

REVIEW

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CSACI guidelines for the ethical, evidence-based and patient-oriented clinical practice of oral immunotherapy in IgE-mediated food allergy

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Abstract

Background: Oral immunotherapy (OIT) is an emerging approach to the treatment of patients with IgE-mediated food allergy and is in the process of transitioning to clinical practice.

Objective: To develop patient-oriented clinical practice guidelines on oral immunotherapy based on evidence and ethical imperatives for the provision of safe and efficient food allergy management.

Materials and methods: Recommendations were developed using a reflective patient-centered multicriteria approach including 22 criteria organized in five dimensions (clinical, populational, economic, organizational and sociopolitical). Data was obtained from: (1) a review of scientific and ethic literature; (2) consultations of allergists, other healthcare professionals (pediatricians, family physicians, nurses, registered dietitians, psychologists, peer supporters), patients and caregivers; and patient associations through structured consultative panels, interviews and on-line questionnaire; and (3) organizational and economic data from the milieu of care. All data was synthesized by criteria in a multicriteria deliberative guide that served as a platform for structured discussion and development of recommendations for each dimension, based on evidence, ethical imperatives and other considerations.

Results: The deliberative grid included 162 articles from the literature and media reviews and data from consultations involving 85 individuals. Thirty-eight (38) recommendations were made for the practice of oral immunotherapy for the treatment of IgE mediated food allergy, based on evidence and a diversity of ethical imperatives. All recommendations were aimed at fostering a context conducive to achieving objectives identified by patients and caregivers with food allergy. Notably, specific recommendations were developed to promote a culture of shared responsibility between patients and healthcare system, equity in access, patient empowerment, shared decision making and personalization of OIT protocols to reflect patients' needs. It also provides recommendations to optimize organization of care to generate capacity to meet demand according to patient choice, e.g. OIT or avoidance. These recommendations were made acknowledging the necessity of ensuring sustainability of the clinical offer in light of various economic considerations.

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Conclusions: This innovative CPG methodology was guided by patients' perspectives, clinical evidence as well as ethical and other rationales. This allowed for the creation of a broad set of recommendations that chart optimal clinical practice and define the conditions required to bring about changes to food allergy care that will be sustainable, equitable and conducive to the well-being of all patients in need.

Keywords: Food allergy, Oral immunotherapy, Clinical practice guidelines, Avoidance, Patient-centered, Evidence, Ethics, Quality of life, Indication, Contraindication, Multi-criteria decision analysis

Background

IgE-mediated food allergy is a condition that imposes food-related restrictions on patients and their caregivers in order to prevent allergic reactions. The burden of disease stems from both the actual and perceived risks of accidental ingestion, including the possibility of a life-threatening allergic reaction. This burden manifests itself in variable levels of anxiety and social limitations and significantly impacts quality of life. The current standard management for food allergy is complete avoidance of the offending allergen in the diet, combined with training on how to recognize and treat allergic reactions. And while avoidance is currently recognized as a safe approach, it has a limited ability to improve a patients' perception of safety or sense of control over the condition and its associated limitations—this leads many to seek alternative management options [1–6].

Oral immunotherapy (OIT) consists of daily ingestion of the offending food allergen (food dosing), starting below a patient's threshold dose (i.e. the minimum amount that would elicit a reaction), and increasing the dose over time with a goal of increasing clinical tolerance to that food. It had been proposed as a potential alternative to avoidance throughout the 20th and into the early 21st centuries [7], yet its development had been limited until recently. This is mainly due to the risk of allergic reactions associated with OIT, which is difficult to reconcile with current practice standards that focus on the avoidance of reactions at all cost and are arguably rooted in a culture of fear.

OIT can be viewed as a disruptive innovation as it challenges the current paradigm of care in food allergy and highlights its limitations in responding to patient needs. There is a need for patient-centered ethical clinical practice guidelines (CPGs) that include patients and caregivers as well as other stakeholders in the consultation and deliberation process, in order to develop best practice recommendations for providing OIT for food allergy. It is essential to understand patient and caregiver perspectives to ensure proper interpretation of published evidence and understand the ethical issues involved.

Previous CPGs on OIT [8–10] have used more traditional approaches, focusing mainly on quantitative

clinical evidence. However, in order to ensure a clear vision of all that OIT entails and to benefit all patients with food allergy in need of care, CPGs must not only be based on experimental data (e.g., clinical trials) but also on observational, economic and sociopolitical data, as well as experiential narrative data from both patients and healthcare professionals. The optimal provision of OIT must also account for ethical and organizational data to promote the equitable, sustainable and responsible development of this treatment. In fact, evidence-based medicine has been defined as “the application of the best available research to clinical care, which requires the integration of evidence with clinical expertise and patient values [11].”

The development of these CPGs on OIT followed the Guidelines International Network 2015 recommendations including a policy for the management of conflicts of interests [12]. They were commissioned by the Canadian Society of Allergy and Clinical Immunology (CSACI), and was developed through a collaboration with the University Hospital Center Sainte-Justine and the methodological support of the Institut National d'Excellence en Santé et Services Sociaux (INESSS). CSACI acted as the sponsor and was responsible for creating a diversified Working Group. This working group and the executive team opted for a reflective multicriteria methodology, which has been used in the past to develop CPGs [13] using the EVIDEM (Evidence and Values Impact on Decision Making) ethical framework [14–17]. This approach encourages the collection of data from diverse sources, including both the scientific literature and consultations, thus offering a 360° view of the subject. This framework was also used to organize, analyze and ultimately integrate the data into a deliberation guide, providing an efficient and consistent approach throughout the project.

Materials and methods

Multidisciplinary team

A multidisciplinary team comprised of experts from a diversity of fields was assembled, including allergists and other healthcare professionals, ethicists, and those with expertise in multicriteria deliberation methodology, literature review, consultations and sociology.

Multicriteria methodology

The aim of the methodological approach was to support reflection by all stakeholders during the development of fair and reasonable recommendations. To this end, a patient-centered and ethics-based multicriteria framework was used throughout the process. The framework was adapted from EVIDEM, included three additional patient focused criteria and organized 22 criteria into five dimensions defined to cover all relevant aspects of OIT. The framework also builds on the Accountability for reasonableness (A4R) conditions set forth by Daniels and Sabin [18] and the Triple Aim of healthcare systems set forth by Berwick and colleagues [19]. The five dimensions of the framework include:

- How the use of OIT can contribute to a socio-politico-cultural context conducive to The Common Good (sociopolitical dimension),
- How OIT contributes to a fair and equitable distribution of services (populational dimension),
- How OIT responds to a need for health and well-being in an adequate way (clinical dimension),
- How the use of OIT can contribute to improve the quality, organization and governance of healthcare services (organizational dimension), and
- How OIT optimizes the use of resources and the associated costs to ensure sustainability of healthcare systems (economic dimension).

Each dimension contains criteria for operationalization, organized into a multicriteria grid. Data from the literature review and consultations were collected and organized per criterion to allow for a comprehensive assessment of OIT and provide a knowledge platform for the development of the CPG recommendations.

All documentation was compiled using a data management software program (CITAVI), which was adapted to organize data by criteria and provided an interactive interface for review by the working group.

Conflict of interest management and respect of persons

To avoid the impact of COI or conflicts of roles on the process, explicit guidelines regarding their declaration, evaluation and management were developed based on the GIN 2015 recommendations (see Additional file 1: Appendix 1) [12]. Each potential participant was required to complete a conflict of interest declaration, which was then analyzed by an ethicist. Participants who were deemed at risk of bias on a particular subject were excluded from the room during the deliberation meeting for the time during which the related recommendations were being discussed.

Every step was taken to ensure that best practices for respect of persons were carried out, with respectful atmosphere created by chairs for each group discussion and by interviewers for each individual interview; as well documentation was provided ahead of time to give each participant time to prepare. All patients completed an informed consent; they were informed that only their perspective on the topic was solicited, not personal clinical data, and that psychological support was available.

Literature review

Sources of data

An extensive literature review was performed. The primary sources of data were peer-reviewed full-text publications retrieved through searching multiple sources, including PubMed, MEDLINE (Ovid), Embase, EBM Reviews, CINAHL and Web of Science bibliographic databases. Searches for OIT clinical data were performed on April 17–18, 2019, and searches for epidemiological and burden of disease data were performed on May 30–31, 2019. Search terms are presented in Additional file 1: Appendix 2A. These searches aimed to collect data for all dimensions of the framework, including the sociopolitical, populational, clinical, organizational and economic dimensions. Bibliographical database searches were supplemented by individually searching the tables of contents of pertinent recent periodicals (up to September 2019), as well as bibliographies of key publications. Websites from government agencies, HTA bodies, professional associations and patient associations were also consulted. In order to capture the perception of OIT in the media, a review of the Canadian news media of the last 5 years was conducted via the FACTIVA Global News Monitoring & Search Engine using ‘oral immunotherapy’ and ‘immunothérapie orale’ (French) as search terms.

Data selection for each dimension

Retrieved records were screened based on title and abstract to select those for further assessment in full-text format. For the clinical dimension, patient focus groups or surveys providing insight on the importance of the therapy and its outcomes for patients, were considered for inclusion in addition to clinical studies (see details below), qualitative studies, and published CPGs. For the sociopolitical dimension, different types of publications on relevant topics such as the history of OIT and regulatory aspects were reviewed. Stakeholder’s positions were collected and informed by the media press review. For the populational dimension, records such as recent systematic reviews of epidemiological studies, original studies conducted in large, representative populations,

preferably in the Canadian context, and recent reviews of qualitative research were considered for inclusion. For the organizational dimension, data concerning the healthcare system's organization and requirements for the provision of OIT was sought. For the economic dimension, data collected included economic studies, such as cost of illness studies or economic analyses, and cost data (i.e., the costs of products and procedures for OIT). An analysis of associated ethical issues was included for each criterion throughout the framework, as applicable.

Selection of clinical studies and assessment of their methodological quality

Clinical studies were selected using eligibility (inclusion/exclusion) criteria listed in Additional file 1: Appendix 2B. Study designs included experimental, comparative studies, randomized [RCTs], non-randomized controlled clinical trials [CCTs], and observational studies reporting outcomes from clinical practice. RCTs are best suited to answer the questions whether an intervention is efficacious and safe, compared to another intervention or management option. These, however, can be limited in their ability to answer certain specific questions that arise in clinical practice, including how patient characteristics may impact outcomes or how to adapt to what happens over the course of treatment [20]. These limits stem from highly selective patient eligibility criteria, rigid study protocols, non-patient-centered end-points, short follow-up durations or small population sizes. A blinded study design, in particular, is not best suited to study personalized care, nor to investigate the impact of a treatment on patient-reported quality of life outcomes—examples include topics such as food-allergy related anxiety and the burden of allergen avoidance, both of which require awareness of the treatment received and the results achieved (e.g., level of desensitization). Observational studies can complement experimental comparative studies, especially when they involve larger less strictly selected patient populations that are closely followed over a long-term horizon in a real world practice setting.

The methodological quality of RCTs was assessed according to the Cochrane risk of bias approach [21], using published risk of bias assessments from systematic reviews, whenever available [22–24]. For case series, the Institute of Health Economics Quality Appraisal of Case Series Studies Checklist was applied [25]. Among its 20 items, 10 core items on study conduct and reporting were selected to operationalize quality assessment. A case series was deemed of high methodological quality (low risk of bias) if all 10 were positive, moderate if 8 to 9 were positive, and low (high risk of bias) if less than 8 were

positive. The methodological quality of meta-analyses was determined by checking whether all eligible studies had been included, and by repeating key analyses based on the data reported in the original publications.

Extraction, analysis and synthesis

Clinical study data was extracted and synthesised in evidence tables in a per-criterion report format. The extraction tool was validated by a clinical expert. The report was validated by two assessors and then reviewed and revised by the Working Group. Clinical data was further synthesized and integrated into the multicriteria grid for the deliberation. Data pertaining to the other dimensions were directly synthesized in the multicriteria grid.

Consultations

Objective

The objective of the consultation process was to capture relevant experiential and contextual data from diverse perspectives to develop a comprehensive understanding of the topic. Data for each dimension of the multicriteria grid was collected through discussions with allergists, patients and other healthcare professionals. Healthcare professionals were able to provide insight into two main aspects: first, to validate and enrich the data collected through the literature review, and second, enhance the data with relevant clinical practice experience that might not have been elucidated from published studies. Patients with food allergy contributed their unique perspective of the condition and its impact, as well as their view and experience of food allergy therapy, including its benefits and its constraints.

General approach

In order to ensure diversity of participants, an open call for applications was posted on the website of applicable patient associations and the CSACI, and targeted calls were made by sending e-mail invitations to relevant professional societies and all CSACI members. The calls provided a short text explaining the objectives of the project, as well as the goals and format of the consultation, followed by a link to a small questionnaire covering the necessary information to enable selecting a diversity of participants to be consulted. The recruitment process was completed by applying a chain-referral sampling strategy. For each potential consultant, the geographical location, gender, general opinion of OIT and, when relevant, the type of practice (e.g. academic vs community, pediatric vs adult) were considered for participant diversification.

Selected participants were contacted and, upon confirmation of participation, asked to complete COI

and consent forms. Subsequent steps differed depending on the format of the consultation for each specific group. Possible steps were discussion panels, individual interviews and an online questionnaire. Discussion panels served to create a debate around the various aspects of OIT from different contexts and viewpoints. Individual interviews allowed for the collection of in-depth data from a specific context and its implications. The online questionnaire allowed for the collection of a broad range of experience from a greater number of experts than would have been possible through discussion panels and interviews alone. For every consultation, participants received a consultation guide with questions adapted to their contexts and expertise, which was based on the multicriteria grid and grouped by criteria, in order to facilitate data collection and analysis. All participants were provided with the consultation document a week prior to the consultation in order to give time to familiarize themselves with it. During the discussion panels, the Chatham House Rule [26] was applied, which guarantees anonymity of all information provided by participants. These panels were led by co-chairs experienced in data appropriation while fostering an environment of respect, attentiveness and constructive exchanges.

Allergists

Consultations with allergists were twofold, with two different groups. A panel discussion was first conducted with the 15 Working Group members to identify key points on which to focus the CPGs. The group was well diversified in terms of experience with OIT: some participants had never offered it, some had offered it only in research settings, and those offering it in clinical practice reported using different methods and protocols. The discussion followed the multicriteria questionnaire, discussing every issue per criteria. Data was collected through recording and notetaking. Secondly, 42 CSACI members completed an online questionnaire, following the same structure. The data obtained from both the panel discussion and the questionnaire were compiled per criteria. Key themes within each criterion were identified through thematic analysis.

Patients and caregivers

Consultations with patients also occurred in two formats to fit two purposes. A panel discussion was held with 8 participants, diversified according to their individual context pertaining to OIT, which included whether or not they had direct experience with it, what their vision of the therapy was and the type and impact of their food allergy condition. Discussions were guided by the

multicriteria grid. Patient perspective narrative data was collected for each of the criteria through recording and notetaking. The second consultation format consisted of individual interviews with 6 participants, following the same diversification criteria and using the same questionnaire as the panel discussion. The data from both sources was then compiled in the same way as the allergist consultations and analyzed thematically to identify key points raised by the patients.

Other healthcare professionals and lay representatives

These consultations served the purpose of obtaining the viewpoints of stakeholders involved in the care of food allergy patients other than allergists, namely family physicians, pediatricians, nurses, registered dietitians, psychologists and caregivers engaged in peer support activities. They were consulted via a discussion panel involving 10 participants diversified by their professions and the differences in their experience with OIT, which followed the same format as the patient panel. Another two healthcare professionals completed an online questionnaire. Representatives from patient associations were also interviewed, via phone, using the same questionnaire as the panel, to provide patient-centered contextual knowledge on OIT. This data was collected through notes and recording, per criteria, compiled in the same way as for the other consulted groups, and thematically analyzed, bringing forward essential notions associated with OIT provision to include in the CPGs.

Data from milieu of care

Data from Canadian clinical practices (milieu of care) was collected in the form of economic data provided by the working group members from their clinical practice offer of OIT, which was extracted and compiled into criteria of the economic dimension.

Deliberation

Data integration

Compiled data from the literature review, consultations and milieu of care were integrated into the deliberation guide in a highly synthesized format in order to facilitate comprehension of the data by all participants during the deliberation. Prior to this integration, the data from the literature review was revised and enriched by the Working Group. Data for each criterion was separated into three sections: literature review data, consultation data and ethical aspects. The deliberation guide consisted of the synthesized data integrated into a multicriteria grid, with an additional column in which participants were invited to add their interpretation of the data provided in order to facilitate discussion. Empty

recommendation boxes at the end of each dimension were also included to allow discussion and the formation of informed recommendations for one subject at a time.

Deliberation process

The participants in the deliberation included the allergists of the Working Group along with selected participants from the consultations, in order to provide relevant data from a global patient perspective. These included two patients with different and longstanding experiences, two family physicians, a pediatrician, a nurse, a registered dietician, a pharmacist and a peer supporter. Each participant received a copy of the deliberation guide 1 week prior to the meeting. The deliberation meeting was chaired by three methodologists who were experts in multicriteria deliberation, multicriteria literature review and synthesis and multicriteria consultations, for a total of 22 participants. The deliberation was divided into four sessions according to the dimensions of the multicriteria grid, during which the literature review and consultation data were presented by the co-chairs. Corresponding recommendations were discussed and determined at the end of each session. All recommendations were based on a group consensus—recommendations for which a COI was identified were based on a consensus of the group excluding those with a COI.

Rationales for recommendations

Recommendations were based on a variety of rationales that included evidence from consultations and scientific studies, ethical imperatives, such as promotion of equity or patient autonomy, and other considerations, such as general standards of clinical care, clinical reasoning, and biological plausibility.

For recommendations that included evidence from clinical studies, the strength of the evidence supporting the recommendation was determined using a method that builds on the approach of the Oxford Centre for Evidence-Based Medicine [8, 27]. The risk of bias was assessed using the Cochrane approach [21] and the Institute for Health Economics (IHE) method for case series [25]. These methods, developed for quantitative data, were adapted to include qualitative data from consultations such that the strength of the evidence supporting the recommendation takes into account:

- risk of bias (study design, including the methodology chose for data collection and analysis can affect the risk of misleading results);
- type of study (meta-analyses, RCTs, non-randomized controlled trials (CCTs), case series); studies could be carried out in usual clinical practice or in a research context;

- consistency of evidence across studies; and
- the level of coherence between evidence from studies and data obtained from the consultation process.

The amount, quality and consistency of the evidence supporting the recommendation is defined at three levels:

- *High* Large amount of consistent evidence from RCTs (or meta-analyses) *and* large studies in clinical practice, ideally at a low risk of bias; *AND* coherence with data from consultations and/or qualitative studies.
- *Moderate* Moderate amount of consistent evidence from RCTs (or meta-analyses) and/or studies in clinical practice, ideally at a moderate or low risk of bias; *AND* coherence with data from consultations and/or qualitative studies.
- *Low* Small amount of evidence *OR* evidence with some incoherence in data from RCTs (or meta-analyses) and/or studies in clinical practice *OR* data at moderate to high risk of bias; *AND* coherence with data from consultations and/or qualitative studies.

Strength of recommendations The strength of recommendations in CPGs is often graded based on the quality of clinical evidence regarding the efficacy and safety of an intervention. However, this approach does not apply to recommendations that do not rest on clinical trial outcomes, but for which the body of evidence from clinical research and practice shows a clear clinical benefit because conducting such trials would neither be reasonable nor ethical [28]. Moreover, grading in such a way does not take into account factors other than clinical outcomes, such as ethical imperatives, social context or economic considerations, which can be key elements of the rationale underlying a recommendation. Therefore, to ensure that all types of recommendations in these CPGs will be regarded on an equal footing, the strength of recommendations was not given a rating. Rather, in the spirit of accountability for reasonableness (A4R) [18], the rationale for each recommendation, the level of supporting evidence, where appropriate, and the necessary contextualization and nuances were all clearly stated.

Results

Multicriteria grid

The multicriteria grid used for this project included five dimensions divided into 22 criteria and is shown in Fig. 1.

Data used as basis for recommendations

The literature review yielded a total of 8157 records; 468 of them were assessed for eligibility in full-text records and 145 were included in the multicriteria grid (Fig. 2).

An additional 17 articles were included from the media press review.

A total of 14 patients or caregivers, 13 allergists and 16 other healthcare professionals or patient association representatives were consulted through panel discussions or individual interviews. In addition, 42 CSACI allergists responded to the online consultation survey.

Data on the economic aspects of OIT was available from three Canadian practices, and data on quality of life impact of OIT was collected from one practice.

The synthesis of the data collected through the literature review, consultations and from the milieu of care is presented by criteria along with complete references in the deliberation guide (Table 1). Detailed clinical evidence tables with results of quality assessments are available in Additional file 1: Appendix 3.

Deliberation guide

The deliberation guide includes the synthesized data for each criterion along with a section prompting participants to interpret and discuss the data. Boxes for

the development of recommendations were added at the end of each dimension.

Recommendations

Recommendations are presented in the following format:

1. A lay summary of the data synthesis that led to the recommendation(s) written in a format that is accessible to a non-physician audience (for the clinical dimension, detailed narrative summaries of the data are available in Additional file 1: Appendix 4).
2. Additional key points discussed during deliberation that led to the recommendation(s)' development.
3. Recommendations and rationales.

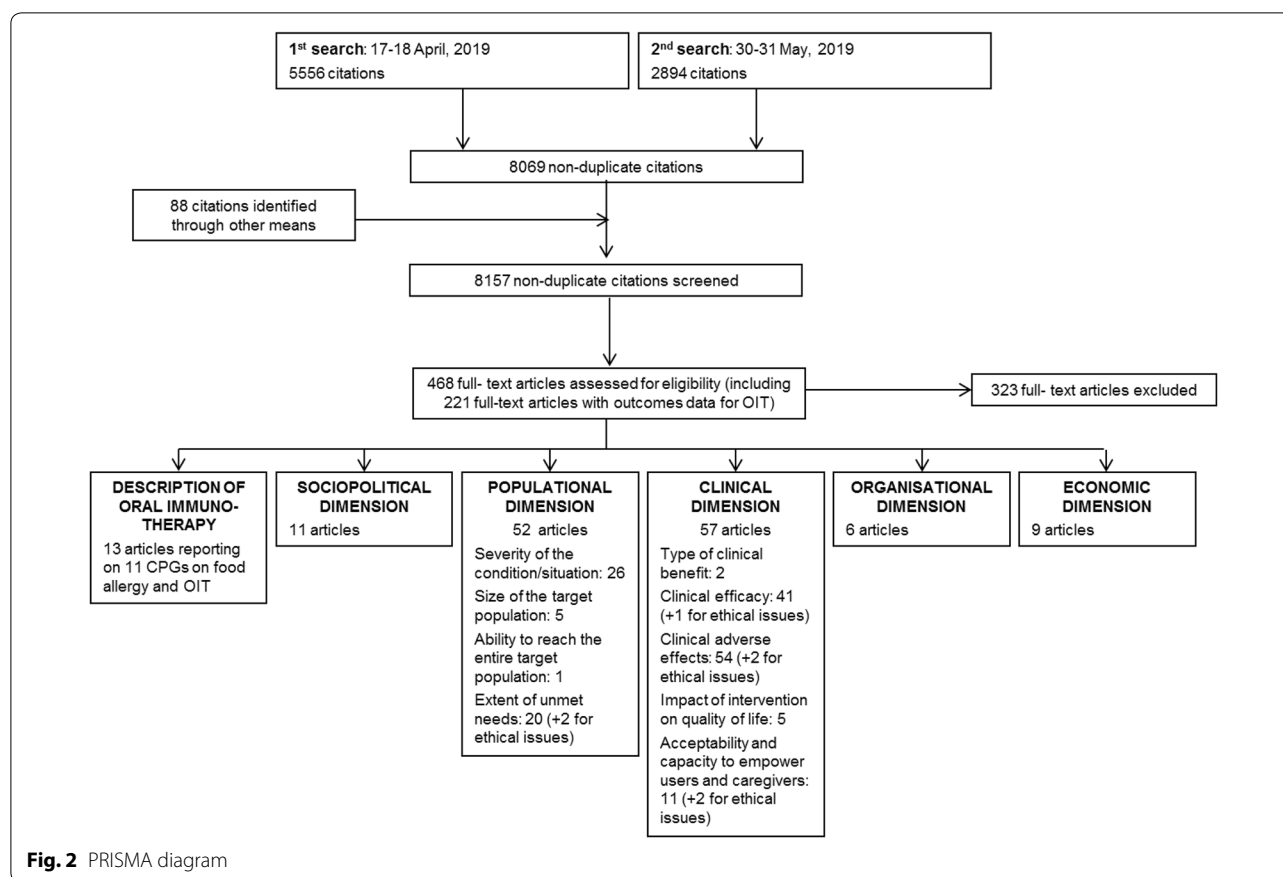
To facilitate the understanding of the presented data, key concepts and definitions pertaining to OIT are illustrated in Fig. 3.

Sociopolitical dimension: promotion of the common good Recommendations for a sociopolitical context for optimized food allergy management

Summary of data synthesis (see details and references in Table 1, Sociopolitical dimension, criteria 1 and 2): Data collected for the sociopolitical dimension illustrates that the main practice in food allergy management is avoidance, in which patients and caregivers carry most of the responsibility. Although this management method is certainly appropriate for some, there has been a growing demand for an interventional approach in food allergy, leading to recent developments in OIT. With OIT treatment growing in popularity, two opposing perceptions have arisen: one of fear and one of hope. Confusing misinformation concerning risks and benefits of OIT further contributes to a polarizing discussion surrounding OIT. Within this unconducive context, OIT has only recently been introduced in a limited number of clinical practices. Access disparities are further exacerbated by increasing demand, the lack of specialized care in urban and, even more so, rural areas, and a potentially inadequate billing system in some Canadian provinces. Additionally, some proponents assert that OIT should only be administered using pharmaceutical products, such as pre-packaged food doses, indented as a life-long treatment, rather than using readily available food for OIT, creating issues that could adversely affect both patients and sustainable development of OIT.

DIMENSIONS	Criteria
SOCIOPOLITICAL <i>Promotion of conditions conducive to common good</i>	C1 - Historical, political, cultural context
	C2 - Stakeholder visions
POPULATIONAL <i>Promotion of equity</i>	C3 - Severity of the condition / situation
	C4 - Size of the target population
	C5 - Ability to reach the entire target population (access)
	C6 - Extent of unmet needs
	C7 - Social priorities
CLINICAL <i>Promotion of health and well-being (outcomes of the intervention)</i>	C8 - Clinical efficacy
	C9 - Clinical adverse effects
	C10 - Type of clinical benefit offered by the intervention
	C11 - Acceptability and capacity to empower users and caregivers
ORGANIZATIONAL <i>Promotion of integrated care</i>	C12 - Impact of the intervention on quality of life and health as perceived by the user
	C13 - Alignment of the intervention with the mandate of the healthcare system
ECONOMIC <i>Promotion of sustainability</i>	C14 - System capacity and appropriate use of intervention
	C15 - Cost of acquiring and maintaining the intervention for the health and social services system
	C16 - Cost in health and social services system resources
	C17 - Costs for the user / caregiver
	C18 - Societal costs
	C19 - Environmental impact
	C20 - Cost-effectiveness
	C21 - Opportunity cost regarding the resources of the healthcare system and financial affordability
	C22 - Opportunity cost regarding the resources of the patient / caregiver / user and financial affordability

Fig. 1 Multicriteria grid: dimensions and criteria



Additional key points from deliberation It is essential that patients with food allergy have the ability to control the management of their condition so that it reflects their needs and objectives. As such, they should be able to access OIT when it is requested. Patients will be able to reach these objectives more effectively when adequately informed about their treatment, to manage anxiety related to food allergy and to prevent

unrealistic expectations about the benefits of OIT or an overestimation of its risks. A fully standardized approach would not be adequate in this context since it cannot respond to each patient's situation and needs—this calls for research designs on food allergy care to be directed towards answering key questions of personalized care, such as long-term outcomes and real-life needs.

- ① Reactivity threshold (dotted red line), corresponds to the amount of food that will trigger a reaction. It varies between patients and can also vary over time.
- ② During the **initial food escalation**, the food allergen (full blue line) is introduced in clinic for the first time to identify a dose below the reactivity threshold to begin daily home dosing.
- ③ The amount of the daily home dose is then increased periodically under medical supervision during **up-dosing visits**.
- ④ Once the target maintenance dose is achieved, the patient is protected against accidental exposure to at least that amount (**protective or partial desensitization**) as long as the food is eaten regularly.
- ⑤ Regular ingestion of the food is paramount. If food dosing is stopped, the reactivity threshold will decrease progressively patient could react upon reintroduction.
- ⑥ In presence of external **co-factors**, which contribute to additional mast cell activation or disturb gastro-intestinal barrier function resulting in spikes of allergen absorption, the reactivity threshold can decrease even below the daily food dose. Patient training and action plan is thus required to recognize and adapt treatment in presence of co-factors.
- ⑦ A **high threshold challenge** can be performed to a higher amount (e.g. 2 full servings of the food) to determine the full extent of protection while on maintenance (**complete desensitization**).
- ⑧ To assess the risk posed by co-factors, a challenge with the allergen can be performed after administering aspirin and alcohol or with concomitant exercise.
- ⑨ Sustained tolerance testing can be performed by progressively increasing the dosing interval and monitoring for return of reactivity.
- ⑩ When stopping food doses after prolonged treatment, some patients will have achieved sustained unresponsiveness to their allergens. Most will find their reactivity threshold to have increased compared to baseline level before treatment.

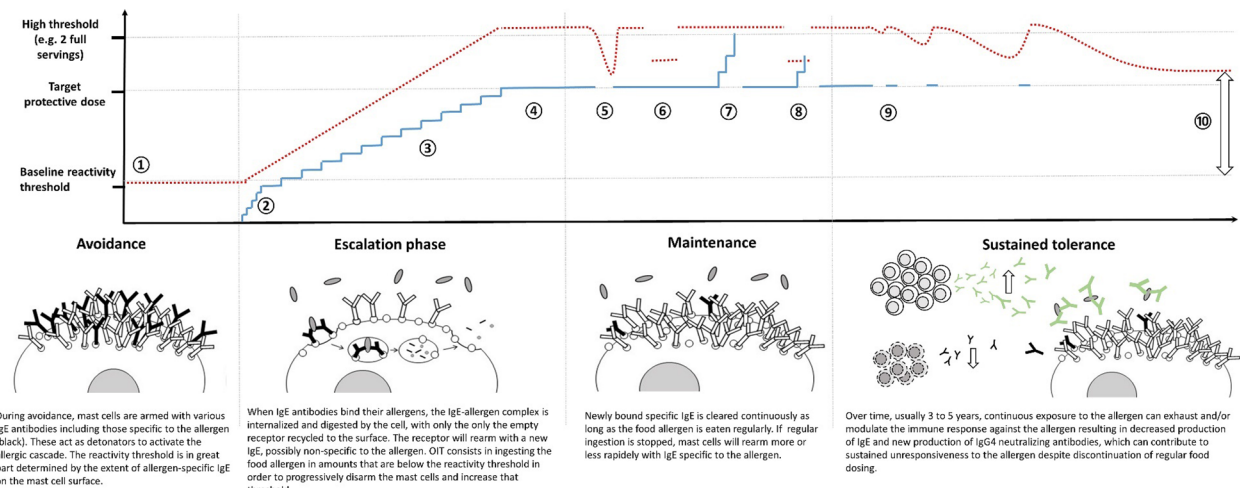


Fig. 3 Key concepts and definitions pertaining to OIT

Box 1: Recommendations for a sociopolitical context for optimized food allergy management

A large number of patients with food allergies are unable to access basic care for proper diagnosis and management, including avoidance or oral immunotherapy, leaving many with inadequate support from the healthcare system. Empowerment of patients and families should be promoted through shared responsibility with the healthcare system, in respect and support of patient choices

A new culture should be fostered to transition from one that is fear-driven towards one that promotes a sense of control in food allergy through accurate information on the condition and the options available

There is inadequate reliable communication between patients, families and healthcare professionals about oral immunotherapy, often accompanied by misinformation. This should be addressed through shared decision-making, and access to trustworthy, clear and transparent information

Oral immunotherapy for food allergy should be developed and practiced in the spirit of personalized care, considering the heterogeneity and specificity of the condition and individual patient contexts

Research should be encouraged to adequately inform clinical practice regarding OIT, through innovative study designs focusing on meaningful patient-centered and long-term outcomes, while appropriately reflecting the need for personalized care in real-world practice

Ethical imperative, data or other considerations in support of the recommendation

This recommendation is based on the principle of *solidarity* of public healthcare systems towards patients to provide necessary care and foster patient and family *autonomy* in their choices and management of their condition

It is supported by data from consultations with stakeholders and key aspects emerging from the literature

This recommendation is based on the principle of *patients' best interest*, as defined by the patients themselves

It is supported by data from consultations with stakeholders and key aspects emerging from the literature

This recommendation is based on the principle of *transparency* to ensure easy access to all relevant and trustworthy knowledge on OIT and safeguard patient and family *decisional autonomy*

It is supported by data from consultations with stakeholders and key aspects emerging from the literature

This recommendation is rooted in the principle of *patient protection*, since failure to adapt to the patient and their individual characteristics can lead to risky or futile interventions

It is supported by data from consultations with stakeholders and key aspects emerging from the literature

This recommendation is rooted in the principle of *patient autonomy*. To ensure informed decision making in OIT, research needs to focus on meaningful patient-centered and long-term outcomes that are coherent with individual realities and objectives

It is supported by data from consultations with stakeholders and key aspects emerging from the literature

It is supported by the previous recommendation for the development and practice of OIT in the spirit of personalized care

Populational dimension: promotion of equity *Recommendations for the equitable provision of OIT*

Summary of data synthesis (see details and references in Table 1, Populational dimension, criteria 3 to 7): The burden of food allergy can be described in two ways: based on the risk of severe reactions which is relatively low or based on its impact on the psychosocial wellbeing of patients and caregivers, which is extensive (see details and references in Table 1). Food allergy affects many spheres of life for patients and their caregivers and may lead to isolation or vulnerability to bullying. These impacts may be lifelong for those in whom food allergy does not resolve naturally with time.

A management strategy based solely on avoidance is often characterized by a number of unmet needs, as patients and caregivers are often left to manage their condition by themselves. Society can help reduce risk and burden with measures such as appropriate food labeling regulations or food restriction/management protocols in schools and restaurants. However, even with these measures in place, patients and caregivers will continue to have many limitations and few options to establish control over their risk of reaction.

Up to 50% is directly or indirectly affected by food allergy, according to some estimates, including patients, family and caregivers, their immediate social circles and society. Despite this, there is low investment in this area by the healthcare system, with a low capacity of care for both accurate diagnosis and management. There are disparities in access to specialized care, which is generally limited, both in urban and rural areas.

Key additional points from the deliberation A culture of fear currently exists regarding food allergy and includes widespread erroneous concept that all allergies should be considered equally dangerous. As a result, many believe that the only acceptable management option is strict avoidance. Instead, the risk of reaction is extremely variable and hard to predict. This results in a disparity between populational epidemiological data and actual individual risk. Individuals vary with respect to their level of comfort with risk as well as their perception of the extent of benefit derived from a treatment. Thus, the decision to pursue OIT should be left to the well-informed patient as much as clinically possible, rather than based on external criteria.

It was strongly felt that in the development of OIT within the healthcare system as an option of care, steps must be taken to ensure that resources in food allergy are

not disproportionately displaced toward OIT, so as to ensure that patients will continue to receive optimal care if opting for the traditional approach of food avoidance.

Box 2: Recommendations for the equitable provision of OIT

Ethical imperative, data or other considerations in support of the recommendation

The notion of severity is inadequate for determining eligibility for OIT, as the risk of a reaction and of it being severe are difficult to predict and does not necessarily correlate with the psychosocial impact on patients and families. The aim should thus be to make OIT available as an option for all patients wishing to receive it, provided there is no contraindication and a clear understanding of individual risks and benefits

This recommendation is based on the principle of *equity in eligibility*. It is supported by data from consultations with stakeholders and key aspects emerging from the literature

A lack of public investment has resulted in a situation of low capacity and disparities in access to care for the accurate diagnosis and proper management of food allergy. This applies to management choices that include both avoidance and OIT

This recommendation is based on the principles of *solidarity and equity of access*. This refers to both regional access and access to food allergy care in general. It is supported by data from consultations with stakeholders and key aspects emerging from the literature

Clinical dimension: promotion of health and well-being *Recommendations on eligible food allergens and types of clinical outcomes that can be achieved by OIT*

Summary of data synthesis (see details and references in Table 1, clinical dimension, criteria 8 to 12): Many studies with OIT to a variety of different food allergens show that a majority of patients can achieve protective levels of desensitization and that a substantial proportion can achieve complete desensitization, which can be maintained with continued consumption of the food. Studies show that many patients do continue consuming the food allergen regularly in the longer term. A variable smaller proportion can maintain tolerance to the food allergen even after a period of prolonged avoidance; however, this data is scarce and only available for the major food allergens.

Patients undergoing OIT will more likely experience allergic reactions than those who are avoiding the food. This is because treatment dictates that they intentionally consume their food allergen. A majority of OIT patients have at least one allergic reaction, varying mild to severe (i.e. anaphylaxis), and some may require the use of epinephrine. According to many studies across different designs and food allergens, the

frequency and/or severity of allergic reactions declines as the treatment progresses. A few studies also observed that the frequency of reactions from accidental exposure declines in patients undergoing OIT.

Even after a prolonged period of maintenance dosing, systemic reactions may occur in some patients. These reactions usually occur in the presence of a cofactor (e.g. exercise, sleep deprivation, illness and fever, certain medications) that transiently increases the likelihood of reaction, but the risk appears to decrease with longer time on maintenance.

While some patients ultimately discontinue OIT due to adverse events, other factors may also result in discontinuations and include anxiety or refusal to ingest the food doses.

avoidance in the short term, the anxiety associated with these is generally manageable because they are expected and can be planned for, which contributes to patients' sense of control. The burden of these reactions is generally offset by the protection granted against unexpected reactions from accidental exposures outside of food dosing, which creates a sense of empowerment by lifting the burden of constant vigilance and provides a sense freedom. For many patients, the burden of these reactions diminishes over time as they learn to self-manage.

The variability in safety outcomes between studies may be due to various factors, including a treatment center's experience in OIT. This will affect the ability of providers to personalize treatment plans, shaping the instructions offered to patients on how to take the dose and manage reactions.

Additional key points from deliberation Although reactions are more frequent during OIT than with

Box 3: Recommendations on eligible food allergens and types of clinical outcomes that can be achieved by OIT

Ethical imperative, data or other considerations in support of the recommendation Level of evidence (applicable when recommendations are based on outcome data from clinical studies)

There is no convincing evidence of a clinically significant difference between food allergens in terms of safety and efficacy outcomes in OIT for the treatment of IgE-mediated food allergy. Therefore, all recommendations in these CPGs are generally applicable to all food allergens, unless there is specific evidence to demonstrate otherwise

OIT is recommended as a treatment to achieve desensitization. A majority of patients will achieve a level desensitization to a daily dose of the allergen that will be sufficient to provide protection against trace exposure, while a sizable proportion of patients will be able to tolerate a full serving

OIT can be recommended for long term management since a sizable proportion of patients will continue to regularly consume a sufficient amount of the food to maintain desensitization after reaching maintenance, without reverting to complete avoidance

OIT may be recommended to achieve sustained unresponsiveness, but data is limited and variable

This recommendation is based on the principle of *equity of eligibility*

It is supported by *large amount of consistent clinical evidence*, considering the absence of demonstrated lack of efficacy or of a consistent safety issue for any specific food despite a large number of clinical studies for a variety of foods [22–24, 29–38]. *Level of evidence: HIGH*
It is also supported by the lack of *biological plausibility* that the mechanism of OIT would differ from one allergen to another.

This recommendation is based on the principle of *beneficence*. Whether or not the outcomes (i.e. desensitization, continued consumption or sustained unresponsiveness) are worth pursuing remains patients' prerogative, in line with the principle of *patient autonomy*
It is supported by a *large amount of consistent clinical evidence*, which includes three meta-analyses [22–24] (together covering 31 published OIT controlled clinical trials), three additional RCTs [31, 34, 39] and two non-randomized controlled clinical trials (CCTs) [36, 38], five large case series in clinical practice (N > 150) [29, 30, 32, 33, 40], and two smaller case series [35, 37]. This body of evidence includes 10 RCTs rated as being at low risk of bias [34, 41–49] and is coherent with data from consultations. *Level of evidence: HIGH*

This recommendation is based on the principle of *beneficence*. Whether or not the outcomes (i.e. desensitization, continued consumption or sustained unresponsiveness) are worth pursuing remains patients' prerogative, in line with the principle of *patient autonomy*
It is supported by a *moderate amount of consistent clinical evidence*, from three long-term, 2-arm follow-up studies of RCTs (high risk of bias due to open-label; mean follow-up 2.5 to 5 years; completeness of follow-up: 77 to 90%) [50–52], three large case series in clinical practice (N ≥ 145) (moderate risk of bias using the IHE tool due to single-center, retrospective design; median follow-up: 1.5 to 6.5 years; completeness of follow-up: 83 to 99%) [33, 53, 54], and four smaller single-arm, follow-up studies (N = 43 to 100) at low to high risk of bias (completeness of follow-up: 82 to 100%) [35–37, 55]. This is coherent with data from consultations. *Level of evidence: MODERATE*

This recommendation is based on the principle of *beneficence*. Whether or not the outcomes (i.e. desensitization, continued consumption or sustained unresponsiveness) are worth pursuing remains patients' prerogative, in line with the principle of *patient autonomy*
It is supported by a *small amount of evidence with some incoherence in findings*, including one meta-analysis (covering 4 RCTs) [22], three additional RCTs [34, 46, 56], one CCT [57], one prospective trial with retrospectively-matched controls [58] and one case series in clinical practice [40]. This is coherent with data from consultation concerning pre-school children. *Level of evidence: LOW*

Recommendations on who could benefit from OIT (indications)

Summary of data synthesis (see details and references in Table 1, Clinical dimension, criteria 8 to 12): The allergists consulted highlighted the need for accurate diagnosis of food allergy before initiating treatment, since many patients are either mislabeled or wrongly believe they are allergic.

Most OIT studies included children and adolescents across a wide age range. Several report that the treatment is very efficacious and well tolerated in toddlers and preschoolers. A few studies focused on adults and suggested that they can also achieve desensitization.

Additional key elements from deliberation An accurate diagnosis of IgE-mediated food allergy may require an oral food challenge, especially if the patient

does not have a convincing medical history or a high food-specific IgE level. In addition to confirming the diagnosis, an advantage of performing a food challenge prior to starting OIT is that it can inform the initial escalation dose. This advantage must be weighed against other practical considerations, including the burden of inducing a highly probable allergic reaction and available resources to perform food challenges.

Toddlers and preschoolers are an attractive group for OIT due to the high efficacy and relative ease of treatment in this group. However, it is important that efforts are not focused solely on an age group where treatment appears to be more cost-effective, as specific clinical expertise should also be developed to address the need in other age groups, including adults. A careful balance must thus be found between the promotion of sustainability and the promotion of equity of access.

Box 4: Recommendations on who could benefit from OIT (indications)

Ethical imperative, data or other considerations in support of the recommendation Level of evidence (applicable when recommendations are based on outcome data from clinical studies)

An accurate diagnosis of IgE-mediated food allergy is essential before proceeding with OIT

Regardless of therapeutic option considered, accurate diagnosis of food allergy is the basis for proper care to avoid futile treatment, including unnecessary avoidance. This recommendation is thus based on the principles of *nonmaleficence* and *sustainability*

OIT is indicated for toddlers and preschoolers

This recommendation is based on the principle of *equity in eligibility* as well as *proportionality* between risks and benefits, considering patient's goals and perspectives

Important consideration While the likelihood of spontaneously outgrowing milk or egg allergy may be greater than for other foods, their impact on patients and families, if not outgrown, is high. Caregivers should be included in shared decision-making about, whether to initiate OIT early for these foods and based on individual prognosis, considering that OIT is well tolerated and has high efficacy in this age group

For *desensitization*, it is supported by a *large amount of consistent clinical evidence*. Many OIT studies (RCTs [34, 41, 43, 47, 49, 59, 60] as well as large clinical practice case series [32, 33, 40, 54]) enrolled children starting from the age of 4 or 5 years; some have started enrolment from age three [29, 61] or one [46, 62]. In addition, there is a moderate amount of consistent evidence specifically for this age group from one RCT of milk OIT (unclear risk of bias—Cochrane) [63], one large (N = 270) prospective, multi-center case series in clinical practice of peanut OIT (low risk of bias—IHE tool) [30] and one small (N = 37) prospective, uncontrolled clinical trial of peanut OIT [58]. This is coherent with data from consultations. *Level of evidence: HIGH*

For *sustained unresponsiveness*, it is supported by a *small amount of clinical evidence* (1 prospective clinical trial of peanut OIT with retrospectively matched controls observing a large effect size [58]) and is overall coherent with data from consultations. *Level of evidence: LOW*

OIT is indicated for school-age children and adolescents

This recommendation is based on the principle of *equity in eligibility* as well as *proportionality* between risks and benefits, considering patient's goals and perspectives.

For *desensitization*, it is supported by a *large amount of consistent clinical evidence*. Most of the evidence for desensitization stems from studies that enrolled children and adolescents with median/mean ages in the range of 6 to 12 years (RCTs [31, 34, 39, 41, 43, 46, 49, 59–61, 64, 65] and large clinical practice case series [32, 33, 40, 54]). In nine RCTs [34, 39, 41, 43, 44, 47, 59, 61, 64] and five large clinical practice case series [29, 32, 33, 40, 54], the upper age limit for enrolment was 16 years or older (up to 27 years [32]). This is coherent with data from consultations. *Level of evidence: HIGH*

For *sustained unresponsiveness*, it is supported by a *small amount of consistent clinical evidence*. Most of the limited evidence that is available for sustained unresponsiveness stems from studies that enrolled children with median/mean ages in the range of 6 to 9 years (RCTs [34, 46, 49, 56, 59, 66], CCT [57] and clinical practice case series [40]). *Level of evidence: LOW*

OIT may be indicated for adults

This recommendation is based on the principle of *equity in eligibility* as well as *proportionality* between risks and benefits, considering patient's goals and perspectives.

For *desensitization*, it is supported by only a *small amount of consistent clinical evidence*. The limited data available for patients 18 years of age and older, from one double-blind RCT that included a small number of adults [47, 67] and one small case series [44] suggest that desensitization is possible in this age group. *Level of evidence: LOW*

Recommendations regarding contraindications

Summary of data synthesis (see details and references in Table 1, Clinical dimension, criteria 8 to 12): A history of anaphylactic reactions to the targeted food allergen was generally not an exclusion criterion in OIT studies. Some studies suggested that a history of anaphylaxis had an impact on OIT outcomes, but most of these patients were able to achieve at least partial desensitization. The number of food allergies a patient has appears to have no effect on treatment efficacy in terms of reaching the target maintenance dose to one food.

Most OIT studies included patients with controlled asthma, but generally excluded patients with uncontrolled or severe asthma (i.e. severe asthma defined as the requirement for extensive medication to achieve control). Patients with asthma tended to have a higher

risk of adverse reactions and, in certain studies, some experienced a worsening of their asthma. Nevertheless, most patients with controlled asthma were able to achieve at least partial desensitization.

OIT requires that patients and their caregivers attend visits regularly and are able to understand and follow instructions regarding how to administer the treatment at home. Patients must also be able to recognize and treat adverse events.

