Position Paper - Oral Immunotherapy for Food Allergy

This document has been developed by ASCIA, the peak professional body of clinical immunology/allergy specialists in Australia and New Zealand. ASCIA information is based on published literature and expert review, is not influenced by commercial organisations and is not intended to replace medical advice.

This document and references will be reviewed and updated once a systematic review on food allergy treatments is completed. In the meantime, a reference list is included at the end of this document.

For patient or carer support contact Allergy & Anaphylaxis Australia or Allergy New Zealand.

Key points

- Oral immunotherapy (OIT) is an emerging treatment for food allergy, but is not a cure for food allergy.
- Food OIT involves daily ingestion of the food(s) to which a person is known to be allergic, under medical guidance. The doses are initially small and are gradually increased in an attempt to reach a target maintenance dose that is then consumed daily at home as a treatment for a prolonged period of time.
- OIT can be effective at inducing desensitisation and, in some people, can induce sustained unresponsiveness (remission):
    - **Achieving desensitisation** means there is a temporary increase in the amount of food allergen that can be consumed before an allergic reaction occurs. Some people who are desensitised can eat a full serving of the food allergen without reacting. As the increased level of protection is temporary, it is necessary to continue regular ingestion of the food (either as OIT or as dietary forms of food) to maintain the desensitisation effect.
    - **Achieving sustained unresponsiveness (remission)** means a person can eat an unrestricted amount of the food allergen after stopping OIT.
- ASCIA recommends that for most patients, strict avoidance of confirmed food allergens remains the recommended standard of care.
- ASCIA acknowledges there is uncertainty about patient-important outcomes of food OIT including safety, long-term effectiveness and overall impact on quality of life.
- ASCIA strongly supports further clinical trials of food OIT and other treatments for food allergy that are underway or planned in Australia and other countries. More data needs to be collected about safety, tolerability, cost-effectiveness, quality of life and long-term outcomes of food OIT.
- Some patients with food allergy may benefit from OIT. Decisions regarding commencing OIT must be made through a shared decision-making process between the patient/family and the patient's clinical immunology/allergy specialist, taking into full consideration the risks, burden and potential benefits involved, and preferably as part of a clinical trial. If it is decided to undertake OIT outside a clinical trial, documentation of informed consent including discussion of the risks and benefits of OIT is strongly advised. The OIT should only be administered under the supervision of an experienced clinical immunology/allergy specialist, with dose increases delivered under medical supervision in a medical facility equipped to manage severe allergic reactions. Anaphylaxis can occur during OIT, most commonly during the initial phase of treatment when doses are being increased. A treating specialist supervising OIT outside a clinical trial should have regular clinical meetings with other qualified allergists/immunologists in order to promote best practice with appropriate peer review.
- Most OIT that is offered to patients around the world uses food products rather than a commercial OIT product that is registered with medicines regulators.

- Food OIT is not the same as using an egg or milk ladder, which may be recommended in people with a mild allergy to minimise unnecessary avoidance of likely tolerated foods. When used in this way, milk and egg ladders involve initially giving the food allergen in a form that is more likely to be tolerated by a patient (such as heated egg or milk in baked foods), and then introducing other forms of the food allergen as tolerance develops over time. This is different from food OIT, where desensitisation is induced by giving doses of a food allergen in a form that the patient is known to be allergic.

Food allergies may be 'outgrown' with time

- At age 12 months more than 10% of children have a challenge-proven food allergy, most commonly to egg[1].
- The prevalence of allergy in school-aged children and adolescents is around 4-5%, most commonly to nuts[2, 3].
- Peanut, tree nut, sesame and crustacean allergies tend to be lifelong as they are less likely to resolve naturally[4].
- When food allergy develops for the first time in adults, it is less likely to resolve.

Possible benefits of food OIT are desensitisation and sustained unresponsiveness (remission)

Published trials show that food OIT can result in successful desensitisation in most people, however only some people may be able to achieve sustained unresponsiveness (remission).

There are two possible beneficial outcomes of food OIT:

- **Desensitisation** is a temporary state that allows a person to consume more of the food allergen than they could prior to OIT. Depending on the OIT regimen and patient factors, desensitisation may allow intake of a full serve of the allergen without an allergic reaction. Continued regular ingestion of the food allergen is required to maintain the desensitised state, as the underlying food allergy is still present and clinical reactivity is only being temporarily suppressed.

