

TreEAT Trial: protocol for a randomised controlled trial investigating the efficacy and safety of early introduction of tree nuts for the prevention of tree nut allergy in infants with peanut allergy.

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Abstract

Introduction: Children with peanut allergy are at increased risk of developing tree nut allergies, which can be severe and for most lifelong. Introduction of peanut in the first year of life can reduce the risk of peanut allergy, however, prevention strategies for tree nut allergies have not been established. We aimed to test the efficacy and safety of a novel strategy, a supervised multi-nut oral food challenge (OFC) compared to standard care for tree nut allergy prevention in infants at high risk of developing tree nut allergy, TreEAT. **Methods and analysis:** TreEAT is a 2-armed, open-label, randomised, controlled trial (RCT). Infants (n=212) aged 4-11months with peanut allergy will be randomised 1:1 at peanut allergy diagnosis to either a hospital-based multi-tree nut (almond, cashew, hazelnut and walnut) OFC using multi-nut butter or standard care (home introduction of individual tree nuts). All infants will be assessed at age 18months, with questionnaires and SPT to peanut and tree nuts. Peanut and tree nut OFCs will be performed as required to determine allergy status for each nut. The primary outcome is tree nut allergy at age 18 months. Secondary outcomes include peanut allergy resolution, proportion and severity of adverse events related to tree nut ingestion, number and frequency of tree nuts ingested, quality of life and parental anxiety and allergy related healthcare visits from randomisation to 18 months of age. Analyses will be performed on an intention-to-treat basis. **Ethics and dissemination** TreEAT was approved by the Royal Children's Hospital Human Research Ethics Committee (#70489). Outcomes will be presented at scientific conferences and disseminated through publication. **Trial registration number:** ClinicalTrials.gov ID: NCT04801823

Title: TreEAT Trial: protocol for a randomised controlled trial investigating the efficacy and safety of early introduction of tree nuts for the prevention of tree nut allergy in infants with peanut allergy.

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Key message

To date strategies for the prevention of tree nut allergy have not been established, particularly for those with peanut allergy who are at higher risk. The TreEat trial is a randomised controlled trial assessing the safety and efficacy of a supervised hospital-based multi- tree nut oral food challenge versus home introduction of individual nuts in infants with peanut allergy to reduce tree nut allergy development.

BACKGROUND

IgE-mediated tree nut allergy in children is common, often serious, and usually lifelong [1]. Australia has the highest reported prevalence of tree nut allergy [2-4]. Accidental ingestion is common, and nuts are the most common trigger of fatal anaphylaxis in <20 year olds [5-7]. Tree nut allergy resolution is very low, at around 10%, [8] hence once established in young children, tree nut allergy is usually life-long and avoidance remains the mainstay of management.

Systematic review and meta-analyses have shown that early peanut and egg introduction reduces the risk of a child developing peanut or egg allergy compared with delaying until after 12 months of age [9]. This has resulted in a paradigm shift in clinical practice, from advice to delay the introduction of peanut and egg, to actively encouraging introduction before 12 months of age. Accordingly, infant feeding guidelines in Europe, Canada, the US and Australia have been revised to recommend the introduction of peanut and egg (and in some countries other common allergens) in the first year of life [10-12].

There are, however, no specific prevention strategies for tree nut allergy. There is emerging evidence from the *HealthNuts* cohort, which observed a protective effect of early cashew introduction with no participants (0%: 95% CI, 0%-2.6%) who were introduced to cashew before 12 months developing cashew allergy by 6 years of age [13], compared to 3.6% (95% CI 2.9-4.4%) cashew allergy in infants who did not consume cashew in the first year. Infants with peanut allergy are at higher risk of developing tree nut allergies, with up to 40% of children with peanut allergy developing one or more tree nut allergies by age 6 [2, 14]. Of concern, the *EarlyNuts study* found that parents of infants at high risk of tree nut allergy (peanut allergic and/or eczema) were more likely to delay tree nut introduction compared to infants without peanut allergy and/or eczema in the first year of life [15].