Additional key elements from deliberation Successful OIT requires a significant commitment from both patients and caregivers – it is essential to ensure all are informed and understand the importance of this commitment. Psychological support can help if there is significant anxiety or other psychological issues and should ideally be sought before beginning OIT.

Box 5: Recommendations regarding contraindications**Ethical imperative, data or other considerations in support of the recommendation****Level of evidence (applicable when recommendations are based on outcome data from clinical studies)**

Previous history of anaphylaxis to the targeted food is not a contraindication for OIT

This recommendation is based on the principle of *equity in eligibility*. It is supported by a *large amount of clinical evidence*. A history of anaphylactic reactions to the targeted food allergen was generally not an exclusion criterion in OIT studies. Some RCTs [43, 46, 47, 49, 59, 63] and clinical practice case series [30] excluded patients with a history of severe anaphylaxis; others included them (RCTs [41, 61, 64]; case series [29, 40]). Evidence from large case series on whether baseline history of anaphylaxis had an impact on OIT outcomes is inconsistent [32, 40, 53, 54], but most patients with a history of anaphylaxis were able to achieve at least partial desensitization [32, 40]. This is coherent with data from consultations. *Level of evidence: HIGH*

Multiple food allergies are not a contraindication to OIT

This recommendation is based on the principle of *equity in eligibility*. It is supported by a *moderate amount of consistent clinical evidence* from two case series (N = 111 and N = 280; moderate risk of bias [IHE tool] [32, 54]) and additional clinical studies targeted towards patients with multiple food allergies [68–71]. *Level of evidence: MODERATE*

Uncontrolled asthma is an absolute contraindication to OIT. Asthma must be controlled before beginning OIT and pro-actively managed during OIT

This recommendation is based on the principle of *nonmaleficence*. In many RCTs [31, 39, 41, 43, 46, 47, 60, 61] and clinical practice case series [30, 32, 54], severe and/or poorly controlled or unstable asthma was an exclusion criterion for OIT. However, most patients with controlled asthma were able to achieve at least partial desensitization [33, 40, 54, 72]. This is coherent with data from consultations. *Level of evidence: HIGH*

Pregnancy is an absolute contraindication for initiating OIT

This recommendation is based on the principle of *nonmaleficence*. It is in line with the current general standard of care in allergen immunotherapy.

Conditions such as active severe atopic dermatitis, pre-existing eosinophilic esophagitis, heart disease, and those requiring the use of beta-blockers or ACE inhibitors are relative contraindications for OIT. A decision to pursue OIT in these patients should be based on clinical judgment, provider expertise and shared decision-making.

This recommendation is based on the principles of *nonmaleficence, equity of eligibility and patient autonomy*. It is in line with the current general standard of care in allergen immunotherapy.

Patient- or caregiver-specific contexts that may jeopardize the safe administration of therapy must be assessed. These include but are not limited to unreliable adherence to protocol, reluctance to use epinephrine, language barrier, severe anxiety, psychiatric barriers, non-collaborative family dynamics, lack of schedule flexibility for proper dosing, and lack of commitment from patient or caregivers. If these cannot be satisfactorily addressed, they constitute contraindications for OIT.

This recommendation is based on the principle of *patient protection*. It is supported by data from consultations with stakeholders.

Recommendations for the safe provision of OIT

Summary of data synthesis (see details and references in Table 1, Clinical dimension, criteria 8 to 12): (see details and references in Table 1, Clinical dimension, criteria 8 to 12): Clinical studies of OIT report that reactions requiring the use of epinephrine, including anaphylaxis, may occur in the clinic as well as during home dosing.

Eosinophilic esophagitis (EoE) is more prevalent in children with food allergy, especially those with milk or egg allergy, as compared to the general pediatric population, and may emerge during OIT. Certain studies report that EoE was managed with dose adjustments, though some patients discontinued OIT because of EoE.

Additional key points from deliberation Some patients have gastro-intestinal symptoms that occur independently of the timing of food dosing. These can often be controlled by modifying the treatment schedule or by adding specific medication. Patients and families should be informed that endoscopy-directed biopsy may be required when symptoms compatible with EoE or eosinophilic gastro-intestinal disease (EGID) arise during OIT.

Box 6: Recommendations for the safe provision of OIT**Ethical imperative, data or other considerations in support of the recommendation**

Level of evidence (applicable when recommendations are based on outcomes data from clinical studies)

OIT providers and patients should be prepared to recognize and treat allergic reactions, including anaphylaxis, during OIT. Food escalation should only be performed in a clinic with appropriate equipment and infrastructure* available to treat anaphylaxis
A personalized action plan should be provided to patients to guide management of reactions occurring at home
Providers should only offer OIT in age groups in which they have training or experience in treating anaphylaxis
(*see Additional file 1: Appendix 5 for guidance on equipment and infrastructure requirements)

Patients should be observed in clinic for 1 h following dose escalation. The observation period can be decreased as appropriate to a minimum of 30 min, based on various factors that include patients who are reliable, confident and comfortable with the management of allergic reactions

Surveillance for the emergence of EoE or EGID should be based on monitoring for the emergence of clinical symptoms (e.g. dysphagia, oesophageal spasms, vomiting, diarrhea). Endoscopy and biopsy should be used to confirm the diagnosis in suspected cases not responding to dose adjustments or medication

This recommendation is based on the principle of *nonmaleficence*. It is supported by a *large amount of consistent clinical evidence* indicating that there is a risk of anaphylactic reactions during OIT [22–24]. A proportion of these reactions occur outside the healthcare setting [29, 32, 36, 38–40]. This is coherent with data from consultations. *Level of evidence: HIGH*

This recommendation is based on the principle of *nonmaleficence*. It is supported by data from consultations with stakeholders

This recommendation is based on the principle of *nonmaleficence*. It is supported by data from consultations with stakeholders

Recommendations on personalized OIT protocols

Summary of data synthesis (see details and references in Table 1, Clinical dimension, criteria 8 to 12): (see details and references in Table 1, Clinical dimension, criteria 8 to 12): The goals of OIT can be achieved with many different types of protocols, which vary in terms of dosing schedules, and food allergen product and preparation (Additional file 1: Appendix 3-Table OIT PROTOCOLS). Most OIT clinical trials and all OIT clinical practice studies used non-pharmaceutical food-based products. There is no evidence that pharmaceutical products offer any additional benefit.

A few studies directly compared different OIT protocols. One study indicated better efficacy and fewer moderate to severe reactions with more gradual up-dosing. Another study observed that patients were more likely to adhere with continued allergen consumption when the maintenance dose was lowered. The frequency of maintenance dosing had an impact on reactions and adherence in one study, while another study found no difference after 1 year of maintenance. When considering clinical factors that could be used to define treatment plan, the only prognostic factor consistently associated with treatment outcome was the baseline allergen-specific IgE level.

When considering multiple food OIT protocols, similar rates of reaction were observed in studies treating up to 5 food allergens simultaneously, as compared to single-food OIT. In addition, time to reach desensitization for all the foods with multiple-food OIT was only a few months longer than for one food with single-food OIT.

Studies have also looked at the use of omalizumab as part of an OIT protocol. A short course of omalizumab combined with an accelerated OIT schedule not only reduced the rate of dosing-related reactions, but helped improve desensitization rates. In contrast, extended use of omalizumab within a standard slow OIT schedule did not improve the final success rate.

Additional key points from deliberation Decisions regarding when to initiate OIT, the initial food escalation, and the rate of escalation should be based on the same factors that help predict reactivity during food challenges and adapted to patient context. For example, it may be appropriate to proceed directly to OIT for a toddler with a recent reaction to relatively high amount of the culprit food whose food allergy has been confirmed with a skin test rather than to delay therapy while waiting for further confirmatory laboratory results. The objective is to respect the time patients and families have available, optimize the use

of limited healthcare resources, and avoid missing a window of opportunity before a potentially unfavorable natural evolution of the disease.

In an ideal world, the rate of dosing escalation would be adjusted to match the patient's change in reactivity threshold, which may not follow a linear trajectory. In practice, however, this is not always feasible for logistical reasons. In addition, fixed up-dosing schedules are also more easily implemented by OIT providers with less experience.

There is limited data on the advantage of a high maintenance dose over a lower dose when long term outcomes are assessed. Conceptually, the demonstrated efficacy of sub-lingual immunotherapy (SLIT) and epicutaneous immunotherapy (EPIT) suggests that a high dose may not be needed to modulate the immune response. Adherence with lower food doses is often easier, and a potentially more important goal than an unproven theoretical benefit a higher dose may have on sustained tolerance. Ultimately, however, determination of the target dose should include a consideration of the patient's goals and preferences.

Treatment objectives can vary between patients as well as over time during therapy for a given patient. Some patients may desire the ability to stop treatment for a prolonged period (i.e., several weeks) without losing tolerance, while others should like to know that they can safely skip treatment for a few days, that they no longer need to be careful of certain co-factors or that they can safely ingest large amount of the food. Oral food challenges are necessary to assess many of these treatment objectives but consume time and resources. Therefore, monitoring plan should be personalized to specifically assess only the treatment outcomes that are relevant to a patient. Measurements of food-specific IgE and IgG4 are inexpensive and may also be helpful in the decision whether to proceed with an oral food challenge to test for these outcomes.

Assessing for sustained unresponsiveness requires a prolonged period of discontinuation of ingestion of the food and carries the risk of unnecessarily losing progress made with desensitization. Unless allergy testing has become negative, the preferred approach is to assess for sustained unresponsiveness is to progressively increase dosing intervals such that that dosing intervals can again be shortened if and when reactivity returns.

Because of its cost, recourse to omalizumab should occur responsibly and judiciously, as widespread unjustified use could jeopardize treatment sustainability. Despite its excellent safety profile, it is an injectable biologic drug, which can limit its acceptability for some patients.

Box 7: Recommendations on personalized OIT protocols**Ethical imperative, data or other considerations in support of the recommendation****Level of evidence (applicable when recommendations are based on outcomes data from clinical studies)**

OIT can be performed with many different food products

This recommendation is based on the principles of *equity of access and sustainability*. Unless the superiority of a specific food product is demonstrated over other forms of the same allergen, choice of the product should be guided by availability, cost and practicality. It is supported by data from consultations with stakeholders. In addition, despite a theoretical concern for the variability of non-standardized food products there is no evidence on the superiority of OIT protocols that use pharmaceutical products. (One meta-analysis of peanut OIT RCTs found that both proprietary and non-proprietary OIT products led to desensitization compared to placebo or usual care [24])

The goals of OIT can be achieved with many different protocols. There is little evidence that specific dosing schedules are superior to others. Reference protocols* can be useful to guide therapy but need to be selected and adapted based on the patient's specific situation

See Additional file 1: Appendix 6 for sample protocols

This general recommendation as well as the specific recommendations (A to D) that follow are supported by data from consultations with stakeholders and a large amount of successful published protocols that follow the same general approach (see OIT protocol variables in clinical studies or published clinical practice in Additional file 1: Appendix 3)

A. The initial dose that will be ingested at home should be determined during an initial dose escalation in clinic (day 1). This consists of a graded introduction of the allergen to identify the highest tolerated dose at baseline. The planned starting and ending doses for the initial escalation in clinic should be below the expected reactivity threshold and determined through shared decision making with patients and families. The objective is not necessarily to identify the reactivity threshold and induce a reaction as this can become a barrier to treatment. An alternative to multi-step escalation is to start treatment directly with a single dose assumed to be below the patient's reactivity

These recommendations are based on the principle of *patient's best interest* to limit the burden of unnecessary visits while preserving patient safety, as well as on the principle of *sustainability* and *best use of healthcare resources*

B. After initiating daily home ingestion of the tolerated dose, up-dosing increments should be adapted to patient evolution throughout therapy. Transient mild local reactions are to be expected in the first days following a dose increase. In the absence of any signs of reaction, the protocol could be accelerated. In the event of persistently recurring, moderate to severe or systemic reactions, dose progression must be decreased. The up-dosing intervals can be prolonged for medical or logistical reasons, or for personal preferences

The use of a flexible approach reflects the key elements of *personalized care* and contributes to *empowering patients* in the self-management of their food allergies. This is in line with earlier recommendations (see Box 1) to practice OIT in the spirit of personalized care and to promote patient empowerment

C. The final target dose for the therapy should be guided by the patient's individual clinical response and personal goals, which can range from protection against accidental exposures to small amounts to unrestricted inclusion of the allergen into the diet. There is a lack of evidence that high maintenance doses will increase the likelihood of sustained unresponsiveness

This recommendation is based on the principle of *autonomy* to allow patients to achieve their individual goals according to their contexts.

D. During follow-up, persistence of desensitization is monitored by documenting a patient's continued consumption of the food allergen. A decision to test for other outcomes should be guided by a patient's personal objectives. Complete desensitization can be assessed by performing a high threshold challenge to the food. The risk of a dosing reactions associated with cofactors can be assessed by performing a food challenge in the presence of cofactors (e.g. alcohol and non-steroidal anti-inflammatory drugs, exercise). Sustained unresponsiveness can be assessed by the progressive increase in dosing intervals

This recommendation is based on the *adequacy of the intervention* in addressing the actual needs of patients

When performing OIT in patients with multiple food allergies, the preferred approach is to treat multiple foods simultaneously

This recommendation is based on the principle of *sustainability* and on practical consideration for patients

It is supported by a *small amount of consistent clinical evidence*: one small non-randomized study observing similar safety outcomes between multiple-food OIT (targeting up to 5 foods simultaneously) as compared to single-food OIT and a small difference in treatment duration [68]. Additional small studies lend further support to suggesting the feasibility of multi-food OIT with [69, 71] or without [70] the concomitant use of omalizumab. This is coherent with data from consultations. *Level of evidence: LOW*

Short-term concomitant use of omalizumab can be considered in challenging cases

This recommendation is based on the principles of *nonmaleficence* and *equity of access* in the specific context of challenging cases. Limiting recourse of omalizumab to such challenging cases is based on the principle of *sustainability*. It is supported by a *moderate amount of consistent clinical evidence* including two small placebo-controlled RCTs rated as being at low-risk of bias, in which, compared to placebo, the concomitant use of omalizumab allowed for more rapid up-dosing with similar or fewer adverse reactions [71, 73]. This is coherent with data from consultations. *Level of evidence: MODERATE*

Recommendations for patient-centered care

Summary of data synthesis (see details and references in Table 1, Clinical dimension, criteria 8 to 12): One of the most important goals patients have regarding the management of their food allergy is to reduce the anxiety and achieve a sense of control by reducing the risk associated with accidental exposure. This can be achieved in different ways, including through OIT.

OIT involves ingesting an allergen that was previously avoided, which can initially be very challenging and an understandable source of anxiety. Reactions can occur with food dosing, and as is the case in all food reactions, including those due to unintentional exposures, both patients and clinicians find it difficult to distinguish between allergic symptoms and symptoms due to anxiety.

OIT is time-consuming for multiple reasons, including the number of clinic visits necessary for up-dosing, and a period of reduced activity that is required before and after food dosing to reduce the risk of reactions. A patient can be bothered by the amount and taste of food they must consume for OIT. Nevertheless, published studies and consultation data suggest that most patients do not consider OIT an overwhelming burden.

Misconceptions regarding risks and outcomes of OIT have the potential to create unrealistic expectations or concerns. Interestingly, one clinical study showed that anxiety was reduced and adherence with OIT improved when the occurrence of mild reactions was presented in a positive light as being part of the process and indicative of progress towards treatment goals.

The majority of studies on OIT show that patients receiving OIT report improved food allergy-related quality of life, particularly with respect to anxiety. A subset of patients can experience a deterioration in quality of life measures at the beginning of treatment, but this tends to resolve upon reaching maintenance. The greatest improvements in quality of life are reported by patients for whom food allergy had the strongest impact on quality of life before starting treatment.

Additional key points from deliberation Shared decision-making is a key component of patient-centered food allergy management. Providers must communicate effectively to explain all treatment options, including continued avoidance and food OIT, so that patients are able to make a choice that aligns with their preferences, values and clinical needs. Communication between patients and their provider before initiating OIT and throughout treatment is of the utmost importance to ensure that patient and

provider treatment goals are aligned, expectations remain realistic, and anxiety is well managed.

During the maintenance phase of OIT, many patients want to be informed about their treatment progress beyond their level of desensitization to the daily doses. This includes information about whether they also have tolerance to food amounts above the treatment dose, the actual risk associated with skipping doses and the relevance of various cofactors in allergic reactions to foods. The observation of longitudinal changes in the underlying immune response is highly relevant to patients and is used in some clinical practices to guide decisions. Monitoring food-specific IgE and IgG4 levels may be useful in that regard; however, more research is needed to clarify the real-life interpretation and relevance of these within the context of OIT.

Research on the impact of other interventions, such as food allergy education, on quality of life would contribute to inform best approaches and optimise care and resource use.

Box 8: Recommendations for patient-centered care

Ethical imperative, data or other considerations in support of the recommendation

The ultimate goal of food allergy care should be the empowerment of patients and their caregivers to manage the risk of food allergy reactions, reduce food-related anxiety and achieve a sense of control over their condition. This can be achieved in different ways for different patients. Tactful and empathic shared decision making with patients, their caregivers and the OIT provider, is necessary before making a decision to proceed with OIT

This recommendation is based on the importance of understanding patients' perspective, with thoughtful consideration for the needs and values of each individual, which is the essence of *empathy*, as well as on the importance of promoting patient empowerment, which reflects the principle of *autonomy*. It is also based on the *adequacy* of the intervention in addressing the actual needs of patients. It is supported by data from consultations with stakeholders and key aspects emerging from the literature.

Informed consent must be obtained before initiating OIT. This should include clear discussion of potential outcomes, risks and benefits, as well as of patients' and their caregivers' concerns, expectations and goals. Patients should be informed on how to recognize and manage reactions during therapy.

This recommendation is based on the principle of *decisional autonomy*. It is supported by data from consultation with stakeholders as well as a *small amount of clinical evidence* (one clinical trial on psychologic intervention in support of OIT [74]). *Level of evidence: LOW*

Throughout treatment, patients' goals and perceived benefits should be reassessed periodically to ensure that clinical decisions continue to reflect their personal objectives. When appropriate, expected mild reactions should be framed in a positive manner that reduces perceived burden of therapy and promotes a sense of control.

Organizational dimension: promotion optimized organization of care

Recommendations for the promotion of optimized organization of care

Summary of data synthesis (see details and references in Table 1, Organizational dimension, criteria 13 and 14): OIT is a viable therapeutic option and so falls within the mandate of the healthcare system. Healthcare resources for food allergy are currently based on an approach to management focused on the complete avoidance of the offending allergen; thus, the implementation of OIT will require a complete reorganization of food allergy care, while also maintaining support for patients who continue with avoidance alone.

All physicians involved in administering OIT must be able to recognize and manage different types of adverse food reactions and must have access to equipment required to treat severe reactions. A multidisciplinary approach to OIT can improve patient outcomes and optimize the use of resources by including other relevant healthcare personnel who can assist the physician, including nurses, registered dietitians and psychologists.

Additional key elements from deliberation A multidisciplinary approach could contribute to improved quality of care and a sustainable wide scale offer of OIT by relieving OIT providers of certain tasks that other healthcare professionals can perform. Nurses can be essential as a point of contact for patients and for coordinating care. Registered dietitians can provide unique support in identifying equivalent food alternatives for home dosing and to monitor nutritional needs. Psychologists can offer support within the context of individual or group interactions. Group interactions have the unique potential to offer professional support within the context of sharing issues with others, supporting others with similar concerns and questions, and collaboratively identifying solutions. Patient groups can also provide an outlet to discuss issues that might not otherwise arise if the patient interacts with healthcare professionals only. Integrating peer supporters into the clinical team can help ensure the alignment of key messages.

Regarding access disparities, offering training and support to pediatricians and family doctors who wish to offer OIT under the direct supervision of a subspecialist allergist could greatly contribute to make the treatment accessible to a much larger number of patients in rural areas, where few or no allergists are available, or in urban areas, where there are not

enough allergists to respond to patient demand. Conditions for the safe provision of OIT (see Box 6) need to be always maintained, including equipment and infrastructure requirements.

The majority of clinical and research OIT initiatives have focused on children to this point which creates a risk of a knowledge deficit in the adult allergy/immunology training curriculum that could impact future capacity to offer treatment in this patient group.

Box 9: Recommendations for the promotion of optimized organization of care

Ethical imperative, data or other considerations in support of the recommendation

To optimize human resources and ensure optimal delivery of quality care in food allergy, a multidisciplinary approach adapted to patient needs should be promoted, and should include nurses, registered dietitians, psychologists and peer supporters, when possible

This recommendation stems from *responsibility* of the healthcare system to deliver the best possible care to all patients while optimizing healthcare resources. It is supported by data from consultations with stakeholders

In areas with limited or no access to allergists, pediatricians and family physicians could provide certain OIT services, after receiving adequate training and under close supervision by an allergist

This recommendation is based on the principle of *equity of access* by adapting available resources to local contexts, and thus minimizing regional disparities in OIT provision. It is supported by data from consultations with stakeholders

Economic dimension: promotion of sustainability

Recommendations for sustainable and responsible provision of OIT

Summary of data synthesis (see details and references in Table 1, Economic dimension, criteria 15 to 21): The price of a commercial product developed for peanut OIT is based on the cost of pharmaceutical development, which makes it approximately 100 times higher in cost a similar non-pharmaceutical-based approach produced within the healthcare system. When using non-pharmaceutical products, the cost of OIT treatment derives primarily from healthcare practitioner's services, whereas when using pharmaceutical product, the commercial food OIT product represents a significant additional and long-term expense without reducing base costs. With the commercially developed peanut OIT product, the economic model assumes lifelong treatment based on the manufacturer's stated indication, while a non-pharmaceutical-based approach assumes that patient can use regular food. This raises ethical issues regarding the best interests of a patient, which

is to have an open diet, and the best interest of the healthcare system, which is to ensure sustainability over the long term.

On the patient side, data shows that avoidance is associated with significant costs to patients, because as one patient said, “fear makes us spend”. OIT, in the short term, will increase cost associated with physician visits (including time off work), which will be reduced and possibly lower than avoidance once on maintenance. From the societal side, OIT is perceived as a good investment which could prevent future healthcare and productivity issues, especially when performed early.

Additional key points from deliberation A pharmaceutical-based approach to OIT carries the risk of diverting limited resources in food allergy care to cover high cost products and away from strengthening treatment capacity within the healthcare system.

The notion of “off-label” use does not apply to food—characterizing the practice of OIT with common food as “off-label” in reference to an alternative commercial product is in neither the best interest of patients nor of the healthcare system. To this point, foods for other medical procedures, including diagnostic food challenges, are currently bought at the grocery store and measured in clinic. The cost of a prepackaged standardized food dose should reflect its true value in clinic, which is ultimately of a practical nature, rather than the fact that it has been categorized as a drug.

Box 10: Recommendations for sustainable provision of OIT	Ethical imperative, data or other considerations in support of the recommendation
In the development of OIT, extreme care should be taken to avoid creating unnecessary financial barriers that could limit access to treatment based on ability to pay	This recommendation is based on the core value of public healthcare systems, which aim at <i>reducing social inequalities in health</i> . It is supported by data from consultations with stakeholders
Investment by the healthcare system in food allergy treatment should be guided by patients' best interests and system sustainability. As such, investments should be encouraged toward measures that contribute to building the capacity for OIT within the system (e.g. multidisciplinary teams, preparation of personalized food products, treatment monitoring) in order to achieve meaningful and cost-effective impacts on patient outcomes	This recommendation stems from the principles of <i>sustainability</i> and a <i>fair and efficient allocation</i> of healthcare resources. It is supported by data from consultations with stakeholders and data from milieu of care

Discussion

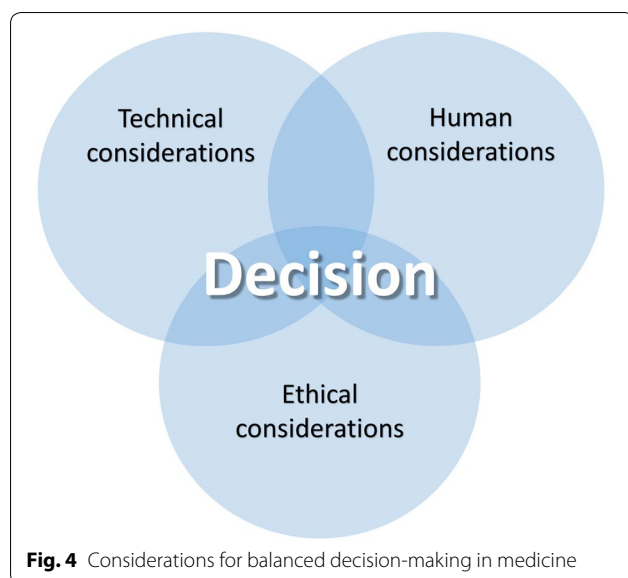
This development process of these CPGs consisted of a comprehensive approach to both the data collection and the collection of perspectives from all stakeholders. This allowed for the collaborative development of 38 recommendations guided by the five principles of the common good, equity, health and wellbeing, optimized organization of care and sustainability of healthcare systems, allowing a 360° view of OIT.

This comprehensive approach included the full extent of a traditional review of the available clinical data. The large number of both RCTs and diverse observational studies provided a rich body of complementary evidence. In addition, the inclusion of patients in both the consultation and the deliberation phases provided key experiential knowledge and contributed to the interpretation of data and the development of recommendations. Similar involvement of first line and allied healthcare professionals ensured a multidisciplinary perspective for optimal organization and provision of care as well as efficient use of healthcare resources. Throughout the aforementioned steps, the multicriteria methodology drove the systematic collection of scientific and experiential knowledge for all dimensions, the sociopolitical, populational, clinical, organizational and economic. This was instrumental in developing balanced recommendations allowing us to address issues beyond what is usually covered by traditional CPGs.

This was critical in the specific context of OIT, which poses challenges beyond its clinical aspects. Offering OIT requires adapting the organization of care in a setting of highly limited resources. It marks a rupture with a culture focusing on avoiding reactions at all cost, which creates confusion and tensions. Competing developments as a drug-based versus a food-based therapy also create a number of ethical issues. The methodology provides an ethics-based framework to identify and address these issues in the elaboration of recommendations.

The 360° approach necessitates a team with diverse expertise in various methodological domains and fields of knowledge to collect and integrate the body of knowledge in the multicriteria grid. Expertise in communicating in lay language and chairing a discussion on all these aspects is essential to ensure an understanding by all. The inclusion of participants with diverging perspectives is important to stimulate individual and group reflection during discussions. A tailored multidisciplinary team and a method that allows for efficient organization of data per criteria are essential to the process and key to promote understanding of numerous complex concepts and fulfill the A4R conditions.

Accountability for Reasonableness (A4R) defines four main conditions that can enhance legitimacy and help



stakeholders develop a mutual basis for decision making; publicity of rationales for choices; relevance of criteria agreed to by a broad range of stakeholders; revisability of the decision in light of new evidence or arguments; and enforcement that means the other conditions are met [14]. The multicriteria approach facilitates meeting these four conditions. The use and publication of the multicriteria grid completed with the data, from which detailed and lay rationales were developed, addresses the publicity and the relevance conditions. The multicriteria grid also offers a pragmatic tool to update the CPGs as significant advancements in knowledge emerges, which contributes to revisability. The implication of a large number of stakeholders, of methodologists and ethicists, the participation of external observers at the deliberation, as well as oversight by the CSACI board contributed to the enforcement of these three conditions.

Clinical recommendations developed here are generally concordant with those from the European Academy of Allergy and Clinical Immunology (EAACI) [8]. That said, in addition to the recommendations made outside the clinical dimension, there are some noteworthy differences between the CPGs, which likely stem from the difference in methodology. The authors of the EAACI guidelines explicitly stated in their discussion that “there is no evidence that the efficacy and safety are affected by the type and nature of the food allergen used in allergen immunotherapy”. However, their methodology resulted in limiting the indication for OIT to milk, egg and peanut only. The current guidelines diverge from

those from EAACI in a few other recommendations, namely regarding the indication for OIT in children less than 4 years of age or in adults and the recognition that OIT can promote sustained unresponsiveness in some patients, over the long term.

There was also a difference in the overall vision surrounding the development of OIT. In the EAACI guidelines, the need for standardized protocols and products was identified as a high priority, while these CPGs emphasize that there is a need for more personalization. Standardization is often seen as a desirable objective in modern medicine because it allows generating quantitative data that can be used as the basis for more recommendations using a traditional CPG methodology. However, the ability to adapt protocols to patients’ needs is essential in OIT. Standardized products and protocols have not been shown to provide clinical benefits over their adaptable alternatives and can actually increase barriers and costs, thus threatening sustainability and access.

Personalized approaches, however, represent a challenge for the transfer of expertise. The development of training initiatives, clinical tools, and organizational models adapted to the delivery of personalized care should therefore be made a priority. Shared decision-making tools should include clear information on food allergy management, consent forms, home dosing instructions, and a reaction management plan. Specific training tools directed toward allergists, primary care physicians and allied healthcare professionals should focus on the biological, psychological and social aspects of the therapy and be included in training curricula and continuing professional development (CPD).

Clinical tools will be developed collaboratively as a second step of these CPGs and made available online at <http://www.csaci.ca/OIT-guidelines>.

These CPGs also identified a number of data gaps that require further research, including:

- long-term patient-centered outcomes
- underrepresented groups, e.g. adults
- optimal use of biomarkers to guide therapy
- optimal use of medication to support treatment
- determinants of reactivity, e.g. cofactors, individual differences in absorption and distribution of allergens
- benefits and optimal use of nutritional, psychological, and peer support
- economic and organizational aspects of the treatment.

Table 1 Multicriteria grid with data from literature review, consultations and milieu of care synthesized by criteria and used for the deliberation

DIMENSION Criteria	Data collected from the literature, milieu and consultations (in italics)
SOCIOPOLITICAL DIMENSION AND PROMOTION OF CONDITIONS CONDUCTIVE TO COMMON GOOD	
C1- Historical, political, cultural context	DOMINANT CULTURE: - Currently in North America, food allergy is most often managed by avoidance of the allergen. Avoidance is therefore the predominant response to food allergy in our society, with all the societal implications of food labeling and food restrictions in social activities. However, recently certain jurisdictions (e.g., British Columbia⁷⁶) encourage exposure of babies to allergens to limit development of food allergies. Avoidance defers the greatest part of the responsibility for food allergy management to patients and their families⁷⁷ (which maybe suited for certain patients), while OIT provides an avenue to treat this condition. OIT DEVELOPMENT: 100-year-old approach: first documented treatment attempt in 1908 (Schofield 1908). Network of allergists: The increasing prevalence of food allergies created a growing demand of patients for interventional approaches, which led allergists to develop immunotherapy protocols and products to alleviate this health issue. Following a death due to dosing error in a clinical trial on subcutaneous peanut immunotherapy (allergy shots) in 1995, there was a shift of focus towards OIT with the beginning of controlled trials. To differentiate themselves from alternative health providers working outside their area of expertise and to legitimize the field of OIT, interested allergists networked to initiate and sustain the production of evidence on OIT, developing different approaches and indications. This has led to the development of two schools of thought, which have contributed to some divisions in the food allergy community. On one side, some centers continue to conduct formal clinical trials, on the other side others have started introducing OIT in practice based on the available evidence. In Canada, opinions appear less polarized with some clinicians combining both approaches. The introduction of OIT as a clinical offer has been made possible via oral food challenges, which is an approved and reimbursed practice in several provinces, and has been sustained by clinicians' enthusiasm ('OIT was the most important things they have done in medicine'⁷⁸). This situation, as well as medical and organizational barriers to meeting the high demand, has led to the desire to formalize and standardize the practice of OIT with the understanding that this is an evolving field. Pharmaceutical industry: More recently, with the promise of a large market for OIT (estimated at billions of dollars⁷⁹), came an interest from investors in the pharmaceutical industry and research investigators to create a product (peanut powder in a capsule or a sachet) to be tested in clinical trials and submitted for FDA approval, leading to the creation of Almmune.⁸⁰ The FDA granted a fast track process and breakthrough therapy designation to this product (Palforzia⁸⁰) and on September 13th, 2019, voted to support its use in children and adolescents. OIT PERCEPTION & NEED OF CLINICAL PRACTICE GUIDELINES Polarized perceptions: Perceptions of OIT are polarized, ranging from being dangerous to being a miracle, creating confusion among patients and healthcare practitioners. Some researchers argue that the risks of allergic reactions with current OIT approaches do not outweigh their benefits and that research into other treatment approaches with an enhanced safety profile should be developed.²⁴ Rapidly evolving situation: Changing perception of OIT from being an experimental treatment towards acceptance as an established service; the recent FDA position contributes to this change. Comprehensive clinical practice guidelines (CPGs): A careful review of up to date evidence as well as a refined understanding of the complexity of the topic in all its dimensions (sociopolitical, clinical, economic, populational and organizational) are essential for providing this service to patients in a safe and sustainable manner. The OIT-CPG Canadian working group and deliberative committee was constituted for that purpose. CANADIAN SETTING Reimbursement: Each province has their own rules around billing codes concerning OIT that can or cannot be used by allergists for this purpose, creating a difficult situation for those seeking to provide the service. Resources for food allergy: currently hospital resources dedicated to food allergy are calculated based on the practice of avoidance and are already saturated with an unmet demand for oral food challenges. Availability of OIT: only few centers are currently offering OIT in Canada. CONSULTATIONS Patients: Access to information for the patients is limited; pediatricians and allergists contradict themselves, which can drive patients to obtain the information elsewhere without the supervision of a doctor. Access to OIT clinics is difficult; toddlers are prioritized, which makes obtaining care for patients of other age ranges challenging. Patients can turn to private clinics, which often offer food challenges only, or offer OIT at a high cost. Some patients have to abandon their culinary traditions since foods from their countries of origin contain many common allergens (i.e. Asian foods often contain peanuts). Allergists: There are two opposing views: for some OIT is an answer to the patients' needs, for others it seems too dangerous. Although we are progressing well compared to other countries, the treatment's development is slow, and its popularity is expanding, which can create problems since it is not well regulated, there is a lack of training and

Table 1 (continued)

DIMENSION Criteria	Data collected from the literature, milieu and consultations (in italics)
	some feel there is not enough evidence. There is a large diversity across the provinces in the way professional services related to OIT (office visits, food challenges) are billed (e.g., in Ontario, billing codes are inadequate since follow-up visits are not billable and oral food challenges are under-compensated, creating a barrier for people who would wish to start offering OIT or making the offer unsustainable, while in Nova Scotia the codes are adequate, since OIT follow-up visits are considered as oral challenges with up-dosing, which are billable in office outside the hospital). With OIT, the overarching goal should be to normalize the diet of patients with food allergies. It is best to do that early in life to avoid the development of severe allergies and the possible need for more complex interventions later on. Other healthcare professionals: Media misinformation on OIT presents two outcomes: some see it as dangerous and refuse treatment without becoming informed, since the news do not inform on the positive sides of OIT, while some can perceive OIT as a 'miracle cure'. Growing popularity of OIT can create issues in social settings; people pushing patients to get treated in an effort not to impose restrictions related to their allergy on people around them, or patients feeling that the availability of OIT being limited is unfair. The government views healthcare as a budget and only sees extra costs in implementing OIT. They might not currently take into account non-budgetary outcomes, but prevention measures are starting to be considered as a second solution. ETHICAL ISSUES • There could be a perceived conflict between the current culture of avoidance oriented towards protection from exposure to the allergen and a potentially evolving culture that seeks to actively take control of the allergy by ingesting the allergen. Both cultures need to cohabit in solidarity, while respecting individual choices. • There is some controversy regarding the commercialization of food products using the usual pharmaceutical channels (e.g. FDA approval). Although the best interest of patients should be the primary objectives, fear of legal jeopardy and the potential market appear to be important drivers of commercial development.^{79,81} • In a vision of OIT as a personalized approach, the OIT protocol should be adapted to each patient; however, traditionally clinical trials require standardized protocols, which creates tension for attempting to address evidence gaps.^{81,82} • The FDA approval of the peanut powder may create a sense of security that is not fully legitimate since FDA approval of the product in itself does not assure that it will be used properly to prevent serious allergic reactions.^{81,83,84}
C2- Stakeholder visions	DIVERGING VISIONS REGARDING FUTURE DEVELOPMENTS TO MAKE OIT ACCESSIBLE: • Commercial approach: Proponents of a standardized drug treatment argue that a drug with an FDA-approved indication and protocol is necessary since some physicians perceive that the benefit-risk ratio of OIT is unclear and do not provide it because the "medicolegal jeopardy [risk of lawsuits] associated with peanut OIT outweighed the benefits",⁸¹ and they do not have a billing code.⁸⁰ Commercialization through approval of a product by regulatory agencies, such as the FDA, is usually made on the basis of randomized controlled trials (RCT) with predefined and standardized protocols. Regulatory approval facilitates reimbursement and the creation of billing codes but comes at the cost of purchasing the commercial product for the healthcare system.⁷⁹ • Personalized approach relying on food products. Proponents of food based OIT- argue that "the key element of food allergy is food, and that food allergy does not need a drug but can be effectively treated with a food". (C Wasserman, 2018⁷⁸) and that the evidence gap should be closed by longitudinal studies of personalized care tailored to each individual.⁸² Several allergists have indeed successfully developed OIT approaches using food products prepared in clinic by skilled staff to support patient needs worldwide^{79,81} and generated evidence in clinical practice and RCTs. Personalized care emphasizing a positive mindset in patients on OIT non-life-threatening symptoms was shown to improve outcomes (RCT⁷⁴). In this vision, clinical practice guidelines should be developed based on evidence and ethical imperatives associated with food allergies and the provision of OIT. MEDIA: The media message evolved from focusing on OIT as being dangerous (e.g., in 1910) to being a hope for patients with food allergies, the rate of which is increasing and who are currently left with the only choice of avoidance and its limitations. At the moment, there is no consensus in the media on OIT, since it is associated with many feelings: excitement, caution and some unanswered questions. Anxiety remains a key issue both for avoidance and OIT (Media Review). The recent FDA decision is spurring a debate on the pros and cons of the commercial approach featuring a lifetime treatment indication for OIT with headings such as: "The US healthcare system found a way to make peanuts cost \$4,200".⁸⁰ CONSULTATIONS Patients: There is confusion concerning the treatment, uncertainties about what exactly is food allergy, and what are the risks associated. Severity is currently defined in the common mind based on the quantity of reactions a patient has had. Different types of reaction can create anxiety for the parents, which can be unfounded due to these misconceptions. What anaphylaxis is and what its treatments are isn't clear for some, who find it worrisome to use adrenaline and prefer going to the emergency room, which isn't always in the best interest of the patient. Allergists: Not applicable Other healthcare professionals: The current priority in the healthcare system is to cut costs. OIT, compared to 'peanut pills', is very cost-effective. The problem is that healthcare professionals can be reluctant to provide it since they are not well informed (especially all non-allergists) and have no clear protocols, which can create trust issues with patients looking to receive OIT. Education for all who could be involved in providing OIT (allergist, pediatricians, registered dietitians, psychologists, family doctors) should be a priority. There has not yet been a consensus amongst allergists on OIT, which can be worrisome for some patients.

Table 1 (continued)

DIMENSION Criteria	Data collected from the literature, milieu and consultations (in italics)									
	<i>Pushing for OIT are: a portion of allergists, healthcare providers, patients and caregivers; pushing against: another portion of allergists, pharmaceutical companies, government officials.</i> ETHICAL ISSUES: • The best interest of patients, which are in need of services, and the sustainability of healthcare systems may come into conflict with commercial interests: regulatory approval of a commercialized product does not come with clinical practice guidelines and may confer a false sense of security to patients and providers. Commercialized products are likely to come at a significant cost to the healthcare system, which may limit patient access.⁷⁹ • The call for more research into other options (so far with limitations) rather than pursuing with OIT may not be well aligned with the patients' perspective of risks and benefits and conflicts with the current high unmet need • The current system facilitates development and reimbursement of standardized treatments through a commercial approach, while the production of a simple food product by the healthcare system is more difficult; the best interest of patients (personalized approach) and of healthcare systems (sustainability associated with simple food-based products) calls for developing system facilitators for non-commercial approaches. MORTALITY • Risk of death: 0.60 to 3.25 deaths per million people with food allergies per year.^{87, 88} • Forty (40) deaths in Ontario over 26 years for food allergy anaphylaxis (16 to peanut), with a declining trend.⁸⁹ MORBIDITY: • Most frequent cause of reactions: inadvertent ingestion, mostly at home (food labeling issues, risky patient behaviour)⁹⁰ • Parent-reported accidental exposures: 12.4 per 100 children with peanut allergy per year (66% moderate or severe).⁹¹ • Anaphylaxis: • Incidence: per 100 people with food allergy per year:⁹²<table><tr><th></th><th>With any medical attention</th><th>With hospital admission</th></tr><tr><td>Children and adolescents (age 0-19)</td><td>0.20</td><td>0.020</td></tr><tr><td>All ages</td><td>0.14</td><td>0.009</td></tr></table> • Yearly recurrence rate: 17.6% among children who had visited emergency departments⁹³ • Healthcare resources (QC): 0.1% of ambulance calls (mostly peanuts),⁹⁴ 0.2 to 0.4%^{95, 96} of hospital emergency room visits in children (1.8% of these with hospitalization⁹⁶) and 0.2% in adults.⁹⁷ HEALTH-RELATED QUALITY OF LIFE (HRQOL): • Fear of accidental exposure: uncertainty, anxiety and distress in parents, children¹⁻³ and adolescents.^{4, 5} Survey: more than 50% of 853 US parents of children with peanut allergy reported to be always afraid of exposure.⁶ • Dealing with reactions by parents: uncertainty, hesitation using epinephrine.^{96, 98} • Constant vigilance and risk of psychological distress, depression and social isolation for patients (including bullying) and caregivers.^{99, 100, 101, 52, 53} • HRQoL lower for food allergy patients than sex /age-matched controls in Sweden: children 0.84 vs 0.94; adolescents: 0.91 vs 1.00, P<0.001 (using EQ-5D).¹⁰² • Factors associated with a worse food-allergy-related QoL (children [age <13 years] in Canada, Italy, Sweden, US, using parent-reported QoL FAQLQ-PF): more severe reactions (history of anaphylaxis,^{2, 103-105} number and severity of symptoms,¹⁰³ hospitalizations²), multiple food allergies,^{103, 106} using² or carrying¹⁰³ an epinephrine auto-injector, a prolonged cow milk-free diet,¹⁰⁴ and older age of the child.¹⁰⁴⁻¹⁰⁶ CONSULTATIONS Patients: Allergy patients live with the fear and risks of severe reactions, which can deeply affect their lives and the people around them, who can also become anxious. Some patients can rightly or wrongly perceive that they can have severe reactions to the smallest traces (perceived airborne risks, contact reactions), making some situations quite difficult, especially with multiple allergies (e.g., restaurant visits, travelling). Contact reactions can prevent parents from kissing their children, sometimes out of anxiety rather than direct risk. Adults who have lived their lives with allergies or parents of young allergic children can develop very serious anxiety, limiting activities and opportunities. Allergists: Depending on the severity of reactions and the number of allergies, the impact of the condition for the patients can be either mild and manageable or socially crippling. Any activity can cause anxiety in parents of young children, since they have no safe way of managing severe or serious reactions by themselves. Other healthcare professionals: Fear of accidental exposure and of death can, in some cases, result in depression or create constant anxiety, which impacts self-esteem and diminishes the quality of life of patients and caregivers. For parents, each phase in their child's development can pose particular challenges: when children are young, they 'touch everything', when they are older, they need to be reminded to be careful of everything, creating a state of perpetual vigilance, when children reach adolescence, they may be not as careful, since 'allergy is not cool'. Patients reaching maturity remain focused on their allergy throughout adulthood. ETHICAL ISSUES: • Every person should be given the opportunity to achieve their full potential in health and well-being; the burden of food allergy, for which there is little support from the		With any medical attention	With hospital admission	Children and adolescents (age 0-19)	0.20	0.020	All ages	0.14	0.009
	With any medical attention	With hospital admission								
Children and adolescents (age 0-19)	0.20	0.020								
All ages	0.14	0.009								
C3-Severity of the condition / situation										

Table 1 (continued)

DIMENSION Criteria	Data collected from the literature, milieu and consultations (in italics)
C4-Size of the target population	healthcare system, interferes with this goal (principle of equity). - The impact of food allergies on the lives of patients and caregivers increases if they had severe allergic reactions; however, history of severe reactions is sometimes used as an exclusion criterion for OIT, which may increase inequity of access. Prevalence of food allergy in Canada (random survey of 5734 Canadians): Any perceived food allergy: 7.5%; probable allergy: children: peanuts (2.2%), tree nuts (1.5%), egg (1.0%), fish (0.9%), shellfish (0.8%), milk, wheat (0.2%); adults: shellfish (1.6%), tree nuts (1.0%), peanut (0.6%), egg, fish (0.5%), milk, wheat, sesame (0.2%).¹⁰⁷ Number of Quebec children with food allergy eligible for OIT: estimate 36 000 (excludes fruits/vegetable allergy and those likely to tolerate a challenge)¹⁰⁸ Population directly or indirectly impacted by food avoidance: caregivers, family, friends, restaurants & school staff,¹⁰⁹⁻¹¹¹ more than 50% of Canadians report that they are directly or indirectly impacted by food allergies.¹¹² CONSULTATIONS Patients: Allergy has a deep impact on patients, but also on their caregivers since they always have to stay informed and prepared to any eventuality. Friend, family, life companions, colleagues, classmates, especially in early childhood environments, and all public services linked to food also feel the burden of allergy and have to be educated and mindful about it. Some parents of other children at school can be unpleasant and reluctant to accept restrictions due to lack of understanding. Allergists: Not applicable Other healthcare professionals: There is a strong impact on the family of a child: the patient(s), their parents and their siblings have to learn about allergy, watching for misconceptions such as comments like: 'just don't eat it' or 'injections are easy to do'. There is a very strong impact on both the parents of an allergic child, in some cases especially on the mother of the patient, who sometimes sees herself in the nourishing role, which can add to the psychological impact of the condition. Patients and their parents also have to quickly develop a response in possible dangerous situations, since allergy also touches schools, kindergartens, workplaces and all social setting of the patient. ETHICAL ISSUES - The burden of food allergies affects not only those who live with food allergies but also their surroundings as well as a sizable proportion of the society and is currently not alleviated by the healthcare system, although it falls under its mandate. - The number of allergists in Canada is small; and the percentage of allergists who practise OIT in Canada is unknown, but this service is currently limited and mostly available in large cities.¹¹³ CONSULTATIONS Patients: Lack of availability of OIT is a problem, which can imply having to travel several hours to a clinic offering it. There are few allergists in rural areas, and fewer offering OIT. Adults wishing to receive OIT can have a difficult time even finding allergists for themselves. People living outside of large cities find it also challenging to stay well informed. Allergists: The Canadian healthcare system is currently unable to provide OIT according to demand, which outweighs the available providers: some of those providing OIT feel that they are not always fairly compensated. We are not yet ready to make OIT a standard treatment, since there are not enough regulations or residency training programs. Other healthcare professionals: Currently, there are not enough allergists to treat all patients in Canada, so improving the number of professionals able to treat allergies would be the first priority. Educating family doctors and pediatricians to administer OIT in addition to allergists could improve access everywhere. ETHICAL ISSUES - The lack of allergists who provide OIT and the fact that the few who provide this service are mostly in large cities creates inequity of access at several levels. The currently dominant practice of food allergy management is avoidance of food allergens: Spontaneous resolution of food allergy in childhood: 49% to 79% (egg, milk, soy & wheat); peanut 20-27%¹¹⁴ and tree nut (9%);¹¹⁵ allergy is less likely to resolve in children with other atopic diseases, high IgE levels, large SPT wheal sizes and symptoms other than only urticaria (hives) or angioedema.¹¹⁵ Feasibility of allergen avoidance in real life: elimination diet often represents "an unrealistic therapeutic option";¹¹⁶ avoidance can fail (packaged food containing undeclared allergens,^{117,118} cross-contamination, social activities involving food at school, work, restaurants and other public places) and requires a team effort, including increased awareness and education to avoid misconceptions and inconsistent knowledge of risks in public places such as restaurants.¹¹¹ Impact of allergen avoidance on health: potentially unnecessary restrictive diets for food-allergic children¹¹⁹ in and their siblings;¹²⁰ risk of inadequate intake of certain nutrients¹²¹ (e.g., calcium with increased risk of osteoporosis¹²²), risk of eating disorders and other psychological problems.¹²³ Psychosocial impact: time-consuming and stressful preparation for social activities, bullying, isolation, fear and uncertainty about the risk of accidental ingestion and severe reaction, psychological distress and depression.^{110,111,116,124-126} Exploratory approaches: Epicutaneous immunotherapy (EPIT): The commercially developed peanut patch (Viaskin®) is not currently available in Canada. It has shown limited clinical efficacy in an RCT (response rate 35% vs 14% placebo (difference, 22% [95% CI, 12%-30%; P < .001]).¹²⁷ Sub-lingual immunotherapy (SLIT): The limited research currently available indicates research lower efficacy (i.e., desensitization) than OIT,¹²⁸ although a recent report
C5-Ability to reach the entire target population (access)	
C6 - Extent of unmet needs	

Table 1 (continued)

DIMENSION Criteria	Data collected from the literature, milieu and consultations (in italics)
	suggested improved efficacy with long-term treatment (3–5 years).¹²⁹ - Diets containing baked milk or eggs: Mainly for milk and egg allergic patient who can tolerate the baked form of the food (although, some approaches also introduce baked milk in small amounts to baked-milk reactive patients¹³⁰). It is currently unclear whether consumption of baked food products can accelerate the development of tolerance to unbaked forms of the food (i.e., liquid milk, raw egg).¹³⁰ Two small RCTs comparing baked-milk and baked egg protocols to OIT found lower rates of desensitization (statistically significant in 1 RCT) with the baked food protocol and similar rates of adverse events.^{56 131} CONSULTATIONS Patients: Current standard management of allergy is avoiding the allergen and epinephrine autoinjectors utilization, both of which require constant surveillance of the patient and a limited diet (avoiding desserts, having to eat at home, vague labeling like 'may contain'). Avoidance can make social activities difficult (dinner with friends, birthdays, travelling, restaurants). This method provides no hope of change, a limited sense of control for the patients and creates a weight on everyday life. Some allergists state awaiting guidelines before providing OIT. Allergists: Avoidance is difficult to maintain (i.e. in restaurants), partly because of the vague food labeling 'may contain'. It doesn't help reduce anxiety, and doesn't always achieve anything long term, although a number of children outgrow milk and egg allergies on avoidance. Desensitization can lead to patients growing out of their allergy. The SLIT and EPIT treatments have higher costs and less efficacy (doses too low for meaningful response) than OIT. These treatments can subject the patient to higher anaphylaxis risks and have fewer potential long-term effects. Other healthcare professionals: The anxiety associated with allergies makes avoidance the first response for many patients, because they feel that this is the only way to proceed. It isn't however a solution, since it doesn't bring any changes and largely limits opportunities for patients and caregivers, depending on how common the allergen is. Avoidance also requires relying on other people and depending on their knowledge of allergy and its seriousness. For patients who are allergic to an uncommon food (shellfish), OIT might not be worth the trouble in their opinion, versus one with an allergy very difficult to avoid, who can see it as a hope for needed change (milk, wheat). Avoiding doesn't however impose as heavy a schedule as OIT (2 hours after administering the dose). ETHICAL ISSUES: - In institutions such as school, food prohibition "may actually increase safety risks posed to students dealing with allergies because of the false sense of security such bans create": in addition, such institution should be exempted from heavy accommodations related to food allergies. Avoiding total bans is in most cases in the best long-term interests of all parties, including allergic students.¹³² - Since currently, there is no treatment for food allergy, emphasis is placed upon behavioral change, which, in a way, aims at empowering the patient, but very often, people are feeling "alone" without sufficient support from the healthcare system and "the treatment seems to rely entirely in [their] responsibility". Management of food allergy in general is not an established social priority in Canada, nor is OIT. CONSULTATIONS Patients: Not applicable Allergists: The Canadian healthcare system is currently unable to provide OIT accordingly, since the demand outweighs the available practitioners, and some of those who provide OIT feel they are not always fairly compensated. We are not yet ready to make OIT a standard treatment, since there are not enough regulations or training programs. Other healthcare professionals: It would be helpful to identify which patients would benefit the most from OIT. ETHICAL ISSUES: - The lack of interest in food allergy by the healthcare system generates a situation where there is a lack of skills for OIT, which further contributes to deepen inequities.
C7-Social priorities	
CLINICAL DIMENSION AND PROMOTION OF HEALTH AND WELL-BEING (OUTCOMES OF THE INTERVENTION)	
CLINICAL PERSPECTIVE	
C8-Clinical efficacy	A. EFFICACY OF OIT IN CLINICAL TRIALS AND CLINICAL PRACTICE FIGURE 1: Summary of Efficacy Data by Outcome And Allergens – see detailed tables in the Appendix 3 Outcomes for each allergen are represented in colors (see below), the types of studies are indicated by symbols (see right side of table); filled symbols represent data for OIT patients, empty symbols data for patients not receiving OIT (control group). Asterisks represents results for OIT patients in studies with no control group; symbol size reflects the size of the study; the risk of bias, assessed using the Cochrane approach,²¹ for RCTs and the IHE checklist²⁶ for case series, is indicated below the figure (H=high, M=medium, L=low). All outcomes from original studies are based on ITT analysis. - Desensitization (increase in reactivity threshold): ability to ingest a partial desensitization (PD) or full (complete desensitization - CD) a serving of the food allergen without having a reaction; for peanuts: greater desensitization (GD) = ability to ingest at least 1 g of peanut protein (4.2 peanuts) - Continued consumption (CC): consuming the food allergen regularly at ≥ 6 months after reaching the maintenance dose

Table 1 (continued)

DIMENSION Criteria

Data collected from the literature, milieu and consultations (*in italics*)

- Sustained unresponsiveness (SU): maintaining desensitization after discontinuing regular consumption of the food allergen; measured with a food challenge after 2 to 8 weeks of food avoidance

The forest plot displays the percentage of patients achieving different outcomes (OIT, Empty control, Large) for eight allergens: Peanut, Chicken's egg, Cow's milk, Wheat, Walnut, Hazelnut, Sesame, and another allergen. The y-axis ranges from 0% to 100%. Symbols represent different study types: filled diamonds for OIT patients, open squares for empty control patients, and crosses for large controlled trials. A legend explains the symbols and their corresponding patient groups.