  The threshold at which an allergic reaction can be triggered in a person who is desensitised can change from day to day and may be influenced by cofactors such as intercurrent illness, menstruation, exercise, sleep deprivation or breaks in treatment. Therefore, patients can react to their daily desensitisation treatment, despite previously tolerating it, and reactions can be severe (anaphylaxis).

  The benefit to people who are desensitised is protection against allergic reactions following accidental exposure to small amounts (generally less than their maintenance dose) of food allergen, while they continue maintenance dosing (indefinitely), and in most cases also adhere to strict allergen avoidance outside their regular dosing. People who are desensitised to a food are still considered allergic, need to carry their adrenaline injector device and should avoid the food allergen (other than their OIT dose).

- **Sustained unresponsiveness (remission)** means that a person can consume a serving size of the food allergen without having an allergic reaction (pass a diagnostic oral food challenge), after having discontinued OIT and avoided all other forms of the food allergen for a period of several weeks.

  If a patient can consume a full serve after this (short) period of avoidance, they can introduce the food into their diet freely and do not have to adhere to strict allergen avoidance or continue regimented maintenance dosing beyond the end of their OIT treatment course. **There is no assurance that the food will be tolerated after longer periods of avoidance** or with other cofactors present.

  Most OIT studies to date do not report on sustained unresponsiveness. Studies that do report on sustained unresponsiveness suggest that less than half of treated patients achieve this outcome. **Achieving sustained unresponsiveness does not indicate that a person's food allergy has been cured.** Some patients who achieve sustained unresponsiveness may still experience allergic reactions to the food for which they received OIT. Patients who have achieved sustained unresponsiveness still need to carry their adrenaline injector and ASCIA Action Plan.

Tolerance is a permanent state of being able to ingest an unlimited amount of the food without experiencing an allergic reaction. This means that a person can tolerate standard serves of the food allergen even after a long period (such as years) of avoidance, similar to what is observed in children who have outgrown food allergies. **There is insufficient data to determine whether OIT can induce tolerance.**

Publications providing a comprehensive review of OIT for peanut allergy, and recent advances

Recent published systematic reviews and meta-analyses have provided comprehensive and rigorous summaries of the evidence available on OIT for peanut and other food allergies.

Chu et al. published a meta-analysis of 12 peanut OIT trials in the Lancet in April 2019[5]. It compared the effectiveness and safety of peanut OIT versus peanut avoidance, combining all the studies where children with peanut allergy had been randomly assigned to either peanut consumption or avoidance (control group). There were 1,041 children in these studies, with approximately two thirds taking peanut OIT and the remainder acting as controls.

Results showed that while peanut OIT can achieve the goal of desensitisation for many people, those who underwent peanut OIT had more frequent allergic reactions, including severe allergic reactions (anaphylaxis) and required more frequent treatment with adrenaline (epinephrine) injectors (such as EpiPen® or Anapen®) than patients who avoided peanut and did not receive peanut OIT (standard care). The analysis also found low certainty evidence that peanut desensitisation may not improve patient quality of life.

The Lancet publication's findings suggest that desensitisation may not be an optimal outcome for patients and highlight the need for food allergy treatment approaches with a better safety profile as well as further trials focused on improving patient-important outcomes such as quality of life. ASCIA supports this view and the importance of further research.

A second meta-analysis published in Scientific Reports by Grzeskowiak et al. in January 2020 analysed the same 12 controlled studies and an additional 15 non-controlled studies[6]. These 27 studies involved 1,488 children receiving peanut OIT. This analysis showed that certain aspects of treatment programs could increase the risk of anaphylaxis, while co-administration of other treatments with OIT may reduce the risk. This analysis also highlights the lack of data collected to date around patient-important outcomes such as protection from accidental reactions for those who have undergone peanut OIT in the past.