Initial recommendations in the US suggested infants with peanut allergy should be screened for tree nut allergies with tests of allergen specific IgE sensitisation (skin prick test or serum IgE) and an individual OFC performed for all sensitised tree nuts to determine allergy status [16]. This approach may minimize parental anxiety and assist with home introduction of the negative tree nuts but the concern is the poor positive predictive value of IgE testing may mean a risk of over diagnosis of tree nut allergy. Given long wait times and limited access to hospital based OFCs, this approach may result in delayed introduction of the sensitised tree nuts, potentially amplifying the risk of developing additional nut allergies [17]. Given this, there is a move towards recommendations against pre-emptive tree nut screening for those with peanut allergy [10, 11].

The current practice in Australia is to advise infants with a diagnosed food allergy to introduce all other food allergens one by one (including tree nuts) via a cautious home introduction protocol without prior allergy testing (screening). Whilst the risk of anaphylaxis in infants via a cautious graded approach is considered low [17], there remains the risk of IgE mediated reactions. Another concern is that it can be labour intensive and time-consuming to introduce each of the 8 individual tree nuts (almond, brazil nut, cashew, hazelnut, macadamia, pecan, pistachio and walnut) in a meal or ground form safe for infants.

We hypothesise a supervised multi-nut OFC (compared to home based individual tree nut introduction) will reduce tree nut allergy prevalence at 18 months of age in infants with peanut allergy, facilitate earlier and ongoing ingestion of tree nuts, improve parental anxiety and quality of life and reduce the healthcare costs associated with the management of multiple nut allergies.

METHODS AND ANALYSIS

Trial design and study setting

TreEAT is a 2-armed, open label, randomised controlled trial (1:1 allocation). Infants (between 4 and 11 months of age) with IgE-mediated peanut allergy will be recruited from public and private allergy clinics in Melbourne, Australia. All study visits and procedures will be undertaken in the Melbourne Children's Trial Centre unit of the Murdoch Children's Research Institute based at the Royal Children's Hospital, Melbourne, Australia.

Participants

Infants with IgE-mediated peanut allergy who meet all the following inclusion criteria and none of the exclusion criteria will be invited to join TreEAT

Inclusion criteria

1. Aged between 4 and 11 months of age
2. IgE-mediated peanut allergy diagnosed by an allergist with positive SPT (≥ 3 mm) or serum sIgE (>0.35 ku/L) to peanut
3. A legally acceptable representative capable of understanding the informed consent document.

Exclusion criteria

1. Any history of severe food induced anaphylaxis (defined as a reaction requiring two or more doses of intramuscular adrenaline)
2. Pre-existing tree nut allergy (parent-reported)
3. Tolerance of any tree nut (ingestion of 1 teaspoon on >3 occasions without reaction)
4. Not commenced or unable to eat solid food
5. Taking beta-blocker medication.

Recruitment and Enrolment

Potential participants will be identified during standard allergy clinic appointments and if family consent to be contacted by the study team, the allergist will complete an electronic referral via REDCap. The nominated contact person of potential participants will be contacted by the study team and screened to ensure inclusion and exclusion criteria are met. If eligible, the study team member will describe the purpose of the study, the randomisation process, the study procedures, and the risks and benefits of participation.

A record of all infants screened, and their enrolment status will be maintained in a separate screening database to adhere to the consolidated standards for the reporting of randomised controlled trials. Deidentified data (age, sex, food allergy status, reason not enrolled) will be kept capturing reasons for participants screened and not enrolled. Families will consent to participate via electronic consent module in REDCap.

Randomisation

Participants will be randomised to either the multi-nut OFC or standard care arms with an allocation ratio of 1:1. Randomisation will be computer generated using permuted blocks of variable length by an independent statistician. The randomisation schedule will remain confidential.