Allergen	OIT (%)	Empty control (%)	Large (%)
Peanut	~85	~40	~70
Chicken's egg	~80	~40	~70
Cow's milk	~80	~40	~70
Wheat	~80	~40	~70
Walnut	~80	~40	~70
Hazelnut	~80	~40	~70
Sesame	~80	~40	~70
(L-5 g protein)	~80	~40	~70

+ Note: This value is based on an additional analysis of 8 RCTs (P=0.02 for all) (5 RCTs: 3 peanut,^{60,61} 1 milk,⁴¹ 1 egg³¹) (1 unpublished) included in the PACE meta-analysis: passing an oral food challenge with a cumulative dose of 400 to 5000 mg peanut protein (1.6–20 peanuts) (median 2700 mg); OIT: 73% (422/574) vs control: 7.0% (21/284)

B. VARIATION OF OIT EFFICACY IN PATIENT SUBGROUPS

B1. BASELINE FOOD ALLERGY-RELATED PARAMETERS

- Clinical studies that included children with a history of severe allergic reactions (severe anaphylaxis) reported that 62 to 90% of children achieved some degree of desensitization compared to 0 to 16% of control children (P<0.02 for all) (5 RCTs: 3 peanut,^{60,61} 1 milk,⁴¹ 1 egg³¹)
- Across three reports of OIT clinical practice, high specific IgE serum levels (milk³³, peanut⁴⁰) and low tolerated dose of food allergen (milk³³) were associated with failure to achieve full desensitization; patients with a history of anaphylactic reactions were less likely to achieve desensitization according to one (milk³²) but not to another (peanut)⁴⁰ report (case series; N=270–296)

B2. AGE

- Age most studied: children starting age 4 to 7 years; median/mean ages about 6 to 12 years.^{31–33, 40, 41, 43, 47, 48, 53, 54, 59, 60, 64, 65}
- Across four reports of OIT clinical practice with children and adolescents (age ≥ 4 years), two found no association between age and reaching the target dose;^{32, 33} one found that older children were less likely to reach the target dose (17% reduction each year after age 5, P<.001),⁴⁰ and one found that children who failed desensitization were younger than those desensitized (median 4.2 vs 6 yrs).³⁴ (case series, N= 145 to 295)

Data from studies in specific age groups:

- Toddlers and pre-school children < 6 years:
- 81 to 90% of children were desensitized to peanuts (1.2–20 kernels) (2 single-arm studies N=37⁵⁸, N=270³⁰); 90% desensitized to 200 mL milk versus 23% control (RCT⁶³; N=30 OIT, 30 controls)

Table 1 (continued)

DIMENSION Criteria	Data collected from the literature, milieu and consultations (in italics)
	78% of children who had had a baseline reaction to peanut tolerated 16 peanuts after 1 year of consuming 1.2 peanuts per day (N=87) (Canadian clinical practice- data on file) 78% reached sustained unresponsiveness to peanuts versus 4% control (retrospectively controlled trial⁵⁸; N=37 OIT, 154 control) 90% continued to consume 200 mL milk per day (RCT⁵³; N=30) Adolescents: 61 to 81% desensitized to peanuts (1.6 to 2.4 kernels) versus 3 to 11% control (1 RCT: N=134 OIT, 35 placebo;^{67,47} 1 RCT: N=21 OIT, 9 controls⁴⁴) Adults: 42% desensitized to peanuts (2.4 kernels) versus 14% control; difference statistically not significant (1 DB-RCT, N=41 OIT, 14 control;^{67, 47}) - Increase in amount of food tolerated to 60-fold for peanuts, 8-fold for milk and 35-fold for eggs (1 single-arm study⁴⁴; N=9 peanuts, 10 milk, 4 eggs) B3. PATIENTS WITH ASTHMA - Most OIT studies excluded patients with severe/poorly controlled or unstable asthma (RCTs^{43, 61, 41, 31, 60, 46, 47}; clinical practice^{32, 30, 54}) - Across four reports of OIT clinical practice, three (milk,³³ peanut^{40, 54}) found no statistical significant difference between patients with or without asthma in reaching the target dose, but one (milk⁷¹) observed they were less likely to achieve full desensitization.⁷² (case series: 2 milk N=244;³³ N=194;⁷² 2 peanut: N=270;⁴⁰ N=145⁵⁴) B4. PATIENTS WITH MULTIPLE FOOD ALLERGIES - Across two reports of OIT clinical practice, there was no correlation between the number of other food allergies and the outcomes of OIT for a targeted food (2 case series: milk, N=280³² peanut, N=111⁵⁴) C. IMPACT OF OIT PROTOCOL PARAMETERS ON EFFICACY OUTCOMES (for a summary of parameters, see Appendix 3) C0. Type of OIT product. There are many different products reported in OIT protocols. Most clinical trials and all clinical practices used non-pharmaceutical food-based products. There are no head-to-head comparisons between pharmaceutical and food-based products. Meta-analysis of peanut OIT RCTs found that both proprietary and non-proprietary OIT products led to desensitization compared to no OIT (placebo or usual care) (non-proprietary: 67% [64/93] vs 7.5% [4/53]; proprietary: 53% [256/481] vs 2.2% [5/231])²⁴ C1. UP-DOSING FREQUENCY - Both conventional and rush OIT protocols (egg, milk, peanut) achieved significantly greater desensitization than control treatments (placebo or usual care) (meta-analysis:²² conventional: 19 controlled trials; rush: 7 controlled trials) - One clinical study of egg OIT found that weekly (30% increments) plus daily (5% increments) up-dosing led to a higher desensitization rate than weekly only up-dosing (30% increments) (96% vs 76%, P = 0.01) and a shorter build-up period (median 65 vs 126 days, P=0.01) (RCT³¹; N=26 weekly plus daily, 62 weekly only) C2. TARGET DOSE (dose reached at the end of the up-dosing phase) - In one clinical study, there was no difference in the rate of desensitization to 4.4 g wheat gluten between low (1.4 g) and high (2.7 g) target dose (52% vs 57%) (RCT³⁴; N=23 low dose, 21 high dose) C3. MAINTENANCE DOSE (dose that will be used regularly to maintain protection following the up-dosing phase, often the same as target dose) - In one report of OIT clinical practice, there were more patients continuing consumption when using a lower (4.8 peanuts) than a higher (12 peanuts) daily maintenance dose (96% vs 72%, P=.001) and no significant difference in maintaining desensitization to 12 peanuts (96% vs 100%).⁵⁴ (consumption: N=76 low, 35 high; desensitization: N=66 low, 22 high) - In one clinical study, there was no difference in the proportion of patients reaching sustained unresponsiveness with low (1.2 peanuts) versus high (12 peanuts daily) maintenance dose (85% vs 71%, P=0.43) among young children (age 9-36 months), (RCT⁵⁶; N=20 low, 17 high, P=0.43) C4. MAINTENANCE FREQUENCY - In one clinical study, there was no difference in maintaining desensitization between eating the maintenance dose daily or every other day (tolerating 1 raw egg white after 6 months of maintenance: 93% vs 83%) (RCT⁵⁵; N=29 daily, 24 every other day) C5. MULTI-FOOD OIT - In one clinical study,⁶⁸ there was no difference in desensitization (reaching 10-fold increase in reaction threshold) between patients undergoing OIT for peanuts plus up three other foods at the same time and patients allergic to peanuts only (88% vs 80%) but patients on multi-food OIT required more time to reach that outcome (14 weeks

Table 1 (continued)

DIMENSION Criteria	Data collected from the literature, milieu and consultations (<i>in italics</i>) earlier with single-food OIT, P=0.04) (non-randomized trial:⁶⁸ N=25 multiple food allergies, N=15 peanuts only) C6. USE OF OMALIZUMAB • Across three randomized controlled clinical trials comparing OIT with omalizumab versus OIT with placebo: • Combination with standard OIT: One study found no significant difference in desensitization at 28 months (10-g milk: 89% omalizumab vs 71% placebo, P=0.18) and no significant difference in sustained unresponsiveness at 32 months (89% omalizumab vs 71% placebo, P=0.42), but there were fewer doses required to achieve maintenance with omalizumab (198 vs 225, P =0.008).¹³³ (N=57, omalizumab discontinued at 28 months) • Combination with accelerated OIT: Two studies observed a higher rate of desensitization with omalizumab than with placebo at 14-28 weeks (8 peanuts: 79% vs 12%, P<0.01; 16 peanuts: 76% vs 12%, P=0.002; 2 g protein of ≥2 foods: 83% vs 33%, P=0.0044).^{71, 73} (N=37 to 48, omalizumab discontinued at 7-8 weeks into OIT) CONSULTATIONS Patients: The possibility, if desensitization is achieved, of a life without allergy, offsets the disadvantages that can be associated with OIT. Age might not need to be considered a factor, since, even though the success rate is seen as higher for children, the treatment also works for adults, provided they are willing to put in time and resources. However, the sooner the better in a patient's life to start the treatment, since they are more trusting and compliant when young. Some allergists include baseline severity as an exclusion factor, since they consider the treatment could be associated with too many complications. Allergists: OIT's effectiveness is mainly good, especially in preschoolers, it can be less effective in older children. Most patients do however reach and tolerate maintenance dose or achieve desensitization, which often leads to improved quality of life for them and their caregivers. Age needs to be taken into account, as OIT is more effective in younger patients, 5 and under, (most efficient at 2-3 years old. Baseline severity of previous reactions doesn't have much of an impact, however some allergens make the protocols slower (sesame, cashew, walnut, wheat). Milk can be more difficult to treat than nuts. Other healthcare professionals: OIT works, depending on the objective (desensitization is more attainable than a complete cure) but like any other treatments, some factors (genetic or otherwise) can create constraints. If a patient's baseline allergy tests are very high, it is less likely for them to achieve desensitization. The treatment is also most efficient with young children. ETHICAL ISSUES: Although desensitization or tolerance achieved with OIT could be lost if regular consumption of the allergen is ceased, OIT can alleviate the burden of food allergy, even if regular consumption of the food allergen is necessary to maintain protection from anaphylactic reactions.⁷⁹																					
C9- Clinical adverse effects	A. CLINICAL ADVERSE EVENTS OF OIT IN CLINICAL TRIALS AND CLINICAL PRACTICE A1. ANY ALLERGIC REACTIONS / LOCAL ADVERSE REACTIONS FIGURE 2: % Of Patients Experiencing Any Allergic Reactions / Local Adverse Reactions – see detailed tables in the Appendix 3 Food allergens are represented in colors (peanut, egg, milk, wheat, walnut, hazelnut); the types of studies are indicated by symbols (see right side of table); filled symbols represent data for OIT patients, empty symbols data for patients not receiving OIT (control group), asterisks represents results for OIT patients in studies with no control group <table><thead><tr><th>Controlled trials</th><th>Peanut</th><th>Egg</th><th>Milk</th><th>Wheat</th><th>Walnut</th><th>Hazelnut</th></tr></thead><tbody><tr><td>Case series</td><td>L</td><td>H</td><td>M</td><td>L</td><td>H</td><td>--</td></tr><tr><td>References</td><td>24 30 40</td><td>23 31 55</td><td>22</td><td>35</td><td>36</td><td>37</td></tr></tbody></table> Additional data: % of doses with any reactions: ◦ Milk clinical practice: 1.9% (N=265)³² ◦ Wheat clinical study: 15% OIT (N=23) vs 5.8% placebo (N=23)³⁴ - Mean number of allergic reactions per patient: ◦ Milk clinical study: any: 17.4; mild: 5.2; moderate: 11.6; severe: 0.5 (N=41)³⁹ Symbols: Filled: OIT patients Empty: control patients	Controlled trials	Peanut	Egg	Milk	Wheat	Walnut	Hazelnut	Case series	L	H	M	L	H	--	References	24 30 40	23 31 55	22	35	36	37
Controlled trials	Peanut	Egg	Milk	Wheat	Walnut	Hazelnut																
Case series	L	H	M	L	H	--																
References	24 30 40	23 31 55	22	35	36	37																

Table 1 (continued)

DIMENSION Criteria	Data collected from the literature, milieu and consultations (<i>in italics</i>)
	A2. ADVERSE EVENTS RELATED TO ACCIDENTAL FOOD ALLERGEN EXPOSURE: - Build-up phase: 11.5% (80/693) peanut OIT vs 19.0% (55/289) placebo; maintenance phase: 9.0% (28/310) peanut OIT vs 20.3% (24/118) placebo (<i>integrated analysis of 2 double-blind RCTs</i>)¹³⁴ 17% peanut OIT vs 45% placebo (P=0.026) (<i>double-blind RCT</i>, N peanut OIT=30, placebo=31)⁶¹ A3. SEVERE REACTIONS AND EPINEPHRINE USE Serious adverse event (SAE): an event that causes death, a life-threatening state, hospitalization, disability, congenital abnormality, or an important medical event such as an urgent intervention to prevent the other outcomes Anaphylaxis: an allergic reaction that involves two or more organ systems, or isolated hypotension with known allergen exposure Epinephrine-treated reaction (ETR): an allergic reaction that is treated with (intramuscular) epinephrine injection Grade 4 reaction: - WAO classification:¹³⁵ Respiratory failure and/or hypotension (and/or profound lethargy – modified) - Sampson classification:¹³⁶ diarrhea and/or hoarseness, “barky” cough, difficulty swallowing, dyspnea, wheezing, cyanosis and/or dysrhythmia and/or mild hypotension and/or “light headedness,” feeling of “pending doom”
	FIGURE 3: Severe Reactions in Patients Undergoing OIT Compared to Patients not Receiving OIT Food allergens are represented in colors (peanut, egg, milk); filled symbols represent data for OIT patients, empty symbols data for patients not receiving OIT (control group), asterisks represents results for OIT patients in studies with no control group (all studies are meta-analyses of controlled clinical trials) - A systemic or anaphylactic reaction was experienced by 16 to 17% of patients treated with OIT for peanut, milk or egg allergies compared to by 2 to 2.6% of control patients^{22,24} (risk of bias: peanut:²⁴ low; milk/egg/peanut: moderate²⁵) - An epinephrine-treated reaction was experienced by 8.4 (egg) to 12% (peanut) of patients treated with OIT compared to 0% and 3.7% of control patients (risk of bias: peanut: low;²⁴ egg high²⁵) - One meta-analysis estimated an approximately doubled risk of serious adverse events with peanut OIT (6.2% vs 3.0% control).²⁴ Quality assessment based on original source publications indicated misclassification of adverse events in some cases, suggesting that the rate of serious adverse events may be similar between OIT and control groups. Note: Rate may be similar between OIT and control groups References: 22 24 23 24 24 CCT: non-randomized controlled clinical trial; RCT: randomized, controlled clinical trial
	Additional data Peanut – clinical practice 2.6% - 2-3 epinephrine doses; no IV (case series:⁴⁰ N=270; moderate risk of bias) 0.6% - 2 epinephrine doses; no IV (case series:²⁹ N=352; moderate risk of bias) 4.1% epinephrine-treated reaction; 0.4% Grade 4 reaction (pre-school children) (case series:³⁰ N=270; low risk of bias) Egg – clinical study - Grade 4: 9.2% build-up, 1.3% maintenance; no dysrhythmia, severe hypotension, hypovolemic shock, laryngeal edema, respiratory or cardiac arrest (RCT: N=76 OIT, 25 control; high risk of bias)³¹ Milk - Clinical practice: one extremely severe case of anaphylaxis (0.3%) (case series: N=295; moderate risk of bias)³³ - Canadian clinical study: events per patient (OIT vs control): anaphylaxis: 5.5 vs 0.1, epinephrine-treated reaction: 0.5 vs 0.1 (RCT: N=52; high risk of bias)³⁹ Wheat – clinical studies - Serious adverse event: 4.3% OIT vs 22% placebo; 0.08% of doses with epinephrine-treated reactions (0.04% severe) OIT vs 0 placebo (RCT: N=23 OIT, 23 placebo; low risk of bias)³⁴ - Severe reactions: 24% (extensive coughing, inspiratory stridor or expiratory wheezing): epinephrine-treated reaction 12% (case series: N=100; low risk of bias)³⁵ Walnut – clinical study - No severe reaction (≥ grade 3) (CCT: N=55 OIT, 18 control; high risk of bias)³⁶ Sesame – clinical study - No severe reaction (≥ grade 3) (CCT: N=60 OIT, 15 control; high risk of bias)³⁶

Table 1 (continued)

DIMENSION
Criteria

Data collected from the literature, milieu and consultations (*in italics*)

FIGURE 4: % of Patients Experiencing Adverse Events During the Build-Up Versus the Maintenance Phase of OIT

Many reports of clinical practice as well as clinical studies across different food allergens observed that **fewer patients experienced severe adverse reactions during the build-up phase (in blue)** than the **maintenance phase (in red)** (see figure below). However, one large peanut OIT clinical study reported a similar percentages of patients experiencing systemic reactions during both phases (**8.5% vs 8.7%**), although the rates of any as well as of serious adverse events related to OIT declined from build-up to maintenance (events per patient-year: any: 60 vs 18; serious 0.02 vs 0.01; double-blind RCT: N=372 OIT, 124 placebo; low risk of bias).⁴⁷

Allergen	Build-up phase (%)	Maintenance phase (%)
Peanut	23	8.5
Chicken's egg	10 (0.07% of doses)	6.4 (0.02% of doses)
Wheat	14.0	8.3
Walnut	20	2.2
Sesame	17	0

Additional studies report as well that the occurrence or severity of allergic reactions declines as the treatment progresses (not in figure).^{30, 39, 40, 61} One long-term study reported that **14%** of patients treated with **milk OIT** experienced anaphylaxis at least once after the build-up phase over 1 to 11 years of follow-up (median 6.5 years) (*case series*: N=237; *moderate risk of bias*).³³

Experiencing epinephrine-treated reactions in the clinic versus at home:

- **17 to 20%** of patients receiving **walnut** or **sesame** OIT experienced an **epinephrine-treated reaction in the clinic** during the build-up phase and **8.3 to 15% at home** (also shown in figure above);^{36, 38} for **milk** OIT, the respective values were **48%** and **17%** (the latter associated with 0.08% of doses).³² Another milk OIT study reported that **66%** of anaphylactic allergic reactions occurred at home vs **34%** in the hospital.³⁹ Similarly, in peanut OIT clinical practice, overall, **63%** (build-up only) to **71%** of epinephrine-treated reactions occurred at home.^{29, 40} During peanut OIT in pre-school children, **0.26%** of doses were associated with an epinephrine-treated reaction in the clinic and **0.016%** at home.³⁰

A4. DISCONTINUATIONS DUE TO ADVERSE EVENTS

- **13%** of patients discontinued **peanut** OIT due to adverse events compared to **3.7%** of control patients (*meta-analysis: low risk of bias*)²⁴
- **6.7 to 15%** discontinued **egg** OIT due to adverse events compared to **0 to 6.7%** of control patients (*RCTs*^{59, 62, 65, 137}).
- Milk OIT clinical practice: **7.5%** (due to anaphylaxis) to **9.6%** (due to adverse events or treatment failure) (*2 case series*, N=280-295)^{32, 33}
- **0 to 18%** of patients discontinued due to adverse events **during the build-up** and **0 to 5.3% during the maintenance phase** of OIT for peanut,⁴⁰ egg,^{55, 137} sesame,³⁸ or walnut⁴⁶ or wheat³⁴ allergy. In one wheat study, 23% of patients discontinued during the build-up and 26% during the maintenance phase; however, discontinuations due to severe reactions declined from 7.0% to 2.6% (*case series*: N=100 build-up, 77 maintenance)³⁵

Table 1 (continued)

DIMENSION Criteria	Data collected from the literature, milieu and consultations (in italics)												
A5. EOSINOPHILIC ESOPHAGITIS (EOE):	• Frequency of biopsy-confirmed EOE among: • Children undergoing OIT for: • peanut: 0.4% OIT (N=719) vs 0% control^{43,45,47,61} • various foods: 2.7% (N=708)¹³⁸ • mostly milk: 5.3% to 6.3% (N=185)¹³⁹⁻¹⁴¹ • Children in general (N=35,528 US): 4.7% with food allergies vs 0.04% general population (highest risk with milk and egg allergy, not significant for peanut)¹⁴² • GI symptoms indicative of EOE (recurrent symptoms & vomiting independent of dosing time) in children undergoing OIT for: • peanut: 14% - 35% of these patients reached the target maintenance dose (case series: N=270, moderate risk of bias);⁴⁰ 1.1% of pre-school children (case series: N=270, low risk of bias)³⁰ • various foods: 8.2% (N=794)¹⁴³ - for these patients, doses were reduced or dose increases deferred or suspended; in long-term follow-up, they were more likely to fail OIT (P=0.04) and less likely to reach full desensitization (P<0.001) compared to patients who did not have such symptoms¹⁴⁴												
A6. LONG-TERM FOLLOW-UP FOR SAFETY AND TOLERABILITY	• Percent of patients in clinical practice who had successfully completed OIT and of whom the majority consumed the food allergen reporting over 1 to 3.6 years: • Epinephrine-treated reaction: peanut: 1.5% (1 case series: N=130),⁵⁴ milk: 2.5 to 6.7% (2 case series, N=158-195),^{33,53} milk/egg/wheat: 1.9% (1 case series: N=108)¹⁴⁵ • Any reaction: milk: 47 to 57% (N=30-195)^{33,53,145} (rate of reactions declined from 0.28 per month during months 1 to 6 of maintenance to 0.15 per month after month 30, P<0.01⁵³); wheat: 59% (N=17);¹⁴⁵ egg: 28% (N=61).¹⁴⁵ Patient-reported precipitating factors included exercise,^{33,53,145} fatigue¹⁴⁵ and illness,¹⁴⁵ such as viral infections.⁵⁴ In one study, these factors were reported by 73% of patients reporting symptoms (1 case series: N=44)¹⁴⁵ • Any objective reaction: peanut: 9.2% (N=130)⁵⁴												
B. VARIATION OF OIT SAFETY OUTCOMES IN PATIENT SUBGROUPS													
B1. BASELINE FOOD ALLERGY-RELATED PARAMETERS	• Retrospective analyses of clinical practice (case series: N=111-280): • High specific IgE serum levels (3 analyses of clinical practice^{30,33,40}) large skin prick wheal size (1 analysis³⁰), history of anaphylactic reactions (2 analyses^{53,54}) and low tolerated dose of food allergen (1 analysis⁵³) were associated with a higher risk of adverse events in some studies. Other analyses did not find an association between safety outcomes and history of anaphylactic reaction,⁵⁴ low tolerated dose of food allergen⁵³ or skin prick wheal size.^{53,54} • Among 13 OIT clinical studies (RCTs with N> 50), five did not exclude children with a history of severe allergic reactions (3 peanut,^{60,61,64} 1 milk,⁴¹ 1 egg³¹). Percentages of patients experiencing following adverse events in these studies:<table><tr><th></th><th>Severe or serious adverse events (SAEs)</th><th>Epinephrine-treated reactions (ETRs)</th></tr><tr><td>Peanut</td><td> • RCT with medium target dose:⁶⁴ 1 case of wheezing (2.0%) • RCT with low target dose:⁶¹ SAEs: 10% OIT vs 16% placebo • RCT with high target dose:⁶⁰ 19% had anaphylactic events, graded as moderate </td><td> • RCT with medium target dose:⁵⁴ 2.0% OIT vs 0 control • RCT with low target dose:⁶¹ no ETR • RCT with high target dose:⁶⁰ 11% OIT vs 0 control </td></tr><tr><td>Egg</td><td> • Grade 4 reactions: 9.2% (build-up), 1.3% maintenance; no dysrhythmia, severe hypotension, hypovolemic shock, laryngeal edema, respiratory or cardiac arrest³¹ • 6.7% of patients visited emergency departments during home dosing⁴¹ </td><td> • 8.0% OIT vs Control: NR³¹ </td></tr><tr><td>Milk</td><td></td><td> • hospital rush phase: 13% OIT vs 0 control; home-dosing: 3.3% OIT vs 0 control⁴¹ </td></tr></table>		Severe or serious adverse events (SAEs)	Epinephrine-treated reactions (ETRs)	Peanut	• RCT with medium target dose:⁶⁴ 1 case of wheezing (2.0%) • RCT with low target dose:⁶¹ SAEs: 10% OIT vs 16% placebo • RCT with high target dose:⁶⁰ 19% had anaphylactic events, graded as moderate	• RCT with medium target dose:⁵⁴ 2.0% OIT vs 0 control • RCT with low target dose:⁶¹ no ETR • RCT with high target dose:⁶⁰ 11% OIT vs 0 control	Egg	• Grade 4 reactions: 9.2% (build-up), 1.3% maintenance; no dysrhythmia, severe hypotension, hypovolemic shock, laryngeal edema, respiratory or cardiac arrest³¹ • 6.7% of patients visited emergency departments during home dosing⁴¹	• 8.0% OIT vs Control: NR³¹	Milk		• hospital rush phase: 13% OIT vs 0 control; home-dosing: 3.3% OIT vs 0 control⁴¹
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B2. AGE	• Most OIT studies enrolled children starting from age 4 to 7 years, with median/mean ages in the range of 6 to 12 years.^{31-33,40,41,43,47,49,53,54,59,60,64,65}; some have started enrollment from age 2^{59,61} or one.^{46,62} • There was no association between baseline age and safety outcomes in four large reports of OIT practice with children and adolescents (age≥4 years)^{32,33,53,54} (case series: N=130 to 295) Data from studies in specific age groups: • Toddlers and pre-school children < 6 years: • 2.7 to 4.1% of children undergoing peanut OIT and 6.7% (vs 0 control) experienced an epinephrine-treated reaction; there was 1 grade 4 reaction (0.4% of children) in one peanut study and no severe reactions in the other two studies (peanut: 2 single-arm studies N=37⁵⁸, N=270;³⁰ milk: RCT: N=30 OIT, 30 controls) • Adolescents: • 19% of peanut OIT patients experienced anaphylaxis compared to 0 control patients (RCT: 21 OIT, 9 controls)⁴⁴												

Table 1 (continued)

DIMENSION Criteria	Data collected from the literature, milieu and consultations (in italics)
	• Adults: • 19.5% of adults undergoing peanut OIT experienced an anaphylaxis/systemic allergic reaction and 4.9% a severe adverse event versus 7.1% (for both outcomes) of control patients (double-blind RCT: N=41 OIT, 14 placebo)¹³⁴ • 17% of OIT patients had an epinephrine-treated reaction (1 single-arm study⁴⁴; N=9 peanuts, 10 milk, 4 eggs) B3. PATIENTS WITH ASTHMA • Asthma-related safety outcomes among children in OIT clinical studies (RCTs with N>50) that had excluded patients who had severe and/or poorly controlled or unstable asthma before OIT: • Egg:³¹ 9.1% of OIT patients withdrew during the build-up phase because of uncontrolled asthma (N=88) • Peanut (low-dose OIT):⁶¹ No difference in asthma-related outcomes between OIT and control (N=62) • Peanut (low-dose OIT):⁴⁷ Asthma exacerbation was recorded as a serious adverse event in 2 OIT patients (0.54%) and no placebo patient (N=372 OIT, 124 placebo) • Across five large retrospective analyses of clinical practice, asthma was statistically significantly associated with a higher risk of epinephrine-treated reactions (milk, N=194⁷¹; peanut, N=270⁴⁵), moderate to severe adverse reactions during the hospital-based rush phase (milk, N=192^{116,63}), eosinophilic esophagitis-like OIT-related syndrome (peanut, N=270⁴⁶), and adverse events during maintenance (peanut, N=104¹⁴⁷); however, one study found no association between asthma and reactions during home-dosing (milk, N=132¹⁴⁸). • One report of clinical practice highlighted 3 cases (2.3% of 130 patients treated for milk or egg allergy) of life-threatening anaphylaxis, all in teenage boys with sub-optimally controlled asthma. These patients had also high baseline sigE levels and poor compliance with OIT and asthma management plans.¹⁴⁹ C. IMPACT OF OIT PROTOCOL PARAMETERS ON SAFETY OUTCOMES C0. Type of OIT product. There are many different products reported in OIT protocols. Most clinical trials and all clinical practices used non-pharmaceutical food-based products. There are no head-to-head comparisons between pharmaceutical and food-based products. Meta-analysis of peanut OIT RCTs found that both proprietary and non-proprietary OIT products increased the rate of anaphylaxis compared to no OIT (placebo or usual care) (non-proprietary: 33% [43/131] vs 5.8% [3/52]; proprietary: 12% [65/522] vs 2.0% [5/245])²⁴ C1. UP-DOSING FREQUENCY • One clinical study of egg OIT found that weekly (30% increments) plus daily (5% increments) up-dosing (N=26) led to higher rate of Grade 1-2 reactions than weekly only up-dosing (30% increments) (N=62) (mean number of reactions per patient: 3.8% vs 24%, P=0.001), but also to lower rate of Grade 3-4 reactions (0.88 vs 1.46, P=0.031) (RCT:³¹ N=26 weekly plus daily, 62 weekly only) C2. TARGET DOSE : No data C3. MAINTENANCE DOSE: No data C4. MAINTENANCE FREQUENCY • In one clinical study of milk OIT, after 1 year of maintenance, there was no difference in frequency of adverse events between patients consuming 150-200 ml milk daily or twice weekly; there were no discontinuations during maintenance (RCT¹⁵⁰, N=38) • In one clinical study of egg OIT, there was a lower rate of reactions per patient with daily maintenance versus every two days (0.76 vs 2.1, P<0.05) and higher adherence to maintenance dosing (completed 1 year: 97% vs 78% (25/32) P value not reported (RCT:⁵⁶ N=29 daily, 24 every other day) C5. MULTI-FOOD OIT • In one clinical study,⁶⁸ there was no difference in reactions per dose between multiple-food OIT (N=15) and single-food OIT (N=25) (non-randomized trial:⁶⁸ N=25 multiple food allergies, N=15 peanuts only) C6. USE OF OMALIZUMAB • 3 RCTs comparing OIT with omalizumab vs OIT with placebo: • Combination with standard milk OIT : Fewer adverse reactions during build-up in patients using omalizumab (% of doses: 2.1% vs 16.1%, P=0.0005, requiring treatment: 0 omalizumab vs 3.8% placebo, P=0.0008) (N=57, omalizumab discontinued at 28 months)¹³³ • Combination with accelerated peanut OIT – No difference in adverse reaction rates (% of OIT doses associated with any reaction: 7.8% omalizumab vs 16.8% placebo, odds ratio=0.57, P=0.15; note: higher peanut doses in omalizumab group; N=37, omalizumab discontinued at 7 weeks)⁷³ • Multiple foods (2-5) – Fewer doses associated with any adverse events (median per patient: 27% omalizumab vs 68% placebo; P=0.0082) during the 8 weeks of OIT

Table 1 (continued)

DIMENSION Criteria	Data collected from the literature, milieu and consultations (in italics)
	when omalizumab was administered, there was no difference thereafter (N=48, omalizumab discontinued at 8 weeks)⁷ C7. TYPE OF PATIENT COMMUNICATION - Patients who were told that non-life-threatening symptoms were a positive signal that peanut OIT was progressing towards desensitization reported being less anxious about symptoms (P= .003), less likely to contact staff about symptoms (9.4% vs 17.5%, P= .036), experienced fewer non-life-threatening symptoms (P < .001), and were less likely to skip/reduce doses (4% vs 21%; P= .065) compared to patients who were told that they were unfortunate side effects of OIT (RCT:⁷⁴ N=50) CONSULTATIONS Patients: There are risks with OIT, although opinions on risks are contradictory. For example: being in a controlled environment makes the reactions less worrying, or the possibility of reactions only increases the patient's anxiety, or they would be willing to participate at the hospital, but not administer from home. Caregivers have to realize how serious what they are doing is. In any case, expecting reactions and getting used to warning signs helps reduce anxiety of accidental exposure on the long term (contact reactions and cross contamination risks are quickly reduced), severe reactions can be managed the same ways patients are already used to (EpiPen, 911), and through educating people around them. Allergists: Avoidance has no side effects until accidental exposure, so OIT brings more reactions and adverse effects, which are mostly mild, whereas accidental exposure can result in severe reactions. However, the biggest improvement with OIT is in patient quality of life. OIT can be suspended if the reactions are severe, the dose can be decreased if breathing issues or GI symptoms arise, and the treatment can be discontinued for severe symptoms such as vomiting, abdominal pains, severe anaphylaxis, that did not stop by reducing the dose. Some will follow the patient's preference, or can discontinue if the patient or their caregiver is not compliant. Other healthcare professionals: Some side effects can be associated with strong stress rather than allergic reactions (vomiting). OIT does provoke reactions on a regular basis, but the inconvenience of it depends on the patient's definition of severity; if having many reactions is a problem for them, OIT might have too many adverse effects, whereas if severity is defined by a severe reaction necessitating emergency action, OIT poses less risk than avoidance. ETHICAL ISSUES: The attitude of equipoise ascertains that OIT is not better than food avoidance due to the reactions occurring during OIT,^{151 152} however, most OIT reactions are not severe and may actually be signals of increasing desensitization,^{74 82} while avoidance reactions mostly generate anxiety and additional diet restrictions. Clarity about the risks associated with each option is thus necessary, and individualized protocols and clear communication on the meaning of allergic reactions during OIT would be beneficial to patients. The potential clinical benefits of OIT are: - Reducing the risk of allergic reactions due to accidental exposure: An increase in the eliciting dose from ≤ 100 mg to 300 mg peanut protein (approx. 1 peanut) may lead to > 95% reduction in the risk of an allergic reaction related to residual peanut protein in packaged foods.^{153 154} - Incorporating the food allergen into the diet - Achieving a definitive resolution of the allergy (sustained unresponsiveness /tolerance) CONSULTATIONS Patients: Patients achieving desensitization see their lives change, they can 'get their futures back'. The families' expectations aren't necessarily big, since the main objective is to reduce risks of accidental exposure, not find a cure. Another objective would be to help children grow out of their allergies. Some want to be able to assure themselves that they are at least trying to find a solution. In any case, OIT offers some security, and can facilitate improvement in the lives of the patients. Allergists: The goals from OIT are oral desensitization to reduce exposure risks, and sustained unresponsiveness where they can tolerate full doses (incorporate in diet), long term. Both can improve quality of life and reduce anxiety for the patients and their caregivers. Pros: providing OIT can help patients and their caregivers feel more in control, it can improve their quality of life, reduce their anxiety, and offer a potential cure. Cons: OIT doesn't have clear regulations, practitioners aren't always adequately compensated, it creates exposure to more frequent reactions, it is time consuming and can entail extra costs for the patients and for the practitioner, and there are concerns about adherence issues on the long term. Other healthcare professionals: OIT can provide a sense of control to the patients, being able to control the setting of the reactions is empowering. It can reduce the patients and caregivers' anxiety to be in a controlled environment, and significantly improves their quality of life. For some allergies that are harder to avoid (milk, wheat, eggs), the possibility of including them in the diet is much bigger a benefit than something that is not as present in many foods.
C10 -Type of clinical benefit offered by the intervention	
USER PERSPECTIVE	
C11- Acceptability and capacity to empower users and caregivers	PATIENTS' GOALS AND EXPECTATIONS may include developing a buffer against reactions due to accidental exposure,¹⁵⁵ translating to increased sense of freedom in daily life,¹⁵⁶ ability to freely eat the food allergen,^{155 157} to consume a limited amount of the food allergen with caution,¹⁵⁵ or to reduce the risk of a fatal food reaction.¹⁵⁷

Table 1 (continued)

DIMENSION Criteria	Data collected from the literature, milieu and consultations (in italics)
C12-Impact of the intervention on quality of life and health as perceived by the user	TREATMENT BURDEN • OIT requires patients (and/or their caregivers) to regularly attend visits, to adhere to the treatment at home (including administering the doses and complying with instructions for reduced activity 2 hours after the dose), and to be able to recognize and treat adverse events.^{8,9,78} • OIT Treatment burden assessment: • Over 80% of peanut OIT study participants (mothers and children) rated the treatment burden as positive (score 1–3, scale 1=extremely positive to 7=extremely negative) (RCT: N=62)⁶¹ • In one high-dose peanut-OIT clinical study, treatment burden was rated as overall moderate (3.7–3.9, scale 0: no burden to 10: massive burden); the highest burden was due to taste/amount of food, but declined after the first year of treatment (Year 1: 6.5 vs Year 2: 5.3, P=0.02); burden due to gastrointestinal adverse reactions declined after year 1 (Year 1: 2.6 vs Year 2: 1.4, P=0.001). (RCT: N OIT=57)⁶⁰ • Impact of taste aversion: • 49% of patients did not reach the target dose (20 peanuts) and 5.3% discontinued peanut OIT due to taste aversion (RCT, N OIT=57)⁶⁰ • 5.1% of patients discontinued peanut OIT during maintenance (8 peanuts), accounting for 41% of all patients who discontinued during maintenance (case series, N=270)⁶⁰ • 2.5 to 3.6% of patients discontinued milk OIT, accounting for 10% to 45% of all patients who discontinued (2 case series, N=280,³² N=295³³) CONSULTATIONS Patients: Mild reactions every 2 weeks during the up-dosing phase is the main adverse effect, and is not necessarily a problem once the routine is established, especially if it means reduced reactions once the treatment completed. It's an investment in the future. What is most problematic is the lack of availability, having to drive multiple hours to get to a clinic providing OIT, for example. Caregivers can find changing their avoiding habits and learning to trust the process to be challenging. Educating themselves and people around the patient is important and vital. The treatment can also be time consuming for the caregivers. Allergists: OIT implies more frequent office visits and reactions happening, however both decrease with time. There is still much more involvement than during avoidance management, shared decision-making is essential. Other healthcare professionals: OIT requires a lot of time, it can involve costs and can create a sense of uncertainty of not knowing the outcome. Patients can be unrealistically informed and expect a cure from OIT, or expect a 'smooth ride' and might be uncomfortable asking the doctors how the treatment is going. The main expectation is the reduction of risks of accidental exposures. ETHICAL ISSUES: Issues relating to disease comprehension and shared decision-making: Information in the media does not always promote informed decision-making. On the other hand, physicians should be careful to avoid information bias, to explain risks and expected outcomes, in order to inform shared decisions.^{158,159} QUALITY OF LIFE (QoL) OUTCOMES SPECIFIC TO FOOD ALLERGY- (see detailed results in the Appendix 3) QoL outcomes after the end of the build-up phase (in controlled clinical OIT trials or large case series) • Parent data as proxy for child QoL (tool FAQLQ-PF validated in food allergy): ◦ 5 published studies: 2 placebo-controlled RCTs (peanut; N=31 OIT, 31 placebo,⁶¹ N=31 OIT, 31 placebo¹⁶⁰), 1 prospective cohort study¹⁶¹ (peanut, egg, sesame, tree nuts; N=175 OIT, 48 control), 1 case series¹⁶² (peanut, N=100), 1 open-label cross-over RCT⁶⁴ (peanut, N=19 OIT, control not reported) ▪ OIT: 4 studies showed significant improvement from baseline in the Total score^{64,160-162} and 3 reported also significant improvement in each domain (Food Anxiety, Social and Dietary Limitations, Emotional Impact).¹⁶⁰⁻¹⁶², 1 placebo-controlled study (peanut) observed no significant improvement from baseline in all measures.⁶¹ ▪ Control: In all 3 of the controlled studies, there were no significant changes from baseline in the control groups. ▪ Comparison OIT-control: no significant difference between OIT and control in 1 study;⁶¹ Improvement in FAQLQ-PF score by ≥ 0.5 (MCID) 3 months post-treatment: OIT: 77%; Placebo: 34%; Absolute risk reduction: 42.2%; NNT = 2.3 (95% CI 1.0 to 2)¹⁶⁰ ◦ Mean utility gain per patient upon completion of OIT: 4.5% (SE 1.1%) based on FAQLQ-PF data from 66 patients mapped onto the generic SF-6D QoL instrument¹⁶³ (data from Canadian clinical practice, published at conference) • Child (FAQLQ-PF) or Teen (FAQLQ-TF) QoL data: ◦ 2 studies (peanuts; 1 placebo-controlled RCT 9 OIT, 8 placebo,⁶¹ case series, N=46 children or adolescents¹⁶²) with significant improvement from baseline in the Total score and in each domain (Allergen avoidance, Risk of accidental exposure, Emotional impact, Dietary restrictions); Control: no significant differences from baseline in the RCT;⁶¹ significant difference OIT vs control only for Risk of exposure and Emotional impact Parental burden • Parental burden data (FAQL-PB): (1 open-label peanut RCT¹⁶⁴) significantly improvement for OIT-group (N=39) (P<0.0001) and control group (N=20) (P=0.004) from baseline to two years, with no significant difference between groups (P=0.57).

