTS OF PEANUT ALLERGY

1.2.1 Increased Prevalence of Peanut Allergy

Peanut allergy has become increasingly prevalent: recent studies demonstrate that the prevalence of peanut allergy has doubled in 10 years and approximates 1.3%–1.5%.² Peanuts are a frequent cause of anaphylaxis for which there is no established treatment except allergen avoidance. Children with peanut allergy additionally have to avoid tree nuts since up to 50% have allergies to individual tree nuts.

Studies eliminating food allergens during pregnancy, lactation, and infancy have consistently failed to reduce IgE-mediated food allergy in children. Two explanations for this failure with respect to peanut allergy include:

1. Sensitization to food allergens does not occur through oral exposure but may occur via other routes. For example, the use of topical preparations containing peanut oil on infants with eczema during the first 6 months of life is associated with a high risk of developing peanut allergy.³ A recent study showed that after subjects had eaten peanut and then washed their hands and cleaned the tabletops, peanut protein was detectable in significant amounts (ten to several hundred micrograms) on hands and on the tabletop surfaces.⁴
2. Early oral exposure may be required to prevent the development of allergy. Oral tolerance induction is well recognized in murine models and has been documented in the clinical literature.^{5,6}

1.2.2 Examples of Oral Tolerance

One study of oral tolerance induction in adults showed that oral intake of keyhole limpet hemocyanin (KLH) results in immunological tolerance to KLH antigen.⁵ The only study that attempted to induce tolerance to a food allergen⁷ was conducted in subjects who already had established milk allergy. The result of this study was promising: 71% of highly allergic children were able to tolerate a daily intake of 200 mL of milk after treatment. However, because this was an uncontrolled study, the possibility that these children would have shown spontaneous resolutions cannot be discounted.

There is some evidence that oral exposure to nickel results in tolerance. Numerous studies, both prospective and retrospective, show that early cutaneous exposure to jewelry, particularly through ear

piercing, is a risk factor for the development of contact dermatitis. In contrast, three independent studies,⁸⁻¹⁰ including one prospective birth cohort study, show that the early application of orthodontic braces made of nickel strongly protects against the development of contact dermatitis to nickel (in one study there was an odds ratio of 0.07). Indeed, after the insertion of fixed orthodontic appliances, the level of nickel both in the saliva and serum of individuals increases significantly, which is thought to result in oral tolerance. Similarly, subjects exposed to pancreatic extract by inhalation or contact develop IgE-mediated allergic reactions, whereas subjects exposed to this extract by oral route do not.¹¹

1.2.3 Epidemiology of Peanut Allergy

Clinical observations from countries in Southeast Asia and Africa, where high amounts of peanuts are consumed in different snack forms during infancy, suggest a low rate of peanut allergy. As these differences could be due to genetics, we have examined these geographical variations more carefully by comparing the prevalence of peanut allergy in Jewish children in the UK and Israel. The relative risk of peanut allergy is 15-fold higher in the UK than in Israel.

There are two components to our ongoing study comparing allergies in Jewish children in the UK and Israel. We initially determined the allergy prevalence data for 4- to 18-year-old Jewish schoolchildren in the UK (n=4031) and in Israel (n=4677). In the second part of the study, we determined the peanut consumption data for 8- to 14-month-old Jewish infants in Israel and the UK.

Data on peanut consumption were prospectively obtained for 218 Jewish infants 8–14 months old (115 infants in the UK, 103 in Israel). Preliminary data suggest that most Israeli infants (81%) had eaten peanut by 1 year of age (median age 10 months), with a median peanut protein consumption of 6.0 g of peanut protein per week (an interquartile range of 0–18 g per week). In contrast, the majority of UK infants (78%) had not been exposed to peanut protein by 1 year of age and significantly lower peanut consumption patterns were recorded, a median of 0 g per week. Thus, there is a statistically significant difference between peanut protein consumption by infants in Israel and infants in the UK, with a *P* value of .0013 for the two-sample Wilcoxon rank-sum test.

We do not have data comparing the prevalence of allergies in Israeli children who have not eaten peanut protein—specifically, the Israeli peanut-containing snack Bamba,—because, such children are very difficult to identify after the age of 2.

Children from 11 Israeli schools and 13 Jewish UK schools participated in this study. The proportion of children of Ashkenazi (Central and Eastern European) and Sephardic (Mediterranean and North African) origin is equivalent in both countries. The return rate in Israeli schools was 83.2% (74%–89%) and 79% (70%–92%) in the UK. In total, 8% of total responders were “late responders” whose questionnaires were completed by postal reminders or telephone interviews. There are no significant demographic differences between early and late responders. An independent and random data entry audit revealed an error rate of <0.1%.

Numerous questions relating to food allergy and atopic disease remain. In this trial, we are primarily interested in a binary measure of peanut allergy, but we also look at an ordinal measure of the increasing likelihood of clinical allergy. Previously, for peanut allergy (as a binary variable), we only used the most stringent definition. Children had to react with at least one typical symptom within 2 hours of eating peanut and were required to avoid foods containing peanut in their diet. Using this definition the prevalence of peanut allergy is 0.11% in Israel and 1.54% in the UK (*P* < 0.001). This tighter definition appears to be extremely accurate. Twenty-six children fulfilling these criteria have been clinically evaluated, and 23 children (88.4%) were found to be peanut allergic. Peanut allergy is always more common in the UK than in Israel, irrespective of the criteria we use, and this difference occurs both in children with and without eczema.

The unadjusted prevalence of peanut allergy is 15 times more common in the UK than in Israel. There is less variation in other atopic diseases, such as eczema, asthma, and allergies to cow's milk, between the UK and Israel. We explore whether the difference in peanut allergy can be explained by the modifying effects of the underlying propensity for atopic disease in the two countries. More formally, we can calculate the relative risk of peanut allergy in the UK as compared with that in Israel after adjusting for a number of factors (see Table 1).

Table 1. Relative risk of peanut allergy in the UK compared with that in Israel

Adjustment	Relative Risk ¹	95% Confidence Interval	P
Unadjusted	14.6	5.8–34.3	<.001
Logistic regression, adjusted for age, sex, eczema, asthma, hay fever, egg allergy, milk allergy	7.3	2.8–18.8	<.001
Stratified analysis, matched on age, sex, eczema, asthma, hay fever and milk or egg allergy (Mantel-Haenszel estimate)	11.2	3.5–36.1	<.001

¹The terms *relative risk* and *odds ratio* are used interchangeably, as the prevalence of peanut allergy in Israel is extremely low.

In conclusion, the questionnaire-based study shows that peanut allergy is many-fold more common among Jewish children in the UK than among Jewish children in Israel. The different prevalence can only partly be explained by a difference in atopic diseases or other food allergies. Even after taking account of these factors, we find that peanut allergy is many times more common in the UK. The result is unlikely to be due to cultural differences in the way the questionnaires were completed. The difference in prevalence remains even when one uses a variety of definitions for peanut allergy, and is seen in both low-risk children (e.g., children without any atopic disease) and high-risk children (e.g., children with eczema or egg allergy).

These data are also consistent with the notion that high-dose, first-time peanut exposure may lead to oral tolerance. Indeed, if a single oral exposure to peanut were to have no effect on promoting or preventing peanut allergy, then one might expect to see numerous children react on subsequent exposures. This is not the case.

1.2.4 Egg, Milk, and Tree-Nut Allergies in Israel and the UK

Egg and milk are useful control allergens to compare to peanut. Although more common in the UK (combined prevalence of 3.8%), egg and milk allergies are nevertheless common in Israel, with a combined prevalence of 1.6%. The unadjusted odds ratio comparing egg and milk allergies between the UK and Israel is 2.5, but after adjusting for hay fever, asthma, and eczema, the odds ratio decreases to 1.6. In contrast, the adjusted odds ratio for peanut allergy remains extremely high, a result due to a country effect rather than to differences in atopy. Importantly, the difference between tree-nut allergies in both countries mirrors the difference seen for peanut. Thus, in the UK, the prevalence of tree-nut allergies is 1.76%, and in Israel, it is 0%.

In our study, as in other studies, 50% of children with peanut allergy had tree-nut allergies and vice versa on questionnaire. This is not surprising since the major peanut allergens Arah1, Arah2, and Arah3 belong respectively to the family of viscillins, conglutinins (2S albumen), and glycinins, highly conserved protein families found in nuts and seeds. Furthermore, there is evidence of extensive cross reactivity between peanut and tree-nut allergens and B-cell epitopes in IgE binding studies. De Leon

and colleagues¹² report that preincubation of sera from peanut-allergic individuals with almond, Brazil nut, or hazelnut resulted in a marked decrease in IgE binding to peanut extract, indicating cross reactivity.

There is also the possibility that similar T-cell epitopes exist for peanut and tree-nut proteins. By doing a protein sequence BLAST search, we have found high levels of sequence homology between the three major peanut allergens and the major allergens in tree nuts. Overall protein homology and amino acid positivity exist in the 30%–50% range. These similarities are heightened when we search for limited domain homology over peptide lengths of 20–25 amino acids (multiple alignment using Clustal W software). Thus, we can identify domain homologies with amino acid identity of 70%–80% and amino acid positivity of 80%–95%. These areas of homology/positivity among the major peanut allergens could potentially explain cross sensitization in the UK population. Similarly, they could account for a cross-tolerizing effect between peanuts and tree nuts in the Israeli population, perhaps because of high dose exposure to peanut protein. This could explain the absence of both peanut and tree-nut allergies in Israel despite the relatively high prevalence of egg and milk allergies.

1.2.5 Analysis of Protein in Bamba

One possible explanation for the differences in the rate of peanut allergy in the UK and Israel is that children in the two countries are exposed to peanut that is processed differently. For example, in China, where people consume boiled peanuts, there is a low prevalence of peanut allergy, and in the U.S., where people consume roasted peanuts, there is a high prevalence of peanut allergy. However, this is unlikely to be the case in Israel given that Bamba is made from roasted peanut sourced from different countries.

To verify this, Dr. Soheila Maleki of the U.S. Department of Agriculture determined and compared the peanut protein content and the amount of each major peanut allergen in Bamba, in a roasted peanut control, and in two different commercial peanut butter preparations available in the UK. She found that 85% of the protein in Bamba derives from peanut (the remainder derives from maize) and that the amount of each major peanut allergen (Arah1, Arah2, and Arah3) in the peanut protein is comparable to the amount of each major allergen in the two peanut butters. Similarly, IgE binding (pooled sera from peanut allergen) was very similar between different samples of Bamba and the two peanut butters (Figure 1). Thus, Bamba contains large amounts of peanut protein, contains all three major peanut allergens in significant quantities, and, as measured by IgE binding, contains peanut protein that is highly allergenic (or just as allergenic as the peanut butter used in the UK).

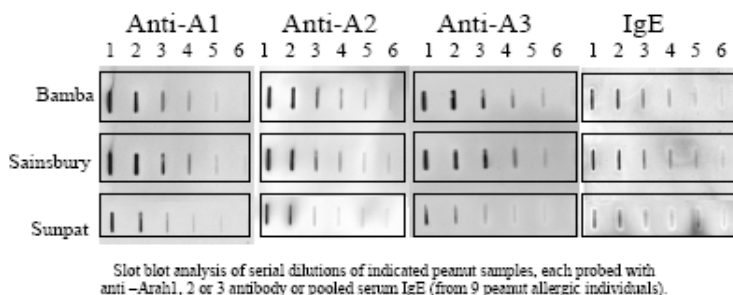


Figure 1. IgE binding of Bamba and two variations of peanut butter

1.3 PRECLINICAL ASPECTS OF PEANUT ALLERGY

Certain murine studies have shown that allergic sensitization to antigen can occur on cutaneous exposure. Saloga and colleagues showed that when microgram quantities of ovalbumen were applied to the abraded skin of mice, the mice had significant anti-OVA IgE responses and positive intradermal

tests.¹³ More recently, Strid and colleagues have shown that when arachis oil is applied to the abraded skin of mice, the mice have significant IgE and T-cell responses to peanut,¹⁴ even if the oil has fewer than 6 µg/mL of peanut protein.

Animal models demonstrate that a high early dose of oral protein antigen is highly effective in inducing tolerance to the respective antigen, even in the case of subsequent administrations of antigen in the presence of potent immune-adjuvants. Over the last 35 years, 33 publications on oral tolerance induction in animal models have documented that a single oral dose of antigen is sufficient to induce tolerance. This phenomenon has been demonstrated for different antigens in different experimental models, but the resulting data are consistent: they uniformly show that a single dose of oral protein administration effectively causes immunological tolerance and prevents the expression of related clinical disease.

Oral tolerance induction in animal models is most potent in its effects on delayed type I hypersensitivity responses; prevention of antibody responses through induction of oral tolerance is less consistent. However, numerous publications point to the fact that in mice a single dose of food allergen (beta-lactoglobulin, ovalbumen, peanut) is particularly effective in preventing the development of subsequent IgE-mediated responses. A recent study¹⁵ showed that naïve mice orally tolerized to beta-lactoglobulin were unable to mount significant IgE responses when they were subsequently sensitized with beta-lactoglobulin injected along with alum intraperitoneally. Similarly, there were no significant T-cell responses to beta-lactoglobulin in the pretolerized animals.

In another study in 2004, Strid and colleagues¹⁶ fed mice a single intragastric feed of defatted peanut flour at doses varying from 0.2 to 100 mg per mouse. Seven days after the feed, the mice were immunized with 100 µg of peanut antigen emulsified with Freund complete adjuvant. Three weeks later, the mice were given a recall immunization with 100 µg of antigen. The mice were assayed for T-cell proliferation to peanut, cytokine production, delayed-type hypersensitivity responses, and antibody responses. Tolerizing doses of 100 mg of peanut protein resulted in significant reduction of delayed-type hypersensitivity responses and inhibition of proliferative responses to peanut. Mice tolerized to 100 mg of peanut protein showed significantly reduced interferon gamma and IL-4 production. Specific IgE responses to peanut following sensitization were almost completely prevented by the single tolerizing dose. However, very low tolerizing doses of peanut, i.e., those below 2 mg per animal, resulted in enhanced delayed-type hypersensitivity responses, T-cell proliferative responses, cytokine production, and IgE production. Doses between 2 and 20 mg of peanut protein induced no difference between the T- and B-cell responses as compared to sham-tolerized animals. Tolerance to peanut was only achieved at doses of 100 mg per animal. Oral tolerance to peanut was shown to be antigen specific. Tolerizing doses of peanut did not promote tolerance to ovalbumen and vice versa.

1.4 RATIONALE FOR TRIAL DESIGN

1.4.1 Population and Stratification

This trial will enroll infants who are at high risk of developing peanut allergy, which is defined by having egg allergy, eczema, or both. The risk of developing peanut allergy is mainly determined by the presence of severe eczema. In determining the degree of eczema severity as a criterion for enrollment, two factors have been shown to be of predictive value for peanut allergy: (1) the required use of topical steroidal creams on children 6 months of age or younger, (D. Hill, personal communication), and (2) parental responses to questionnaires describing the nature of the skin condition (G. Lack, unpublished data).

In addition, participants will be stratified into risk groups based on skin-test reactivity to assess the effect of peanut consumption in those with moderate skin-test reactivity and those with minimal skin-test reactivity.

1.4.2 Open-Label Design

In an ideal world, we would address the study hypothesis using a randomized, placebo-controlled, double-blind design. The inclusion of a placebo has been considered in great detail. The main reason for not including a placebo snack is the impossibility of guaranteeing that it would be free from peanut since it would be manufactured in the same factories as the peanut snack. Furthermore, the cost of producing a placebo snack would be substantial, and there would be no guarantee of its nutritional equivalence to the peanut-containing snack. Finally, the children eating the placebo snack that tastes of peanut may develop a taste for peanut and may want to eat other foods that contain peanut, which would make adherence to the study advice impossible.

The obvious disadvantage of not including a placebo snack is that children will know which study arm they are assigned to. This disadvantage is offset by the fact that peanut allergy will be diagnosed on the basis of three objective measures: double blind, placebo-controlled food challenge (DBPCFC); specific IgE; and skin-prick testing to peanut. On peanut challenge, neither the physician, the nurse, nor the participant will know the participant's dose (peanut or placebo), so it will be impossible for the outcome of the challenge to be influenced by that knowledge. Skin-prick testing and specific IgE are highly objective measures, and the person reporting the specific IgE level will not know the status of the participant.

1.4.3 Administration of Baseline Peanut Challenge

More than 90% of the peanut-allergic children seen in our clinics react on first known exposure to peanut. It is extremely unlikely for a child to react on the second or third exposure, having tolerated peanut the first time. In the rare instances where a reaction occurs on subsequent exposure, it usually occurs because, on the first occasion, the child was only exposed to very small amounts of peanut at home and only tolerated a small amount. We believe that these participants are already allergic on first or second exposure but have not reached a threshold dose for clinical reaction; their aversion to peanut has prevented them from eating a sufficient dose. In the current trial, children with preexisting allergy will be screened from further administration of peanut by giving those who are initially randomized to the peanut consumption group a baseline peanut challenge.

1.4.4 Determination of Peanut Allergy

The main goal of this trial is to determine the proportion of participants with peanut allergy. It is important that as many participants as possible are evaluable for this assessment. Food challenge will be the main method of assessment, as it is recognized as the gold standard for diagnosis of peanut allergy. However, given the importance of this assessment, for those in whom food challenge is not possible, additional information will be considered, including dietary history, skin prick testing, and allergen-specific IgE levels. The algorithm for determination is presented in Figure 3 and Figure 4.

We will first determine if, at 60 months of age, the participant meets the criteria for open challenge. These criteria are intended to identify participants who are less likely to be allergic. Such participants who have a negative open challenge will be considered tolerant, since the gold standard for tolerance is the open challenge. Children with a positive open challenge will be invited to undergo a double blind challenge, which is the gold standard for determination of allergy. Because we insist on no symptoms for a participant to be considered tolerant, indeterminate results may occur. In addition, positive symptoms during an open challenge may be difficult to interpret. Therefore, all such participants will be invited to DBPCFC.

Participants who do not meet the criteria for an open challenge will undergo the DBPCFC. A participant who also reacts positively to the DBPCFC will be considered allergic. A participant who

passes the DBPCFC will be considered tolerant, bearing in mind the last step of the DBPCFC is an unblinded administration of peanut protein.

It is anticipated that as many participants as possible active in the study at 60 months of age will have an outcome determined based on food challenge. However, in order to maximize the number of individuals who can be accurately evaluated for the primary endpoint, for the remaining participants we will diagnose peanut allergy or tolerance if the outcome can be determined with a high degree of accuracy.

Participants who are not available for either open challenge or DBPCFC, or participants who have indeterminate results, will be evaluated using dietary history, SPT, and peanut-specific IgE. For such participants, these evaluations determine allergic status with greater than 95% accuracy.

The general approach is that a strongly suggestive history can be combined with highly predictive ($\geq 95\%$) SPT and/or IgE results to give a determination of tolerance or allergy. Even an excellent history on its own is only 70%–80% accurate in establishing a diagnosis of allergy or tolerance. There are cutoff values, however, for both SPT and IgE above and below which one can respectively establish a diagnosis of allergy or tolerance with $\geq 95\%$ predictive value. Because it is unknown if the cutoff value varies with the ingestion of Bamba, these cutoff values will be used together with history. As a general rule, if there is a contradiction in our data set between history and the SPT/IgE results, or even between the SPT and IgE results, the participant will be considered nonevaluable in the absence of a challenge. The algorithm to do so is outlined in Figure 4.

A dietary and reaction history can be categorized in four ways with respect to the degree to which it supports tolerance or allergy.

1. For a participant with a history strongly suggestive of peanut tolerance, see the upper left hand quadrant of Figure 4. A strongly suggestive history is one in which there is good documentation that a participant has been eating significant quantities of peanut at home. In the current trial, this will be assessed by a supervised 4-g peanut ingestion at home without difficulty. Such ingestion, without symptoms, will nearly always establish tolerance, except for the scenario where SPT or IgE is contradictory.
2. For a participant with a history consistent with peanut tolerance, see the lower left-hand quadrant of Figure 4. A history consistent with tolerance is one in which the participant has had more than trace exposure to peanut without difficulty, but where there is no good documentation of significant dietary exposure. Here, negative IgE or SPT is required because this history is not as robust as in case 1 above.
3. For a participant with a history strongly suggestive of peanut allergy, see the upper right-hand quadrant of Figure 4. A strongly suggestive history is one in which there is good documentation that a participant has had symptoms related to peanut exposure. A high IgE or SPT is nevertheless required to establish a diagnosis of allergy.
4. For a participant with indeterminate history consistent with allergy, see the lower right-hand quadrant of Figure 4. An indeterminate history consistent with allergy is one in which the participant has not had more than trace exposure to peanut and where there is no good documentation of symptoms related to dietary exposure. Here, a very high level of IgE or SPT is required to determine allergy and a very low level of IgE or SPT is required to establish tolerance.

Participants for whom allergic or tolerant status cannot be determined with at least 95% certainty will be considered nonevaluable. Such participants include those in whom data are not strong enough on either the allergic or the tolerant side to make a clear determination. They also include those for whom there is a contradiction among the history, the skin test result, and the IgE measurement. For example,

this would occur when the dietary and reaction history suggests tolerance but the SPT or IgE results suggest an allergic response.

1.4.5 Eczema Severity

In this clinical trial, we will enroll children with a high risk of developing peanut allergy based on their eczema severity. We will use three different criteria for assessing eczema severity. The first criterion will be the parents or guardians' description of their child's eczema severity. The second criterion will be the use of topical creams and ointments containing corticosteroids or calcineurin inhibitors. The third criterion will be a modified SCORAD (Scoring Atopic Dermatitis System) evaluation.

Eczema (atopic dermatitis) is an itchy, inflammatory skin condition with a predilection for the skin flexures. It is characterized by poorly defined erythema with edema, vesicles, and weeping in the acute stage and skin thickening (lichenification) in the chronic stage.

Assessing disease severity is problematic when there is no objective marker. The many severity scales used in clinical trials have generally not been studied for association with peanut allergy.

Lack et al.³ found that rash over joints and skin creases as well as oozing, crusted rash had a significant association with peanut allergy. They also found a trend toward an association between the severity of rash in the first 6 months of life and the prevalence of peanut allergy.³

Recently, in the same cohort they noticed a risk of peanut allergy of approximately 20% among children whose parents described their rash as "very bad" (G. Lack, unpublished data). Hill found that peanut allergy is associated with eczema severity when severity was defined as days of topical steroid use each month (D. Hill, personal communication).

The use of modified SCORAD objective criteria will permit the inclusion of children who may not have had access to topical anti-inflammatory medications or whose parents cannot recall or report the severity of their child's eczema. Epidemiological studies using the SCORAD in European countries in older children show mean overall SCORAD scores of 21/103 and 20/103, respectively.^{17,18} The European task Force of Atopic Dermatitis, using only the objective components of SCORAD, classified scores of <15, 15–40, and >40 as mild, moderate, or severe eczema, respectively, out of a possible total score of 83.¹⁹

1.5 RATIONALE FOR IMMUNOLOGICAL ASSESSMENTS

This clinical trial of oral tolerance induction in children will be accompanied by a comprehensive series of studies that will permit us to identify the following:

- Biomarkers that predict susceptibility to oral tolerance induction.
- Molecular mechanisms associated with the development of oral tolerance induction to peanut allergen.
- Indicators of an active (immunomodulatory) response to oral tolerance induction during the course of therapy.
- Biomarkers of underlying allergen tolerance.

Our strategy for identifying these biomarkers, molecular mechanisms, and indicators will involve retrospective comparisons between individual allergen immune-response profiles of peanut-tolerant vs. peanut-allergic individuals. Qualitative, quantitative, and time-dependent changes in allergen immune-response profiles of participants who do or do not develop tolerance to peanut will provide data for testing current hypotheses and generating new hypotheses to explain underlying tolerogenesis mechanisms. To identify the biomarkers associated with underlying tolerance mechanisms in operation

at the time of sampling, we will perform a cross-sectional analysis of the immune-response profiles at screening and at 12, 30, and 60 months of age. Integration of biological data with clinical outcomes will provide a means to identify potential biomarkers of oral induced tolerance to peanut. Mechanistic studies will focus on T cell responses (CD4, T_{REG}) and B-cell responses (IgE epitopes, peanut specific IgE and IgG4, FAP assay). Specimens may also be used in future immune response or biomarker assays to reevaluate biological response as research tests are developed.

1.6 KNOWN AND POTENTIAL RISKS

1.6.1 Peanut Consumption Group

Potential risks associated with the consumption of a peanut-containing snack are worsening of eczema, weight gain, nutritional compromise, metabolic abnormalities, and an increased risk of allergy to peanut or other allergens.

Four different studies show that the median age of reacting to peanuts is between 14 and 24 months of age. The vast majority of patients react upon first known exposure to peanut.^{3,20,21} This argues strongly against the possibility that peanut allergy is caused by eating peanuts and provides some reassurance that we will not induce peanut allergy by feeding participants peanuts.

1.6.2 Peanut Avoidance Group

Avoidance of peanut may result in an increased risk of allergy to peanut or other allergens.

1.6.3 Both Groups

Undergoing laboratory assessments may involve a low risk of hemorrhage, hematoma, and infection at the venipuncture site. Risks associated with the planned peanut challenges include nausea, vomiting, itching, urticaria, angioedema, asthma, other respiratory symptoms, and anaphylaxis, which can be life-threatening.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

To assess whether oral administration of a peanut-containing snack can induce tolerance in children at high risk for peanut allergy.

2.2 SECONDARY OBJECTIVES

To assess the effect of a peanut-containing snack on additional allergy outcomes, as outlined in section 3.3.

To assess the safety of administration of peanut protein in this population.

To define the mechanisms through which the ingestion of peanut protein may induce tolerance to peanut.

3. STUDY DESIGN

3.1 DESCRIPTION

This is a randomized, controlled trial that will enroll children at high risk for peanut allergy as demonstrated by eczema, egg allergy, or both. As shown in Figure 2, participants will be stratified based on their skin prick test (SPT) results for peanut: those with a wheal diameter of 0, 1, or 2 mm will be in the SPT two-minus stratum and those with a wheal diameter of 3 or 4 mm will be in the SPT three-plus stratum. Participants in each stratum will be randomly assigned to receive a peanut-containing snack or to avoid peanut. Those assigned to receive the peanut-containing snack will receive at least 2 g of peanut protein three times per week until they reach 60 months of age. The prevalence of peanut allergy at that time will be compared between the peanut consumption and peanut avoidance groups.

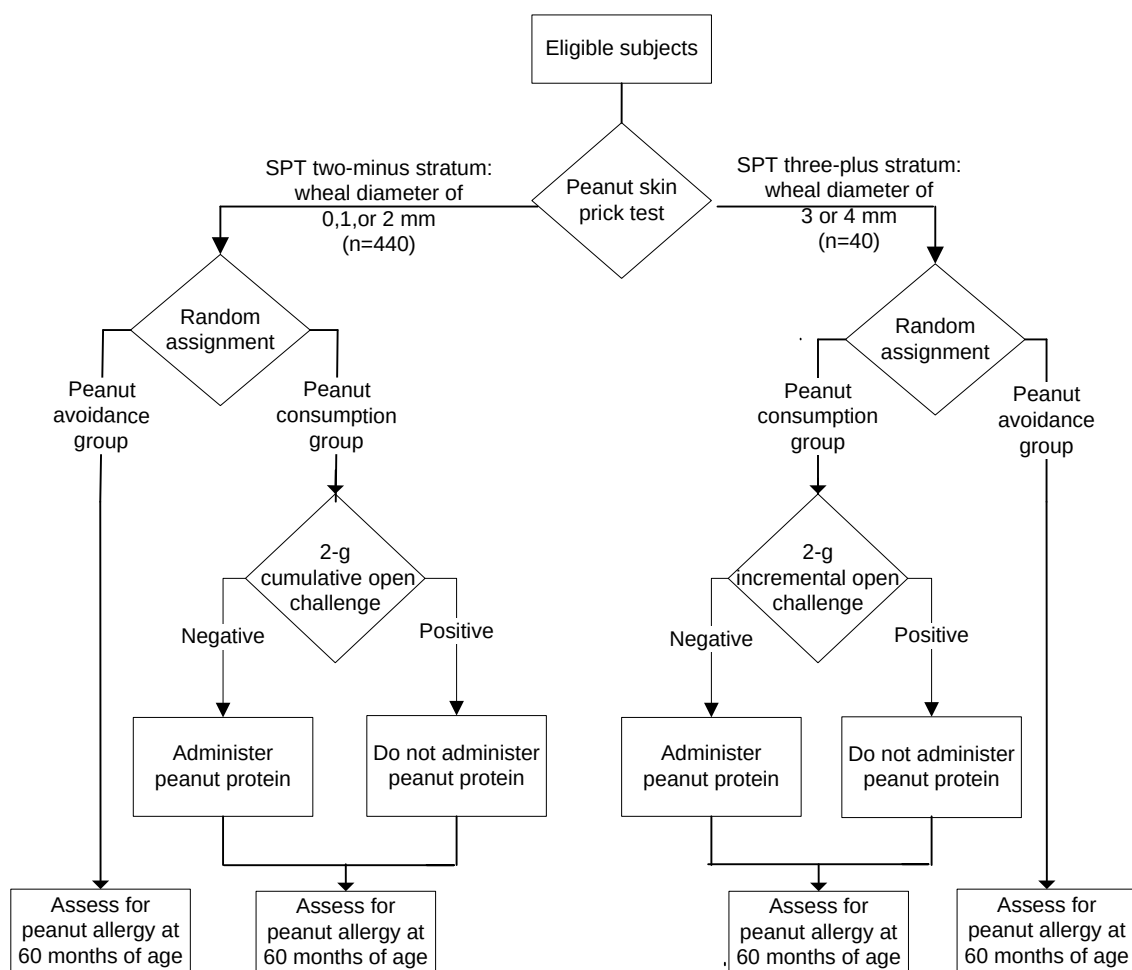


Figure 2. Study design

3.2 PRIMARY ENDPOINT

The proportion of participants with peanut allergy at 60 months of age.

3.3 SECONDARY ENDPOINTS

1. At 30 and 60 months of age: the proportion of participants with allergic sensitization to selected ingested allergens and inhaled allergens, and with seasonal rhinoconjunctivitis, perennial rhinoconjunctivitis, and asthma.
2. At 60 months of age: the proportion of participants with type 1 immediate onset food allergy to selected ingested allergens.
3. Incidence of adverse events and laboratory abnormalities; nutritional evaluations.
4. Results of cellular and humoral assessments of immune response related to the development of allergy or tolerance to specific allergens.

3.4 DETERMINATION OF PEANUT ALLERGY

Figure 3 and Figure 4 provide the algorithm for determination of peanut allergy.

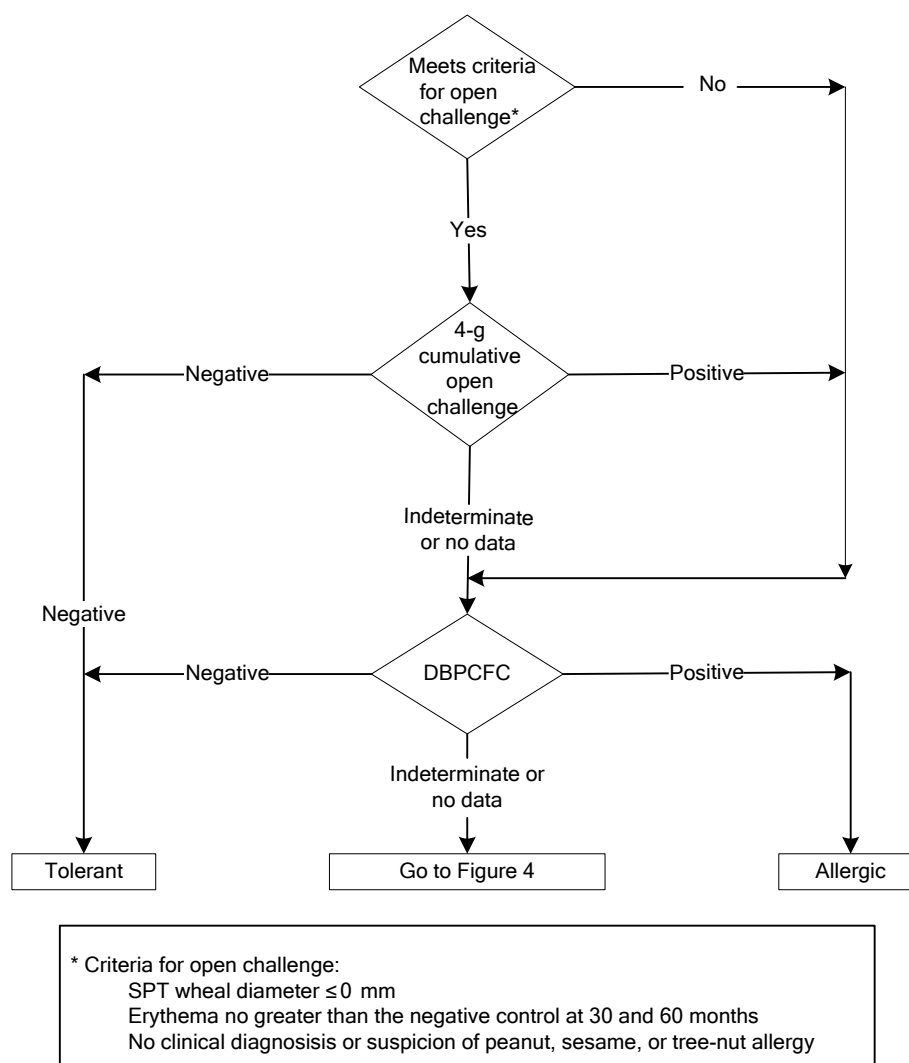


Figure 3. Determination of peanut allergy using challenges performed in the clinic

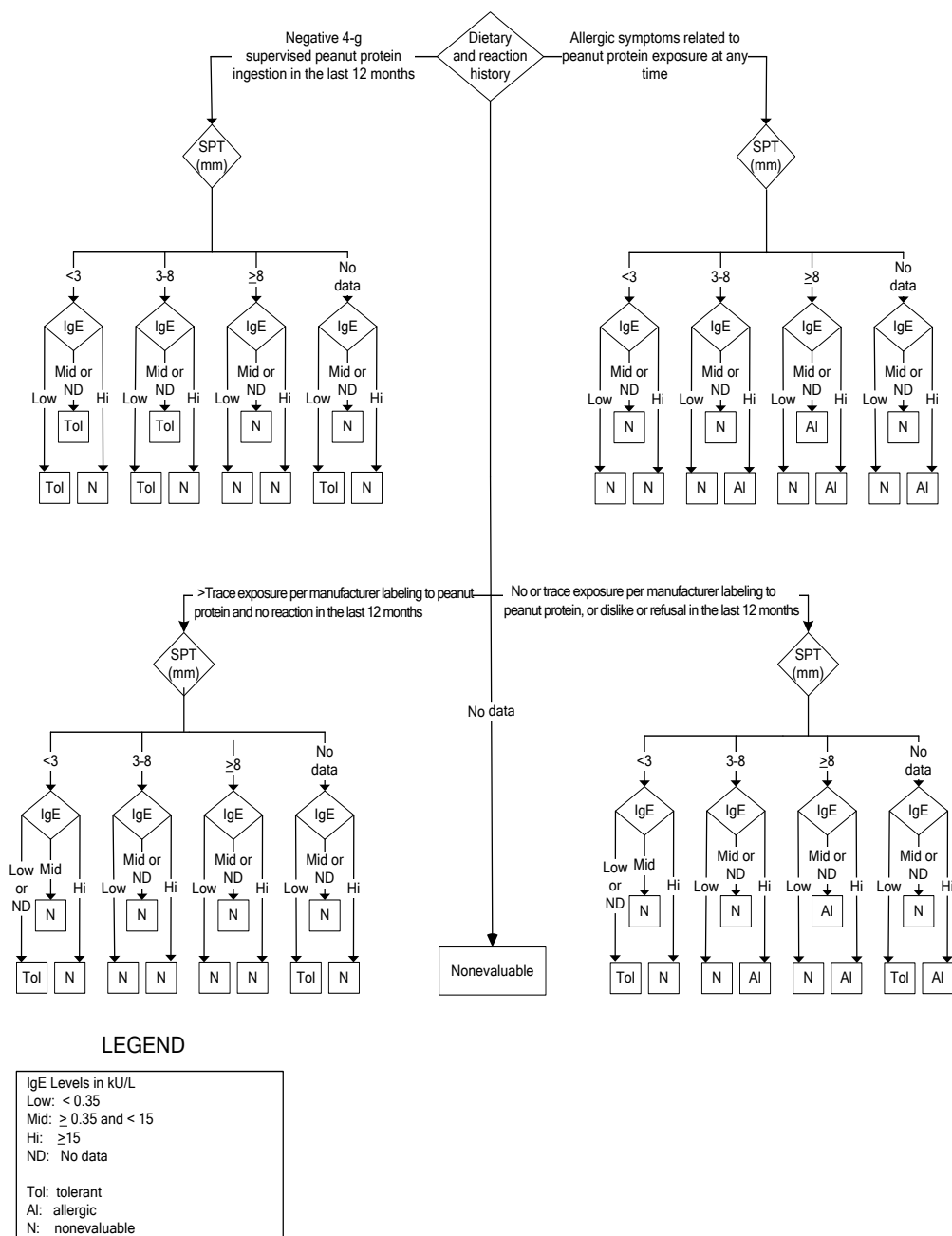


Figure 4. Determination of peanut allergy in the absence of peanut-challenge results using dietary and reaction history, SPT, and IgE

3.4.1 Example Assessment Scenarios

An interpretable outcome for either the DBPCFC or the 4-g cumulative open challenge performed in clinic is sufficient for a determination of allergy status (Figure 3).

- If there is no such outcome, peanut allergy will be assessed via interpretation of dietary history, SPT wheal diameter, and IgE levels (Figure 4).

Consider the following examples for a participant at age 5:

- A participant undergoes the DBPCFC and exhibits one or more of the indications listed in Table 3. This participant would be counted as allergic.
- A participant undergoes the 4-g cumulative open challenge performed in clinic and does not exhibit any of the indications listed in Table 3. This participant would be counted as tolerant.
- A participant is not available for in-clinic challenge (“no data”). For such participants, dietary and reaction history shall be reviewed (Figure 4). Some possible scenarios follow:
 - A participant has a dietary and reaction history of a negative 4-g supervised peanut protein ingestion in the last 12 months. This result directs the assessment to the upper left quadrant of Figure 4. The participant’s SPT = 2 mm. The participant’s IgE = 3 kU/L (“Mid”). This leads us to a box labeled “Tol,” that is, the participant will be counted as tolerant.
 - Dietary history indicates that a participant has exhibited allergic symptoms related to peanut protein exposure. This result directs the assessment to the upper right quadrant of Figure 4. The participant’s SPT = 5 mm, and IgE = 17 kU/L. This leads us to a box labeled “Al”; that is, the participant will be counted as allergic.
 - Dietary history indicates that a participant has had more than trace exposure to peanut protein in the last 12 months and has exhibited no reaction. This result directs the assessment to the lower left quadrant of Figure 4. As in the above scenario, this participant’s SPT = 5 mm and IgE = 17 kU/L. This participant will be considered nonevaluable because the high IgE, which is strongly suggestive of allergy, contradicts the history, suggesting tolerance.
 - Dietary history indicates that during the last 12 months a participant has had only trace exposure to peanut protein or has persistently refused or exhibited dislike of peanut. This result directs the assessment to the lower right quadrant of Figure 4. There are no data for SPT, but the participant’s IgE = 0.2 kU/L. This participant will be counted as tolerant.
 - Dietary history for a participant is not available. This participant will be considered nonevaluable.