Interventions

Standard Care Arm – Home based introduction

Parents are advised that each tree nut be introduced individually in graded amounts over 5 consecutive days in a blended or paste form added to solids (Smear to inside of lip, 1/8 teaspoon (tsp) $\frac{1}{4}$ tsp, $\frac{1}{2}$ tsp, 1 tsp). Tolerated tree nuts are advised to be continued in the diet with no specified amount or frequency.

Intervention Arm – Multi Nut OFC

A multi-tree nut butter recipe was developed by the study dietitian that contains almond, cashew, hazelnut and walnut providing 1gram of each nut protein in a 20-gram (4 teaspoon) food challenge. This will be administered over 6 graded doses at 15-minute intervals (smear, 1/8tsp, 1/4tsp, $\frac{1}{2}$ tsp, 1 tsp, reminder of 4 teaspoon dose).

The nuts selected were the most common tree nuts eaten in Australia and a 1g top dose of each nut protein was considered representative of nut ingestion in a toddler diet.

The nut butter was trialled as part of the pilot study (n=20) and was found to be palatable and taken well by participants. The pilot study nut butter was prepared by the study dietitian but for the current trial it will be manufactured offsite by a food manufacturing company (Royal Nut Company^R) who prepare commercially available nut butter products. The nut butter is prepared on machinery that does not manufacture peanut containing products and tested to ensure it was free of peanut protein.

Primary Outcome- IgE-mediated tree nut allergy at 18 months of age.

The algorithm for classifying tree nut allergy at 18 months is outlined below and in figure 1:

1. Definite tree nut allergy- has evidence of tree nut sensitization (SPT[?]3mm) and either a positive OFC or parental report of a reaction consistent with IgE-mediated food allergy to an individual tree nut via the home introduction protocol
2. Probable tree nut allergy – Based on review by study clinician panel. Participants will be referred to review panel if there is: 1) evidence of tree nut sensitization (SPT[?]3mm) AND 2) OFC result is missing (declined by parent) AND 3) has either a history of reaction that is unclear or reports a late reaction after the OFC has ceased.
3. Tree nut tolerant- has a negative individual tree nut OFC or successfully tolerated the tree nut via home introduction (ingested 1 teaspoon on >3 occasions).
4. Probable tree nut tolerance – not sensitised (SPT <3mm) but no known ingestion or negative multi-nut OFC and no further tree nut ingestion.
5. Inconclusive –sensitised (SPT[?]3mm) but ingestion has not occurred, and participant declines OFC.

Figure 1. Algorithm for determining Tree Nut Allergy at 18 months

Secondary Outcomes

Difference between the 2 treatment arms in:

1. The proportion of participants with persistent peanut allergy at 18 months of age. Defined as i) ongoing peanut sensitisation > 8mm OR ii) peanut SPT 3-8mm and a reaction consistent with IgE mediated peanut allergy since randomisation or iii) positive formal OFC.
2. The proportion and severity of reported adverse events (AE) related to tree nut ingestion as assessed by standardised predetermined criteria, related to tree nut ingestion from randomization to 18 months of age collected via parent questionnaire and medical history.
3. The number and frequency of tree nuts ingested, measured via parent questionnaire.
4. Mean difference from baseline to 18 months of age of quality of life and parental anxiety scores measured via Food Allergy Quality of Life Questionnaire (FAQLQ-PF) and the State/Trait Anxiety Inventory (STAI).
5. The number of allergy related healthcare visits from randomization to 18 months of age, captured per number of hospitalisations, emergency room visits, physician office visits and medication prescriptions.

Exploratory Objective - To explore tree nut diagnostic methods including extract versus fresh nut SPT and new cellular and antibody diagnostic methods that may improve tree nut allergy diagnosis in the future.