Table 1 (continued)

DIMENSION Criteria	Data collected from the literature, milieu and consultations (in italics)																		
	GENERIC QUALITY OF LIFE OUTCOMES (Pediatric Quality of Life Inventory Version 4.0 (PedsQL 4.0, not validated in food allergy; 1 peanut RCT¹⁶⁴ (N= OIT: 39, Control 20) • Child QoL: OIT: significant improvement ($P < 0.001$) from baseline to two years; no change in control; difference between groups not significant ($P = 0.12$). • Parent as proxy of child QoL: significant improvement ($P < 0.001$) from baseline to two years; no change in control; difference between groups significant ($P = 0.02$) Study Limitations: • RCT evidence: 3 RCTs with comparator data available, of which only 2 used the FAQLQ questionnaire and only 1 measured QoL at multiple times after baseline; relatively small sample size, particularly for the children; blinding of treatment assignment (placebo-based design) may fail to fully capture the subjective impact of treatment on QoL (e.g., for domains Food anxiety or Allergen avoidance), incomplete QoL data • Non-RCT evidence: lack of comparator groups EVOLUTION OF QOL OUTCOMES DURING THE COURSE OF OIT • Parent data (FAQLQ-PF scores) from prospective cohort study of 191 children with various food allergies:¹⁶¹ improvement from baseline through mid-up-dosing to maintenance and further to 6 months post-maintenance, with the greatest improvements between the latter two time points • Subset of patients: deterioration in QoL during mid-up-dosing with a return to baseline levels upon reaching maintenance.																		
	FACTORS ASSOCIATED WITH GREATER IMPROVEMENT IN FOOD-ALLERGY-RELATED QOL WITH OIT <table> <tr> <th>Factor</th><th>Significant association?</th></tr> <tr> <td>worse pre-OIT QoL (FAQLQ-PF)*</td><td>✓</td></tr> <tr> <td>history of anaphylactic reactions†</td><td>✓</td></tr> <tr> <td>younger age‡</td><td>✓</td></tr> <tr> <td>single food allergy (rather than multiple)*</td><td>✓</td></tr> <tr> <td>type of food allergy (treated asthma status)</td><td>No</td></tr> <tr> <td>achieving sustained unresponsiveness</td><td>No</td></tr> <tr> <td>duration of up-dosing</td><td>✓</td></tr> <tr> <td>frequency and severity of allergic reactions during OIT</td><td>No</td></tr> </table> * Significant in linear regression analysis; † Significant only in single-factor analysis; ‡ Only significant in subgroup of 158 children who reached full desensitization CONSULTATIONS Patients: OIT can help reduce parents' anxiety, depending on the results of the treatment, as well as simplify interactions with schools, kindergartens, or workplaces. The stress associated with children's allergies is becoming more and more of a problem, since the parents worry in any and all situations (planes, metro, restaurant, etc.). The diminishing anxiety and risks of accidental exposure can positively impact quality of life on the long term. In the short term, it is difficult for the parents to administer doses to their children, they require support. Allergic parents reaching desensitization or sustained unresponsiveness can have an opportunity to provide their children with a more varied diet. Allergists: There is a tremendous improvement in many patients and caregivers' quality of life, since it can reduce anxiety and suppress the effects of the allergies on social life, in comparison to avoidance. Other healthcare professionals: Quality of life can be positively impacted by the treatment, reducing anxiety, increasing confidence, and providing a sense of control to the patients since they learn how to recognize a reaction is coming and how to handle it without panicking. Parents can have higher expectations for the treatments than children or teenagers, who might not have as much of a long-term vision as their parents, these expectations need to be aligned with realistic goals achievable through OIT. ETHICAL ISSUES: Not applicable	Factor	Significant association?	worse pre-OIT QoL (FAQLQ-PF)*	✓	history of anaphylactic reactions†	✓	younger age‡	✓	single food allergy (rather than multiple)*	✓	type of food allergy (treated asthma status)	No	achieving sustained unresponsiveness	No	duration of up-dosing	✓	frequency and severity of allergic reactions during OIT	No
Factor	Significant association?																		
worse pre-OIT QoL (FAQLQ-PF)*	✓																		
history of anaphylactic reactions†	✓																		
younger age‡	✓																		
single food allergy (rather than multiple)*	✓																		
type of food allergy (treated asthma status)	No																		
achieving sustained unresponsiveness	No																		
duration of up-dosing	✓																		
frequency and severity of allergic reactions during OIT	No																		
	ORGANIZATIONAL DIMENSION AND PROMOTION OF INTEGRATED CARE • OIT is aligned with the mandate of the healthcare system. • The Canada Health Care Act stipulates 5 guiding principles: portability, accessibility, universality, comprehensiveness, and public administration. Comprehensiveness is defined as: The provincial and territorial plans must insure all medically necessary services provided by hospitals, medical practitioners and dentists working within a hospital setting. (Government of Canada 209) CONSULTATIONS Patients: Not applicable Allergists: Not applicable Other healthcare professionals: OIT is a viable option, so it would be aligned with the mandate of the healthcare system. ETHICAL ISSUES: Not applicable • Reorganization of the care of food-allergic individuals is necessary to improve access to allergy specialists, time to diagnosis and children's quality of life.¹⁶⁵																		
C13–Alignment of the intervention with the mandate of the healthcare system																			
C14–System																			

Table 1 (continued)

DIMENSION Criteria	Data collected from the literature, milieu and consultations (in italics)		
	Expertise / training requirements	Recommendations or reported practices for OIT in clinical practice	Reference
capacity and appropriate use of intervention	Implementation of OIT requires consideration of several factors explored below:	Staff training for sourcing and preparing of foods Experience in patient education and communication Experience in performing oral food challenges Training and experience in treating allergic reactions, including anaphylaxis	FAST, 2018 ⁸⁶ - USA EAACI, 2018 ⁸ - Europe
	Medications and equipment required	Steriloscope, sphygmomanometer, pulse oximeter, oxygen, spirometer, peak flow meter, laryngoscope, intubation tubes, ventilation bags, heart defibrillator; epinephrine, antihistamine (oral and parenteral), inhaled beta2-agonist, corticosteroids (oral, parenteral), IV lines and IV fluids	EAACI, 2018 ⁸ - Europe
	Logistics of patient education, communication and shared decision-making	Schedule a 30 to 60 minute discussion before initiating OIT At every visit, educate patients on how to identify and manage reactions (including criteria for epinephrine use) Provide individualized schedule and interventional protocol in the event of allergic reactions at home clearly written in simple non-medical language Provide convenient means for reporting allergic reactions and incidents during treatment (forms, web-sites, phone apps?)	FAST, 2018 ⁸⁶ - USA Blaiss, 2019 ⁸¹ - USA Nachshon, 2015 ¹⁶⁶ - Israel SEICAP, 2017 ⁹ - Spain EAACI, 2018 ⁸ - Europe
	Logistics of food allergen dose administration	First OIT dose typically administered by allergist; dedicated nurse monitors the patient and may administer later doses (up-dosing) Observation requires 1 to 2 hours of use of an examination room or food challenge area Personnel should be able to provide at least 12 hours of observation in case of adverse reactions related to OIT. Prolonged monitoring units (up to 24 hours) in the medical center in the event of severe anaphylaxis (or in pediatric department in the case of children)	Blaiss et al, 2019 ⁸¹ - USA EAACI, 2018 ⁸ - Europe SEICAP, 2017 ⁹ - Spain
	Logistics of food allergen dose preparation and storage	Purchase: at local groceries or online Preparation: On site (highly sensitive scale) or out-source to compounding pharmacies Storage: refrigeration or freezing (no stability testing needed) Home doses are packaged for storage	FAST, 2018 ⁸⁶ - USA Blaiss, 2019 ⁸¹ - USA
CONSULTATIONS			
Patients: Constantly available support for the patients would be appropriate, in the case of more than anticipated severe reactions. Different healthcare professionals could help on different aspects of the treatment. Telephone support 24h would be reassuring, more so than a chat system, since talking to someone makes it more trustworthy. The current HCS organization isn't equipped for OIT; since some allergists, and many family doctors, aren't familiar with OIT, or willing to administer it. Allergists: To administer OIT, it is necessary to have allergist training and experience in order to be able to treat anaphylaxis, or any other reaction. It is also needed to master oral challenges and be able to understand and educate the patients and their caregivers. Some patients feel that it would be important for the provider to be willing to be available at all times. The allergist should see the patient at the initial consultation (and then yearly), even if via a videoconference, and develop the initial treatment plan. This plan can be delivered by a local family physician under continuing guidance of the allergist (e.g., through telephone calls) in certain cases. To perform OIT, it is necessary to have a dedicated nursing staff to assist, adequate safety equipment, access to epinephrine, clinic space to monitor patients and for a waiting room, and resuscitation facilities. It should be done in a hospital context. For increased OIT access, there needs to be increased access to allergists for easier diagnostics, more allergists need to be educated to perform OIT, billing codes should be revised to encourage the practice, and more hospital-based clinics should be created for OIT to be provided in. Other healthcare professionals: For the treatment administration, education should be made available to family doctors and pediatricians in addition to allergists would be best, in order to make sure the method used is the best one (understanding of challenges, understanding of the patient's issues, understanding of different types of reactions and how to manage them). There should at least be the possibility of access to registered dietitians in order to help the patients and caregivers develop an appropriate diet that is kept varied. There should also be offered psychological support, especially in the form of group discussion, which would minimize costs, and allow the patients to benefit from peer support which would help solve issues more than one patient encounter, or help children discuss things with people other than their parents. Some issues might come out more effectively this way, amongst people sharing their experiences, which would help add res them in the best way. For the more complex cases, individual support by a psychologist would also be ideal. Pharmacists could be involved in the process as advisors, in order to answer questions for the patients, or to compound and measure doses. Necessary resource would include: a doctor on site at all times, access to a secure environment (oxygen, stretchers) and available trained medical staff, especially nurses able to assist patients with inquiries concerning the treatment, either in person, or via phone or e-mail. Necessary infrastructure would include: a space to receive the patients, a space to prepare the doses and access to a service corridor to transport patients reacting badly.			
ETHICAL ISSUES: Not applicable			

Table 1 (continued)

DIMENSION Criteria	Data collected from the literature, milieu and consultations (in italics)
C15- Cost of acquiring and maintaining the intervention for the health and social services system (e.g., medication, software)	COST OF FOOD PRODUCTS Non-commercial approach: - Acquisition cost of allergen food product acquisition for OIT: estimates between less than \$10 to \$50 per patient (data on file from two Canadian OIT clinics). - Cost of producing peanut doses by skilled staff in healthcare system (25 mg or 125 mg peanut protein): \$0.025 (suspension) to \$0.214 (flour cups) per dose⁶⁷ (data from 1 Canadian OIT clinic) Commercial approach: - Acquisition cost of commercialized peanut product (estimate): US\$3600 to US\$4800 per year (ICER, 2019⁶⁵); lifetime treatment (i.e., for 10 years = US\$36,000 to US\$48,000) COST OF OMALIZUMAB AS AN ADJUNCT THERAPY Omalizumab is sometimes used to increase the threshold of adverse reactions while providing OIT, in a temporary manner (usually between 2 to 6 months), with the objective of allowing a safe and rapid progression of food dosages that will provide protection once omalizumab is weaned - Estimated cost: \$309 to \$3,708 every 4 weeks (based on a cost of, is \$618 per 150-mg vial for sub-cutaneous injection (RAMQ, 15 August, 2019 and dosing depending on body weight and ranging from 75 mg every 4 weeks to 450 mg every 2 weeks⁶⁸) COST OF AVOIDANCE No cost to the healthcare system CONSULTATIONS Not applicable ETHICAL ISSUES: High cost options may create access issues and inequity.
C16- Cost in health and social services system resources	HEALTHCARE RESOURCES COST FOR OIT - Cost of OIT physician visits per patient (Canada): estimates between \$972 to \$2153 per patient; based on an average number of clinic visits per patient of 5.6 to 15.4 visits with the latter including 2.6 visits for oral food challenge (data on file from 3 Canadian OIT clinics) - Costs of clinical visits for dose escalation during the first 6 months of peanut OIT (USA): estimated at US\$4,495 per patient (ICER,⁶) HEALTHCARE RESOURCES COST FOR AVOIDANCE There are significant hidden costs related to food allergen avoidance, such as emergency department visits, physician visits and pharmacotherapy.^{124 168} OIT VS AVOIDANCE In theory, reducing outpatient and emergency department visits and the need for rescue therapy with epinephrine, could lead to lower direct medical cost for patients with food allergy (Cannon, 2018); However, data from RCT do not support the idea that patients would have less reactions overall and consume less care, but rather to be cost-neutral. CONSULTATIONS Patients: In the short term, implementing OIT at a great scale would imply an important budget in the therapeutic field of allergy. On the long term, there could be possible reductions in doctor visits, in reactions, in possible ambulance emergencies, in ER visits, in other medical expenses related to the effects of allergies (psychological, nutrition) or in EpiPen use, which might reduce costs compared to now. Preventive costs are essential. If reactions were too frequent with OIT, it could be too costly Allergist: OIT is considered a moderate to high cost treatment, since it requires some resources (staff, infrastructure to have sufficient space) in order to ensure the patients' safety. OIT will be cost-adding in the first years of treatment (also because of an increased frequency of reactions) and if sustained unresponsiveness cannot be achieved. In this case, the benefit lies in the improvement of QoL. In the long term, cost savings may come from a reduced need for psychiatrists, psychologists or registered dietitians associated with avoidance. Other healthcare professionals: The burden of cost is currently mainly on the patients, so they would be the ones feeling changes the most. Patients would still need to carry an epinephrine autoinjector, so there wouldn't be changes that way, but if a large part of the allergic population used OIT, there would be an impact on the number of ER visits.
C17- Costs for the user / caregiver	ETHICAL ISSUES: Not applicable COST OF OIT TO PATIENTS & FAMILIES May include costs associated with regular appointments (transportation, parking, taking time off from work and school), cost of buying the food allergen (may be significant for shellfish), and co-payments for any prescribed adjuvants (such as omalizumab), if these are used, and for medications to treat adverse reactions (e.g., autoinjectable epinephrine, antihistamines).

Table 1 (continued)

DIMENSION Criteria	Data collected from the literature, milieu and consultations (in italics)																								
	COST OF AVOIDANCE TO PATIENTS & FAMILIES - Includes cost of allergen-free food, medications (e.g., autoinjectable epinephrine, antihistamines), lost time and earnings due to allergic reactions and consultations with health professionals, changing job etc.,^{81,102,168,169} which can be financially burdensome, especially for low income families.^{86,110,168} Annual out-of-pocket costs for families with an allergic child: €3961-€4792 (for milk, eggs or wheat allergy in Sweden)⁸⁰ and US\$931 (US, any food allergy).¹⁶⁹ Average annual costs of lower work productivity of caregivers due to their child's allergy: US\$2399 per child, which affected 9.1% of caregivers (4.9% of caregivers reported quitting a job, 2.5% had to change jobs, and 1.9% lost their jobs).^{124,169} CONSULTATIONS Patients: <i>For the patients and their caregivers, going to see their allergists regularly for a limited period (the time of the treatment) will be less costly on the long term than their current situations, in which 'fear makes us spend'. Visits could end up being globally less numerous if young children are desensitized. Shared costs between the HCS and the patients would be acceptable. Private clinics options do create higher costs, and allergen-safe foods can be expensive.</i> Allergists: Not applicable Other healthcare professionals: <i>Time off work transportation and parking would be the possible costs involved. Finding food containing allergens would be easier than avoiding them, and would reduce parents' time spent preparing the food for the children.</i> ETHICAL ISSUES: The cost associated with avoidance, which are borne by the patients, can be a financial burden for low income families, contributing to inequity in food allergy management. OIT, being the financial responsibility of the healthcare system, would allow reducing inequities. OIT: No data AVOIDANCE - The burden of managing avoidance (or lack of) in schools and daycares is hard to quantify but is very well described in qualitative studies. CONSULTATIONS Patients: <i>Investing in the display of allergies is important, and is perceived to be driven by fear and anxiety, while investment in the OIT is seen as bringing hope for change. Reactions cost everyone money.</i> Allergists: Not applicable Other healthcare professionals: <i>If all patients used OIT, there would be savings to schools or workplaces, but otherwise, measures might be reduced but would have to remain.</i> ETHICAL ISSUES: Not applicable OIT - If services are limited to city centers, long distances travelled by car or plane can contribute to carbon emissions. AVOIDANCE - Some adult patients identify their nut or legume allergy as a barrier to adopt a more ecologically sensitive diet. Cost-effectiveness model of the Institute for Clinical And Economic Review of commercially developed OIT (AR101) for peanut allergy⁶ Base case results: <i>perspective of the US healthcare system; lifetime horizon; costs and outcomes discounted at 3% per year; patients who were successfully desensitized were assumed to remain on OIT for lifetime; peanut product (AR101) cost: US\$4200 per year; month 1-6 clinical visits for dose escalation US\$4495 (number of visits not reported)</i> <table><tr><th></th><th>OIT-AR101</th><th>Avoidance</th><th>Difference: OIT-AR101 – Avoidance</th></tr><tr><td>Therapy cost (includes cost of peanut pill and clinical visits for escalation during months 1-6)</td><td>US\$65,000</td><td>US\$6,000</td><td>US\$65,000</td></tr><tr><td>Other costs (adverse events, accidental exposure)</td><td>US\$7,000</td><td></td><td>US\$1,000</td></tr><tr><td>Total cost</td><td>US\$72,000</td><td>US\$6,000</td><td>US\$66,000</td></tr><tr><td>Quality-adjusted life-years (QALYs)</td><td>27.19</td><td>26.44</td><td>0.75</td></tr><tr><td>Incremental cost per QALY (incremental cost-effectiveness ratio, ICER)</td><td></td><td></td><td>\$88,000</td></tr></table> - No difference in life-years between treatments Sensitivity analyses: - ICER was sensitive to utilities (QoL weights) and AR101 costs - Varying the number of weekly OIT visits did not have a significant impact on the ICER (base case: 0.2 visits per week, sensitivity analysis: 0.16 to 0.24) ETHICAL ISSUES: Not applicable		OIT-AR101	Avoidance	Difference: OIT-AR101 – Avoidance	Therapy cost (includes cost of peanut pill and clinical visits for escalation during months 1-6)	US\$65,000	US\$6,000	US\$65,000	Other costs (adverse events, accidental exposure)	US\$7,000		US\$1,000	Total cost	US\$72,000	US\$6,000	US\$66,000	Quality-adjusted life-years (QALYs)	27.19	26.44	0.75	Incremental cost per QALY (incremental cost-effectiveness ratio, ICER)			\$88,000
	OIT-AR101	Avoidance	Difference: OIT-AR101 – Avoidance																						
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C18 - Societal costs																									
C19- Environmental impact																									
C20- Cost-effectiveness																									

Table 1 (continued)

DIMENSION Criteria	Data collected from the literature, milieu and consultations (<i>in italics</i>)
C21- Opportunity cost regarding the resources of the healthcare system and financial affordability	CONSULTATIONS Patients: Allergies affect lots of people, children being the first concerned, which makes the first objective taking preventive measures. OIT can be seen as an investment in the future, seeking to improve quality of life for all concerned, which could lead to reductions in expenses associated with reactions, and could help society at large since reduced anxiety could allow the patients to become more productive. The insufficient actual investment in allergy treatments could be considered unfair compared to other conditions which impact day to day life and nutrition (i.e. diabetes). Allergists: It might be too costly to offer it on a global scale, but it could be manageable with an age cut-off. However, this would need to be balanced with the needs of older patients with severe persistent disease. It may require a reorganization of the allergists' clinical office with a delegation of less specialized but lucrative interventions to other health professionals. Some say the government could afford providing the resources for administering OIT. Other healthcare professionals: Allergy resources are underfunded and should be more prioritized, but there is no certainty in the HC system's capacity to afford OIT. ETHICAL ISSUES: Not applicable CONSULTATIONS Patients: Although some have doubts as to its efficacy, with proof and additional data, patients express OIT would be worthy of investing in, even if the process may be expensive, they feel the treatment's possible results could be worth it. Allergists: Not applicable Other healthcare professionals: Not applicable ETHICAL ISSUES: Not applicable
C22- Opportunity cost regarding the resources of the patient / caregiver / user and financial affordability	ETHICAL ISSUES: Not applicable CONSULTATIONS Patients: Although some have doubts as to its efficacy, with proof and additional data, patients express OIT would be worthy of investing in, even if the process may be expensive, they feel the treatment's possible results could be worth it. Allergists: Not applicable Other healthcare professionals: Not applicable ETHICAL ISSUES: Not applicable

Conclusion

These guidelines bring to the forefront the critical importance and value of placing patients at the center of the development of clinical practice guidelines. Here, this approach was instrumental to developing recommendations for the responsible implementation of OIT in clinical practice, adapted to individual patient needs. The multicriteria approach offers an alternative to technocentric approaches in CPG development by balancing human, ethical and technical considerations in decision making (Fig. 4).

Technocentric approaches tend to create a pressure to standardize patient care in order to generate quantitative data, which may not always be in patients' best interest. Rather than adapting patient care to meet methodological needs for quantitative data, the methodology should be adapted to patients' needs for best care. As the saying goes, 'Not everything that counts can be counted, and not everything that can be counted counts [75].'

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s13223-020-0413-7>.

Additional file 1. Supplementary appendices.

Abbreviations

A4R: Accountability for reasonableness; CCT: Controlled clinical trial; CPG: Clinical practice guidelines; CSACI: Canadian Society of Allergy and Clinical Immunology; EAACI: European Academy of Allergy and Clinical Immunology; EoE: Eosinophilic esophagitis; EPIT: Epicutaneous Immunotherapy; IHE: Institute for Health Economics; OIT: Oral immunotherapy; RCT: Randomized controlled clinical trial; SLIT: Sub-lingual Immunotherapy.

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Authors' contributions

P. Bégin, E. S. Chan, H. Kim, E. M. Abrams, M. Ben-Shoshan, S. B. Cameron, S. Carr, D. Fischer, A. Haynes, S. Kapur, M. N. Primeau, J. Upton, T. K. Vander Leek are members of the OIT CPG working group, in alphabetical order except for the executive team. MSC adapted the EVIDEM framework to transform it into a patient-centered ethical framework. MMG reorganized the criteria of the EVIDEM framework into five dimensions and adapted the framework to a qualitative MCDA approach (no weighting and no scoring) to deepen the reflective aspects of the framework. HK, ESC, PB, MW, MMG were responsible for executive decisions throughout the development of the clinical practice guidelines. MW performed the review of the literature to which all authors contributed, except for the ethical aspects, which was performed by CFG. MSC, MW, MMG and PB performed consultations and chaired consultations panels. MSC organized and analyzed the consultations. MMG performed the data integration. All authors had full access to all of the data collected through the literature review and consultations. MSC, MW, MMG and PB take responsibility for the accuracy of the data synthesis. All authors contributed to the analysis and interpretation of data. MSC, MW, MMG and PB drafted the deliberation guide. MSC, MW and MMG chaired the deliberation committee. All authors drafted the recommendations during the deliberation. MSC, MMG, MW, and PB drafted the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Additional data is included in the supplemental repository. Clinical tools for implementation in practice will be made available at <http://www.csaci.ca/OIT>.

Ethics approval and consent to participate

The study was performed according to the current practices at INESSS for clinical practice guidelines; patients consulted on their perspectives of the different dimensions of OIT completed an informed consent.

Consent for publication

Not applicable.

Competing interests

Direct competing interests related to the topic of the guidelines P. Bégin and J. Upton are non-remunerated investigators on an investigator-instigated trial sponsored by the Canadian Institutes of Health on the use of omalizumab in oral immunotherapy (in-kind contribution of investigative drug product by Novartis worth > \$100,000 CAD). They were excluded from the room for the discussion and deliberations on recommendations related to the use of omalizumab in oral immunotherapy. M. Ben-Shoshan was a principal investigator on a trial on the use of pharmaceutical peanut flour preparations in OIT sponsored by Aimmune Therapeutics (> \$100,000 CAD in grant support). J. Upton was a non-remunerated sub-investigator on clinical trial sponsored by Aimmune Therapeutics on the use of pharmaceutical peanut flour preparations in OIT. They were excluded from the room for the discussion and deliberations on recommendations related to the use of pharmaceutical food products in OIT.

Direct competing interests unrelated to the topic of the guidelines P. Bégin reports speaker and/or advisor fees from Food Allergy Canada, Novartis, Pfizer, Sanofi, ALK and Aralez Pharmaceuticals, as well as research grant support from Canadian Institutes for Health Research, Fonds de Recherche en Santé du Québec, Canadian Allergy, Asthma and Immunology Foundation, DBV technologies, CHU Ste-Justine Foundation, Regeneron and Sanofi outside the submitted work. M. Ben-Shoshan reports advisor fees from Food Allergy Canada, as well as research grant support from Canadian Institutes for Health Research, Fonds de recherche en Santé du Québec and Canadian Foundation of Allergy and Clinical Immunology outside the submitted work. S. B. Cameron reports an unrestricted educational grant from Pfizer outside the submitted work. S. Carr reports speaker and/or advisor fees from Aralez, Pfizer, Nutricia, Meda (Mylan), Sanofi, GSK, ALK, and Pediapharm. E. S. Chan reports speaker and/or advisor fees from Pfizer, Kaleo, Food Allergy Canada, Pediapharm, Leo and DBV technologies as well as research grant support from DBV Technologies outside the submitted work. D.

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Indirect competing interests related to the topic of the guidelines E. M. Abrams is a pediatric allergist currently offering OIT in clinic. She has contributed to a national cohort study published on the topic. She is on the national advisory board of Food Allergy Canada. P. Bégin is an adult-trained allergist currently offering OIT in the academic setting. He pursues clinical research projects on OIT. He is the director of a pilot public OIT program funded through philanthropy and government support. He collaborates with a parent committee doing fundraising for a public-funded OIT program in the province of Quebec. He is a clinician-scientist with a research program including clinical trials, epidemiologic and health technology assessment studies on food allergy and OIT. He has published original research as well as editorials and review articles on the topic of OIT. He is a member of the advisory board for Food Allergy Canada. He has given public and scientific lectures on the topic of OIT. M. Ben-Shoshan is a pediatric allergist currently not offering OIT outside research. He is a clinician-scientist with a research program including clinical trials OIT. He has previously published on the topic of OIT. He is on the national advisory board of Food Allergy Canada. A. Boisvert is a peer-supporter at byebyeallergies.ca and Food Allergy Canada. M. J. Cadieux, is a peer-supporter at Déjouer-les-allergies. S. B. Cameron is a pediatric allergist currently offering OIT in clinic. He has contributed to a national cohort study and a review published and has given scientific lectures on the topic. S. Carr is a pediatric allergist currently offering OIT in clinic. He has contributed to a national cohort study and a review published and has given scientific lectures on the topic. E. S. Chan is a pediatric allergist currently offering OIT in the academic setting. He collaborates with a parent committee doing fundraising for a public-funded OIT program in Vancouver. He has contributed to a national cohort study published on the topic. He is a member of the advisory board for Food Allergy Canada, is an eosinophilic esophagitis guideline member for the Joint Task Force/American Gastroenterological Association, and was an expert panel and coordinating committee member of the National Institute of Allergy and Infectious Diseases-sponsored Guidelines for Peanut Allergy Prevention. D. Fischer is an adult-trained allergist currently not offering OIT in clinic. He has given scientific lectures on the topic. B. Francoeur is a family physician from a region without allergist with a practice focus on allergy. He currently follows patients on OIT but does not initiate treatment himself. H. Kim is an adult-trained allergist currently offering OIT in clinic. He has published an editorial on the topic of OIT. He is the president of Canadian Society of Allergy and Clinical Immunology. A. Haynes is a pediatric allergist currently not offering OIT in clinic. S. Kapur is a pediatric allergist currently offering OIT in clinic. He has previously contributed to a national cohort study published on the topic. G. Parizeault is a pediatrician with a practice focus on allergy in a region without allergist. He is currently offering OIT in clinic. S. Pernice, is a registered dietician practicing in an academic allergy clinic offering OIT. M.N. Primeau is a pediatric allergist currently not offering OIT in clinic. J. Upton is an adult-trained allergists currently not offering OIT outside research. She is a clinician with a research program including clinical trials OIT. She is on the national advisory board of Food Allergy Canada. She has given public and scientific lectures on the topic of OIT. C. Vaillancourt is a family physician with a practice focus on allergy in a region without allergist. He is currently offering OIT in clinic. T. K. Vander Leek is a pediatric allergists currently offering OIT in clinic. He has previously contributed to a national cohort study published on the topic. Other authors and members of the deliberative committee declared no indirect conflicts of interest.

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Appendix 1: Management of conflict of interests and roles

Orientations for the implementation of Guidelines International Network (GIN) principles - OIT Guideline development

	(GIN) (2015) Principles	Proposed orientations for the implementation of GIN principles - OIT Guideline development
Defining and declaring COIs	<i>Principle 2: The definition of COI and its management applies to all members of a guideline development group, regardless of the discipline or stakeholders they represent, and this should be determined before a panel is constituted.</i>	1. <u>Definitions:</u> Conflict of interests (COI): situations in which the professional judgement of an individual involved in developing the CPG can be unduly influenced by an opportunity to derive personal benefit. A specific interest is related to the topic under evaluation. 2. The declarant must declare his/her own interests as well as the interests of spouses living in the same residence as the declarant, children, parents (father and mother) and siblings. Interests from friends, other family members, and business partners must also be declared, if they are known to the declarant and could affect impartiality and independence of the declarant's judgment. Interests of organizations in which the declarant holds a managerial position must also be declared. 3. The principles and orientations proposed apply to every person working on the OIT Guideline development, including the members of: the Clinical Practice Guideline Development Executive Team; the CSACI Oral Immunotherapy CPG Working Group; the Scientific Support team; the Deliberative Committee; and the individuals (experts/advisors/patients) consulted as part of the consultations activities.
	<i>Principle 3: A guideline development group should use standardized forms for disclosure of interests</i>	4. The declaration is made via a declaration of interests form. It must be renewed at least every year. Any change which places the declarant in a situation conducive to the development of conflicts of interest or roles must be declared as soon as possible. 5. The types of interests that are to be declared include: a. Financial or non-financial interests or roles, specific or non-specific to the object of the work; b. Personal, professional or institutional activities, past, present or future (already planned), actual, apparent or potential. 6. Interests held in the 36 months preceding the declaration, and those foreseeable, are to be declared.

	<i>Principle 4: A guideline development group should disclose all relevant interests publicly, and these should be easily accessible for users of the guideline.</i>	7. The COIs of every person working on the OIT Guideline development, the reasons for including conflicted members and the management of COIs, will be disclosed explicitly and publicly, i.e. they will be published and described with the Guideline. 8. The funding source of the Guideline will be disclosed and published along with the Guideline. The funding for the OIT Guideline development comes from the membership to the Canadian Society of Allergy and Clinical Immunology. No industry money is used to fund the activities. 9. The role of the sponsor(s) and the support provided for the development of the guideline will be described within the Guideline.
	<i>Principle 5: All members of a guideline development group should declare and update any changes in interests at each meeting of the group and at regular intervals (for example, annually for standing guideline development groups).</i>	10. The declaration of interests must be renewed every year. Any change which places the declarant in a situation conducive to the development of conflicts of interest must be declared at the earliest opportunity, for example, orally at the start of meetings and/or by updating the original form.
Oversight Committee	<i>Principle 9: An oversight committee should be responsible for developing and implementing rules related to COIs.</i>	11. The CSACI Guidelines Selection Committee, designated by the CSACI executive, reviews the written declarations of COIs from CSACI members who volunteered to be part of the CSACI OIT CPG Working Group. 12. The Committee reviews written COIs declarations from the Clinical Practice Guideline Development Executive Team, the CSACI OIT CPG Working Group, the Scientific Support team, the Deliberative Committee and the individuals (experts/advisors/patients) consulted. 13. The Committee evaluates the interests declared applying the following criteria, using an evaluation grid (to be developed): 1) interest or role (nature, value, nature of the organization involved, specificity, seniority, duration, repetition); 2) the declarant (holder of the interest, nature of the link with an outside organization); 3) the mandate of the declarant;

		4) the potential consequences of the conflict of interests or roles. 14. The Committee determines one of three potential responses to a conflict of interest: - No action other than open disclosure - Partial exclusion (e.g., include only for consultation but not for deliberation, i.e., decision-making, or if included in deliberation, exclude from voting on specific recommendations) - Complete exclusion 15. The Committee retains the declaration forms five years after the publication of the guidelines 16. The Committee takes action if a conflict of interest was not identified, declared or managed appropriately.
GDG composition	<i>Principle 1: Guideline developers should make all possible efforts to not include members with direct financial or relevant indirect COIs.</i>	17. Members of the CSACI Oral Immunotherapy CPG Working Group, the CPG Development Executive Team, the Scientific support team, the Deliberative Committee, and all individuals consulted must submit a disclosure of interests form. 18. More than one third of persons participating at the OIT Guideline Development should not have COIs (financial or non-financial; specific or non-specific to the object of the work; personal, professional or institutional - including, but not limited to: patents; stocks; equity positions; gifts; consulting agreements, employment arrangements, research grants/ contracts, and travel reimbursement and honorariums sponsored by industry; representation of an association whose purpose, mission or interests that are related to the objects of evaluation; advocacy). The inclusion of conflicted persons should be explicitly justified (e.g. irreplaceable expertise, geographical representation).
	<i>Principle 8: No member of the guideline development group deciding about the direction or strength of a recommendation should have a direct financial COI.</i>	19. When a member of the deliberative Committee has a financial COI directly related to a specific recommendation, he/she will be excluded from the discussion (physically absent) on this particular recommendation. Financial COIs include, but are not limited to, patents, stocks, equity positions, gifts, consulting agreements, employment arrangements, research grants/ contracts, and travel reimbursement and honorariums sponsored by industry as well as interests that relate to the development, manufacture or marketing of products that may be considered by the committee. 20. Individuals who are likely to be excluded from more than half of the Deliberative Committee's

		discussions because of financial COIs should not be appointed as members of the Deliberative committee. 21. More than half of the Deliberative Committee members who deliberate on a specific recommendation should not have any COIs related to this recommendation (financial or non-financial; specific or non-specific to the objects of the work; personal, professional or institutional - including, but not limited to: patents; stocks; equity positions; gifts; consulting agreements, employment arrangements, research grants/ contracts, and travel reimbursement and honorariums sponsored by industry; representation of an association whose purpose, mission or interests are related to the objects of evaluation ; public comments, testimony, and previously published opinions including policy positions; leadership role on a panel; substantial career efforts/ interests relating to the services, interventions, products, or delivery of care to be considered within the scope of the guideline; advocacy). The inclusion of conflicted participants should be justified (e.g. irreplaceable expertise).
	<i>Principle 6: Chairs of guideline development groups should have no direct financial or relevant indirect COIs.</i> <i>When direct or indirect COIs of a chair are unavoidable, a co-chair with no COIs who leads the guideline panel should be appointed.</i>	22. The Chair and the co-chair of the Deliberative Committee should have no COIs: - o no direct financial interests including, but not limited to: patents; stocks; equity positions; gifts; consulting agreements, employment arrangements, research grants/ contracts, and travel reimbursement and honorariums sponsored by industry; interests that relates to the development, manufacture or marketing of products that may be consider by the committee. - o no other relevant interests including, but not limited to: representation of an association whose purpose, mission or interests are related to the objects of evaluation; public comments, testimony, and previously published opinions including policy positions; leadership role on a panel; substantial career efforts/ interests relating to the services, interventions, products, or delivery of care to be considered within the scope of the guideline; advocacy.
	<i>Principle 7: Experts with relevant COIs and specific knowledge or expertise may be permitted to participate in discussion of individual topics, but there should be an appropriate balance of opinion among those sought to provide</i>	23. All individuals consulted (experts/advisers/patients) must declare their interests. 24. Individuals with relevant COIs and specific knowledge or expertise may be consulted and participate in the discussion of the Deliberative Committee. 25. If consulted individuals with COIs are invited to a meeting of the Deliberative Committee, they should declare their interests at each meeting they attend before giving their testimony. 26. The consultation process seeks to capture a diversity of opinions.

	<i>input.</i>	
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Appendix 2: Literature review details

Appendix 2A: Bibliographical database search strategy and terms

First search: Outcomes of oral immunotherapy

PubMed 17 April 2019

#1	Food Hypersensitivity[MH]
#2	Hypersensitivity[MH] OR allerg*[TIAB] OR hypersensitiv*[TIAB] OR hyper-sensitiv*[TIAB] OR hyperresponsiv*[TIAB] OR hyper-responsiv*[TIAB] OR allerg*[OT] OR hypersensitiv*[OT] OR hyper-sensitiv*[OT] OR hyperresponsiv*[OT] OR hyper-responsiv*[OT]
#3	Food[Mesh] OR additive[TIAB] OR additives[TIAB] OR almond*[TIAB] OR apple[TIAB] OR apples[TIAB] OR apricot*[TIAB] OR arachis hypogaea[TIAB] OR avocado*[TIAB] OR banana*[TIAB] OR barley[TIAB] OR beef[TIAB] OR berries[TIAB] OR berry[TIAB] OR blackberr*[TIAB] OR blueberr*[TIAB] OR buckwheat*[TIAB] OR cacao[TIAB] OR calamari[TIAB] OR carrot*[TIAB] OR cashew*[TIAB] OR celery[TIAB] OR cherries[TIAB] OR cherry[TIAB] OR chestnut*[TIAB] OR chicory[TIAB] OR chocolat*[TIAB] OR cilandro[TIAB] OR clam[TIAB] OR clams[TIAB] OR cockle*[TIAB] OR coconut[TIAB] OR coconuts[TIAB] OR conch[TIAB] OR conchs[TIAB] OR coriander[TIAB] OR corn[TIAB] OR crab[TIAB] OR crabs[TIAB] OR cranberr*[TIAB] OR crawfish*[TIAB] OR crayfish*[TIAB] OR crustacea*[TIAB] OR cucumber*[TIAB] OR dairy[TIAB] OR dairies[TIAB] OR edamame*[TIAB] OR egg[TIAB] OR eggplant*[TIAB] OR eggs[TIAB] OR fig[TIAB] OR figs[TIAB] OR fish[TIAB] OR fishes[TIAB] OR flaxseed*[TIAB] OR food[TIAB] OR foods[TIAB] OR fruit[TIAB] OR fruits[TIAB] OR grape[TIAB] OR grapes[TIAB] OR hazelnut*[TIAB] OR kiwi[TIAB] OR kiwis[TIAB] OR lactose[TIAB] OR legume*[TIAB] OR lobster[TIAB] OR lobsters[TIAB] OR mango*[TIAB] OR meat[TIAB] OR melon[TIAB] OR melons[TIAB] OR milk[TIAB] OR mollusc*[TIAB] OR multifoood[TIAB] OR mushroom*[TIAB] OR mussel[TIAB] OR mussels[TIAB] OR mustard[TIAB] OR nut[TIAB] OR nuts[TIAB] OR oat[TIAB] OR oats[TIAB] OR octopus[TIAB] OR "oral allergy syndrome"[TIAB] OR orange*[TIAB] OR oyster[TIAB] OR oysters[TIAB] OR parsley[TIAB] OR pea[TIAB] OR peach*[TIAB] OR peanut*[TIAB] OR pear[TIAB] OR pears[TIAB] OR peas[TIAB] OR pecan*[TIAB] OR periwinkle*[TIAB] OR pineapple*[TIAB] OR pistachio*[TIAB] OR plum[TIAB] OR plums[TIAB] OR pork[TIAB] OR potato*[TIAB] OR prawn[TIAB] OR prawns[TIAB] OR raspberr*[TIAB] OR rice[TIAB] OR rye[TIAB] OR salmon[TIAB] OR scallop[TIAB] OR scallops[TIAB] OR seafood*[TIAB] OR sesame[TIAB] OR shellfish*[TIAB] OR shrimp[TIAB] OR shrimps[TIAB] OR snail[TIAB] OR snails[TIAB] OR soja[TIAB] OR soybean*[TIAB] OR soy[TIAB] OR soybean*[TIAB] OR soybean*[TIAB] OR squid[TIAB] OR squid[TIAB] OR strawberr*[TIAB] OR sunflower seed*[TIAB] OR tomato*[TIAB] OR vegetable*[TIAB] OR walnut*[TIAB] OR wheat[TIAB] OR wheats[TIAB] OR whelk[TIAB] OR whelks[TIAB] OR zucchini*[TIAB] OR additive[OT] OR additives[OT] OR almond*[OT] OR apple[OT] OR apples[OT] OR apricot*[OT] OR arachis hypogaea[OT] OR avocado*[OT] OR banana*[OT] OR barley[OT] OR beef[OT] OR berries[OT] OR berry[OT] OR blackberr*[OT] OR blueberr*[OT] OR buckwheat*[OT] OR cacao[OT] OR calamari[OT] OR carrot*[OT] OR cashew*[OT] OR celery[OT] OR cherries[OT] OR cherry[OT] OR chestnut*[OT] OR chicory[OT] OR chocolat*[OT] OR cilandro[OT] OR clam[OT] OR clams[OT] OR cockle*[OT] OR coconut[OT] OR coconuts[OT] OR conch[OT] OR conchs[OT] OR coriander[OT] OR corn[OT] OR crab[OT] OR crabs[OT] OR cranberr*[OT] OR crawfish*[OT] OR crayfish*[OT] OR crustacea*[OT] OR cucumber*[OT] OR dairy[OT] OR dairies[OT] OR edamame*[OT] OR egg[OT] OR eggplant*[OT] OR eggs[OT] OR fig[OT] OR figs[OT] OR fish[OT] OR fishes[OT] OR flaxseed*[OT] OR food[OT] OR foods[OT] OR fruit[OT] OR fruits[OT] OR grape[OT] OR grapes[OT] OR hazelnut*[OT] OR kiwi[OT] OR kiwis[OT] OR lactose[OT] OR legume*[OT] OR lobster[OT] OR lobsters[OT] OR mango*[OT] OR meat[OT] OR melon[OT] OR melons[OT] OR milk[OT] OR mollusc*[OT] OR multifoood[OT] OR mushroom*[OT] OR mussel[OT] OR mussels[OT] OR mustard[OT] OR nut[OT] OR nuts[OT] OR oat[OT] OR oats[OT] OR octopus[OT] OR "oral allergy syndrome"[OT] OR orange*[OT] OR oyster[OT] OR oysters[OT] OR parsley[OT] OR pea[OT] OR peach*[OT] OR peanut*[OT] OR pear[OT] OR pears[OT] OR peas[OT] OR pecan*[OT] OR periwinkle*[OT] OR pineapple*[OT] OR pistachio*[OT] OR plum[OT] OR plums[OT] OR pork[OT] OR potato*[OT] OR prawn[OT] OR prawns[OT] OR raspberr*[OT] OR rice[OT] OR rye[OT] OR salmon[OT] OR scallop[OT] OR scallops[OT] OR seafood*[OT] OR sesame[OT] OR shellfish*[OT] OR shrimp[OT] OR shrimps[OT] OR snail[OT] OR snails[OT] OR soja[OT] OR soybean*[OT] OR soy[OT] OR soya[OT] OR soybean*[OT] OR soybean*[OT] OR squid[OT] OR strawberr*[OT] OR sunflower seed*[OT] OR tomato*[OT] OR vegetable*[OT] OR walnut*[OT] OR wheat[OT] OR wheats[OT] OR whelk[OT] OR whelks[OT] OR zucchini*[OT]
#4	Desensitization, Immunologic[MH] OR desensitisation*[TIAB] OR desensitization*[TIAB] OR hypo-sensitisation*[TIAB] OR hyposensitisation*[TIAB] OR hypo-sensitization*[TIAB] OR hyposensitization*[TIAB] OR immunotherap*[TIAB] OR "oral induction"[TIAB] OR oral tolerance[TIAB] OR OIT[TIAB] OR up dosing[TIAB] OR desensitisation*[OT] OR desensitization*[OT] OR hypo-sensitisation*[OT] OR hyposensitisation*[OT] OR hypo-sensitization*[OT] OR hyposensitization*[OT] OR immunotherap*[OT] OR "oral induction"[OT] OR oral tolerance[OT] OR OIT[OT] OR up dosing[OT]
#5	English[lang] OR French[lang] OR Italian[lang] OR Spanish[lang] OR German[lang]
#6	(#1 OR (#2 AND #3)) AND #4 AND #5

#7	#6 AND ("1998/01/01"[PDAT] : "3000/12/31"[PDAT]) 2417 results
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Medline (OVID) 17 April 2019

1	Exp Food Hypersensitivity/
2	Exp Hypersensitivity/ OR (allerg* OR hypersensitiv* OR hyper-sensitiv* OR hyperresponsiv* OR hyper-responsiv*).ti,ab,kw,kf
3	Exp Food/ OR (additive OR additives OR almond* OR apple OR apples OR apricot* OR arachis hypogaea OR avocado* OR banana* OR barley OR beef OR berries OR berry OR blackberr* OR blueberr* OR buckwheat* OR cacao OR calamari OR carrot* OR cashew* OR celery OR cherries OR cherry OR chestnut* OR chicory OR chocolat* OR cilandro OR clam OR clams OR cockle* OR coconut OR coconuts OR conch OR conchs OR coriander OR corn OR crab OR crabs OR cranberr* OR crawfish* OR crayfish* OR crustacea* OR cucumber* OR dairy OR dairies OR edamame* OR egg OR eggplant* OR eggs OR fig OR figs OR fish OR fishes OR flaxseed* OR food OR foods OR fruit OR fruits OR grape OR grapes OR hazelnut* OR kiwi OR kiwis OR lactose OR legume* OR lobster OR lobsters OR mango* OR meat OR melon OR melons OR milk OR mollusc* OR multifoood OR mushroom* OR mussel OR mussels OR mustard OR nut OR nuts OR oat OR oats OR octopus OR "oral allergy syndrome" OR orange* OR oyster OR oysters OR parsley OR pea OR peach* OR peanut* OR pear OR pears OR peas OR pecan* OR periwinkle* OR pineapple* OR pistachio* OR plum OR plums OR pork OR potato* OR prawn OR prawns OR raspberr* OR rice OR rye OR salmon OR scallop OR scallops OR seafood* OR sesame OR shellfish* OR shrimp OR shrimps OR snail OR snails OR soja OR sojabean* OR soy OR soya OR soyabean* OR soybean* OR squid OR strawberr* OR sunflower seed* OR tomato* OR vegetable* OR walnut* OR wheat OR wheats OR whelk OR whelks OR zucchini*).ti,ab,kw,kf
4	Exp Desensitization, Immunologic/ OR (desensitisation* OR desensitization* OR hypo-sensitisation* OR hyposensitisation* OR hypo-sensitization* OR hyposensitization* OR immunotherap* OR "oral induction" OR oral tolerance OR OIT OR up dosing).ti,ab,kw,kf
5	(English OR French OR Italian OR Spanish OR German).la
6	(1 OR (2 AND 3)) AND 4 AND 5
7	Limit 6 to yr="1998 -Current" 2469 results