3.5 STUDY DEFINITIONS

Allergic sensitization. Either allergen-specific IgE ≥ 0.35 kU/L, as defined by the CAP System™ (Pharmacia Diagnostics AB); or positive SPT, defined as SPT wheal diameter ≥ 3 mm with appropriate controls.

Asthma. A history of cough, wheeze, or shortness of breath that (1) was responsive to therapy with bronchodilators on two or more occasions in the previous 24 months, (2) required one visit to a physician in the previous 24 months, and (3) occurred during the night, during early morning, or upon exercising in the intervals between exacerbations at any time in the previous 12 months.

Egg allergy. Either (1) an SPT wheal diameter ≥ 6 mm from exposure to raw hen’s egg white and no history of previous egg tolerance, or (2) an SPT wheal diameter ≥ 3 mm from exposure to pasteurized hen’s egg white and allergic symptoms related to exposure to hen’s egg.

Failure to thrive. Weight decrease across ≥ 2 deciles from the initial baseline weight.

Life-threatening anaphylaxis. An allergic reaction accompanied by any of the following: hypoxia, as evidenced by central cyanosis or oxygen saturation $\leq 89\%$; hypotension; loss of consciousness; or admission to intensive care.

Peanut allergy. IgE-mediated immediate hypersensitivity symptoms to peanut allergen.

Perennial rhinoconjunctivitis. Sensitization to a perennial allergen and clinical history of rhinoconjunctivitis symptoms experienced when exposed to the relevant allergen.

Seasonal rhinoconjunctivitis. Sensitization to a seasonal allergen and clinical history of rhinoconjunctivitis symptoms experienced during the relevant season.

Severe eczema. A rash that

- required the application of a topical creams and ointments containing corticosteroids or calcineurin inhibitors and if the participant is
 - ≤ 6 months of age, lasted for at least 12 out of 30 days on two occasions, or
 - > 6 months of age, lasted for at least 12 out of 30 days on two occasions in the last 6 months; or
- has been described by the participant's parent or guardian in a pre-enrollment questionnaire as "a very bad rash in joints and creases" or "a very bad itchy, dry, oozing, or crusted rash"; or
- is currently or was previously graded > 40 using the modified SCORAD evaluation.

3.6 STOPPING RULES

3.6.1 Ongoing Review

The protocol chair, the NIAID medical monitor, the ITN clinical trial physician, and the NIAID Allergy and Asthma Data and Safety Monitoring Board (DSMB) will review safety data on an ongoing basis. The DSMB may stop enrollment or participation in the trial at any time if it concludes that there are significant safety concerns.

3.6.2 Review of Specific Adverse Events

3.6.2.1 Stopping Enrollment

Enrollment in the trial will be stopped pending review if any death occurs or if two participants are admitted to an intensive care unit for an adverse event related to study participation.

3.6.2.2 Stopping Enrollment and Administration of Peanut-containing Snack

Enrollment in the trial and further administration of the peanut protein-containing snack will be stopped pending review if either of the following occurs for the SPT two-minus stratum:

- An analysis performed when 50 such participants in the peanut consumption group have been followed for 3 weeks demonstrates that the lower bound of the 95% confidence interval for the proportion of participants in the peanut consumption group with peanut allergy as determined in an unscheduled clinic visit (see section 6.7) is greater than 15%.
- An analysis performed when 50 such participants per group have been followed for 12 months demonstrates that the rate of serious adverse events is significantly greater at the 0.05 significance level in the peanut consumption group than in the peanut avoidance group.

Enrollment in the trial and further administration of peanut protein-containing snack to participants in the SPT three-plus stratum will be stopped pending review if either of the following occurs:

- One of the first 5, 2 of the first 10, or 3 of the first 15 such participants randomly assigned to the peanut consumption group experiences life-threatening anaphylaxis (see section 3.5) during the first 3 weeks of administration of the peanut protein-containing snack.
- An analysis performed when 10 such participants in the peanut consumption group have been followed for 12 months demonstrates that 4 or more participants have experienced a serious adverse event.

3.7 STUDY DURATION

Enrollment is expected to take 24 months. Participation is approximately 54 months. Study duration is expected to be 78 months.

4. ELIGIBILITY

4.1 INCLUSION CRITERIA

1. Children ≥ 4 to < 11 months old who have had solids successfully introduced into their diet.
2. Egg allergy, severe eczema, or both.
3. Informed consent obtained from parent or guardian.

4.2 EXCLUSION CRITERIA

1. Clinically significant chronic illness, except for eczema or recurrent wheeze.
2. Positive skin prick test for peanut allergen with a wheal diameter > 4 mm in the presence of a negative saline control.
3. Previous or current consumption of peanut protein that exceeds 0.2 g of peanut protein on at least one occasion or 0.5 g over a single week.
4. Investigator-suspected allergy to peanut protein.
5. Investigator-suspected allergy to peanut protein in a care provider or current household member.
6. Diagnosis of persistent asthma.
7. AST (SGOT), ALT (SGPT), or bilirubin > 2 times the upper limit of age-related normal value.
8. BUN or creatinine > 1.25 times the upper limit of age-related normal value.
9. WBC $< 3.5 \times 10^3/\text{mL}$, polymorphonuclear cell count $< 1500/\text{mL}$, platelet count $< 100,000/\text{mL}$, or hemoglobin < 9 g/dL.
10. Unwillingness or inability to comply with study requirements and procedures.

4.3 REASSESSMENT FOR ELIGIBILITY

Participants who fail to meet the criteria for enrollment in the trial may be reassessed for eligibility. Such participants may be enrolled at the time of reassessment if they meet all criteria for enrollment.

4.4 PREMATURE TERMINATION

4.4.1 Premature Termination of Trial Interventions

Trial intervention will be prematurely terminated for a participant if, in the judgment of the investigator, further participation in the trial would be deleterious to the participant's health; or if an independent dietary assessment reveals that the study intervention has led to body mass index BMI exceeding the 95th percentile for the participant's age (Table 2)²² or has led to failure to thrive.

Table 2. UK National BMI percentile classification

Age (years)	Boys (95%) Obese	Girls (95%) Obese
2	19.10	18.84
2.5	18.77	18.56
3	18.51	18.42
3.5	18.27	18.35
4	18.08	18.32
4.5	17.97	18.31
5	17.95	18.35
5.5	17.99	18.46
6	18.10	18.65
10	20.42	21.52
10.5	20.79	21.94

4.4.2 Premature Termination from the Trial

Participants will be prematurely terminated from the trial for either of the following:

- withdrawal of consent, or
- failure to return.

Such participants will not be replaced.

5. STUDY INTERVENTION

5.1 PEANUT ADMINISTRATION OR AVOIDANCE

Participants assigned to the peanut consumption group will be fed at least 6 g of peanut protein per week, distributed over at least three meals per week during study participation. The preferred peanut source will be Bamba. There are 17 g of Bamba per serving, which provides 2 g of peanut protein. Thus, the specified amount corresponds to three servings per week. However, peanut butter may be substituted. Participants assigned to the peanut avoidance group will avoid exposure to peanut protein during study participation.

5.2 ASSESSMENT OF COMPLIANCE WITH STUDY INTERVENTION

Dietitians will monitor participant peanut protein consumption using a validated peanut frequency questionnaire in accordance with the schedule of events (see Appendix 1).

5.3 MODIFICATION OR DISCONTINUATION OF STUDY INTERVENTION

Participants in the peanut consumption group will discontinue consumption of the peanut protein-containing snack if a confirmed allergic reaction to peanut protein or an adverse nutritional consequence attributable to consumption of peanut protein is experienced.

These participants will remain in the study to receive a status assessment at 60 months of age.

6. STUDY PROCEDURES

6.1 VISIT WINDOWS

Visits described in the schedule of events should occur as follows:

- Visit 0: no more than 21 days following visit -1.
- Visits 12 and 30: within ± 3 months of the planned visit date.
- Dietary consultations:
 - Between visits 0 and 12: ± 3 days.
 - Between visits 12 and 30: ± 7 days.
 - Between visits 30 and 60: ± 14 days.
- Visit 60: within ± 6 months of the planned visit date.

6.2 GENERAL ASSESSMENTS

These general assessments will be performed at the site:

- Informed consent. Written informed consent will be obtained before any study assessments or procedures are performed.
- Randomization to the peanut consumption or peanut avoidance group. In each stratum, individual assignments to either the peanut consumption or peanut avoidance group will be obtained by authorized site personnel by calling the PPDI Interactive Voice Response System (IVRS) once and entering their unique personal identification number (PIN). The IVRS will assign the study participant a randomization number based on the randomization schedule.
- Dietary education. Dieticians will provide written and verbal information and advice regarding peanut protein consumption or avoidance to the respective groups. Advice on avoidance will be provided in accordance with the Department of Health Guidelines for those in the peanut avoidance group.
- Physical examination. Temperature, blood pressure, pulse, respiration, skin fold thickness, weight, height, and waist circumference.
- Medical history. A history will be taken to determine if the participant has had any clinically significant diseases or medical procedures other than the disease under study.
- Adverse events. Participants will be assessed for adverse events. All adverse events will be recorded on the case report forms (CRFs).
- Concomitant medications. All concomitant medications will be recorded on the CRFs.

- Dietary history. A dietary history will be obtained using a 3-day food diary that captures typical food consumption and provides a breakdown of macro- and micronutrient intake and total energy intake.
- Food reaction history. A history will be taken to determine if the participant has had any clinically significant food-induced, immediate-onset allergic reactions.
- Eczema evaluation. Both subjective and objective eczema severity criteria will be recorded. At screening, eczema severity will be determined using the criteria described in section 1.4.5. The modified SCORAD evaluation alone will be used for all remaining eczema evaluations.
- Rhinitis evaluation. Symptoms in accordance with the study definitions for seasonal and perennial rhinoconjunctivitis will be recorded.
- Asthma evaluation. Symptoms in accordance with the study definition for asthma will be recorded..

6.3 LABORATORY ASSESSMENTS

Routine hematologic and chemistry laboratory assessments, which are detailed below, will be performed at the investigation site and recorded on CRFs.

- Hematology includes CBC with differential and platelets.
- Serum chemistries include Ca, PO₄, BUN, Cr, total protein, and albumin.
- Fasting serum lipids include cholesterol, triglycerides, and high- and low-density lipoproteins.
- Fasting glucose and insulin.
- Skin and nasal swab culture.

6.4 ALLERGY ASSESSMENTS

6.4.1 Allergens Assessed

The following allergy assessments will be performed:

- SPT for ingested allergens includes peanut, raw hen's egg white, pasteurized hen's egg white, cow's milk, sesame, and Soya.
- SPT for tree nuts includes Brazil nut, hazel nut, cashew, almond, and walnut.
- IgE for ingested allergens includes peanut, hen's egg white, cow's milk, sesame, Brazil nut, hazel nut, cashew, almond, and walnut.
- IgE for inhalant allergens includes house dust mite (*Dermatophagoides pteronyssinus*), cat dander, dog dander, timothy grass pollen, alternaria mold, and birch tree pollen.
- Oral food challenges for sesame, Brazil nut, hazel nut, cashew, and walnut will be given when clinical history and the results of SPT and IgE for these allergens are inconclusive. These challenges will be performed according to standard clinical practice.

6.4.2 Skin Prick Testing: Procedures and Interpretation

Prior to testing, ensure that the participant has not received short-acting antihistamine medications for at least 48 hours and/or long-acting antihistamine medications for at least 7 days.

The SPT for raw hen's egg white will be performed using Red Lion salmonella-free egg. The other SPTs will be performed using Soluprick® extracts (ALK-Abelló). Lyophilized peanut extract (ALK-Abelló) will be analyzed for total protein and major peanut allergen concentration (Arah1, Arah2, and Arah3). The extract will be stored at -72°C and will be used for SPT evaluations to peanut throughout the study. Saline 0.9% will be used as a negative control, and histamine (concentration of 1 mg/mL of saline) will be used as the positive control.

Tests will be performed on the forearm unless unaffected eczema-free skin patches are not available, in which case the skin on the participants back will be used for testing. Using a standardized lancet (ALK-Abelló), the skin will be pricked through a drop of the extract, which will then be absorbed.

Skin test sites should be measured after 15 minutes. The wheal and erythema should be measured at their widest diameters and recorded separately. Tests will be interpreted based on the widest wheal diameter.

The positive and negative control tests should be performed and measured prior to allergen SPT.

- If the saline negative control test is ≥ 3 mm, then it should be repeated immediately. If the repeat test remains ≥ 3 mm, the testing should be rescheduled for approximately 7 days' time.
- If the histamine positive control is ≤ 3 mm, then it should be repeated immediately. If the repeat test remains ≤ 3 mm, then the testing should be rescheduled for approximately 7 days' time.

For peanut measurements, the following rules apply:

- The SPT will be performed in duplicate.
- If one result is <3 mm and one is ≥ 3 mm, a third SPT will be performed.
- If two of three results are <3 mm, their mean will be recorded as the final result.
- If two of three results are ≥ 3 mm, their mean will be recorded as the final result.

6.5 PEANUT CHALLENGES

6.5.1 Scheduled Challenges

For participants who are randomly assigned to the peanut arm, a 2-g open challenge will be performed after random assignment (see Figure 2).

For all participants, an in-clinic challenge will be scheduled at the end of study participation for determination of the primary endpoint. This challenge will be either DBPCFC or open challenge by the criteria shown in Figure 3.

6.5.2 Unscheduled Challenges

Unscheduled challenges will be performed as indicated at unscheduled clinic visits (see section 6.7).

6.5.3 Repeat Challenges

If a participant fails to complete a challenge, he/she may be offered an opportunity to repeat the challenge at the investigator's discretion.

6.5.4 Procedure

6.5.4.1 Step 1: Perform Clinical Assessment

All children will be assessed by a pediatric allergy specialist to determine their suitability for a challenge. A participant's eligibility for a challenge is guided by the following criteria:

- The child has had no acute exacerbation of allergic signs or symptoms within the last week.
- The child has not received
 - short-acting beta-2 agonists for 12 hours,
 - long-acting beta-2 agonists for 24 hours,
 - short-acting antihistamines in the last 48 hours, or
 - long-acting antihistamines in the last 7 days.
- The child has no concurrent illness.

Prior to conducting challenges, do the following:

- Inform PICU of the challenge taking place.
- Ensure that both oxygen and suction are in working order in the clinical trials unit.
- Ensure that all steps of the anaphylaxis protocol are in place and that all emergency drugs are prescribed.
- Check that the drug box containing emergency medications is complete and that it is readily available.
- Record baseline observations, including temperature, pulse, respiration, SaO₂, auscultation of the chest, and peak expiratory flow rate (PEFR), if the child is reliably able to perform PEFR.
- Record blood pressure on all participants older than 12 months.
- Cannulate the following participants:
 - peanut-sensitized children (see section 3.5), and
 - children with a history of previous anaphylaxis to foods.
- Ensure that a child with a latex allergy or suspected latex allergy avoids all latex products.

6.5.4.2 Step 2: Prepare the Food to be used in the Challenge

The dietician will prepare the challenge foods containing peanut protein and any carrier foods on the day of admission. The foods will be labeled and dated in the ward kitchen.

6.5.4.3 Step 3: Perform the Challenge

6.5.4.3.1 Double-blind, placebo-controlled challenge

Dose assessments and adjustments:

- Prior to the administration of each meal, the child will be evaluated for signs of reaction and vital signs (temperature, pulse, respiratory rate, blood pressure, SaO₂, and PEFR, if the child is reliably able to perform PEFR) will be monitored.

- The challenge should be discontinued at any stage if a reaction occurs (as described in Table 3), and action will be taken according to local hospital guidelines.
- The meals will be blinded by a computer-generated random code known to the dietician but not to the participant, nurse, or doctor. After discussion with an investigator, a blinded dose may be repeated if any of the following occurs:
 - abdominal pain,
 - nausea,
 - chest tightness or pain,
 - abnormal oropharyngeal sensation, or
 - unexplained behavioral change.

Perform a **mixed challenge** as follows:

- Administer six doses each of peanut protein and placebo in randomly alternating, increasing increments of 0.1, 0.25, 0.5, 1.0, 2.0, and 4.0 g in 12 separate meals over the course of 1 day.
- After each dose, observe the child for 20 minutes.
- If the top dose is reached with no allergic reaction, wait 20 minutes and administer an additional 2 g of peanut protein in an unblinded fashion.
- An additional dose pair comprising a repeat of the previous dose and a placebo in random order may be given at the discretion of the investigator.

If an allergic reaction occurs following a placebo dose, perform a **separate challenge** as follows:

Day 1:

- Administer six doses in increasing increments of 0.1, 0.25, 0.5, 1.0, 2.0, and 4.0 g, all of which are either peanut protein or placebo.
- After each dose, observe the child for 20 minutes.

Day 2:

- Administer six doses in increasing increments of 0.1, 0.25, 0.5, 1.0, 2.0, and 4.0 g, all of which are either peanut protein or placebo. If peanut protein was administered on day 1, then administer placebo on day 2, or vice versa.
- After each dose, observe the child for 20 minutes.
- If the top dose is reached with no allergic reaction, wait 20 minutes and administer an additional 2 g of peanut protein in an unblinded fashion.
- A dose may be repeated at the discretion of the investigator.

6.5.4.3.2 Open challenges

Open challenges will be performed at various times in the trial, as shown in Figures 2, 3, and 5. These challenges may be incremental for participants who are at minimal risk for reaction or cumulative for participants who are at more than minimal risk for reaction.

Incremental open challenge (2 or 4 g):

- Administer five doses of peanut protein of 0.1, 0.25, 0.5, 1.0, and 2.0 g in separate meals.
- If the child is ≥ 36 months of age, administer a sixth dose of 4.0 g of peanut protein.

- After each dose, observe the child for 20 minutes. If there is no reaction do a full set of dose assessments (temperature, pulse, respiratory rate, blood pressure, SaO₂ and PEFr—if the child is reliably able to perform PEFr) and proceed to the cumulative open challenge.

Cumulative open challenge (2 or 4 g):

- Administer at least 2 g of peanut protein within a 6-hour period, *or*
- If the child is ≥ 36 months of age, administer at least 4 g of peanut protein within a 6-hour period.
- Observe the child during the challenge and for 1 hour after completion of the cumulative dose.

No particular feeding regimen is required. Peanut meals may vary and be used interchangeably.

6.5.4.4 Step 4: Determine the Outcome

Outcome of the challenge will be determined by evaluating the participant using the criteria in Table 3.

A positive food challenge will be defined by the presence of either of the following:

- One or more major criteria.
- Two or more minor criteria.

An indeterminate food challenge will be defined by the presence of one minor criterion.

A negative food challenge will be defined by the absence of major or minor criteria.

All symptoms should be of new onset and not due to ongoing disease. Symptoms must occur no later than 2 hours after the last dose.

Table 3. Criteria for determining the outcome of food challenge

Major Criteria
Confluent erythematous pruritic rash
Respiratory signs (at least one of the following): wheezing inability to speak stridor dysphonia aphonia
≥ 3 urticarial lesions
≥ 1 site of angioedema
Hypotension for age not associated with vasovagal episode
Evidence of severe abdominal pain (such as abnormal stillness or doubling over) that persists for ≥ 3 minutes
Minor Criteria
Vomiting
Diarrhea
Persistent rubbing of nose or eyes that lasts for ≥ 3 minutes
Persistent rhinorrhea that lasts for ≥ 3 minutes
Persistent scratching that lasts for ≥ 3 minutes

6.5.4.5 Step 5: Consult with the Family

If the result is negative:

- Advise the family that the child may include peanut protein in the diet.
- No emergency plan is required.
- If the challenge was performed at a time other than the study termination visit, advise the family to continue feeding the child according to the protocol for participants in the peanut consumption group.

If the result is positive:

- Advise the family that the child must avoid all peanut and tree-nut protein in the diet.
- Provide a detailed written emergency management plan.
- Provide education on peanut protein and tree-nut avoidance strategies.
- Provide training in Epi-Pen administration.
- Review the child's inhaler technique if appropriate.
- Encourage the parents to join the UK Anaphylaxis Campaign and Medic-Alert.
- Schedule a follow up appointment for the participant in an appropriate allergy clinic.
- If the challenge was performed at a time other than the study termination visit, advise the family of the procedures and visit schedule for participants in the peanut consumption group who have reacted positively to challenge.

6.5.4.6 Step 6: Discharge the Participant

Observe the child until:

- 2 hours have elapsed since the top dose of the challenge.
- All symptoms have resolved (if the result was positive).
- The clinician confirms that the child is ready for discharge.

After the observation period is over, remove the cannula if one was installed.

6.6 PEANUT CONSUMPTION

Maternal peanut protein consumption history. Information on the mother's peanut protein consumption during pregnancy and breastfeeding will be obtained at the baseline visit.

Participant peanut protein consumption monitoring. A peanut frequency questionnaire (PFQ) will be completed to ascertain the peanut protein consumption of the participant. The information provided on the questionnaire will be converted to grams of peanut protein for entry on the case report forms. Additionally, at home visits, the dieticians will observe the feeding of participants assigned to the peanut consumption group.

Household peanut protein consumption monitoring. Peanut protein consumption of all household members will be assessed in order to determine environmental exposure to peanut.

The **4-g supervised peanut protein ingestion** will be performed for participants who:

- Have eaten 3 g of peanut protein within a 7-day period in the last 28 days.
- Have no evidence of allergic sensitization at age 30 months (see section 3.5).

The ingestion of 4 g of peanut protein will be supervised at home by a nurse.

6.7 UNSCHEDULED CLINIC VISITS

An unscheduled clinic visit may be conducted at any time for either of the following:

- Aversion to peanut protein, refusal of peanut protein, or both for those in the peanut consumption group.
- Suspected peanut allergy.

Assessments to be performed at unscheduled visits are described in Figure 5. Independent of the result of these assessments, participants will continue with all subsequent study assessments.

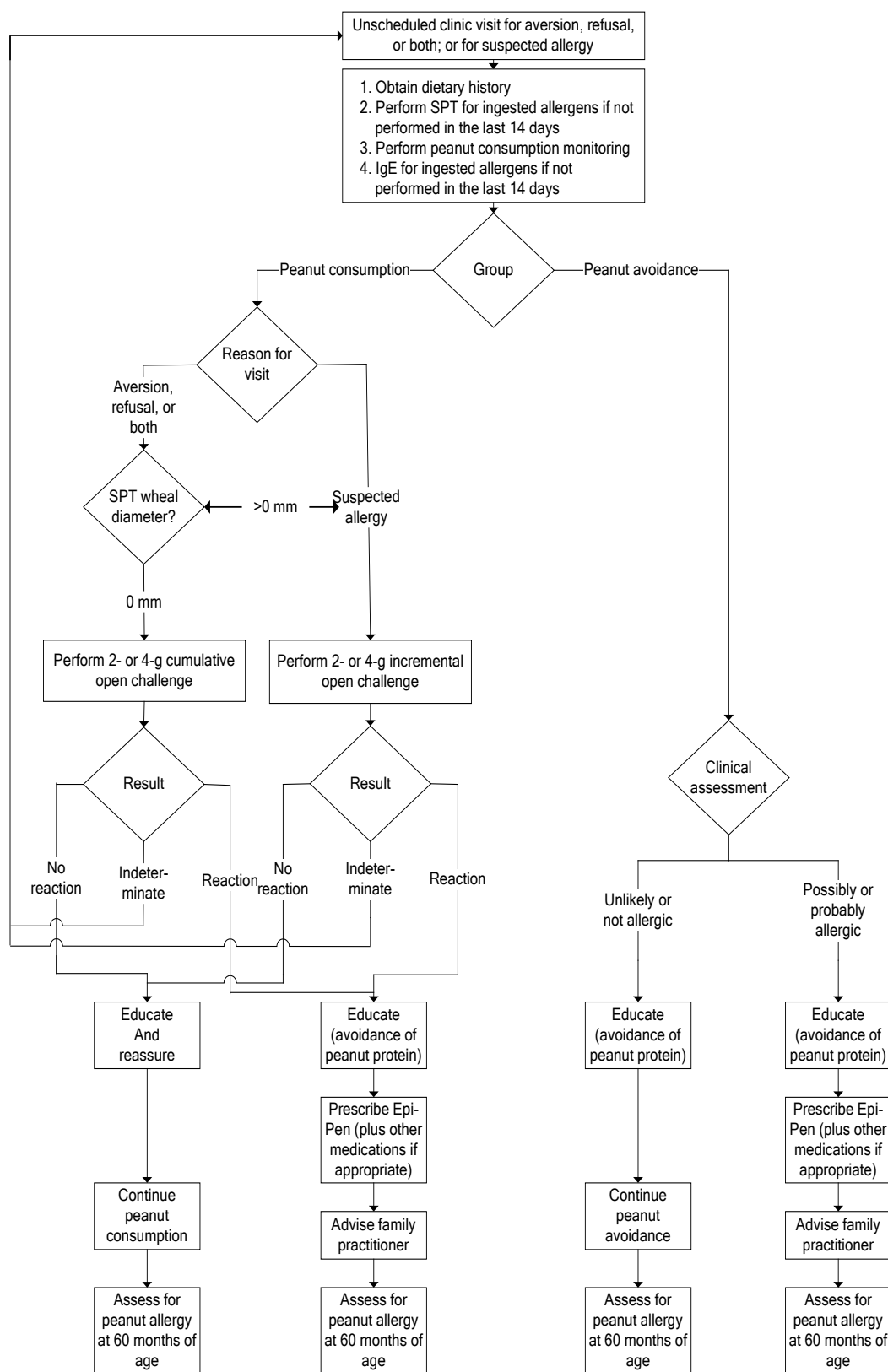


Figure 5. Assessments to be performed at unscheduled clinic visits

7. TOLERANCE ASSAYS

7.1 FROZEN PBMC T-CELL ASSAY

7.1.1 Overview

Cryobanked PBMCs will be used in assays monitoring functional changes in T cells. Samples will be cultured in vitro and stimulated with peanut antigen to see if there is peanut-specific lymphocyte proliferation and to measure cytokines secreted in response to these antigens. Cells from the stimulated cultures will be pelleted and banked in RNeasy[®] for RNA extraction by the ITN core lab and the supernatants frozen for future secreted cytokine profiling.

7.1.2 Gene Expression Profiling

Gene expression profiling will be performed using RNA isolated from non-stimulated versus in vitro stimulated cells. In this case, genes expressed in response to peanut antigen will be compared in participants believed to be tolerant versus those who go on to develop peanut allergy. Genes of interest include IL-4, IL-5, IL-13, and IFN γ to determine if an allergic participant's T-cell responses are more T_H2-like; whereby a tolerant participant's T cells may respond to antigen in a more T_H1-like fashion. Alternatively, genes involved in mediating immune regulation by T regulatory cells may also be differentially expressed. Of particular interest is FoxP3, which will also be analyzed and directly compared to intracellular cytokine staining. Recently IRF-4, IRF-5, and IRF-7 have been shown to be associated with Toll-like receptor signaling and inflammatory responses. These, among other genes, are potential candidates for study.

7.1.3 Secreted Cytokines

Cytokines secreted by in vitro stimulated cells will be monitored with the Luminex platform, a multiplex assay currently allowing for detection of 30 cytokines and chemokines from very small volumes of cell culture supernatant or serum. This analysis will be compared with gene expression and ICS data to determine if cytokines produced by T cells are released and to examine the difference between secreted cytokine profiles of peanut-tolerant and allergic participants.

7.1.4 Antigen-specific Proliferative and Cytokine Responses

Antigen-specific proliferative and cytokine responses will be assessed using in vitro cultures with peanut antigen as described above. Using CFSE dye as a label, we will determine how many cell divisions have occurred in response to peanut antigen in vitro and determine the phenotype of proliferating cells with multicolor flow cytometry. Proliferative responses may be lower in peanut tolerant versus allergic participants if active regulation is occurring for example. Additionally, intracellular cytokine production will be measured with ICS to determine profiles of cytokines secreted by the proliferating and nonproliferating T cells.

7.1.5 Regulatory T cells

Regulatory T cells play an important role in down modulating active or inflammatory immune responses. In this case, early antigen exposure may induce tolerance by activating antigen specific regulatory T cells. Currently, regulatory T cells are isolated using CD4 and CD25 surface markers, specifically gating on CD25⁺ hi cells. CD4⁺CD25⁺ cells are mixed with CD4⁺CD25⁻ cells to evaluate the impact of regulatory T cells on antigen-specific proliferative responses by CD25⁻ cells. Again, if tolerance to peanut allergens is achieved, there may be increased regulatory T-cell activity. This assay

is likely to evolve given the use of FoxP3 and potentially other markers for enumeration and isolation of regulatory T cells.

7.2 PLASMA ALLERGEN-SPECIFIC IGG AND IGE

7.2.1 ELISA-based Techniques

ELISA-based techniques will be used to measure peanut-specific IgG4 and total IgE at baseline and at several time points during the study using cryobanked plasma samples. Previous studies have shown that children who are sensitized but not allergic to peanut have higher IgG4/IgE ratios than those who are allergic to peanut. Interestingly, the fact that both sensitized and allergic children are IgE positive suggests active regulation by T cells, which results in the higher IgG4 levels in the nonallergic, sensitized patients. Higher IgG4/IgE ratios found in sensitized versus allergic patients should correlate with peanut-induced tolerance in this study.

7.2.2 Facilitated Antigen Presentation Inhibition

Facilitated antigen presentation (FAP) inhibition is a flow cytometric-based assay that can detect participants who have allergen-specific IgG antibodies that interfere with FAP. In FAP, IgE facilitates the presentation of antigen to B cells, subsequently causing allergy-related, T-cell activation. Immunotherapy induces IgG, which competes for allergen-bound IgE, thus inhibiting allergen/IgE complexes from binding Fc receptors on antigen presentation cells (in this case, a B-cell line). Peanut consumption will increase peanut-specific IgG, especially IgG4, which interferes with FAP. The time course and magnitude of changes in plasma FAP inhibitory activity will be compared with clinical symptoms, clinical scores, and allergen-specific IgG levels.

7.3 WHOLE BLOOD DNA-HLA GENOTYPES

There are some indications that HLA class II genetic polymorphism may be associated with susceptibility to peanut allergy. DNA will be isolated from peripheral blood of trial participants, subjected to sequence-based class II typing, and genotyped for potential SNPs associated with persons susceptible to allergic responses.

8. ADVERSE EVENTS

8.1 OVERVIEW

Safety data will be recorded on a CRF specifically designed for this purpose. All serious adverse events (SAEs) will be reported on an SAE report form as well as on individual CRFs. All data will be reviewed periodically by the data safety and monitoring board (DSMB). In addition, SAEs will be reported locally. The DSMB has the authority to withdraw any participants and/or terminate the study because of safety findings.

Adverse events that are classified as serious according to the definition of health authorities must be reported promptly and appropriately to the ITN, NIAID, the IND sponsor NIAID, principal investigators in the trial, institutional review boards (IRBs), and health authorities. This section defines the types of adverse events and outlines the procedures for appropriately collecting, grading, recording, and reporting them. 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*, and applies the standards set forth in the National Cancer Institute (NCI), *Common Terminology Criteria for Adverse Events (CTCAE)*, Version 3.0 (December 12, 2003).

8.2 DEFINITIONS

8.2.1 Adverse Event

An adverse event is any occurrence or worsening of an undesirable or unintended sign, symptom, laboratory finding, or disease that occurs during participation in the trial.

An adverse event will be followed until it resolves or until 30 days after a participant terminates from the study, whichever comes first.

8.2.2 Serious Adverse Event

An SAE or reaction is defined as “any adverse event that suggests a significant hazard, contraindication, side effect, or precaution.” This includes but is not limited to any of the following events:

1. Death: A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up after the completion of therapy must be reported whether it is considered treatment related or not.
2. A life-threatening event: A life-threatening event is any adverse therapy experience that, in the view of the investigator, places the participant at immediate risk of death from the reaction as it occurred.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant disability.
5. An event that requires intervention to prevent permanent impairment or damage. An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.
6. Congenital anomaly or birth defect.
7. Other conditions specified in the protocol.

Regardless of the relation of the adverse event to study participation, the event must be reported as a serious adverse event if it meets any of the above definitions.

8.2.3 Unexpected Adverse Event

An adverse event is considered “unexpected” when its nature (specificity) or severity is not consistent with a normal reaction to the study intervention.

8.3 COLLECTING ADVERSE EVENTS

8.3.1 Methods of Collection

Adverse events will be collected from the time the participant provides consent until the time the event resolves or until 30 days after the participant completes study treatment, whichever comes first.

Adverse events may be discovered through any of these methods:

- Observing the participant.

- Questioning the participant in an objective manner.
- Receiving an unsolicited complaint from the participant.

An abnormal value or result from a clinical or laboratory evaluation (e.g., a radiograph, an ultrasound, or an electrocardiogram) can also indicate an adverse event. If this is the case, then the evaluation that produced the value or result should be repeated until that value or result returns to normal or can be explained and the participant's safety is not at risk. If an abnormal value or result is determined by the investigator to be clinically significant, it must be recorded as an adverse event on the appropriate laboratory evaluation form(s).

8.3.2 Collecting Serious Adverse Events

Serious adverse events will be collected from the time the participant provides consent until 30 days after he/she completes study participation or until 30 days after he/she prematurely withdraws from the study.

8.3.3 Recording Adverse Events

Throughout the study, the investigator will record all adverse events on the appropriate adverse event CRF regardless of their severity or relation to study medication or study procedure. The investigator will treat participants experiencing adverse events appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes.

8.3.4 Recording Serious Adverse Events

Serious adverse events will be recorded on the adverse event CRF and on the SAE form, and health authorities will be notified as outlined in section 8.5.2.

8.4 GRADING AND ATTRIBUTION OF ADVERSE EVENTS

8.4.1 Grading Criteria

The study site will grade the severity of adverse events experienced by ITN study participants according to the criteria set forth in the NCI-CTCAE Version 3.0. This document provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events.

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.

All adverse events will be reported and graded whether they are or are not related to disease progression or treatment.

8.4.2 Attribution Definitions

The relation, or attribution, of an adverse event to study participation will be determined by the site investigator. The site investigator will also record the determination of attribution on the appropriate CRF and/or SAE reporting form. The relation of an adverse event to the study treatment will be determined using the descriptors and definitions provided in Table 4. 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>.

Table 4. NCI-CTCAE attribution of adverse events

Code	Descriptor	Definition
Unrelated Category		
1	Unrelated	The adverse event is clearly not related to study participation.
Related Categories		
2	Unlikely	The adverse event is doubtfully related to study participation.
3	Possible	The adverse event may be related to study participation.
4	Probable	The adverse event is likely related to study participation.
5	Definite	The adverse event is clearly related to study participation.

8.5 REPORTING SERIOUS ADVERSE EVENTS

8.5.1 Reporting Timeline

The following process for reporting a serious adverse event ensures compliance with the ICH guidelines. When an investigator identifies a serious adverse event (as defined in section 8.2.2), he or she must notify the Pharmaceutical Product Development, Inc. (PPDI) Safety Reporting Center within 24 hours of discovering the event using the PPDI 24-Hour SAE Reporting Hotline (1-800-201-8725). In addition to being reported by telephone, these events will be entered on the serious adverse event form and the adverse event CRF. Both forms will be faxed to the PPDI Safety Reporting Center within 24 hours. PPDI is responsible for notifying the study sponsor.

8.5.2 Options for Reporting Serious Adverse Events

After the serious adverse event has been assessed by the investigator, there are three options for reporting an event to the appropriate health authorities:

- No requirement to report. This option applies if the adverse event is deemed not serious by the PPDI Safety SAEC/medical liaison, the medical monitor and the NIAID medical officer.
- Standard reporting is required (report in the IND annual report). This option applies if the adverse event is classified as one of the following: (a) serious, expected, and participation related; (b) serious, expected, and not treatment related; or (c) serious, unexpected and not treatment related.
- Expedited reporting is required. This option applies if the adverse event is considered serious, unexpected, and treatment related. These events must be reported by the sponsor to the appropriate health authorities within 15 days; fatal or life-threatening events must be reported within 7 days. For expedited SAEs, all sites must attach the notification letter and MedWatch/CIOMS to the current investigator's brochure.

All investigators must report serious adverse events to their respective IRBs as mandated by them.

8.5.3 Reporting Serious Adverse Events to the Data Safety Monitoring Board

The DSMB will be provided listings of all SAEs on an ongoing basis. Furthermore, the DSMB will be informed of expedited SAEs by the NIAID medical monitor at the same time as health authorities.

9. STATISTICS

9.1 ANALYSIS SAMPLES

The following groups will form samples for analysis.

- Intent-to-treat (ITT): all randomly assigned participants who are evaluable for peanut allergy at age 60 months.
- Safety: all participants who either receive any peanut protein-containing food or are in the peanut avoidance group.
- Per-protocol (PP): participants in compliance with the dietary regimen for their assigned group and evaluable for peanut allergy at age 60 months. Compliance is defined as the consumption of peanut protein in the first 24 months of life:
 - In the peanut consumption group, compliance is consumption of at least 3 g of peanut protein per week for at least 50% of the weeks enrolled and consumption of at least 2 g of peanut protein on at least one occasion in both the first and second years of life.
 - In the peanut avoidance group, compliance is consumption of less than 0.2 g of peanut protein on any one occasion and less than 0.5 g over a single week.

9.2 ANALYSIS OF ENDPOINTS

9.2.1 Analysis of Primary Endpoint

9.2.1.1 SPT Two-minus Stratum

The main analysis will evaluate participants in the ITT sample of the SPT two-minus stratum. In an additional analysis, the same comparison will be made in the PP sample. It will compare the proportion of participants with peanut allergy in the peanut and observation arms at 60 months of age using a two-tailed, chi-square test at the 0.05 level of significance.

9.2.1.2 SPT Three-plus Stratum

Peanut allergy incidence in the safety and PP samples will be evaluated in the SPT three-plus stratum. The difference in peanut allergy incidence rates at 60 months of age will be described using the difference in proportions between the two groups and a two-tailed, 95% confidence interval.

9.2.2 Analysis of Secondary Endpoints

The incidence of adverse events and laboratory abnormalities at 5 years of age will be compared between the peanut consumption and avoidance groups in the safety sample using a two-tailed chi-

square test at the 0.05 level of significance. Additional specific secondary endpoints are described in section 3.3.

9.2.3 Additional Analyses

Additional analyses of the risk associated with peanut allergy in the treatment groups will be performed using multiple logistic regression to identify possible associations of risk with baseline participant characteristics and selected clinical and dietary measures. These analyses will be performed on the incidence of peanut allergy at ages 30 months and 60 months.

9.3 SAMPLE SIZE

For participants in the SPT two-minus stratum, the null hypothesis states that there is no difference in the proportion of individuals with peanut allergy in the peanut consumption group as compared to the peanut avoidance group. We assume the true rate of peanut allergy in the peanut avoidance group is at least 15% and that treatment will reduce that rate to 4.5 % or less in the peanut consumption group. Assuming a 20% dropout rate, enrolling 220 participants in each group will provide 91% power to detect such differences between the groups using a two-tailed, chi-square test.

For participants in the SPT three-plus stratum, current resources allow for 20 participants to be enrolled per group. Allowing for a 20% dropout rate, 16 evaluable participants allow for the half-width of the two-sided 95% confidence interval on the difference in proportions to be a minimum of 0.25 in the range of rates expected for the primary endpoint.

