

Randomized controlled trial of slow peanut oral immunotherapy in young children: SmaChO study protocol

To the Editor,

Peanut allergy is the main cause of anaphylaxis and affects approximately 2%.¹ In oral immunotherapy (OIT), allergic individuals start eating very low doses of the allergen and gradually increase it up to a maintenance dose. The goal is to induce desensitization or, preferably, tolerance to the allergen. In a study of 496 children (4–17 years) receiving peanut OIT, 67% achieved desensitization for ≥ 600 mg peanut protein after 1 year of treatment with 300 mg peanut protein/day.²

Mild allergic reactions are common adverse events during OIT and anaphylaxis sometimes occurs. A study of OIT in younger children (9–36 months) indicates that OIT might be more successful and safer in younger children. No anaphylaxis was observed, and 85% tolerated peanuts at a challenge 4 weeks after discontinuing OIT.³ It seems that intervention early in life may affect the immune system towards development of tolerance. Studies about immunological markers in blood and faeces predicting or correlating the outcome of OIT treatment in young children are sparse.^{4,5} How the intestinal microbiome changes over time in young children with or without OIT is to a large part unknown.

In this Letter, we report the protocol of a clinical open-labelled randomized controlled trial (RCT) with peanut OIT treatment or avoidance (ratio 2:1) in peanut-allergic children aged 1–3 years. The overall aim is to study whether oral immunotherapy with a low dose and slow up-dosing strategy in 50 peanut-allergic young children (1–3 years) is safe and effective.

The study has been approved by the Swedish Ethical Review Authority (2019–04645, 2020–04559, 2022–040107-02) and registered in Clinical trials (NCT04511494). The primary outcome is sustained unresponsiveness (tolerance) to 750 mg peanut protein (cumulative dose) after 3 years of OIT and 4 weeks of avoidance. Secondary outcomes are adverse events among peanut-allergic children with OIT or avoidance and changes in the health-related quality of life (QoL) parameters and immunological markers in blood and faeces.

IgE-antibodies (IgE-ab) to peanut/Ara h 2 for children 1–3 years from the Karolinska University Laboratory are used to identify potential participants. An information letter is sent to families of

children with IgE-ab to peanut extract or Ara h 2 > 0.1 kU_A/l. Families interested in attending the study are invited to a screening visit after a written consent. Thereafter, an open peanut challenge will be performed. Children reacting to ≤ 250 mg peanut protein will be randomized 2:1 to peanut OIT (group 1, $n=50$) or avoidance (group 2, $n=25$). Children with other serious illness will be excluded, details are shown here <https://osf.io/kf523/>. Children with a negative challenge will be followed up with blood tests and QoL (group 4, n =unknown). Non-allergic children will be included as a control group for immunological markers, gut microbiome and QoL (group 3, $n=30$). STATA software version 15.1 is used to generate the random allocation sequence.

The peanut baseline challenge starts with 0.3 mg peanut protein and continues stepwise up to 250 mg peanut protein (Table 1). If no objective symptoms are seen, the next dose is given every 30 min up to a maximum cumulative dose of 277.8 mg peanut protein. The first three doses are thoroughly mixed peanut flour and oat flour, the fourth dose is peanut butter. The challenge is considered as positive if any objective allergic symptom occurs during the observation time, 2 h after last dose. During the baseline challenge the following assessments are performed: clinical examination, weight and height, temperature, faecal samples (collected at home by the parents, kept frozen until arrival at the clinic). For safety reasons, all children will receive a peripheral venous catheter (PVC) after local anaesthesia. From the PVC, blood samples for immunoglobulins, blood status and immunological markers (21 mL) are drawn. A health-related QoL questionnaire (FAQLQ-PF) is filled out by the parents.

Children randomized to OIT treatment (group 1, $n=50$) start with a mini challenge for safety reasons. Four doses will be given at the study centre at 20–30 min intervals. The last dose corresponds to $\frac{1}{4}$ of the dose that gave the reaction at the baseline challenge and will be ingested daily at home for the next 4–6 weeks if tolerated at the study centre (Table 2). The study participants are provided with peanuts in appropriate quantity and form from the study centre. For doses up to 24 mg peanut protein, a mix of peanut and oat flour is used (4.6% peanut protein). For all other doses, BAMBA (Osem Food Industries), a peanut-coated corn puff containing 50% peanut that dissolves in the mouth, is used. BAMBA was previously used in the

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LEAP study.⁶ The OIT is performed with slow up-dosing with visits every 4th to 6th week until a maintenance dose of 285 mg peanut protein (3 BAMBA) daily (Table 2). Clinical examination is performed at all visits before the dose is given and the child is observed after the dose (90 min during up-dosing and 30 min during maintenance). The total time for OIT will be 3 years and follow-up visits are scheduled every 3rd month during maintenance. The parents fill out a daily diary at home with information of the dose taken, allergic symptoms or illness. The diary is reviewed at the visits.

All participants will get an 'emergency kit' with adrenaline autoinjector, oral antihistamine and if they have asthma beta agonist-inhalation. Peroral corticosteroids will be provided for families living far away from hospital. Parents receive written instruction and practical demonstration on how/when to use the medications and are informed about co-factors for allergic reaction such as hot bath, infections and physical activity. In case of adverse events, participants may come to the clinic more often and the dose may be temporarily lowered or interrupted.

Children in the avoidance group (group 2, $n=25$), without OIT treatment, continue avoiding peanuts and their parents answer a monthly survey concerning allergic reactions to peanuts or other allergens.