In January 2022, a multidisciplinary task force including patient representatives, published a systematic review and meta-analysis of allergen-specific immunotherapy trials for food allergy, to inform updated guidelines from the Global Allergy and Asthma European Network (GA^{2}LEN)[7]. This paper included 36 OIT trials, with most being for peanut (13 trials, of which 7 were OIT), cow's milk (11 trials, 8 OIT) or hen's egg (7 trials, all OIT) allergy. The meta-analysis reported with high certainty that peanut OIT was effective at inducing desensitisation. There was low certainty evidence that peanut OIT may induce sustained unresponsiveness in a smaller proportion of children.

Taken together, these publications indicate that while OIT is effective at inducing desensitisation, more research is required to identify approaches for treating food allergy that are more effective and safer and provide longer-lasting protection and greater improvement in patient-important outcomes than current approaches.

Commercial OIT versus food products

It is important that patients are aware that most food OIT practised globally uses food products, rather than registered commercial products that are approved by regulators of therapeutic goods in the relevant jurisdictions.

Palforzia™, developed by Aimmune Therapeutics, is a commercial OIT product which uses standardised amounts of peanut allergen powder contained in capsules. It has received approval for use in peanut desensitisation by medicines regulators in the USA, Europe and UK, and is the only commercial product to have done so to date.

There are no commercial OIT products registered or approved to induce sustained unresponsiveness (remission) or tolerance in any jurisdiction.

There is currently no commercial OIT product approved or registered by the TGA in Australia or Medsafe in New Zealand.

There is no evidence that registered commercial OIT products are inherently more effective and/or safer than other evidence-based, standardised protocols using food products.

Safety and Efficacy

Food OIT safety issues include:

- More allergic and adverse reactions compared with the standard care of allergen avoidance.
- OIT patients can have allergic reactions to OIT doses, even after achieving desensitisation, particularly in the presence of co-factors, such as illness, exercise, sleep deprivation.
- Even after achieving desensitisation or sustained unresponsiveness (remission), people can have allergic reactions due to the allergen, whether exposure is accidental or intentional.
- Eosinophilic oesophagitis (EoE), presenting with dysphagia, regurgitation, reflux oesophagitis and food impaction, triggered by the OIT target allergen, can develop in an estimated 1-5% of patients receiving food OIT[8, 9, 10]. Unlike EoE outside the context of OIT, which is usually chronic, OIT-related EoE generally resolves when the OIT is stopped.

The efficacy and safety of food OIT is highly variable and unpredictable; some children experience severe side effects requiring discontinuation of OIT and achieve no long-term benefit, while others achieve sustained unresponsiveness with few treatment-related side effects. Available data suggest that children who achieve sustained unresponsiveness (remission) experience fewer allergic reactions and have better quality of life in the long-term than children who are only desensitised[11].

There is emerging evidence that infants and pre-school children may benefit from immunomodulation with early peanut OIT. Jones et al. found that among pre-school children, those who initiated peanut OIT at a younger age were more likely to achieve sustained unresponsiveness[12]. Shaker et al. reported modelling that pre-school peanut OIT was associated with cost savings while improving quality-adjusted life-years, compared to a non-immunotherapy approach[13].

When considering OIT, it is essential that there is shared decision-making between patients/families and the clinical immunology/allergy specialist, ensuring that there is thorough discussion and weighing up of the potential benefits, safety issues and impact on quality of life, including the burden of undergoing OIT. If a clinical immunology/allergy specialist is supervising OIT outside a clinical trial, they should have regular clinical meetings with other qualified allergists/immunologists in order to promote best practice with appropriate peer review.

Considerations prior to commencing OIT for food allergy

Food OIT should be given in a consistent way, supported by evidence-based treatment protocols with sufficient resources available, and overseen by a clinical immunology/allergy specialist. Being in a food OIT clinical trial ensures these requirements are in place, and usually requires frequent visits to hospital, possible food challenge to the allergen before commencing OIT, blood tests and other investigations over many months or years. Any future provision of food OIT as part of clinical practice (outside a food allergy clinical research trial) will require similar resources and commitment from patients and families to maximise the chances of its effectiveness and minimise the risk of side effects.

Because of the importance of consistent dosing, the long duration of treatment, the medical investigations and oversight required, undertaking food OIT may present difficulties for people who plan to go on holidays, overnight excursions, camps, or board overnight at school. There will also be some inconveniences, potential costs (such as travel and time off work), lifestyle disruptions and restrictions that need to be carefully considered and these may vary widely for different age groups.