9.4 STRATIFICATION

Participants will be randomly assigned to treatment within each of the two strata using a centrally administered randomization scheme. One stratum comprises participants with skin prick tests for peanut at time of study entry of 0, 1 or 2 mm, whereas the second stratum comprises those with skin prick tests to peanut of 3 or 4 mm. In the first stratum, 440 participants will be randomly assigned, whereas in the second stratum 40 participants will be randomly assigned.

9.5 REPORTING DEVIATIONS FROM THE ORIGINAL STATISTICAL PLAN

The principal features of the study design and the plan for statistical analysis of the data are outlined in this protocol and will be described in more detail in the subsequent statistical analysis plan (SAP). Any changes in these features will require a protocol or an SAP amendment, which will be subject to review by the independent DSMB and the study sponsor. These changes will be described in the final report as appropriate.

10. IDENTIFICATION AND ACCESS TO SOURCE DATA

10.1 IDENTIFYING SOURCE DATA

The investigator is required to keep accurate records to ensure that the conduct of the study is fully documented (see section 11). The results of all clinical and clinical laboratory evaluations will be maintained in the participant's medical records and the data will be transferred to clinical CRFs.

Safety data will be recorded on CRFs specifically designed for this purpose. All the SAEs will be reported on an SAE report form as well as on individual CRFs. All data will be reviewed periodically

by the DSMB and IRB. The DSMB and/or the IRB have the authority to withdraw any participants and/or terminate the study because of safety findings.

10.2 PERMITTING ACCESS TO SOURCE DATA

The investigational site participating in this study will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from the participants in this clinical trial. Medical and research records should be maintained at each site in the strictest confidence. However, as a part of the quality assurance and legal responsibilities of an investigation, the investigational site must permit authorized representatives of the sponsor(s) and health authorities to examine (and when required by applicable law, to copy) clinical records for the purpose of quality assurance reviews, audits, and evaluations of the study safety and progress. Unless required by the laws that permit copying of records, only the coded identity associated with documents or with other participant data may be copied (and all personally identifying information must be obscured). Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that is linked to identified individuals. The investigational site will normally be notified before auditing visits occur.

11. QUALITY CONTROL AND QUALITY ASSURANCE

The investigator is required to keep accurate records to ensure that the conduct of the study is fully documented.

The sponsor is responsible for regularly reviewing the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness, consistency, and accuracy of all documented data.

11.1 DATA HANDLING

The investigator is required to ensure that all CRFs are legibly completed for every participant entered in the trial. To ensure the reliability of the data recorded in the database, double-data entry will be used for all fields on the CRF. The data will be verified by a series of computerized edit checks, and all relevant data queries will be resolved regularly. When the CRFs are complete, they will be reviewed and signed by the investigator and returned to the sponsor or designees. All data from the original signed CRF will be entered in the database, and a comparison program will be run again. All discrepancies will be reviewed, and any resulting queries will be resolved with the investigator and amended in the database. All elements of data entry (i.e., time, date, verbatim text, and the name of the person performing the data entry) will be recorded in an electronic audit trail to allow all data changes in the database to be monitored and maintained in accordance with federal regulations.

12. ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

12.1 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 an appropriate ethics committee or IRB. Any amendments to the protocol or to the consent materials must also be approved before they are implemented.

Ethical approval for the study will also be obtained locally from the relevant Multicentre Research Ethics Committee. All relevant trusts within the National Health System in England will also be informed of the study.

12.2 INFORMED CONSENT AND ASSENT

The informed consent form is a means of providing information about the trial to a prospective participant and allows for an informed decision about participation in the study. All participants (or their legally acceptable representative) must read, sign, and date a consent form before entering the study or undergoing any study-specific procedures. Consent materials for participants who do not speak or read English must be translated into the participants' appropriate language.

The informed consent form must be revised whenever important new safety information is available, whenever the protocol is amended, and/or whenever any new information becomes available that may affect participation in the trial.

A copy of the informed consent will be given to a prospective participant for review and signature. The attending physician, in the presence of a witness, will review the consent and answer questions. The prospective participant 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.

12.3 PRIVACY AND CONFIDENTIALITY

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a sequential identification number, and these numbers rather than names will be used to collect, store, and report participant information.

13. PUBLICATION POLICY

The ITN policy on the publication of study results will apply to this trial. Authorized participants can find details of the policy statement on the ITN website at <http://www.immunetolerance.org>.

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Appendix 1. Schedule of Events

Age in months	4–10	4–10	4–11	12	13–29	30	31–59	60	Unscheduled
Visit	-1	0	0.01–0.36	12	12.01–12.39	30	30.01–30.30	60	99
			Weekly phone dietary consultation ¹		Biweekly phone dietary consultation		Monthly phone dietary consultation		UCV ²
Informed consent	X								
Randomization		X							
Dietary education		X	X	X	X	X	X	X	X
General Assessments									
Physical examination	X	X		X		X		X	X
Medical history	X			X		X		X	X
Adverse events		X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Dietary history		X	X ³	X	X ³	X		X	X
Food reaction history			X	X	X	X	X	X	X
Eczema evaluation	X			X		X		X	
Rhinitis evaluation						X		X	
Asthma evaluation						X		X	
Laboratory Assessments									
Hematology	X							X	
Serum chemistries	X							X	
Fasting serum lipids								X	
Fasting glucose and insulin								X	
Skin and nasal swab culture		X		X		X		X	
Allergy Assessments									
SPT for ingested allergens	X			X		X		X	X
SPT for tree nuts								X	
IgE for ingested allergens	X			X		X		X	X
IgE for inhalant allergens						X		X	
Oral food challenges ⁴								X	X
Peanut challenges ⁵		X						X	X
Peanut Consumption									
Maternal peanut protein consumption history		X							
Participant peanut protein consumption monitoring	X	X	X ³	X	X ³	X	X	X	
Household peanut protein consumption monitoring		X	X ³	X	X ³	X		X	X
4-g supervised peanut protein ingestion							X ⁶		
Immunologic Assessments									
Frozen PBMC T-cell assay	X			X		X		X	
Plasma allergen-specific IgG and total IgE	X			X		X		X	
Whole blood DNA-HLA genotypes	X ⁷			X ⁷				X ⁷	

¹ In addition to telephone dietary consultations, an in-home dietary consultation will occur at 9 months of age for participants enrolled before 6 months of age and at 21 months of age for all participants.

² An unscheduled clinic visit may be conducted at any time for aversion to peanut, refusal of peanut, or both, or for suspected peanut allergy. Section 6.6 specifies which assessments are required for particular participants.

³ To be performed only at the in-home dietary consultation.

⁴ Oral food challenges will be performed as indicated in section 6.4.1.

⁵ Peanut challenges will be performed as indicated in sections 6.5.1 and 6.7.

⁶ Should occur between 48 and 60 months.

⁷ To be performed at one of the listed time points.

Appendix 2. Predictive Values: Food Allergen-Specific IgE Levels and Food Allergen Skin Prick Tests

Predictive value of specific IgE levels ¹⁻³		
Food	≥kU/L	≥PPV
Egg	7	95
Infants ≤24 months ⁴	2	95
Milk	15	95
Infants ≤24 months ⁵	5	95
Peanut ⁶	15	95
Fish	20	95
Tree nuts ^{6,7}	15	95
Predictive value of skin prick tests ^{8,9}		
Food	≥Wheal size (mm)	≥PPV
Milk	8	95
Infants ≤24 months	6	95
Egg	7	95
Infants ≤24 months	5	95
Peanut ^{6,9}	8	95

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Protocol ITN032AD

Induction of Tolerance through Early Introduction of Peanut in High-Risk Children

Short Title: Tolerance to Peanut in High-Risk Children

Version 7.0 (July 18, 2011)

This clinical study is supported and conducted by the Immune Tolerance Network, which is sponsored by the National Institute of Allergy and Infectious Diseases.

Protocol Approval

Protocol ITN032AD	Version: 7.0 (July 18, 2011)
	Protocol Chair: Gideon Lack, MD
Short Title: <i>Tolerance to Peanut in High-Risk Children</i>	
I have read protocol ITN032AD and I approve it. As the principal investigator, I agree to conduct this protocol using good clinical practices, as delineated in <i>ICH Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance</i> (April 1996), and according to the criteria specified in the protocol. _____ Principal Investigator (Print) _____ Principal Investigator (Signature) _____ Date _____	

Synopsis

Title	Induction of Tolerance Through Early Introduction of Peanut in High-Risk Children
Short Title	Tolerance to Peanut in High-Risk Children
Sponsored by	National Institute of Allergy and Infectious Diseases
Conducted by	Immune Tolerance Network
Protocol Chair	Gideon Lack, MD
Participating Site(s)	Evelina Children's Hospital, Guys and St. Thomas' NHS Foundation Trust, King's College, London, UK
Accrual Objective	640 participants
Study Design	This is a randomized controlled trial in which children at high risk for peanut allergy, as demonstrated by eczema, egg allergy, or both, are enrolled. Participants are stratified based on skin prick test (SPT) results for peanut into those with a wheal diameter of 0 mm (SPT-negative stratum), and those with a wheal diameter of 1, 2, 3, or 4 mm (SPT-positive). Participants in each stratum are randomly assigned to receive a peanut-containing snack or to avoid peanut. The group assigned to receive a peanut-containing snack will eat at least 2 g of peanut protein three times per week until 60 months of age. The prevalence of peanut allergy at that time is compared between the peanut consumption and the avoidance groups.
Study Duration	84 months
Primary Endpoint	The proportion of participants with peanut allergy at 60 months of age.
Secondary Endpoints	At 30 and 60 months of age: the proportion of participants with allergic sensitization to selected ingested and inhaled allergens, and with seasonal rhinoconjunctivitis, perennial rhinoconjunctivitis, and asthma. At 60 months of age: the proportion of participants with type-1 immediate onset food allergy to selected ingested allergens. Incidence of adverse events and laboratory abnormalities; nutritional evaluations. Results of cellular and humoral assessments of immune response related to the development of allergy or tolerance to specific allergens.

Inclusion Criteria	1. Children ≥ 4 to < 11 months old who have had solids successfully introduced into their diet. 2. Egg allergy, severe eczema, or both. 3. Informed consent obtained from parent or guardian.
Exclusion Criteria	1. Clinically significant chronic illness, except for eczema or recurrent wheeze. 2. Positive skin prick test for peanut allergen with a wheal diameter > 4 mm in the presence of a negative saline control. 3. Previous or current consumption of peanut protein that exceeds 0.2 g of peanut protein on at least one occasion or 0.5 g over a single week 4. Investigator-suspected allergy to peanut protein. 5. Investigator-suspected allergy to peanut protein in care provider or current household member. 6. Diagnosis of persistent asthma. 7. ALT (SGPT) or bilirubin > 2 times the upper limit of age-related normal value. 8. BUN or creatinine > 1.25 times the upper limit of age-related normal value. 9. Platelet count $< 100,000/\text{mL}$, hemoglobin $< 9 \text{ g/dL}$, or investigator-suspected immunocompromise. 10. Unwillingness or inability to comply with study requirements and procedures.
Study Intervention	Participants assigned to the peanut consumption group will be fed at least 2 g of peanut protein 3 times per week. The preferred peanut source will be Bamba, although peanut butter may be substituted. Participants assigned to the peanut avoidance group will avoid exposure to peanut protein during study participation.

Glossary of Abbreviations

BMI	body mass index
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 food challenge
DSMB	data safety monitoring board
FAP	facilitated antigen presentation
GCP	good clinical practice
ICH	International Conference on Harmonization
IND	investigational new drug
IRB	institutional review board
ITN	Immune Tolerance Network
KLH	keyhole limpet hemocyanin
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Diseases
PEFR	peak expiratory flow rate
Rho Fed	Rho Federal Systems Division, Inc. (Clinical Research Organization)
SAE	serious adverse event
SAP	statistical analysis plan
SPT	skin prick test
UCSF	University of California, San Francisco
UK	United Kingdom

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1. BACKGROUND

1.1 SUMMARY AND RATIONALE FOR TRIAL

Peanut allergy is an increasingly prevalent cause of serious allergic reactions and is a recognized public health concern. Dietary avoidance of peanut in early life has been recommended in many countries. In the United Kingdom (UK), for example, infants identified as at risk are advised to avoid peanut for the first 3 years of life.(1) However, there is evidence that the prevalence of peanut allergy is decreased in countries where children are fed peanut beginning at an early age.(2) This raises the possibility that avoidance guidelines may promote the development of peanut allergy by preventing the induction of oral tolerance in infants exposed to high levels of environmental peanut. This trial proposes to compare the two approaches in a population of high-risk children. In addition, it will allow the mechanisms that underpin antigen-specific oral tolerance induction to be addressed.

1.2 CLINICAL ASPECTS OF PEANUT ALLERGY

1.2.1 Increased Prevalence of Peanut Allergy

Peanut allergy has become increasingly prevalent: recent studies demonstrate that the prevalence of peanut allergy has doubled in 10 years and approximates 1.3%–1.5%.(3) Peanuts are a frequent cause of anaphylaxis for which there is no established treatment except allergen avoidance. Children with peanut allergy additionally have to avoid tree nuts since up to 50% have allergies to individual tree nuts.

Studies eliminating food allergens during pregnancy, lactation, and infancy have consistently failed to reduce IgE-mediated food allergy in children. Two explanations for this failure with respect to peanut allergy include:

1. Sensitization to food allergens does not occur through oral exposure but may occur via other routes. For example, the use of topical preparations containing peanut oil on infants with eczema during the first 6 months of life is associated with a high risk of developing peanut allergy.(4) A recent study showed that after subjects had eaten peanut and then washed their hands and cleaned the tabletops, peanut protein was detectable in significant amounts (ten to several hundred micrograms) on hands and on the tabletop surfaces. (5)
2. Early oral exposure may be required to prevent the development of allergy. Oral tolerance induction is well recognized in murine models and has been documented in the clinical literature. (6-7)

1.2.2 Examples of oral tolerance

One study of oral tolerance induction in adults showed that oral intake of keyhole limpet hemocyanin (KLH) results in immunological tolerance to KLH antigen.(6) The only study that attempted to induce tolerance to a food allergen(8) was conducted in subjects who already had established milk allergy. The result of this study was promising: 71% of highly allergic children were able to tolerate a daily intake of 200 mL of milk after treatment. However, because this was an uncontrolled study, the possibility that these children would have shown spontaneous resolutions cannot be discounted.

There is some evidence that oral exposure to nickel results in tolerance. Numerous studies, both prospective and retrospective, show that early cutaneous exposure to jewelry, particularly through ear piercing, is a risk factor for the development of contact dermatitis. In contrast, three independent studies,(9-11) including one prospective birth cohort study, show that the early application of orthodontic braces made of nickel strongly protects against the development of contact dermatitis to nickel (in one study there was an odds ratio of 0.07). Indeed, after the insertion of fixed orthodontic appliances, the level of nickel both in the saliva and serum of individuals increases significantly, which is thought to result in oral tolerance. Similarly, subjects exposed to pancreatic extract by

inhalation or contact develop IgE-mediated allergic reactions, whereas subjects exposed to this extract by oral route do not.(12)

1.2.3 Epidemiology of Peanut Allergy

Clinical observations from countries in Southeast Asia and Africa, where high amounts of peanuts are consumed in different snack forms during infancy, suggest a low rate of peanut allergy. As these differences could be due to genetics, we have examined these geographical variations more carefully by comparing the prevalence of peanut allergy in Jewish children in the UK and Israel. The relative risk of peanut allergy is 15-fold higher in the UK than in Israel.

There are two components to our ongoing study comparing allergies in Jewish children in the UK and Israel. We initially determined the allergy prevalence data for 4- to 18-year-old Jewish schoolchildren in the UK (n=4031) and in Israel (n=4677). In the second part of the study, we determined the peanut consumption data for 8- to 14-month-old Jewish infants in Israel and the UK.

Data on peanut consumption were prospectively obtained for 218 Jewish infants 8–14 months old (115 infants in the UK, 103 in Israel). Preliminary data suggest that most Israeli infants (81%) had eaten peanut by 1 year of age (median age 10 months), with a median peanut protein consumption of 6.0 g of peanut protein per week (an interquartile range of 0–18 g per week). In contrast, the majority of UK infants (78%) had not been exposed to peanut protein by 1 year of age and significantly lower peanut consumption patterns were recorded, a median of 0 g per week. Thus, there is a statistically significant difference between peanut protein consumption by infants in Israel and infants in the UK, with a P value of .0013 for the two-sample Wilcoxon rank-sum test.

We do not have data comparing the prevalence of allergies in Israeli children who have not eaten peanut protein—specifically, the Israeli peanut-containing snack Bamba,—because, such children are very difficult to identify after the age of 2.

Children from 11 Israeli schools and 13 Jewish UK schools participated in this study. The proportion of children of Ashkenazi (Central and Eastern European) and Sephardic (Mediterranean and North African) origin is equivalent in both countries. The return rate in Israeli schools was 83.2% (74%–89%) and 79% (70%–92%) in the UK. In total, 8% of total responders were “late responders” whose questionnaires were completed by postal reminders or telephone interviews. There are no significant demographic differences between early and late responders. An independent and random data entry audit revealed an error rate of <0.1%.

Numerous questions relating to food allergy and atopic disease remain. In this trial, we are primarily interested in a binary measure of peanut allergy, but we also look at an ordinal measure of the increasing likelihood of clinical allergy. Previously, for peanut allergy (as a binary variable), we only used the most stringent definition. Children had to react with at least one typical symptom within 2 hours of eating peanut and were required to avoid foods containing peanut in their diet. Using this definition the prevalence of peanut allergy is 0.11% in Israel and 1.54% in the UK ($P < 0.001$). This tighter definition appears to be extremely accurate. Twenty-six children fulfilling these criteria have been clinically evaluated, and 23 children (88.4%) were found to be peanut allergic. Peanut allergy is always more common in the UK than in Israel, irrespective of the criteria we use, and this difference occurs both in children with and without eczema.

The unadjusted prevalence of peanut allergy is 15 times more common in the UK than in Israel. There is less variation in other atopic diseases, such as eczema, asthma, and allergies to cow’s milk, between the UK and Israel. We explore whether the difference in peanut allergy can be explained by the modifying effects of the underlying propensity for atopic disease in the two countries. More formally, we can calculate the relative risk of peanut allergy in the UK as compared with that in Israel after adjusting for a number of factors (see Table 1).

Table 1. Relative risk of peanut allergy in the UK compared with that in Israel

Adjustment	Relative Risk ¹	95% Confidence Interval	P
Unadjusted	14.6	5.8–34.3	<.001
Logistic regression, adjusted for age, sex, eczema, asthma, hay fever, egg allergy, milk allergy	7.3	2.8–18.8	<.001
Stratified analysis, matched on age, sex, eczema, asthma, hay fever and milk or egg allergy (Mantel-Haenszel estimate)	11.2	3.5–36.1	<.001

¹The terms *relative risk* and *odds ratio* are used interchangeably, as the prevalence of peanut allergy in Israel is extremely low.

In conclusion, the questionnaire-based study shows that peanut allergy is many-fold more common among Jewish children in the UK than among Jewish children in Israel. The different prevalence can only partly be explained by a difference in atopic diseases or other food allergies. Even after taking account of these factors, we find that peanut allergy is many times more common in the UK. The result is unlikely to be due to cultural differences in the way the questionnaires were completed. The difference in prevalence remains even when one uses a variety of definitions for peanut allergy, and is seen in both low-risk children (e.g., children without any atopic disease) and high-risk children (e.g., children with eczema or egg allergy).

These data are also consistent with the notion that high-dose, first-time peanut exposure may lead to oral tolerance. Indeed, if a single oral exposure to peanut were to have no effect on promoting or preventing peanut allergy, then one might expect to see numerous children react on subsequent exposures. This is not the case.

1.2.4 Egg, Milk, and Tree-Nut Allergies in Israel and the UK

Egg and milk are useful control allergens to compare to peanut. Although more common in the UK (combined prevalence of 3.8%), egg and milk allergies are nevertheless common in Israel, with a combined prevalence of 1.6%. The unadjusted odds ratio comparing egg and milk allergies between the UK and Israel is 2.5, but after adjusting for hay fever, asthma, and eczema, the odds ratio decreases to 1.6. In contrast, the adjusted odds ratio for peanut allergy remains extremely high, a result due to a country effect rather than to differences in atopy. Importantly, the difference between tree-nut allergies in both countries mirrors the difference seen for peanut. Thus, in the UK, the prevalence of tree-nut allergies is 1.76%, and in Israel, it is 0%.

In our study, as in other studies, 50% of children with peanut allergy had tree-nut allergies and vice versa on questionnaire. This is not surprising since the major peanut allergens Arah1, Arah2, and Arah3 belong respectively to the family of viscillins, conglutinins (2S albumen), and glycinins, highly conserved protein families found in nuts and seeds. Furthermore, there is evidence of extensive cross reactivity between peanut and tree-nut allergens and B-cell epitopes in IgE binding studies. de Leon and colleagues(13) report that preincubation of sera from peanut-allergic individuals with almond, Brazil nut, or hazelnut resulted in a marked decrease in IgE binding to peanut extract, indicating cross reactivity.

There is also the possibility that similar T-cell epitopes exist for peanut and tree-nut proteins. By doing a protein sequence BLAST search, we have found high levels of sequence homology between the three major peanut allergens and the major allergens in tree nuts. Overall protein homology and amino acid positivity exist in the 30%–50% range. These similarities are heightened when we search for limited domain homology over peptide lengths of 20–25 amino acids (multiple alignment using

Clustal W software). Thus, we can identify domain homologies with amino acid identity of 70%–80% and amino acid positivity of 80%–95%. These areas of homology/positivity among the major peanut allergens could potentially explain cross sensitization in the UK population. Similarly, they could account for a cross-tolerizing effect between peanuts and tree nuts in the Israeli population, perhaps because of high dose exposure to peanut protein. This could explain the absence of both peanut and tree-nut allergies in Israel despite the relatively high prevalence of egg and milk allergies.

1.2.5 Analysis of Protein in Bamba

One possible explanation for the differences in the rate of peanut allergy in the UK and Israel is that children in the two countries are exposed to peanut that is processed differently. For example, in China, where people consume boiled peanuts, there is a low prevalence of peanut allergy, and in the U.S., where people consume roasted peanuts, there is a high prevalence of peanut allergy. However, this is unlikely to be the case in Israel given that Bamba is made from roasted peanut sourced from different countries.

To verify this, Dr. Soheila Maleki, of the U.S. Department of Agriculture, determined and compared the peanut protein content and the amount of each major peanut allergen in Bamba, in a roasted peanut control, and in two different commercial peanut butter preparations available in the UK. She found that 85% of the protein in Bamba derives from peanut (the remainder derives from maize) and that the amount of each major peanut allergen (Arah1, Arah2, and Arah3) in the peanut protein is comparable to the amount of each major allergen in the two peanut butters. Similarly, IgE binding (pooled sera from peanut allergen) was very similar between different samples of Bamba and the two peanut butters (Figure 1). Thus, Bamba contains large amounts of peanut protein as well as all three major peanut allergens in significant quantities, and, as measured by IgE binding, peanut protein is highly allergenic (or just as allergenic as the peanut butter used in the UK). These findings were unpublished data at the time of study design; they have since been published.(2)

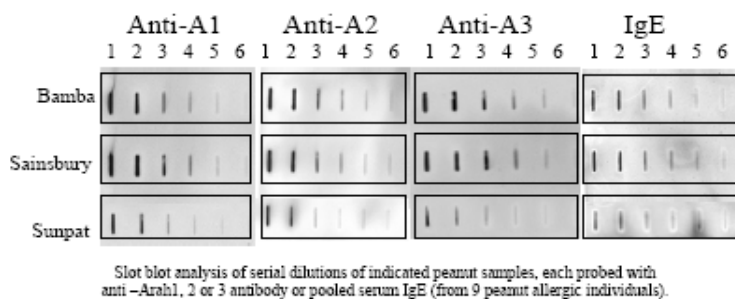


Figure 1. IgE binding of Bamba and two variations of peanut butter

1.3 PRECLINICAL ASPECTS OF PEANUT ALLERGY

Certain murine studies have shown that allergic sensitization to antigen can occur on cutaneous exposure. Saloga and colleagues showed that when microgram quantities of ovalbumin were applied to the abraded skin of mice, the mice had significant anti-OVA IgE responses and positive intradermal tests.(14) More recently, Strid and colleagues have shown that when arachis oil is applied to the abraded skin of mice, the mice have significant IgE and T-cell responses to peanut,(15) even if the oil has fewer than 6 µg/mL of peanut protein.

Animal models demonstrate that a high early dose of oral protein antigen is highly effective in inducing tolerance to the respective antigen, even in the case of subsequent administrations of antigen in the presence of potent immune-adjuvants. Over the last 35 years, 33 publications on oral tolerance induction in animal models have documented that a single oral dose of antigen is sufficient to induce tolerance. This phenomenon has been demonstrated for different antigens in different experimental models, but the resulting data are consistent: they uniformly show that a single dose of oral protein

administration effectively causes immunological tolerance and prevents the expression of related clinical disease.

Oral tolerance induction in animal models is most potent in its effects on delayed type I hypersensitivity responses; prevention of antibody responses through induction of oral tolerance is less consistent. However, numerous publications point to the fact that in mice a single dose of food allergen (beta-lactoglobulin, ovalbumin, peanut) is particularly effective in preventing the development of subsequent IgE-mediated responses. A recent study(16) showed that naïve mice orally tolerized to beta-lactoglobulin were unable to mount significant IgE responses when they were subsequently sensitized with beta-lactoglobulin injected along with alum intraperitoneally. Similarly, there were no significant T-cell responses to beta-lactoglobulin in the pretolerized animals.

In another study in 2004, Strid and colleagues (17) fed mice a single intragastric feed of defatted peanut flour at doses varying from 0.2 to 100 mg per mouse. Seven days after the feed, the mice were immunized with 100 µg of peanut antigen emulsified with Freund complete adjuvant. Three weeks later, the mice were given a recall immunization with 100 µg of antigen. The mice were assayed for T-cell proliferation to peanut, cytokine production, delayed-type hypersensitivity responses, and antibody responses. Tolerizing doses of 100 mg of peanut protein resulted in significant reduction of delayed-type hypersensitivity responses and inhibition of proliferative responses to peanut. Mice tolerized to 100 mg of peanut protein showed significantly reduced interferon gamma and IL-4 production. Specific IgE responses to peanut following sensitization were almost completely prevented by the single tolerizing dose. However, very low tolerizing doses of peanut, i.e., those below 2 mg per animal, resulted in enhanced delayed-type hypersensitivity responses, T-cell proliferative responses, cytokine production, and IgE production. Doses between 2 and 20 mg of peanut protein induced no difference between the T- and B-cell responses as compared to sham-tolerized animals. Tolerance to peanut was only achieved at doses of 100 mg per animal. Oral tolerance to peanut was shown to be antigen specific. Tolerizing doses of peanut did not promote tolerance to ovalbumin and vice versa.

1.4 RATIONALE FOR TRIAL DESIGN

1.4.1 Population and Stratification

This trial will enroll infants who are at high risk of developing peanut allergy, which is defined by having egg allergy, eczema, or both. The risk of developing peanut allergy is mainly determined by the presence of severe eczema. In determining the degree of eczema severity as a criterion for enrollment, two factors have been shown to be of predictive value for peanut allergy: (1) the required use of topical steroidal creams on children 6 months of age or younger (D. Hill, personal communication) and (2) parental responses to questionnaires describing the nature of the skin condition (G. Lack, unpublished data).

In addition, participants will be stratified into risk groups based on skin-test reactivity to assess the effect of peanut consumption in those with moderate skin-test reactivity and those with minimal skin-test reactivity.

The first version of this protocol (version 1.0) specified for the purpose of this risk group stratification that moderate skin-test reactivity would be defined by a skin-prick wheal size of 3 or 4 mm and minimal skin-test reactivity by a skin-prick wheal size of 0, 1, or 2 mm. New information made available in the first few weeks after protocol opening (D. Hill, personal communication), however, pointed out that even children with wheal sizes of 1 or 2 mm have a risk of peanut allergy much higher than average. Version 2.0 therefore specified that moderate skin-test reactivity would be defined by a skin-prick wheal size of 1, 2, 3, or 4 mm and minimal skin-test reactivity by a skin-prick wheal size of 0 mm.

1.4.2 Open-label Design

In an ideal world, we would address the study hypothesis using a randomized, placebo-controlled, double-blind design. The inclusion of a placebo has been considered in great detail. The main reason for not including a placebo snack is the impossibility of guaranteeing that it would be free from peanut since it would be manufactured in the same factories as the peanut snack. Furthermore, the cost of producing a placebo snack would be substantial, and there would be no guarantee of its nutritional equivalence to the peanut-containing snack. Finally, the children eating the placebo snack that tastes of peanut may develop a taste for peanut and may want to eat other foods that contain peanut, which would make adherence to the study advice impossible.

The obvious disadvantage of not including a placebo snack is that children will know which study arm they are assigned to. This disadvantage is offset by the fact that peanut allergy will be diagnosed on the basis of three objective measures: double blind, placebo-controlled food challenge (DBPCFC); specific IgE; and skin-prick testing to peanut. On peanut challenge, neither the physician, the nurse, nor the participant will know the participant's dose (peanut or placebo), so it will be impossible for the outcome of the challenge to be influenced by that knowledge. Skin-prick testing and specific IgE are highly objective measures, and the person reporting the specific IgE level will not know the status of the participant.

1.4.3 Administration of Baseline Peanut Challenge

More than 90% of the peanut-allergic children seen in our clinics react on first known exposure to peanut. It is extremely unlikely for a child to react on the second or third exposure, having tolerated peanut the first time. In the rare instances where a reaction occurs on subsequent exposure, it usually occurs because, on the first occasion, the child was only exposed to very small amounts of peanut at home and only tolerated a small amount. We believe that these participants are already allergic on first or second exposure but have not reached a threshold dose for clinical reaction; their aversion to peanut has prevented them from eating a sufficient dose. In the current trial, children with preexisting allergy will be screened from further administration of peanut by giving those who are initially randomized to the peanut consumption group a baseline peanut challenge.

1.4.4 Determination of Peanut Allergy

The main goal of this trial is to determine the proportion of participants with peanut allergy. It is important that as many participants as possible are evaluable for this assessment. Food challenge will be the main method of assessment, as it is recognized as the gold standard for diagnosis of peanut allergy. However, given the importance of this assessment, for those in whom food challenge is not possible, additional information will be considered, including dietary history, skin prick testing, and allergen-specific IgE levels. The algorithm for determination is presented in Figure 3 and Figure 4.

We will first determine if, at 60 months of age, the participant meets the criteria for a 5-g cumulative open challenge. These criteria are intended to identify participants who are less likely to be allergic. Such participants who have a negative open challenge will be considered tolerant, since the gold standard for tolerance is the open challenge. Children with a positive open challenge will be invited to undergo a double blind challenge, which is the gold standard for determination of allergy. Because we insist on no symptoms for a participant to be considered tolerant, indeterminate results may occur. In addition, positive symptoms during an open challenge may be difficult to interpret. Therefore, all such participants will be invited to DBPCFC.

Participants who do not meet the criteria for an open challenge will undergo the DBPCFC. A participant who also reacts positively to the DBPCFC will be considered allergic. A participant who passes the DBPCFC will be considered tolerant, bearing in mind the last step of the DBPCFC is an unblinded administration of peanut protein.

It is anticipated that as many participants as possible active in the study at 60 months of age will have an outcome determined by food challenge. However, in order to maximize the number of individuals

who can be accurately evaluated for the primary endpoint, for the remaining participants, we will diagnose peanut allergy or tolerance if the outcome can be determined with a high degree of accuracy.

Participants who are not available for either open challenge or DBPCFC, or participants who have indeterminate results, will be evaluated using dietary history, SPT, and peanut-specific IgE. For such participants, these evaluations determine allergic status with greater than 95% accuracy.

The general approach is that a strongly suggestive history can be combined with highly predictive ($\geq 95\%$) SPT and/or IgE results to give a determination of tolerance or allergy. Even an excellent history on its own is only 70%–80% accurate in establishing a diagnosis of allergy or tolerance. There are cutoff values, however, for both SPT and IgE above and below which one can respectively establish a diagnosis of allergy or tolerance with $\geq 95\%$ predictive value. Because it is unknown if the cutoff value varies with the ingestion of Bamba, these cutoff values will be used together with history. As a general rule, if there is a contradiction in our data set between history and the SPT/IgE results, or even between the SPT and IgE results, the participant will be considered nonevaluable in the absence of a challenge. The algorithm to do so is outlined in Figure 4.

A dietary and reaction history can be categorized in three ways with respect to the degree to which it supports tolerance or allergy.

1. For a participant with a history consistent with peanut tolerance, see the left-hand side of Figure 4. A history consistent with tolerance is one in which the participant has had more than trace exposure to peanut without difficulty, but where there is no good documentation of significant dietary exposure. Here, negative IgE or SPT is required because this history is not robust.
2. For a participant with a history strongly suggestive of peanut allergy, see the upper right-hand quadrant of Figure 4. A strongly suggestive history is one in which there is good documentation that a participant has had symptoms related to peanut exposure. A high IgE or SPT is nevertheless required to establish a diagnosis of allergy.
3. For a participant with indeterminate history consistent with allergy, see the lower right-hand quadrant of Figure 4. An indeterminate history consistent with allergy is one in which the participant has not had more than trace exposure to peanut and where there is no good documentation of symptoms related to dietary exposure. Here, a very high level of IgE or SPT is required to determine allergy and a very low level of IgE or SPT is required to establish tolerance.

Participants for whom allergic or tolerant status cannot be determined with at least 95% certainty will be considered nonevaluable. Such participants include those in whom data are not strong enough on either the allergic or the tolerant side to make a clear determination. They also include those for whom there is a contradiction among the history, the skin test result, and the IgE measurement. For example, this would occur when the dietary and reaction history suggests tolerance but the SPT or IgE results suggest an allergic response.

1.4.5 Eczema Severity

In this clinical trial, we will enroll children with a high risk of developing peanut allergy based on their eczema severity. We will use three different criteria for assessing eczema severity. The first criterion will be the parents or guardians' description of their child's eczema severity. The second criterion will be the use of topical creams and ointments containing corticosteroids or calcineurin inhibitors. The third criterion will be a modified SCORAD (Scoring Atopic Dermatitis System) evaluation.

Eczema (atopic dermatitis) is an itchy, inflammatory skin condition with a predilection for the skin flexures. It is characterized by poorly defined erythema with edema, vesicles, and weeping in the acute stage and skin thickening (lichenification) in the chronic stage.

Assessing disease severity is problematic when there is no objective marker. The many severity scales used in clinical trials have generally not been studied for association with peanut allergy.

Lack et al. found that rash over joints and skin creases as well as oozing, crusted rash had a significant association with peanut allergy. (4) They also found a trend toward an association between the severity of rash in the first 6 months of life and the prevalence of peanut allergy. (4)

Recently, in the same cohort they noticed a risk of peanut allergy of approximately 20% among children whose parents described their rash as “very bad” (G. Lack, unpublished data). Hill found that peanut allergy is associated with eczema severity when severity was defined as days of topical steroid use each month (D. Hill, personal communication).

The use of modified SCORAD objective criteria will permit the inclusion of children who may not have had access to topical anti-inflammatory medications or whose parents cannot recall or report the severity of their child’s eczema. Epidemiological studies using the SCORAD in European countries in older children show mean overall SCORAD scores of 21/103 and 20/103, respectively. (18-19) The European task Force of Atopic Dermatitis, using only the objective components of SCORAD, classified scores of <15, 15–40, and >40 as mild, moderate, or severe eczema, respectively, out of a possible total score of 83. (20)

1.5 RATIONALE FOR IMMUNOLOGICAL ASSESSMENTS

This clinical trial of oral tolerance induction in children will be accompanied by a comprehensive series of studies that will permit us to identify the following:

- Biomarkers that predict susceptibility to oral tolerance induction.
- Molecular mechanisms associated with the development of oral tolerance induction to peanut allergen.
- Indicators of an active (immunomodulatory) response to oral tolerance induction during the course of therapy.
- Biomarkers of underlying allergen tolerance.

Our strategy for identifying these biomarkers, molecular mechanisms, and indicators will involve retrospective comparisons between individual allergen immune-response profiles of peanut-tolerant vs. peanut-allergic individuals. Qualitative, quantitative, and time-dependent changes in allergen immune-response profiles of participants who do or do not develop tolerance to peanut will provide data for testing current hypotheses and generating new hypotheses to explain underlying tolerogenesis mechanisms. To identify the biomarkers associated with underlying tolerance mechanisms in operation at the time of sampling, we will perform a cross-sectional analysis of the immune-response profiles at screening and at 12, 30, and 60 months of age. Integration of biological data with clinical outcomes will provide a means to identify potential biomarkers of oral induced tolerance to peanut. Mechanistic studies will focus on T cell responses (CD4, T_{REG}) and B-cell responses (IgE epitopes, peanut specific IgE and IgG4, FAP assay). Specimens may also be used in future immune response or biomarker assays to reevaluate biological response as research tests are developed.

1.6 KNOWN AND POTENTIAL RISKS

1.6.1 Peanut Consumption Group

Potential risks associated with the consumption of a peanut-containing snack are worsening of eczema, weight gain, nutritional compromise, metabolic abnormalities, and an increased risk of allergy to peanut or other allergens.

Four different studies show that the median age of reacting to peanuts is between 14 and 24 months of age. The vast majority of patients react upon first known exposure to peanut. (4, 21-22) This argues strongly against the possibility that peanut allergy is caused by eating peanuts and provides some reassurance that we will not induce peanut allergy by feeding participants peanuts.

1.6.2 Peanut Avoidance Group

Avoidance of peanut may result in an increased risk of allergy to peanut or other allergens.

1.6.3 Both Groups

Undergoing laboratory assessments may involve a low risk of hemorrhage, hematoma, and infection at the venipuncture site. Risks associated with the planned peanut challenges include nausea, vomiting, itching, urticaria, angioedema, asthma, other respiratory symptoms, and anaphylaxis, which can be life threatening.

Protocol versions 1 through 6 specified that children with suspected peanut allergy and children with a history of anaphylaxis to foods should be cannulated, that is, have intravenous access established, prior to peanut challenge. Beginning with version 7.0 in 2011 when additional information and experience became available, this specification was modified to include only children with both suspected peanut allergy as defined and other specific risk factors for a severe reaction described in the protocol. Version 7.0 also supplied a definition of suspected peanut allergy. The reasons for this narrower specification for establishment of venous access are described below.

Published studies

Recent publications have examined the outcomes of oral food challenges and treatment approaches for positive reactions. In a review of 253 positive food challenges including 71 to peanut, the Johns Hopkins group reported that no deaths or hospitalizations occurred. They reported that all reactions resolved without treatment or could be treated with oral or intramuscular antihistamines, oral steroids, intramuscular epinephrine or nebulized albuterol (23). Intravenous medications or fluids were not required.

In another review of 436 positive food challenges, including 38 to peanut, the Mt. Sinai group focused on the use of epinephrine, reporting that 50 of the positive challenges required intramuscular epinephrine. Only 3 of those required a second epinephrine dose. These were reactions to wheat, milk and pistachio. Intravenous fluids were given for severe emesis in 14 (3.2%) of positive challenges. In this study steroids, if required, were administered intravenously. Fifty (11%) reactions were treated with steroids (24).

A report from Australia examined predictors for severe reactions in 55 peanut challenges. In 27 positive challenges, 6 did not result in anaphylaxis and resolved without treatment; 21 resulted in anaphylaxis and resolved with oral antihistamine, oral steroids, inhaled salbutamol or intramuscular epinephrine. Higher IgE and larger skin prick test wheal sizes were predictive of more severe reactions (25). The high frequency of anaphylaxis as a positive challenge outcome reflected the fact that in this study challenges were not stopped for mild non-anaphylactic reactions; instead additional peanut was given up to 11.7 grams or until a moderate to severe reaction occurred. In the current study, however, if an interpretable reaction as defined in section 6.5.4.4 occurs the challenge will be stopped.