Study Visits

Participants will attend an initial study visit at peanut allergy diagnosis (>12 months of age) which will

include parent questionnaires, allergy history, eczema assessment and a blood test. Without prior allergy testing for tree nuts, the multi-nut OFC group will undergo multi-nut OFC and the home introduction of tree nut group will receive instructions for home introduction of individual tree nuts. Blood samples will be taken at this visit to allow retrospective analysis of tree nut sensitisation prior to tree nut introduction. Any participants reacting to multi-nut OFC or to a tree nut on home introduction will return for tree nut SPT. An individual tree nut OFC will be offered for any sensitised tree nuts ($\geq 3\text{mm}$). All participants will return for follow up at 18 months of age. This visit will include parent questionnaires, allergy history, eczema assessment, SPT and a blood test. The study assessment schedule is outlined in Table 1 and a study overview in Figure 2.

Study Period	Pre-Study Phone screen	Prior to V1	T1	(T2) (Multi Nut OFC group only)	T4(+) Follow Up Visit	Additional individual tree nut OFC (T3/T5) (as req ^d)
Interval	Day -14 to -1	Day -14 to 1	Day 1 (+28 days)	Day (V1 +7 to 30 days)	Aged 18mths (+90 days)	Aged 18 months (+180 days)
Venue	Home	Home	MCRI clinical trials unit	MCRI clinical trials unit	MCRI clinical trials unit	MCRI clinical trials unit
Invitation to participate	X					
Informed Consent	X	X (returned)				
Inclusion/Exclusion Criteria	X					
Randomisation		X				
Skin Prick test		X	X (Peanut SPT if not performed by RCH Allergy clinic)	X (full tree nut panel)	X (peanut and full tree nut panel)	
Bloods			X		X	
Allergy History			X		X	X
Eczema Examination			X		X	X
Questionnaires						
Parent questionnaire		X			X	
Food Allergy Specific Quality of Life Questionnaire (FASQL)		X			X	
State Trait Anxiety Questionnaire		X			X	
Home Introduction instructions for tree nuts			X (Home intro group only)			
Multi-nut OFC			X (Multi Nut OFC group only)			
Additional single tree nut OFC				X (if SPT positive to one or more tree nuts)		X (if SPT positive to one or more tree nuts)
Peanut OFC					X (if SPT $\geq 3\text{mm}$ - 8mm)	
Review of adverse events and tree nut ingestion history			X	X	X	X
Review of SAEs (if applicable)			X	X	X	X