All EBM Reviews 17 April 2019

1	Exp Food Hypersensitivity/
2	Exp Hypersensitivity/ OR (allerg* OR hypersensitiv* OR hyper-sensitiv* OR hyperresponsiv* OR hyper-responsiv*).ti,ab,kw,kf
3	Exp Food/ OR (additive OR additives OR almond* OR apple OR apples OR apricot* OR arachis hypogaea OR avocado* OR banana* OR barley OR beef OR berries OR berry OR blackberr* OR blueberr* OR buckwheat* OR cacao OR calamari OR carrot* OR cashew* OR celery OR cherries OR cherry OR chestnut* OR chicory OR chocolat* OR cilandro OR clam OR clams OR cockle* OR coconut OR coconuts OR conch OR conchs OR coriander OR corn OR crab OR crabs OR cranberr* OR crawfish* OR crayfish* OR crustacea* OR cucumber* OR dairy OR dairies OR edamame* OR egg OR eggplant* OR eggs OR fig OR figs OR fish OR fishes OR flaxseed* OR food OR foods OR fruit OR fruits OR grape OR grapes OR hazelnut* OR kiwi OR kiwis OR lactose OR legume* OR lobster OR lobsters OR mango* OR meat OR melon OR melons OR milk OR mollusc* OR multifoood OR mushroom* OR mussel OR mussels OR mustard OR nut OR nuts OR oat OR oats OR octopus OR "oral allergy syndrome" OR orange* OR oyster OR oysters OR parsley OR pea OR peach* OR peanut* OR pear OR pears OR peas OR pecan* OR periwinkle* OR pineapple* OR pistachio* OR plum OR plums OR pork OR potato* OR prawn OR prawns OR raspberr* OR rice OR rye OR salmon OR scallop OR scallops OR seafood* OR sesame OR shellfish* OR shrimp OR shrimps OR snail OR snails OR soja OR sojabean* OR soy OR soya OR soyabean* OR soybean* OR squid OR strawberr* OR sunflower seed* OR tomato* OR vegetable* OR walnut* OR wheat OR wheats OR whelk OR whelks OR zucchini*).ti,ab,kw,kf
4	Exp Desensitization, Immunologic/ OR (desensitisation* OR desensitization* OR hypo-sensitisation* OR hyposensitisation* OR hypo-sensitization* OR hyposensitization* OR immunotherap* OR "oral induction" OR oral tolerance OR OIT OR up dosing).ti,ab,kw,kf
5	(English OR French OR Italian OR Spanish OR German).la
6	(1 OR (2 AND 3)) AND 4 AND 5
7	Limit 6 to yr="1998 -Current" 432 results

Embase 18 April 2019

1	Exp food allergy OR food allergen/
2	Exp Hypersensitivity/ OR (allerg* OR hypersensitiv* OR hyper-sensitiv* OR hyperresponsiv* OR hyper-responsiv*).ti,ab,kw
3	Exp food/ OR (additive OR additives OR almond* OR apple OR apples OR apricot* OR arachis hypogaea OR avocado* OR banana* OR barley OR beef OR berries OR berry OR blackberr* OR blueberr* OR buckwheat* OR cacao OR calamari OR carrot* OR cashew* OR celery OR cherries OR cherry OR chestnut* OR chicory OR chocolat* OR cilandro OR clam OR clams OR cockle* OR coconut OR coconuts OR conch OR conchs OR coriander OR corn OR crab OR crabs OR cranberr* OR crawfish* OR crayfish* OR crustacea* OR cucumber* OR dairy OR dairies OR edamame* OR egg OR eggplant* OR eggs OR fig OR figs OR fish OR fishes OR flaxseed* OR food OR foods OR fruit OR fruits OR grape OR grapes OR hazelnut* OR kiwi OR kiwis OR lactose OR legume* OR lobster OR lobsters OR mango* OR meat OR melon OR melons OR milk OR mollusc* OR multifoood OR mushroom* OR mussel OR mussels OR mustard OR nut OR nuts OR oat OR oats OR octopus OR "oral allergy syndrome" OR orange* OR oyster OR oysters OR parsley OR pea OR peach* OR peanut* OR pear OR pears OR peas OR pecan* OR periwinkle* OR pineapple* OR pistachio* OR plum OR plums OR pork OR potato* OR prawn OR prawns OR raspberr* OR rice OR rye OR salmon OR scallop OR scallops OR seafood* OR sesame OR shellfish* OR shrimp OR shrimps OR snail OR snails OR soja OR sojabean* OR soy OR soya OR soyabean* OR soybean* OR squid OR strawberr* OR sunflower seed* OR tomato* OR vegetable* OR walnut* OR wheat OR wheats OR whelk OR whelks OR zucchini*).ti,ab,kw
4	Exp desensitization/ OR (desensitisation* OR desensitization* OR hypo-sensitisation* OR hyposensitisation* OR hypo-sensitization* OR hyposensitization* OR immunotherap* OR "oral induction" OR oral tolerance OR OIT OR up dosing).ti,ab,kw
5	(English OR French OR Italian OR Spanish OR German).la
6	(1 OR (2 AND 3)) AND 4 AND 5
7	Limit 6 to yr="1998 -Current"
8	conference abstract.pt.
9	7 not 8 3260 results

CINAHL 18 April 2019

S1	MH(Food Hypersensitivity+)
S2	MH(Hypersensitivity+) OR TI(allerg* OR hypersensitiv* OR hyper-sensitiv* OR hyperresponsiv* OR hyper-responsiv*) OR AB(allerg* OR hypersensitiv* OR hyper-sensitiv* OR hyperresponsiv* OR hyper-responsiv*)
S3	MH(food+) OR TI(additive OR additives OR almond* OR apple OR apples OR apricot* OR arachis hypogaea OR avocado* OR banana* OR barley OR beef OR berries OR berry OR blackberr* OR blueberr* OR buckwheat* OR cacao OR calamari OR carrot* OR cashew* OR celery OR cherries OR cherry OR chestnut* OR chicory OR chocolat* OR cilandro OR clam OR clams OR cockle* OR coconut OR coconuts OR conch OR conchs OR coriander OR corn OR crab OR crabs OR cranberr* OR crawfish* OR crayfish* OR crustacea* OR cucumber* OR dairy OR dairies OR edamame* OR egg OR eggplant* OR eggs OR fig OR figs OR fish OR fishes OR flaxseed* OR food OR foods OR fruit OR fruits OR grape OR grapes OR hazelnut* OR kiwi OR kiwis OR lactose OR legume* OR lobster OR lobsters OR mango* OR meat OR melon OR melons OR milk OR mollusc* OR multifoood OR mushroom* OR mussel OR mussels OR mustard OR nut OR nuts OR oat OR oats OR octopus OR "oral allergy syndrome" OR orange* OR oyster OR oysters OR parsley OR pea OR peach* OR peanut* OR pear OR pears OR peas OR pecan* OR periwinkle* OR pineapple* OR pistachio* OR plum OR plums OR pork OR potato* OR prawn OR prawns OR raspberr* OR rice OR rye OR salmon OR scallop OR scallops OR seafood* OR sesame OR shellfish* OR shrimp OR shrimps OR snail OR snails OR soja OR sojabean* OR soy OR soya OR soyabean* OR soybean* OR squid OR strawberr* OR sunflower seed* OR tomato* OR vegetable* OR walnut* OR wheat OR wheats OR whelk OR whelks OR zucchini*) OR AB(additive OR additives OR almond* OR apple OR apples OR apricot* OR arachis hypogaea OR avocado* OR banana* OR barley OR beef OR berries OR berry OR blackberr* OR blueberr* OR buckwheat* OR cacao OR calamari OR carrot* OR cashew* OR celery OR cherries OR cherry OR chestnut* OR chicory OR chocolat* OR cilandro OR clam OR clams OR cockle* OR coconut OR coconuts OR conch OR conchs OR coriander OR corn OR crab OR crabs OR cranberr* OR crawfish* OR crayfish* OR crustacea* OR cucumber* OR dairy OR dairies OR edamame* OR egg OR eggplant* OR eggs OR fig OR figs OR fish OR fishes OR flaxseed* OR food OR foods OR fruit OR fruits OR grape OR grapes OR hazelnut* OR kiwi OR kiwis OR lactose OR legume* OR lobster OR lobsters OR mango* OR meat OR melon OR melons OR milk OR mollusc* OR multifoood OR mushroom* OR mussel OR mussels OR mustard OR nut OR nuts OR oat OR

S4	oats OR octopus OR "oral allergy syndrome" OR orange* OR oyster OR oysters OR parsley OR pea OR peach* OR peanut* OR pear OR pears OR peas OR pecan* OR periwinkle* OR pineapple* OR pistachio* OR plum OR plums OR pork OR potato* OR prawn OR prawns OR raspberr* OR rice OR rye OR salmon OR scallop OR scallops OR seafood* OR sesame OR shellfish* OR shrimp OR shrimps OR snail OR snails OR soja OR sojabean* OR soy OR soya OR soyabean* OR soybean* OR squid OR strawberr* OR sunflower seed* OR tomato* OR vegetable* OR walnut* OR wheat OR wheats OR whelk OR whelks OR zucchini*) MH(Desensitization, Immunologic) OR TI(desensitisation* OR desensitization* OR hypo-sensitisation* OR hyposensitisation* OR hypo-sensitization* OR hyposensitization* OR immunotherap* OR "oral induction" OR oral tolerance OR OIT OR up dosing) OR AB(desensitisation* OR desensitization* OR hypo-sensitisation* OR hyposensitisation* OR hypo-sensitization* OR hyposensitization* OR immunotherap* OR "oral induction" OR oral tolerance OR OIT OR up dosing)
S5	LA(English OR French OR Italian OR Spanish OR German)
S6	(S1 OR (S2 AND S3)) AND S4 AND S5 limiters publication date 19980101-20191231 437 results

Web of Science 18 April 2019

#1	TS=(allerg* OR hypersensitiv* OR hyper-sensitiv* OR hyperresponsiv* OR hyper-responsiv*)
#2	TS=(additive OR additives OR almond* OR apple OR apples OR apricot* OR arachis hypogaea OR avocado* OR banana* OR barley OR beef OR berries OR berry OR blackberr* OR blueberr* OR buckwheat* OR cacao OR calamari OR carrot* OR cashew* OR celery OR cherries OR cherry OR chestnut* OR chicory OR chocolat* OR cilandro OR clam OR clams OR cockle* OR coconut OR coconuts OR conch OR conchs OR coriander OR corn OR crab OR crabs OR cranberr* OR crawfish* OR crayfish* OR crustacea* OR cucumber* OR dairy OR dairies OR edamame* OR egg OR eggplant* OR eggs OR fig OR figs OR fish OR fishes OR flaxseed* OR food OR foods OR fruit OR fruits OR grape OR grapes OR hazelnut* OR kiwi OR kiwis OR lactose OR legume* OR lobster OR lobsters OR mango* OR meat OR melon OR melons OR milk OR mollusc* OR multifoood OR mushroom* OR mussel OR mussels OR mustard OR nut OR nuts OR oat OR oats OR octopus OR "oral allergy syndrome" OR orange* OR oyster OR oysters OR parsley OR pea OR peach* OR peanut* OR pear OR pears OR peas OR pecan* OR periwinkle* OR pineapple* OR pistachio* OR plum OR plums OR pork OR potato* OR prawn OR prawns OR raspberr* OR rice OR rye OR salmon OR scallop OR scallops OR seafood* OR sesame OR shellfish* OR shrimp OR shrimps OR snail OR snails OR soja OR sojabean* OR soy OR soya OR soyabean* OR soybean* OR squid OR strawberr* OR sunflower seed* OR tomato* OR vegetable* OR walnut* OR wheat OR wheats OR whelk OR whelks OR zucchini*)
#3	TS=(desensitisation* OR desensitization* OR hypo-sensitisation* OR hyposensitisation* OR hypo-sensitization* OR hyposensitization* OR immunotherap* OR "oral induction" OR oral tolerance OR OIT OR up dosing)
#4	(#1 AND #2 AND #3) AND LANGUAGE: (English OR French OR German OR Italian OR Spanish) Timespan=1998-2019 4121 results

After the removal of duplicates, there were a total of 5556 records retrieved on April 18th 2019.

Second search: Epidemiology, burden of illness, impact on quality of life

PubMed 30 Mai 2019

#1	Food Hypersensitivity[MH]
#2	Hypersensitivity[MH] OR allerg*[TIAB] OR hypersensitiv*[TIAB] OR hyper-sensitiv*[TIAB] OR hyperresponsiv*[TIAB] OR hyper-responsiv*[TIAB] OR allerg*[OT] OR hypersensitiv*[OT] OR hyper-sensitiv*[OT] OR hyperresponsiv*[OT] OR hyper-responsiv*[OT]
#3	Food[Mesh] OR additive[TIAB] OR additives[TIAB] OR almond*[TIAB] OR apple[TIAB] OR apples[TIAB] OR apricot*[TIAB] OR arachis hypogaea[TIAB] OR avocado*[TIAB] OR banana*[TIAB] OR barley[TIAB] OR beef[TIAB] OR berries[TIAB] OR berry[TIAB] OR blackberr*[TIAB] OR blueberr*[TIAB] OR buckwheat*[TIAB] OR cacao[TIAB] OR calamari[TIAB] OR carrot*[TIAB] OR cashew*[TIAB] OR celery[TIAB] OR cherries[TIAB] OR cherry[TIAB] OR chestnut*[TIAB] OR chicory[TIAB] OR chocolat*[TIAB] OR cilandro[TIAB] OR clam[TIAB] OR clams[TIAB] OR cockle*[TIAB] OR coconut[TIAB] OR coconuts[TIAB] OR conch[TIAB] OR conchs[TIAB] OR coriander[TIAB] OR corn[TIAB] OR crab[TIAB] OR crabs[TIAB] OR cranberr*[TIAB] OR crawfish*[TIAB] OR crayfish*[TIAB] OR crustacea*[TIAB] OR cucumber*[TIAB] OR dairy[TIAB] OR dairies[TIAB] OR edamame*[TIAB] OR egg[TIAB] OR eggplant*[TIAB] OR eggs[TIAB] OR fig[TIAB] OR figs[TIAB] OR fish[TIAB] OR fishes[TIAB] OR flaxseed*[TIAB] OR food[TIAB] OR foods[TIAB] OR fruit[TIAB] OR fruits[TIAB] OR grape[TIAB] OR grapes[TIAB] OR hazelnut*[TIAB] OR kiwi[TIAB] OR kiwis[TIAB] OR lactose[TIAB] OR legume*[TIAB] OR lobster[TIAB] OR lobsters[TIAB] OR mango*[TIAB] OR meat[TIAB] OR melon[TIAB] OR melons[TIAB] OR milk[TIAB] OR

	mollusc*[TIAB] OR multifoood[TIAB] OR mushroom*[TIAB] OR mussel[TIAB] OR mussels[TIAB] OR mustard[TIAB] OR nut[TIAB] OR nuts[TIAB] OR oat[TIAB] OR oats[TIAB] OR octopus[TIAB] OR "oral allergy syndrome"[TIAB] OR orange*[TIAB] OR oyster[TIAB] OR oysters[TIAB] OR parsley[TIAB] OR pea[TIAB] OR peach*[TIAB] OR peanut*[TIAB] OR pear[TIAB] OR pears[TIAB] OR peas[TIAB] OR pecan*[TIAB] OR periwinkle*[TIAB] OR pineapple*[TIAB] OR pistachio*[TIAB] OR plum[TIAB] OR plums[TIAB] OR pork[TIAB] OR potato*[TIAB] OR prawn[TIAB] OR prawns[TIAB] OR raspberr*[TIAB] OR rice[TIAB] OR rye[TIAB] OR salmon[TIAB] OR scallop[TIAB] OR scallops[TIAB] OR seafood*[TIAB] OR sesame[TIAB] OR shellfish*[TIAB] OR shrimp[TIAB] OR shrimps[TIAB] OR snail[TIAB] OR snails[TIAB] OR soja[TIAB] OR soybean*[TIAB] OR soy[TIAB] OR soya[TIAB] OR soyabean*[TIAB] OR soybean*[TIAB] OR squid[TIAB] OR strawberr*[TIAB] OR sunflower seed*[TIAB] OR tomato*[TIAB] OR vegetable*[TIAB] OR walnut*[TIAB] OR wheat[TIAB] OR wheats[TIAB] OR whelk[TIAB] OR whelks[TIAB] OR zucchini*[TIAB] OR additive[OT] OR additives[OT] OR almond*[OT] OR apple[OT] OR apples[OT] OR apricot*[OT] OR arachis hypogaea[OT] OR avocado*[OT] OR banana*[OT] OR barley[OT] OR beef[OT] OR berries[OT] OR berry[OT] OR blackberr*[OT] OR blueberr*[OT] OR buckwheat*[OT] OR cacao[OT] OR calamari[OT] OR carrot*[OT] OR cashew*[OT] OR celery[OT] OR cherries[OT] OR cherry[OT] OR chestnut*[OT] OR chicory[OT] OR chocolat*[OT] OR cilandro[OT] OR clam[OT] OR clams[OT] OR cockle*[OT] OR coconut[OT] OR coconuts[OT] OR conch[OT] OR conchs[OT] OR coriander[OT] OR corn[OT] OR crab[OT] OR crabs[OT] OR cranberr*[OT] OR crawfish*[OT] OR crayfish*[OT] OR crustacea*[OT] OR cucumber*[OT] OR dairy[OT] OR dairies[OT] OR edamame*[OT] OR egg[OT] OR eggplant*[OT] OR eggs[OT] OR fig[OT] OR figs[OT] OR fish[OT] OR fishes[OT] OR flaxseed*[OT] OR food[OT] OR foods[OT] OR fruit[OT] OR fruits[OT] OR grape[OT] OR grapes[OT] OR hazelnut*[OT] OR kiwi[OT] OR kiwis[OT] OR lactose[OT] OR legume*[OT] OR lobster[OT] OR lobsters[OT] OR mango*[OT] OR meat[OT] OR melon[OT] OR melons[OT] OR milk[OT] OR mollusc*[OT] OR multifoood[OT] OR mushroom*[OT] OR mussel[OT] OR mussels[OT] OR mustard[OT] OR nut[OT] OR nuts[OT] OR oat[OT] OR oats[OT] OR octopus[OT] OR "oral allergy syndrome"[OT] OR orange*[OT] OR oyster[OT] OR oysters[OT] OR parsley[OT] OR pea[OT] OR peach*[OT] OR peanut*[OT] OR pear[OT] OR pears[OT] OR peas[OT] OR pecan*[OT] OR periwinkle*[OT] OR pineapple*[OT] OR pistachio*[OT] OR plum[OT] OR plums[OT] OR pork[OT] OR potato*[OT] OR prawn[OT] OR prawns[OT] OR raspberr*[OT] OR rice[OT] OR rye[OT] OR salmon[OT] OR scallop[OT] OR scallops[OT] OR seafood*[OT] OR sesame[OT] OR shellfish*[OT] OR shrimp[OT] OR shrimps[OT] OR snail[OT] OR snails[OT] OR soja[OT] OR soybean*[OT] OR soy[OT] OR soya[OT] OR soyabean*[OT] OR soybean*[OT] OR squid[OT] OR strawberr*[OT] OR sunflower seed*[OT] OR tomato*[OT] OR vegetable*[OT] OR walnut*[OT] OR wheat[OT] OR wheats[OT] OR whelk[OT] OR whelks[OT] OR zucchini*[OT]
#4	Psychology[Mh:noexp] OR Psychology[sh] OR Stress, Psychological[Mh] OR Adaptation, Psychological[Mh:noexp] OR Quality of Life[Mh] OR Family Health[Mh] OR Social*[TIAB] OR Psychosocial*[TIAB] OR Psycholog*[TIAB] OR Quality of Life[TIAB] OR Life quality[TIAB] OR QoL[TIAB] OR HRQoL[TIAB] OR burden*[TIAB] OR Social*[OT] OR Psychosocial*[OT] OR Psycholog*[OT] OR Quality of Life[OT] OR Life quality[OT] OR QoL[OT] OR HRQoL[OT] OR burden*[OT]
#5	Epidemiology[mh] OR Epidemiology[sh:noexp] OR Incidence[Mh] OR Prevalence[Mh] OR "Costs and Cost Analysis"[Mh] OR economics[sh] OR Epidemiolog*[TIAB] OR prevalence*[TIAB] OR Frequenc*[TIAB] OR occurrence*[TIAB] OR incidence*[TIAB] OR cost*[tiab] OR expens*[tiab] OR expenditure*[tiab] OR economic*[tiab] OR financ*[tiab] OR budget*[tiab] OR spending*[tiab] OR Epidemiolog*[OT] OR prevalence*[OT] OR Frequenc*[OT] OR occurrence*[OT] OR incidence*[OT] OR cost*[OT] OR expens*[OT] OR expenditure*[OT] OR economic*[OT] OR financ*[OT] OR budget*[OT] OR spending*[OT]
#6	Canada[Mesh] OR Canad*[TIAB] OR Alberta*[TIAB] OR Calgary[TIAB] OR Edmonton[TIAB] OR British Columbi*[TIAB] OR Vancouver[TIAB] OR Manitoba*[TIAB] OR New Brunswick[TIAB] OR Newfoundland[TIAB] OR Labrador[TIAB] OR Northwest Territor*[TIAB] OR Nova Scotia*[TIAB] OR Nunavut[TIAB] OR Ontari*[TIAB] OR Toronto[TIAB] OR Ottawa[TIAB] OR Prince Edward Island[TIAB] OR Quebec*[TIAB] OR Montreal[TIAB] OR Saskatchewan[TIAB] OR Yukon[TIAB] OR Canad*[OT] OR Alberta*[OT] OR Calgary[OT] OR Edmonton[OT] OR British Columbi*[OT] OR Vancouver[OT] OR Manitoba*[OT] OR New Brunswick[OT] OR Newfoundland[OT] OR Labrador[OT] OR Northwest Territor*[OT] OR Nova Scotia*[OT] OR Nunavut[OT] OR Ontari*[OT] OR Toronto[OT] OR Ottawa[OT] OR Prince Edward Island[OT] OR Quebec*[OT] OR Montreal[OT] OR Saskatchewan[OT] OR Yukon[OT]
#7	Systematic review[Pt] OR Systematic Reviews as Topic[Mh] OR Meta-Analysis[Pt] OR Meta-Analysis as Topic[mh] OR ((systematic*[tiab] OR Umbrella[tiab]) AND (review*[tiab] OR overview*[tiab] OR synthes*[tiab])) OR meta-analys*[tiab] OR metaanalys*[tiab] OR ((systematic*[OT] OR umbrella[OT]) AND (review*[OT] OR overview*[OT] OR synthes*[OT])) OR meta-analys*[OT] OR metaanalys*[OT]
#8	English[lang] OR French[lang] OR Italian[lang] OR Spanish[lang] OR German[lang]
#9	(#1 OR (#2 AND #3)) AND (#4 OR (#5 AND (#6 OR #7))) AND #8
#10	#9 AND ("2014/01/01"[PDAT] : "2019/05/30"[PDAT]) 1233 results

Medline (OVID) 30 Mai 2019

1	Exp Food Hypersensitivity/
2	Exp Hypersensitivity/ OR (allerg* OR hypersensitiv* OR hyper-sensitiv* OR hyperresponsiv* OR hyper-responsiv*).ti,ab,kw,kf
3	Exp Food/ OR (additive OR additives OR almond* OR apple OR apples OR apricot* OR arachis hypogaea OR avocado* OR banana* OR barley OR beef OR berries OR berry OR blackberr* OR blueberr* OR buckwheat* OR cacao OR calamari OR carrot* OR cashew* OR celery OR cherries OR cherry OR chestnut* OR chicory OR chocolat* OR cilandro OR clam OR clams OR cockle* OR coconut OR coconuts OR conch OR conchs OR coriander OR corn OR crab OR crabs OR cranberr* OR crawfish* OR crayfish* OR crustacea* OR cucumber* OR dairy OR dairies OR edamame* OR egg OR eggplant* OR eggs OR fig OR figs OR fish OR fishes OR flaxseed* OR food OR foods OR fruit OR fruits OR grape OR grapes OR hazelnut* OR kiwi OR kiwis OR lactose OR legume* OR lobster OR lobsters OR mango* OR meat OR melon OR melons OR milk OR mollusc* OR multifoood OR mushroom* OR mussel OR mussels OR mustard OR nut OR nuts OR oat OR oats OR octopus OR "oral allergy syndrome" OR orange* OR oyster OR oysters OR parsley OR pea OR peach* OR peanut* OR pear OR pears OR peas OR pecan* OR periwinkle* OR pineapple* OR pistachio* OR plum OR plums OR pork OR potato* OR prawn OR prawns OR raspberr* OR rice OR rye OR salmon OR scallop OR scallops OR seafood* OR sesame OR shellfish* OR shrimp OR shrimps OR snail OR snails OR soja OR soyabean* OR soy OR soya OR soyabean* OR soybean* OR squid OR strawberr* OR sunflower seed* OR tomato* OR vegetable* OR walnut* OR wheat OR wheats OR whelk OR whelks OR zucchini*).ti,ab,kw,kf
4	Psychology/ OR Psychology.fs OR exp Stress, Psychological/ OR Adaptation, Psychological/ OR exp Quality of Life/ OR exp Family Health/ OR (Social* OR Psychosocial* OR Psycholog* OR Quality of Life OR Life quality OR QoL OR HRQoL OR burden*).ti,ab,kw,kf
5	Exp Epidemiology/ OR Epidemiology.fs OR exp Incidence/ OR exp Prevalence/ OR exp "Costs and Cost Analysis"/ OR economics.fs OR (Epidemiolog* OR prevalence* OR Frequenc* OR occurrence* OR incidence* OR cost* OR expens* OR expenditure* OR economic* OR financ* OR budget* OR spending*).ti,ab,kw,kf
6	Exp Canada/ OR (Canad* OR Alberta* OR Calgary OR Edmonton OR British Columbi* OR Vancouver OR Manitoba* OR New Brunswick OR Newfoundland OR Labrador OR Northwest Territor* OR Nova Scotia* OR Nunavut OR Ontari* OR Toronto OR Ottawa OR Prince Edward Island OR Quebec* OR Montreal OR Saskatchewan OR Yukon).ti,ab,kw,kf
7	Systematic review.pt OR Systematic Reviews as Topic/ OR Meta-Analysis.pt OR Meta-Analysis as Topic/ OR (((systematic* OR Umbrella) AND (review* OR overview* OR synthes*)) OR meta-analys* OR metaanalys*).ti,ab,kw,kf
8	(English OR French OR Italian OR Spanish OR German).lg
9	(1 OR (2 AND 3)) AND (4 OR (5 AND (6 OR 7))) AND 8
10	limit 9 to yr="2014 - 2019" 1298 results

All EBM Reviews 30 Mai 2019

1	Exp Food Hypersensitivity/
2	Exp Hypersensitivity/ OR (allerg* OR hypersensitiv* OR hyper-sensitiv* OR hyperresponsiv* OR hyper-responsiv*).ti,ab,kw,kf
3	Exp Food/ OR (additive OR additives OR almond* OR apple OR apples OR apricot* OR arachis hypogaea OR avocado* OR banana* OR barley OR beef OR berries OR berry OR blackberr* OR blueberr* OR buckwheat* OR cacao OR calamari OR carrot* OR cashew* OR celery OR cherries OR cherry OR chestnut* OR chicory OR chocolat* OR cilandro OR clam OR clams OR cockle* OR coconut OR coconuts OR conch OR conchs OR coriander OR corn OR crab OR crabs OR cranberr* OR crawfish* OR crayfish* OR crustacea* OR cucumber* OR dairy OR dairies OR edamame* OR egg OR eggplant* OR eggs OR fig OR figs OR fish OR fishes OR flaxseed* OR food OR foods OR fruit OR fruits OR grape OR grapes OR hazelnut* OR kiwi OR kiwis OR lactose OR legume* OR lobster OR lobsters OR mango* OR meat OR melon OR melons OR milk OR mollusc* OR multifoood OR mushroom* OR mussel OR mussels OR mustard OR nut OR nuts OR oat OR oats OR octopus OR "oral allergy syndrome" OR orange* OR oyster OR oysters OR parsley OR pea OR peach* OR peanut* OR pear OR pears OR peas OR pecan* OR periwinkle* OR pineapple* OR pistachio* OR plum OR plums OR pork OR potato* OR prawn OR prawns OR raspberr* OR rice OR rye OR salmon OR scallop OR scallops OR seafood* OR sesame OR shellfish* OR shrimp OR shrimps OR snail OR snails OR soja OR soyabean* OR soy OR soya OR soyabean* OR soybean* OR squid OR strawberr* OR sunflower seed* OR tomato* OR vegetable* OR walnut* OR wheat OR wheats OR whelk OR whelks OR zucchini*).ti,ab,kw,kf

4	Psychology/ OR Psychology.fs OR exp Stress, Psychological/ OR Adaptation, Psychological/ OR exp Quality of Life/ OR exp Family Health/ OR (Social* OR Psychosocial* OR Psycholog* OR Quality of Life OR Life quality OR QoL OR HRQoL OR burden*).ti,ab,kw,kf
5	Exp Epidemiology/ OR Epidemiology.fs OR exp Incidence/ OR exp Prevalence/ OR exp "Costs and Cost Analysis"/ OR economics.fs OR (Epidemiolog* OR prevalence* OR Frequenc* OR occurrence* OR incidence* OR cost* OR expens* OR expenditure* OR economic* OR financ* OR budget* OR spending*).ti,ab,kw,kf
6	Exp Canada/ OR (Canad* OR Alberta* OR Calgary OR Edmonton OR British Columbi* OR Vancouver OR Manitoba* OR New Brunswick OR Newfoundland OR Labrador OR Northwest Territor* OR Nova Scotia* OR Nunavut OR Ontari* OR Toronto OR Ottawa OR Prince Edward Island OR Quebec* OR Montreal OR Saskatchewan OR Yukon).ti,ab,kw,kf
7	Systematic review.pt OR Systematic Reviews as Topic/ OR Meta-Analysis.pt OR Meta-Analysis as Topic/ OR (((systematic* OR Umbrella) AND (review* OR overview* OR synthes*)) OR meta-analys* OR metaanalys*).ti,ab,kw,kf
8	(English OR French OR Italian OR Spanish OR German).lg
9	(1 OR (2 AND 3)) AND (4 OR (5 AND (6 OR 7))) AND 8
10	limit 9 to yr="2014 - 2019" 170 results

Embase 31 Mai 2019

1	Exp food allergy OR food allergen/
2	Exp Hypersensitivity/ OR (allerg* OR hypersensitiv* OR hyper-sensitiv* OR hyperresponsiv* OR hyper-responsiv*).ti,ab,kw
3	Exp food/ OR (additive OR additives OR almond* OR apple OR apples OR apricot* OR arachis hypogaea OR avocado* OR banana* OR barley OR beef OR berries OR berry OR blackberr* OR blueberr* OR buckwheat* OR cacao OR calamari OR carrot* OR cashew* OR celery OR cherries OR cherry OR chestnut* OR chicory OR chocolat* OR cilandro OR clam OR clams OR cockle* OR coconut OR coconuts OR conch OR conchs OR coriander OR corn OR crab OR crabs OR cranberr* OR crawfish* OR crayfish* OR crustacea* OR cucumber* OR dairy OR dairies OR edamame* OR egg OR eggplant* OR eggs OR fig OR figs OR fish OR fishes OR flaxseed* OR food OR foods OR fruit OR fruits OR grape OR grapes OR hazelnut* OR kiwi OR kiwis OR lactose OR legume* OR lobster OR lobsters OR mango* OR meat OR melon OR melons OR milk OR mollusc* OR multifoood OR mushroom* OR mussel OR mussels OR mustard OR nut OR nuts OR oat OR oats OR octopus OR "oral allergy syndrome" OR orange* OR oyster OR oysters OR parsley OR pea OR peach* OR peanut* OR pear OR pears OR peas OR pecan* OR periwinkle* OR pineapple* OR pistachio* OR plum OR plums OR pork OR potato* OR prawn OR prawns OR raspberr* OR rice OR rye OR salmon OR scallop OR scallops OR seafood* OR sesame OR shellfish* OR shrimp OR shrimps OR snail OR snails OR soja OR sojabean* OR soy OR soya OR soyabean* OR soybean* OR squid OR strawberr* OR sunflower seed* OR tomato* OR vegetable* OR walnut* OR wheat OR wheats OR whelk OR whelks OR zucchini*).ti,ab,kw
4	Psychology/ OR metal stress/ OR exp coping behavior/ OR exp "Quality of Life"/ OR Family Health/ OR (Social* OR Psychosocial* OR Psycholog* OR Quality of Life OR Life quality OR QoL OR HRQoL OR burden*).ti,ab,kw
5	Epidemiology/ OR ep.fs OR exp Incidence/ OR exp Prevalence/ OR exp Cost/ OR (Epidemiolog* OR prevalence* OR Frequenc* OR occurrence* OR incidence* OR cost* OR expens* OR expenditure* OR economic* OR financ* OR budget* OR spending*).ti,ab,kw
6	Exp Canada/ OR (Canad* OR Alberta* OR Calgary OR Edmonton OR British Columbi* OR Vancouver OR Manitoba* OR New Brunswick OR Newfoundland OR Labrador OR Northwest Territor* OR Nova Scotia* OR Nunavut OR Ontari* OR Toronto OR Ottawa OR Prince Edward Island OR Quebec* OR Montreal OR Saskatchewan OR Yukon).ti,ab,kw
7	"systematic review (topic)"/ OR " Meta-Analysis (topic)"/ OR (((systematic* OR Umbrella) AND (review* OR overview* OR synthes*)) OR meta-analys* OR metaanalys*).ti,ab,kw
8	limit 5 to (meta analysis or "systematic review")
9	(English OR French OR Italian OR Spanish OR German).la

10	(1 OR (2 AND 3)) AND (4 OR 8 OR (5 AND (6 OR 7))) AND 9
11	limit 10 to yr="2014 - 2019"
12	conference abstract.pt.
13	11 not 12 1710 results

CINAHL 31 Mai 2019

S1	MH(Food Hypersensitivity+)
S2	MH(Hypersensitivity+) OR TI(allerg* OR hypersensitiv* OR hyper-sensitiv* OR hyperresponsiv* OR hyper-responsiv*) OR AB(allerg* OR hypersensitiv* OR hyper-sensitiv* OR hyperresponsiv* OR hyper-responsiv*)
S3	MH(food+) OR TI(additive OR additives OR almond* OR apple OR apples OR apricot* OR arachis hypogaea OR avocado* OR banana* OR barley OR beef OR berries OR berry OR blackberr* OR blueberr* OR buckwheat* OR cacao OR calamari OR carrot* OR cashew* OR celery OR cherries OR cherry OR chestnut* OR chicory OR chocolat* OR cilandro OR clam OR clams OR cockle* OR coconut OR coconuts OR conch OR conchs OR coriander OR corn OR crab OR crabs OR cranberr* OR crawfish* OR crayfish* OR crustacea* OR cucumber* OR dairy OR dairies OR edamame* OR egg OR eggplant* OR eggs OR fig OR figs OR fish OR fishes OR flaxseed* OR food OR foods OR fruit OR fruits OR grape OR grapes OR hazelnut* OR kiwi OR kiwis OR lactose OR legume* OR lobster OR lobsters OR mango* OR meat OR melon OR melons OR milk OR mollusc* OR multifoood OR mushroom* OR mussel OR mussels OR mustard OR nut OR nuts OR oat OR oats OR octopus OR "oral allergy syndrome" OR orange* OR oyster OR oysters OR parsley OR pea OR peach* OR peanut* OR pear OR pears OR peas OR pecan* OR periwinkle* OR pineapple* OR pistachio* OR plum OR plums OR pork OR potato* OR prawn OR prawns OR raspberr* OR rice OR rye OR salmon OR scallop OR scallops OR seafood* OR sesame OR shellfish* OR shrimp OR shrimps OR snail OR snails OR soja OR sojabean* OR soy OR soya OR soyabean* OR soybean* OR squid OR strawberr* OR sunflower seed* OR tomato* OR vegetable* OR walnut* OR wheat OR wheats OR whelk OR whelks OR zucchini*) OR AB(additive OR additives OR almond* OR apple OR apples OR apricot* OR arachis hypogaea OR avocado* OR banana* OR barley OR beef OR berries OR berry OR blackberr* OR blueberr* OR buckwheat* OR cacao OR calamari OR carrot* OR cashew* OR celery OR cherries OR cherry OR chestnut* OR chicory OR chocolat* OR cilandro OR clam OR clams OR cockle* OR coconut OR coconuts OR conch OR conchs OR coriander OR corn OR crab OR crabs OR cranberr* OR crawfish* OR crayfish* OR crustacea* OR cucumber* OR dairy OR dairies OR edamame* OR egg OR eggplant* OR eggs OR fig OR figs OR fish OR fishes OR flaxseed* OR food OR foods OR fruit OR fruits OR grape OR grapes OR hazelnut* OR kiwi OR kiwis OR lactose OR legume* OR lobster OR lobsters OR mango* OR meat OR melon OR melons OR milk OR mollusc* OR multifoood OR mushroom* OR mussel OR mussels OR mustard OR nut OR nuts OR oat OR oats OR octopus OR "oral allergy syndrome" OR orange* OR oyster OR oysters OR parsley OR pea OR peach* OR peanut* OR pear OR pears OR peas OR pecan* OR periwinkle* OR pineapple* OR pistachio* OR plum OR plums OR pork OR potato* OR prawn OR prawns OR raspberr* OR rice OR rye OR salmon OR scallop OR scallops OR seafood* OR sesame OR shellfish* OR shrimp OR shrimps OR snail OR snails OR soja OR sojabean* OR soy OR soya OR soyabean* OR soybean* OR squid OR strawberr* OR sunflower seed* OR tomato* OR vegetable* OR walnut* OR wheat OR wheats OR whelk OR whelks OR zucchini*)
S4	MH(Psychology) OR MW(PH) OR Mh(Stress, Psychological+) OR MH(Adaptation, Psychological+) OR MH(Quality of Life+) OR MH(Family Health) OR TI(Social* OR Psychosocial* OR Psycholog* OR Quality of Life OR Life quality OR QoL OR HRQoL OR burden*) OR AB(Social* OR Psychosocial* OR Psycholog* OR Quality of Life OR Life quality OR QoL OR HRQoL OR burden*)
S5	MH(Epidemiology+) OR MW(EP) OR MH(Incidence) OR MH(Prevalence) OR MH("Costs and Cost Analysis"+) OR MW(EC) OR TI(Epidemiolog* OR prevalence* OR Frequenc* OR occurrence* OR incidence* OR cost* OR expens* OR expenditure* OR economic* OR financ* OR budget* OR spending*) OR AB(Epidemiolog* OR prevalence* OR Frequenc* OR occurrence* OR incidence* OR cost* OR expens* OR expenditure* OR economic* OR financ* OR budget* OR spending*)
S6	MH(Canada+) OR TI(Canad* OR Alberta* OR Calgary OR Edmonton OR British Columbi* OR Vancouver OR Manitoba* OR New Brunswick OR Newfoundland OR Labrador OR Northwest Territor* OR Nova Scotia* OR Nunavut OR Ontari* OR Toronto OR Ottawa OR Prince Edward Island OR Quebec* OR Montreal OR Saskatchewan OR Yukon) OR AB(Canad* OR Alberta* OR Calgary OR Edmonton OR British Columbi* OR Vancouver OR Manitoba* OR New Brunswick OR Newfoundland OR Labrador OR Northwest Territor* OR Nova Scotia* OR Nunavut OR Ontari* OR Toronto OR Ottawa OR Prince Edward Island OR Quebec* OR Montreal OR Saskatchewan OR Yukon)
S7	PT(Systematic review) OR MH(Systematic Review) OR PT(Meta-Analysis) OR MH(Meta-Analysis) OR TI(((systematic* OR Umbrella) AND (review* OR overview* OR synthes*))) OR meta-analys* OR metaanalys*) OR AB(((systematic* OR Umbrella) AND (review* OR overview* OR synthes*))) OR meta-analys* OR metaanalys*)

S8	LA(English OR French OR Italian OR Spanish OR German)
S9	(S1 OR (S2 AND S3)) AND (S4 OR (S5 AND (S6 OR S7))) AND S8 limiters publication date 20140101-20191231 506 results

Web of Science 31 Mai 2019

#1	TS=(allerg* OR hypersensitiv* OR hyper-sensitiv* OR hyperresponsiv* OR hyper-responsiv*)
#2	TS=(additive OR additives OR almond* OR apple OR apples OR apricot* OR arachis hypogaea OR avocado* OR banana* OR barley OR beef OR berries OR berry OR blackberr* OR blueberr* OR buckwheat* OR cacao OR calamari OR carrot* OR cashew* OR celery OR cherries OR cherry OR chestnut* OR chicory OR chocolat* OR cilandro OR clam OR clams OR cockle* OR coconut OR coconuts OR conch OR conchs OR coriander OR corn OR crab OR crabs OR cranberr* OR crawfish* OR crayfish* OR crustacea* OR cucumber* OR dairy OR dairies OR edamame* OR egg OR eggplant* OR eggs OR fig OR figs OR fish OR fishes OR flaxseed* OR food OR foods OR fruit OR fruits OR grape OR grapes OR hazelnut* OR kiwi OR kiwis OR lactose OR legume* OR lobster OR lobsters OR mango* OR meat OR melon OR melons OR milk OR mollusc* OR multifoood OR mushroom* OR mussel OR mussels OR mustard OR nut OR nuts OR oat OR oats OR octopus OR "oral allergy syndrome" OR orange* OR oyster OR oysters OR parsley OR pea OR peach* OR peanut* OR pear OR pears OR peas OR pecan* OR periwinkle* OR pineapple* OR pistachio* OR plum OR plums OR pork OR potato* OR prawn OR prawns OR raspberr* OR rice OR rye OR salmon OR scallop OR scallops OR seafood* OR sesame OR shellfish* OR shrimp OR shrimps OR snail OR snails OR soja OR sojabean* OR soy OR soya OR soyabean* OR soybean* OR squid OR strawberr* OR sunflower seed* OR tomato* OR vegetable* OR walnut* OR wheat OR wheats OR whelk OR whelks OR zucchini*)
#3	TS=(Social* OR Psychosocial* OR Psycholog* OR Quality of Life OR Life quality OR QoL OR HRQoL OR burden*)
#4	TS=(Epidemiolog* OR prevalence* OR Frequenc* OR occurrence* OR incidence* OR cost* OR expens* OR expenditure* OR economic* OR financ* OR budget* OR spending*)
#5	TS=(Canad* OR Alberta* OR Calgary OR Edmonton OR British Columbi* OR Vancouver OR Manitoba* OR New Brunswick OR Newfoundland OR Labrador OR Northwest Territor* OR Nova Scotia* OR Nunavut OR Ontari* OR Toronto OR Ottawa OR Prince Edward Island OR Quebec* OR Montreal OR Saskatchewan OR Yukon)
#6	TS=((systematic* OR Umbrella) AND (review* OR overview* OR synthes*)) OR meta-analys* OR metaanalys*)
#7	(#1 AND #2 AND (#3 OR (#4 AND (#5 OR #6)))) AND LANGUAGE: (English OR French OR German OR Italian OR Spanish) Timespan=1998-2019 1438 results

After the removal of duplicates, there were a total of 2894 records retrieved.