Published studies thus indicate that positive food challenges including those to peanut can be effectively treated. Antihistamines are the mainstays of management for mild and moderate reactions that do not result in anaphylaxis. Epinephrine is the treatment of choice for anaphylaxis, with a recommended dosage 0.01 mg/kg given intramuscularly (26). High-flow oxygen and inhaled beta-agonists are also important for management of respiratory symptoms. Because onset of action is slow, steroids are not useful for acute management and can be given orally or intravenously (27). Positive reactions very rarely require intravenous access for medication or fluid administration.

Guy's and St. Thomas' experience

Considerable experience in our research unit and in our clinical practice acquired over the last several years supports the idea that intravenous access is not required to safely perform food challenges. In the current trial, open challenges with two grams of peanut were performed at visit 0 on 320 children

assigned to peanut consumption. All participants safely completed this baseline peanut challenge regardless of their SPT result. Participants who reacted were all successfully managed with oral antihistamines. Neither intramuscular epinephrine nor intravenous access for fluid was required.

In a related clinical trial exploring early food introduction termed the EAT Study, performed in the same Clinical Trials Unit at Guy's and St. Thomas' as this trial and using identical treatment procedures, 81 food challenges in 3-4 month old sensitised infants were performed of which 35 were positive (2 to peanut). Reactions were all successfully managed with oral medications. Neither intramuscular epinephrine nor intravenous access for fluid was required.

In our clinical NHS practice at Guy's and St. Thomas' Hospital we have over the past 4 years performed 1924 food challenges of which 174 were positive (54 were to peanut). Intramuscular epinephrine was required on 2 occasions (peanut = 1, milk=1). Again neither intramuscular epinephrine nor intravenous access for fluid was required.

In summary, in our research and clinical experience at Guy's and St. Thomas' Hospital, over the past several we have performed 2325 oral food challenges in young children. Of over 200 positive challenges, all were effectively managed without the requirement for intravenous access for administration of fluid or medication.

Conclusion

A recent review synthesized published information and clinical experience into comprehensive recommendations regarding food challenges in clinical practice. They listed situations that may warrant obtaining intravenous access prior to food challenge, including a past history of anaphylaxis, a past history of severe emesis, severe asthma, difficult intravenous access and anticipated need for intravenous medications (28). These recommendations were intended for broad clinical application including settings in which only limited information might be available about individual subjects.

In the current study we adopt the first two of these recommendations for children with suspected peanut allergy. In contrast to the broad clinical scenarios envisioned by the work group, in the current trial we will have detailed histories of laboratory and clinical parameters for all subjects. This will allow us to sort them into those with suspected peanut allergy and other features. This evaluation is built into the protocol specification for cannulation.

Published studies and our clinical experience indicate that asthma is effectively treated with inhaled therapies and oral steroids. It is not practical to judge difficult intravenous access; in addition the clinical centre where the trial is performed is very close to a pediatric intensive care unit, and, if necessary, children will be transferred to this pediatric intensive care unit for further management. As reviewed above we do not anticipate a need for intravenous medications.

Although the typical manifestations of severe anaphylaxis in young children are respiratory, fluid replacement may rarely be required for example in a child with suspected peanut allergy and a history of a food reaction involving severe emesis. Such a participant in the current trial would have intravenous access established prior to the challenge.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

To assess whether oral administration of a peanut-containing snack can induce tolerance in children at high risk for peanut allergy.

2.2 SECONDARY OBJECTIVES

To assess the effect of a peanut-containing snack on additional allergy outcomes, as outlined in section 3.3.

To assess the safety of administration of peanut protein in this population.

To define the mechanisms through which the ingestion of peanut protein may induce tolerance to peanut.

3. STUDY DESIGN

3.1 DESCRIPTION

This is a randomized, controlled trial that will enroll children at high risk for peanut allergy as demonstrated by eczema, egg allergy, or both. As shown in Figure 2, participants will be stratified based on their skin prick test (SPT) results for peanut: those with a wheal diameter of 0 mm will be in the SPT-negative stratum and those with a wheal diameter of 1, 2, 3, or 4 mm will be in the SPT-positive stratum. Participants in each stratum will be randomly assigned to receive a peanut-containing snack or to avoid peanut. Those assigned to receive the peanut-containing snack will receive at least 2 g of peanut protein three times per week until they reach 60 months of age. The prevalence of peanut allergy at that time will be compared between the peanut consumption and peanut avoidance groups.

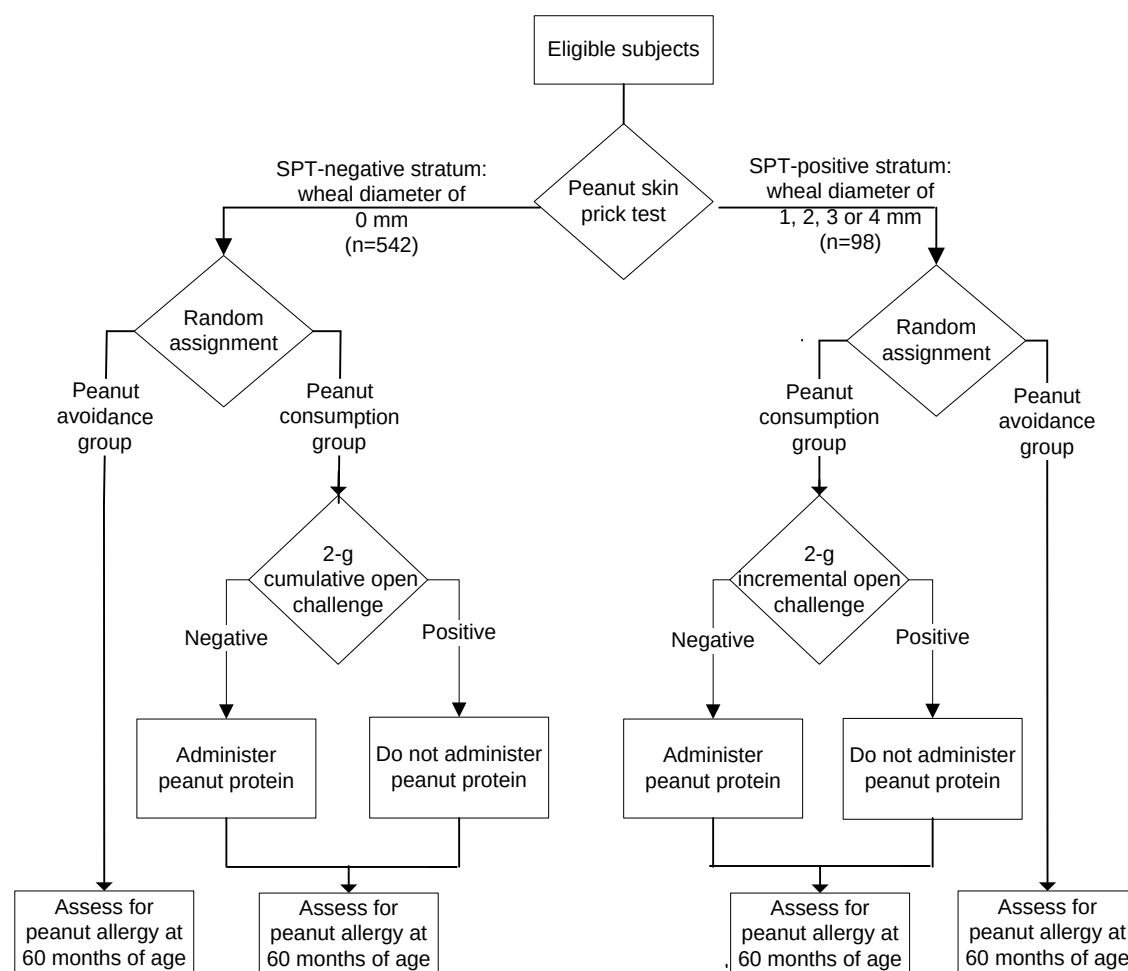


Figure 2. Study design

3.2 PRIMARY ENDPOINT

The proportion of participants with peanut allergy at 60 months of age.

3.3 SECONDARY ENDPOINTS

1. At 30 and 60 months of age: the proportion of participants with allergic sensitization to selected ingested allergens and inhaled allergens, and with seasonal rhinoconjunctivitis, perennial rhinoconjunctivitis, and asthma.

At 60 months of age: the proportion of participants with type 1 immediate onset food allergy to selected ingested allergens.

Incidence of adverse events and laboratory abnormalities; nutritional evaluations.

Results of cellular and humoral assessments of immune response related to the development of allergy or tolerance to specific allergens.

3.4 DETERMINATION OF PEANUT ALLERGY

Figure 3 and Figure 4 provide the algorithm for determination of peanut allergy.

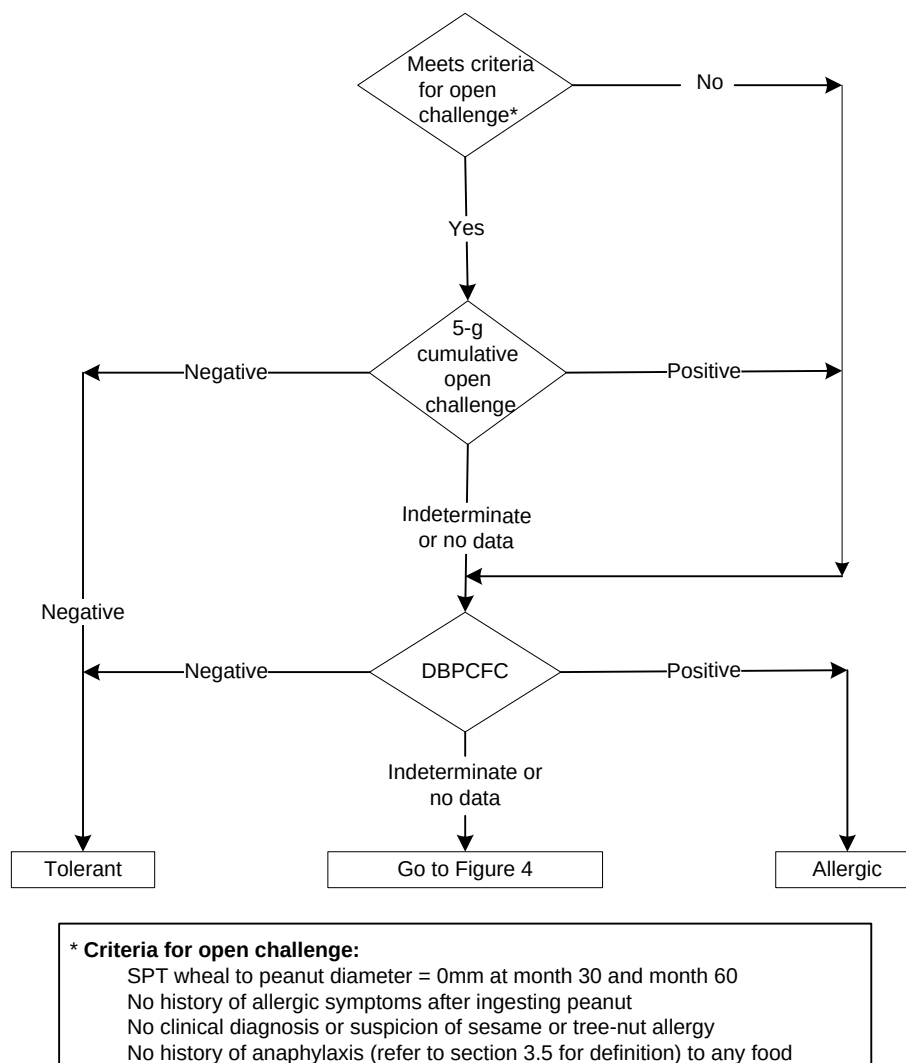


Figure 3. Determination of peanut allergy using open challenge and DBPCFC

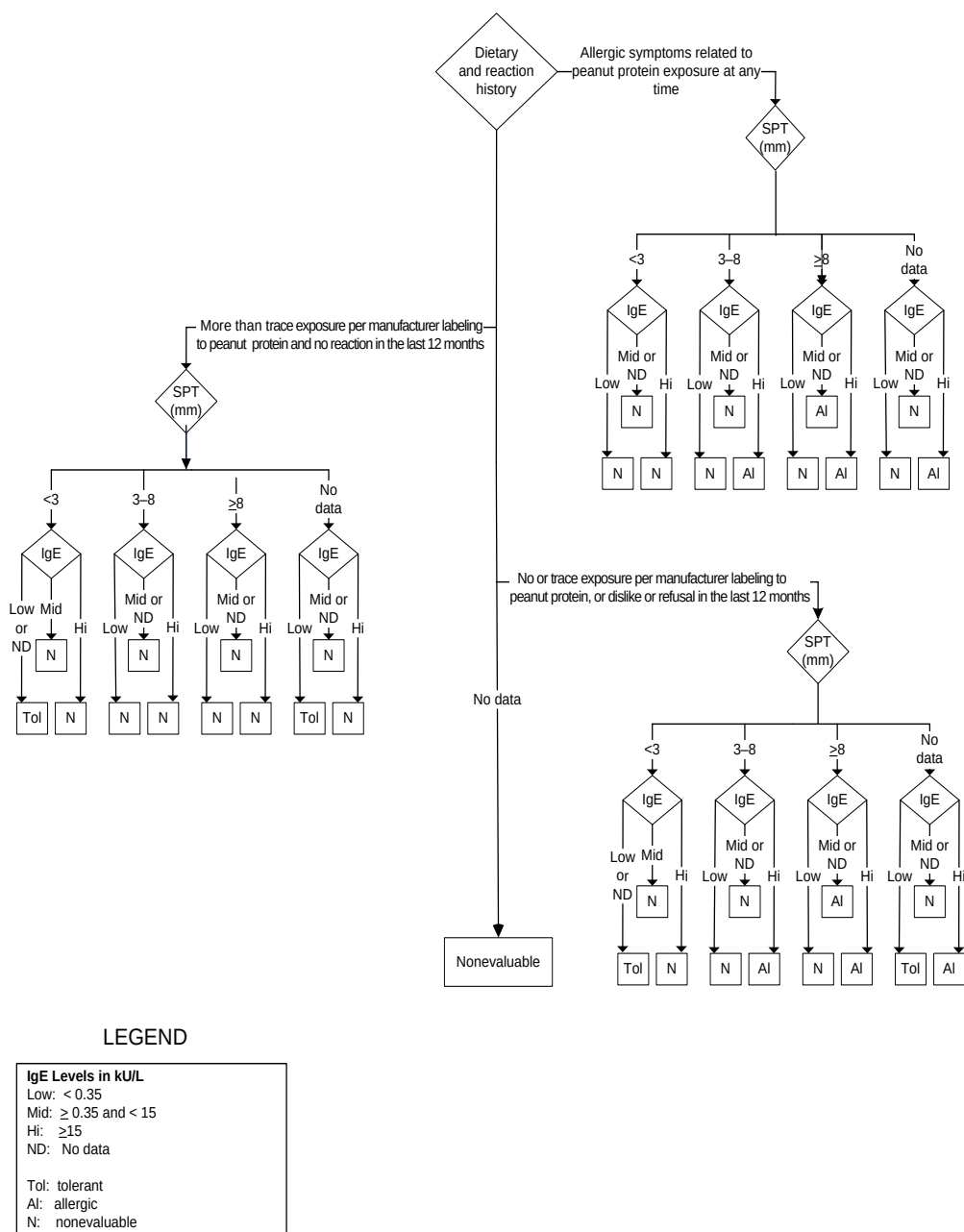


Figure 4. Determination of peanut allergy in the absence of peanut-challenge results using dietary and reaction history, SPT, and IgE

3.4.1 Example Assessment Scenarios

An interpretable outcome for either the DBPCFC or the 5-g cumulative open challenge performed in clinic is sufficient for a determination of allergy status (Figure 3).

- If there is no such outcome, peanut allergy will be assessed via interpretation of dietary history, SPT wheal diameter, and IgE levels (Figure 4).

Consider the following examples for a participant at age 5:

- A participant undergoes the DBPCFC and exhibits one or more of the allergic signs listed in Table 2. This participant would be counted as allergic.

- A participant undergoes the 5-g cumulative open challenge, which is positive (per criteria in Table 2) or indeterminate. This participant will then be invited for a DBPCFC (per Figure 3).
- A participant undergoes the 5-g cumulative open challenge and does not exhibit any of the allergic signs listed in Table 2. This participant would be counted as tolerant.
- A participant is not available for challenge (“no data”). For such participants, dietary and reaction history shall be reviewed (Figure 4). Some possible scenarios follow:
 - Dietary history indicates that a participant has exhibited allergic symptoms related to peanut protein exposure. This result directs the assessment to the upper right quadrant of Figure 4. The participant’s SPT = 5 mm, and IgE = 17 kU/L. This leads us to a box labeled “A1”; that is, the participant will be counted as allergic.
 - Dietary history indicates that a participant has had more than trace exposure to peanut protein in the last 12 months and has exhibited no reaction. This result directs the assessment to the lower left quadrant of Figure 4. As in the above scenario, this participant’s SPT = 5 mm and IgE = 17 kU/L. This participant will be considered nonevaluable because the high IgE, which is strongly suggestive of allergy, contradicts the history, suggesting tolerance.
 - Dietary history indicates that during the last 12 months a participant has had only trace exposure to peanut protein or has persistently refused or exhibited dislike of peanut. This result directs the assessment to the lower right quadrant of Figure 4. There are no data for SPT, but the participant’s IgE = 0.2 kU/L. This participant will be counted as tolerant.
 - Dietary history for a participant is not available. This participant will be considered nonevaluable.

3.5 STUDY DEFINITIONS

Anaphylaxis. Systemic allergic reaction with cardiovascular and/or respiratory compromise.

Allergic sensitization. Either allergen-specific IgE ≥ 0.35 kU/L, as defined by the CAP System™ (Pharmacia Diagnostics AB); or positive SPT, defined as SPT wheal diameter ≥ 3 mm with appropriate controls.

Asthma. A history of cough, wheeze, or shortness of breath that (1) was responsive to therapy with bronchodilators on two or more occasions in the previous 24 months, (2) required one visit to a physician in the previous 24 months, and (3) occurred during the night, during early morning, or upon exercising in the intervals between exacerbations at any time in the previous 12 months.

Egg allergy. Either (1) an SPT wheal diameter ≥ 6 mm from exposure to raw hen’s egg white and no history of previous egg tolerance, or (2) an SPT wheal diameter ≥ 3 mm from exposure to pasteurized hen’s egg white and allergic symptoms related to exposure to hen’s egg.

Failure to thrive. Weight decrease across >2 centile lines from the initial baseline weight.

Life-threatening anaphylaxis. An allergic reaction accompanied by any of the following: hypoxia, as evidenced by central cyanosis or oxygen saturation $\leq 89\%$; hypotension; loss of consciousness; or admission to intensive care.

Peanut allergy. IgE-mediated immediate hypersensitivity symptoms to peanut allergen.

Perennial rhinoconjunctivitis. Sensitization to a perennial allergen and clinical history of rhinoconjunctivitis symptoms experienced when exposed to the relevant allergen.

Seasonal rhinoconjunctivitis. Sensitization to a seasonal allergen and clinical history of rhinoconjunctivitis symptoms experienced during the relevant season.

Severe eczema. A rash that

- required the application of a topical creams and ointments containing corticosteroids or calcineurin inhibitors and if the participant is
 - ≤ 6 months of age, lasted for at least 12 out of 30 days on two occasions, or
 - > 6 months of age, lasted for at least 12 out of 30 days on two occasions in the last 6 months; or
- has been described by the participant's parent or guardian in a pre-enrollment questionnaire as "a very bad rash in joints and creases" or "a very bad itchy, dry, oozing, or crusted rash"; or
- is currently or was previously graded ≥ 40 using the modified SCORAD evaluation.

Suspected peanut allergy. Any of the following at any time during the study: SPT wheal diameter to peanut of at least 1 mm, IgE of at least 0.1 kU/L, or a history of allergic symptoms after ingesting peanut.

3.6 STOPPING RULES

3.6.1 Ongoing Review

The protocol chair, the NIAID medical monitor, the ITN clinical trial physician, and the NIAID Allergy and Asthma Data and Safety Monitoring Board (DSMB) will review safety data on an ongoing basis. The DSMB may stop enrollment or participation in the trial at any time if it concludes that there are significant safety concerns.

3.6.2 Review of Specific Adverse Events

3.6.2.1 Stopping Enrollment

Enrollment in the trial will be stopped pending review if any death occurs or if two participants are admitted to an intensive care unit for an adverse event related to study participation.

3.6.2.2 Stopping Enrollment and Administration of Peanut-containing Snack

Enrollment in the trial and further administration of the peanut protein-containing snack will be stopped pending review if either of the following occurs for the SPT-negative stratum:

- An analysis performed when 50 such participants in the peanut consumption group have been followed for 3 weeks demonstrates that the lower bound of the 95% confidence interval for the proportion of participants in the peanut consumption group with peanut allergy as determined in an unscheduled clinic visit (see section 6.7) is greater than 15%.
- An analysis performed when 50 such participants per group have been followed for 12 months demonstrates that the rate of serious adverse events is significantly greater at the 0.05 significance level in the peanut consumption group than in the peanut avoidance group.

Enrollment in the trial and further administration of peanut protein-containing snack to participants in the SPT-positive stratum will be stopped pending review if either of the following occurs:

- One of the first 5, 2 of the first 10, or 3 of the first 15 such participants randomly assigned to the peanut consumption group experiences life-threatening anaphylaxis (see section 3.5) during the first 3 weeks of administration of the peanut protein-containing snack.
- An analysis performed when 10 such participants in the peanut consumption group have been followed for 12 months demonstrates that 4 or more participants have experienced a serious adverse event.

3.7 STUDY DURATION

Enrollment is expected to take 24 months. Participation is approximately 54 months. Study duration is expected to be 78 months.

4. ELIGIBILITY

4.1 INCLUSION CRITERIA

1. Children ≥ 4 to <11 months old who have had solids successfully introduced into their diet.

Egg allergy, severe eczema, or both.

Informed consent obtained from parent or guardian.

4.2 EXCLUSION CRITERIA

1. Clinically significant chronic illness, except for eczema or recurrent wheeze.

Positive skin prick test for peanut allergen with a wheal diameter >4 mm in the presence of a negative saline control.

Previous or current consumption of peanut protein that exceeds 0.2 g of peanut protein on at least one occasion or 0.5 g over a single week.

Investigator-suspected allergy to peanut protein.

Investigator-suspected allergy to peanut protein in a care provider or current household member.

Diagnosis of persistent asthma.

ALT (SGPT) or bilirubin >2 times the upper limit of age-related normal value.

BUN or creatinine >1.25 times the upper limit of age-related normal value.

Platelet count $<100,000/\text{mL}$, hemoglobin <9 g/dL, or investigator-suspected immunocompromise.

Unwillingness or inability to comply with study requirements and procedures.

4.3 REASSESSMENT FOR ELIGIBILITY

Participants who fail to meet the criteria for enrollment in the trial or fail to complete the screening process within the designated visit window may be reassessed once for eligibility. Such participants may be enrolled at the time of reassessment if they meet all criteria for enrollment.

4.4 PREMATURE TERMINATION

4.4.1 Premature Termination of Trial Interventions

Trial intervention will be prematurely terminated for a participant if, in the judgment of the investigator, further participation in the trial would be deleterious to the participant's health; or if an independent dietary assessment reveals that the study intervention has led to body mass index BMI exceeding the International Obesity Task Force's proposed cutoff points for obesity in children at varying ages according to the BMI charts currently being used (29) or has led to failure to thrive.

4.4.2 Premature Termination from the Trial

Participants will be prematurely terminated from the trial for either of the following:

- withdrawal of consent, or

- failure to return.

Such participants will not be replaced.

5. STUDY INTERVENTION

5.1 PEANUT ADMINISTRATION OR AVOIDANCE

Participants assigned to the peanut consumption group will be fed at least 6 g of peanut protein per week, distributed over at least three meals per week during study participation. The preferred peanut source will be Bamba. There are 17 g of Bamba per serving, which provides 2 g of peanut protein. Thus, the specified amount corresponds to three servings per week. However, peanut butter may be substituted. Participants assigned to the peanut avoidance group will avoid exposure to peanut protein during study participation.

5.2 ASSESSMENT OF COMPLIANCE WITH STUDY INTERVENTION

Dieticians will monitor participant peanut protein consumption using a validated peanut frequency questionnaire in accordance with the schedule of events (see Appendix 1).

Participants enrolled in the LEAP study will be invited to participate in a separate additional study of dietary compliance. Separate consent will be obtained and participant's family will be asked to collect dust from the child's bed 2-4 weeks before their V60. Peanut protein levels in the dust will be used as an independent marker of peanut consumption and it is hypothesised that the peanut levels in dust in the peanut consumption group will be significantly higher than in the peanut avoidance group. These data will be linked to the LEAP database and any future follow-on study in the LEAP cohort for further exploratory analyses of compliance.

5.3 MODIFICATION OR DISCONTINUATION OF STUDY INTERVENTION

Participants in the peanut consumption group will discontinue consumption of the peanut protein-containing snack if a confirmed allergic reaction to peanut protein or an adverse nutritional consequence attributable to consumption of peanut protein is experienced.

These participants will remain in the study to receive a status assessment at 60 months of age.

6. STUDY PROCEDURES

6.1 VISIT WINDOWS

Visits described in the schedule of events should occur as follows:

- Visit 0: No more than 21 days following visit -1.
- Visits 12 and 30: Within ± 3 months of the planned visit date.
- Dietary consultations:
 - o Between visits 0 and 12: ± 3 days.
 - o Between visits 12 and 30: ± 7 days.
 - o Between visits 30 and 60: ± 14 days.
- Visit 60: within ± 6 months of the planned visit date.

6.2 GENERAL ASSESSMENTS

These general assessments will be performed at the site:

- Informed consent. Written informed consent will be obtained before any study assessments or procedures are performed.

- Randomization to the peanut consumption or peanut avoidance group. In each stratum, individual assignments to either the peanut consumption or peanut avoidance group will be obtained by authorized site personnel via a web-based response system or a phone-based response system whereby authorized site personnel will contact Rho Fed support staff by telephone for treatment assignments.
- Dietary education. Dieticians will provide written and verbal information and advice regarding peanut protein consumption or avoidance to the respective groups. Advice on avoidance will be provided in accordance with the Department of Health Guidelines for those in the peanut avoidance group.
- Physical examination. Temperature, pulse, respiration, skin fold thickness, weight, height, and waist circumference.
- Medical history. A history will be taken to determine if the participant has had any clinically significant diseases or medical procedures other than the disease under study.
- Adverse events. Participants will be assessed for adverse events. All adverse events will be recorded on the case report forms (CRFs).
- Concomitant medications. All concomitant medications will be recorded on the CRFs.
- Dietary history. A dietary history will be obtained using a 3-day food diary that captures typical food consumption and provides a breakdown of macro- and micronutrient intake and total energy intake.
- Food reaction history. A history will be taken to determine if the participant has had any clinically significant food-induced, immediate-onset allergic reactions.
- Eczema evaluation. Both subjective and objective eczema severity criteria will be recorded. At screening, eczema severity will be determined using the criteria described in section 1.4.5. The modified SCORAD evaluation alone will be used for all remaining eczema evaluations.
- Rhinitis evaluation. Symptoms in accordance with the study definitions for seasonal and perennial rhinoconjunctivitis will be recorded.
- Asthma evaluation. Symptoms in accordance with the study definition for asthma will be recorded.

6.3 LABORATORY ASSESSMENTS

Routine hematologic and chemistry laboratory assessments, which are detailed below, will be performed at the investigation site and recorded on CRFs.

- Hematology includes CBC with differential and platelets.
- Serum chemistries include Ca, PO₄, BUN, Cr, total protein, and albumin.
- Skin and nasal swab culture.

6.4 ALLERGY ASSESSMENTS

6.4.1 Allergens Assessed

The following allergy assessments will be performed:

- SPT for ingested allergens includes peanut, raw hen's egg white, pasteurized hen's egg white, cow's milk, sesame, and Soya.
- SPT for tree nuts includes Brazil nut, hazel nut, cashew, almond, and walnut.
- IgE for ingested allergens includes peanut, hen's egg white, cow's milk, sesame, Brazil nut, hazel nut, cashew, almond, and walnut.

- IgE for inhalant allergens includes house dust mite (*Dermatophagoides pteronyssinus*), cat dander, dog dander, timothy grass pollen, alternaria mold, and birch tree pollen.
- Oral food challenges for sesame, Brazil nut, hazel nut, cashew, and walnut will be given when clinical history and the results of SPT and IgE for these allergens are inconclusive. These challenges will be performed according to standard clinical practice.

6.4.2 Skin Prick Testing: Procedures and Interpretation

Prior to testing, ensure that the participant has not received short-acting antihistamine medications for at least 48 hours and/or long-acting antihistamine medications for at least 7 days.

The SPT for raw hen's egg white will be performed using Red Lion salmonella-free egg. The other SPTs will be performed using Soluprick® extracts (ALK-Abelló, where available). Lyophilized peanut extract (ALK- Abelló) will be analyzed for total protein and major peanut allergen concentration (Arah1, Arah2, and Arah3). The extract will be stored at -72°C and will be used for SPT evaluations to peanut throughout the study. Saline 0.9% will be used as a negative control, and histamine (concentration of 1 mg/mL of saline) will be used as the positive control.

Tests will be performed on the forearm unless unaffected eczema-free skin patches are not available, in which case the skin on the participants back will be used for testing. Using a standardized lancet (ALK Abelló), the skin will be pricked through a drop of the extract, which will then be absorbed.

Skin test sites should be measured after 15 minutes. The wheal and erythema should be measured at their widest diameters and recorded separately. Tests will be interpreted based on the widest wheal diameter.

The positive and negative control tests should be performed and measured prior to allergen SPT.

- If the saline negative control test is ≥ 3 mm, then it should be repeated immediately. If the repeat test remains ≥ 3 mm, the testing should be rescheduled for approximately 7 days' time.
- If the histamine positive control is ≤ 3 mm, then it should be repeated immediately. If the repeat test remains ≤ 3 mm, then the testing should be rescheduled for approximately 7 days' time.

For peanut measurements, the following rules apply:

- The SPT will be performed in duplicate and the mean of the two tests will be recorded.
- If both results are ≥ 1 mm and there is a > 2 mm difference between the results, a third SPT will be performed and the mean of the two closest results will be recorded.
- If one result is < 1 mm and one result is > 1 mm, a third SPT will be performed. If two of three results are < 1 mm, 0 mm will be recorded as the final result. If two of three results are ≥ 1 mm, the mean of those two results will be recorded as the final result.
- For V12, V30 and V 60 – when both SPT > 4 mm, the average of the two peanut SPTs will be recorded without necessitating a 3rd SPT even if the difference between the 2 SPT's is > 2 mm. If the 1st or 2nd SPT ≤ 4 mm the existing protocol rules for a 3rd SPT apply.

6.5 PEANUT CHALLENGES

6.5.1 Scheduled Challenges

For participants who are randomly assigned to the peanut arm, a 2-g open challenge will be performed after random assignment (see Figure 2).

For all participants, a 5-g cumulative challenge will be scheduled at the end of study participation for determination of the primary endpoint. This challenge will be either DBPCFC or open challenge by the criteria shown in Figure 3.

6.5.2 Unscheduled Challenges

Unscheduled challenges will be performed as indicated at unscheduled clinic visits (see section 6.7).

6.5.3 Repeat Challenges

If a participant fails to complete a challenge, he/she may be offered an opportunity to repeat the challenge at the investigator's discretion.

6.5.4 Procedure

6.5.4.1 Step 1: Perform Clinical Assessment

All children will be assessed by a pediatric allergy specialist to determine their suitability for a challenge. A participant's eligibility for a challenge is guided by the following criteria:

- The child has had no acute exacerbation of allergic signs or symptoms within the last week.
- The child has not received
 - short-acting beta-2 agonists for 12 hours,
 - long-acting beta-2 agonists for 24 hours,
 - short-acting antihistamines in the last 48 hours, or
 - long-acting antihistamines in the last 7 days.
- The child has no concurrent illness.
- For open challenges all safety criteria listed in Figure 3 must be confirmed.

Prior to conducting challenges, do the following:

- Inform PICU of the challenge taking place, except for home-based open challenges described in Section 6.5.4.3.2.
- Ensure that both oxygen and suction are in working order in the clinical trials unit, except for home-based open challenges described in Section 6.5.4.3.2 .
- Ensure that all steps of the anaphylaxis protocol are in place and that all emergency drugs are prescribed.
- Check that the drug box containing emergency medications is complete and that it is readily available.
- Record baseline observations, including temperature, pulse, respiration, SaO₂, auscultation of the chest, and peak expiratory flow rate (PEFR), if the child is reliably able to perform PEFR.
- Record blood pressure on all participants older than 12 months.
- Cannulation (intravenous access)

- The following individuals should have a cannula placed prior to the challenge: participants with suspected peanut allergy as defined in section 3.5 and a history of
 - life-threatening anaphylaxis to any food, or
 - a reaction to any food which caused dehydration and required intravenous fluid resuscitation.
- If cannulation is unsuccessful for such patients, challenge will not be performed.
- Ensure that a child with a latex allergy or suspected latex allergy avoids all latex products.

6.5.4.2 Step 2: Prepare the Food to be used in the Challenge

The dietician will prepare the challenge foods containing peanut protein and any carrier foods on the day of admission. The foods will be labeled and dated in the ward kitchen.

6.5.4.3 Step 3: Perform the Challenge

6.5.4.3.1 Double-blind, placebo-controlled challenge

Dose assessments and adjustments:

- Prior to the administration of each meal, the child will be evaluated for signs of reaction and vital signs (temperature, pulse, respiratory rate, blood pressure, SaO₂, and PEFr, if the child is reliably able to perform PEFr) will be monitored.
- The challenge should be discontinued at any stage if a reaction occurs (as described in Table 2), and action will be taken according to local hospital guidelines.
- The meals will be blinded by a computer-generated random code known to the dietician but not to the participant, nurse, or doctor. After discussion with an investigator, a blinded dose may be repeated if any of the following occurs:
 - abdominal pain,
 - nausea,
 - chest tightness or pain,
 - abnormal oropharyngeal sensation, or
 - unexplained behavioral change.

Perform a **mixed challenge** as follows:

- Administer five doses each of peanut protein, randomly interspersed with 3 placebo doses of equivalent portion size to the previous peanut dose, in increasing increments of 0.1, 0.25, 0.5, 1.0, and 2.5, g in 8 separate meals over the course of 1 day.
- After each dose, observe the child for at least 15 minutes.
- If the top dose is reached with no allergic reaction, wait at least 15 minutes and administer an additional 5 g of peanut protein in an unblinded fashion.
- An additional dose pair comprising a repeat of the previous dose and a placebo in random order may be given at the discretion of the investigator.

If an allergic reaction occurs following a placebo dose, perform a **separate challenge** as follows:

Day 1:

- Administer five doses in increasing increments of 0.1, 0.25, 0.5, 1.0, and 2.5g, all of which are either peanut protein or placebo.
- After each dose, observe the child for at least 15 minutes.

Day 2:

- Administer five doses in increasing increments of 0.1, 0.25, 0.5, 1.0, and 2.5 g, all of which are either peanut protein or placebo. If peanut protein was administered on day 1, then administer placebo on day 2, or vice versa.
- After each dose, observe the child for at least 15 minutes.
- If the top dose is reached with no allergic reaction, wait 20 minutes and administer an additional 5 g of peanut protein in an unblinded fashion.
- A dose may be repeated at the discretion of the investigator.

6.5.4.3.2 Open challenges

Open challenges will be performed at various times in the trial, as shown in Figures 2, 3, and 5. These challenges will be incremental for participants who are at more than minimal risk for reaction and cumulative for participants who are at minimal risk for reaction.

A 5-g cumulative open challenge will be performed at the 60-month visit in all participants who meet the safety criteria in Figure 3. If children are unable to come to hospital for this visit, the challenge may be performed at home by a study nurse.

Incremental open challenge

For children less than or equal to 36 months of age (4 g):

- Administer five doses of peanut protein of 0.1, 0.25, 0.5, 1.0, and 2.0 g in separate meals.
- After each dose, observe the child for at least 15 minutes. If there is no reaction do a full set of dose assessments (temperature, pulse, respiratory rate, blood pressure—for participants over 12 months of age—SaO₂, and PEFr—if the child is reliably able to perform PEFr).

For children greater than 36 months of age (9.35 g):

- Administer six doses of peanut protein of 0.1, 0.25, 0.5, 1.0, 2.5, and 5.0 g in separate meals.
- After each dose, observe the child for at least 15 minutes. If there is no reaction do a full set of dose assessments (temperature, pulse, respiratory rate, blood pressure—for participants over 12 months of age—SaO₂, and PEFr—if the child is reliably able to perform PEFr).

Cumulative open challenge

For children less than or equal to 36 months of age (2 g):

- Administer at least 2 g of peanut protein within a 6-hour period.
- Observe the child during the challenge and for 1 hour after completion of the cumulative dose.

For children greater than 36 months of age (5 g):

- Administer at least 5 g of peanut protein within a 6-hour period.
- Observe the child during the challenge and for 1 hour after completion of the cumulative dose.

No particular feeding regimen is required. Peanut meals may vary and be used interchangeably.

6.5.4.4 Step 4: Determine the Outcome

Outcome of the challenge will be determined by evaluating the participant using the criteria in Table 2.

A positive food challenge will be defined by the presence of either of the following:

- One or more major criteria.
- Two or more minor criteria.

An indeterminate food challenge will be defined by the presence of one minor criterion.

A negative food challenge will be defined by the absence of major or minor criteria.

All symptoms should be of new onset and not due to ongoing disease. Symptoms must occur no later than 2 hours after the last dose.

Table 2 Criteria for determining the outcome of food challenge

Major Criteria
Confluent erythematous pruritic rash Respiratory signs (at least one of the following): - Wheezing - Inability to speak - Stridor - Dysphonia - Aphonia ≥ 3 Urticarial lesions ≥ 1 Site of angioedema - Hypotension for age not associated with vasovagal episode - Evidence of severe abdominal pain (such as abnormal stillness or doubling over) that persists for ≥ 3 minutes
Minor Criteria
- Vomiting - Diarrhea - Persistent rubbing of nose or eyes that lasts for ≥ 3 minutes - Persistent rhinorrhea that lasts for ≥ 3 minutes - Persistent scratching that lasts for ≥ 3 minutes

6.5.4.5 Step 5: Consult with the Family

If the result is negative:

- Advise the family that the child may include peanut protein in the diet.
- No emergency plan is required.
- If the challenge was performed at a time other than the study termination visit, advise the family to continue feeding the child according to the protocol for participants in the peanut consumption group.

If the result is positive:

- Advise the family that the child must avoid all peanut and tree-nut protein in the diet.
- Provide a detailed written emergency management plan.
- Provide education on peanut protein and tree-nut avoidance strategies.
- Provide training in Epi-Pen administration.
- Review the child's inhaler technique if appropriate.
- Encourage the parents to join the UK Anaphylaxis Campaign and Medic-Alert.
- Schedule a follow up appointment for the participant in an appropriate allergy clinic.
- If the challenge was performed at a time other than the study termination visit, advise the family of the procedures and visit schedule for participants in the peanut consumption group who have reacted positively to challenge.