Table 1. Visit Schedule

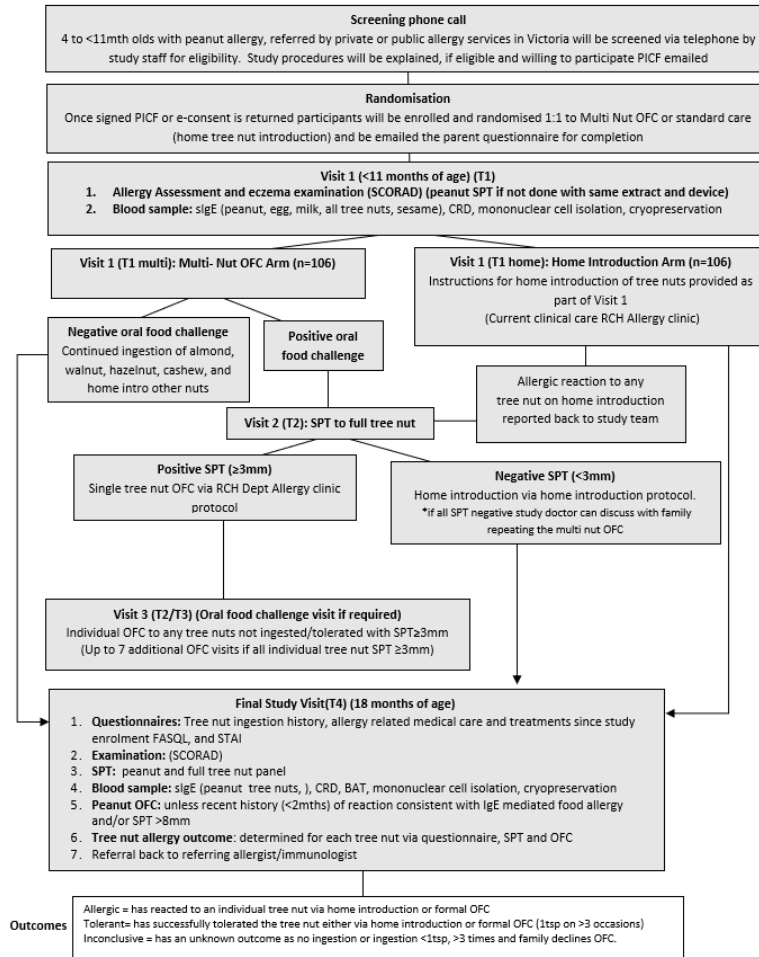


Figure 2: TreEAT trial Visits and Procedures

Study Procedures

Eczema Assessment

Eczema will be clinically assessed using the standardised and validated SCORing Atopic Dermatitis (SCORAD) clinical tool assessment method [18] at enrolment and 18 months of age. Use of any emollients and/or eczema treatments will also be recorded.

Allergy Assessment and other Questionnaires

Parent-completed questionnaires will be administered via REDCap capturing data on atopic history, infant feeding, allergen exposure and associated risk factors for food allergy (family history of allergy, number of siblings, pet ownership, season of birth, parents' country of birth). Participant quality of life will be measured by parent proxy using the Food Allergy Quality of Life-Parent Form (FAQL-PF) [19]. The food allergy-related quality of life questionnaire is a widely used, validated questionnaire to measure quality of life specific to food allergy. Parent reported anxiety will be measured via the State-Trait Anxiety Inventory (STAI) which is a validated questionnaire to measure parental anxiety that has been used in paediatric food allergy research previously [20, 21].

Blood samples

At baseline and follow up visits, 10mL of venous blood will be collected by trained study staff. The blood will be processed for plasma, peripheral blood mononuclear cells, and granulocytes within 4 hours of receiving the sample. Plasma will be stored at -80C for batched analysis of specific IgE and specific IgG4 against whole peanut/tree nuts and corresponding components by ImmunoCAP (Phadia AB, Uppsala, Sweden). Peripheral blood mononuclear cells and granulocytes will be isolated using a Ficoll-paque density gradient and stored in liquid nitrogen for exploratory immunological studies. In addition, follow up visit blood samples will have Basophil Activation Tests (BATs) performed within 4 hours, with basophils isolated and tested for expression of activation markers CD63 and CCR3+ following specific peanut/tree nut allergen stimulation in vitro.

Skin Prick Testing

Tree nut SPT will include both fresh tree nuts and commercial extracts almond, cashew pecan (Greer), brazil nut, pistachio, walnut (ALK USA) and hazelnut and macadamia (Immunotek)]. Peanut SPT will be via commercial extract only (Greer). Any participant reacting to the multi-nut OFC or on home introduction of an individual tree nut will undergo SPT to tree nuts. At 18 months of age follow up peanut and tree nut SPT will be performed regardless of ingestion or allergy history to capture sensitized tolerant participants.

Allergens will be applied to the child's back and standard single lancet technique will be used with a Quintip device. Wheal size will be calculated as the average of the length and width of the wheal after 15 minutes. A positive SPT will be defined as a wheal diameter at least 3 mm greater than that produced by the negative control solution at 15 minutes. For allergens tested with extract and fresh nuts, a mean wheal diameter [?]3 mm for either method will be considered positive.

Individual Nut Oral Food Challenge s

Participants sensitized to peanut or any tree nut will undergo individual nut OFC using a modified version of the Australasian Society of Clinical Immunology and Allergy (ASCIA) Peanut or Tree Nut Challenge Protocols [22]. The top dose has been reduced from 2 teaspoons to one teaspoon for the TreEAT trial due to the younger age of participants. The individual peanut or tree nut OFC will consist of 6 increasing doses at 20minute intervals (Smear, 1/16tsp, 1/8tsp, 1/4 tsp, 1/2tsp and 1 tsp).