Each dose of OIT carries a risk of an allergic reaction, including anaphylaxis. Exercise around OIT doses increases the risk of allergic reactions, and therefore OIT doses should be administered at a time when a child can rest and be observed by a parent or responsible guardian for at least 2 hours after a dose. When students are on overnight school excursions or camps, there can be changes in sleep patterns, busy activity schedules, lower ratios of carers to students and remote or unfamiliar locations, all of which can increase the risk of allergic reaction (including anaphylaxis) from an OIT dose. Co-factors such as infection, menstruation, poorly controlled asthma and allergic rhinitis can also increase the risk.

Therefore, people on food OIT may need to choose between attending school activities and interrupting OIT, depending on discussions with schools and camps or other factors. These factors should also be considered for people going on holidays or participating in other activities with their family or friends.

There are added risks when recommencing food OIT after a long interruption. For this reason, the OIT clinical trial doctor or treating clinical immunology/allergy specialist may recommend that this occurs in a supervised medical setting. While clinical trials will have facilities and resources to accommodate these situations in extenuating circumstances, a treating clinical immunology/allergy specialist may not be able to offer rapid access to a suitable setting for recommencing OIT when interruptions occur.

All patients and participants in food OIT clinical trials should remain under the regular care of a clinical immunology/allergy specialist in addition to the research team. The patient's specialist plays a particularly important role in ongoing management decisions once a patient finishes a clinical research trial, in consultation with the patient's GP.

Food allergy treatments offered in clinical research trials may not be available for participants when the trial finishes. It is important for patients to discuss tentative plans for management after the trial with their regular clinical immunology/allergy specialist when deciding whether to participate in a clinical trial.

Current ASCIA recommendations for management of food allergy

For most patients, with the exception of patients with egg and milk allergy who tolerate those foods in baked forms, strict avoidance of confirmed food allergens remains the standard of care. This recommendation will remain in place until the long-term efficacy and safety of food OIT or other treatments are optimised, and long-term patient-important and other clinically relevant outcomes are shown to be improved by OIT or other treatments.

There remains potential for OIT to provide long term benefits for patients with food allergy. ASCIA strongly supports the provision of clinical trials to address this data gap and increased access to OIT in clinical trials for those patients and families who wish to undertake OIT.

While ASCIA recommends that food OIT should be undertaken in the context of a clinical trial, these opportunities may not always be available to patients. If food OIT is being considered outside of a clinical trial, ASCIA recommends a shared decision-making process with appropriate expert consultation and documentation of informed consent, and that OIT is provided under the supervision of a clinical immunology/allergy specialist, as part of a multidisciplinary team with expertise in food OIT. In these circumstances, ASCIA recommends that standardised measures of safety, effectiveness and patient-reported outcomes are collected to address the current gaps in knowledge.

If such therapy is undertaken, OIT should be performed using published peer reviewed treatment protocols. Dose increases must take place with qualified staff in a facility that has the necessary equipment to treat anaphylaxis. Prior to commencing OIT, a clinical diagnosis of allergy to the food in question must be established; a diagnosis cannot be based on skin tests or blood tests in isolation. A supervised oral food allergen challenge in an appropriate setting may be needed to confirm the diagnosis or to establish a reaction threshold.

Any patient receiving OIT should have an adrenaline injector available at all times. Comprehensive anaphylaxis education regarding the recognition and management of anaphylaxis should be provided for the patient and/or their carers and a written management plan should be provided. Clear written information about when to avoid a dose (for example, prior to exercise) should be provided.

Key Recommendations

Food OIT should only be administered by a clinical immunology/allergy specialist.

When food OIT is provided through a clinical trial, the patient's usual treating clinical immunology/allergy specialist plays a critical role in supporting the patient.

Food OIT increases the likelihood of allergic reactions (including anaphylaxis) and patients with food allergy must be prepared for managing allergic reactions, whether or not they undertake OIT:

- Know the signs and symptoms of mild to moderate allergic reactions and anaphylaxis.
- Know what to do when an allergic reaction occurs.
- Read and understand food labels for food allergy.
- Inform wait staff that they have food allergy when eating out.
- Be aware of cross contamination and contact with food allergens when preparing food.
- Carry their prescribed adrenaline injector/s and their ASCIA Action Plan.