6.5.4.6 Step 6: Discharge the Participant

Observe the child until:

- 2 hours have elapsed since the top dose of an incremental challenge or 1 hour has elapsed since a cumulative challenge (see cumulative open challenge in section 6.5.4.3.2).
- All symptoms have resolved (if the result was positive).
- The clinician confirms that the child is ready for discharge.

After the observation period is over, remove the cannula if one was installed.

6.6 PEANUT CONSUMPTION

Maternal peanut protein consumption history. Information on the mother's peanut protein consumption during pregnancy and breastfeeding will be obtained at the baseline visit.

Participant peanut protein consumption monitoring. A peanut frequency questionnaire (PFQ) will be completed to ascertain the peanut protein consumption of the participant. The information provided on the questionnaire will be converted to grams of peanut protein for entry on the case report forms. Additionally, at home visits, the dieticians will observe the feeding of participants assigned to the peanut consumption group.

Household peanut protein consumption monitoring. Peanut protein consumption of all household members will be assessed in order to determine environmental exposure to peanut.

6.7 UNSCHEDULED CLINIC VISITS

An unscheduled clinic visit may be conducted at any time for either of the following:

- Aversion to peanut protein, refusal of peanut protein, or both for those in the peanut consumption group.

- Suspected peanut allergy.

Assessments to be performed at unscheduled visits are described in Figure 5. Independent of the result of these assessments, participants will continue with all subsequent study assessments.

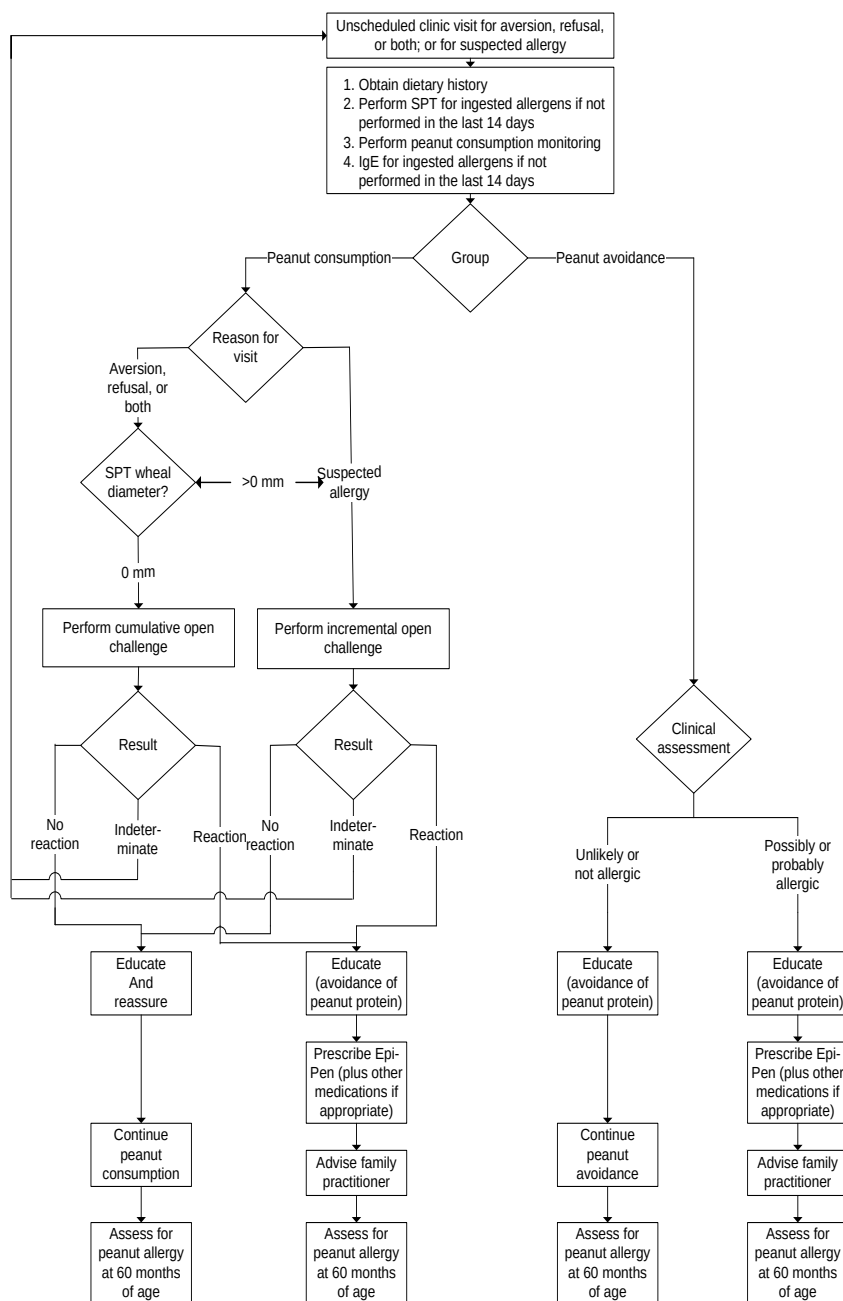


Figure 5. Assessments to be performed at unscheduled clinic visits

7. TOLERANCE ASSAYS

7.1 FROZEN PBMC T-CELL ASSAY

7.1.1 Overview

Cryobanked PBMCs will be used in assays monitoring functional changes in T cells. Samples will be cultured in vitro and stimulated with peanut antigen to see if there is peanut-specific lymphocyte proliferation and to measure cytokines secreted in response to these antigens. Cells from the stimulated cultures will be pelleted and banked for RNA extraction by the ITN core lab and the supernatants frozen for future secreted cytokine screening.

7.1.2 Gene Expression Profiling

Gene expression profiling will be performed using RNA isolated from non-stimulated versus in vitro stimulated cells. In this case, genes expressed in response to peanut antigen will be compared in participants believed to be tolerant versus those who go on to develop peanut allergy. Genes of interest include IL-4, IL-5, IL-13, and IFN γ to determine if an allergic participant's T-cell responses are more T_H2-like; whereby a tolerant participant's T cells may respond to antigen in a more T_H1-like fashion. Alternatively, genes involved in mediating immune regulation by regulatory T cells may also be differentially expressed. Of particular interest is FoxP3, which will also be analyzed and directly compared to intracellular cytokine staining. Recently IRF-4, IRF-5, and IRF-7 have been shown to be associated with Toll-like receptor signaling and inflammatory responses. These, among other genes, are potential candidates for study.

7.1.3 Secreted Cytokines

Cytokines secreted by in vitro stimulated cells will be monitored with the Luminex platform, a multiplex assay currently allowing for detection of 30 cytokines and chemokines from very small volumes of cell culture supernatant or serum. This analysis will be compared with gene expression and ICS data to determine if cytokines produced by T cells are released and to examine the difference between secreted cytokine profiles of peanut-tolerant and allergic participants.

7.1.4 Antigen-specific Proliferative and Cytokine Responses

Antigen-specific proliferative and cytokine responses will be assessed using in vitro cultures with peanut antigen as described above. Using CFSE dye as a label, we will determine how many cell divisions have occurred in response to peanut antigen in vitro and determine the phenotype of proliferating cells with multicolor flow cytometry. Proliferative responses may be lower in peanut tolerant versus allergic participants if active regulation is occurring for example. Additionally, intracellular cytokine production will be measured with ICS to determine profiles of cytokines secreted by the proliferating and nonproliferating T cells.

7.1.5 Regulatory T cells

Regulatory T cells play an important role in down modulating active or inflammatory immune responses. In this case, early antigen exposure may induce tolerance by activating antigen specific regulatory T cells. Currently, regulatory T cells are isolated using CD4 and CD25 surface markers, specifically gating on CD25⁺ hi cells. CD4⁺CD25⁺ cells are mixed with CD4⁺CD25⁻ cells to evaluate the impact of regulatory T cells on antigen-specific proliferative responses by CD25⁻ cells. Again, if tolerance to peanut allergens is achieved, there may be increased regulatory T-cell activity. This assay is likely to evolve given the use of FoxP3 and potentially other markers for enumeration and isolation of regulatory T cells.

7.2 SERUM/PLASMA ALLERGEN-SPECIFIC IgG, IgG4, IgA AND IgE

7.2.1 ELISA-based Techniques

ELISA-based techniques will be used to measure peanut-specific IgG, IgG4, IgA, and total IgE at baseline and at several time points during the study using serum samples. Previous studies have shown that children who are sensitized but not allergic to peanut have higher IgG4/IgE ratios than those who are allergic to peanut. Interestingly, the fact that both sensitized and allergic children are IgE positive suggests active regulation by T cells, which results in the higher IgG4 levels in the nonallergic, sensitized patients. Higher IgG4/IgE ratios found in sensitized versus allergic patients should correlate with peanut-induced tolerance in this study.

7.2.2 Facilitated Antigen Presentation Inhibition

Facilitated antigen presentation (FAP) inhibition is a flow cytometric-based assay that can detect participants who have allergen-specific IgG antibodies that interfere with FAP. In FAP, IgE facilitates the presentation of antigen to B cells, subsequently causing allergy-related, T-cell activation. Immunotherapy induces IgG, which competes for allergen-bound IgE, thus inhibiting allergen/IgE complexes from binding Fc receptors on antigen presentation cells (in this case, a B-cell line). Peanut consumption will increase peanut-specific IgG, especially IgG4, which interferes with FAP. The time course and magnitude of changes in FAP inhibitory activity will be compared with clinical symptoms, clinical scores, and peanut-specific IgG levels.

7.3 WHOLE BLOOD DNA-HLA GENOTYPES

There are some indications that HLA class II genetic polymorphism may be associated with susceptibility to peanut allergy. DNA will be isolated from trial participants, subjected to sequence-based class II typing, and genotyped for potential SNPs associated with persons susceptible to allergic responses.

8. ADVERSE EVENTS

8.1 OVERVIEW

Safety data will be recorded on a CRF specifically designed for this purpose. All serious adverse events (SAEs) will be reported on an SAE report form as well as on individual CRFs. All data will be reviewed periodically by the data safety and monitoring board (DSMB). In addition, SAEs will be reported locally. The DSMB has the authority to withdraw any participants and/or terminate the study because of safety findings.

Adverse events that are classified as serious according to the definition of health authorities must be reported promptly and appropriately to the ITN, the NIAID, the IND sponsor, principal investigators in the trial, institutional review boards (IRBs), and health authorities. This section defines the types of adverse events and outlines the procedures for appropriately collecting, grading, recording, and reporting them. 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*, and applies the standards set forth in the National Cancer Institute (NCI), *Common Terminology Criteria for Adverse Events* (CTCAE), Version 3.0 (December 12, 2003).

8.2 DEFINITIONS

8.2.1 Adverse Event

An adverse event is any occurrence or worsening of an undesirable or unintended sign, symptom, laboratory finding, or disease that occurs during participation in the trial.

An adverse event will be followed until it resolves or until 30 days after a participant terminates from the study, whichever comes first.

8.2.2 Serious Adverse Event

An SAE or reaction is defined as “any adverse event that suggests a significant hazard, contraindication, side effect, or precaution.” This includes but is not limited to any of the following events:

1. **Death:** A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up after the completion of therapy must be reported whether it is considered treatment related or not.

A life-threatening event: A life-threatening event is any adverse therapy experience that, in the view of the investigator, places the participant at immediate risk of death from the reaction as it occurred.

Inpatient hospitalization or prolongation of existing hospitalization.

Persistent or significant disability.

An event that requires intervention to prevent permanent impairment or damage. An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Congenital anomaly or birth defect.

Other conditions specified in the protocol.

Regardless of the relation of the adverse event to study participation, the event must be reported as a serious adverse event if it meets any of the above definitions.

8.2.3 Unexpected Adverse Event

An adverse event is considered “unexpected” when its nature (specificity) or severity is not consistent with a normal reaction to the study intervention.

8.3 COLLECTING ADVERSE EVENTS

8.3.1 Methods of Collection

Adverse events will be collected from the time the participant provides consent until the time the event resolves or until 30 days after the participant completes study treatment, whichever comes first.

Adverse events may be discovered through any of these methods:

- Observing the participant.
- Questioning the participant in an objective manner.
- Receiving an unsolicited complaint from the participant.

An abnormal value or result from a clinical or laboratory evaluation (e.g., a radiograph, an ultrasound, or an electrocardiogram) can also indicate an adverse event. If this is the case, then the evaluation that produced the value or result should be repeated until that value or result returns to normal or can be explained and the participant’s safety is not at risk. If an abnormal value or result is determined by the investigator to be clinically significant, it must be recorded as an adverse event on the appropriate laboratory evaluation form(s).

8.3.2 Collecting Serious Adverse Events

Serious adverse events will be collected from the time the participant provides consent until 30 days after he/she completes study participation or until 30 days after he/she prematurely withdraws from the study.

8.3.3 Recording Adverse Events

Throughout the study, the investigator will record all adverse events on the appropriate adverse event CRF regardless of their severity or relation to study medication or study procedure. The investigator will treat participants experiencing adverse events appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes.

8.3.4 Recording Serious Adverse Events

Serious adverse events will be recorded on the adverse event CRF and on the SAE form, and health authorities will be notified as outlined in section 8.5.2.

8.4 GRADING AND ATTRIBUTION OF ADVERSE EVENTS

8.4.1 Grading Criteria

The study site will grade the severity of adverse events experienced by ITN study participants according to the criteria set forth in the NCI-CTCAE Version 3.0. This document provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events.

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.

All adverse events will be reported and graded whether they are or are not related to disease progression or treatment.

8.4.2 Attribution Definitions

The relation, or attribution, of an adverse event to study participation will be determined by the site investigator. The site investigator will also record the determination of attribution on the appropriate CRF and/or SAE reporting form. The relation of an adverse event to the study treatment will be determined using the descriptors and definitions provided in Table 3. 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>.

Table 3. NCI-CTCAE attribution of adverse events

Code	Descriptor	Definition
Unrelated Category		
1	Unrelated	The adverse event is clearly not related to study participation.
Related Categories		

2	Unlikely	The adverse event is doubtfully related to study participation.
3	Possible	The adverse event may be related to study participation.
4	Probable	The adverse event is likely related to study participation.
5	Definite	The adverse event is clearly related to study participation.

8.5 REPORTING SERIOUS ADVERSE EVENTS

8.5.1 Reporting Timeline

When an investigator identifies an SAE (as defined in section **8.2.2**), he or she must complete the study specific AE/SAE CRF and submit to Rho Product Safety within 24 hours of discovering the event. This report may be sent by fax or through a 21 CFR part 11 compliant electronic data capture system. A confirmation e-mail will be sent to the investigator within 1 business day. The investigator should contact Rho Product Safety if this confirmation is not received. This process and timeline applies to both initial and follow-up SAEs.

SAEs should be **FAXED** to Rho Product Safety at (1-888-746-3293). General questions about SAE reporting may be directed to Rho Product Safety by **TELEPHONE** (1-888-746-7231) or **E-MAIL** (rho_productsafety@rhoworld.com).

Reporting Criteria for SAEs

After the SAE has been assessed, the event will be reported in the required manner based on the following criteria:

Standard reporting as SAE. This requirement applies if the adverse event is classified as any of the following:

- Serious, drug related, and expected.
- Serious, *not* drug related.

Expedited reporting. This requirement applies if the adverse event is considered serious, drug related, and unexpected. This type of SAE must be reported by the sponsor to the appropriate health authorities within 15 days; fatal or life-threatening events must be reported within 7 days.

All investigators must report adverse events to their IRBs as mandated by their IRBs.

8.5.3 Reporting Serious Adverse Events to the Data Safety Monitoring Board

The DSMB will be provided listings of all SAEs on an ongoing basis. Furthermore, the DSMB will be informed of expedited SAEs by the NIAID medical monitor.

9. STATISTICS

9.1 ANALYSIS SAMPLES

The following groups will form samples for analysis.

- Intent-to-treat (ITT): all randomly assigned participants who are evaluable for peanut allergy at age 60 months.
- Safety: all participants who either receive any peanut protein-containing food or are in the peanut avoidance group.
- Per-protocol (PP): participants in compliance with the dietary regimen for their assigned group and evaluable for peanut allergy at age 60 months. Compliance is defined as the consumption of peanut protein in the first 24 months of life:

- o In the peanut consumption group, compliance is consumption of at least 3 g of peanut protein per week for at least 50% of the weeks recorded and consumption of at least 2 g of peanut protein on at least one occasion in both the first and second years of life.
- o In the peanut avoidance group, compliance is consumption of less than 0.2 g of peanut protein on any occasion and less than 0.5 g over a single week.
- o At least 50% of compliance information must be available for the required visits in order to be included in the PP sample.

9.2 ANALYSIS OF ENDPOINTS

9.2.1 Analysis of Primary Endpoint

9.2.1.1 SPT-negative Stratum

The main analysis will evaluate participants in the ITT sample of the SPT-negative stratum. In an additional analysis, the same comparison will be made in the PP sample. It will compare the proportion of participants with peanut allergy in the peanut and observation arms at 60 months of age using a two-tailed, chi-square test at the 0.05 level of significance.

9.2.1.2 SPT-positive Stratum

Peanut allergy incidence in the ITT sample will be evaluated in the SPT-positive stratum. The peanut allergy incidence rates at 60 months of age will be compared between the two groups using a two-tailed test at the 0.05 level of significance. A similar analysis will be performed in the PP sample.

9.2.2 Analysis of Secondary Endpoints

The incidence of adverse events and laboratory abnormalities at 5 years of age will be compared between the peanut consumption and avoidance groups in the safety sample using a two-tailed, chi-square test at the 0.05 level of significance. All AEs will be classified by body system and preferred term according to a standardized thesaurus (MedDRA version 11.1). Additional specific secondary endpoints are described in section 3.3.

9.2.3 Additional Analyses

Additional analyses of the risk associated with peanut allergy in the treatment groups will be performed using multiple logistic regression to identify possible associations of risk with baseline participant characteristics and selected clinical and dietary measures. These analyses will be performed on the incidence of peanut allergy at ages 30 months and 60 months.

9.3 SAMPLE SIZE

9.3.1 Original Sample Size Calculation

We assumed in versions 1.0 and 2.0 of the protocol that the true rate of peanut allergy in the peanut avoidance group would be at least 15% and that treatment would reduce that rate to 4.5 % or less in the peanut consumption group. Assuming a 20% dropout rate, enrolling 220 participants in each group would have provided 91% power to detect such differences between the groups using a two-tailed, chi-square test.

Versions 1.0 and 2.0 of the protocol also allowed for 20 participants in the SPT-positive stratum to be enrolled per group. This group size was determined by available resources. We also expected that only a small number infants screened would turn out to be SPT-positive. Allowing for a 20% dropout rate, 16 evaluable participants would allow for the half-width of the two-sided 95% confidence

interval on the difference in proportions to be a minimum of 0.25 in the range of rates expected for the primary endpoint.

9.3.2 Need for Revision of Original Sample Size Calculation

We have since obtained evidence suggesting that the sample size should be increased in the SPT-negative and SPT-positive strata. This decision is justified below and is based largely data that emerged from the enrollment characteristics of participants recruited early in the trial.

SPT-negative stratum

Prior to beginning the current trial, we assumed that only 10% of those who would eventually develop peanut allergy would have skin tests either in the 1- to 4-mm or > 4-mm range at enrollment. In contrast, we actually found that 13% of high-risk infants screened early in the conduct of this trial had a skin test of 1 to 4 mm and 14% had a skin test > 4 mm. Thus, a higher fraction of screened subjects than expected was excluded from the SPT-negative stratum and from the trial entirely. When we take into account this 27% rate of exclusion of screened subjects from the negative stratum, we have to reduce our estimate for those who would have peanut allergy at 5 years of age. Using this information we can predict that the rate of peanut allergy in the peanut avoidance group will be about 10%.

Additional data obtained early in the trial, however, suggested that the actual rate of peanut allergy at 5 years of age could be even lower. We found that infants enrolled into the trial at ≥ 6 months of age had only an 18% rate of IgE sensitization, defined as peanut-specific IgE ≥ 0.35 kU/L, compared to 38% for infants enrolled at < 6 months of age.

Enrollment age early in the trial was skewed towards infants older than 6 months, with 92% of the first 189 subjects screened falling into this age group. This skewing meant that there would be relatively fewer infants with IgE sensitization, as defined above, than there would be if enrollment were more balanced with respect to age. This, in turn, suggested that there would be a lower rate of peanut allergy in the peanut avoidance group than previously expected. This can be illustrated by using peanut-specific IgE at screening to estimate the chance of peanut allergy in each subject at age 5 years, with the additional assumption that 25% of the children will outgrow their allergy.

In table 4, the predicted rates of peanut allergy at age 5 years are estimated from the peanut-specific IgE at screening using data from the first 189 subjects who passed screening and had skin prick tests to peanut of 0 mm. In these first 189 subjects, 80, 74, 15, 1, and 3 were ≥ 6 months of age at enrollment and fell into the respective IgE ranges—0–0.01, > 0.01–0.7, > 0.7–3.5, > 3.5–17.5, and > 17.5 kU/L—and 8, 2, 2, 3, and 1 were < 6 months of age at enrollment and fell into the same respective IgE ranges.

Using those distributions and estimating the chance of peanut allergy at age 5 years according to peanut-specific IgE level, with the additional assumption that 25% of children will outgrow their allergy, the predicted rate of peanut allergy in subjects enrolled at < 6 months or ≥ 6 months can be made as shown in Table 4.

The estimates of the rate of peanut allergy corresponding to various levels of peanut-specific IgE are based on previous data from the United Kingdom(30) and the United States. (31) In Table 4, the allergy rates associated with levels of peanut-specific IgE from 0 to 3.5 kU/L have been reduced to more conservative values compared to the rates in references 23 and 24. This is because our clinical experience suggests that the prediction of allergy rates by low levels of IgE is less accurate in the very young infants of the current trial than in the older populations described in references 23 and 24.

Table 4 includes three estimates of the probability of peanut allergy at peanut-specific IgE levels > 3.5 kU/L to illustrate that small changes in these levels do not substantially affect the final predicted rate of peanut allergy, mainly because relatively few subjects with such levels are enrolled.

Table 4 Early enrollees and predicted rates of clinical peanut allergy at age 5 years

Predicted rates of peanut allergy at screening by peanut-specific IgE, with children not outgrowing clinical allergy						Predicted rates of peanut allergy at age 5 years by enrollment age, with 25% of children outgrowing clinical allergy			
Peanut-specific IgE ranges						Enrollment age		All subjects with age mix	
IgE (kU/L)	0–0.01	>0.01–0.7	>0.7–35	>35–175	>175	< 6 mo	≥ 6 mo	< 6 mo 8%; ≥ 6 mo 92%	< 6 mo 25%; ≥ 6 mo 75%
Number of early enrollees in different peanut-specific IgE ranges									
< 6 mo	8	2	2	3	1	16			
≥ 6 mo	80	74	15	1	3		173		
Predicted rates of peanut allergy									
Case 1	0%	10%	30%	60%	90%	16.41%	6.59%	7.37%	9.04%
Case 2	0%	10%	30%	70%	100%	18.28%	6.76%	7.68%	9.64%
Case 3	0%	10%	30%	80%	100%	19.69%	6.81%	7.84%	10.03%

Given a mix of ages with 8% less than and 92% greater than or equal to 6 months at enrollment, and using the most conservative estimates for probability of peanut allergy (case 1, Table 4), we estimated that the rate of peanut allergy at age 5 years could be as low as 7.37%. If this were true, it would severely diminish the power of the trial to see a statistically significant difference between the two groups.

We now propose to focus enrollment efforts to change the age distribution of those enrolled to increase the percentage of less than 6-month old infants to 25%. If this is possible, we estimate that the rate of peanut allergy in the peanut avoidance group will be increased to 9.04% (Table 4).

We also now expect to see a lower rate of peanut allergy in the intervention group. The higher than expected rate of positive skin prick tests to peanut at screening will remove more subjects destined to be peanut allergic away from this group at enrollment. At enrollment we are now expecting only a 1% rate of positive peanut challenges in this group. Data from Israel (section 1.2.4) suggest that the rate of peanut allergy in a country with a high rate of peanut consumption in infants is very low. Assuming that the true rate of new peanut allergy during follow up is 1% (allowing for this being a high risk group), we will have a 2% rate of peanut allergy at aged 5 years in the intervention group.

To have adequate power to detect a statistical difference in the rate of peanut allergy between the two groups, in addition to changing the age distribution, the number of participant enrolled into the SPT-negative stratum needs to be increased.

SPT-positive stratum

As we have already stated, a very high proportion of eligible infants screened (13%) had a skin test to peanut in the 1- to 4-mm range and therefore fell into the SPT-positive stratum. This meant that half of the infants in the population who become allergic to peanut at 5 years of age would be derived from this SPT-positive stratum. Using baseline data from the subjects successfully screened in the first 6 months of the trial, we estimated that 50% of the peanut avoidance group in the SPT-positive stratum would be peanut allergic at age 5 years. This assumed a 70% rate of allergy with a 3- to 4-mm skin test, a 50% rate for a 1- to 2- mm skin test, and a 25% rate of outgrowing allergy.

Using a similar approach, we estimated that the rate of peanut allergy in the peanut consumption group in the SPT- positive stratum would be 20%. This assumed that at enrollment we would expect a 20% rate of positive peanut challenges in this group. It also assumed 7% of the subjects would develop peanut allergy during follow-up and 25% of the subjects would outgrow their allergy.

The planned number of subjects in early versions of the protocol was not sufficient to have sufficient power to show an effect of intervention in this stratum assuming rates in the groups of 50% and 20%. We therefore concluded that an increase in the size of the SPT-positive stratum would also be needed to determine whether the study intervention would have a significant effect on the prevalence of peanut allergy in this important group.

9.3.3 Revised Sample Size Calculations for Both Strata

9.3.3.1 SPT-negative Stratum

For participants in the SPT-negative stratum, the null hypothesis states that there is no difference in the proportion of individuals with peanut allergy in the peanut consumption group as compared to the peanut avoidance group. We assume that the true rate of peanut allergy in the peanut avoidance group is at least 9.04% and that treatment will reduce that rate to 2% or less in the peanut consumption group. Assuming a 20% dropout rate, enrolling 271 participants in each group will provide 89% power to detect such differences between the groups using a two-tailed, chi-square test (without the continuity correction).

9.3.3.2 SPT-positive Stratum

For participants in the SPT-positive stratum, we assume the true rate of peanut allergy in the peanut avoidance group is at least 50% and that treatment will reduce that rate to 20% or less in the peanut consumption group. Assuming a 20% dropout rate, enrolling 49 participants in each group will provide 80% power to detect such differences between the groups using a two-tailed, chi-square test (without the continuity correction). If the true rate in the intervention group is actually 15%, 49 participants will provide 92% power.

9.4 STRATIFICATION

Participants will be randomly assigned to treatment within each of the two strata using a centrally administered randomization scheme. One stratum comprises participants with skin prick tests for peanut of 0 mm at time of study entry, whereas the second stratum comprises those with skin prick tests for peanut of 1, 2, 3, or 4 mm. In the first stratum, 542 participants will be randomly assigned, whereas in the second stratum 98 participants will be randomly assigned. Counting both strata, a total of 640 participants will be recruited into the trial.

9.5 REPORTING DEVIATIONS FROM THE ORIGINAL STATISTICAL PLAN

The principal features of the study design and the plan for statistical analysis of the data are outlined in this protocol and will be described in more detail in the subsequent statistical analysis plan (SAP). Any changes in these features will require a protocol or an SAP amendment, which will be subject to review by the independent DSMB and the study sponsor. These changes will be described in the final report as appropriate.

10. IDENTIFICATION AND ACCESS TO SOURCE DATA

10.1 IDENTIFYING SOURCE DATA

The investigator is required to keep accurate records to ensure that the conduct of the study is fully documented (see section 11). The results of all clinical and clinical laboratory evaluations will be maintained in the participant's medical records and the data will be transferred to clinical CRFs.

Safety data will be recorded on CRFs specifically designed for this purpose. All the SAEs will be reported on an SAE report form as well as on individual CRFs. All data will be reviewed periodically by the DSMB and IRB. The DSMB and/or the IRB have the authority to withdraw any participants and/or terminate the study because of safety findings.

10.2 PERMITTING ACCESS TO SOURCE DATA

The investigational site participating in this study will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from the participants in this clinical trial. Medical and research records should be maintained at each site in the strictest confidence. However, as a part of the quality assurance and legal responsibilities of an investigation, the investigational site must permit authorized representatives of the sponsor(s) and health authorities to examine (and when required by applicable law, to copy) clinical records for the purpose of quality assurance reviews, audits, and evaluations of the study safety and progress. Unless required by the laws that permit copying of records, only the coded identity associated with documents or with other participant data may be copied (and all personally identifying information must be obscured). Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that is linked to identified individuals. The investigational site will normally be notified before auditing visits occur.

11. QUALITY CONTROL AND QUALITY ASSURANCE

The investigator is required to keep accurate records to ensure that the conduct of the study is fully documented.

The sponsor is responsible for regularly reviewing the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness, consistency, and accuracy of all documented data.

11.1 DATA HANDLING

The investigator is required to keep accurate records to ensure that the conduct of the study is fully documented. The investigator is required to ensure that all CRFs are completed for every participant entered in the trial. The sponsor is responsible for regular inspection of the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness, consistency, and accuracy of all documented data. The CRFs will be completed online via a Web-based electronic data capture (EDC) system that has been validated and is compliant with Part 11 Title 21 of the Code of Federal Regulations. Study staff at the site will enter information into the electronic CRFs, and the data will be stored remotely at a central database. Data quality will be ensured through the EDC system's continuous monitoring of data and real-time detection and correction of errors. All elements of data entry (i.e., time, date, verbatim text, and the name of the person performing the data entry) will be recorded in an electronic audit trail to allow all changes in the database to be monitored and maintained in accordance with federal regulations.

12. ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

12.1 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 an appropriate ethics committee or IRB. Any amendments to the protocol or to the consent materials must also be approved before they are implemented.

Ethical approval for the study will also be obtained locally from the relevant Multicentre Research Ethics Committee. All relevant trusts within the National Health System in England will also be informed of the study.

12.2 INFORMED CONSENT AND ASSENT

The informed consent form is a means of providing information about the trial to a prospective participant and allows for an informed decision about participation in the study. All participants (or their legally acceptable representative) must read, sign, and date a consent form before entering the study or undergoing any study-specific procedures. Consent materials for participants who do not speak or read English must be translated into the participants' appropriate language.

The informed consent form must be revised whenever important new safety information is available, whenever the protocol is amended, and/or whenever any new information becomes available that may affect participation in the trial.

A copy of the informed consent will be given to a prospective participant for review and signature. The attending physician, in the presence of a witness, will review the consent and answer questions. The prospective participant 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.

12.3 PRIVACY AND CONFIDENTIALITY

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a sequential identification number, and these numbers rather than names will be used to collect, store, and report participant information.

13. PUBLICATION POLICY

The ITN policy on the publication of study results will apply to this trial. Authorized participants can find details of the policy statement on the ITN website at <http://www.immunetolerance.org>.

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Appendix 1. Schedule of Events

Age in months	4–10	4–10	4–11	12	13–29	30	31–59	60	
Visit	–1	0	0.01–0.36	12	12.01–12.39	30	30.01–30.30 ¹	60	Unscheduled 99
			Weekly phone dietary consultation ²		Biweekly phone dietary consultation		Monthly phone dietary consultation		USV ³
Informed consent	X								
Randomization		X							
Dietary education		X	X	X	X	X	X	X	X
General Assessments									
Physical examination	X	X		X		X		X	X
Medical history	X								
Adverse events		X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Dietary history		X	X ⁴	X	X ³	X		X	X
Food reaction history			X	X	X	X	X	X	X
Eczema evaluation	X			X		X		X	
Rhinitis evaluation						X		X	
Asthma evaluation						X		X	
Laboratory Assessments									
Hematology	X							X	
Serum chemistries	X							X	
Skin and nasal swab culture		X		X		X		X	
Allergy Assessments									
SPT for ingested allergens	X			X		X		X	X
SPT for tree nuts								X	
IgE for ingested allergens	X			X		X		X	X
IgE for inhalant allergens						X		X	
Oral food challenges ⁵								X	X
Peanut challenges ⁶		X						X	X
Peanut Consumption									
Maternal peanut protein consumption history		X							
Participant peanut protein consumption monitoring	X	X	X	X	X	X	X	X	X
Household peanut protein consumption monitoring		X	X ³	X	X ³	X		X	X
Immunologic Assessments									
PBMC T-cell assay	X			X		X		X	
Serum allergen-specific immunoglobulins	X			X		X		X	
Serum total IgE	X					X		X	
Plasma allergen archive	X			X		X		X	
Whole blood DNA-HLA genotypes	X			X					

¹ Additional monthly phone dietary consultation visits (30.31 – 30.36) are allowed during the protocol window for V60 i.e. ±6 months

² In addition to telephone dietary consultations, an in-home dietary consultation will be performed at 9 months of age for participants enrolled younger than 6 months of age and at 21 months of age for all participants.

³ An unscheduled clinic visit may be conducted at any time for aversion to peanut, refusal of peanut, or both, or for suspected peanut allergy. Section 6.6 specifies which assessments are required for particular participants.

⁴ To be performed only at the in-home dietary consultation.

⁵ Oral food challenges will be performed as indicated in section 6.4.

⁶ Peanut challenges will be performed as indicated in sections 6.5 and 6.7.

Appendix 2. Predictive Values: Food Allergen-Specific IgE Levels and Food Allergen Skin Prick Tests

Predictive value of specific IgE levels ¹⁻³		
Food	≥ kU/L	≥ PPV
Egg	7	95
Infants ≤ 24 months ⁴	2	95
Milk	15	95
Infants ≤ 24 months ⁵	5	95
Peanut ⁶	15	95
Fish	20	95
Tree nuts ^{6,7}	15	95
Predictive value of skin prick tests ^{8,9}		
Food	≥ Wheal size (mm)	≥ PPV
Milk	8	95
Infants ≤ 24 months	6	95
Egg	7	95
Infants ≤ 24 months	5	95
Peanut ⁶⁻⁹	8	95

¹ Sampson HA. Food allergy - accurately identifying clinical reactivity. *Allergy*. 2005;60 (Suppl 79):S19–S24.

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³ Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol*. 2001;107(5):891-896.

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⁷ Clark AT, Ewan PW. Interpretation of tests for nut allergy in one thousand patients, in relation to allergy or tolerance. *Clin Exp Allergy*. 2003;33(8):1041–1045.

⁸ Hill DJ, Heine RG, Hosking CS. The diagnostic value of skin prick testing in children with food allergy. *Pediatr Allergy Immunol*. 2004;15(5):435–441.

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LEAP Study SAP (ITN032AD) – summary of changes

The LEAP Study SAP Version 1.0 was prepared by the Statistical and Data Coordinating Center (at PPD) in collaboration with Dr. Lack, the site team and the ITN in 2007.

The Statistical and Data Coordinating Center contract was subsequently awarded to Rho Federal Systems Division and the study data and documents were transitioned to Rho in 2008. Please note that the Version 1.0 signature pages indicate Version 2.0, but the body of the document indicates that the document is Version 1.0 of the SAP and is the earliest version of the SAP available.

The LEAP Study SAP underwent a series of updates prior to database lock, as follows:

Version 1.0, 2 November 2007 (original)

Version 2.2, 12 June 2014

Version 3.0, 04 September 2014 (final)

Summary of changes from Version 1.0 to Version 2.2

The SAP was updated from the original document created by PPD in 2007.

The study team incorporated hypothesis and statistical methodology for analyses of mechanistic data not collected in the eCRFs as a series of attachments.

Summary of changes from Version 2.2 to Version 3.0

The study team removed the description of mechanistic data analyses for data not collected in the eCRFs as these analyses were to be performed in collaboration with the Biomarker Discovery Research (BDR) and Bioinformatics (BIG) Groups of the Immune Tolerance Network. BDR and BIG detailed these analyses in a separate mechanistic statistical analysis plan (MSAP).

Study Sponsor: National Institute of Allergy and Infectious Diseases (NIAID)
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Statistical Analysis Plan
PROTOCOL ITN032AD

Induction of Tolerance through Early Introduction of Peanut in
High-Risk Children (Version 2.0, 17 April 2007)

Prepared by:

PPD, Inc.
929 North Front Street
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Issued by:

Sarah Thieling

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Date: 04 / Nov / 2007

Approved by:

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Senior Reviewer
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Date: ____ / ____ / ____

Upon review of this document, including table, listing and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing and figure production can begin.

Approved by:

Date: ____ / ____ / ____

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Date: ____/____/____

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Date: ____/____/____

Upon review of this document, including table, listing and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing and figure production can begin.

Approved by:

Carson Northrup

Date: 11 / 06 / 07

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List of Abbreviations

AE	adverse event
BMI	body mass index
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DBPCFC	Double-blind placebo-controlled food challenge
DSMB	Data Safety Monitoring Board
ITN	Immune Tolerance Network
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities [®]
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Diseases
PP	Per protocol
PPDI	Pharmaceutical Products Development, Inc.
SAE	serious adverse event
SAP	statistical analysis plan
SCORAD	<u>Scoring Atopic Dermatitis</u> System
SD	standard deviation
SE	standard error
SPT	skin-prick test
WHO	World Health Organization
UK	United Kingdom

1 Introduction

Peanut allergy is an increasingly prevalent cause of serious allergic reactions and is a recognized public health concern. Dietary avoidance of peanut in early life has been recommended in many countries. In the United Kingdom (UK), for example, infants identified as at risk are advised to avoid peanut for the first 3 years of life. However, there is evidence that the prevalence of peanut allergy is decreased in countries where children are fed peanut beginning at an early age. This raises the possibility that avoidance guidelines may promote the development of peanut allergy by preventing the induction of oral tolerance in infants exposed to high levels of environmental peanut. This trial proposes to compare the two approaches in a population of high-risk children. In addition, it will allow the mechanisms that underpin antigen-specific oral tolerance induction to be addressed.

2 Study Administrative Structure

This study is being conducted by the Immune Tolerance Network (ITN) under the sponsorship of the National Institute of Allergy and Infectious Diseases (NIAID) in accordance with applicable standard operating procedures. Clinical monitoring, pharmacovigilance, data management and statistical analyses are being performed under contract with Pharmaceutical Products Development, Inc. (PPDI), in collaboration with NIAID.

The Clinical, Data Management and Biostatistics departments at PPDI will work to ensure that the data collected and analyzed for this study are of the highest quality possible. This will be accomplished in part by having very thorough edit checks written, programmed, and updated as needed to guarantee high quality data. Edit checks will be reviewed by the statistician on an ongoing basis to evaluate whether any additional edit checks need to be added.

All analyses will be conducted using SAS[®] (SAS Institute, Cary, NC, Version 8 or later) software.

3 Study Objectives

3.1 Primary Objective

To assess whether oral administration of a peanut-containing snack can induce tolerance in children at high risk for peanut allergy.