Appendix 2B: Eligibility criteria for inclusion of clinical studies

	Inclusion / exclusion criteria
INCLUSION	
Patient population	Patients of any age with clinician-diagnosed IgE-mediated food-allergy (confirmed through positive skin prick test, specific IgE level and/or oral food challenge test) including eggs, peanuts, milk, wheat, soy, tree nuts, or other
Intervention	Oral immunotherapy using food products (including patented food-based products) <i>Note: Sublingual (SLIT) and epicutaneous (EPIT) immunotherapy was only to be discussed in terms of background information</i>
Comparators	- Routine care (allergen avoidance and prescription of epinephrine injection device), no treatment, placebo - OIT with different protocols
Outcomes	Efficacy: - desensitization - continued consumption - sustained unresponsiveness - Impact of patient characteristics and protocol variables on efficacy outcomes Adverse effects: - Severe reactions (systemic reactions, anaphylaxis, serious adverse events, intra-muscular epinephrine use) - Any reactions (mild, local reactions) - Discontinuations due to adverse events - Long-term follow-up for safety and tolerability - Eosinophilic esophagitis - Impact of patient characteristics and protocol variables on safety outcomes Impact on QoL: - Changes in disease-specific and generic health-related quality of life measured using validated instruments Patient perspectives on the intervention: - Acceptability, burden of treatment, impact on autonomy, values, preferences, expectations and goals of treatment

Study design	Generally included: • Meta-analyses published since 2015 • Randomized controlled clinical trials (RCTs) OIT vs placebo or avoidance with N (enrolled) > 50 not included in meta-analyses • Large (N>150) observational studies of OIT in clinical practice or and non-randomized, controlled, parallel group intervention studies (controlled, clinical trials, CCTs) Studies not fulfilling the above criteria were included if they addressed the following data gaps or questions concerning patient selection or OIT protocol parameters: • Long-term follow-up of controlled trials (with control arm) and observational studies (≥ 6 months after reaching maintenance) • Impact of patients' age on the outcomes of OIT / studies in adults or adolescents • Impact of other patient characteristics on OIT outcomes • Multi-food OIT • Less common allergens (e.g., wheat, soy, walnut) • Baked food product protocols • Studies focusing on EoE and its impact on the outcomes of OIT • Patient-reported outcomes (PROs): quality of life, burden-of-treatment • Impact of different modes of communication and shared decision-making on clinical or PRO outcomes: • RCTs exploring OIT with adjuvant therapy (e.g., biologics, probiotics) • Studies comparing different OIT protocols
EXCLUSION	
Outcomes	• Studies reporting immunological outcomes only (surrogate outcomes) (<i>Note: immunological outcomes were extracted if reported by otherwise included studies</i>)
Design	• Case reports
Language	• Language other than French or English
Completeness of reporting	• Conference papers (excluded due to incomplete reporting and lack of peer-review)
Time of publication	• Articles published before 1998

Appendix 3: Detailed clinical evidence tables

OIT PROTOCOL VARIABLES IN CLINICAL STUDIES OR PUBLISHED CLINICAL PRACTICE

	Allergen food preparation	Single starting dose in initial dose escalation	Build-up phase starting dose (per day)	Target dose (per day)	Up-dosing interval during build-up phase	Length of build-up phase (months)	Maintenance phase
Peanut							
RCTs with N> 50	Peanut flour (Anagnostou, 2014; ¹ Blumchen, 2019; ² Reier-Nilsen, 2019a ³ ; Tang, 2015 ⁴), AR101 powder (Bird, 2018 ⁵ ; Vickery, 2018 ⁶) <u>Adjuvant</u> : <i>Lactobacillus rhamnosus</i> CGMCC 1.3724 (Tang, 2015 ⁴)	0.1-0.5 mg PP (Bird, 2018 ⁵ ; Tang, 2015 ⁴ ; Vickery, 2018 ⁶)	No initial dose escalation: 1-5 mg (Anagnostou, 2014; ¹ Reier-Nilsen, 2019a ³) 0.1-30 mg PP depending on eliciting dose (Blumchen, 2019 ²) With initial dose escalation: 3 mg PP (Vickery, 2018 ⁶) 6 mg PP (Bird, 2018 ⁵ , 25 mg PP (Tang, 2015 ⁴)	125 or 250 mg PP depending on eliciting dose (Blumchen, 2019 ²) 300 mg PP (Bird, 2018 ⁵ ; Vickery 2018 ⁶) 800 mg PP (Anagnostou, 2014 ¹) 2000 mg PP (Tang, 2015 ⁴) 5000 mg PP (Reier-Nilsen, 2019 ³)	2-3 weeks	6 (Anagnostou, 2014 ¹) 4.6 to 7.8 (Bird, 2018 ⁵) 13 median (range 10-14) (Blumchen, 2019 ²) 11.5 to 18.0 (Reier-Nilsen, 2019 ³) 8 (Tang, 2015 ⁴) ~6.4 (Vickery, 2018 ⁶)	5000 mg PP daily for 36 months (Reier-Nilsen, 2019a ³) 2000 mg PP daily for 10 months (Tang, 2015 ⁴) 300 mg PP daily for 24 weeks (Vickery, 2018 ⁶) 50-250 mg PP daily; median (observed): 125 mg for 8±2 weeks (Blumchen, 2019 ²)
Large case series	Peanut flour ; peanuts for doses ≥ 300 mg PP (Nachshon, 2018 ⁷) Peanut flour ; for higher doses peanuts , peanut butter, and other processed peanut food products (Wasserman, 2019 ⁸) Peanut flour , Bamba [®] (peanut flour puffs), peanut butter powder compounded at local pharmacies into capsules with inert filler (to be opened) (Soller, 2019 ⁹)	0.1 mg PP (Nachshon, 2018 ⁷) 2.5 µg PP (Wasserman, 2019 ⁸) 0.1 mg PP (Soller, 2019 ⁹)	Median: 20 mg PP (IQR 7.5-100) - single highest tolerated dose during initial dose escalation (Nachshon, 2018 ⁷) Individualized (Wasserman, 2019 ⁸) No initial dose escalation: 10 to 12 mg PP (Soller, 2019 ⁹) With initial dose escalation: individualized (Soller, 2019 ⁹)	3000 mg PP or ≥ 300 mg for patients with difficulty reaching 3000 mg PP (Nachshon, 2018 ⁷) 3000 mg PP (Wasserman, 2019 ⁸) 300-320 PP (Soller, 2019 ⁹)	Monthly (Nachshon, 2018 ⁷) 1-2 weeks (Wasserman, 2019 ⁸) 2 weeks (Soller, 2019 ⁹)	8.7 median (IQR: 3.8 – 12.8) (Nachshon, 2018 ⁷) NR-Individualized (Wasserman, 2019 ⁸) 3.7 to 5.1 (16-22 weeks) (Soller, 2019 ⁹)	3000 or 1200 mg PP daily for unlimited time (Nachshon, 2018 ⁷) 2000 mg of PP once or twice a day for a minimum of 3 years (Wasserman, 2019 ⁸) 300-320 PP (Soller, 2019 ⁹)
Cow's milk							
RCTs with N> 50	Milk , diluted or whole (Longo, 2008; ¹⁰ Martorell, 2011; ¹¹ Morisset, 2007; ¹² de Schryver, 2019 ¹³)	0.5 mg CMP (=0.017 mL milk) (Longo, 2008 ¹⁰) 0.3 mg CMP (=0.010 mL milk) (De Schryver, 2019 ¹³)	≤ 20 mL milk (individualized) (Longo, 2008 ¹⁰) 4 mL milk (=120 mg CMP) (Martorell, 2011 ¹¹) 1 mL milk (=30 mg CMP) (Morisset, 2007 ¹²) 2.5 mL (=75 mg CMP) De Schryver, 2019 ¹³)	4500 mg CMP (150 mL milk) (Longo, 2008 ¹⁰) 6400 mg CMP (200 mL milk) (Martorell, 2011; De Schryver, 2019 ¹³) 7500 mg CMP (250 mL milk) and dairy products (Morisset, 2007 ¹²)	2 days (Longo, 2008 ¹⁰) 1 week (Martorell, 2011; ¹¹ Morisset, 2007; ¹²) (De Schryver, 2019 ¹³)	12 (Longo, 2008 ¹⁰) 3.7 (Martorell, 2011 ¹¹) 1.4 (Morisset, 2007 ¹²)	150 – 200 mL milk daily plus dairy products ad libitum (Longo, 2008; ¹⁰ Martorell, 2011; ¹¹ 200 mL/d for 1 month, afterwards ≥ 200 mL twice a week plus dairy products ad

	Allergen food preparation	Single starting dose in initial dose escalation	Build-up phase starting dose (per day)	Target dose (per day)	Up-dosing interval during build-up phase	Length of build-up phase (months)	Maintenance phase
Large case series	Powdered formula ; 3% fat milk for doses ≥ 90 mg of CMP (Levy, 2014 ¹⁴) Milk diluted in water (Kauppila, 2014 ¹⁵)	0.3 mg CMP (=0.010 mL milk) (Levy, 2014 ¹⁴)	No initial dose escalation: 0.5 mg CMP (=0.017 mL milk) (Kauppila, 2014 ¹⁵) With initial dose escalation: Median 52.5 mg CMP (=1.75 mL milk) (Levy, 2014 ¹⁴)	7200 mg CMP (240 mL milk) (Levy, 2014 ¹⁴) 6400 mg CMP (200 mL milk) (Kauppila, 2014 ¹⁵)	Monthly (Levy, 2014 ¹⁴) 1-2 weeks (Kauppila, 2014 ¹⁵)	4-6 (Kauppila, 2014 ¹⁵)	libitum (De Schryver, 2019 ¹³) 4500 mg CMP daily (150 mL milk) plus ad libitum milk products for unlimited time (Elizur, 2016 ¹⁶) 6400 mg CMP daily (200 mL milk) for unlimited time (Kauppila, 2014 ¹⁵)
Chicken's egg							
RCTs with N> 50	Dried egg white powder/dehydrated egg white (Burks, 2012, ¹⁷ Escudero, 2015 ¹⁸) Powdered pasteurised egg (Fuentes-Aparicio, 2013 ¹⁹) Pasteurized egg white (Martin-Munoz, 2019a ²⁰) Hard-boiled egg (Morisset, 2007 ¹²)	0.1 mg dried egg white powder (Burks, 2012 ¹⁷) 0.08 mg EWP (Escudero, 2015 ¹⁸) 1 mg powdered pasteurised egg (Fuentes-Aparicio, 2013 ¹⁹) 0.11 mg EWP (Martin-Munoz, 2019a ²⁰)	3-50 mg dried egg white powder (individualized) (Burks, 2012 ¹⁷) 0.02 mg EWP (Escudero, 2015 ¹⁸) 30 mg powdered pasteurised egg (Fuentes-Aparicio, 2013 ¹⁹) Individualized, based on last tolerated dose in initial dose escalation (Martin-Munoz, 2019a ²⁰) 1 g of hard-boiled egg yolk (Morisset, 2007 ¹²)	2 g of egg-white powder (~1/3 egg) (Burks, 2012 ¹⁷) 2.808 g EWP (Escudero, 2015 ¹⁸) 10 g powdered pasteurised egg (~1 egg) (Fuentes-Aparicio, 2013 ¹⁹) 30 mL pasteurized egg white (3.3 g EWP, ~1 egg) (Martin-Munoz, 2019a ²⁰) 4 g of egg yolk and 4 g of egg white plus foods containing eggs	1-2 weeks Weekly plus daily or weekly only (Martin-Munoz, 2019a)	10 (Burks, 2012 ¹⁷) 3 (planned), 1 (observed) (Escudero, 2015 ¹⁸) 3 (range 1.2-8.2) (Fuentes-Aparicio, 2013 ¹⁹) 2-3 (Morisset, 2007 ¹²)	2 g of egg-white powder (~1/3 egg) daily for 12 months (Burks, 2012 ¹⁷) ≥ 1 undercooked egg every 2 days plus any other foods containing egg ad libitum (Escudero, 2015 ¹⁸) Normal, egg-containing diet (Fuentes-Aparicio, 2013 ¹⁹) 30 mL pasteurized egg white (3.3 g EWP, ~1 egg) daily or every 2 days (Martin-Munoz, 2019b ²¹)
Multi-food OIT							
Single-arm clinical study, Begin, 2014a ²² (N=40)	Food flours/powders (milk powder; egg powder; peanut, walnut, cashew, almond, pecan, hazelnut, pecan, wheat, soy, and sesame seed flours)	0.1 mg of each food allergen protein (i.e., 0.5 mg total food allergen protein for a patient with 5 allergies treated)	Highest tolerated dose at initial dose escalation (≤6 mg total food allergen protein) divided evenly among the treated food allergens	4000 mg food allergen protein per allergen (up to 20,000 mg for those with 5 allergies)	2 weeks	Individualized; median time to reach 1000 mg dose: approx. 16 months; 4000 mg:>20 months	4000 mg food allergen protein per allergen (i.e., 20,000 mg total food allergen protein for a patient with 5 allergies treated)
Single-arm clinical study, Begin, 2014b ²³ (with omalizumab, N=25)		5 mg total food allergen protein divided evenly among the treated food allergens (e.g., 1 mg of each allergen for a patient with 5 allergies treated)	Highest tolerated dose at initial dose escalation (≤1250 mg total food allergen protein) divided evenly among the treated food allergens	4000 mg food allergen protein per allergen (up to 20,000 mg for those with 5 allergies)	2 weeks	Individualized; median time to reach maintenance dose was 4.14 months (range 1.6–8.3)	4000 mg food allergen protein per allergen

CMP: cow's milk protein; EWP: egg white protein; PP: peanut protein

Note: 1 peanut corresponds to approximately 250 mg peanut protein; 1 mL milk corresponds to 30 mg milk protein; 1 egg corresponds to 4g egg white protein or 30 mL pasteurized egg white or 6 g of egg-white powder

Summary table

Allergen food preparation	Adjuvants	Single starting dose in initial dose escalation	Build-up phase starting dose (per day)	Target dose (per day)	Up-dosing interval during build-up phase	Length of build-up phase (months)	Maintenance dose
Peanut: Peanut flour, AR101 powder, peanuts, peanut butter and other processed peanut products (e.g., peanut flour puffs), compounded peanut butter powder Milk: milk, diluted or whole; powdered (formula) Egg: Dried / dehydrated egg white powder; pasteurized egg white; hard-boiled egg Multi-food OIT: Food flours/powders	Lactobacillus, omalizumab	Peanut: 0.0025-0.5 mg peanut protein Milk: 0.3-0.5 mg milk protein Egg: 0.1-1 mg egg white powder or egg protein Multi-food OIT: 0.1 mg of each food allergen protein	Peanut: <u>No initial dose escalation:</u> 0.1-30 mg peanut protein <u>With initial dose escalation:</u> 3-100 mg peanut protein Milk: <u>No initial dose escalation:</u> 0.5 mg milk protein <u>With initial dose escalation:</u> 30-120 mg milk protein Egg: 0.02-50 mg egg white powder or egg protein	Peanut: 800 -5000 mg peanut protein (low dose OIT: 125-320 mg) Milk: 150-250 mL milk (4500-7200 mg milk protein) Egg: ~1 egg or ~1/3 egg Multi-food OIT: 4000 mg food allergen protein per allergen (up to 20,000 mg for those with 5 allergies)	Most common: 2-3 weeks; range: 2 days to 1 month	Peanut: 3.7 to 18 Milk: 1.4 to 12 Egg: 3 to 10 Multi-food OIT: No omalizumab median > 20 With omalizumab: 1.6-8.3, median 4.14	Peanut: 1200-5000 mg peanut protein /d (low dose OIT: 50-320 mg/d) Milk: 150-200 mL daily or at least twice weekly (4500-6500 cow milk protein) Egg: 3.3 g egg white protein (~1 egg) or 2 g of egg-white powder (~1/3 egg) or ≥ 1 undercooked egg daily or every 2 days

Protocols for other food allergens

	Nowak-Wegrzyn, 2019 ²⁴ (RCT, N=46) - wheat	Kulmala, 2018 ²⁵ (prospective, single-arm study, N=100) -wheat	Elizur, 2019 ²⁶ (CCT, N=73)-walnut	Barni, 2019 ²⁷ (case series, N=43) - hazelnut	Nachshon, 2019 ²⁸ (CCT) N=75 - sesame
Age	Median, 8.7 years; range, 4.2-22.3	Mean 11.6 years, range, 6.1-18.6	Mean 7.9 years OIT, 6.8 years control; range 4-20	Mean 10 years, range: 5-16	Mean 7.5 years, ≥4, (IQR: 5.8-11.6)
Diagnosis	DBPCFC	Open OFC (not performed in 15 patients with an immediate reaction within the previous 3 months)	OFC, unless an immediate, recent (past year) reaction was documented	OFC	OFC or reaction within past year together with positive skin prick test (SPT) result and/or specific serum IgE (>0.35 kUA/L)
OIT protocol	Biweekly escalation for up to 44 weeks to a maximum of 1445 mg of wheat protein (WP), followed by daily home maintenance dosing. After 52 weeks of treatment (≥ 8 weeks of maintenance dosing), DBPCFC for a cumulative dose of 7443 of WP (2-3 slices of bread). Subjects continued OIT for another year and underwent a year 2 DBPCFC and, if passed, a subsequent off therapy DBPCFC. Placebo-treated subjects crossed over to high-dose OIT (maximum, 2748 mg of WP).	Well-cooked wheat spaghetti was consumed every day for 17 weeks, increasing every 1-2 weeks from 0.3 to 2000 mg of wheat protein, followed by 3-month maintenance and 9-month follow-up Patients received antihistamine every day	Initial 4-day dose-escalation phase to establish the single highest tolerated dose, which was consumed daily at home for 24 days; subsequent monthly dose escalations were repeated until 4000 mg walnut protein was achieved. Patients who were desensitized to walnut continued to consume 1200 mg walnut protein daily for 6 months as maintenance.	Initial hospital OFC followed by hazelnut intake at home 3 times/ week with a dose equal to the maximum dose tolerated during hospital stay, up-dosing every 3 months at the hospital until 2.5 g hazelnut (cumulative dose) was reached	The initial 2 days of first dose-escalation round served as an entry OFC up to 4800 mg sesame protein (non-reacting patients were excluded). The single highest tolerated dose (SHTD) was then consumed at least once daily at home for 24 days. ubsequently, patients returned for monthly dose escalations performed in an ambulatory day care setting, Patients who could tolerate the target dose of 4000 mg sesame protein at the end build-up, were considered fully desensitized and were instructed to consume a daily maintenance dose of 1200 mg sesame protein (5g Tahini) plus ad-lib consumption of sesame products Patients who tolerated ≥ 240 mg sesame protein (~1 g of Tahini) but<4000 mg were considered partially desensitized and instructed to consume their achieved dose for an unlimited time

CLINICAL EFFICACY

Desensitization: increase in reactivity threshold

Data for peanut, milk and egg allergies

Meta-analyses			RCT not included in meta-analyses with N>50	
Nurmatov, 2017 ²⁹ – chicken’s egg, cow’s milk, peanut and others	Romantsik, 2018 ³⁰ – chicken’s egg	Chu, 2019 ³¹ – peanut	Martin-Munoz, 2019a ²⁰ (Spain) – chicken’s egg N=101 Age: 6-9 years Diagnosis confirmed with OFC: yes	De Schryver, 2019 ¹³ (Canada) – cow’s milk N=52 Age: 6-18, mean 12.1 years Diagnosis confirmed with OFC: yes (single-blind)
Desensitization in patients assessed in DBPCFC: All OIT trials - 17 RCTs^{1,10-12,18,19,32-42} and 5 CCTs⁴³⁻⁴⁷ OIT: 75% (432/573) Control 11% (44/409) RR (Control/OIT) = 0.14 (95% CI 0.08, 0.24) <u>OIT RCTs only:</u>^{1,10-12,18,19,32-42} OIT: 71% (291/410) Control: 13% (43/334) RR (Control/OIT) = 0.18 (95% CI 0.10, 0.32) - 5.55 <u>Diagnosis confirmed by DBPCFC:</u> OIT: 73% (412/565) Control: 13% (43/334) RR (Control/OIT) = 0.15 (95% CI 0.09, 0.27) P<0.0001 Chicken's egg: - 9 RCTs^{12,18,19,32,34,35,37,39,48} (1 SLIT⁴⁸) and 1 CCT⁴⁷ OIT: 74% (251/339) Control: 17% (36/208), P<.0001 RR (Control/OIT) = 0.22 (95% CI 0.11, 0.45)	Induction of immunologic tolerance and/or ability to tolerate a full serving of egg as assessed in 9 RCTs^{18,19,32,34,35,37,51-53} and 1 CCT:⁵⁴ OIT: 45% (112/249) Control: 10% (19/190) RR: 4.25 (95% CI 2.77, 6.53) <i>GRADE assessment: low quality of evidence</i> Ingestion of a partial serving of egg (1 g to 7.5 g) as assessed in 8 RCTs^{18,19,32,34,35,37,51,53} and 1 CCT:⁵⁴ OIT: 82% (192/234) Control: 10% (18/176) RR= 7.48 (95% CI 4.91, 11.38) <i>GRADE assessment: low quality of evidence</i>	Passing an OFC at the highest dose tested (8 RCTs^{1,2,4-6,42,55}, 1 unpublished): • <i>Original analysis:</i> median cumulative dose 4250 mg PP (range 1043-5000 mg) = 17 (4.2-20) peanuts OIT: 56% (320/574) Control: 3.2% (9/284) RR=12.42 (95% CI 6.82, 22.61), P<.001 <i>GRADE assessment: High quality of evidence</i> • <i>Corrected analysis:</i> median cumulative dose 3022 mg PP (range 1043-5000 mg) = 12 (4.2-20) peanuts OIT: 55% (315/574) Control: 2.8% (8/284) – see Section 8.1 <i>Alternative analysis: achieving at least partial desensitization:</i> passing an OFC with a cumulative dose of 400 to 5000 mg PP (1.6-20 peanuts) (median 2700 mg) across 8 RCTs^{1,2,4-6,42,55} (1 unpublished): OIT: 73% (422/574) Control: 7.0% (21/284)	Passing DBPCFC at 12 months with 3.3 g pasteurized raw egg white protein (cumulative) or reaching target dose of 3.3 g pasteurized raw egg white egg white protein (equivalent to 1 egg): OIT: 84% (64/76) Control: 16% (4/25) P=0.000 <i>Cochrane risk of bias: high (MW assessment)</i>	OIT patients: reaching maintenance dose (200 mL) (8.8 g milk protein) Control patients: passing a single-blind OFC with a cumulative dose of 200 mL milk (8.8 g milk protein): OIT: 69% (18/26) Control: 0 (0/26) Difference: 69% (95% CI: 48%, 91%)

Meta-analyses			RCT not included in meta-analyses with N>50	
Nurmatov, 2017 ²⁹ – chicken’s egg, cow’s milk, peanut and others	Romantsik, 2018 ³⁰ – chicken’s egg	Chu, 2019 ³¹ – peanut	Martin-Munoz, 2019a ²⁰ (Spain) – chicken’s egg N=101 Age: 6-9 years Diagnosis confirmed with OFC: yes	De Schryver, 2019 ¹³ (Canada) – cow’s milk N=52 Age: 6-18, mean 12.1 years Diagnosis confirmed with OFC: yes (single-blind)
<u>Cow’s milk</u> - 9 RCTs^{10,11,33,36,38-41,48} (1 SLIT⁴⁸) and 4 CCTs^{43,44,46,47} – tolerance to median 45 to 250 mL (=1340-7500 mg milk protein) milk (median 200 mL=6000 mg) across trials OIT: 78% (262/336) Control: 7.8% (15/193), P<.0001 RR (Control/OIT) = 0.12 (95% CI 0.06, 0.25) <u>Peanut</u> - 2 OIT^{1,42} and 2 SLIT^{49,50} RCTs OIT: 73% (65/89) Control: 3.7% (3/82), P<.0001 RR (Control/OIT) = 0.11 (95% CI 0.04, 0.31)				

DBPCFC: double-blind, placebo-controlled food challenge; IQR: inter-quartile range; OFC: oral food challenge; OIT: oral immunotherapy; PP: peanut protein; RR: risk ratio; SLIT: sublingual immunotherapy
Note: approximate correspondence: 1 peanut = 250 mg peanut protein; 1 mL milk = 30 mg milk protein; 1 egg white=4g egg white protein
*An additional 15 patients continued to receive increasing amounts of cow milk at date of data cut-off (i.e., had not completed the build-up phase).

Case series (clinical practice) with N>150				
Levy, 2014¹⁴ (Israel)– cow's milk N=265* Age: 4-27 (7.5 median) years Diagnosis confirmed with OFC: not for all patients	Kaupilla, 2019¹⁵ (Finland) – cow's milk N=295 Age: 5-17 (median 7.5) years Diagnosis confirmed with OFC: yes	Soller, 2019⁹ (Canada) – peanut N=270 Age: 0.75-5.9 (median 1.9, IQR : 1.25-2.75) years Diagnosis confirmed with OFC: for 31% of patients	Wasserman, 2019⁸ (USA) – peanut N=270 Age: 4-18 (mean: 8.1) years Diagnosis confirmed with OFC: no	Wasserman, 2014⁵⁶ (USA and Israel)-peanut N=352 Age: 3-24 years Diagnosis confirmed with OFC: 97% of patients
Completion of treatment program and ability to freely consume milk or milk products (> 7.2 g milk protein): 60% (160/265) Ability to tolerate ≥ 180 mg of milk protein (6 mL of milk): 85% (226/265)	Consuming ≥200 mL/d of milk (6.4 g milk protein) 3 months after reaching the maintenance dose of 200 mL: 71% (209/295); Consuming <200 mL (10-190 mL): 18% (54/295) <i>Consuming ≥ 10 mL milk: 89% (263/295)</i> Avoiding milk consumption: or lost to follow-up: 11% (32/295)	Reaching the target maintenance dose of 300-320 mg PP (1.2-1.3 peanuts): 90% (243/270)	Reaching the target dose of 3000 mg PP: 78% (211/270) (an additional 3 patients reached a planned target dose of 2000 mg PP) Passing an OFC with 6000 mg PP: 78% (210/270)	Reaching the target dose of 415-8000 mg PP: 85% (298/352)

DBPCFC: double-blind, placebo-controlled food challenge; IQR: inter-quartile range; OFC: oral food challenge; OIT: oral immunotherapy; PP: peanut protein; RR: risk ratio

Note: approximate correspondence: 1 peanut = 250 mg peanut protein; 1 mL milk = 30 mg milk protein; 1 egg white=4g egg white protein

*An additional 15 patients continued to receive increasing amounts of cow milk at date of data cut-off (i.e., had not completed the build-up phase).

Data for other food allergies

	Nowak-Wegrzyn, 2019²⁴ (RCT, N=46) -wheat	Kulmala, 2018²⁵ (prospective, single-arm study, N=100) -wheat	Elizur, 2019²⁶ (CCT, N=73)-walnut	Barni, 2019²⁷ (case series, N=43) - hazelnut	Nachshon, 2019²⁸ (CCT) N=75 - sesame
Age	Median, 8.7 years; range, 4.2-22.3	Mean 11.6 years, range, 6.1-18.6	Mean 7.9 years OIT, 6.8 years control; range 4-20	Mean 10 years, range: 5-16	Mean 7.5 years, ≥4, (IQR: 5.8-11.6)
Diagnosis	DBPCFC	Open OFC (not performed in 15 patients with an immediate reaction within the previous 3 months)	OFC, unless an immediate, recent (past year) reaction was documented	OFC	OFC or reaction within past year together with positive skin prick test (SPT) result and/or specific serum IgE (>0.35 kUA/L)
Desensitization	At year 1, 12/23 (52%) low-dose VWG OIT-treated and none of 23 placebo-treated subjects consumed successfully ≥ 4443 mg of WP (primary end point) (P < .0001); median doses successfully consumed were 4443 and 143 mg, respectively. Among placebo-treated subjects who crossed over to high-dose VWG OIT, 12/21 (57%) were desensitized after 1 year (median dose, 7443 mg of WP; nonsignificant vs low-dose VWG OIT).	At the end of the 17-week build-up period, 64% (64/100) patients reached the target dose of 2000 mg /d WP (24 strands of spaghetti). Among the remaining 36 patients (including 23 who had discontinued), the median maximum tolerated dose was 5.5 strands of spaghetti (445 mg WP, range 1–1760) After 3 month maintenance, 47 patients consumed 2000 mg/d WP, 25 consumed a median of 330 mg (range 5–1750) and 5 had discontinued	Passing an OFC with 4000 mg of walnut protein (26-g walnut): 49/55 (89%) patients in the OIT group compared to 0/18 patients in the control group (odds ratio 9.2, 95% CI 4.3–19.5; P<.0001). Nine (50%) control patients began walnut OIT, and 7 (78%) were desensitized to 4000 mg walnut protein All patients who were co-allergic to pecan (n=46) were also desensitized to pecan. Additionally, 18/30 (60%) patients who were co-allergic to hazelnut or cashew, and 14/15 (93%) patients who were co-allergic to hazelnut alone, were either fully desensitized or responded to treatment.	65% (28/43) reached the cumulative dose of 2.5 g hazelnut (0.375 g hazelnut protein) 35% (15/43) ongoing, tolerating a mean dose of 255 mg hazelnut Average time to complete treatment was 5 months (range 3-12)	Full desensitization (4000 mg sesame protein): 88% (53/60) vs 0% (0/15) (median time to achieving maintenance dose was 6.5 (IQR, 3.8-12.8) months) At least partial desensitization (≥ 240 mg sesame protein): 100% (60/60) vs 0% (0/15) Control (eligible, but did not undergo OIT due to non-clinical reasons, eg., long distance from clinic): 0% (0/15)

DBPCFC: double-blind, placebo-controlled food challenge; SCD: successfully consumed dose; VWG: vital wheat gluten

Note: 7 walnuts correspond to approx. 28.3 g (1 ounce serving); 12 hazelnuts correspond to approx. 28.3 g (1 ounce serving), with 1 hazelnut weighting about 2.4 g

Assessment of the quality of evidence

		Risk of bias (Cochrane tool ⁵⁷ for interventional comparative studies; IHE tool ⁵⁸ for case series)	Level of evidence (Oxford Centre for Evidence-based medicine) - adapted using the approach of the European Academy of Allergy and Clinical Immunology ⁵⁹
Peanut	Interventional comparative studies (RCTs, CCTs): Chu meta-analysis (8 RCTs ^{1,2,4-6,42,55} , 1 unpublished)	Low - 8 RCTs of which 5 were rated as being at low risk of bias and 3 as high risk of bias for this outcome*	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series: Soller, 2019 ⁹ , Wasserman, 2019, ⁸ Wasserman, 2014 ⁵⁶	Moderate – 3 case series: 2 with retrospective study design; 1 single center; OFC as outcome in 1 study only	
Egg	Interventional comparative studies (RCTs, CCTs): Romantsik, 2018 ³⁰ meta-analysis (9 RCTs ^{18,19,32,34,35,37,51-53} and 1 CCT ⁵⁴) plus 1 RCT (Martin-Munoz, 2019a ²⁰)	High – All RCTs rated as being at overall high risk of bias by ≥1 analysis	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series	--	
Milk	Interventional comparative studies (RCTs, CCTs): meta-analysis (9 RCTs ^{10,11,33,36,38-41,48} (1 SLIT ⁴⁸) and 4 CCTs ^{43,44,46,47}) plus 1 RCT (De Schryver, 2019 ¹³)	High – meta-analysis: of the 9 RCTs, 5 were rated as being at high risk of bias and 2 at unclear risk of bias; RCT not in meta-analysis- high risk of bias	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series: Levy, 2014 ¹⁴ and Kauppi, 2019 ¹⁵ (clinical practice)	Moderate – 2 case series from clinical practice, main limit: retrospective study design, no OFC as outcome; 1 was conducted at a single center	
Wheat	Interventional comparative studies (RCTs, CCTs): Nowak-Wegrzyn, 2019 ²⁴	Low – 1 RCT	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series: 1 prospective case series in research context (Kulmala, 2018 ²⁵)	Low – 1 prospective case series	
Walnut	Interventional comparative studies (RCTs, CCTs): Elizur, 2019 ²⁶ (CCT, N=73)	High – non-randomized control group,** unblinded	Level II two groups, non-randomized studies
	Case series: NA		
Hazelnut	Interventional comparative studies (RCTs, CCTs): NA	--	Level III: one group non-randomized
	Case series: Barni, 2019 ²⁷ (clinical practice)	High - 1 case series from clinical practice, limits: retrospective study design, single center, unclear recruitment and eligibility criteria	
Sesame	Interventional comparative studies (RCTs, CCTs): Nachshon, 2019 ²⁸	High – non-randomized control group,*** unblinded	Level II two groups, non-randomized studies
	Case series: NA	--	

*Note: Sensitivity analyses that adjusted for risk of bias yielded similar results to the main analysis (Chu et al, 2019³¹).

** Treatment assignment was based on the order in which patients presented at to the clinic, with the first patients starting OIT and the remaining patients being managed by observation and strict dietary exclusion (control group).

*** Controls were patients eligible for OIT but refrained from treatment during the study period for nonmedical reasons, such as a large travel distance to the clinic or previous obligations at the time of their invite to treatment.

Continued allergen food consumption

Data for peanut, milk and egg allergies

LTFU of RCTs (with control arm data)			Large case series (N≥145)		
Jones, 2016⁶⁰ – LTFU of Burks, 2012 (egg)³² Diagnosis confirmed with OFC: no	Hsiao, 2017⁶¹ – LTFU of Tang 2015 (peanut):⁴ Diagnosis confirmed with OFC: no	Meglio, 2017⁶² – LTFU of Meglio 2013 (egg)³⁷ Diagnosis confirmed with OFC (DBPCFC)	Kaupilla, 2019¹⁵ (Finland) – cow’s milk N=295 Age: 5-17 (median 7.5) years Diagnosis confirmed with OFC	Elizur, 2016¹⁶ (Israel) - cow’s milk N=196 Age: >6, mean 10 years Diagnosis confirmed with OFC for patients without an anaphylactic reaction in the preceding year	Nachshon, 2018⁷ (Israel)-peanut* N=145 Age: ≥4 (median 5.8) years Diagnosis confirmed with OFC for patients without an anaphylactic reaction in the preceding year
Patients followed: All patients who started OIT or control therapy Follow-up: Point 1: approx. 5 years after study enrolment; Point 2: 1 year later Completeness of follow-up: OIT: 85% (34/40); placebo: 73% (11/15) at both time points <u>Among patients with follow-up:</u> Eating baked or unbaked egg: At point 1: OIT: 82% (28/34) vs placebo: 36% (4/11), P=.007; At point 2: OIT: 85% (28/33) vs placebo: 67% (8/12), P=.22 Eating baked and unbaked egg: At point 1: OIT: 68% (23/34) vs placebo: 18% (2/11), P=.006; At point 2: OIT: 64% (21/33) vs placebo: 25% (3/12), P=.04 <i>Sensitivity analysis (all lost to FU assumed to avoid):</i> <i>At point 1:</i> <i>OIT: 58% (23/40) vs placebo: 13% (2/15);</i> <i>At point 2: OIT: 53% (21/40) vs</i>	Patients followed: All patients who started OIT or control therapy Follow-up: Mean of 4.2 years (SD 0. 7) from treatment cessation Completeness of follow-up: 77% (OIT: 24/31; placebo: 24/31) of patients <u>Among patients with follow-up:</u> Eating peanuts: OIT: 67% (16/24) vs Control 4.2% (1/24) P=.001 <i>Sensitivity analysis (all lost to FU assumed to avoid):</i> <i>OIT: 52% (16/31) vs Control 3.2% (1/31)</i> Eating peanuts at least weekly: OIT: 46% (11/24) vs Control 4.2% (1/24) P=NR <i>Sensitivity analysis (all lost to FU assumed to avoid):</i> <i>OIT: 35% (11/31) vs Control 3.2% (1/31)</i> Eating > 2000 mg PP:	Patients followed: All patients who started OIT or control therapy Follow-up: Mean of 2.5 (SD 0.3) and 7 (SD 0.9) years after original study start Completeness of follow-up: 2.5 years: 9/10 OIT, 10/10 control; 7 years: 9/10 OIT, 9/10 control <u>Among patients with follow-up:</u> Being able to eat raw and/or cooked egg at least once a week without symptoms: OIT group: 7/9 children (78%) at both time points Control: 2.5-year FU: 3/10 (30%), P<.05; 7-year FU: 3/9 (33%), P=n.s. (2 control children started OIT) <i>Sensitivity analysis (all lost to FU assumed to avoid):</i> <i>OIT: 70% (7/10) vs Control 30% (3/10)</i>	Patients followed: All patients who started OIT Follow-up: median 6.5 years (range 1-11) Completeness of follow-up: 83% (244/295) of patients <u>Among patients with follow-up:</u> Consuming ≥200 mL milk/d: 56% (136/244) – SA: 46% (136/295) Consuming ≥200 mL milk/d with no self-reported milk-related side effects in the last year: 26% (77/244) Consuming <200 mL (10-190 mL) milk/d: 18% (44/244) Avoiding milk consumption: 26% (65/244) of patients Any milk consumption (≥ 10 mL/d): 74% (180/244) <i>Sensitivity analysis (all lost to FU assumed to avoid): 61% (180/295)</i>	Patients followed: Patients who reached full cow milk protein consumption Follow-up: ≥ 6 months after completing build-up phase; median: 24.8 (range 6–41) months Completeness of follow-up: 195/196 (99%) of patients <u>Among patients with follow-up:</u> Consuming ≥ 4.5 g of cow milk protein ≥3 times per week: 93% (181/195) of patients <i>Sensitivity analysis (all lost to FU assumed to avoid): 92% (181/196)</i> Discontinued milk consumption: 7.2% (14/195) of patients	Patients followed: All patients who started OIT Follow-up: ≥ 6 months after completing build-up phase; median: 18 (range 6–75) months Completeness of follow-up: 142/145 (98%) of all patients 130/133 (98%) of patients reaching 3000 mg (n=113) or 300-2400 mg (n=20) PP at end of up-dosing Eating peanuts regularly (≥300 mg peanut protein/d): All patients with follow-up: 113/142 patients (80%) <i>Sensitivity analysis (all lost to FU assumed to avoid): 78% (113/145)</i> Patients who reached maintenance: 87% (113/130) <i>Sensitivity analysis (all lost to FU assumed to avoid): 85% (113/133)</i> Discontinued eating peanuts (among patients who reached maintenance): 17/130 (13%)

LTFU of RCTs (with control arm data)			Large case series (N≥145)		
Jones, 2016⁶⁰ – LTFU of Burks, 2012 (egg)³² Diagnosis confirmed with OFC: no	Hsiao, 2017⁶¹ – LTFU of Tang 2015 (peanut):⁴ Diagnosis confirmed with OFC: no	Meglio, 2017⁶² – LTFU of Meglio 2013 (egg)³⁷ Diagnosis confirmed with OFC (DBPCFC)	Kaupilla, 2019¹⁵ (Finland) – cow's milk N=295 Age: 5-17 (median 7.5) years Diagnosis confirmed with OFC	Elizur, 2016¹⁶ (Israel) - cow's milk N=196 Age: >6, mean 10 years Diagnosis confirmed with OFC for patients without an anaphylactic reaction in the preceding year	Nachshon, 2018⁷ (Israel)- peanut* N=145 Age: ≥4 (median 5.8) years Diagnosis confirmed with OFC for patients without an anaphylactic reaction in the preceding year
<i>placebo: 20% (3/15)</i> 20 OIT patients had demonstrated SU at some point over 4 years of treatment; 18 of them responded to the FU survey and all (100%) reported consumption of all forms of egg at points 1 and 2.	OIT: 52% (12/23) Placebo: 4% (1/24) P=.001 23 OIT patients had demonstrated SU at 18 months of treatment; 20 of them responded to the FU survey. 16/20 (80%) reported regular consumption of peanuts at FU, 1 had discontinued due to taste aversion and 3 failed subsequent DBPCF				Reasons for discontinuation: food aversion (13/17), treatment burden (3/17), heartburn (1/17) Failed OIT (did not reach maintenance dose): 12/142 (8.5%)

PP: peanut protein

Data for other food allergies

	Nowak-Wegrzyn, 2019²⁴ (RCT, N=46) -wheat	Kulmala, 2018²⁵ (prospective, single-arm study, N=100) -wheat	Elizur, 2019²⁶ (CCT, N=73)-walnut	Barni, 2019²⁷ (case series, N=43) - hazelnut	Nachshon, 2019²⁸ (CCT) N=75 - sesame
Age	Median, 8.7 years; range, 4.2-22.3	Mean 11.6 years, range, 6.1-18.6	Mean 7.9 years OIT, 6.8 years control; range 4-20	Mean 10 years, range: 5-16	Mean 7.5 years, ≥4, (IQR: 5.8-11.6)
Diagnosis	DBPCFC	Open OFC (not performed in 15 patients with an immediate reaction within the previous 3 months)	OFC, unless an immediate, recent (past year) reaction was documented	OFC	OFC or reaction within past year together with positive skin prick test (SPT) result and/or specific serum IgE (>0.35 kUA/L)
Long-term follow-up	No data	After 9 month maintenance: 39/100 consumed ≥2000 mg/d WP 18/100 consumed a median of 500 mg (range 83–1000) WP (1-12 strands of spaghetti) 43/100 had discontinued	45 of 56 patients who had been desensitized to walnut had follow-up data (≥ 6 months after end of OIT) and were consuming a daily dose of 1200 mg walnut protein – 70% (45/64) of patients who had initiated OIT	At 1-year follow-up, all patients who had completed treatment continued to consume hazelnut, at a dose of ≤ 2.5 g ≥ 1 time a week, without adverse reactions	Follow-up ≥6 months after reaching the maintenance dose (median 8, range 5.5-34.6) months Completeness of FU: 100% (56/56-4 patients had not yet reached ≥6 months) for regular consumption, 82% (46/56) for OFC Regular consumption (ITT analysis): ≥1200 mg sesame protein : 88% (49/56) ≥480 mg sesame protein : 93% (52/56) OFC with 4000 mg sesame protein: 82% (46/56)

Assessment of the quality of evidence

		Risk of bias (Cochrane tool ⁵⁷ for interventional comparative studies; IHE tool ⁵⁸ for case series)	Level of evidence (Oxford Centre for Evidence-based medicine) - adapted using the approach of the European Academy of Allergy and Clinical Immunology ⁵⁹
Peanut	Interventional comparative studies (RCTs, CCTs) - Hsiao, 2017 ⁶¹	High - 1 LTFU on RCT, limitations: open-label and loss to follow-up	Level II two groups, non-randomized studies
	Case series - Nachshon, 2018 ⁷	Moderate – 1 case series; main limits: single-center, retrospective data collection	
Egg	Interventional comparative studies (RCTs, CCTs) - Jones 2016 ⁶⁰ , Meglio 2017 ⁶²	High - 2 LTFU on RCTs, limitations: open-label and loss to follow-up	Level II two groups, non-randomized studies
	Case series	--	
Milk	Interventional comparative studies (RCTs, CCTs):	--	Level III: one group non-randomized
	Case series: - Kauppila 2019 ¹⁵ , Elizur 2016 ¹⁶	Moderate – 2 large case series; main limits: single-center, retrospective data collection	
Wheat	Interventional comparative studies (RCTs, CCTs)	--	Level III: one group non-randomized
	Case series: 1 prospective case series in research context (Kulmala, 2018 ²⁵)	Low – 1 prospective case series of low risk of bias	
Walnut	Interventional comparative studies (RCTs, CCTs): Elizur, 2019 ²⁶ (CCT, N=73)	High – non-randomized control group,** unblinded	Level II two groups, non-randomized studies
	Case series: NA		
Hazelnut	Interventional comparative studies (RCTs, CCTs): NA	--	Level III: one group non-randomized
	Case series: Barni, 2019 ²⁷ (clinical practice)	High - 1 small case series from clinical practice, limits: retrospective study design, single center, unclear recruitment and eligibility criteria and follow-up	
Sesame	Interventional comparative studies (RCTs, CCTs): Nachshon, 2019 ²⁸	High – single-arm follow-up, unblinded	Level III: one group non-randomized

Sustained unresponsiveness

Data for peanut, milk, egg allergies

Meta-analyses : Nurmatov, 2017²⁹
Ability to safely consume foods containing the allergen in question after discontinuing as assessed in 3 egg RCTs (Burks 2012, ³² Caminiti, 2015, ³⁴ Escudero, 2015, ¹⁸) and 1 milk/egg RCT (Staden, 2007 ⁴¹) with DBPCFC - approx. 88% of patients were treated for egg allergy, period of avoidance was 1-3 months across studies OIT: 34% (36/113) Control: 11% (9/81) RR (Control/OIT)=0.29 (95% CI 0.08, 1.13) P < 0.074 DBPCFC: double-blind controlled food challenge

RCTs (N≥50) not included in meta-analyses

Study	Age (years)	Design	Intervention (N initiated treatment)	Comparator (N initiated treatment)	Allergy confirmed with DBPCFC?	Interval between treatment initiation and SU assessment	Intervening period of allergen avoidance	SU assessment	SU – ITT analysis
Sampson, 2019 [abstract], ⁶³ USA – egg*	Mean 8 (range 3.5–16.8)	RCT	OIT (N=23)	Baked egg products consumption (N=27)	Yes	24 months (2 years)	8-10 weeks	DBPCFC - 7.4 g egg-white protein (1.9 egg whites), cumulative	44% (10/23) vs 11% (3/27), P=.009
Tang, 2015, ⁴ (OIT with probiotic <i>Lactobacillus</i>) Australia – peanut	Mean 6 (SD 2.4)	Double-blind, placebo-controlled RCT	OIT + probiotic (<i>Lactobacillus rhamnosus</i> CGMCC 1.3724) (N=31)	Placebo (N=31)	For a subset of participants	18 months	2-5 weeks	DBPCFC -2 g peanut protein (8 peanuts), cumulative	74% (23/31) vs 3.2% (1/31), P=0.001

**Even though this study was published only as abstract, it was included for the SU endpoint due to scarcity of data on SU (data reporting validated by checking data posted on Clinical trials.gov)*

Note: 1 egg white contains about 4 g of protein; 1 peanut contains about 250 mg of protein

Case series and prospective cohort studies (single arm)

- Wasserman, 2019⁸ (case series, N=270) – peanut: Patients were invited to test for SU if they had ≥ 36 months of maintenance dosing (a total of 105 patients), no ETRs within 2 years, ≥ 90% fall in peanut-specific IgE level or a prechallenge peanut-specific IgE < 1.0 kU/mL. After an avoidance period of 1 month, 19 patients were challenged (including 8 who did not meet these criteria) with 6 g peanut protein (24 peanuts); 74% (14/19) passed – among all patients who had ≥ 36 months of maintenance dosing: **13% (14/105)**
- Vickery, 2014⁶⁴ (prospective cohort studies, age 1-16 years) – peanut: Of the 39 subjects originally enrolled, 12 (31%, 12/39) successfully passed a challenge with 5000 mg of peanut protein one month after stopping OIT.

ADDITIONAL EVIDENCE

Smaller RCTs, CCTs or retrospective case-control studies (ITT analyses)

Study	Design	Food allergen	Intervening period of allergen avoidance	SU – ITT analysis	
				OIT	Comparator
Nagakura, 2018 ⁶⁵ , low-dose OIT	Prospective cohort study with historical control	Peanut	2 weeks	33% (8/24)	Historical controls: 0 (0/23)
Narisety 2015 ⁶⁶	RCT	Peanut	4 weeks	27% (3/11)	SLIT 10% (1/10)
Takahashi, 2016 ⁶⁷	CCT	Milk	2 weeks	21% (7/31) – 1 year 45% (14/31) -2 years	Untreated: 0/17 (1 year)
Vickery, 2017, ⁶⁸ USA age 9-36 months	RCT comparing different maintenance doses with a substudy that retrospectively identified and matched standard of care controls	Peanut	4 weeks	85% (17/20) low dose maintenance 71% (12/17) high dose maintenance, Overall: 78% (29/37)	Historical matched controls: 3.9% (6/154), P<0.001
Yanagida 2016 ⁶⁹ , low-dose OIT	RCT	Egg	2 weeks	71% (15/21) – 1/32 of one whole egg 33% (7/21) - 1/2 of one whole egg	Control: 0 (0/12) for both outcomes

Allergens other than milk, egg and peanut

	Nowak-Wegrzyn, 2019²⁴ (RCT, N=46) -wheat	Kulmala, 2018²⁵ (prospective, single-arm study, N=100) -wheat	Elizur, 2019²⁶ (CCT, N=73)-walnut	Barni, 2019²⁷ (case series, N=43) - hazelnut	Nachshon, 2019²⁸ (CCT) N=75 - sesame
Age	Median, 8.7 years; range, 4.2-22.3	Mean 11.6 years, range, 6.1-18.6	Mean 7.9 years OIT, 6.8 years control; range 4-20	Mean 10 years, range: 5-16	Mean 7.5 years, ≥4, (IQR: 5.8-11.6)
Diagnosis	DBPCFC	Open OFC (not performed in 15 patients with an immediate reaction within the previous 3 months)	OFC, unless an immediate, recent (past year) reaction was documented	OFC	OFC or reaction within past year together with positive skin prick test (SPT) result and/or specific serum IgE (>0.35 kUA/L)
Sustained unresponsiveness	At year 2, 7/23 (30%) low-dose VWG OIT-treated subjects were desensitized to 7443 mg of WP At year 2, 3/23 (13%) low-dose VWG OIT-treated subjects achieved SU 8 to 10 weeks off therapy to (SCD, 7443 mg of WP in DBPCFC)	NA	No data on SU - (45 of 56 patients who had been desensitized to walnut had follow-up data (≥ 6 months after end of OIT) all of them (100%) maintained walnut desensitization for ≥6 months after reaching maintenance (passed OFC with single dose of 4000 mg walnut protein) – 70% (45/64) of patients who had initiated OIT)	NA	NA

DBPCFC: double-blind, placebo-controlled food challenge; SCD: successfully consumed dose; VWG: vital wheat gluten

Note: 7 walnuts correspond to approx. 28.3 g (1 ounce serving); 12 hazelnuts correspond to approx. 28.3 g (1 ounce serving), with 1 hazelnut weighting about 2.4 g

Assessment of the quality of evidence

		Risk of bias (Cochrane tool ⁵⁷ for interventional comparative studies; IHE tool ⁵⁸ for case series)	Level of evidence (Oxford Centre for Evidence-based medicine) - adapted using the approach of the European Academy of Allergy and Clinical Immunology ⁵⁹
Peanut	Interventional comparative studies (RCTs, CCTs) - Tang 2015 ⁴	Low - 1 RCT considered at low risk of bias	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series – Wasserman, 2019 ⁸	High – 1 case series; main limits: single-center, retrospective data collection, only a small proportion of patients was assessed for SU	
Egg	Interventional comparative studies (RCTs, CCTs) – meta-analysis (88% /12% milk): including Burks 2012, ³² Caminiti, 2015, ³⁴ Escudero, 2015, Staden, 2007 ⁴¹) *	Moderate – 4 RCTs, of which at least 2 are considered being at high risk of bias	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series	--	
Milk	Interventional comparative studies (RCTs, CCTs): Takahashi, 2016 ⁶⁷	High – 1 small open-label CCT**	Level II two groups, non-randomized studies
	Case series: - NA	--	
Wheat	Interventional comparative studies (RCTs, CCTs): Nowak-Wegrzyn, 2019 ²⁴	Medium – 1 small RCT with no control data	Level III: one group non-randomized
	Case series: NA	--	
Walnut	Interventional comparative studies (RCTs, CCTs)	--	
	Case series: NA	--	
Hazelnut	Interventional comparative studies (RCTs, CCTs): NA	--	
	Case series: NA	--	
Sesame	Interventional comparative studies (RCTs, CCTs): NA	--	
	Case series: NA	--	

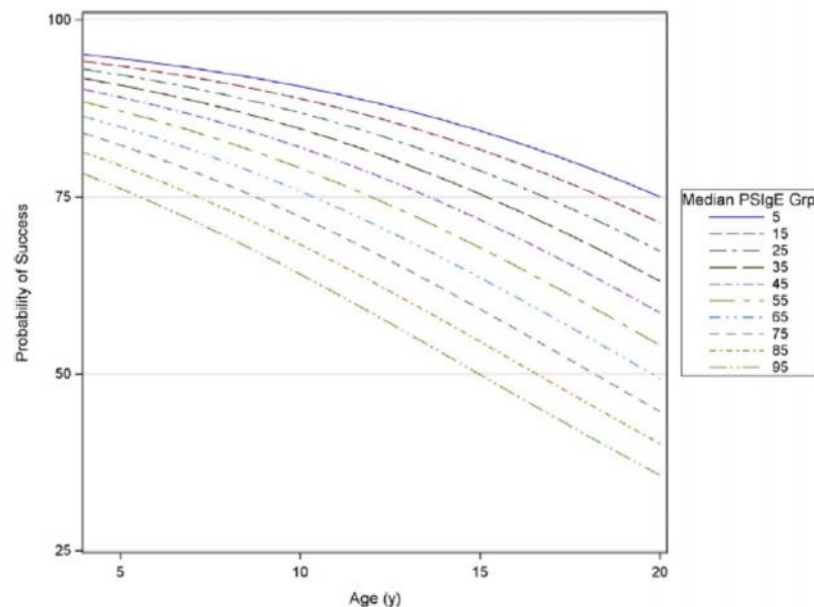
*The quality of the study published in abstract form only (Sampson, 2019⁶³) was not assessed

** The control group were patients who did not want to undergo OIT

Impact of patient characteristics on efficacy outcomes

- Most OIT studies enrolled children and adolescents starting from age 4 to 7 years, with median/mean ages in the range of 6 to 12 years (Anagnostou, 2014;¹ Bird, 2018;⁵ Burks, 2012;³² Elizur, 2016;¹⁶ Escudero, 2015;¹⁸ Fuentes-Aparicio, 2013;¹⁹ Kaupila, 2019;¹⁵ Levy, 2014;¹⁴ Longo, 2008;¹⁰ Martin-Munoz, 2019;²⁰ Nachshon, 2018;⁷ Reier-Nilsen, 2019;³ Vickery, 2018⁶ and Wasserman, 2019⁸). Three studies enrolled peanut-allergic children starting from a younger age, three years (Blumchen, 2019;² Wasserman, 2014⁵⁶) or one year (Tang, 2015⁴). One study enrolled children for milk or egg OIT starting from the age of one year (Morisset, 2007¹²).
- **Older children, adolescents and adults**

- Association between baseline age and likelihood of achieving efficacy outcomes in large case series of children and adolescents (N: 145 to 295):
 - i. Wasserman (2019⁸) reported (based on multivariate analysis) that among a cohort of 270 **4- to 18-year** old children and adolescents with **peanut** allergy (mean age 8.1 years), older age at the initiation of therapy significantly reduced the likelihood of reaching the target maintenance dose by 17% for each year after the age 5 years (odds ratio 0.83 [95% CI 0.75-0.93], $P < .001$) (see figure below).