A positive multi nut or individual nut food challenge will be defined based on modified PRACTALL criteria [23] and in summary will consist of any one of the following: [?]3 concurrent non-contact urticarial wheals, facial angioedema, vomiting and /or anaphylaxis (respiratory or cardiovascular symptoms) within 1 hour of the last dose.

Sample size calculation

Based on data from the *HealthNuts* study [2] it is assumed that 36% of children with peanut allergy will have a tree nut allergy at age 18 months of age. A sample size of 95 per arm will provide 80% power to detect a relative reduction of 50% or greater (to 18% in the multi-nut OFC group) based on a 2-sided chi-squared test with no continuity correction. To allow for 10% loss to follow-up we require a total of 212 infants, 106 per arm.

Families may withdraw their involvement in the trial at any time, without explanation and without implications to their future care. Where possible, the reason for withdrawal will be recorded. Participants who discontinue or are withdrawn will not be replaced.

Statistical analysis

The primary analysis will follow the intention to treat (ITT) principle with all participants analysed according to their random allocation. All statistical tests will be two-sided with a significance level of $\alpha = 0.1$, unless otherwise specified. Data will be summarized using descriptive statistics (sample mean, median, standard deviation, minimum, maximum) for continuous variables and frequencies and percentages for discrete variables.

The primary end point, proportion of participants with tree nut allergy at 18 months will be compared between treatment groups using a logistic regression model . The estimate of interest is the odds ratio between the two arms estimated via logistic regression and will be presented with its 95% confidence interval and a two-sided p-value. Secondary outcomes (peanut allergy resolution, adverse event frequency, number of tree nuts ingested and frequency of tree nuts ingested) will also be analysed as difference in proportion between the two treatment arms using logistic regression with 95% confidence intervals and a two sided p value. Differences in Quality of Life (FAQLQ-PF) and parental anxiety (STAI) total scores will be analysed as difference between the two treatment groups using logistic regression with 95% confidence intervals and a two-sided p value. If there is very little missing data (<5% in the primary outcome) then the analysis will be based on the available cases. If, however, there is more than 5% missing data in the primary outcome, and there is evidence that the data are missing at random, then multiple imputation will be used to handle the missing data.

Data and data monitoring

Study data will be collected and managed using REDCap (Research Electronic Data Capture), an electronic data capture tool hosted at the Murdoch Children’s Research Institute. [24, 25].

Study co-ordinator will monitor recruitment, staffing, protocol adherences and data entry, and will report the findings to the principal investigator via monthly meetings and quarterly investigator meetings.

Safety

Tree nuts have the potential to trigger severe allergic reactions in susceptible children and there is a risk of reaction in both the multi nut and home introduction arms of the TreEAT trial. To date there is a paucity of data on the type and severity of tree nut reactions in infancy and on first exposure. However, low risk of severe reactions on first exposure have been reported to peanut [26] and it has been suggested that the risk of severe reactions may be age related [17]. Our published data for cashew nut challenges indicate that <2% of positive cashew nut challenges involve the development of anaphylaxis [27].

In the home introduction arm, the risk and severity of potential reactions will be minimised by following the cautious graded home introduction protocol with dose escalation daily. All participants will be provided with an ASCIA Allergy Action Plan [28] outlining the signs and symptoms of an allergic reaction, and appropriate treatment including the use of antihistamines and adrenaline auto injectors if required. This information is also included on the Home introduction of tree nuts TreEAT trial information provided to families.

It is not known if giving tree nuts together in a mixed nut butter in the multi nut OFC group may increase the risk or severity of an allergic reaction. However, the overall dose of each tree nut protein in the multi-nut butter is lower than that given in an individual nut OFC (1g versus 2-4g depending on OFC top dose). The risks are mitigated with specialised allergy trained nursing and medical staff supervising the OFCs and anaphylaxis rescue medication (adrenaline) and full resuscitation equipment on standby. Additionally, the multi-nut OFCs will be done in the Melbourne Children’s Trial Centre which is co-located at Australia’s largest tertiary paediatric children’s hospital, Royal Children’s Hospital Melbourne.