3.2 Secondary Objectives

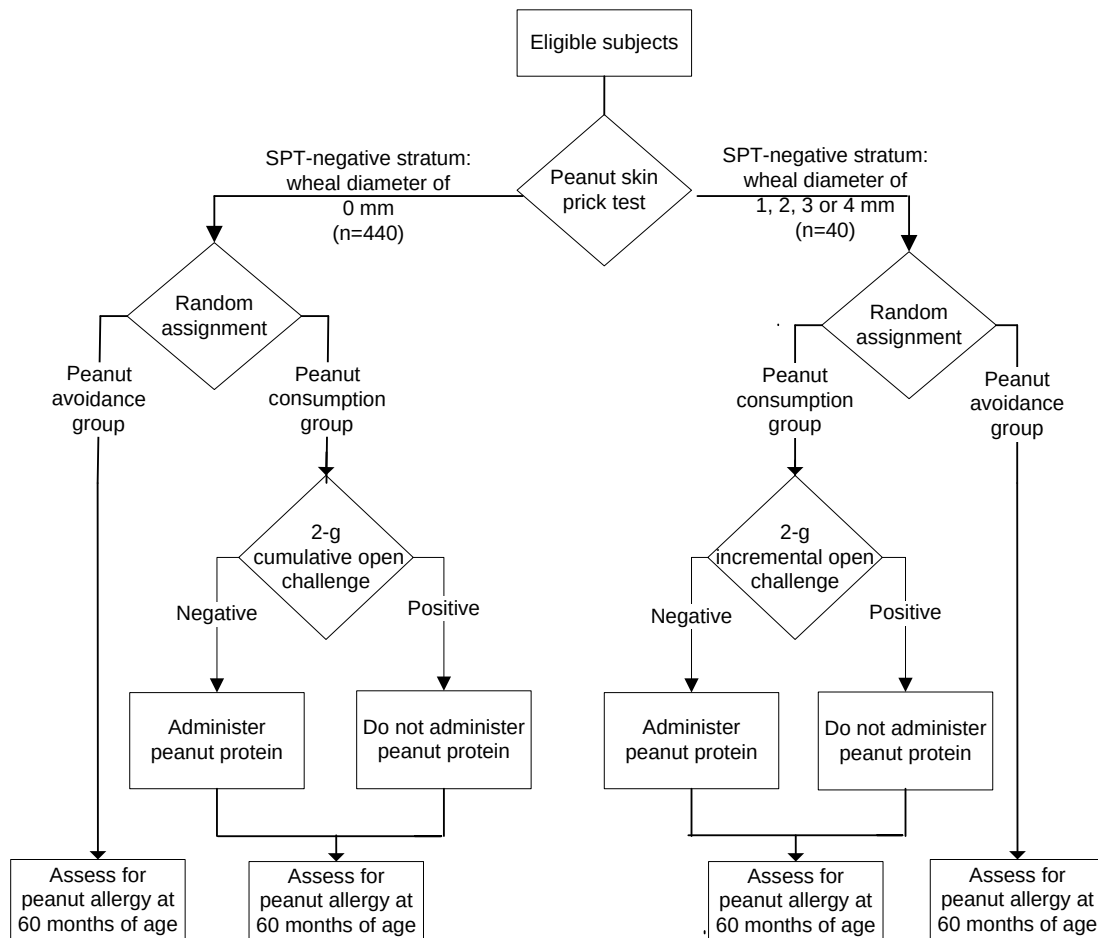
- To assess the effect of a peanut-containing snack on additional allergy outcomes.

- To assess the safety of administration of peanut protein in this population.
- To define the mechanisms through which the ingestion of peanut protein may induce tolerance to peanut.

4 Investigational Plan

4.1 Study Design

This is a randomized, controlled trial that will enroll children at high risk for peanut allergy as demonstrated by eczema, egg allergy, or both. As shown in Figure 2 in the protocol, which is shown below, participants will be stratified based on their skin prick test (SPT) results for peanut: those with a wheal diameter of 0 mm will be in the SPT-negative stratum and those with a wheal diameter of 1, 2, 3 or 4 mm will be in the SPT-positive stratum. Participants in each stratum will be randomly assigned to receive a peanut-containing snack or to avoid peanut. Those assigned to receive the peanut-containing snack will receive at least 2 g of peanut protein three times per week until they reach 60 months of age. The prevalence of peanut allergy at that time will be compared between the peanut consumption and peanut avoidance groups.



4.2 Study Endpoints

4.2.1 Primary Endpoint

The proportion of participants with peanut allergy at 60 months of age.

4.2.2 Secondary Endpoints

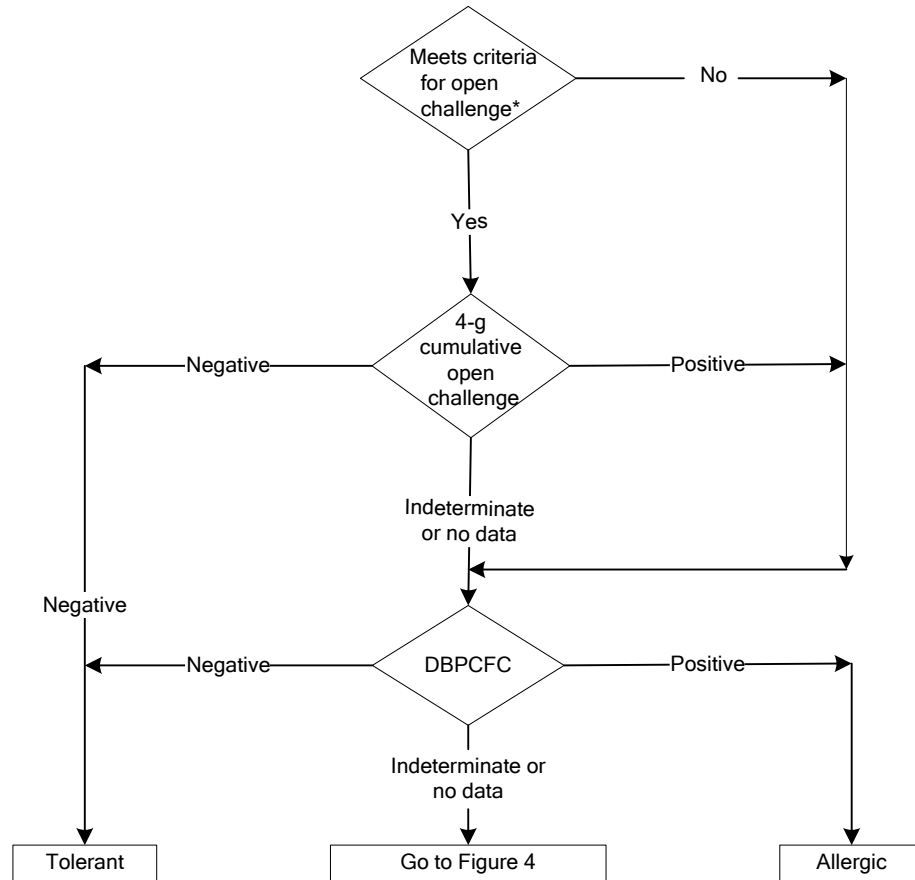
The secondary endpoints are:

1. At 30 and 60 months of age: the proportion of participants with allergic sensitization to selected ingested allergens and inhaled allergens, and with seasonal rhinoconjunctivitis, perennial rhinoconjunctivitis, and asthma.
2. At 60 months of age: the proportion of participants with type 1 immediate onset food allergy to selected ingested allergens.
3. Incidence of adverse events and laboratory abnormalities; nutritional evaluations.
4. Results of cellular and humoral assessments of immune response related to the development of allergy or tolerance to specific allergens.

4.3 Determination of Peanut Allergy

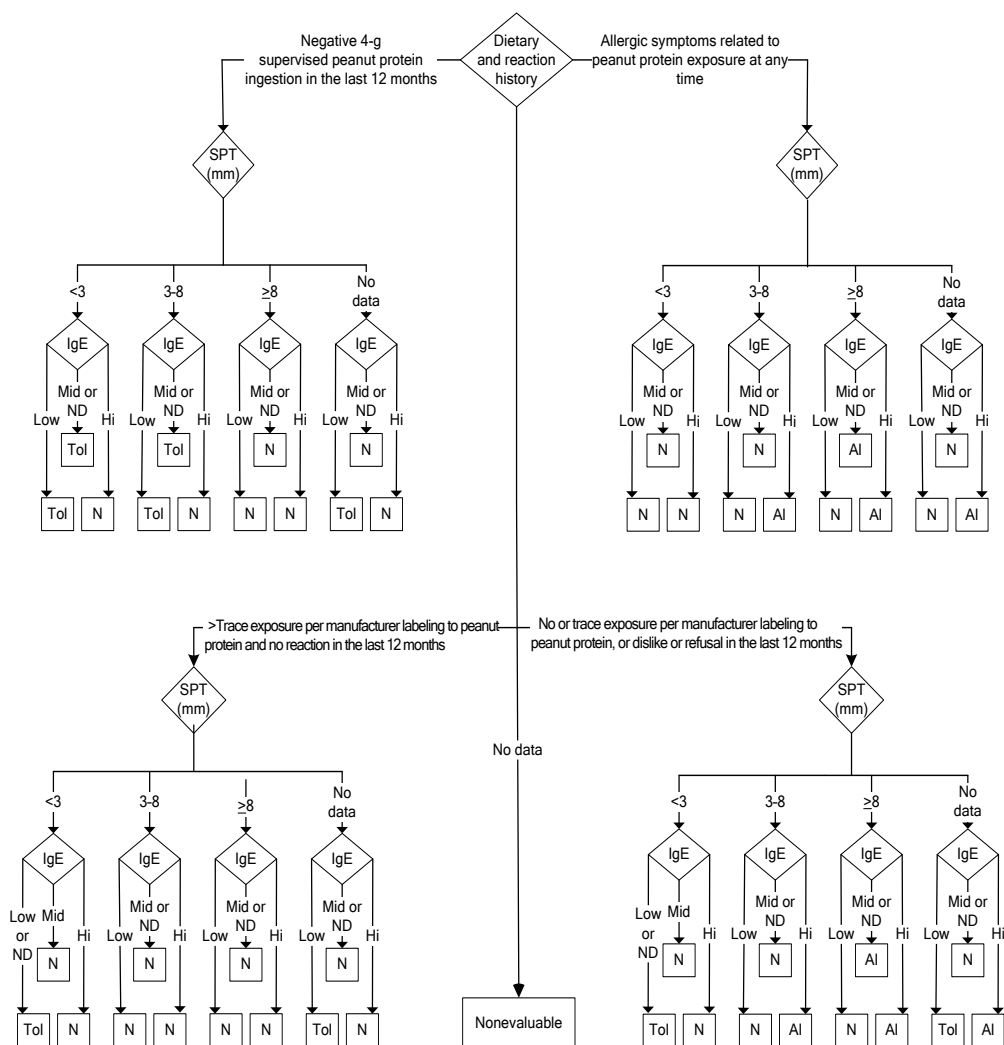
Peanut allergy is determined following the algorithm outlined in Figures 3 and 4 in the protocol, which are shown below. The first figure describes how a determination of peanut allergy is made based on peanut challenges. An interpretable outcome for either the double-blind placebo-controlled food challenge (DBPCFC) or the 4-g cumulative open challenge performed in clinic is sufficient for a determination of allergy status. If there is no such outcome the second figure illustrates how a determination can be made using dietary history, SPT wheal diameter, and IgE levels.

Determination of peanut allergy using challenges performed in the clinic



* Criteria for open challenge:
SPT wheal diameter ≤ 0 mm
Erythema no greater than the negative control at 30 and 60 months
No clinical diagnosis or suspicion of peanut, sesame, or tree-nut allergy

Determination of peanut allergy in the absence of peanut-challenge results using dietary and reaction history, SPT, and IgE



LEGEND

IgE Levels in kU/L
 Low: < 0.35
 Mid: ≥ 0.35 and < 15
 Hi: ≥ 15
 ND: No data

 Tol: tolerant
 AI: allergic
 N: nonevaluable

4.4 Participant Selection and Identification

In each stratum, individual assignments to either the peanut consumption or peanut avoidance group will be obtained by authorized site personnel by calling the PPDI Interactive Voice Response System (IVRS) once and entering their unique personal identification number. The IVRS will assign the study participant a randomization number based on the randomization schedule.

At enrollment, each participant will be assigned a unique participant identification number, to be used for the remainder of the study. The number will consist of the site number concatenated with the participant randomization number.

4.5 Strata Definitions for Statistical Analyses

Version 2.0 of the protocol (dated 17April2007) implemented a change in the definition of the strata due to new information being available regarding sensitivity to peanut. Prior to version 2.0, the strata were defined as follows

- SPT two-minus stratum: SPT values of 0, 1, and 2,
- SPT three-plus stratum: SPT values of 3 and 4.

With the approval of version 2.0, the strata were redefined as

- SPT-negative stratum: SPT value of 0,
- SPT-positive stratum: SPT values of 1, 2, 3, and 4.

The IVRS data was updated to re-stratify participants who were randomized before the implementation of the version 2.0 definitions so that all participants are stratified using the SPT-negative and positive definitions. This change ensured that the appropriate number of participants was enrolled in each stratum.

For all statistical analyses, the strata will be SPT-negative and SPT-positive. Participants will be stratified using the actual SPT wheal value as entered in IVRS.

For participants whose stratum was changed, the “Randomization” CRF at visit 0 will indicate that they were in stratum 1 (originally the SPT two-minus Stratum, now the SPT-negative stratum). This stratum value will be compared to the actual SPT wheal value to identify participants in stratum 1 with a wheal greater than 0 which will identify participants whose stratum was changed. Participants whose stratum assignment was changed are identified in **Listing 4.3.1**.

4.5 Procedures for Removing Participants from Study

4.5.1 Premature Termination of Trial Interventions

Trial intervention will be prematurely terminated for a participant if, in the judgment of the investigator, further participation in the trial would be deleterious to the participant’s health; or if an independent dietary assessment reveals that the study

intervention has led to body mass index (BMI) exceeding the 95th percentile for the participant's age (Table 2 of the protocol, shown below) or has led to failure to thrive.

UK National BMI percentile classification

Age (years)	Boys (95%) Obese	Girls (95%) Obese
2	19.10	18.84
2.5	18.77	18.56
3	18.51	18.42
3.5	18.27	18.35
4	18.08	18.32
4.5	17.97	18.31
5	17.95	18.35
5.5	17.99	18.46
6	18.10	18.65
10	20.42	21.52
10.5	20.79	21.94

4.5.2 Premature Termination from the Trial

Participants will be prematurely terminated from the trial for either of the following:

- withdrawal of consent, or
- failure to return.

Such participants will not be replaced.

5 General Statistical Considerations

Percentages are used throughout this analysis plan and in the tables, listings, and figures instead of proportions.

All hypothesis tests, unless specified otherwise, will be performed as two-sided using a Type I error rate of $\alpha=0.05$. P-values will be rounded to three decimal places; however, any p-values rounding to 0 or 1 (to the nearest 0.001) will be reported as "<0.001" or ">0.999," respectively.

Summaries of results will be done by stratum and peanut consumption group. All data will be displayed in the listings sorted by stratum, treatment group, participant and, where applicable, time point.

Continuous data will be summarized using n, mean, standard deviation (SD), median, minimum and maximum. Discrete data will be summarized using counts and percents. When a count is zero, the corresponding percent will be suppressed, to draw attention to the non-zero percents. Unless indicated otherwise, the denominator for each percent will be the number of participants with non-missing values in that treatment group within the sample of interest. If the percent pertains to a particular

visit, the denominator will be the number of participants with non-missing values at that visit unless indicated otherwise. A row denoted "Missing" will be included in count tabulations when missing values are encountered.

In summaries of categorical data, if categories are specified on the CRF (*e.g.*, discontinuation reason), or if categories are ordered intervals (*e.g.*, age groups), then all categories will be presented, even if no participants are found for any particular category. For other categorical data (*e.g.*, adverse events and medications), only categories with at least one participant will be presented.

If no data are available for a table or appendix, an empty page with the title will be produced with suitable text (*e.g.*, "There are no observations for this table/appendix.").

Means, least-squares (LS) means and medians will be rounded in presentations to 1 more decimal place than the recorded data. SDs and standard errors (SE) will be rounded to 2 more decimal places than the recorded data. Minimum and maximum values will be presented using the same number of decimal places as the recorded data.

Confidence intervals will be rounded using the same number of decimal places as the parameter estimate (*e.g.*, mean). Percents will be presented to 1 decimal place.

Summary tables will be accompanied by data appendices (listings) sorted by stratum, treatment, and participant number. All data available from the CRFs along with some derived variables will be listed. For relevant dates, the actual day relative to randomization will also be listed. Dates will be presented in the format of "DDMONYYYY."

5.1 Sample Size

For participants in the SPT-negative stratum, the null hypothesis states that there is no difference in the percentage of individuals with peanut allergy in the peanut consumption group as compared to the peanut avoidance group. We assume the true rate of peanut allergy in the peanut avoidance group is at least 15% and that treatment will reduce that rate to 4.5 % or less in the peanut consumption group. Assuming a 20% dropout rate, enrolling 220 participants in each group will provide 91% power to detect such differences between the groups using a two-tailed, chi-square test.

For participants in the SPT-positive stratum, current resources allow for 20 participants to be enrolled per group. Allowing for a 20% dropout rate, 16 evaluable participants allow for the half-width of the two-sided 95% confidence interval on the difference in percentages to be a minimum of 25% in the range of rates expected for the primary endpoint.

5.3 Analysis Samples

Data analysis and summarization will be done on the analysis samples defined below.

- All Enrolled: all randomly assigned participants.
- Intent-to-treat (ITT): all randomly assigned participants who are evaluable for peanut allergy at age 60 months.
- Safety: all participants who either receive any peanut protein-containing food or are in the peanut avoidance group.
- Per-protocol (PP): participants in compliance with the dietary regimen for their assigned group and evaluable for peanut allergy at age 60 months. Compliance is defined as the consumption of peanut protein in the first 24 months of life:
 - In the peanut consumption group, compliance is consumption of at least 3 g of peanut protein per week for at least 50% of the weeks enrolled and consumption of at least 2 g of peanut protein on at least one occasion in both the first and second years of life.
 - In the peanut avoidance group, compliance is consumption of less than 0.2 g of peanut protein on any one occasion and less than 0.5 g over a single week.

5.4 Definitions of Day 0 and Screening and Baseline Values

Day 0 for the participants randomized to the peanut consumption arm is defined as the date of the administration of 2 gram peanut challenge at visit 0. Day 0 for the participants randomized to peanut avoidance arm is defined as the date of randomization. The screening and baseline values are defined as the measurements from protocol defined visits -1 or 0, respectively.

5.5 Stopping Rules

5.5.1 Ongoing Review

The protocol chair, the NIAID medical monitor, the ITN clinical trial physician, and the NIAID Allergy and Asthma Data and Safety Monitoring Board (DSMB) will review safety data on an ongoing basis. The DSMB may stop enrollment or participation in the trial at any time if it concludes that there are significant safety concerns.

5.5.2 Review of Specific Adverse Events

5.5.2.1 Stopping Enrollment

Enrollment in the trial will be stopped pending review if any death occurs or if two participants are admitted to an intensive care unit for an adverse event related to study participation.

5.5.2.1 Stopping Enrollment and Administration of Peanut-containing Snack

Enrollment in the trial and further administration of the peanut protein-containing snack will be stopped pending review if either of the following occurs for the SPT-negative stratum:

- An analysis performed when 50 such participants in the peanut consumption group have been followed for 3 weeks demonstrates that the lower bound of the 95% confidence interval for the percentage of participants in the peanut consumption group with peanut allergy as determined in an unscheduled clinic visit is greater than 15%. This will occur if at least 14 of the first 50 participants have peanut allergy.
- An analysis performed when 50 such participants per group have been followed for 12 months demonstrates that the rate of serious adverse events is significantly greater at the 0.05 significance level in the peanut consumption group than in the peanut avoidance group.

Enrollment in the trial and further administration of peanut protein-containing snack to participants in the SPT-positive stratum will be stopped pending review if either of the following occurs:

- One of the first 5, 2 of the first 10, or 3 of the first 15 such participants randomly assigned to the peanut consumption group experiences life-threatening anaphylaxis during the first 3 weeks of administration of the peanut protein-containing snack.
- An analysis performed when 10 such participants in the peanut consumption group have been followed for 12 months demonstrates that 4 or more participants have experienced a serious adverse event.

Table 5.5.2.1.1 will present the number of deaths and the death rate for all randomized participants in the SPT-negative stratum at the time of the analysis. The table will also present the number of participants out of the first 50 in the peanut consumption group with peanut allergy and the rate of peanut allergy with the 95% exact confidence interval based on the binomial distribution.

Table 5.5.2.1.2 will present the number of deaths and the death rate for all randomized participants in the SPT-negative stratum at the time of the analysis. The table will also present the serious adverse event rate at 12 months post-randomization for the first 50 participants in each group in the SPT-negative stratum. A two-sided exact p-value will be presented comparing the rates between the groups. The treatment difference (peanut avoidance – peanut consumption) and two-sided 95% exact confidence interval, computed using the binomial distribution, will also be presented.

Table 5.5.2.1.3 will present the number of deaths and the death rate for all randomized participants in the SPT-positive stratum at the time of the analysis. The table will also present the number and rate of participants who experienced life-threatening anaphylaxis within 3 weeks post-randomization out of the first 5, 10, and 15 participants in the SPT-positive stratum randomized to peanut consumption who consumed peanut.

Table 5.5.2.1.4 will present the number of deaths and the death rate for all randomized participants in the SPT-positive stratum at the time of the analysis. The table will also present the serious adverse event rate at 12 months post-randomization for the first 10 participants in the SPT-positive stratum randomized to peanut consumption who consumed peanut.

Data related to whether or not an adverse event resulted in admittance to an intensive care unit are not currently captured in the clinical database. This information will be added to the CRF in the future. After the addition is made, the data will be included in the stopping rule analysis. Until the addition is made, these data will be included in the summary of the stopping rule analysis but not in the tables or listings.

6.1 Inclusion/Exclusion Criteria

Sections 4.1 and 4.2 of the protocol describe the inclusion and exclusion criteria participants must satisfy for entry and randomization. The CRFs contains data relating to whether each participant met all inclusion criteria and did not meet any of the exclusion criteria. These data will be shown in **Listing 6.1**. Participants will be listed separately by stratum.

6.2 Participant Disposition and Discontinuation

Table 6.2.1 will summarize participant disposition and discontinuation for all randomized participants in the SPT-negative stratum. It will summarize the number of participants randomized, completed, and discontinued. It will further summarize the number of participants in each analysis sample (ITT, Safety, and Per-Protocol). A participant who is discontinued from the study may still be followed for study endpoints. The table will summarize the primary reason for permanent discontinuation from study participation. It will also summarize the primary reason a participant is no longer followed and whether the participants who are no longer

followed were clinically obese or failing to thrive. Percentages will be calculated from the total number of participants in each treatment group.

Table 6.2.1 will summarize participant disposition and discontinuation for participants in the SPT-negative stratum who are not evaluable for peanut allergy at age 60 months.

Listing 6.2.1 will show participant disposition, analysis samples, and discontinuations/terminations for all randomized participants in the SPT-negative stratum.

Tables 6.2.3 and **6.2.4** will present participant disposition and discontinuation data for all randomized participants in the SPT-positive stratum and all participants in the SPT-positive stratum who are not evaluable for peanut allergy at age 60 months, respectively. **Listing 6.2.2** will present participant disposition and discontinuation data for participants in the SPT-positive stratum.

Listing 6.2.3 will present all protocol deviations separated by strata.

7 Demographics and other Baseline Characteristics

All demographics and baseline characteristics will be summarized by randomized treatment group and overall within each stratum for all enrolled participants. Summaries of continuous data will present n, mean, median, standard deviation, minimum and maximum. Any participants with missing data will be excluded from the corresponding summaries. Summaries of categorical data will present counts and percents. Percentages will be calculated from the total number of participants in each treatment group.

7.1 Demographics

Demographics of all participants are collected at visit -1. **Table 7.1.1** will summarize age, gender, and ethnicity for all randomized participants in the SPT-negative stratum. Age will be calculated using date of visit -1. In the summary of ethnicity, only the main ethnicity categories will be summarized; subcategories will only be listed. **Table 7.1.2** will present demographic characteristics for participants in the SPT-negative stratum who are not evaluable for peanut allergy at age 60 months.

Listing 7.1.1 will show demographic characteristics for all randomized participants in the SPT-negative stratum.

Tables 7.1.3 and **7.1.4** and **Listing 7.1.2** will present demographic data for the SPT-positive stratum.

7.2 Medical History

Table 7.2.1 will display the number and percent of all randomized participants in the SPT-negative stratum with clinically significant diseases including allergies, or current or past medical procedures other than the disease under study, by body system, at screening. **Listing 7.2.1** will list medical history for all randomized participants in the SPT-negative stratum.

Table 7.2.2 and **Listing 7.2.2** will present the same medical history information for the SPT-positive stratum.

7.3 Eczema Evaluation

The participant's eczema status, severity category, age of onset (months), and current Scoring Atopic Dermatitis System (SCORAD) data are collected at screening. In addition, SCORAD and the age at which eczema was resolved for the participants who entered the study with eczema are collected at post-screening visits. **Table 7.3.1** will display the number and percent for eczema status and severity category and, descriptive statistics for age of onset, current SCORAD, and age at which eczema was resolved, for all randomized participants in the SPT-negative stratum. **Listing 7.3.1** will show eczema evaluation data for all randomized participants in the SPT-negative stratum.

Table 7.3.2 and **Listing 7.3.2** will present eczema data for the participants in the SPT-positive stratum.

7.4 Family History

Family history collected at baseline includes participant's birth history, parents' smoking history, nursery/daycare history, pet exposure, feeding method, and allergy history of participant's relatives. Solid foods introduced and allergy history of the participant's relatives will only be listed. **Table 7.4.1** will display the descriptive statistics for all other family history data for all randomized participants in the SPT-negative stratum. **Listings 7.4.1** and **7.4.2** will show family history data for all randomized participants in the SPT-negative stratum.

Table 7.4.2 and **Listings 7.4.3** and **7.4.4** will summarize family history data for the SPT-positive stratum participants.

7.5 Participant's Allergy and Allergy Related Family History

Participant's food allergy history collected at baseline includes allergies to different types of food, age (allergy was) first noticed, and age when the allergy resolved or if ongoing. The age allergy was first noticed, and age when the allergy resolved will only be listed. **Table 7.5.1** will display the descriptive statistics for allergies to

different types of food for all randomized participants in the SPT-negative stratum. **Listings 7.5.1 and 7.5.2** will show the participant's allergy and allergy related family history data for all randomized participants in the SPT-negative stratum.

Table 7.5.2 and Listings 7.5.3 and 7.5.4 will summarize allergy history data for the SPT-positive stratum.

7.6 Maternal Peanut Protein Consumption History

Maternal peanut protein consumption history collected at baseline includes mother's weekly peanut protein consumption whilst pregnant and whilst breastfeeding.

Table 7.6.1 will display the descriptive statistics for all randomized participants in the SPT-negative stratum. **Listing 7.6.1** will show maternal peanut protein consumption history data for all randomized participants in the SPT-negative stratum.

Table 7.6.2 and Listing 7.6.2 will present maternal peanut protein consumption history for the SPT-positive stratum.

8 Prior and Concomitant Medications

Medications taken at entry or during the course of the study are recorded in the CRF. All medications will be classified by preferred name and drug class according to the World Health Organization (WHO) Drug Dictionary (version 2005, 2Q).

Any medication with a stop date prior to the date of randomization will be considered prior. Medication with a stop date after the date of randomization or ongoing at the date of randomization will be considered concomitant. Prior and concomitant drug usage will be summarized by the number and percentage of participants receiving each medication by preferred name and drug class in **Tables 8.1 and 8.2**, respectively, for participants in the Safety sample in the SPT-negative stratum. Multiple usage of the same medication within drug class will be counted once only. Percentages will be calculated from the total number of participants in each treatment group. All prior and concomitant medications will be listed in **Listing 8.1**.

Tables 8.3 and 8.4 and Listing 8.2 will summarize medications for participants in the SPT-positive stratum.

9 Analyses of Endpoints

All CIs and p-values will be reported based on 2-sided statistical tests. CIs will have confidence coefficients of 95%. The type I error rate will be 5%. No adjustments for multiplicity will be made.

Alternative analysis methods may be considered if significant deviations from analytic assumptions are suspected. The reasons for any changes to the planned analyses will be documented.

9.1 Analyses of Primary Endpoint

Tables summarizing the primary endpoint of the study will include the appropriate p-value and the treatment difference (peanut avoidance – peanut consumption) along with the appropriate 95% confidence interval. For the analysis of the SPT-negative stratum, SPT-positive stratum, and the analysis of the combined SPT-negative and positive strata, an exact p-value for testing the null hypothesis that the percentages are equal between the two groups will be presented. The 95% exact confidence intervals will be calculated using the binomial distribution.

The primary endpoint of the study is the percentage of participants in the ITT sample with peanut allergy at 60 months of age in the SPT-negative stratum. **Table 9.1.1** will display the percentage of participants with peanut allergy at 60 months and a 95% CI for peanut consumption and peanut avoidance groups. This analysis will be repeated for the per-protocol sample and summarized in **Table 9.1.2**.

Peanut allergy incidence in the safety and PP samples will be evaluated in the SPT-positive stratum. The table summarizing peanut allergy incidence in the safety sample will be included in section 10 of this analysis plan. **Table 9.1.3** will display percentage of participants in the SPT-positive stratum with peanut allergy at 60 months for the peanut consumption and peanut avoidance groups for the PP sample.

Listing 9.1.1 will include the peanut allergy status at 60 months for all participants in the SPT-negative stratum. **Listing 9.1.2** will list the results of all peanut challenges for all randomized participants in the SPT-negative stratum.

Listings 9.1.3 and **9.1.4** will present peanut allergy status at 60 months and the results of all peanut challenges, respectively, for all per protocol participants in the SPT-positive stratum.

Tables 9.1.4 and **9.1.5** will present the percentage of ITT and Safety sample participants, respectively, with peanut allergy at 60 months for the SPT-negative and SPT-positive strata combined. The tables will include a 95% exact CI for the peanut consumption and peanut avoidance groups along with an exact p-value testing whether the percentages are equal between the two groups. It is assumed that the relative distribution of the randomized study participants by strata reflects the distribution of the eligible screened study participants. If the recruitment of participants in the SPT-positive stratum is capped, weighting may be needed.

9.1.1 Sensitivity Analysis: Peanut Allergy Determined by Food Challenge Alone

As a sensitivity analysis, peanut allergy at 60 months will be determined using only the results of the DBPCFC or the 4-g cumulative open challenge. Participants with

indeterminate or no data will be excluded from the analysis. **Table 9.1.1.1** will present the results of this analysis for participants in the ITT sample in the SPT-negative stratum. **Table 9.1.1.2** will present the same analysis for the PP sample in the SPT-positive stratum.

9.1.2 Sensitivity Analysis: Age at Entry into Study

The effect of a participant's age at entry into the study on peanut allergy at 60 months will be examined. Age at entry will be included in a logistic regression model as a continuous covariate. Table 9.1.2.1 will present the results of this analysis for participants in the ITT sample in the SPT-negative stratum. A second logistic regression model will examine age at entry split into two groups: participants less than or equal to 6 months of age and participants greater than 6 months of age. **Table 9.1.2.2** will present the results of this analysis for participants in the ITT sample in the SPT-negative stratum. **Tables 9.1.2.3** and **9.1.2.4** will present similar analyses for participants in the SPT-positive stratum.

9.1.3 Sensitivity Analysis: Compliance with Regimen

An exploratory analysis will be considered based on available data to relate the extent of compliance with the treatment regimen to peanut allergy at 60 months.

9.2 Analyses of Secondary Endpoints

For the secondary endpoints the treatment difference (peanut avoidance – peanut consumption) and 95% confidence interval will only be presented for the composite rather than for each component of the secondary endpoint. For the SPT-negative stratum, the 95% confidence interval for the treatment difference will be calculated using the normal approximation to the binomial for discrete measures. For the SPT-positive stratum, the 95% exact confidence interval based on the binomial distribution will be presented for discrete measures. Percentages will be calculated from the total number of participants in each treatment group.

Analyses of the following secondary endpoints for the study are described in this section.

- At 30 and 60 months of age: the percentage of participants with allergic sensitization to selected ingested allergens and inhaled allergens, and with seasonal rhinoconjunctivitis, perennial rhinoconjunctivitis, and asthma.
- At 60 months of age: the percentage of participants with type 1 immediate onset food allergy to selected ingested allergens.
- Nutritional evaluations

The analysis of cellular and humoral assessments of immune response related to the development of allergy or tolerance to specific allergens will not be discussed in this

plan as PPDI is not performing the statistical analysis of mechanistic assay data for this trial.

The following safety related secondary endpoints will be described in section 10 of this plan.

- Incidence of adverse events at 60 months of age.
- Incidence of laboratory abnormalities at 60 months of age.

9.2.1 Participants with Allergic Sensitization

The wheal and flare measurements from the skin prick test for ingested allergens are recorded at screening and all post-screening visits. **Tables 9.2.1.1** and **9.2.1.2** will display the descriptive statistics for the wheal and flare, respectively, for all randomized participants in the SPT-negative stratum. **Listing 9.2.1.1** will show skin prick test data for all randomized participants in the SPT-negative stratum. **Tables 9.2.1.3** and **9.2.1.4** and **Listing 9.2.1.2** will present the skin prick data for the SPT-positive stratum. The treatment difference and 95% confidence interval will be presented for measurements taken at visits 30 and 60.

The tests for immunoglobulins and plasma allergens are performed at screening and at all post-screening visits. **Table 9.2.1.5** will display the descriptive statistics for all immunoglobulin test results for all ITT participants in the SPT-negative stratum. **Table 9.2.1.6** will display descriptive statistics for all plasma allergens for all ITT participants in the SPT-negative stratum. **Listing 9.2.1.3** will show immunoglobulin test data all randomized participants in the SPT-negative stratum. **Listing 9.2.1.4** will show plasma allergens test data all randomized participants in the SPT-negative stratum. For the SPT-positive stratum, the immunoglobulin and plasma allergies will be presented in **Tables 9.2.1.7** and **9.2.1.8** and **Listings 9.2.1.5** and **9.2.1.6**. The treatment difference and 95% confidence interval will be presented for measurements taken at visits 30 and 60.

Skin and nasal swab cultures are done at baseline and at all post-baseline visits. If the results are positive, organisms are recorded. **Tables 9.2.1.9** and **9.2.1.10** will display the descriptive statistics (counts and percents) for culture results for all ITT participants in the SPT-negative and SPT-positive strata, respectively. The treatment difference and 95% confidence interval will be presented for measurements taken at visits 30 and 60. Organisms and staphylococcus data will only be listed in **Listings 9.2.1.7** and **9.2.1.8** together with skin and nasal swab culture results for all randomized participants in the SPT-negative and SPT-positive strata, respectively.

A skin prick test for tree nut allergies is performed at visit 60. Both wheal and flare measurements are collected. **Table 9.2.1.11** and **Listing 9.2.1.9** will summarize this data for the SPT-negative stratum. **Table 9.2.1.12** and **Listing 9.2.1.10** will summarize this data for the SPT-positive stratum. The treatment difference and 95% confidence interval will be presented for measurements taken at visits 30 and 60.

An oral food challenge testing Sesame, Brazil nut, Hazel nut, Cashew, and Walnut is performed at visit 60 and positive and negative test results are recorded. **Table 9.2.1.13** will summarize the positive and negative test results for the SPT-negative stratum including the treatment difference and 95% confidence interval. **Listing 9.2.1.11** will summarize the test results for the SPT-negative stratum. **Table 9.2.1.14** and **Listing 9.2.1.12** will present the same data for the SPT-positive stratum.

IgE data for inhalant allergens including house dust mite, cat dander, dog dander, Timothy grass pollen, birch tree pollen, and Alternaria mold is collected at visits 30 and 60. **Tables 9.2.1.15** and **9.2.1.16** will summarize the IgE data for the SPT-negative and Positive strata, respectively, with supporting data provided in **Listings 9.2.1.13** (SPT-negative stratum) and **9.2.1.14** (SPT-positive Stratum). The treatment difference and 95% confidence interval will be presented for measurements taken at visits 30 and 60.

Each participant will undergo the 4 gram supervised peanut protein ingestion between months 48 and 60. The details of this ingestion and well as the percentage of participants experiencing an allergic reaction will be summarized in **Table 9.2.1.17** for the participants in the SPT-negative stratum. The treatment difference and 95% confidence interval will be presented for the percentage of participants experiencing a positive result. **Listing 9.2.1.15** will present the corresponding participant data related to this ingestion including the symptoms experienced. **Table 9.2.1.18** and **Listing 9.2.1.16** will present the same data for the SPT-positive stratum.

9.2.2 Participants with Seasonal and Perennial Rhinoconjunctivitis

Data regarding seasonal and perennial rhinoconjunctivitis and the symptoms experienced are captured at visits 30 and 60. The percentage of participants with seasonal and perennial rhinoconjunctivitis as well as the percentage of participants experiencing specific symptoms will be presented in **Table 9.2.2.1** and **Listing 9.2.2.1** for the SPT-negative stratum. **Table 9.2.2.2** and **Listing 9.2.2.2** will present the same data for the SPT-positive stratum. The treatment difference and 95% confidence interval will be presented for season and perennial rhinoconjunctivitis.

9.2.3 Participants with Asthma

Table 9.2.3.1 will summarize the percentage of participants with asthma at visit 30 and visit 60 as well as the symptoms experienced by the participants. The treatment difference and 95% confidence interval will be presented. **Listing 9.2.3.1** will list the asthma related data for all participants in the SPT-negative stratum.

Table 9.2.3.2 and **Listing 9.2.3.2** will summarize the asthma data for the SPT-positive stratum.

9.2.4 Percentage of Participants with Type 1 Immediate Onset Food Allergy to Selected Ingested Allergens

Food reaction history collected at baseline and at all post-baseline visits includes the responses to the questions whether the participant was observed eating 2 grams of peanut protein and whether there is a history of clinically significant food-induced immediate onset allergic reaction. **Table 9.2.4.1** will display the descriptive statistics for all responses for all ITT participants in the SPT-negative stratum. The treatment difference and 95% confidence interval will be presented for the percentages of participants with clinically significant food-induced immediate-onset allergic reaction. **Listing 9.2.4.1** will show food reaction history data for all randomized participants in the SPT-negative stratum. **Table 9.2.4.2** and **Listing 9.2.4.2** will present food reaction data for the SPT-positive stratum.

9.2.5 Nutritional Evaluations

The participant's dietary history collected at baseline and at all post-baseline visits includes the nutrients, energy, protein, total carbohydrate, total fat, and sodium, and sub-nutrients within these as well. Further, micronutrient intake that is lower or higher than UK dietary reference values are also collected. Micronutrient intake will only be listed. **Table 9.2.5.1** will display the descriptive statistics and the treatment difference and 95% confidence interval for nutrients for all randomized participants in the SPT-negative stratum. **Listing 9.2.5.1** will show dietary history data for all randomized participants in the SPT-negative stratum.

Participant and household peanut protein consumption collected at baseline and at all post-baseline visits include peanut protein consumption for the participant, participant's mother, and all household members except the mother and the participant, for the previous week, and the total number of household members except the mother and the participant. Total peanut exposure will be summarized as well. Total peanut exposure is defined as the sum of the participant's mother's peanut consumption and peanut consumption for all household members other than the participant and the participant's mother. **Table 9.2.5.2** will display the descriptive statistics and the treatment difference and 95% confidence interval for all ITT participants in the SPT-negative stratum. **Listing 9.2.5.2** will show participant and household peanut protein consumption for all randomized participants in the SPT-negative stratum.

Table 9.2.5.3 and **Listing 9.2.5.3** and **Table 9.2.5.4** and **Listing 9.2.5.4** will present the participant's dietary history and participant and household peanut protein consumption, respectively, for participants in the SPT-positive stratum.