- ii. Other case series did not find such an association:
 1. Kauppila (2019¹⁵) observed (based on logistic regression analysis) that baseline age (<7 versus ≥7 years) was **not** a statistically significant predictor of treatment failure among 296 patients **5 to 17** years of age (median **7.5**) undergoing **milk** OIT.
 2. Levy (2014¹⁴) reported that among 280 **4- to 27-year** old patients (median **7.5** years) undergoing **milk** OIT there was no difference in median age between those who did or did not achieve the full dose ($P=0.69$).
 3. Nachshon (2018⁷) following 145 patients undergoing **peanut** OIT (age ≥ 4 years, median 5.8, interquartile range: 4.5-7, **88% were between 4 and 10** years old, 4.1% were >18 years old) observed that the 12 patients who failed desensitization were significantly younger than the 133 patients who were partially or fully desensitized (median 4.2 vs 6 yrs).

- A double-blind, placebo-controlled RCT included 169 **adolescents** (age 12 to 17) and 55 **adults** (age 18 to 55) with peanut allergy (Burks, 2018;⁷⁰ Vickery 2018⁶), with the percentage of adults who could tolerate ≥ 600 mg as a single dose being pre-specified as a secondary endpoint. There was no statistically significant difference between the OIT and the placebo groups in reaching this end-point.

Age range (years)	Proportion of patients who tolerated ≥ 600 mg peanut protein as a single dose: OIT versus placebo (n/N) – ITT analysis	Difference between OIT and placebo groups (95% CI)
4 to 11	70.6% (168/238) versus 4.5% (4/89)	66.1% (53.9 to 78.3), $P<0.0001$
12 to 17	61.2% (82/134) versus 2.9% (1/35)	58.3% (39.7 to 76.9), $P<0.0001$
18 to 55	41.5% (17/41) versus 14.3% (2/14)	27.2% (-1.7 to 56.0), $P=0.07$

- Double-blind, placebo-controlled RCT of **adolescents** with peanut allergy (mean age 15 years, range 12-18; age at diagnosis: 3 years) (Fauquert, 2018⁵⁵): Peanut (or placebo) capsules were ingested daily over 24 weeks with increments every 2 weeks from 2 to 400 mg of peanut protein. ITT analysis: at DBPCFC, unresponsiveness to 400 mg of peanut protein was achieved in 81% (17/21) of OIT and 11% (1/9) of placebo patients ($P<0.001$, absolute difference = 0.7, 95%IC 0.43 0.96).
- Case series of 23 **adults** with OFC-confirmed IgE-mediated allergies who were treated with OIT (10 milk, 9 peanut, 4 egg) (Mantyla, 2018⁷¹): The median period of OIT was 515 days. The median dose of protein that could be tolerated increased from baseline 60-fold, 8-fold, and 35-fold in peanut, milk and egg-allergic subjects, respectively.

- **Toddlers and pre-school children:**

- Vickery et al (2017⁶⁸) randomized 37 children aged 9 to 36 months with OFC-confirmed peanut allergy to OIT with a maintenance dose of 300 or 3000 mg peanut protein per day. In the ITT analysis, 81% were desensitized to 20 peanuts (5000 mg peanut protein, OFC). Over a median of 29 months, an overall of 78% (29/37) children achieved a 4-week SU with 5000 mg of peanut protein (20 peanuts) (300 mg arm: 17/20 [85%]; 3000 mg, 12/17 [71%], $P=0.43$. Among 154 retrospectively identified matched control children who received standard care (avoidance), 6 demonstrated SU (3.9%), which was significantly lower than for the OIT group ($P<0.001$).
- Martorell et al (2011¹¹) randomized 60 children aged 24 to 36 months with OFC-confirmed milk allergy to OIT or avoidance. After one year, 90% (27/30) of OIT patients tolerated 200 mL milk compared to 23% (7/30) of control patients.
- Soller et al 2019 (prospective multi-center study) reported that of 270 pre-school children (age 0.75-5.9 years, median 1.9 years) initiating peanut OIT, 243 (90%) reached the maintenance dose of 300-320 mg peanut protein (1.2-1.3 peanuts). ⁹ Of these, 87 patients had had a baseline reaction and an OFC after ~1 year of ingesting ~300mg peanut protein daily and 68 of them passed the OFC (78% = 68/87). For the 19 (21.9%) who reacted at the 1-year OFC, median cumulative dose increased from 12 mg (IQR: 10, 75) at baseline to 4000 mg (IQR: 4000 to 4000) at the 1-year OFC (change from baseline: 3988 mg [IQR: 3920, 3995]). (unpublished data on file from Canadian clinical practice)

Correlations between baseline parameters and OIT efficacy outcomes

Outcomes of RCTs with N≥ 50 that included children with a history of severe reactions:

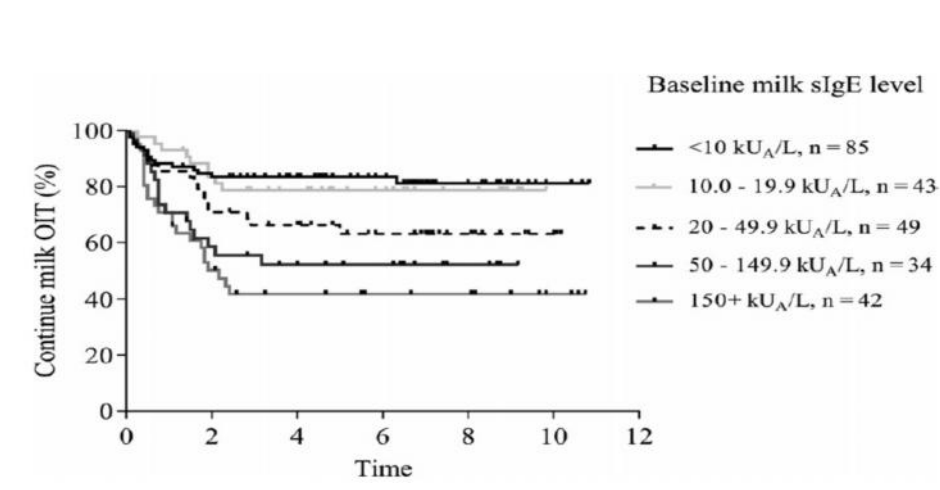
- **Anagnostou, 2014¹ (peanut RCT, N=99, baseline worst clinical reaction WAO score grade 3 or 4: control 22.5% vs active 8.1%): 62% (24/39; 95% CI 45–78)** of patients were desensitized in the active group and none of the control group (0/46; 95% CI 0–9; P<0.001). 84% (95% CI 70–93) of the active group tolerated daily ingestion of 800 mg protein (5 peanuts). Median increase in peanut threshold after OIT was 1345 mg (range 45–1400; P<0.001) or 25.5 times (range 1.82–280; P<0.001).
- **Blumchen, 2019² (peanut, N2=62: 31 OIT, 31 control):** At baseline, 53% of children in the OIT group and 58% in the control group had a history of severe allergic reactions to peanut (grade IV or V⁷²). The median sIgE was 81.5 kU/L (range 0.57-624 kU/L) and the median maximum tolerated single dose at the initial OFC was 30 mg peanut protein (range 1-3,000 mg). At the completion of the maintenance phase, 23/31 patients (**74%**) in the OIT group tolerated ≥ 300 mg peanut protein compared to 5/31 patients (**16%**) in the placebo group (P<.001); 13 (42%) patients in the OIT group tolerated 4.5 g peanut protein vs 1 patient (3.2%) in the placebo group (P<.001).
- **Longo, 2008¹⁰ (milk RCT, N=30 OIT, N=30 control):** Included children with a baseline sIgE level > 85 kUA/L who had a positive history of at least one severe allergic reaction (defined as class 4 and 5 by Clark's classification) after accidental exposure to milk or dairy products requiring emergency treatment. After 1 year, 11/30 (**36%**) children receiving OIT achieved a daily intake of cow's milk of at least 150 mL, **54%** (16/30) were able to consume 5 to 150 mL of milk daily, and 10% (3/30) discontinued due to adverse reactions (respiratory or abdominal). No desensitization was observed in the control group.
- **Martin-Munoz, 2019a²⁰ (egg, RCT N=101 Age: 6-9 years):** Passing DBPCFC at 12 months with 3.3 g pasteurized raw egg white protein (cumulative) or reaching target dose of 3.3 g pasteurized raw egg white egg white protein (equivalent to 1 egg): OIT: **84%** (64/76) Control: **16%** (4/25)
- **Reier-Nilsen, 2019a³ (peanut, N=77: 57 OIT, 20 control):** At baseline, 79% of children had a history of anaphylaxis to peanut and all children reacted with anaphylaxis during the baseline DBPCFC. At the end of the study, **21%** (12/57) of the OIT children reached the maintenance dose of 5000 mg peanut protein, **54%** (31/57) reached a lower maintenance dose (250-4000 mg) and 25% (14/57) had discontinued. The only significant predictor of reaching a maintenance dose was the baseline peanut sIgG4/sIgE ratio (P=0.02).

Large case series

Baseline parameter	Outcome and correlation	Reference
History of anaphylactic reaction	Proportion (n/N) of patients with history of anaphylaxis (n) among all patients achieving the following outcomes (N): • Achieving the full target dose: 64% (102 [with history of anaphylaxis]/160 [all patients achieving this outcome]) • Achieving a partial dose: 91% (60/66) • Did not achieve any cow milk protein consumption: 82% (30/39) (P<0.001)	Levy, 2014 ¹⁴ (milk, N=280)
	In multivariate analysis, history of anaphylaxis was not associated with reaching the maintenance dose.	Wasserman, 2019 ⁸ (peanut, N=270)
Specific IgE serum levels	In logistic regression analysis, treatment failure (< 200 mL milk daily in long-term follow-up) was related to milk sIgE before OIT (P=0.000)	Kauppiila, 2019 ¹⁵ (milk, N=296)

	An increase of 1 KU/L in the pre-treatment peanut-specific IgE level led to a 2% decrease ($P<.001$) in the likelihood of reaching the target dose	Wasserman, 2019 ⁸ (peanut, N=270)
Maximum tolerated dose of food allergen	Starting dose: median 120 mg cow milk protein; range (10-7200 mg). In multivariate logistic regression analysis, the most important independent predictors for achieving the full dose included a maximal tolerated starting dose ≥ 30 mg of cow milk protein (OR: 4.6, $P<.001$).	Levy, 2014 ¹⁴ (milk, N=280)

Kauppila, 2019¹⁵



Wasserman, 2019⁹⁴

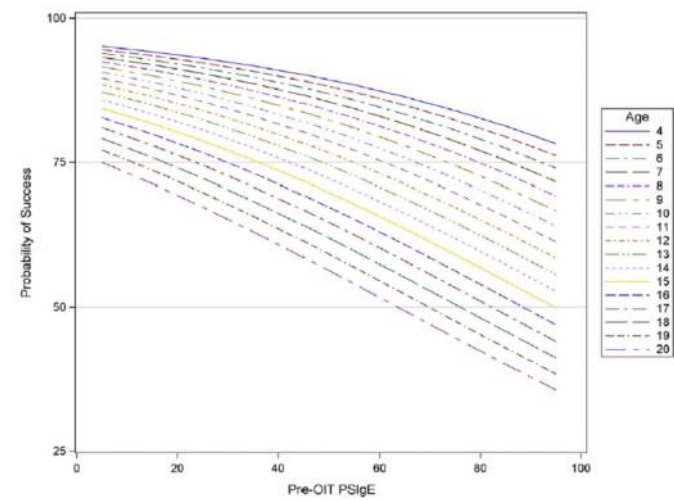


FIGURE 4. The probability of reaching the escalation target based on pretreatment PSigE level and age at the start of therapy.

ADDITIONAL EVIDENCE - RCTs, CCTs and smaller case series

Baseline parameter	Outcome and correlation	Reference
History of anaphylactic reaction	History of anaphylaxis was <u>not</u> a potential predictor of food challenge results at 4 months.	Escudero, 2015 ³² (RCT egg , N=30 OIT, N=31 control)
Specific IgE blood levels	In Tobit regression analysis, the baseline total IgE and the baseline sIgE were associated with the amount of peanut protein tolerated after OIT (P<0.001 for all).	Anagnostou, 2014 ² (RCT peanut , N=49 OIT, N=50 control)
	Desensitization was slower in patients with higher baseline sIgE levels: 9/10 (90%) patients in with sIgE <3.5 kU/L, 7/15 (50%) of patients with sIgE=3.5-17 kU/L, and 3/8 (30%) of patients with sIgE=17-50 kU/L achieved desensitization in < 3 months (P = 0.04).	Garcia-Ara, 2013 ⁴³ (CCT, milk , N=36 OIT; N=19 control)
Maximum tolerated dose of food allergen	In Tobit regression analysis, the amount of peanut protein tolerated at baseline was associated with the amount of peanut protein tolerated after OIT (P<0.001 for all).	Anagnostou, 2014 ² (RCT peanut , N=49 OIT, N=50 control)
	The dose that triggered symptoms at baseline was <u>not</u> a potential predictor of food challenge results at 4 months.	Escudero, 2015 ³² (RCT egg , N=30 OIT, N=31 control)
	Baseline maximum dose allergen dose tolerated on the first day was <u>not</u> predictive of sustained unresponsiveness.	Burks, 2012 ³² (RCT egg , N=40 OIT, N=15 control)

Correlations between baseline asthma status and OIT outcomes

Large case series

Outcome and correlation	Proportion of patients with asthma	Reference
Compared to patients without asthma (N=93), patients with asthma (N= 101) were less likely to reach full desensitization (7200 mg CMP) (52% vs 69%, P =.019). Among patients with asthma, need for controller therapy (initiated before or during OIT) was associated with lower likelihood of reaching full desensitization (P=0.001). Overall, 86% of all patients with asthma (87/101) and ≥ 82% of the sub-group requiring asthma controller therapy reached a dose likely protective against accidental exposure (>180 mg CMP).	101 patients with asthma, 93 no asthma	Elizur, 2015 ⁷³ (milk , N=194)
Baseline asthma was not a statistically significant predictor of treatment failure.	asthma: 73%	Kauppila, 2019 ¹⁵ (milk , N=244)
History of asthma (intermittent, P=.291, or persistent, P = .170) was not a statistically significant predictor of reaching the target dose.	asthma: persistent: 43%, intermittent: 21%	Wasserman, 2018 ⁸ (peanut , N=270)
Although more children with asthma (23%) vs without asthma (5.6%) had a single highest tolerated dose <5 mg peanut protein (P=.003), the two groups were comparable in pre-OIT reaction severity and in the course and outcome of OIT .	asthma: 56/145 [39%], controller therapy before OIT or initiated at the start of OIT: 34/145 [23%], uncontrolled asthma excluded	Nachshon, 2018, ⁷ (peanut , N=145)

Correlations between baseline multiple food allergies single-food OIT outcomes in large case series

Outcome and correlation	Reference
Percent of patients with other food allergies within the following outcome groups: - Achieved the full target dose: 18% - Achieved partial dose: 17% - Did not achieve any cow milk protein consumption: 13%, P=0.42	Levy, 2014 ¹⁴ (milk, N=280)
Other food allergies: - Continued treatment: 49% (47/97) - Stopped treatment: 21% (3/14), P=0.08	Nachshon, 2018 ⁷ (peanut, N=111)

CLINICAL SAFETY

Severe reactions /Systemic reactions/ anaphylaxis / serious adverse events / epinephrine use

Data for peanut, milk, egg allergies

Meta-analyses		
Nurmatov, 2017²⁹ – chicken’s egg, cow’s milk, peanut Absence of systemic reactions as assessed in 4 RCTs ^{34,36,38,42} and 1 CCT: ⁴⁶ - milk/egg/peanut: 61%/21%/19% OIT: 84%% (73/87) Control: 98% (62/63) RR (C/OIT) = 1.16 (95% CI 1.03, 1.30) <i>Proportion of patients with systemic reactions:</i> <i>OIT: 16% (14/87)</i> <i>Control: 1.6% (1/63), P: significant</i>	Romantsik, 2018³⁰ – chicken's egg Proportion of participants with serious AEs (defined as ETR) as assessed in 9 RCTs ^{18,19,32,34,35,37,51-53} and 1 CCT: ⁵⁴ OIT: 8.4% (21/249) Control: 0 (0/190) RR= NA <i>GRADE assessment: low quality of evidence</i>	Chu, 2019³¹ – peanut Proportion of participants with ETRs as assessed in 9 RCTs ^{1-6,42,55,66} OIT: 12% (78/660) Control: 3.7% (12/324) RR= 2.21 (1.27 to 3.83) <i>GRADE assessment (overall certainty of evidence): High</i> Proportion of participants with anaphylaxis as assessed in 9 RCTs ^{1,3-6,42,55,66} (1 unpublished): OIT: 17% (108/653) Control: 2.6% (8/297) RR=3.12 (95% CI 1.76, 5.55) <i>GRADE assessment (overall certainty of evidence): High</i> Proportion of participants with serious AEs* as assessed in 9 RCTs ^{1-6,42,55,66} (3 unpublished) OIT: 6.2% (43/699) Control: 3.0% (10/338) RR=1.92 (95% CI 1.00, 3.66) <i>GRADE assessment (overall certainty of evidence): Moderate</i> <i>Re-analysis to correct misclassification: see section 8.2</i> OIT: 21/699 (3.0%) Control: 11/338 (3.3%)

ELORS: eosinophilic esophagitis-like oral immunotherapy- related syndrome; ETR: epinephrine-treated reaction; DBPCFC: double-blind placebo-controlled food challenge; RR: risk ratio (random effects model)
*Serious adverse events defined by US FDA as: causing death, a life-threatening state, hospitalization, disability, congenital abnormality, or an important medical event such as an urgent intervention to prevent the other outcomes) and if they caused treatment discontinuation

Case series with N> 150

Levy, 2014¹⁴ (Israel)– cow’s milk N=265 Age: 4-27 (7.5 median) years Diagnosis confirmed with OFC: not for all patients	Kaupilla, 2019¹⁵ (Finland) – cow’s milk N=295 Age: 5-17 (median 7.5) years Diagnosis confirmed with OFC: yes	Soller, 2019⁹ (Canada) – peanut N=270 Age: 0.75-5.9 (median 1.9, IQR : 1.25-2.75) years Diagnosis confirmed with OFC: for 31% of patients	Wasserman, 2019⁸ (USA) – peanut N=270 Age: 4-18 (mean: 8.1) years Diagnosis confirmed with OFC: no	Wasserman, 2014⁵⁶ (USA and Israel)-peanut N=352 Age: 3-24 years Diagnosis confirmed with OFC: 97% of patients
Follow-up: ≥ 10 months after start of OIT ETRs during induction cycles (in clinic): 48% (128/265) of patients ETRs during home-dosing phase: 17% (44/265) of patients (58 ETRs per 77,098 doses= 0.08%) % of ETRs at home= 58/186=31% SEAs: not reported	Follow-up: median 6.5 (range 1-11) years after start of OIT Anaphylaxis at least once <u>after build-up phase</u>: 14% (34/237)- data missing from 59/295 patients Possible SEAs: One extremely severe anaphylaxis occurred in a patient after consumption of milk yogurt with a high concentration of cow's milk protein (8 g/100 mL), while he was on the aimed maintenance dose	Follow-up: median 20.0 weeks (build-up only) Possible SAE: Grade 4 (severe symptoms) (respiratory failure or hypotension or profound lethargy): 0.4% (1/270) (1 per 2,321 doses administered in the office=0.04%) ETR during <u>build-up phase</u>: 4.1% (11/270) of patients (12 ETRs per 41,020 doses = 0.029% of doses with ETR) ETRs during in-office build-up: 6 per 2,321 doses = 0.26% ETRs during home dosing build-up: 6 per 38,699 doses = 0.016% 50% of ETRs occurred at home 1.1% (3/270) of patients visited emergency departments for AEs, all of which were Grade 2. Grading according to Cox 2010⁷⁴ (modified)	Follow-up: ≥ 1 month after reaching maintenance and up to 8 years ETRs during <u>build-up phase</u>: 23% (63/270) of patients (100 ETRs in total [37%] occurred in clinic) SAEs: 5 of 100 ETRs required 2 epinephrine doses and 2 required 3 doses; no ETR required > 3 epinephrine doses or intravenous fluids ETRs during <u>maintenance phase</u>: 13% (28/214) of patients (63 ETRs in total, 40% occurred during the first 6 months) - sub-group: patients treated for ≥ 3 years of maintenance: 17% (18/105) (43 ETRs) Incidence of ETRs during maintenance phase: 9.9/100 patient-years	Follow-up: from a few weeks to >7 after reaching maintenance ETRs during <u>build-up phase</u>: 10% (36/352) of patients (57 ETRs per 79,726 doses = 0.07% of doses with ETR - <i>corresponds to 26.1 ETRs per 100 patient-years, assuming 1 dose per day</i>) ETRs during <u>maintenance phase</u>: 6.4% (19/298) of patients (38 ETRs per 160,265 doses, 0.02% - <i>corresponds to 8.7 ETRs per 100 patient-years, assuming 1 dose per day</i>) Proportion of all ETRs that occurred in clinic: 29% (28/95) Possible SAEs: 3 patients received 2 doses of epinephrine for a single ETR; no patient required intravenous fluids for hypotension or other manifestations of shock.

RCTs with N>50 not included in meta-analyses

Martin-Munoz, 2019a²⁰ (Spain) – chicken’s egg N (OIT)=76 (88 including cross-over) Age: 6-9 years Diagnosis confirmed with OFC: yes	De Schryver, 2019¹³ (Canada) – cow’s milk N (OIT) = 26 (41 including cross-over), 26 control (4 of them withdrew) Age: 6-18, mean 12.1 years Diagnosis confirmed with OFC: yes (single-blind)
<i>Data from non-comparative phase:</i> ETRs during build-up phase: OIT: 8.0% (7/88) of patients Control: NR Grade 4 dosing adverse reactions during build-up phase: OIT: 9.2% (7/76) of patients (15 DARs per 8448 doses, 0.2%) Control: NR Grade 4 dosing adverse reactions during maintenance phase: OIT: 1.3% (1/76) of patients (1 reaction) Control: NR No patient had moderate or severe adverse reactions because of egg consumption once they had finished the OIT. Possible SAEs: <u>Build-up phase:</u> No patient developed dysrhythmia and/or severe hypotension, hypovolemic shock, laryngeal edema, or respiratory or cardiac arrest <u>Maintenance phase:</u> One patient developed a grade 4 reaction after 2 months on maintenance after stopping OIT for 4 days due to intercurrent illness. Grading according to Sampson 2003⁷⁵	<i>Data from comparative phase (first year of study):</i> Anaphylactic allergic reactions (multi-organ reaction or hypotension): OIT (N=26): mean 5.5 reactions per patient Control (N=22): 2 moderate reactions per 22 patients (mean 0.1 per patient) ETRs: OIT (N=26): mean 0.5 per patient (SD 0.9) Control (N=22): 2/22 patients (mean 0.1 per patient) <i>Data from non-comparative phase:</i> Anaphylaxis: OIT (N=41): Number of anaphylactic reactions per patient: mean 6.0 (245 reactions per 41 patients), median 4 (range 0-21, IQR 1-10, SD 3.5) Severe anaphylactic reactions: OIT (N=41): 2 severe anaphylactic reactions in 2 patients: 4.9% (2/41) of patients ETRs: OIT (N=41): mean 0.6 per patient (SD 1.2) Grading according to Muraro 2007⁷⁶

Allergens other than milk, egg and peanut

	Nowak-Wegrzyn, 2019²⁴ (RCT, N=46) -wheat	Kulmala, 2018²⁵ (case series, N=100) -wheat	Elizur, 2019²⁶ (CCT, N=73)-walnut	Barni, 2019 (case series, N=43) -hazelnut	Nachshon, 2019²⁸ (CCT) N=75 -sesame
Age	Median, 8.7 years; range, 4.2-22.3	Mean 11.6 years, range, 6.1-18.6	Mean 7.9 years OIT, 6.8 years control; range 4-20	Mean 10 years, range: 5-16	Mean 7.5 years, ≥4, (IQR: 5.8-11.6)
Diagnosis	DBPCFC	Open OFC (not performed in 15 patients with an immediate reaction within the previous 3 months)	OFC, unless an immediate, recent (past year) reaction was documented	OFC	OFC or reaction within past year together with positive skin prick test (SPT) result and/or specific serum IgE (>0.35 kUA/L)
Adverse reactions	Among 7822 low-dose OIT doses in year 1, 15% were associated with adverse reactions: 0.04% were	Allergic symptoms occurred in 94/100 children: mild in 34, moderate in 36 and severe in 24 (24%). 12 patients	47/55 (85%) patients had an adverse reaction (mostly Grade 1 or 2) during up-dosing in the clinic and 40 (73%)	20/43 patients (46.5%) had no reactions and 23/43 patients had a total of 55 reactions: 34 (61.8%) oral	<u>Build-up phase:</u> Adverse reactions occurred in 127 of 2,720 (4.7%) induction doses and 253

	severe, and 0.08% (were ETRs. Among 7921 placebo doses, 5.8% were associated with adverse reactions; none were severe. SAEs: Low-dose OIT: 2/23 (including 1 patient who was not randomized) Placebo: 5/23	(12%) had 13 ETRs % of patients with severe reactions by phase: Build-up (17 weeks – 3.3 months): 14% (14/100) Maintenance 1 (3 months): 7.8% (6/77) Maintenance 2 (9 months): 8.3% (6/72) Severe reactions were defined as objective respiratory symptoms, such as extensive coughing, inspiratory stridor or expiratory wheezing, and cardiovascular symptoms such as unconsciousness, lethargy, collapse, drop in blood pressure or tachycardia, alone or in combination with other symptoms. During the study, only bronchial wheezing, coughing, and laryngeal stridor occurred; no patient experienced a drop in blood pressure or cardiovascular collapse.	during the home-dosing phase The reactions were mostly mild (Grade 1 or 2) and occurred in response to 109 (4%) of the doses in clinic and 244 (2%) of home doses ETRs: 11 (20%) during the in-hospital study phase and 8 patients had an ETR in response to a dose at home. During the maintenance phase, 1/45 patients had 1 ETR No severe reactions ($\geq$ grade 3) were recorded during the study.	allergy syndrome, 8 (14.5%) rash, 6 (10.9%) abdominal pain, 2 (3.6%) urticaria, 2 (3.6%) angioedema, and 3 (5.4%) dyspnea	of 13,170 (2%) home doses ETR during the hospital build-up phase: 10 patients (16.7%) for 13/127 (9.4%) reactions ETR during home treatment: 5 patients (8.3%) for 7/ 253 (2.8%) reactions. No reactions worse than Grade I or II (WAO) occurred <u>Maintenance phase:</u> No ETR Grading according to Cox 2010⁷⁴ (modified)
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ETR: epinephrine-treated reaction; DBPCFC: double-blind, placebo-controlled food challenge; SCD: successfully consumed dose; VWG: vital wheat gluten

Assessment of the quality of evidence

		Risk of bias (Cochrane tool ⁵⁷ for interventional comparative studies; IHE tool ⁵⁸ for case series)	Level of evidence (Oxford Centre for Evidence-based medicine) - adapted using the approach of the European Academy of Allergy and Clinical Immunology ⁵⁹
Peanut	Interventional comparative studies (RCTs, CCTs): meta-analysis (8 RCTs ^{1,2,4-6,42,55} , 1 unpublished)	Low - 9 RCTs of which 8 rated as being at overall low risk of bias for ETRs and anaphylaxis	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series: Soller, 2019 ⁹ , Wasserman, 2019, ⁸ Wasserman, 2014 ⁵⁶	Moderate – 3 case series: 2 with retrospective study design	
Egg	Interventional comparative studies (RCTs, CCTs): Romantsik, 2018 ³⁰ (9 RCTs ^{18,19,32,34,35,37,51-53} and 1 CCT ⁵⁴)	High – 10 RCTs of which all were rated as being at overall high risk of bias by ≥1 analysis	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series	--	
Milk/egg/peanut	Interventional comparative studies (RCTs, CCTs): meta-analysis (4 RCTs ^{34,36,38,42} and 1 CCT)	Moderate – RCTs (3 low, 1 high risk of bias) and 1 CCT (moderate risk of bias)	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
Milk	Interventional comparative studies (RCTs, CCTs): 1 RCT (De Schryver, 2019 ¹³)	High – unblinded, 4 control patients withdrew	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series: Levy, 2014 ¹⁴ and Kauppila, 2019 ¹⁵ (clinical practice)	Moderate – 2 case series, main limit: retrospective study design	
Wheat	Interventional comparative studies (RCTs, CCTs): Nowak-Wegrzyn, 2019 ²⁴	Low – 1 RCT	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series: 1 prospective case series in research context (Kulmala, 2018 ²⁵)	Low – 1 prospective case series	
Walnut	Interventional comparative studies (RCTs, CCTs): Elizur, 2019 ²⁶ (CCT, N=73)	High – non-randomized control group,** unblinded	Level II (two groups, non-randomized studies)
	Case series: NA	--	
Hazelnut	Interventional comparative studies (RCTs, CCTs): NA	--	Level II (two groups, non-randomized studies)
	Case series: Barni, 2019 ²⁷ (clinical practice)	High - 1 case series from clinical practice, limits: retrospective study design, single center, unclear recruitment and eligibility criteria	
Sesame	Interventional comparative studies (RCTs, CCTs): Nachshon, 2019 ²⁸	High – non-randomized control group,*** unblinded	Level II (two groups, non-randomized studies)
	Case series: NA	--	

Any adverse reactions / any allergic reactions / local reactions

Data for peanut, milk and egg allergy

Meta-analyses			RCT with N>50		Case series with N> 150		
Nurmatov, 2017 ²⁹ – chicken’s egg and cow’s milk	Romantsik, 2018 ³⁰ – chicken’s egg	Chu, 2019 ³¹ – peanut	Martin-Munoz, 2019 ^{20,21} – chicken’s egg	De Schryver, 2019 ¹³ (Canada) – cow’s milk N (OIT) = 26 (41 including cross-over), 26 control (4 of them withdrew) Age: 6-18, mean 12.1 years Diagnosis confirmed with OFC: yes (single-blind)	Levy, 2014 ¹⁴ (Israel)– cow’s milk N=265 Age: 4-27 (7.5 median) years Diagnosis confirmed with OFC: not for all patients	Wasserman, 2019 ⁸ (USA) – peanut N=270 Age: 4-18 (mean: 8.1) years Diagnosis confirmed with OFC: no	Soller, 2019 ⁹ (Canada) – peanut N=270 Age: 0.75-5.9 (median 1.9, IQR : 1.25-2.75) years Diagnosis confirmed with OFC: for 31% of patients
Absence of local reactions as assessed in 6 RCTs ^{11,12,32,34,37,38} and 1 CCT: ⁴⁶ (Fig S21) - egg/milk: 61%/39% OIT: 49% (89/183) Control: 98% (133/136) RR (C/OIT) = 2.14 (95% CI 1.47, 3.12) <i>Proportion of patients <u>with</u> local reactions:</i> OIT: 51% (94/183) Control: 2.2% (3/136), P: significant	Number of participants with mild to severe AEs as assessed in 9 RCTs ^{18,19,32,34,35,37,51-53} and 1 CCT: ⁵⁴ OIT: 75% (187/249) Control: 6.8% (13/190) RR (OIT/C) = 8.35 (95% CI 5.31, 13.12) <i>GRADE assessment: low quality of evidence</i>	Vomiting ^{††} as assessed in 6 RCTs ^{2,4-6} (2 unpublished): OIT: 39% (201/519) Control: 19% (44/236) RR=1.79 (95% CI 1.35, 2.38) <i>GRADE assessment (overall certainty of evidence): High</i> Angioedema ^{††} as assessed in 5 RCTs: ⁴⁻⁶ (2 unpublished) OIT: 10% (51/489) Control: 3.9% (8/205) RR=2.25 (95% CI 1.13, 4.47) <i>GRADE assessment (overall certainty of evidence): High</i> Nasal congestion or blockage ^{§§} as assessed in 6 RCTs: ^{4-6,55} (2 unpublished) OIT: 29% (149/510) Control: 18% (38/214) RR=1.36 (95% CI 1.02, 1.81) <i>GRADE assessment (overall certainty of evidence): Moderate</i> Any allergic/adverse	Dose-adverse reactions (DARs): OIT: 87% (66/76) Control: 32% (8/25) P<.001 DARs decreased in number and severity throughout the OIT and throughout the study (P < 0.05). DARs during build-up phase: OIT: 91% (67/76) of patients (420 DARs per 8448 doses, 4.9%) Control: NR DARs during maintenance phase: OIT: 71% (54/76) of patients (87 DARs) Control: NR	No comparative data for non-anaphylactic reactions	Frequency of reactions during home-dosing phase which were <u>not</u> treated: OIT: 0.6% (476 reactions per 77,098 doses) Frequency of reactions during home-dosing phase which were <u>treated</u> with an antihistamine or a bronchodilator: OIT: 1.2% (960 reactions per 77,098 doses)	Proportion of patients who reported reactions that did <u>not</u> require epinephrine use: OIT: 58% (157/270) patients (330 reactions)	≥ 1 allergic reaction during buildup phase: 68% (183/270) Grade 1 (mild) symptoms: 36% Grade 2 (moderate) symptoms: 31% Number of allergic reactions per patient: 1.99 (=538/270)

Meta-analyses			RCT with N>50		Case series with N> 150		
Nurmatov, 2017 ²⁹ – chicken’s egg and cow’s milk	Romantsik, 2018 ³⁰ – chicken’s egg	Chu, 2019 ³¹ – peanut	Martin-Munoz, 2019 ^{20,21} – chicken’s egg	De Schryver, 2019 ¹³ (Canada) – cow’s milk N (OIT) = 26 (41 including cross-over), 26 control (4 of them withdrew) Age: 6-18, mean 12.1 years Diagnosis confirmed with OFC: yes (single-blind)	Levy, 2014 ¹⁴ (Israel)– cow’s milk N=265 Age: 4-27 (7.5 median) years Diagnosis confirmed with OFC: not for all patients	Wasserman, 2019 ⁸ (USA) – peanut N=270 Age: 4-18 (mean: 8.1) years Diagnosis confirmed with OFC: no	Soller, 2019 ⁹ (Canada) – peanut N=270 Age: 0.75-5.9 (median 1.9, IQR : 1.25-2.75) years Diagnosis confirmed with OFC: for 31% of patients
		reaction: 86% OIT (N=639) vs 61% control (N=278), RR=1.34 (1.12 to 1.60)					

††Similar findings for abdominal pain, mouth itching, and any allergic or adverse reaction. ‡‡Similar findings for urtica . §§ Similar findings for asthma attack or wheeze

Allergens other than milk, egg and peanut

	Nowak-Wegrzyn, 2019 ²⁴ (RCT, N=46) -wheat	Kulmala, 2018 ²⁵ (case series, N=100) -wheat	Elizur, 2019 ²⁶ (CCT, N=73)-walnut	Barni, 2019 (case series, N=43) - hazelnut	Nachshon, 2019 ²⁸ (CCT) N=75 - sesame
Age	Median, 8.7 years; range, 4.2-22.3	Mean 11.6 years, range, 6.1-18.6	Mean 7.9 years OIT, 6.8 years control; range 4-20	Mean 10 years, range: 5-16	Mean 7.5 years, ≥4, (IQR: 5.8-11.6)
Diagnosis	DBPCFC	Open OFC (not performed in 15 patients with an immediate reaction within the previous 3 months)	OFC, unless an immediate, recent (past year) reaction was documented	OFC	OFC or reaction within past year together with positive skin prick test (SPT) result and/or specific serum IgE (>0.35 kUA/L)
Adverse reactions	Among 7822 low-dose OIT doses in year 1, 15% were associated with adverse reactions: 0.04% were severe, and 0.08% (were ETRs. Among 7921 placebo doses, 5.8% were associated with adverse reactions; none were severe. SAEs: Low-dose OIT: 2/23 (including 1 patient who was not randomized) Placebo: 5/23	Allergic symptoms occurred in 94/100 children: mild in 34, moderate in 36 and severe in 24 (24%). 12 patients (12%) had 13 ETRs % of patients with severe reactions by phase: Build-up: 14% (14/100) Maintenance 1 (3 months): 7.8% (6/77) Maintenance 2 (9 months): 8.3% (6/72)	47/55 (85%) patients had an adverse reaction (mostly grade 1 or 2) during up-dosing in the clinic and 40 (73%) during the home-dosing phase The reactions were mostly mild (grade 1 or 2) and occurred in response to 109 (4%) of the doses in clinic and 244 (2%) of home doses ETRs: 11 (20%) during the in-hospital study phase and 8 patients had an ETR in response to a dose at home. During the maintenance phase, 1/45	20/43 patients (46.5%) had no reactions and 23/43 patients had a total of 55 reactions: 34 (61.8%) oral allergy syndrome, 8 (14.5%) rash, 6 (10.9%) abdominal pain, 2 (3.6%) urticaria, 2 (3.6%) angioedema, and 3 (5.4%) dyspnea	<u>Build-up phase:</u> Adverse reactions occurred in 127 of 2,720 (4.7%) induction doses and 253 of 13,170 (2%) home doses ETR during the hospital build-up phase: 10 patients (16.7%) for 13/127 (9.4%) reactions ETR during home treatment: 5 patients (8.3%) for 7/ 253 (2.8%) reactions. No reactions worse than grade I or II

			patients had 1 ETR No severe reactions ($\geq$ grade 3) were recorded during the study.		(WAO) occurred <u>Maintenance phase:</u> No ETR Grading according to Cox 2010⁷⁴ (modified)
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ETR: epinephrine-treated reaction; DBPCFC: double-blind, placebo-controlled food challenge; SCD: successfully consumed dose; VWG: vital wheat gluten

Assessment of the quality of evidence

		Risk of bias (Cochrane tool ⁵⁷ for interventional comparative studies; IHE tool ⁵⁸ for case series)	Level of evidence (Oxford Centre for Evidence-based medicine) - adapted using the approach of the European Academy of Allergy and Clinical Immunology ⁵⁹
Peanut	Interventional comparative studies (RCTs, CCTs): meta-analysis (Chu, 2019 ³¹)	Low	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series: Soller, 2019 ⁹ , Wasserman, 2019 ⁸	Low – 2 case series, of which 1 had a low and the other a moderate risk of bias	
Egg	Interventional comparative studies (RCTs, CCTs): Romantsik, 2018 ³⁰ (9 RCTs ^{18,19,32,34,35,37,51-53} and 1 CCT ⁵⁴) plus 1 RCT (Martin-Munoz, 2019 ^{20,21})	High —RCTs overall rated as being at high risk of bias	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series	--	
Egg / milk: 61%/39%	Interventional comparative studies (RCTs, CCTs): meta-analysis: 6 RCTs ^{11,12,32,34,37,38} and 1 CCT ⁴⁶	Moderate – of the 6 RCTs in the meta-analysis, 3 low, 2 high, and 1 unclear risk of bias) plus 1 CCT	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
Milk	Interventional comparative studies (RCTs, CCTs): NA	--	Level III: one group non-randomized
	Case series: Levy, 2014 ¹⁴ (clinical practice)	Moderate – 1 case series, main limit: retrospective study design	
Wheat	Interventional comparative studies (RCTs, CCTs): Nowak-Wegrzyn, 2019 ²⁴	Low – 1 RCT	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series: 1 prospective case series in research context (Kulmala, 2018 ²⁵)	Low – 1 prospective case series	
Walnut	Interventional comparative studies (RCTs, CCTs): Elizur, 2019 ²⁶ (CCT, N=73)	High – non-randomized control group,** unblinded	Level II (two groups, non-randomized studies)
	Case series: NA	--	
Hazelnut	Interventional comparative studies (RCTs, CCTs): NA	--	Level II (two groups, non-randomized studies)
	Case series: Barni, 2019 ²⁷ (clinical practice)	High - 1 case series from clinical practice, limits: retrospective study design, single center, unclear recruitment and eligibility criteria	
Sesame	Interventional comparative studies (RCTs, CCTs): Nachshon, 2019 ²⁸	High – non-randomized control group,*** unblinded	Level II (two groups, non-randomized studies)

	Case series: NA	--	
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Discontinuations due to adverse events

Data for peanut, milk and egg allergy

Meta-analyses : Chu, 2019 ³¹ – peanut	RCT with N> 50 not included in meta-analysis	Case series with N> 150		
		Levy, 2014 ¹⁴ (Israel)– cow’s milk N=280* Age: 4-27 (7.5 median) years Diagnosis confirmed with OFC: not for all patients	Kaupilla, 2019 ¹⁵ (Finland) – cow’s milk N=295 Age: 5-17 (median 7.5) years Diagnosis confirmed with OFC: yes	Wasserman, 2019 ⁸ (USA) – peanut N=270 Age: 4-18 (mean: 8.1) years Diagnosis confirmed with OFC: no
Discontinuations due to AEs as assessed in 9 RCTs ^{1-6,42,55,66} (3 unpublished): OIT: 12% (87/699) Control: 2.4% (8/338) RR=2.55 (95% CI 1.20, 5.42) <i>GRADE assessment (overall certainty of evidence): high</i>	<u>Martin-Munoz, 2019^{20,21} - egg</u> Discontinuations due to AEs during <u>build-up phase</u> : OIT: 18% (16/88) Control: not reported <u>Maintenance phase</u> : not clear <u>Burks, 2012¹⁷ - egg :</u> <u>Before maintenance</u> : OIT: 13% (5/40) (4 allergic reaction, 1 anxiety) Placebo: 6.7% (1/15) (1 allergy symptoms) <u>During maintenance</u> : OIT: 2.9% (1/35) (allergic reactions) (no maintenance for placebo) <u>Overall: 15% (6/40) <u>Escudero, 2015¹⁸ - egg</u> OIT: 6.7% (2/30) (persistent mild reactions) Control: 0/31 <u>Fuentes-Aparicio, 2013¹⁹ – egg :</u> OIT: 7.5% (3/40) (persistent GI symptoms, including a case of confirmed EOE) Control: 0/32 <u>Morisset, 2007¹² – milk :</u> OIT : 7.1% (2/28) Control : 0/32</u>	Follow-up: ≥ 10 months after start of OIT Total discontinuations due to AEs or treatment failure: 9.6% (27/280): Primary failures (stopped OIT during the 1st week): 1.8% (5/280) (3 extreme sensitivity, 2 parental or psychological reasons-not AE) Recurrent anaphylaxis: 5.7% (16/280, 59% [16/27 of all]) GI symptoms with peripheral blood eosinophilia: 2.9% (8/280) Food aversion: 3.6% (10/280, percent of patients who discontinued after 1 st week: 45% [10/22]) Total discontinuations: 14% (39/280)	Follow-up: median 6.5 (range 1-11) years after start of OIT Over median FU of 6.5 years 24% (71/295) of patients discontinued OIT (data missing from 15% [44/295] of patients) GI symptoms were the most common self-reported reason for discontinuation: 16% (41/252), 58% (41 of 71 discontinuations) Other reasons: cutaneous (34/71, 48%), respiratory (24/71, 34%), anaphylaxis (22/71, 31% - 7.5% of 295), oropharyngeal (21/71, 30%), food aversion (7/71, 10%), ocular (5/71, 7%), lack of progress (4/71, 6%), and miscellaneous (8/71, 11%).	Follow-up: ≥ 1 month after reaching maintenance and up to 8 years <u>Build-up phase</u> Loss to FU: 2.0% (6/270) Discontinuations, total: 16% (42/270) ETR: 3.0% (8/270, 19% of discontinuations) ELORS: 7.8% (21/270, 50% of discontinuations) Other AEs: 1.9% (5/270, 12% of discontinuations) Total discontinuations due to AEs: 13% (34/270, 81% of discontinuations) Food aversion: 0.7% (2/270, 4.8% of discontinuations) Other (anxiety, burden of care, perception, sibling with OIT): 2.2% (6/270, 14% of discontinuations) <u>Maintenance phase</u> Loss to FU: 15% (33/214) Discontinuations, total: 12% (25/214) of patients (- sub-group: patients treated for ≥ 3 years of maintenance: 11% [12/105]) ETR: 1.4% (3/214, 12% of discontinuations) ELORS: 0.5% (1/214, 4.0% of discontinuations) Other AEs: 1.9% (4/214, 16% of discontinuations) Total discontinuations due to AEs:

Meta-analyses : Chu, 2019 ³¹ – peanut	RCT with N> 50 not included in meta-analysis	Case series with N> 150		
		Levy, 2014 ¹⁴ (Israel)– cow’s milk N=280* Age: 4-27 (7.5 median) years Diagnosis confirmed with OFC: not for all patients	Kauppila, 2019 ¹⁵ (Finland) – cow’s milk N=295 Age: 5-17 (median 7.5) years Diagnosis confirmed with OFC: yes	Wasserman, 2019 ⁸ (USA) – peanut N=270 Age: 4-18 (mean: 8.1) years Diagnosis confirmed with OFC: no
				3.7% (8/214, 32% of discontinuations) Food aversion: 5.1% (11/214, 44% of discontinuations) Other (perception, irregular dosing, failed SU): 2.8% (6/214, 24% of discontinuations) Incidence of discontinuations: 3.9/100 patient-years Discontinuations due to AEs in both phases combined: 42/270=17.5%

* At date of data cut-off, 15 patients continued to receive increasing amounts of cow milk (i.e., have not completed the build-up phase).