There is a risk of discomfort and minor bruising, swelling or bleeding following a blood test. Finally, there is the inconvenience to the families of attending clinic and possible additional OFC appointments. We assess that the study benefits outweigh the potential risks.

Adverse Events

Information on the duration, severity, frequency, outcome and relationship of adverse events (AEs) to trial intervention will be captured at visits 1-4 and from parent report between randomisation to 18 month follow up and recorded in REDCap. Severity grading for allergic reactions will be based upon the NIH NIAID Consortium for Food Allergy Research specific grading system for allergic reactions [29]. Severity grading for non-allergic reactions will be as follows:

- Mild - The symptom is easily tolerated by the subject, causes minimal discomfort and does not interfere with everyday activities.
- Moderate - The symptom causes sufficient discomfort to interfere with normal, everyday activities and may require over the counter medications
- Severe - The symptom causes significant discomfort preventing everyday activities and may require medical intervention.

An independent Safety Monitoring Committee consisting of three senior medical clinicians annually reviews all studies involving food allergy OFCs within our institution. For the TreEAT trial, the chair will be informed within 48 hours via email of any case of anaphylaxis due to home introduction of tree nuts or severe anaphylaxis (2 or more doses of adrenalin) during an OFC. Study monitoring will take place annually and be performed by Melbourne Children’s Trial Centre.

Ethics

Ethical approval has been granted from the Royal Children’s Hospital Human Research Ethics Committee (HREC) approval number HREC/70489.

Sharing

Once the primary trial results have been published, the TreEAT trial data will be available for data sharing. Data sharing requests will need approval by the trial investigators. Please send requests to lead investigator Kirsten Perrett (kirsten.perrett@rch.org.au).

Dissemination

All investigators will be integral in the communication of the results from the TreEAT trial. The trial findings will be submitted for peer-reviewed publication and for presentation at appropriate local and international conferences, as well as to the general public through various forms of media and public presentations on food allergy and allergy prevention. In addition, the trial findings will be disseminated to participants through a one-page lay summary. The TreEAT trial has been designed with the translational plan that the outcomes will inform clinical guidelines on tree nut introduction for infants with peanut irrespective of whether the hypothesis is correct.

Conclusion

To our knowledge this is the first trial to explore a novel pragmatic strategy for the primary prevention of tree nut allergy in infants at highest risk of tree nut allergy, and if effective will provide evidence for a management guideline for direct translation into clinical practice for reducing the risk of development of multiple nut allergies for infants with peanut allergy. It is expected that supervised introduction of several tree nuts in the first year of life will prevent tree nut allergy, facilitate ongoing ingestion, improve parental anxiety and quality of life and reduce the healthcare costs associated with the management of multiple nut allergies.

CURRENT TRIAL STATUS

The first participant was randomised in June 2021. Recruitment for the TreEAT trial is expected to be completed by December 2022. The final participant primary outcome assessments are expected to be completed by December 2023.

AUTHORS’ CONTRIBUTIONS

KP conceived the trial and KP and VM developed the trial design. KL advised on sample size calculations. KP and VM drafted the protocol, all authors contributed to refinement of the TreEAT trial and approved the final manuscript.

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DISCLAIMER

The funders have no role in the study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication and have no authority over any of these activities.

COMPETING INTERESTS STATEMENT

VM reports speaker honoraria and advisory panel consultancy, outside the submitted work for Nutricia, Abbott and Nestle. KP is Chair of the scientific advisory board for AllergyPal and her institution has received research grants from the National Health and Medical Research Council, Immune Tolerance Network, DBV Technologies, Novartis and Siolta and consultant fees from Aravax; outside the submitted work. All other authors have nothing to disclose.

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