9.3 Analyses of Risk Associated with Peanut Allergy

Additional analyses of the risk associated with peanut allergy in the treatment groups will be performed using multiple logistic regression to identify possible associations of risk with baseline participant characteristics and selected clinical and dietary measures. These analyses will be performed on the incidence of peanut allergy at ages 30 months and 60 months. **Tables 9.3.1** and **9.3.2** will present results for the SPT-negative stratum for 30 and 60 months, respectively. The coefficients, p-values for testing the statistical significance of the coefficients, odds ratios, and 95% confidence intervals for the odds ratios will be presented. In addition to treatment group, the following explanatory variables will be considered

- age at enrollment
- sex
- ethnicity
- whether or not the participant was breastfed
- age stopped breast feeding
- gestation at birth
- mother has asthma
- father has asthma
- father has allergic rhinoconjunctivitis
- dog in home
- household member smokes
- severe eczema onset before 6 months of age

Testing for the strength of association with key risk variables will be done for one risk variable at a time. A multiple logistic regression model will also be fitted; backwards selection will be used to identify explanatory variables to be included in the model from those listed above.

Tables 9.3.3 and **9.3.4** will present results for the combined SPT-negative and SPT-positive stratum.

9.4 Analyses of Risk Associated with Secondary Endpoints

Additional analyses of the risk associated with the select secondary endpoints in the treatment groups will be performed using regression models to identify possible associations of risk with SCORAD measured at visit -1, environmental peanut exposure at visit 0, and positive skin and nasal swab cultures for staphylococcus at visit 0 in addition to treatment group. These analyses will be performed on the following secondary endpoints at 60 months of age: SPT wheal and flare for peanut, peanut specific IgE, asthma, and seasonal and perennial rhinoconjunctivitis. **Tables 9.4.1-9.4.4** will present results for the SPT-negative stratum and **Tables 9.4.5-9.4.8** will present results for the SPT-positive stratum for each of the above secondary endpoints.

10 Safety Analyses

This section describes the planned analysis for the safety related primary and secondary endpoints as well as adverse events, hematology, serum chemistry, fasting serum lipids, physical examinations, and vital signs. All safety analyses will be based on the Safety sample.

10.1 Safety Related Primary Endpoints

Peanut allergy incidence in the safety sample will be evaluated in the SPT-positive stratum. **Table 10.1** will display percentage of participants in the SPT-positive stratum with peanut allergy at 60 months for the peanut consumption and peanut avoidance groups for the safety sample. This table will further show the difference in percentages (peanut avoidance group - peanut consumption group) and a 95% exact confidence interval for the difference computed using the binomial distribution.

10.2 Safety Related Secondary Endpoints

10.2.1 Adverse Events Through 60 Months of Age

Table 10.2.1.1 will present the prevalence of adverse events at 60 months of age for participants in the SPT-negative stratum. The treatment difference (peanut avoidance – peanut consumption) and 95% confidence interval calculated using the normal approximation to the binomial will be presented in this table.

Table 10.2.1.2 will present the prevalence of adverse events for the SPT-positive stratum. The treatment difference (peanut avoidance – peanut consumption) and 95% exact confidence interval calculated using the binomial distribution will be presented.

10.2.2 Laboratory Abnormalities at 60 Months of Age

Table 10.2.2.1 will summarize laboratory abnormalities at 60 months of age for participants in the SPT-negative stratum. The treatment difference (peanut avoidance – peanut consumption) and 95% confidence interval calculated using the normal approximation to the binomial will be presented in this table.

Table 10.2.2.2 will present the incidence of laboratory abnormalities for the SPT-positive stratum along with the treatment difference (peanut avoidance – peanut consumption) and 95% exact confidence interval based on the binomial distribution.

10.3 Adverse Events

Adverse events (AE) will be collected from the time the participant provides consent until 30 days after the participant completes study treatment. An AE will be followed

until it resolves or until 30 days after the participant terminates from the study, whichever comes first.

AEs will be coded using the Medical Dictionary for Regulatory Activities[®] (MedDRA) Version 9.1. Severity of AEs will be graded according to the criteria set forth in the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 3.0.

AE summary tables will include counts of participants. If a participant experiences more than one episode of a particular AE, the participant will be counted only once for that event. If a participant has more than one AE that codes to the same preferred term, the participant will be counted only once for that preferred term. Similarly, if a participant has more than one AE within a body system category, the participant will be counted only once in that body system category. In AE summaries, body systems will be arranged alphabetically, and preferred terms within each body system will be arranged by descending total frequency across the treatment groups. Percents of participants experiencing AEs in each body system and preferred term will be presented.

For participants in the SPT-negative and positive strata, all AEs by body system and preferred term are summarized in section 10.2.1 of this plan. **Table 10.3.1** will summarize all AEs by body system and preferred term. **Table 10.3.2** will summarize all AEs by severity. In the summary, if a participant experiences more than one AE within a preferred term or system organ class, only the most extreme severity will be presented at each summary level. If the severity of an AE is missing, the severity will be “Severe” in the summary, and will be missing in the listing. **Table 10.3.3** will summarize AEs by relationship to study participation by body system. If a participant experiences more than one AE within a preferred term or system organ class, the AE most closely related to study participation will be presented at each summary level. If the relationship is missing, the relationship in the summary table will be presented as “Probable” and the relationship in the listing will be missing. **Table 10.3.4** will summarize serious adverse events (SAE) and **Table 10.3.5** will summarize AEs leading to study intervention discontinuation.

All AEs will be presented by system organ class and preferred term ordered by participant in **Listing 10.3.1** for participants in the SPT-negative stratum. The listing will include the start and stop dates of AEs. Any AEs unresolved at the time of study completion or early termination will be noted as ongoing.

Tables 10.3.6-10.3.10 and **Listing 10.3.2** will summarize adverse events for the SPT-positive stratum in a manner similar to those for the SPT-negative stratum.

10.4 Deaths

Listing 10.4.1 will list all deaths for participants in the SPT-negative stratum occurring during the study, including the date, study day, cause of death, whether an

autopsy was performed, and the relationship to study intervention. **Listing 10.4.2** will list deaths for the SPT-positive stratum.

10.5 Laboratory Evaluations

Hematology and serum chemistry tests are performed at screening and visit 60 and fasting serum lipids are collected at visit 60. Laboratory variables will be summarized using descriptive statistics for each visit. Hematology data will be summarized in **Table 10.5.1**, and presented in **Listing 10.5.1** for the SPT-negative stratum, and serum chemistry data will be summarized in **Table 10.5.2**, and presented in **Listing 10.5.2** for the SPT-negative stratum. **Table 10.5.3** will summarize the fasting serum lipids and **Listing 10.5.3** will present the fasting serum lipid data for the SPT-negative stratum. **Figures 10.5.1** and **10.5.2** will display participant line graphs for each hematology and serum chemistry test, respectively, over time for the participants in the SPT-negative stratum. Separate figure panels will be presented side-by-side for each treatment group.

Tables 10.5.4, 10.5.5 and 10.5.6, Listings 10.5.4, 10.5.5, and 10.5.6, and Figures 10.5.3 and 10.5.4 will present the hematology and serum chemistry data for the SPT-positive stratum.

10.6 Physical Examinations and Vital Signs

Physical examinations are performed at screening, baseline, and at all post-baseline visits. At the screening visit, findings are recorded as “Normal,” “Abnormal,” or “Not Done.” At all other visits including baseline, findings are recorded as “No Change,” “Improved,” “Worsened,” or “Not Done” as determined by the investigator compared to the previous visit.

Table 10.6.1 will summarize the physical examination at screening for the SPT-negative stratum. This table will display the number and percent of participants in the Safety sample with normal or abnormal body systems, or number and percent of participants with response “Not Done,” if the physical examination is not performed for a given body system. Physical examinations at other visits will only be listed.

Systolic blood pressure, diastolic blood pressure, SaO₂, pulse, respiration, body mass index, BMI percentile, temperature, length, weight, waist circumference, tricep skin fold thickness, subscapula skin fold thickness, and expected weight for height are collected during the physical examination. Descriptive statistics of these vital signs will be displayed in **Table 10.6.2** for participants in the safety sample in the SPT-negative stratum for all visits.

Listing 10.6.1 will list physical examination data, and **Listing 10.6.2** will list vital signs for all randomized participants in the SPT-negative stratum.

Figure 10.6.1 will present participant line graphs for participants in the SPT-negative stratum. Each parameter will be graphed over time with each treatment group presented in separate figure panels displayed side-by-side.

Tables 10.6.3 and 10.6.4, Listings 10.6.3 and 10.6.4, and Figure 10.6.2 will present the physical examination data and vital signs for the SPT-positive stratum.

11 Interim Analysis

Per protocol version 2.0, there are not any planned interim analyses for this study.

The protocol chair, the NIAID medical monitor, the ITN clinical trial physician, and the NIAID Allergy and Asthma Data and Safety Monitoring Board (DSMB) will review safety data on an ongoing basis. The DSMB may stop enrollment or participation in the trial at any time if it concludes that there are significant safety concerns. Stopping rules are described in Section 3.6 of the protocol and Section 5.5 of this statistical analysis plan (SAP).

12 Amendments to the Planned Analyses

Any SAP revisions made after protocol approval but before database lock will be described and justified in this section.

Table of Contents: Tables, Listing, and Figures

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STATISTICAL ANALYSIS PLAN
04 September 2014

Induction of Tolerance through Early Introduction of Peanut in High-Risk Children

PROTOCOL NUMBER ITN032AD

SPONSOR

This clinical study is supported and conducted by the Immune Tolerance Network, which is sponsored by the National Institute of Allergy and Infectious Diseases.

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DOCUMENT VERSION CONTROL

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3.0	04 September 2014	Updated from Version 2.2 to remove mechanistic analyses from data not collected in eCRFs. These analyses will be performed by BDR/BIG and detailed in the MSAP.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
BMI	Body Mass Index
BUN	Blood Urine Nitrogen
CI	Confidence Interval
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DBPCFC	Double-blind placebo-controlled food challenge
DSMB	Data Safety Monitoring Board
ITN	Immune Tolerance Network
IRB	Institutional Review Board
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities®
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Diseases
PP	Per protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCORAD	<u>Scoring Atopic Dermatitis</u> System
SD	Standard Deviation
SE	Standard Error
SGPT	Serum Glutamic Oxaloacetic Transaminase
SI	International System of Units
SOC	System Organ Class
SPT	Skin-Prick Test
TADA	Tolerance Assay and Data Analysis
UK	United Kingdom
WHO	World Health Organization

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1. PROTOCOL SYNOPSIS

Study Design	This is a randomized controlled trial in which children at high risk for peanut allergy, as demonstrated by eczema, egg allergy, or both, are enrolled. Participants are stratified based on skin prick test (SPT) results for peanut into those with a wheal diameter of 0 mm (SPT-negative stratum), and those with a wheal diameter of 1, 2, 3, or 4 mm (SPT-positive). Participants in each stratum are randomly assigned to receive a peanut-containing snack or to avoid peanut. The group assigned to receive a peanut-containing snack will eat at least 2 g of peanut protein three times per week until 60 months of age. The prevalence of peanut allergy at that time is compared between the peanut consumption and the avoidance groups.
Study Duration	84 months
Primary Endpoint	The proportion of participants with peanut allergy at 60 months of age.
Secondary Endpoints	- At 30 and 60 months of age: the proportion of participants with allergic sensitization to selected ingested and inhaled allergens, and with seasonal rhinoconjunctivitis, perennial rhinoconjunctivitis, and asthma. - At 60 months of age: the proportion of participants with type-1 immediate onset food allergy to selected ingested allergens - Incidence of adverse events and laboratory abnormalities; nutritional evaluations - Results of cellular and humoral assessments of immune response related to the development of allergy or tolerance to specific allergens.
Inclusion Criteria	- Children ≥ 4 to <11 months old who have had solids successfully introduced into their diet. - Egg allergy, severe eczema, or both. - Informed consent obtained from parent or guardian.
Exclusion Criteria	- Clinically significant chronic illness, except for eczema or recurrent wheeze. - Positive skin prick test for peanut allergen with a wheal diameter >4 mm in the presence of a negative saline control. - Previous or current consumption of peanut protein that exceeds 0.2 g of peanut protein on at least one occasion or 0.5 g over a single week - Investigator-suspected allergy to peanut protein. - Investigator-suspected allergy to peanut protein in care provider or current household member. - Diagnosis of persistent asthma. - ALT (SGPT) or bilirubin >2 times the upper limit of age-related normal value. - BUN or creatinine >1.25 times the upper limit of age-related normal value. - Platelet count $<100,000/\text{mL}$, hemoglobin <9 g/dL, or investigator-suspected immunocompromise. - Unwillingness or inability to comply with study requirements and procedures.
Study Intervention	Participants assigned to the peanut consumption group will be fed at least 2 g of peanut protein 3 times per week. The preferred peanut source will be Bamba, although peanut butter may be substituted. Participants assigned to the peanut avoidance group will avoid exposure to peanut protein during study participation.

2. INTRODUCTION

This statistical analysis plan mainly includes analyses related to the clinical endpoints. However, certain mechanistic analyses will be specified in this SAP. Additional mechanistic analyses may also be performed at the ITN, and a separate analysis plan will be created to detail those planned analyses. Relevant clinical data from the study will be submitted to the ITN Biomarker and Discovery Research (BDR) to augment mechanistic analyses. In addition, relevant mechanistic data from the study will be submitted to Rho to augment clinical analyses.

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following analyses and reporting conventions will be used:

- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form n (%). Percentages will be rounded to 1 decimal place.
- Numeric variables will be summarized using n, mean, standard deviation (SD), median, min, max. The min/max will be reported at same level of significance as original data. The mean and median will be reported at 1 more significant digit than the precision of the data and SD will be reported at 2 more significant digits than the precision of the data. Descriptive statistics will be displayed in the order: n, mean, SD, median, min, max
- The median will be reported as the average of the two middle numbers if the dataset contains even numbers.
- Test statistics including *t* and *z* test statistics will be reported to two decimal places.
- *P*-values will be reported to 3 decimal places if greater than or equal to 0.001. If less than 0.001 then report '<0.001'.

If departures from these general conventions are present in the specific evaluations section of this SAP then those conventions will take precedence over these general conventions.

4. ANALYSIS SAMPLES

- All Enrolled (E): All randomly assigned participants
- Intent-to-treat (ITT): all randomly assigned participants who are evaluable for peanut allergy at age 60 months
- As Treated (AS): All evaluable subjects, analyzed according to peanut consumption, regardless of their randomized assignment.
- Safety (SS): all participants who either receive any peanut protein-containing food or are in the peanut avoidance group
- Per-protocol (PP): participants in compliance with the dietary regimen for their assigned group and evaluable for peanut allergy at age 60 months. Compliance is defined as the consumption of peanut protein in the first 24 months of life:
 1. In the peanut consumption group, compliance is consumption of at least 3 g of peanut protein per week for at least 50% of the weeks recorded and consumption of at least 2 g of peanut protein on at least one occasion in both the first and second years of life
 2. In the peanut avoidance group, compliance is consumption of less than 0.2 g of peanut protein on any occasion and less than 0.5 g over a single week.
 3. At least 50% of compliance information must be available for the required visits in order to be included in the PP sample.

5. STUDY SUBJECTS

Study Strata

Version 2.0 of the protocol (dated 17 April 2007) implemented a change in the definition of the strata due to new information being available regarding sensitivity to peanut. Prior to version 2.0, the strata were defined as follows

- SPT two-minus stratum: SPT values of 0, 1, and 2,
- SPT three-plus stratum: SPT values of 3 and 4.

With the approval of version 2.0, the strata were redefined as

- SPT-negative stratum: SPT value of 0,
- SPT-positive stratum: SPT values of 1, 2, 3, and 4.

The Interactive Voice Response System (IVRS) data was updated to re-stratify participants who were randomized before the implementation of the version 2.0 definitions so that all participants are stratified using the SPT-negative and positive definitions. This change ensured that the appropriate number of participants was enrolled in each stratum.

For all statistical analyses, the strata will be SPT-negative and SPT-positive. Participants will be stratified using the actual SPT wheal value as entered in IVRS. Enrollment is now closed and the SPT-negative stratum has been fixed at 542 randomized (272 Peanut Consumption, 270 Peanut Avoidance), and the SPT-positive stratum at 98 randomized (47 Peanut Consumption, 51 Peanut Avoidance), meeting the target enrollment of 640 total participants.

For participants whose stratum was changed, the “Randomization” CRF at visit 0 will indicate that they were in stratum 1 (originally the SPT two-minus Stratum, now the SPT-negative stratum). This stratum value will be compared to the actual SPT wheal value to identify participants in stratum 1 with a wheal greater than 0 which will identify participants whose stratum was changed. Participants whose stratum assignment was changed are identified in a listing.

Disposition of Subjects

The disposition and discontinuation for all randomized participants will be summarized. A participant who is discontinued from the study may still be followed for study endpoints. The primary reason for permanent discontinuation from study participation, the reasons for discontinuing study treatment, and whether the participants who are no longer followed were obese or failing to thrive will also be presented. Percentages will be calculated from the total number of participants in each treatment group within and across strata.

The disposition and discontinuation for participants in each study stratum who are not evaluable for peanut allergy at age 60 months will also be summarized.

Demographic and other Baseline Characteristics

- Summary descriptive statistics for baseline and demographic characteristics will be reported by stratum, randomized treatment group, and overall within each stratum for all randomized participants. Continuous data (e.g. age) will be summarized descriptively by mean, standard deviation, median, minimum, and maximum; while categorical data (e.g., sex and ethnicity) will be presented as frequencies and percentages.
- Demographic Data:
 - Age
 - Gender
 - Race/Ethnicity
- Baseline Characteristics:
 - Medical History: clinically significant diseases including allergies, current or past medical procedures other than the disease under study
 - By body system
 - Family History: Birth history, parent's smoking history, nursery/daycare history, pet exposure, feeding method, allergy history of participant's relatives
 - Solid foods introduced and allergy history of participant's relatives will be listed
 - Allergy and Allergy Related Family History: age allergy was first noticed, age allergy resolved or ongoing, allergies to different types of food
 - Age allergy was first noticed and age when allergy resolved will be listed
 - Eczema Evaluation: Severity, age of onset, scoring atopic dermatitis system (SCORAD) score, age eczema was resolved, eczema medication usage.
 - Maternal Peanut Protein Consumption History: mother's weekly peanut protein consumption while pregnant and breast feeding

6. STUDY OPERATIONS

Protocol Deviations

Protocol deviations will be listed by strata with information such as type of violation, severity of the deviation (major or non-major), date of occurrence, and the reason for the deviation. Protocol deviations will be summarized in tabular format by type of violation.

Study Drug Administration

6.1.1 Treatment Compliance

An exploratory analysis will be considered based on available data to relate the extent of compliance with the treatment regimen to peanut allergy at 60 months. A multivariate logistic regression model will be used to explore how the following variables and their interaction relate to peanut allergy at 60 months: peanut exposure as measured by the peanut frequency questionnaire (PFQ), witnessed peanut consumption, peanut protein concentration in dust collected from the participant's bed, peanut specific IgG, IgG4, and IgA.

Since the peanut protein concentration in dust collected from the participant's bed will likely be influenced by household peanut consumption, the PFQ data from all household members will also be considered when assessing treatment compliance. For example, the information provided on the questionnaires will be converted to grams of peanut protein. A regression model will be constructed whereby the PFQ data from the household and the participant is used to predict the peanut protein concentration in dust. Participants with high residuals (i.e. cases where an individual's data deviates from the model's predictions) will be identified as potential non-compliers, and these subgroups will be investigated within the multivariate logistic regression model. This statistical methodology will also be implemented using the other variables related to compliance (i.e. IgG, IgG4, and IgA).

Assessment Time Windows

Day 0 for the participants randomized to the peanut consumption arm is defined as the date of the administration of 2 gram peanut challenge at visit 0. Day 0 for the participants randomized to peanut avoidance arm is defined as the date of randomization. The screening and baseline values are defined as the measurements from protocol defined visits -1 or 0, respectively.

Visits described in the schedule of events should occur as follows:

- Visit 0: No more than 21 days following visit -1 (screening).
- Visits 12 and 30: Within ± 3 months of the planned visit date.
- Dietary consultations:

- o Between visits 0 and 12: ± 3 days.
- o Between visits 12 and 30: ± 7 days.
- o Between visits 30 and 60: ± 14 days.
- Visit 60: within ± 6 months of the planned visit date.

Unscheduled visits may also occur throughout the study.

7. ENDPOINT EVALUATION

Primary Endpoint

The primary efficacy endpoint is the proportion of participants with peanut allergy at 60 months of age.

7.1.1 Computation of the Primary Endpoint

Peanut allergy is determined following the algorithm outlined in Figures 3 and 4 from the protocol, which are shown below. The first figure describes how a determination of peanut allergy is made based on peanut challenges. An interpretable outcome for either the double-blind placebo-controlled food challenge (DBPCFC) or the 5-g cumulative open challenge performed in clinic is sufficient for a determination of allergy status. If there is no such outcome the second figure illustrates how a determination can be made using dietary history, SPT wheal diameter, and IgE levels.

Consider the following examples for a participant at age 5:

- A participant undergoes the DBPCFC and exhibits one or more of the allergic signs listed in Table 1. This participant would be counted as allergic.
- A participant undergoes the 5-g cumulative open challenge, which is positive (per criteria in Table 1) or indeterminate. This participant will then be invited for a DBPCFC (per Figure 3).
- A participant undergoes the 5-g cumulative open challenge and does not exhibit any of the allergic signs listed in Table 1. This participant would be counted as tolerant.
- A participant is not available for challenge (“no data”). For such participants, dietary and reaction history shall be reviewed (Figure 4). Some possible scenarios follow:
 - Dietary history indicates that a participant has exhibited allergic symptoms related to peanut protein exposure. This result directs the assessment to the upper right quadrant of Figure 4. The participant’s SPT = 5 mm, and IgE = 17 kU/L. This leads us to a box labeled “A1”; that is, the participant will be counted as allergic.
 - Dietary history indicates that a participant has had more than trace exposure to peanut protein in the last 12 months and has exhibited no reaction. This result directs the assessment to the lower left quadrant of Figure 4. As in the above scenario, this participant’s SPT = 5 mm and IgE = 17 kU/L. This participant will be considered nonevaluable because the high IgE, which is strongly suggestive of allergy, contradicts the history, suggesting tolerance.
 - Dietary history indicates that during the last 12 months a participant has had only trace exposure to peanut protein or has persistently refused or exhibited dislike of peanut. This result directs the assessment to the lower right quadrant of Figure 4. There are no data for SPT, but the

participant's IgE = 0.2 kU/L. This participant will be counted as tolerant.

- o Dietary history for a participant is not available. This participant will be considered nonevaluable.

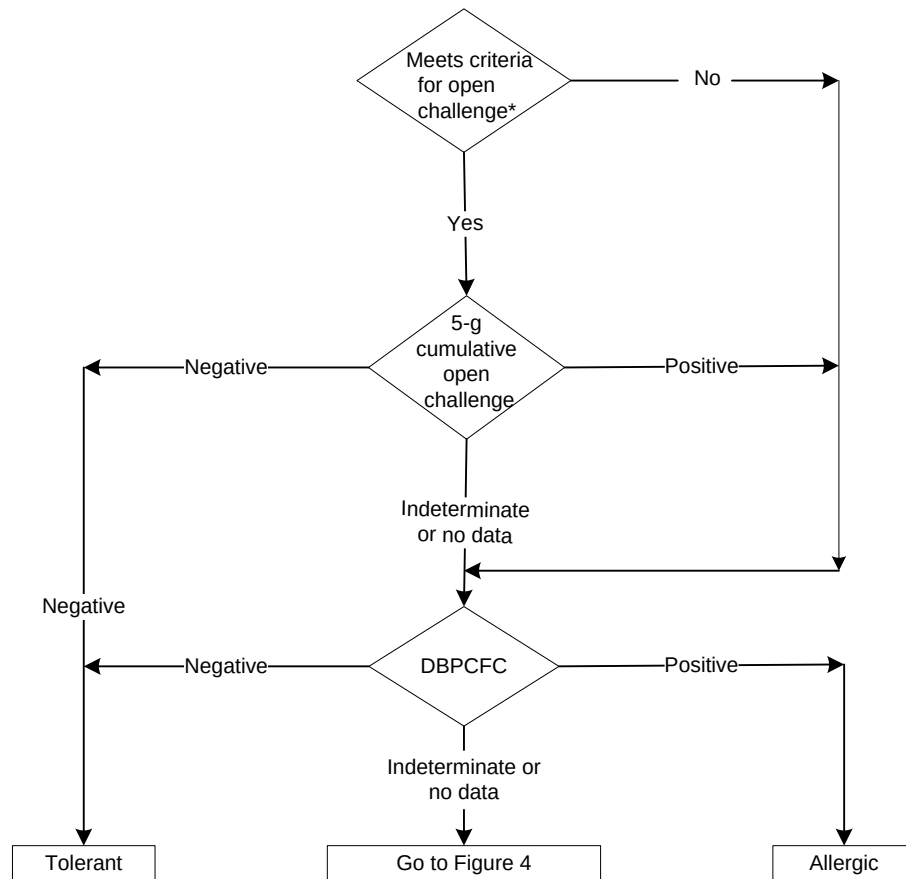
Table 1: Criteria for Determining the Outcome of Food Challenge

Outcome of the challenge will be determined by evaluating the participant using the criteria in Table 1.

- A positive food challenge will be defined by the presence of either of the following:
 - o One or more major criteria.
 - o Two or more minor criteria.
- An indeterminate food challenge will be defined by the presence of one minor criterion.
- A negative food challenge will be defined by the absence of major or minor criteria.
- All symptoms should be of new onset and not due to ongoing disease. Symptoms must occur no later than 2 hours after the last dose.

Major Criteria
Confluent erythematous pruritic rash Respiratory signs (at least one of the following): Wheezing Inability to speak Stridor Dysphonia Aphonia ≥ 3 Urticarial lesions ≥ 1 Site of angioedema Hypotension for age not associated with vasovagal episode Evidence of severe abdominal pain (such as abnormal stillness or doubling over) that persists for ≥ 3 minutes
Minor Criteria
Vomiting Diarrhea Persistent rubbing of nose or eyes that lasts for ≥ 3 minutes Persistent rhinorrhea that lasts for ≥ 3 minutes Persistent scratching that lasts for ≥ 3 minutes

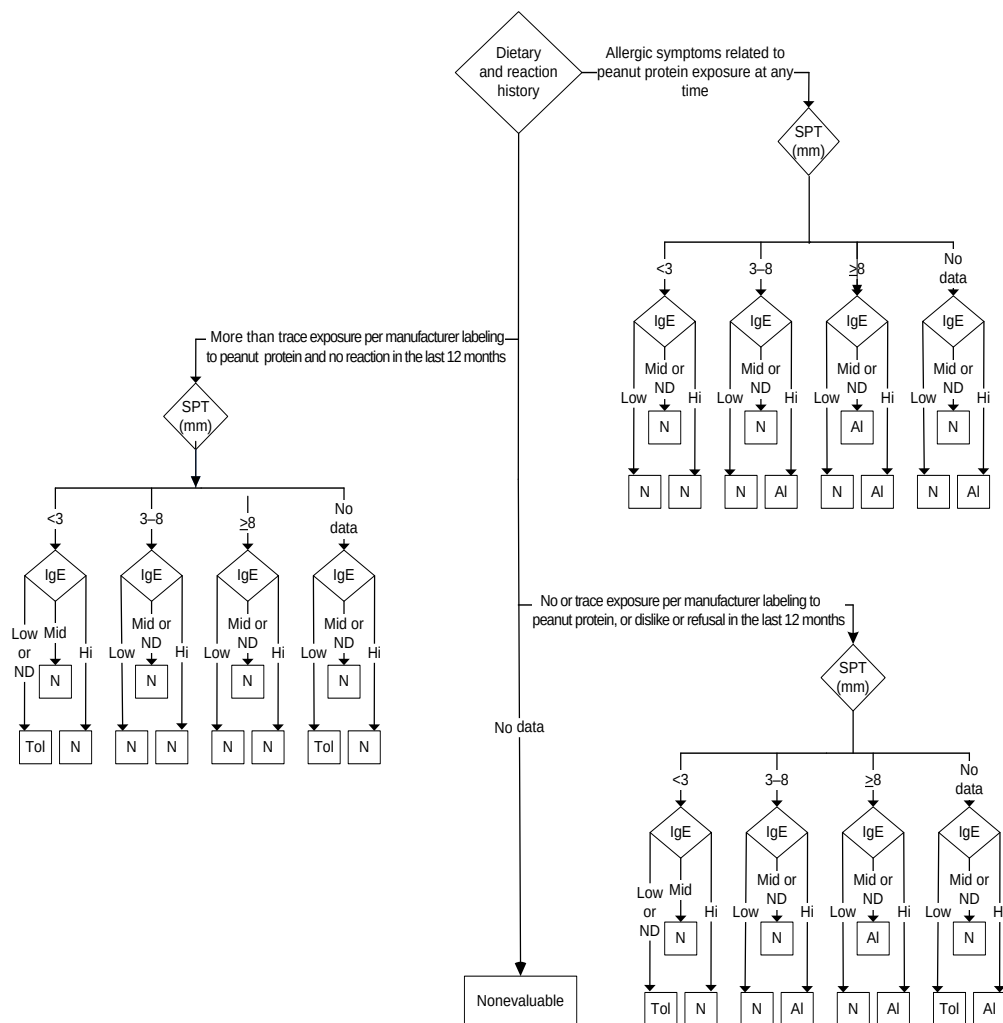
Figure 3: Determination of peanut allergy using open challenge or DBPCFC



*** Criteria for open challenge:**

- SPT wheal to peanut diameter = 0mm at month 30 and month 60
- No history of allergic symptoms after ingesting peanut
- No clinical diagnosis or suspicion of sesame or tree-nut allergy
- No history of anaphylaxis (refer to section 3.5 for definition) to any food

Figure 4: Determination of peanut allergy in the absence of peanut-challenge results using dietary and reaction history, SPT, and IgE



LEGEND

IgE Levels in kU/L
 Low: < 0.35
 Mid: ≥ 0.35 and < 15
 Hi: ≥ 15
 ND: No data
 Tol: tolerant
 AI: allergic
 N: nonevaluable

7.1.2 Handling Dropouts and Missing Data

All efforts will be made via the querying and monitoring phases to avoid missing data.

The handling of missing data, including planned sensitivity analysis for the primary endpoint, will be outlined.

If missing data are not equally distributed between groups, biases can be created. For example, if a significantly greater proportion of dropout occurs in the treatment arm, this arm will have a larger proportion of imputed treatment failures than the placebo arm. This imbalance could tend to underestimate a treatment effect. Conversely, if a significantly greater proportion of dropout occurs in the placebo arm, this could tend to overestimate a treatment effect. These opposing hypothetical biases will be investigated by examining the distribution of missing data as well as the factors associated with missing data.

Once the factors associated with the missing data are identified, they will be incorporated into multivariate models and adjustments of the treatment effect will be described via sensitivity analyses. Moreover, optimistic, pessimistic, and data-driven imputation methods will be used to provide bounds of potential biases that could result from missing data. These sensitivity analyses will provide a measure of robustness of the treatment effect as it relates to the consequences of missing data. The following statistical methodologies may be used to create sensitivity analyses of the missing data: Multiple Imputation, multivariate linear and logistic regression, propensity scoring, Markov chain Monte Carlo methods.

7.1.3 Primary Analysis of the Primary Endpoint

The primary endpoint of the study is the percentage of participants in the ITT sample with peanut allergy at 60 months of age in the SPT-negative stratum. The percentage of participants with peanut allergy at 60 months and a 95% CI for peanut consumption and peanut avoidance groups will be displayed. Tables summarizing the primary endpoint of the study will include the p-value and the treatment difference (peanut avoidance – peanut consumption) along with a 95% confidence interval. For the analysis of the SPT-negative stratum, SPT-positive stratum, and the analysis of the combined SPT-negative and positive strata, an exact p-value for testing the null hypothesis that the percentages are equal between the two groups will be presented. The 95% exact confidence intervals will be calculated using the binomial distribution.

In order to supplement the primary analysis, the same statistical methodology will be repeated for all analysis samples and will be presented separately by strata and by combining the strata.

7.1.4 Secondary Analyses of the Primary Endpoint

7.1.4.1 Sensitivity Analysis: Peanut Allergy Determined by Food Challenge Alone

As a sensitivity analysis, peanut allergy at 60 months will be determined using only the results of the DBPCFC or the 5-g cumulative open challenge. Participants with indeterminate or no data will be excluded from the analysis.

7.1.4.2 Sensitivity Analysis: Age at Entry into Study

The effect of a participant's age at entry into the study on peanut allergy at 60 months will be examined. Age at entry will be included in a logistic regression model as a continuous covariate and data-driven cutpoints of age will be estimated using ROC and regression tree analyses. A second logistic regression model will examine age at entry split into two groups: participants less than or equal to 6 months of age and participants greater than 6 months of age.

7.1.4.3 Analyses of Risk Associated with Peanut Allergy

Additional analyses of the risk associated with peanut allergy in the treatment groups will be performed using multiple logistic regression to identify possible associations of risk with baseline participant characteristics and selected clinical and dietary measures. These analyses will be performed on the incidence of suspected peanut allergy at 30 months and diagnosed peanut allergy at 60 months. Results will be presented by study stratum (SPT-positive and SPT-negative) and overall for 30 and 60 months, respectively. The coefficients, p-values for testing the statistical significance of the coefficients, odds ratios, and 95% confidence intervals for the odds ratios will be presented. In addition to treatment group, other explanatory variables will be considered, for example:

General characteristics

- age at enrolment
- sex
- race/ethnicity

Family history

- Parental allergy (asthma, rhinoconjunctivitis, food allergy)
- Maternal age

Prenatal factors

- Maternal smoking
- Perinatal stress
- Gestational age

Hygiene hypothesis

- Parity
- Mode of delivery
- Antibiotics
- Socioeconomic
- Ethnicity – natively born

Nutrition

- Maternal consumption during pregnancy or early years
- Whether or not the participant was breastfed
- Age participant stopped breastfeeding
- Consumption of nuts

Paracetamol / NSAID

Environmental factors

- Season of birth
- Eczema creams
- Smoking
- Pets

Associated atopic diseases

- Eczema and severe eczema onset before 6 months of age
- Hayfever
- Asthma or wheeze
- Angioedema or urticaria

Testing for the strength of association with key risk variables will be done for one risk variable at a time. A multiple logistic regression model will also be fitted; backwards selection will be used to identify explanatory variables to be included in the model from those listed above. In addition, a variety of statistical techniques may be implemented to develop a risk prediction model of peanut allergy including: data reduction methods, cross-validation, classification and regression trees (CART), random forest, and ROC analyses.

Secondary Endpoints

For the secondary endpoints the treatment difference (peanut avoidance – peanut consumption) and 95% confidence interval will be presented for the secondary endpoints. For the SPT-negative stratum, the 95% confidence interval for the treatment difference will be calculated using the normal approximation to the binomial for discrete measures. For the SPT-positive stratum, the 95% exact confidence interval based on the binomial distribution will be presented for discrete measures. Percentages will be calculated from the total number of participants in each treatment group.

Analyses of the following secondary endpoints for the study are described in this section.

1. At 30 and 60 months of age: the proportion of participants with allergic sensitization to selected ingested and inhaled allergens, and with seasonal rhinoconjunctivitis, perennial rhinoconjunctivitis, and asthma.
2. At 60 months of age: the proportion of participants with type-1 immediate onset food allergy to selected ingested allergens
3. Nutritional evaluations: The following nutritional measurements collected throughout the study will be compared with respect to the randomized groups using parametric and non-parametric tests (e.g. Wilcoxon and t-tests): energy, protein, total carbohydrate, starch, sugars, total fat, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, omega 3, omega 6, sodium, peanut protein, micronutrients, and vitamin D. The data will first be tested to determine normality. If the data are not normal then a Wilcoxon test will be run. If the data are normal then tests will be run to determine if the variances are equal between the two groups. If the variances are equal, a two sample t-test assuming equal variances will be used; otherwise, a two sample t-test assuming unequal variances will be used.
4. Results of cellular and humoral assessments of immune response related to the development of allergy or tolerance to specific allergens is detailed in Attachment 1 at the end of this document.

The following safety related secondary endpoints will also be described

5. Incidence of adverse events at 60 months of age.
6. Incidence of laboratory abnormalities at 60 months of age.

7.1.5 Allergic Sensitization

The wheal and flare measurements from the skin prick test for ingested allergens are recorded at screening and post-screening visits. Descriptive statistics and listings with skin prick data will be displayed for the wheal and flare, respectively, for all randomized participants in the SPT-negative and SPT-positive strata. The treatment difference and 95% confidence interval will be presented for measurements taken at visits 30 and 60.

The tests for allergen-specific immunoglobulins are performed at screening and at all post-screening visits. Tables and listings will display the descriptive statistics and test results for all allergen-specific immunoglobulin evaluations for all participants in the SPT-negative and SPT-positive strata. The treatment difference and 95% confidence interval will be presented for measurements taken at visits 30 and 60.

Skin and nasal swab cultures are done at baseline and at all post-baseline visits. If the results are positive, organisms are recorded. Tables will display the descriptive statistics (counts and percents) for culture results for all participants. The treatment difference and

95% confidence interval will be presented for measurements taken at visits 30 and 60. Organisms and staphylococcus data will be listed together with skin and nasal swab culture results for all randomized participants in the SPT-negative and SPT-positive strata, respectively.

A skin prick test for tree nut allergies is performed at visit 60. Both wheal and flare measurements are collected. Tables and listings will summarize this data for the SPT-negative and SPT-positive strata. The treatment difference and 95% confidence interval will be presented for measurements taken at visits 30 and 60.

An oral food challenge testing Sesame, Brazil nut, Hazel nut, Cashew, and Walnut is performed at visit 60 and positive and negative test results are recorded. Tables and listings will summarize the positive and negative test results for the SPT-negative and SPT-positive strata including the treatment difference and 95% confidence interval.

IgE data for inhalant allergens including house dust mite, cat dander, dog dander, Timothy grass pollen, birch tree pollen, and Alternaria mold is collected at visits 30 and 60. Tables will summarize the IgE data for the SPT-negative and positive strata, respectively, with supporting data provided in listings. The treatment difference and 95% confidence interval will be presented for measurements taken at visits 30 and 60.

Each participant will undergo the 5 gram supervised peanut protein ingestion between months 48 and 60. The details of this ingestion and well as the percentage of participants experiencing an allergic reaction will be summarized for the participants. The treatment difference and 95% confidence interval will be presented for the percentage of participants experiencing a positive result. Listings will present the corresponding participant data related to this ingestion including the symptoms experienced.

7.1.5.1 Participants with Seasonal and Perennial Rhinoconjunctivitis

Data regarding seasonal and perennial rhinoconjunctivitis and the symptoms experienced are captured at visits 30 and 60. The percentage of participants with seasonal and perennial rhinoconjunctivitis as well as the percentage of participants experiencing specific symptoms will be presented for both SPT-negative and SPT-positive strata. The treatment difference and 95% confidence interval will be presented for season and perennial rhinoconjunctivitis.

7.1.5.2 Participants with Asthma

The percentage of participants with asthma at visit 30 and visit 60 as well as the symptoms experienced by the participants will be summarized for the SPT-negative and SPT-positive strata. The treatment difference and 95% confidence interval will be presented.