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For more information go to www.allergy.org.au/hp/food-allergy

To support immunology/allergy research go to www.allergyimmunology.org.au/donate

References

1. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. Journal of Allergy and Clinical Immunology. 2011;127(3):668-76.e2. https://doi.org/10.1016/j.jaci.2011.01.039

2. Peters RL, Koplin JJ, Gurrin LC, Dharmage SC, Wake M, Ponsonby A-L, et al. The prevalence of food allergy and other allergic diseases in early childhood in a population-based study: HealthNuts age 4-year follow-up. Journal of Allergy and Clinical Immunology. 2017;140(1):145-53.e8. https://doi.org/10.1016/j.jaci.2017.02.019

3. Sasaki M, Koplin JJ, Dharmage SC, Field MJ, Sawyer SM, McWilliam V, et al. Prevalence of clinic-defined food allergy in early adolescence: The SchoolNuts study. Journal of Allergy and Clinical Immunology. 2018;141(1):391-8.e4. https://doi.org/10.1016/j.jaci.2017.05.041

4. Savage J, Sicherer S, Wood R. The Natural History of Food Allergy. J Allergy Clin Immunol Pract. 2016;4(2):196-203; quiz 4. https://doi.org/10.1016/j.jaip.2015.11.024

5. Chu DK, Wood RA, French S, Fiocchi A, Jordana M, Waserman S, et al. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. Lancet. 2019;393(10187):2222-32. https://doi.org/10.1016/S0140-6736(19)30420-9

6. Grzeskowiak LE, Tao B, Knight E, Cohen-Woods S, Chataway T. Adverse events associated with peanut oral immunotherapy in children - a systematic review and meta-analysis. Sci Rep. 2020;10(1):659. https://doi.org/10.1038/s41598-019-56961-3

7. de Silva D, Rodriguez Del Rio P, de Jong NW, Khaleva E, Singh C, Nowak-Wegrzyn A, et al. Allergen immunotherapy and/or biologicals for IgE-mediated food allergy: A systematic review and meta-analysis. Allergy. 2022;77(6):1852-62. https://doi.org/10.1111/all.15211

8. Lucendo AJ, Arias Á, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. Annals of Allergy, Asthma & Immunology. 2014;113(6):624-9. https://doi.org/10.1016/j.anai.2014.08.004

9. Nilsson C, Scurlock AM, Dellon ES, Brostoff JM, Pham T, Ryan R, et al. Onset of eosinophilic esophagitis during a clinical trial program of oral immunotherapy for peanut allergy. J Allergy Clin Immunol Pract. 2021;9(12):4496-501. https://doi.org/10.1016/j.jaip.2021.07.048

10. Petroni D, Spergel JM. Eosinophilic esophagitis and symptoms possibly related to eosinophilic esophagitis in oral immunotherapy. Annals of Allergy, Asthma & Immunology. 2018;120(3):237-40. e4. https://doi.org/10.1016/j.anai.2017.11.016

11. Loke P, Orsini F, Lozinsky AC, Gold M, O'Sullivan MD, Quinn P, et al. Probiotic peanut oral immunotherapy versus oral immunotherapy and placebo in children with peanut allergy in Australia (PPOIT-003): a multicentre, randomised, phase 2b trial. Lancet Child Adolesc Health. 2022;6(3):171-84. https://doi.org/10.1016/S2352-4642(22)00006-2

12. Jones SM, Kim EH, Nadeau KC, Nowak-Wegrzyn A, Wood RA, Sampson HA, et al. Efficacy and safety of oral immunotherapy in children aged 1–3 years with peanut allergy (the Immune Tolerance Network IMPACT trial): a randomised placebo-controlled study. The Lancet. 2022;399(10322):359-71. https://doi.org/10.1016/S0140-6736(21)02390-4

13. Shaker M, Chan ES, Protudjer JLP, Soller L, Abrams EM, Greenhawt M. The Cost-Effectiveness of Preschool Peanut Oral Immunotherapy in the Real-World Setting. J Allergy Clin Immunol Pract. 2021;9(7):2876-84 e4. https://doi.org/10.1016/j.jaip.2021.02.058