Peanut challenges (Table 1), up to a maximum cumulative dose of 5000 mg peanut protein, are performed after 1 year (group 1 and 2), 3 years (group 1 and 2) and after 3 years and 4 weeks (group 1). The latter to evaluate sustained unresponsiveness. The challenge is stopped when any objective allergic symptom occurs or when the highest dose is reached. Children in group 1 performing the 3 years challenge and tolerating at least a cumulative dose of 750 mg peanut protein discontinue OIT and are instructed to strictly avoid peanut for 4 weeks and thereafter the final peanut challenge will be performed Table 1. Children passing this challenge are considered peanut tolerant. Families will be advised to continue giving peanuts regularly (3–7 times a week) but decide themselves.

Children in the peanut avoidance group perform a peanut challenge 1 and 3 years after study start. However, if they tolerate the dose 250 mg of peanut protein, they will continue the challenge doses made for group 1 (Table 1). After the last peanut challenge, the participants will be offered peanut OIT, if current knowledge recommends OIT treatment.

The non-allergic control group (group 3) will be age-matched children ($n=30$). Their medical and allergic history is reviewed.

Blood samples are collected at the peanut challenges from children in group 1 and 2 and in group 3 at baseline and after 3 years. Peripheral blood mononuclear cells (PBMC) are separated from the blood and stored in liquid nitrogen together with the serum and plasma until analysis. Allergen- and component-specific antibodies, for example, IgE-ab and IgG4-ab as well as immune markers like cytokines and chemokines, will be analysed throughout the study period. Phenotypical as well as functional characteristics of PBMC populations will be evaluated at DNA, RNA and protein levels with flow cytometry-, multiplex- and sequencing platforms.

Key messages

- This is a study protocol for a trial of low-dose, slow up-dosing peanut oral immunotherapy.
- We will evaluate safety and effectiveness of the intervention in children aged 1–3 years.
- Primary outcome is sustained unresponsiveness to ≥ 750 mg peanut protein after 3 years of immunotherapy.

TABLE 1 Peanut challenges.

Baseline challenges (and for group 2 also after 1 and 3 years)	
Dose	Peanut protein
1	0.3 mg
2	2.5 mg
3	25 mg
4	250 mg
Challenge after 1 and 3 years (only for group 1 ^a)	
Dose	Peanut protein
1	250 mg
2	500 mg
3	1000 mg
4	1000 mg
5	1000 mg
6	1250 mg

Note: The challenge will be discontinued if/when objective symptoms are observed.

^aIf a child in the avoidance group tolerates 250 mg peanut protein they will continue with the higher doses until objective allergic symptoms.

Faecal samples are collected, and parents will complete a quality-of-life questionnaire (FAQLQ-PF) at baseline (group 1, 2 and 3), after 1 (group 1 and 2) and 3 years (group 1, 2 and 3). The samples will be analysed using sequencing-based methods and metabolomic platforms to monitor possible changes in the gut microbiota composition and function related to the treatment.

For safety, stopping rules for both individual and for the whole study population, are used. If more than two anaphylaxes occur in a participant due to OIT a strong recommendation is to consider cessation of intervention. Stopping criteria for the whole study are if more than 50% of the participants experience at least two OIT-related anaphylaxes or if a fatal reaction to peanut occurs among any of the participants in the OIT-group. The whole study group stopping criteria will be discussed with the members of the security board.

If this study is successful, we hope to give young peanut-allergic children a possible treatment and alternative to avoidance. OIT early in life with a slow up-dosing regimen and a low maintenance dose may lead to peanut tolerance and fewer adverse reactions. In the

TABLE 2 Slow up-dosing for OIT every 4th to 6th week.

Dose	Amount of peanut protein in mg	Amount of peanut flour 10% ^a in mg (4.6% peanut protein)	Amount of peanut in mg (one peanut approx. 800mg)	Pieces of Bamba (700 mg/piece, protein content 17.5%)
1	0.8	17	3.2	
2	1.5	33	5.6	
3	3	65	11	
4	6	130	22	
5	12	260	44	
6	24	521	88	
7	48	1043	176	1/3
8	71	1543	264	1/2
9	95	2065	352	1
10	144	3130	528	1 + 1/2
11	190	4130	704	2
12	238	5173	880	2 + 1/2
13	285	6196	1056	3

Note: Start dose at $<1/4$ of the dose causing reaction at baseline challenge.

^aMix 1 g Peanut powder with 9 g oat flour.

future, it may be possible to start treatment as soon as a child is diagnosed with a peanut allergy.

AUTHOR CONTRIBUTIONS

AA and CN are responsible to the conception and trial design. ME, BPV, MJM, ESE and CU contributed to trial design. CU, AA, ESE and CN drafted the manuscript. All authors were involved in critical revision of the article for important intellectual content and were involved in final approval of the article. AA is principal investigator (PI) and CN is senior PI of SmaChO. The PI is responsible for study design; collection, management, analysis and interpretation of data; and the decision to submit the report for publication.

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KEYWORDS

food allergy, peanut allergy, oral immunotherapy, treatment

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

The SmaChO study has been approved the Swedish Ethical Review Authority (2019-04645, 2020-04559, 2022-040107-02). It is registered in Clinical trials (NCT04511494). A written informed consent has been signed by all the study participants' parents. The data that support the findings of this study are available from the corresponding author upon reasonable request

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