7.1.6 Type-1 Immediate Onset Food Allergy

Food reaction history collected at baseline and at all post-baseline visits includes the responses to the questions whether the participant was observed eating 2 grams of peanut protein and whether there is a history of clinically significant food-induced immediate onset allergic reaction. Tables will display the descriptive statistics for all responses for all participants in the SPT-negative and SPT-positive strata. Furthermore, listings will show food reaction history data for all randomized participants in the SPT-negative and positive strata. The treatment difference and 95% confidence interval will be presented for the percentages of participants with clinically significant food-induced immediate-onset allergic reaction.

7.1.7 Nutritional Evaluation

The participant's dietary history collected at baseline and at all post-baseline visits includes the nutrients, energy, protein, total carbohydrate, total fat, and sodium, and sub-nutrients within these as well. Further, micronutrient intake that is lower or higher than UK dietary reference values are also collected. Micronutrient intake will be listed. Tables will display the descriptive statistics and the treatment difference and 95% confidence interval for nutrients while listings will show dietary history data for all randomized participants in the SPT-negative and SPT-positive strata.

Participant and household peanut protein consumption collected at baseline and at all post-baseline visits include peanut protein consumption for the participant, participant's mother, and all household members except the mother and the participant, for the previous week, and the total number of household members except the mother and the participant.

Total peanut exposure will be summarized as well. Total peanut exposure is defined as the sum of the participant's mother's peanut consumption and peanut consumption for all household members other than the participant and the participant's mother. Tables will display the descriptive statistics and the treatment difference and 95% confidence interval for all participants in the SPT-negative and SPT-positive strata; while listings will show participant and household peanut protein consumption for all randomized participants.

7.1.8 Analyses of Risk Associated with Secondary Endpoints

Additional analyses of the risk associated with the select secondary endpoints in the treatment groups will be performed using regression models to identify possible associations of risk with SCORAD measured at visit -1, environmental peanut exposure at visit 0, and positive skin and nasal swab cultures for staphylococcus at visit 0 in addition to treatment group. These analyses will be performed on the following secondary endpoints at 60 months of age: SPT wheal and flare for peanut, peanut specific IgE, asthma, and seasonal and perennial rhinoconjunctivitis. Tables will present results for the SPT-negative and SPT-positive strata for each of the above secondary endpoints.

7.1.9 Adverse Events through 60 Months of Age

Tables will summarize the incidence of adverse events at 60 months of age for participants in the SPT-negative and SPT-positive strata. The treatment difference (peanut avoidance – peanut consumption) and 95% confidence will be presented.

7.1.10 Laboratory Abnormalities at 60 Months of Age

Tables will summarize laboratory abnormalities at 60 months of age for participants in the SPT-negative and SPT-positive strata. The treatment difference (peanut avoidance – peanut consumption) and 95% confidence interval will be presented.

8. SAFETY EVALUATION

This section describes the planned analysis for the safety related primary and secondary endpoints as well as adverse events, hematology, serum chemistry, fasting serum lipids, physical examinations, and vital signs. All safety analyses will be based on the Safety sample.

Overview of Safety Analysis Methods

All safety analysis will be carried out using the safety sample defined in Section 4 unless otherwise noted. Missing safety information will not be imputed. Safety will be analyzed in each dose group through the reporting of adverse events, vital signs, physical examinations, and changes in routine laboratory values.

Peanut allergy incidence in the safety sample will be evaluated in the SPT-positive stratum. **The** percentage of participants in the SPT-positive stratum with peanut allergy at 60 months for the peanut consumption and peanut avoidance groups for the safety sample will be presented in a table. This table will further show the difference in percentages (peanut avoidance group - peanut consumption group) and a 95% exact confidence interval for the difference computed using the binomial distribution

Listings will be prepared for all safety measurements.

Adverse Events

All adverse events will be classified by system organ class and preferred term, according to a standardized thesaurus (MedDRA version 11.1). The severity of AEs will be classified using the National Cancer Institute's Common Toxicity Criteria for Adverse Events (NCI-CTCAE) Version 3.0. Each adverse event is entered on the CRF once at the highest severity. As such, no additional data manipulation is needed to identify events.

Adverse events (AE) will be collected from the time the participant provides consent until 30 days after the participant completes study treatment. An AE will be followed until it resolves or until 30 days after the participant terminates from the study, whichever comes first.

AE summary tables will include counts of participants. If a participant experiences more than one episode of a particular AE, the participant will be counted only once for that event. If a participant has more than one AE that codes to the same preferred term, the participant will be counted only once for that preferred term. Similarly, if a participant has more than one AE within a body system category, the participant will be counted only once in that body system category. In AE summaries, body systems will be arranged alphabetically, and preferred terms within each body system will be arranged by descending total frequency across the treatment groups. Percent of participants experiencing AEs in each body system and preferred term will be presented.

An overall summary table will be developed to report the number of events and the number and percentage of participants having at least one event in the following categories:

- AEs
- AEs indicated as serious (SAEs)
- AEs that lead to study drug discontinuation
- AEs with an outcome of death
- AEs that were reported as having a definite/certain or possible relation to a study drug
- AEs reported by maximum severity

In addition, adverse events classified by MedDRA system organ class and preferred term will be summarized for each study group and overall for each of the following:

- All AEs
- AEs by maximum severity
- AEs by relationship to study drug.

The summary tables will present the total number of events, the number and percentage of participants experiencing the events, the prevalence of events for participants in each strata (SPT-negative vs SPT-positive), the treatment difference (peanut avoidance – peanut consumption), and the 95% confidence. When reporting the number of AEs, if the same AE occurs for a participant on multiple occasions the event will be counted once for each occurrence. When reporting the number of participants experiencing the events, a participant will only be counted once if they ever experience an event within the particular system organ class or preferred term. Percentages will be based on the number of participants in the analysis population.

All AEs will be presented by system organ class and preferred term ordered by participant in listings for participants in the SPT-negative and SPT-positive strata. The listing will include the start and stop dates of AEs. Any AEs unresolved at the time of study completion or early termination will be noted as ongoing.

Deaths and Serious Adverse Events

SAEs will be listed and summarized in the same manner described in section 8.2. Separate displays listing and summarizing death, including time to death and cause of death will also be created for both the SPT-negative and SPT-positive strata. Tables will also be created to capture the following information:

- The number of deaths and the death rate for all randomized participants in the SPT-negative stratum at the time of the analysis. The table will also present the number of participants out of the first 50 in the peanut consumption group with

peanut allergy and the rate of peanut allergy with the 95% exact confidence interval based on the binomial distribution.

- The number of deaths and the death rate for all randomized participants in the SPT-positive stratum at the time of the analysis. The table will also present the number and rate of participants who experienced life-threatening anaphylaxis within 3 weeks post-randomization out of the first 5, 10, and 15 participants in the SPT-positive stratum randomized to peanut consumption who consumed peanut.
- The number of deaths and the death rate for all randomized participants in the SPT-negative stratum at the time of the analysis. The table will also present the serious adverse event rate at 12 months post-randomization for the first 50 participants in each group in the SPT-negative stratum. A two-sided exact p-value will be presented comparing the rates between the groups. The treatment difference (peanut avoidance – peanut consumption) and two-sided 95% exact confidence interval, computed using the binomial distribution, will also be presented.
- The number of deaths and the death rate for all randomized participants in the SPT-positive stratum at the time of the analysis. The table will also present the serious adverse event rate at 12 months post-randomization for the first 10 participants in the SPT-positive stratum randomized to peanut consumption who consumed peanut.

Data related to whether or not an adverse event resulted in admittance to an intensive care unit are not currently captured in the clinical database. This information will be added to the CRF in the future. After the addition is made, the data will be included in the stopping rule analysis. Until the addition is made, these data will be included in the summary of the stopping rule analysis but not in the tables or listings.

Clinical Laboratory Evaluation

Clinical laboratory measurements include serum chemistry and hematology are performed at screening and visit 60; fasting serum lipids are collected at visit 60. Results will be standardized to the international system of units (SI), where possible. For numeric laboratory results, descriptive statistics of laboratory values and the change from baseline of laboratory values will be presented for each study group and overall. For character laboratory results, the number and percentage of participants reporting each result will be presented for each study group and overall. Data listings will also be provided for clinical laboratory measurements. They will be sorted by stratum, treatment group, participant ID, laboratory parameter and time of assessment. Laboratory normal ranges will be included and out-of-range flags (H or L) will be used to denote abnormal values.

Laboratory data will be plotted to show patterns over time. For each test with a numeric result, data will be plotted as a spaghetti plot where each participant's values will be plotted and connected by line segments, forming one line per participant. For each test with a numeric result, quantile plots with treatment group means (or medians) as well as 10th and 90th percentiles plotted over time will be created. Tests with qualitative results (such as 'present' or 'positive') will not be plotted.

Vital Signs, Physical Findings, and Other Observations Related to Safety

8.1.1 Vital Signs

Descriptive statistics of vital signs results and change from baseline of vital signs will be summarized for each study group and overall. Data listings will be provided for vital signs measurements.

Systolic blood pressure, diastolic blood pressure, SaO₂, pulse, respiration, body mass index, BMI percentile, temperature, length, weight, waist circumference, tricep skin fold thickness, subscapula skin fold thickness, and expected weight for height are collected during the physical examination. Descriptive statistics of these vital signs will be displayed in the safety sample for both the SPT-negative and SPT-positive strata for all visits.

Figures will present participant line graphs for participants in both the SPT-negative and SPT-positive strata. Each parameter will be graphed over time with each treatment group presented in separate figure panels displayed side-by-side.

8.1.2 Physical Examinations

Physical examination results of normal, abnormal, and not done will be summarized as frequencies and percentages by body system and visit. Data listings will be provided for physical examination results and sorted by stratum, treatment group, participant, body system and time of assessment.

9. OTHER ANALYSES

9.1.1 Stopping Enrollment and Administration of Peanut-containing Snack

Enrollment in the trial will be stopped pending review if any death occurs or if two participants are admitted to an intensive care unit for an adverse event related to study participation.

Enrollment in the trial and further administration of the peanut protein-containing snack will be stopped pending review if either of the following occurs for the SPT-negative stratum:

- An analysis performed when 50 such participants in the peanut consumption group have been followed for 3 weeks demonstrates that the lower bound of the 95% confidence interval for the percentage of participants in the peanut consumption group with peanut allergy as determined in an unscheduled clinic visit is greater than 15%. This will occur if at least 14 of the first 50 participants have peanut allergy.
- An analysis performed when 50 such participants per group have been followed for 12 months demonstrates that the rate of serious adverse events is significantly greater at the 0.05 significance level in the peanut consumption group than in the peanut avoidance group.

Enrollment in the trial and further administration of peanut protein-containing snack to participants in the SPT-positive stratum will be stopped pending review if either of the following occurs:

- One of the first 5, 2 of the first 10, or 3 of the first 15 such participants randomly assigned to the peanut consumption group experiences life-threatening anaphylaxis during the first 3 weeks of administration of the peanut protein-containing snack.
- An analysis performed when 10 such participants in the peanut consumption group have been followed for 12 months demonstrates that 4 or more participants have experienced a serious adverse event.

10.INTERIM ANALYSES AND DATA MONITORING

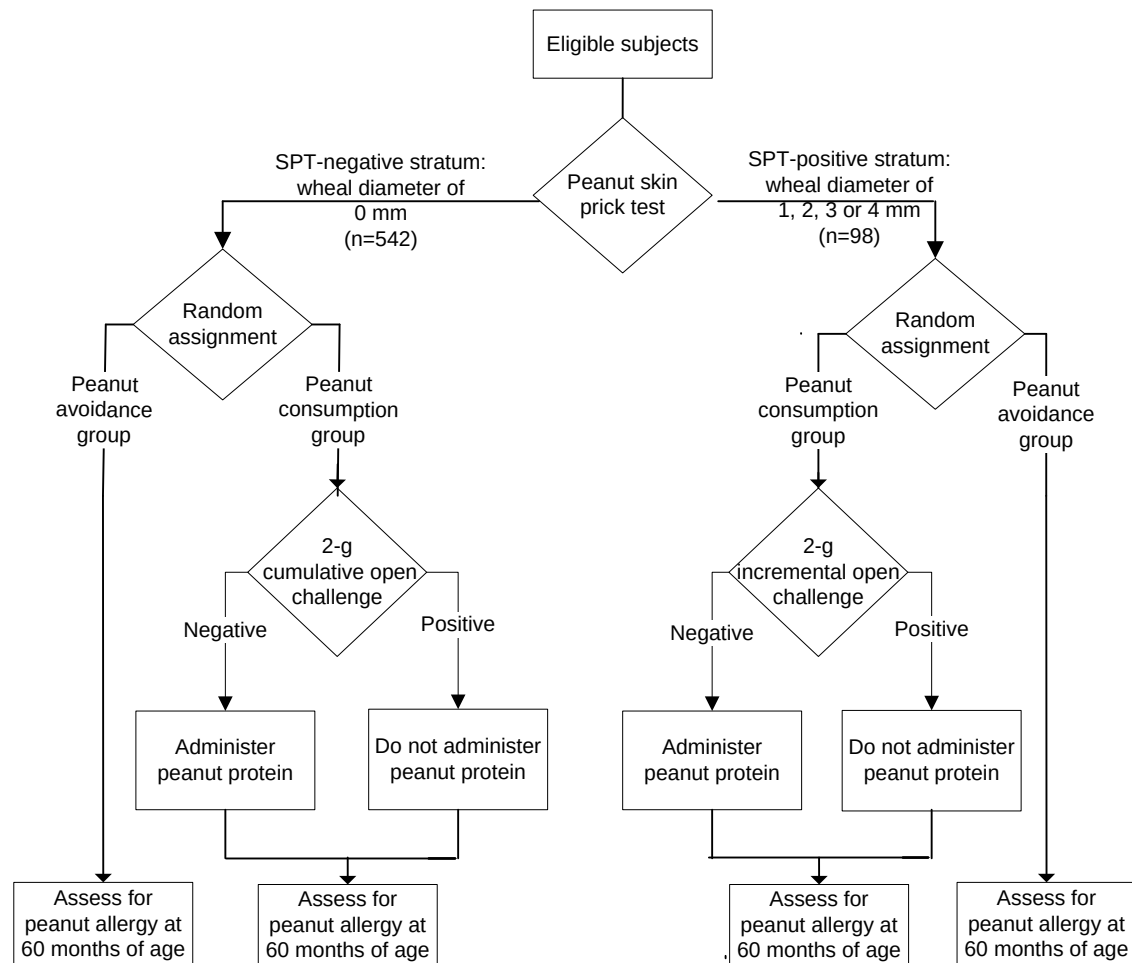
The protocol chair, the NIAID medical monitor, the ITN clinical trial physician, and the NIAID Allergy and Asthma Data and Safety Monitoring Board (DSMB) will review safety data on an ongoing basis. The DSMB may stop enrollment or participation in the trial at any time if it concludes that there are significant safety concerns. Stopping rules are described in Section 3.6 of the protocol and Section 9.1.2 of this statistical analysis plan (SAP).

11. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

No substantial changes have been made in this SAP compared to the protocol.

12. APPENDICES

Study Flow Chart



Schedule of Events

Age in months	4–10	4–10	4–11	12	13–29	30	31–59	60	
Visit	–1	0	0.01–0.36	12	12.01–12.39	30	30.01–30.30 ¹	60	Unscheduled 99
			Weekly phone dietary consultation ²		Biweekly phone dietary consultation		Monthly phone dietary consultation		USV ³
Informed consent	X								
Randomization		X							
Dietary education		X	X	X	X	X	X	X	X
General Assessments									
Physical examination	X	X		X		X		X	X
Medical history	X								
Adverse events		X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Dietary history		X	X ⁴	X	X ³	X		X	X
Food reaction history			X	X	X	X	X	X	X
Eczema evaluation	X			X		X		X	
Rhinitis evaluation						X		X	
Asthma evaluation						X		X	
Laboratory Assessments									
Hematology	X							X	
Serum chemistries	X							X	
Skin and nasal swab culture		X		X		X		X	
Allergy Assessments									
SPT for ingested allergens	X			X		X		X	X
SPT for tree nuts								X	
IgE for ingested allergens	X			X		X		X	X
IgE for inhalant allergens						X		X	
Oral food challenges ⁵								X	X
Peanut challenges ⁶		X						X	X
Peanut Consumption									
Maternal peanut protein consumption history		X							
Participant peanut protein consumption monitoring	X	X	X	X	X	X	X	X	X
Household peanut protein consumption monitoring		X	X ³	X	X ³	X		X	X
Immunologic Assessments									
PBMC T-cell assay	X			X		X		X	
Serum allergen-specific immunoglobulins	X			X		X		X	
Serum total IgE	X					X		X	
Plasma allergen archive	X			X		X		X	
Whole blood DNA-HLA genotypes	X			X					

¹ Additional monthly phone dietary consultation visits (30.31 – 30.36) are allowed during the protocol window for V60 i.e. +6 months

² In addition to telephone dietary consultations, an in-home dietary consultation will be performed at 9 months of age for participants enrolled younger than 6 months of age and at 21 months of age for all participants.

³ An unscheduled clinic visit may be conducted at any time for aversion to peanut, refusal of peanut, or both, or for suspected peanut allergy. Section 6.6 specifies which assessments are required for particular participants.

⁴ To be performed only at the in-home dietary consultation.

⁵ Oral food challenges will be performed as indicated in section 6.4.

⁶ Peanut challenges will be performed as indicated in sections 6.5 and 6.7.

Predictive Values: Food Allergen-Specific IgE Levels and Food Allergen Skin Prick Tests

Predictive value of specific IgE levels ¹⁻³		
Food	≥ kU/L	≥ PPV
Egg	7	95
Infants ≤ 24 months ⁴	2	95
Milk	15	95
Infants ≤ 24 months ⁵	5	95
Peanut ⁶	15	95
Fish	20	95
Tree nuts ^{6,7}	15	95
Predictive value of skin prick tests ^{8,9}		
Food	≥ Wheal size (mm)	≥ PPV
Milk	8	95
Infants ≤ 24 months	6	95
Egg	7	95
Infants ≤ 24 months	5	95
Peanut ⁶⁻⁹	8	95

¹ Sampson HA. Food allergy - accurately identifying clinical reactivity. *Allergy*. 2005;60 (Suppl 79):S19–S24.

² Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol*. 1997;100(4):444–451.

³ Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol*. 2001;107(5):891–896.

⁴ Boyano MT, Garcia-Ara C, Diaz-Pena JM, Munoz FM, Garcia SG, Esteban MM. Validity of specific IgE antibodies in children with egg allergy. *Clin Exp Allergy*. 2001;31(9):1464–1469.

⁵ Garcia-Ara MC, Boyano-Martinez MT, Az-Pena JM, Martin-Munoz MF, Martin-Esteban M. Cow's milk-specific immunoglobulin E levels as predictors of clinical reactivity in the follow-up of the cow's milk allergy infants. *Clin Exp Allergy*. 2004; 34(6):866–870.

⁶ Roberts G, Lack G. Diagnosing peanut allergy with skin prick and specific IgE testing. *J Allergy Clin Immunol*. 2005;115(6):1291–1296.

⁷ Clark AT, Ewan PW. Interpretation of tests for nut allergy in one thousand patients, in relation to allergy or tolerance. *Clin Exp Allergy*. 2003;33(8):1041–1045.

⁸ Hill DJ, Heine RG, Hosking CS. The diagnostic value of skin prick testing in children with food allergy. *Pediatr Allergy Immunol*. 2004;15(5):435–441.

⁹ Sporik R., Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. *Clin Exp Allergy*. 2000;30(11):1540–1546.

13. ATTACHMENTS

Hypotheses

A number of groups of different hypotheses are considered: (i) are the children allergic to peanut; (ii) longitudinal changes in mechanistic results; (iii) the impact of peanut consumption; (iv) sustained as opposed to transient tolerance; (v) IgG, IgG4 and IgA hypotheses.

Hypotheses for IgG, IgG4, and IgA

1. The consumption group will acquire an overall increase in levels of specific IgG, IgG4 and IgA to peanut over time in comparison to the avoidance group.
2. Children in the consumption group who have specific IgE to peanut at V-1 will develop specific IgG, IgG4 and IgA to peanut to a greater extent than sensitised children in the avoidance group.
3. Acquisition of high specific IgG, IgG4 and IgA titers to peanut by v12 will be associated with a failure to develop IgE component spreading in children in the consuming group.
4. The induction of IgG and IgG4 antibodies alone to peanut will be seen in individuals who developed transient peanut desensitisation (tolerant v60 but reactive at v72).
5. Children in the consumption group who have specific IgE to peanut at V-1 who develop long term tolerance, there will be evidence of IgA to peanut as well as IgG4 and IgG to peanut developing along the way.
6. IgG, IgG4 and IgA molecules to peanut in children will be associated with level of peanut consumption and also with a level of peanut dust in the infant's bed. This will hold most for IgG but also for the other isotypes.
7. Children of non-Caucasian ethnicity will show a different pattern of IgE sensitisation at V-1 to Caucasian infants. The non-Caucasian infants will have higher specific IgE levels to peanut and be more likely to be directed against Ara h8 and CCD than to Ara h1, h2, h3, and h9.

Statistical Methodology for Mechanistic Hypotheses

Three categories of statistical methodology (cross-sectional, longitudinal, and data mining) will be applied to the mechanistic hypotheses depending on the type, distribution, and the analysis objectives of the data. Generally, statistical tests will be two-sided at the $\alpha = 0.05$ level of significance. Normality will be assessed by a combination of methods including graphical analysis (e.g. normal probability plots, histograms, and quantile-quantile plots) and formal hypothesis tests (e.g. Kolmogorov-Smirnov test and Shapiro-Wilk test). A two stage testing strategy will be used for many

of the cross-sectional mechanistic hypothesis tests. For example, the data will first be tested for normality. If the data are not normal then a Wilcoxon test will be used. If the data are normal then a test will be run to determine if the variances are equal in both groups. If the variances are equal a two-sample t-test assuming equal variances will be used. If the variances are not equal a two sample t-test assuming unequal variances will be used. Moreover, data transformation techniques may be performed so that parametric methods can be utilized. For example, Ig data will be log base 10 transformed before applying a statistical model where the normality assumption is required.

Signal detection methods will be applied to the diagnostic hypotheses to discern between information-bearing patterns (signals) and random patterns (noise). Prediction models will be built using ROC analyses, confusion matrices, decision-trees (including bootstrap forests and boosted trees), and logistic regression. Cross-validation techniques will be used to evaluate performance of the prediction models. Specifically, training, validation, and test datasets will be created and cross-validated r-squared values will be used to prevent over-fitting and address external model validity. In addition, the PAS study will be used to assess external model validity by testing model performance on a distinct but similar patient population (see PAS Protocol as an addendum).

Statistical tests for presence vs. absence of a mechanistic marker between binary clinical outcomes will use chi-squared tests. Generally, the presence or absence of a marker will be defined as above or below the lower limit of detection, respectively, but other thresholds may be considered from the laboratory's reference ranges and the literature on this topic. In addition, ROC analyses will be performed to determine the optimal cutpoints which predict clinical outcomes.

Changes in mechanistic measurements overtime will be analyzed by longitudinal repeated measures mixed effects models. Plots of the mean values by groups of interest (e.g. randomised group, OFC outcome) over time will be used to illustrate how the treatment effect is manifested and to illustrate the best type of mean structure to fit to the data, i.e., linear vs. curvilinear. We will initially consider a structure that includes multiple sources of variation – fixed effects, random effects, serial correlation, and measurement error. We will then determine the best fitting and most parsimonious model for the data using likelihood ratio tests. The models will be fit by maximum likelihood methods using all available data. We will also perform a likelihood ratio test between a model with time as categorical and a model with time as continuous to see if a linear trend is consistent with the data. If a linear trend is not consistent with the data, a group by time interaction will be examined to determine if a two-way analysis of covariance model that allows the treatment or group effect to vary from one time point to another is more appropriate than analyzing the effect of treatment as constant over time. Moreover,

simplified paired t-test methodology will be utilized when time-points conform to the pre/post analysis setting.

Contingency tables, bar graphs, and parallel plots will be used to display associations between ordinal data (e.g. number of positive Ara h-components and visit number) across a grouping variable (e.g. randomised group assignment or OFC outcome). Cochran-Mantel-Haenszel statistics will be reported as well as p-values from generalized estimating equations (GEE) when repeated measures outcome data are ordinal or binary. The continuous Ara h data will also be analyzed using multivariate analysis of covariance (MANCOVA) methodology. For example, increased reactivity to peanut components of Ara h1, Ara h2, Ara h3 and Ara h9 will be modeled as multivariate continuous outcomes with time and peanut OFC status at V60 as covariates in a repeated measures MANCOVA model.

The relationship between increased reactivity to peanut components and clinical outcomes will be investigated by defining transitions of mechanistic components at each study time point (i.e. for each component a transition from 'absent to present' or 'present to absent' or 'unchanged' will be derived for each component and subject at each time-point). The transitions occurring at each study visit will be associated with the OFC outcome at month 60 and the randomisation assignment. The objective is to determine if gaining or losing certain components across time is associated with peanut consumption or avoidance and ultimately the development of peanut allergy.

Finally, data mining and machine learning techniques will be used to identify mechanistic and allergy phenotypes. A number of data reduction, categorization, and cluster analysis techniques may be used to elucidate the relationship between these mechanistic measures and clinical allergy. Specifically, unsupervised and supervised hierarchical clustering, discriminate function analyses, factor analyses, recursive partitioning, relative importance, random forest, and other exploratory high-dimensional nonparametric analyses may be performed to characterize distinct mechanistic allergy phenotypes. These exploratory analyses will attempt to uncover underlying patterns within these complex, high-dimensional, longitudinal data sets.

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1. Given Name (First Name) Henry	2. Surname (Last Name) Bahnsen	3. Date 11-January-2015
4. Are you the corresponding author? ☐ Yes ☒ No		Corresponding Author's Name Gideon Lack
5. Manuscript Title Randomized Trial of Peanut Consumption in Infants at Risk of Peanut Allergy		
6. Manuscript Identifying Number (if you know it) 14-14850		

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Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☒ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
NIAID/NIH	☐	☐	☐	☒	Contract #HHSN272200800029C

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Are there any relevant conflicts of interest? ☐ Yes ☒ No

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Mr. Bahnson reports other support from the NIAID/NIH during the conduct of the study.

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4. Are you the corresponding author? ☐ Yes ☒ No		Corresponding Author's Name Gideon Lack
5. Manuscript Title Randomized Trial of Peanut Consumption in Infants at Risk of Peanut Allergy		
6. Manuscript Identifying Number (if you know it) 14-14850		

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Are there any relevant conflicts of interest? ☒ Yes ☐ No

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Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
National Institute of Allergy and Infectious Diseases (NIAID, NIH)	☒	☐	☐	☒	NO1-AI-15416 (contract) and UM1AI109565 (grant), covering salary
Food Allergy & Research Education (FARE)	☐	☐	☐	☒	Contribution to NIAID contract/grant
MRC & Asthma UK Centre	☐	☐	☐	☒	Contribution to KCL Division of Asthma, Allergy & Lung Biology (of which Pediatric Allergy Research is a part)
UK Dept of Health through NIHR	☐	☐	☐	☒	BRC award to Guy's and St. Thomas' NHS Foundation
National Peanut Board (NPB)	☐	☐	☐	☒	Support for Paediatric Allergy Clinical Trial's Unit
Osem	☐	☐	☐	☒	Bamba peanut snack purchased at discounted rate
UK Food Standards Agency (FSA)	☒	☐	☐	☐	Additional support for phlebotomy

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Ms. Basting reports grant support from the UK Food Standards Agency (FSA), grant and other support from the National Institute of Allergy and Infectious Diseases (NIAID, NIH), and other support from Food Allergy & Research Education (FARE), MRC & Asthma UK Centre, UK Dept of Health through NIHR, National Peanut Board (NPB), and Osem during the conduct of the study.

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Food Allergy & Research Education (FARE)	☐	☐	☐	☒	Contribution to NIAID contract/grant
MRC & Asthma UK Centre	☐	☐	☐	☒	Contribution to KCL Division of Asthma, Allergy & Lung Biology (of which Pediatric Allergy Research is a part)
UK Dept of Health through NIHR	☐	☐	☐	☒	BRC award to Guy's and St. Thomas' NHS Foundation
National Peanut Board (NPB)	☐	☐	☐	☒	Support for Paediatric Allergy Clinical Trial's Unit

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Food Allergy & Research Education (FARE)	☒	☐	☐	☐	NCT01744990 study
Action Medical Research (AMR)	☒	☐	☐	☐	S/P/4529
Stallergenes	☐	☐	☒	☐	Study materials (SPT) for NCT01744990
Thermo Scientific	☐	☐	☒	☐	Study materials (ImmunoCAP) for NCT01744990
Meridien Foods	☐	☐	☒	☐	Study materials for NCT01744990

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4. Intellectual Property.

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Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name) George	2. Surname (Last Name) Du Toit	3. Date 16-January-2015
4. Are you the corresponding author? ☐ Yes ☒ No		Corresponding Author's Name Gideon Lack
5. Manuscript Title Randomized Trial of Peanut Consumption in Infants at Risk of Peanut Allergy		
6. Manuscript Identifying Number (if you know it) 14-14850		

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☒ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
National Institute of Allergy and Infectious Diseases (NIAID, NIH)	☒	☐	☐	☒	NO1-AI-15416 (contract) and UM1AI109565 (grant), covering salary
Food Allergy & Research Education (FARE)	☐	☐	☐	☒	Contribution to NIAID contract/grant
MRC & Asthma UK Centre	☐	☐	☐	☒	Contribution to KCL Division of Asthma, Allergy & Lung Biology (of which Pediatric Allergy Research is a part)
UK Dept of Health through NIHR	☐	☐	☐	☒	BRC award to Guy's and St. Thomas' NHS Foundation
National Peanut Board (NPB)	☐	☐	☐	☒	Support for Paediatric Allergy Clinical Trial's Unit
Osem	☐	☐	☐	☒	Bamba peanut snack purchased at discounted rate
UK Food Standards Agency (FSA)	☒	☐	☐	☐	Additional support for phlebotomy

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Are there any relevant conflicts of interest? ☐ Yes ☒ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☒ No

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name) Mary	2. Surname (Last Name) Feeney	3. Date 16-January-2015
4. Are you the corresponding author? ☐ Yes ☒ No		Corresponding Author's Name Gideon Lack
5. Manuscript Title Randomized Trial of Peanut Consumption in Infants at Risk of Peanut Allergy		
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Are there any relevant conflicts of interest? ☒ Yes ☐ No

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UK Dept of Health through NIHR	☐	☐	☐	☒	BRC award to Guy's and St. Thomas' NHS Foundation
National Peanut Board (NPB)	☐	☐	☐	☒	Support for Paediatric Allergy Clinical Trial's Unit
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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name) Margarita	2. Surname (Last Name) Gomez Lorenzo	3. Date 07-January-2015
4. Are you the corresponding author? ☐ Yes ☒ No		Corresponding Author's Name Gideon Lack
5. Manuscript Title Early Peanut Consumption and Subsequent Allergy in High-Risk Infants		
6. Manuscript Identifying Number (if you know it) 14-14850		

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Are there any relevant conflicts of interest? ☐ Yes ☒ No

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Dr. Gomez Lorenzo has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name)
Gideon

2. Surname (Last Name)
Lack

3. Date
15-January-2015

4. Are you the corresponding author? ☒ Yes ☐ No

5. Manuscript Title
Randomized Trial of Peanut Consumption in Infants at Risk of Peanut Allergy

6. Manuscript Identifying Number (if you know it)
14-14850

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DBV Technologies	☐	☐	☐	☒	Stock/stock options

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1. Given Name (First Name) Deborah	2. Surname (Last Name) Phippard	3. Date 16-January-2015
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Are there any relevant conflicts of interest? ☒ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
National Institute of Allergy and Infectious Diseases (NIAID, NIH)	☒	☐	☐	☒	N01-AI-15416 (contract) and UM1AI09565 (grant)
Food Allergy & Research Education (FARE)	☒	☐	☐	☒	Contribution to Immune Tolerance Network

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☒ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☒ No

ICMJE Form for Disclosure of Potential Conflicts of Interest

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Section 6. Disclosure Statement

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Dr. Phippard reports grant and other support from the National Institute of Allergy and Infectious Diseases (NIAID, NIH) and Food Allergy & Research Education (FARE) during the conduct of the study.

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Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name)

Marshall

2. Surname (Last Name)

Plaut

3. Date

07-January-2015

4. Are you the corresponding author?

☐ Yes ☒ No

Corresponding Author's Name

Gideon Lack

5. Manuscript Title

Randomized Trial of Peanut Consumption in Infants at Risk of Peanut Allergy

6. Manuscript Identifying Number (if you know it)

14-14850

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☒ No

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Are there any relevant conflicts of interest? ☐ Yes ☒ No

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Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☒ No

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Dr. Plaut has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name) Suzana	2. Surname (Last Name) Radulovic	3. Date 16-January-2015
4. Are you the corresponding author? ☐ Yes ☒ No		Corresponding Author's Name Gideon Lack
5. Manuscript Title Randomized Trial of Peanut Consumption in Infants at Risk of Peanut Allergy		
6. Manuscript Identifying Number (if you know it) 14-14850		

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☒ Yes ☐ No

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National Institute of Allergy and Infectious Diseases (NIAID, NIH)	☒	☐	☐	☒	NO1-AI-15416 (contract) and UM1AI109565 (grant), covering salary
Food Allergy & Research Education (FARE)	☐	☐	☐	☒	Contribution to NIAID contract/grant
MRC & Asthma UK Centre	☐	☐	☐	☒	Contribution to KCL Division of Asthma, Allergy & Lung Biology (of which Pediatric Allergy Research is a part)
UK Dept of Health through NIHR	☐	☐	☐	☒	BRC award to Guy's and St. Thomas' NHS Foundation
National Peanut Board (NPB)	☐	☐	☐	☒	Support for Paediatric Allergy Clinical Trial's Unit
Osem	☐	☐	☐	☒	Bamba peanut snack purchased at discounted rate
UK Food Standards Agency (FSA)	☒	☐	☐	☐	Additional support for phlebotomy

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☒ No

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Dr. Radulovic reports grant support from the UK Food Standards Agency (FSA), grant and other support from the National Institute of Allergy and Infectious Diseases (NIAID, NIH), and other support from Food Allergy & Research Education (FARE), MRC & Asthma UK Centre, UK Dept of Health through NIHR, National Peanut Board (NPB), and Osem during the conduct of the study.

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Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name) Graham	2. Surname (Last Name) Roberts	3. Date 12-January-2015
4. Are you the corresponding author? ☐ Yes ☒ No		Corresponding Author's Name Gideon Lack
5. Manuscript Title Randomized Trial of Peanut Consumption in Infants at Risk of Peanut Allergy		
6. Manuscript Identifying Number (if you know it) 14-14850		

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☒ Yes ☐ No

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National Institute of Allergy and Infectious Diseases (NIAID, NIH)	☒	☐	☐	☒	NO1-AI-15416 (contract) and UM1AI109565 (grant)
Food Allergy & Research Education (FARE)	☐	☐	☐	☒	Contribution to NIAID contract/grant

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name) Alexandra	2. Surname (Last Name) Santos	3. Date 13-January-2015
4. Are you the corresponding author? ☐ Yes ☒ No		Corresponding Author's Name Gideon Lack
5. Manuscript Title Randomized Trial of Peanut Consumption in Infants at Risk of Peanut Allergy		
6. Manuscript Identifying Number (if you know it) 14-14850		

Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☒ Yes ☐ No

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National Institute of Allergy and Infectious Diseases (NIAID)	☒	☐	☐	☐	NO1-AI-15416 (contract) and UM1AI109565 (grant), covering part of salary
Food Allergy & Research Education (FARE)	☐	☐	☐	☒	Contribution to NIAID contract/grant
MRC & Asthma UK Centre	☐	☐	☐	☒	Contribution to KCL Division of Asthma, Allergy & Lung Biology (of which Pediatric Allergy Research is a part)
UK Dept of Health through NIHR	☐	☐	☐	☒	BRC award to Guy's and St. Thomas' NHS Foundation
National Peanut Board (NPB)	☐	☐	☐	☒	Support for Paediatric Allergy Clinical Trial's Unit
Medical Research Council (MRC)	☒	☐	☐	☐	G0902018 (grant number); MRC Centenary Early Career Award
UK Food Standards Agency (FSA)	☒	☐	☐	☐	Additional support for phlebotomy

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This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

5. Relationships not covered above.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

Definitions.

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Other: Anything not covered under the previous three boxes

Pending: The patent has been filed but not issued

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Licensed: The patent has been licensed to an entity, whether earning royalties or not

Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name) Peter	2. Surname (Last Name) Sayre	3. Date 14-January-2015
4. Are you the corresponding author? ☐ Yes ☒ No		Corresponding Author's Name Gideon Lack
5. Manuscript Title Randomized Trial of Peanut Consumption in Infants at Risk of Peanut Allergy		
6. Manuscript Identifying Number (if you know it) 14-14850		

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☒ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
National Institute of Allergy and Infectious Diseases (NIAID, NIH)	☒	☐	☐	☒	N01-AI-15416 (contract) and UM1AI09565 (grant), covering salary
Food Allergy & Research Education (FARE)	☒	☐	☐	☒	Contribution to Immune Tolerance Network

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☐ Yes ☒ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☒ No

ICMJE Form for Disclosure of Potential Conflicts of Interest

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Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Sayre reports grant and other support from the National Institute of Allergy and Infectious Diseases (NIAID, NIH) and Food Allergy & Research Education (FARE) during the conduct of the study.

Evaluation and Feedback

Please visit <http://www.icmje.org/cgi-bin/feedback> to provide feedback on your experience with completing this form.

ICMJE Form for Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.

1. Identifying information.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes".

3. Relevant financial activities outside the submitted work.

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Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name) Michelle	2. Surname (Last Name) Sever	3. Date 09-January-2015
4. Are you the corresponding author? ☐ Yes ☒ No		Corresponding Author's Name Gideon Lack
5. Manuscript Title Randomized Trial of Peanut Consumption in Infants at Risk of Peanut Allergy		
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Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
NIAID/NIH	☐	☐	☐	☒	Contract # HHSN272200800029C

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Are there any relevant conflicts of interest? ☐ Yes ☒ No

Section 4. Intellectual Property -- Patents & Copyrights

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Dr. Sever reports other support from NIAID/NIH during the conduct of the study.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name) Victor	2. Surname (Last Name) Turcanu	3. Date 16-January-2015
4. Are you the corresponding author? ☐ Yes ☒ No		Corresponding Author's Name Gideon Lack
5. Manuscript Title Randomized Trial of Peanut Consumption in Infants at Risk of Peanut Allergy		
6. Manuscript Identifying Number (if you know it) 14-14850		

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Are there any relevant conflicts of interest? ☒ Yes ☐ No

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Food Allergy & Research Education (FARE)	☐	☐	☐	☒	Contribution to NIAID contract/grant
MRC & Asthma UK Centre	☐	☐	☐	☒	Contribution to KCL Division of Asthma, Allergy & Lung Biology (of which Pediatric Allergy Research is a part)
UK Dept of Health through NIHR	☐	☐	☐	☒	BRC award to Guy's and St. Thomas' NHS Foundation
National Peanut Board (NPB)	☐	☐	☐	☒	Support for Paediatric Allergy Clinical Trial's Unit
Osem	☐	☐	☐	☒	Bamba peanut snack purchased at discounted rate
UK Food Standards Agency (FSA)	☒	☐	☐	☐	Additional support for phlebotomy

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Dr. Turcanu reports grant support from the UK Food Standards Agency (FSA), grant and other support from the National Institute of Allergy and Infectious Diseases (NIAID, NIH), and other support from Food Allergy & Research Education (FARE), MRC & Asthma UK Centre, UK Dept of Health through NIHR, National Peanut Board (NPB), and Osem during the conduct of the study.

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