Allergens other than milk, egg and peanut

	Nowak-Wegrzyn, 2019 ²⁴ (RCT, N=46) -wheat	Kulmala, 2018 ²⁵ (case series, N=100) -wheat	Elizur, 2019 ²⁶ (CCT, N=73)-walnut	Barni, 2019 (case series, N=43) - hazelnut	Nachshon, 2019 ²⁸ (CCT) N=75 - sesame
Age	Median, 8.7 years; range, 4.2-22.3	Mean 11.6 years, range, 6.1-18.6	Mean 7.9 years OIT, 6.8 years control; range 4-20	Mean 10 years, range: 5-16	OFC or reaction within past year together with positive skin prick test (SPT) result and/or specific serum IgE (>0.35 kUA/L)
Discontinuations	11/46 (24%) subjects discontinued the study: 1 subject in the low-dose VWG OIT group discontinued after completing the year 2 OFC, 6 subjects discontinued the study before week 52 and were counted as failures for the primary end point; 4 in the active VWG OIT arm (3 because of dosing-related symptoms and 1 because of	Total: 43% (43/100) Build-up: 23/100 (23%) – dropouts due to severe reaction: 7.0% (7/100) (14 had severe reaction) Maintenance phase 1 (3 months): 6.5% (5/77) – dropouts due to severe reaction: 1/77 (1.3%) (6 had severe reaction) Follow-up (maintenance phase 2: 9 months): 21% (15/72) – dropouts due to severe reaction: 1/72 (1.4%) (6 had	one patient of those who had an ETR discontinued 1.8% (1/55)	Not reported	<u>Build-up phase:</u> No discontinuation <u>Maintenance phase:</u> No discontinuation due to AEs (2 discontinued because of treatment burden, 2 because of food aversion)

	participant's decision) and 2 in the placebo arm (1 because of participant's decision and 1 because of nonadherence). In addition, in the high-dose crossover group 2 subjects discontinued participation because of dosing symptoms (1 was given a diagnosis of both ulcerative colitis and EoE) and 1 because of nonadherence. Discontinuation due to AEs in low-dose VWG during the build-up phase: 3/23 (13%) OIT vs 0 placebo In maintenance phase: 1/19 (5.3%)	severe reaction) Combining both maintenance phases: 26% (20/77) – dropouts due to severe reaction: 2/77 (2.6%) (6 had severe reaction) 34/ 43 (79%) had objective or objective and subjective symptoms and 8/43 (16%) only had subjective symptoms			
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ETR: epinephrine-treated reaction; DBPCFC: double-blind, placebo-controlled food challenge; SCD: successfully consumed dose; VWG: vital wheat gluten

Assessment of the quality of evidence

		Risk of bias (Cochrane tool ⁵⁷ for interventional comparative studies; IHE tool ⁵⁸ for case series)	Level of evidence (Oxford Centre for Evidence-based medicine) - adapted using the approach of the European Academy of Allergy and Clinical Immunology ⁵⁹
Peanut	Interventional comparative studies (RCTs, CCTs): meta-analysis (Chu, 2019 ³¹)	Low	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series: Wasserman, 2019 ⁸	Moderate – 1 case series, main limit: retrospective study design	
Egg	Interventional comparative studies (RCTs, CCTs): Burks, 2012 ¹⁷ , Escudero, 2015 ¹⁸ Fuentes-Aparicio, 2013 ¹⁹	Moderate – 3 RCTs: 1 low, 1 high, 1 unclear risk of bias	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series	--	
Milk	Interventional comparative studies (RCTs, CCTs): Morisset, 2007 ¹²	High – 1 RCT at high risk of bias	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series: Levy, 2014 ¹⁴ (clinical practice)	Moderate – 1 case series, main limit: retrospective study design	
Wheat	Interventional comparative studies (RCTs, CCTs): Nowak-Wegrzyn, 2019 ²⁴	Low – 1 RCT	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series: 1 prospective case series in research context (Kulmala, 2018 ²⁵)	Low – 1 prospective case series	
Walnut	Interventional comparative studies (RCTs, CCTs): Elizur, 2019 ²⁶ (CCT, N=73)	High – non-randomized control group,** unblinded	Level II (two groups, non-randomized studies)
	Case series: NA	--	
Hazelnut	Interventional comparative studies (RCTs,	--	--

Sesame	CCTs):NA		Level II (two groups, non-randomized studies)
	Case series: NA	--	
	Interventional comparative studies (RCTs, CCTs): Nachshon, 2019 ²⁸	High – non-randomized control group,*** unblinded	
	Case series: NA	--	

Long-term FU for safety and tolerability

LTFU of RCTs (with control arm)			Large observational studies (case series)			
Jones, 2016⁶⁰ – LTFU of Burks, 2012 (egg)³² Diagnosis confirmed with OFC: no	Hsiao, 2017⁶¹ – LTFU of Tang 2015 (peanut):⁴ Diagnosis confirmed with OFC: no	Meglio, 2017⁶² – LTFU of Meglio 2013 (egg)³⁷ Diagnosis confirmed with OFC: yes (DBPCFC)	Manabe, 2019⁷⁷ (Japan)* - egg, cow's milk, or wheat N=130 Age: 6-NR (children) Diagnosis confirmed with OFC: yes (DBPCFC)	Kaupilla, 2019¹⁵ (Finland) – cow's milk N=295 Age: 5-17 (median 7.5) years Diagnosis confirmed with OFC: yes	Elizur, 2016¹⁶ (Israel) - cow's milk N=196 Age: >6, mean 10 years Diagnosis confirmed with OFC: yes, for patients who did not have an anaphylactic reaction in the preceding year	Nachshon, 2018⁷ (Israel)-peanut N=145 Age: ≥4 (median 5.8) years Diagnosis confirmed with OFC: yes, for patients who did not have an anaphylactic reaction in the preceding year
Patients followed: All patients who started OIT or control therapy Follow-up: Point 1: approx. 5 years after study enrolment; Point 2: 1 year later Completeness of follow-up: OIT: 85% (34/40); placebo: 73% (11/15) at both time points Year 3 and 4 after initiation of OIT: 3 egg-related reactions, 2 in OIT-desensitized subjects including 1 ETR in a patient who had achieved SU 19.4 months prior and reported unrestricted egg consumption.	Patients followed: All patients who started OIT or control therapy Follow-up: Mean of 4.2 years (SD 0. 7) from treatment cessation Completeness of follow-up: 77% (OIT: 24/31; placebo: 24/71) of patients No ETR, no anaphylaxis Estimated number of reactions per 10 person-years: OIT: 1.1 (99.9 person-year of FU) Placebo: 0.9 (102 person-years of FU)	Patients followed: All patients who started OIT or control therapy Follow-up: Mean of 2.5 (SD 0.3) and 7 (SD 0.9) years after original study start Completeness of follow-up: 2.5-year follow up: 19/20; 7-year follow-up: 18/20 No ETR, no need for emergency care	Patients followed: Patients who achieved a 2-week SU within 2 years after starting OIT Follow-up: ≥ 1 year (median 3.6) since achieving a 2-week SU Completeness of follow-up: 85% (108/130) <u>Adverse reactions in follow-up period among patients with follow-up:</u> Any medication-treated symptoms: 44/108 (41%) - Egg: 17/61 (28%); Cow's milk: 17/30 (57%); Wheat: 10/17 (59%) Any moderate or severe medication-treated symptoms: 24/108 (22%) ETRs: 2 (1 egg, 1 wheat)/108 (1.9%) 73% (32/44) patients	Patients followed: All patients who started OIT Follow-up: median 6.5 years (range 1-11) Completeness of follow-up: 83% (244/295) of patients <u>ETRs in the past year among the patients with follow-up:</u> Patients consuming ≥200 mL/d milk: 1.6% (2/122) Patients consuming <200 mL/d milk: 5.6% (2/36) <u>Patients consuming any milk:</u> 2.5% (4/158) Patients avoiding milk: 8.9% (4/45) P=0.09 <u>Any milk-related side-effect in the past year among the patients with follow-up:</u> Patients consuming ≥200 mL/d milk: 37% (45/122) Patients consuming <200	Patients followed: Patients who reached full cow milk protein consumption Follow-up: ≥ 6 months after completing up-dosing phase; median: 24.8 (range 6–41) months Completeness of follow-up: 195/196 (99%) of patients <u>Adverse reactions during follow-up period:</u> ETRs: 13/195 (6.7%) Any AE due to cow milk: 100/195 patients (51%) Respiratory: 57/195 (29%) GI: 17/195 (8.7%) Rate of AEs following completion of up-dosing: Month 6–15 months (n=29): 0.28/month Month 15–30 months (n=39): 0.21/month After > 30 months (n=28):	Patients followed: All patients who started OIT Follow-up: ≥ 6 months after completing build-up phase; median: 18 (range 6–75) months Completeness of follow-up: 142/145 (98%) of all patients 130/133 (98%) of patients reaching 3000 mg (n=113) or 300-2400 mg (n=20) PP at end of up-dosing <u>Adverse reactions during follow-up period among patients consuming 300-3000 mg PP :</u> ETRs: 2/130 (1.5%) Any objective reaction: 12/130 (9.2%)

			reporting symptoms attributed their symptoms to co-factors such as exercise, fatigue or illness 59% (22/ 37) of patients with clear responses) experienced their first symptoms ≥2 years after 2-week SU	mL/d milk: 81% (29/36) <i>Patients consuming any milk:</i> 47% (74/158) Patients avoiding milk: 67% (30/45) P=0.000 Among patients who consumed ≥200 mL/d milk, those with longer follow-up tended to have fewer side effects (P = 0.07)	0.15/month P < .01	
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*Included for this outcome event though N<150 for each allergen because of scarcity of long-term data after SU

ASSESSMENT OF THE QUALITY OF EVIDENCE

		Risk of bias (Cochrane tool ⁵⁷ for interventional comparative studies; IHE tool ⁵⁸ for case series)	Level of evidence (Oxford Centre for Evidence-based medicine) - adapted using the approach of the European Academy of Allergy and Clinical Immunology ⁵⁹
Peanut	Interventional comparative studies (RCTs, CCTs): Hsiao, 2017 ⁶¹	High - 1 LTFU on RCT, limitations: open-label and loss to follow-up	Level II two groups, non-randomized studies
	Case series: Nachshon, 2018 ⁷	Moderate – 1 case series, main limit: retrospective study design, single center	
Egg	Interventional comparative studies (RCTs, CCTs): Jones, 2016 ⁶⁰ , Meglio, 2017 ⁶²	High – 2 LTFU on RCTs, limitations: open-label and loss to follow-up	Level II two groups, non-randomized studies
	Case series	--	
Milk	Interventional comparative studies (RCTs, CCTs):	--	Level III: one group non-randomized
	Case series: Kauppila, 2019 ¹⁵ , Elizur, 2016 ¹⁶ , Manabe, 2019 ⁷⁷	Moderate – 3 case series, main limit: retrospective study designs, single center	
Wheat	Interventional comparative studies (RCTs, CCTs): NA	--	Level III: one group non-randomized
	Case series: Manabe, 2019 ⁷⁷	Moderate – 1 case series, main limit: retrospective study designs, single center	
Walnut	Interventional comparative studies (RCTs, CCTs): NA	--	--
	Case series: NA	--	
Hazelnut	Interventional comparative studies (RCTs, CCTs): NA	--	--
	Case series: NA	--	
Sesame	Interventional comparative studies (RCTs, CCTs): NA	--	--
	Case series: NA	--	

Eosinophilic esophagitis

Meta-analyses		Large case series (N> 150)			
Chu, 2019 ³¹ – peanut	Lucendo, 2014 ⁷⁸ – chicken's egg, cow's milk, peanut and others	Goldberg, 2017 ⁷⁹ (Israel) - milk, peanut, egg, sesame N=794 Age: median 83 months (IQR 60-126) Diagnosis confirmed with OFC: yes, for patients who did not have an anaphylactic reaction in the preceding year	Wasserman, 2019 ⁸ (USA) – peanut N=270 Age: 4-18 (mean: 8.1) years Diagnosis confirmed with OFC: no	Kauppila, 2019 ¹⁵ (Finland) – cow's milk N=295 Age: 5-17 (median 7.5) years Diagnosis confirmed with OFC: yes:	Soller, 2019 ⁹ (Canada) – peanut N=270 Age: 0.75-5.9 (median 1.9, IQR : 1.25-2.75) years Diagnosis confirmed with OFC: for 31% of patients
3 events of EOE occurred in 3 RCTs; another 2 RCTs reported explicitly that no EOE occurred (N=719), all in the OIT group – <i>no statistical analysis performed</i>	Meta-analysis of 9 studies (8 retrospective case series, 1 RCT, published up to March 2014) that reported on a total of 708 patients receiving OIT (including baked milk introduction), indicated that 2.7% of patients undergoing OIT newly developed EOE (95% CI 1.7% to 4.0%).	Recurrent GI symptoms (abdominal pain and/or vomiting) independent of the timing to dose administration: 8.2% (65/794) Milk: 9.0% (55/614) Peanut: 6.9% (9/130) Egg: 2.4% (1/41) 39% (25/65) of cases occurred within the first month and 86% (56/65) within the first 3 months of OIT 69% (45/65) resumed OIT and 42 did not redevelop symptoms* No dysphagia, no food impaction. 3 patients underwent biopsy showing increased esophageal eosinophilic counts In all cases in which the dosage was reduced or stopped, symptoms subsided, and peripheral eosinophil counts decreased. Patients with recurrent GI symptoms had higher peripheral eosinophil counts at baseline (P=0.046) and higher increases in peripheral eosinophil counts during OIT (P<0.001) compared to other patients, but did not differ in age and sex.	ELORS: EOE-like OIT-related syndrome: episodic vomiting occurring > 2 hours after dosing <u>Build-up phase:</u> Proportion of patients with ELORS: 14% (37/270) (documented increase in peripheral blood eosinophils: 4.8% (13/270), only 16 of 37 tested) Biopsies were performed in 2/37 patients (results not reported); 18/37 patients were treated with a PPI for 1-4 weeks and 1/37 with an oral corticosteroid for < 14 days Proportion of patients with ELORS who: -discontinued: 57% (21/37) -reached target maintenance dose: 35% (13/37) -Discontinued for other reasons or transferred care: 8.1% (3/37) None of the 35 patients with ELORS with follow-up (2 transferred care) had persistent symptoms or required prolonged therapy. <u>Maintenance phase:</u> Proportion of patients with ELORS during maintenance phase: 0.5% (1/214) – discontinued OIT	One patient with vomiting and failure to thrive underwent endoscopy, which was negative for EOE; the examination was performed after OIT discontinuation while the patient was on a milk-avoidance diet.	1.1% (3/270) of patients experienced symptoms suggestive of EoE, 1 biopsy performed (no EoE) An additional case of EoE identified incidentally during a biopsy to rule out celiac disease (the EoE persisted despite stopping OIT)

			Incidence of ELORs during maintenance phase: 0.16/100 patient-years		
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* Goldberg (2019⁸⁰) reported details on the management and the treatment course of these patients: the cumulative daily dose was reduced by a median of 50% in 66% (43/65) of patients, dose increases were deferred in 3.1% (2/65) of patients, or treatment was temporarily suspended in 28% (18/65) of patients. Symptoms and eosinophilia abated on dose modification, allowing for resumption of dose increases for 34 patients or reinitiation of treatment for 9 patients. OITIGER reoccurred 18.5% (10/54) of patients and resolved after further dose modification. In long-term follow-up (>3-26 months), patients with OITIGER had a higher OIT failure rate (P=.004) and were less likely to reach full desensitization (P < .001).

Smaller case series	
Echeverria-Zudaire, 2016⁸¹ (Spain) - milk (N=97) or egg (31) N=128 Age: children Diagnosis confirmed with OFC: yes (open)	Gomez Torrijos, 2017⁸² and Rodriguez, 2014⁸³ (Spain) – milk N=57 Age: children Diagnosis confirmed with OFC: NR
Biopsy-confirmed EOE: 6.3% (8/128) 6 patients developed EOE at a median of 29 months (range 15-48) after OIT(all with cow's milk); 2 developed EOE during OIT (egg and milk plus egg) Most of the 8 patients were males between 3 and 14 years of age. EOE with oesophageal involvement only: 4.5% (6/128) 5/6 continued OIT with PPI (n=3) or PPI plus fluticasone (n=2); 4/5 underwent follow-up endoscopy: 3 histological remission, 1 continued EOE. Histological remission was confirmed in the patient who discontinued OIT. EOE - plus duodenal or colon involvement: 1.6% (2/128) Both discontinued OIT and underwent follow-up endoscopy which showed histological remission in both cases	Biopsy-confirmed EOE: 5.3% (3/57) of patients treated with OIT for cow milk allergy All three patients were males and developed symptoms (including dysphagia) after reaching complete desensitization and/or while on maintenance. All patients discontinued milk intake, redeveloped sensitization and started avoiding milk. Biopsies performed 6-24 months after starting avoidance showed resolution of EOE.

Impact of patient characteristics on safety outcomes

- Most OIT studies enrolled children and adolescents starting from age 4 to 7 years, with median/mean ages in the range of 6 to 12 years (Anagnostou, 2014;¹ Bird, 2018;⁵ Burks, 2012;³² Elizur, 2016;¹⁶ Escudero,2015;¹⁸ Fuentes-Aparicio, 2013;¹⁹ Kauppila, 2019;¹⁵ Levy, 2014;¹⁴ Longo, 2008;¹⁰ Martin-Munoz, 2019;²⁰ Nachshon, 2018;⁷ Reier-Nilsen, 2019;³ Vickery, 2018⁶ and Wasserman, 2019⁸). Three studies enrolled peanut-allergic children starting from a younger age, three years (Blumchen, 2019;² Wasserman, 2014⁵⁶) or one year (Tang, 2015⁴). One study enrolled children for milk or egg OIT starting from the age of one year (Morisset, 2007¹²).
- **Older children, adolescents and adults**
 - No association between baseline age and safety outcomes in large case series of children and adolescents (N 130 to 295) (Wasserman 2019⁸, Elizur, 2016;¹⁶ Kauppila, 2019;¹⁵ Levy 2014¹⁴)
 - A double-blind, placebo-controlled RCT included 55 adults (18 to 55) and 169 adolescents (age 12 to 17) with peanut allergy (Burks, 2018;⁷⁰ Vickery 2018⁶). There was no apparent difference between age groups in the proportion of patients with treatment-emergent hypersensitivity adverse events.

Age range (years)	N (OIT)	N (placebo)	Proportion of patients experiencing event OIT versus placebo			
			Treatment-emergent allergic hypersensitivity adverse events	Severe adverse event	Serious adverse events	Anaphylaxis/Systemic allergic reaction
4 to 11	238	89	86.1% versus 69.7%	4.3% vs 0.8%	2.4% vs 0.8%	14.2% vs 3.2%
12 to 17	134	35	89.6% versus 68.6%			
18 to 55	41	14	87.8% versus 78.6%	4.9% vs 7.1%	4.9% vs 7.1%	19.5% vs 7.1%

- Double-blind, placebo-controlled RCT of adolescents with peanut allergy (mean age 15 years, range 12-18; age at diagnosis: 3 years) (Fauquert, 2018⁵⁵): Peanut (or placebo) capsules were ingested daily over 24 weeks with increments every 2 weeks from 2 to 400 mg of peanut protein. **Five severe multi-system reactions (grades 3a and 3b) occurred in 4 OIT patients (19%= 4/21) and in none (0) in the placebo group.**
- Case series of 23 adults with OFC-confirmed IgE-mediated allergies who were treated with OIT (10 milk, 9 peanut, 4 egg) (Mantyla, 2018⁷¹): The median period of OIT was 515 days. **ETRs: 17% (4/23); emergency room treatments: 13% (3/23).**
- **Toddlers and pre-school children:**
 - Vickery et al (2017⁶⁸) randomized 37 preschool children aged 9 to 36 months with OFC-confirmed peanut allergy to OIT with a maintenance dose of 300 or 3000 mg peanut protein per day. One ETR occurred in the high dose group (5.9%, 1/17) and none in the low-dose group. **There were no treatment-related severe adverse events.**
 - Martorell et al (2011¹¹) randomized 60 children aged 24 to 36 months with OFC-confirmed milk allergy to OIT or avoidance. **Two ETRs occurred in 2 children in the OIT group (6.7%, 2/30); no severe reactions occurred.**
 - Soller et al (2019,⁹ prospective multi-center study) reported that of 270 pre-school children (age 0.75-5.9 years, median 1.9 years) undergoing peanut OIT 36% (98/270) experienced grade 1 (mild) symptoms, 31% (84/270) grade 2 (moderate), and 0.4% (1/270) grade 4 (severe) symptoms graded according to the World Allergy Organization Subcutaneous

Immunotherapy Systemic Reaction Grading System⁷⁴). Eleven patients (4.1%, 11/270) experienced a total of 12 ETRs during build-up (11 for grade 2 reactions and 1 for a grade 4 reaction). Half of the ETRs (6) occurred in the clinic during up-dosing and the other half at home. Overall, a total of 0.029% of doses during build-up were associated with an ETR.

Impact of baseline food allergy-related parameters on safety outcomes

Inclusion of patients with a history of severe reactions in OIT studies:

- Among 13 RCTs with N> 50, 6 excluded patients with a history of severe anaphylaxis (Burks, 2012;³² Escudero, 2015;³² Martorell, 2011;³² Tang, 2015;⁴ Bird, 2018;⁵ Vickery, 2018;⁶ Sampson, 2019⁶³), which was commonly defined as hypotension, neurological and/or respiratory compromise. Other RCTs (Longo, 2008,¹⁰ Martin-Munoz, 2019a,²⁰ Reier-Nilsen, 2019a³) either did not list anaphylaxis among their exclusion criteria or, additionally, specifically stated that they did not exclude children with a history of severe allergic reactions (Blumchen, 2019;² Anagnostou, 2014²). (For another 2 studies [Fuentes-Aparicio, 2013, Morisset, 2007], inclusion of patients with severe anaphylaxis was not clear.
 - In peanut RCTs, inclusion criteria for the minimum serum peanut-specific IgE level ranged from 0.35 to 15 kU/L; there was no maximum sIgE level specified (Chu, 2019).³¹
- Large case series (clinical practice) generally did not exclude patients with a history of anaphylaxis; two of them explicitly state that no patient was excluded because of the severity of their previous reactions or their sIgE levels (Wasserman, 2018;⁹⁴ Wasserman, 2014⁵⁶).

Outcomes of RCTs with N≥ 50 that included children with a history of severe reactions:

- **Anagnostou, 2014² (peanut RCT, N=99, baseline worst clinical reaction WAO score grade 3 or 4: control 22.5% vs active 8.1%):** ETRs occurred after 0.01% of doses (1 participant); OIT vs placebo: 2.0% (1/49) vs 9 (0/50). There were no SAEs.
- **Blumchen, 2019² (peanut RCT, N2=62: 31 OIT, 31 control):** At baseline, 53% of children in the OIT group and 58% in the control group had a history of severe allergic reactions to peanut (grade IV or V⁷²). The median sIgE was 81.5 kU/L (range 0.57-624 kU/L) and the median maximum tolerated single dose at the initial OFC was 30 mg peanut protein (range 1-3,000 mg). Wheezing was the only objective symptom reported significantly more often in the OIT group (8 events in 6 patients) than in the placebo group (1 patient; P=.045). There were no ETRs; the rate of serious AEs was 10% (3/30) in the OIT group and 16% (5/31) in the placebo group.
- **Longo, 2008¹⁰ (milk RCT, N=30 OIT, N=30 control):** Included children with a baseline sIgE level > 85 kUA/L who had a positive history of at least one severe allergic reaction (defined as class 4 and 5 by Clark's classification) after accidental exposure to milk or dairy products requiring emergency treatment. In the OIT group, almost all patients had allergic reactions; 4 ETRs occurred in 4 OIT patients (13%) during the initial hospital-based rush phase and 1 ETR (3.3%) during the home dosing phase. During the home dosing phase, 2/30 (6.7%) children attended the emergency department. In the control group, 6/30 (20%) children had mild adverse reactions caused by accidental exposure to milk.
- **Martin-Munoz, 2019a²⁰ (egg, RCT):** (N=88 OIT, 25 controls) ETRs: 8.0% OIT vs Control: NR; No SAEs
- **Reier-Nilsen, 2019a³ (peanut, N=77: 57 OIT, 20 control):** At baseline, 79% of children had a history of anaphylaxis to peanut and all children reacted with anaphylaxis during the baseline DBPCFC. During up-dosing, 11/57 (19%) of children in the OIT group experienced 11 anaphylaxis events (classified as moderate), including 6 ETRs; the control group did not experience any anaphylactic reactions to peanut.

Correlations between baseline parameters and OIT safety and tolerability outcomes

LARGE CASE SERIES

Baseline parameter	Outcome and correlation	Reference
History of anaphylactic reaction	Associated with adverse reactions after the completion of treatment (median follow-up 24.8, range 6-41) months after completion of the build-up phase (OR=2.1, P=.033)	Elizur, 2016 ¹⁶ (milk, N=197)
	History of anaphylaxis among the following sub-groups by outcome: - Continued treatment: 39% (38/97) - Stopped treatment: 71% (10/14), P=0.04	Nachshon, 2018 ⁷ (peanut, N=111)
	In multivariate analysis, history of anaphylaxis was not associated with ELORS or ETRs	Wasserman, 2018 ⁹⁴ (peanut, N=270)
Specific IgE serum levels	In logistic regression analysis, milk-related anaphylaxis after buildup was related to milk sIgE before OIT; for every additional sIgE doubling, the risk of anaphylaxis increased by 60% (OR 1.6) (P=0.000)	Kaupilla, 2019 ¹⁵ (milk, N=296)
	Higher sIgE increased the risk of ELORS (P <.001) and of ETRs (P=0.19) occurring during escalation	Wasserman, 2018 (peanut, N=270)
	In a multivariable logistic regression model those with a higher baseline IgE were more likely to drop out during P-OIT buildup (odds ratio [OR], 1.03; 95% CI, 1.01-1.05) and were more likely to receive epinephrine (ETR) (OR, 1.03; 95% CI, 1.011.06)	Soller, 2019 ⁹ (peanut, N=270)
SPT wheal size	In a multivariable logistic regression model, patients with a higher baseline SPT were more likely to receive epinephrine (ETR) (OR, 1.35; 95% CI, 1.051.75)	Soller, 2019 ⁹ (peanut, N=270)
	No significant difference between those who continued or stopped treatment (P=0.62)	Nachshon, 2018 ⁷ (peanut, N=111)
	Not associated with occurrence of adverse reactions following completion of OIT (P=0.087)	Elizur, 2016 ¹⁶ (milk, N=197)
Maximum tolerated dose of food allergen	MITD not associated with occurrence of adverse reactions following completion of OIT (P=0.087)	Elizur, 2016 ¹⁶ (milk, N=197)
	Starting dose: median 120 mg cow milk protein; range (10-7200 mg). ETRs were significantly more frequent in with a lower maximal tolerated starting dose (P <.0001).	Levy, 2014 ¹⁴ (milk, N=280)

RCTs, CCTs AND SMALLER CASE SERIES

Baseline parameter	Outcome and correlation	Reference
Specific IgE blood levels	Patients who dropped out had higher egg sIgE serum antibody levels (P < 0.05).	Martin-Munoz, 2019a ²⁰ (RCT egg , N=76 OIT, 25 control)
	Higher baseline sIgE levels were associated with OIT discontinuation or persistent reactions to OIT dosing. Optimal predictive cut-off levels were: egg-white sIgE: 9.41 kU/L; ovalbumin-sIgE: 6.49 kU/L and ovomucoid-sIgE: 8.85 kU/L.	Vazquez-Ortiz, 2014 ⁵⁴ (CCT egg , N=50 OIT, N=32 control)
	Fewer patients with lower sIgE levels (<3.5 kU/L) experienced adverse events (6/10, 60%) compared to 13/17 (76%) of patients with higher sIgE levels >3.5 kU/L (P=NR).	Garcia-Ara, 2013 ⁴³ (CCT, milk , N=36 OIT; N=19 control)
	Cox proportional hazards multivariate regression model identified sIgE ≥50 kU/L (HR 2.59, 95% CI 1.4-4.78, P=0.002) as independent risk factor for persistence of allergic reactions.	Vazquez-Ortiz, 2013 ⁸⁴ (case series, milk , N=81)

SPT	Peanut SPT was the only significant predictor of the rate of GI AEs, both before and after adjusting for sex, age, asthma, log peanut-specific IgE, atopic dermatitis, and AR. Rates of GI AEs increased 1.8-fold (95% CI: 1.4, 2.4, p-value: <0.001) for every 5 mm increase in SPT size.	Virkud, 2017 ⁸⁵ (retrospective pooled analysis of 3 RCTs, peanut , N=104)
Maximum tolerated dose of food allergen	Patients who dropped out had lower baseline threshold response dose (P < 0.05).	Martin-Munoz, 2019a ²⁰ (RCT egg , N=76 OIT, 25 control)

Impact of baseline asthma status on safety outcomes

In many interventional (Bird, 2018;⁵ Blumchen, 2019;² Longo, 2008;¹⁰ Martin-Munoz, 2019;²⁰ Reier-Nilsen, 2019;³ Tang, 2015;⁴ Vickery, 2018⁶) and in some observational (Levy, 2014;¹⁴ Nachshon, 2018;⁷) studies severe and/or poorly controlled or unstable asthma was an exclusion criterion for OIT.

Asthma-related outcomes in RCTs with N>50:

- Martin-Munoz, 2019a²⁰ (Spain – **egg**, age 6-9 years, N=101, asthma 30/101 [30%], severe or uncontrolled asthma at baseline excluded): Among all patients who started OIT (N=88) 8 (9.1%) withdrew during the build-up phase because of uncontrolled asthma.
- Blumchen, 2019 (Germany– **peanut**, age 3.2-17.8 years, N=62, uncontrolled asthma excluded, asthma: 65% placebo, 42% OIT) : After the course of OIT, no difference was found with respect to newly diagnosed atopic diseases (bronchial asthma, atopic dermatitis, allergic rhinoconjunctivitis) or worsening established atopic diseases at baseline.
- Vickery, 2018⁶(**peanut**, poorly controlled asthma excluded, 53% of patients had asthma at baseline): Asthma exacerbation was recorded as an SAE in 2 OIT patients (4-17 years, N=372, 0.54%) and no placebo (N=124) patient.

Correlations between baseline asthma status and OIT safety / tolerability outcomes in large case series

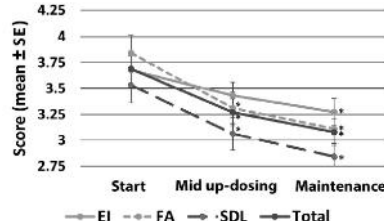
Outcomes and Correlations	Proportion of patients with asthma	Reference
Compared to patients without asthma (N=93), patients with asthma (N= 101) had more ETRs during up-dosing (61% vs 34% of patients, mean ETRs per patient: 1.1 [SD 1.2] vs 0.4 [SD 0.7], P < .001) and at home (26% vs 4.2% of patients, mean ETRs per patient: 0.4 [SD 0.8] vs 0.1 [SD 0.5], P < .001).	101 patients with asthma, 93 no asthma	Elizur, 2015 ⁷³ (milk , N=194)
During the initial 10-day hospital-based “rush” phase, there was a significant association between the incidence of moderate to severe reactions and history of asthma (P=0.01). During OIT dosing phase at home, there was no significant correlation between the presence of asthma and/or viral wheezing and the total number of reactions or reactions requiring nebulised epinephrine.	asthma: 66%, viral wheezing: 34%	Barbi, 2012b ⁸⁶ and Barbi, 2012a ⁸⁷ (milk , N=132)
History of intermittent asthma increased the risk of ETRs (P = .035) and ELORs (P = .014) during dose escalation.	asthma: persistent: 43%, intermittent: 21%	Wasserman, 2018 ⁸ (peanut , N=270)
While asthma was not significant in predicting rates of AEs overall, the presence of asthma significantly increased AE rates by 2.3 times during maintenance (P=0.03)	asthma: 44%	Virkud, 2017 ⁸⁵ (retrospective pooled analysis of 3 RCTs, peanut , N=104)
3 cases (2.3% of 130) of life-threatening anaphylaxis all in teenage boys with persistent asthma under suboptimal control, high milk- or egg-specific IgE levels , and risk-taking behaviors , including poor compliance to OIT and/or to asthma management plans	35% of patients (45/130) were on steps 3 to 4 of asthma treatment and 10% were adolescents (13-18 years old)	Vazquez-Ortiz, 2014 ⁸⁸ (egg, milk , N=130)

IMPACT ON QUALITY OF LIFE

Study – food allergen	OIT protocol variables	PRO data collection	Number and age of patients enrolled	PRO Results (n: number of patients with valid responses)	Factors that influenced QoL outcomes	Main findings and study limitations																														
Study design																																				
Anagnostou 2014 ¹ - peanut Crossover, open-label RCT	Target dose: 800 mg/d PP Up-dosing interval: 2-3 weeks Length of build-up phase: 26 weeks	FAQLQ-PF at end of OIT (26 weeks) – parent proxy	N=99 (49 OIT, 50 control) Age: 7–16, median 12.4 FAQLQ-PF completed by parents of children of 7-12 yrs old	Median (range) change in FAQLQ-PF score from baseline to post-treatment: OIT: (n=19): -1.61 (-4.87 to 0.24), P<0.001 (Wilcoxon signed rank test) Control after crossing over to OIT (n=20): -1.41 (-4.83 to 1.38)	NR	OIT was associated with improvement in the parental FAQLQ-PF total score compared to baseline. <u>Limitations:</u> No comparator Only parent report (no children), Measured at one time point only No information about the different domains of QoL																														
Dunn Galvin, 2018 ⁸⁹ , Tang, 2015 ⁴ – peanut DBPCRT	Target dose 2000 mg/d PP Up-dosing interval: 2 weeks Length of build-up phase: 8 months Maintenance dose and duration: 2000 mg/d PP for 10 months	FAQLQ-PF and FAIM (– parent proxy) at: T0 (baseline) T1 (end-of treatment, 18 months from T0 and before assessment of SU) T3 (3 months post-treatment) T4 (12 month post-treatment)	N=62 (31 OIT, 31 placebo) Age: 1–10, mean 6	<table><tr><td colspan="3">Mean (95% CI) change in FAQLQ-PF total score from T0 to:</td></tr><tr><td></td><td>OIT</td><td>Placebo</td></tr><tr><td>End of treatment (T1)</td><td colspan="2">No statistically significant improvement</td></tr><tr><td>T3: 3 months after T1</td><td>(n=24): +0.8 (0.001 to 1.7), P=0.05*</td><td>(n=27): 0.4 (-0.3 to 1.1), P=0.3</td></tr><tr><td>T4: 12 months after T1</td><td>(n=20): +1.3 (0.4 to 2.1), P=0.005*</td><td>(n=22): -0.6 (-0.8 to 0.7), P=0.8</td></tr></table> Improvement in FAQLQ-PF score by ≥0.5 (MCID) 3 months post-treatment (T3): OIT: 77%; Placebo: 34%; Absolute risk reduction: 42.2%; NNT = 2.3 (95% CI 10 to 2) Improvement (mean difference from baseline) by subscale: <table><tr><td></td><td>T3</td><td>T4</td></tr><tr><td>FA</td><td>1.1, P = .003*</td><td>1.4, P = .001*</td></tr><tr><td>SDL</td><td>0.9, P = .09</td><td>1.2, P = .005*</td></tr><tr><td>EI</td><td>0.6, P = .1</td><td>1.1, P = .01*</td></tr></table> Mean (95% CI) change in FAIM score from T0 to: <table><tr><td></td><td>OIT</td><td>Placebo</td></tr></table>	Mean (95% CI) change in FAQLQ-PF total score from T0 to:				OIT	Placebo	End of treatment (T1)	No statistically significant improvement		T3: 3 months after T1	(n=24): +0.8 (0.001 to 1.7), P=0.05*	(n=27): 0.4 (-0.3 to 1.1), P=0.3	T4: 12 months after T1	(n=20): +1.3 (0.4 to 2.1), P=0.005*	(n=22): -0.6 (-0.8 to 0.7), P=0.8		T3	T4	FA	1.1, P = .003*	1.4, P = .001*	SDL	0.9, P = .09	1.2, P = .005*	EI	0.6, P = .1	1.1, P = .01*		OIT	Placebo	In the OIT group, 23 patients attained SU, 5 patients failed to achieve SU and 3 withdrew. Patients who did not achieve SU (n=NR) showed no improvement in FAQLQ-PF scores at 3 or 12 months post-treatment (Mean Difference T0-T3 0.58, t = 1.05, P =0.4; Mean Difference T0-T4 0.2, t =0.23, P =0 .8). Patients who achieved SU (n=NR) reported a significant improvement in FAQLQ-PF scores across all subscales at 3 (T3)	In a placebo-controlled trial, OIT was associated with clinically-important improvement of parental FAQLQ-PF scores compared to baseline 3 months and 12 months after the end of treatment, while there was no change in the placebo group. Improvements were recorded in each of the 3 domains of the FAQLQ-PF, with the greatest improvement in the domain “food avoidance”. Improvements were positively associated with achieving SU. <u>Limitations:</u> *Incomplete FU: by 12 months post-treatment, FAQLQ-PF data is only available from approx. 2/3 of the patients originally enrolled. *No statistical analysis to compare change in FAQLQ-PF scores between the OIT and the placebo group.
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Study – food allergen	OIT protocol variables	PRO data collection	Number and age of patients enrolled	PRO Results (n: number of patients with valid responses)			Factors that influenced QoL outcomes	Main findings and study limitations
Study design								
				End of treatment (T1)	(n=29): +0.8 (0.4 to 1.3), P=0.002*	(n=28): -0.2 (-0.5 to 0.2), P=0.3	and 12 (T4) months post-treatment (Mean Difference T0-T3 1.3, t = 2.8, P = .01; Mean Difference T0-T4 1.8, t = 2.7, P = .001).	*Only parental report (no children) *Placebo-controlled (up to T1?): Subjective impact of OIT may not be fully captured in the absence of assurance of successful treatment
				T3: 3 months after T1	(n=24): +0.5 (0.04 to 1.0), P=0.03*	(n=27): -0.3 (-0.6 to 0.04), P=0.02		
				T4: 12 months after T1	(n=20): +0.4 (0.1 to 0.8), P=0.04*	(n=22): -0.13 (-0.4 to 0.1), P=0.3		
				Improvement (mean difference from baseline) by subscale:				
				Chance of:	T3	T4		
				Severe reaction, FAIM-2	1.0, P=.03*	0.8, P=.04*		
				Dying from allergen ingestion, FAIM 3	1.0, P=.1	1.2, P=.01*		
				Accidentally eating allergen, FAIM-1	0.9, P=.02*	0.7, P=.04*		
				Minimal improvement, FAIM-4	P=0.3			
Blumchen, 2019 ² - peanut DBPCRT	Target dose: 125-250 mg PP Build-up interval: 2 weeks Build-up duration: up to 14 months Maintenance dose and duration: median: 125 mg/d for 8±2 weeks	FAQLQ-PF (for mothers of children age 3-12) at a median of 9.5 weeks (IQR, 5-15.3) after final OFC FAQLQ-CF (for children age 8-12) at a median of 11 weeks (IQR, 7-16) after final OFC	N=62 (31 OIT, 31 placebo) Age: 3.2-17.8, median 6.8 FAQLQ-PF: OIT: 27, placebo: 21 FAQLQ-CF: OIT: 11, placebo: 9 BOT: OIT : 50 mothers of children (3-12 years), 21 children (8-12 years)	FAQLQ-PF (mothers) Total score: median change from baseline not statistically significant in both OIT (n=20) and placebo (n=18) groups No statistically significant change in all sub-scales No statistically significant difference in changes between OIT and placebo. FAQLQ-CF (children age, 8-12 years) Total score: median change from baseline statistically significant in OIT group (n=9): -1.0 [IQR -2.7 to -0.5]; not statistically significant in placebo group (n=8): -0.1 [IQR-1.2-0.7], but difference between OIT and placebo not statistically significant (P=0.1) By subscale, statistically significant improvement from baseline for: • RAE (-2.0 [IQR -3.3 to -0.9]) • EI (-1.8 [IQR -2.8 to -0.9]), and • AA (-1.9 [-3 to -0.1]), but not for DR. Changes statistically different from placebo only for “risk of accidental exposure” and “emotional impact” (P=0.02 for both)			Not reported	In a placebo-controlled RCT, at approx. 3 months post-treatment there was no significant change of parental FAQLQ-PF scores compared to baseline or to placebo. However, children (age 8-12) in the OIT group reported clinically important and statistically significant improvements from baseline in the FAQLQ-CF total score and in all domains, except “dietary restrictions”. There were no significant changes from baseline in the children’s placebo group; differences between the two groups were not statistically significant, except for “risk of accidental exposure” and “emotional impact”. <u>Limitations:</u> *Incomplete FU *Small sample size, particularly for the children (20 in total) *Outcomes measured at one time point only *Placebo-controlled: Subjective impact of OIT on QoL may not be fully captured in the absence of assurance of successful treatment
Reier-Nilsen,	Target dose:	PedsQL 4.0	N=77 (57	Mean (95% CI) PedsQL 4.0 scores from baseline to Y2:			In multivariate robust	Mean generic PedsQL 4.0 scores improved

Study – food allergen	OIT protocol variables	PRO data collection	Number and age of patients enrolled	PRO Results (n: number of patients with valid responses)			Factors that influenced QoL outcomes	Main findings and study limitations																		
Study design 2019b ⁹⁰ and 2019a ³ - peanut RCT-open label	5000 mg PP Build-up interval: 2 weeks Build-up duration: 50-78 weeks Maintenance dose and duration planned: 5000 mg/d for 36 months; observed: mean 3322 mg PP (range 350 to 5000)	(parents and children) at enrolment (Y0), after 1 year (end of up-dosing) (Y1) and after 2 years (Y2) of OIT FAQL-PB (parents)	OIT, 20 control) Age: 5-15, median 10.1 OIT and 8.9 control	<table><tr><th>OIT (n=39)</th><th>Control (n=20)</th><th>Between groups</th></tr><tr><td>Children</td><td></td><td></td></tr><tr><td>from 82.1 to 86.7: +4.4 (0.5, 8.3) P<.0001*</td><td>from 83.4 to 82.2: -0.9 (-7.9, 6.11), P=0.8</td><td>P= 0.12</td></tr><tr><td>Parents</td><td></td><td></td></tr><tr><td>from 78.7 to 83.7: +9.3 (4.3, 14.3) P<.0001*</td><td>from 81.7 to 82.1: +0.4 (4.3, 14.3), P=0.9</td><td>P=0.02*</td></tr></table> Parents' FAQL-PB improved significantly among both the OIT-group by -9.9 (95% CI -14.6, -5.3) (P<0.0001) and the control group by -9.4 (-15.3, -3.6) (P=0.004) from Y0 to Y2, with no significant difference between groups (P=0.57)	OIT (n=39)	Control (n=20)	Between groups	Children			from 82.1 to 86.7: +4.4 (0.5, 8.3) P<.0001*	from 83.4 to 82.2: -0.9 (-7.9, 6.11), P=0.8	P= 0.12	Parents			from 78.7 to 83.7: +9.3 (4.3, 14.3) P<.0001*	from 81.7 to 82.1: +0.4 (4.3, 14.3), P=0.9	P=0.02*	regression analysis, none of the factors examined (age, gender, maintenance dose, perceived burden of GI AEs and perceived burden of taste/amount) were associated with a change in PedsQL4.0 (child), PedsQL4.0 (parent) or FAQL-PB (parents) scores.	significantly from baseline to Y2 in both children and parents, while no significant difference was seen in controls. Compared to controls, the improvement was significantly different among parents only. <u>Limitations:</u> *Incomplete FU: Data not available for 32% (18/57) of the children who discontinued OIT *Small sample size *Children completed a generic QoL instrument only *No information about the different domains of QoL					
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Epstein Rigbi, 2019 ⁹¹ - milk, peanut, egg, sesame, or tree nuts Prospective cohort study	Target doses (mg protein): Milk: 7,200; egg: 12,000; peanut: 3,000; sesame: 5,000; tree nuts: 4,000 4 weeks (1 month) Planned: 8 months; observed: mean 7.8 (SD 5.7) months Maintenance (mg protein): Peanut, sesame, and tree nuts:	FAQLQ-PF (parents) at OIT initiation, mid up-dosing (4 months of OIT), after reaching maintenance (end of treatment), and 6 months into maintenance	N=191 (consecutive patients initiating OIT), 48 control group (matched for age and allergenic foods) Age: 4-12, mean 6.3	<table><tr><th>FAQLQ-PF</th><th>OIT start</th><th>Reaching maintenance or treatment cessation</th><th></th></tr><tr><td>Total score</td><td>3.69</td><td>3.19</td><td>P < .001*</td></tr><tr><td>EI</td><td>3.66</td><td>3.32</td><td>P=0.001*</td></tr><tr><td>FA</td><td>3.90</td><td>3.32</td><td>P<0.001*</td></tr><tr><td>SDL</td><td>3.50</td><td>2.94</td><td>P<0.001*</td></tr></table> No significant changes in the control group (n=48) between 2 time points (mean interval 13.3 [SD11.2] months) in any of the domains or in the total score. The 14 patients who reached a partial maintenance dose (150-2700 mg protein) experienced a significant improvement in mean FA (P=0.001), SDL (P=0.036), and total (P=0.015), scores, but not for EI (P=0.12) from start of OIT to maintenance. The 3 patients who failed OIT reported no significant change from the start of OIT to treatment cessation (range, 2.6-4.3 months). Among 85 patients (of 96 eligible for mid-point assessment, 88.5%	FAQLQ-PF	OIT start	Reaching maintenance or treatment cessation		Total score	3.69	3.19	P < .001*	EI	3.66	3.32	P=0.001*	FA	3.90	3.32	P<0.001*	SDL	3.50	2.94	P<0.001*	In linear regression analysis, a single food allergy (P<0.001 SDL and total P=0.01EI, P=0.003 FA), and a worse baseline FAQLQ-PF score (P<0.001, all domains and total) predicted a greater improvement in FAQLQ-PF scores from start to maintenance/ cessation of treatment. History of anaphylaxis was associated with greater improvement in single-factor analysis (<.05) Not significant: asthma, food allergy treated,	In a prospective cohort study, parents' FAQLQ-PF scores significantly improved in all dimensions from OIT initiation to reaching full and/or partial maintenance, whereas there was no change in controls. Worse baseline QOL, a single food allergy, and younger age predicted greater QOL improvements. Among the subset of patients whose FAQLQ-PF total score deteriorated from baseline to mid up-dosing, FAQLQ-PF scores returned to near-baseline upon reaching maintenance. Additional significant improvement in QOL was observed 6 months after reaching maintenance. <u>Limitations:</u>
FAQLQ-PF	OIT start	Reaching maintenance or treatment cessation																								
Total score	3.69	3.19	P < .001*																							
EI	3.66	3.32	P=0.001*																							
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SDL	3.50	2.94	P<0.001*																							

Study – food allergen	OIT protocol variables	PRO data collection	Number and age of patients enrolled	PRO Results (n: number of patients with valid responses)	Factors that influenced QoL outcomes	Main findings and study limitations																				
Study design																										
	1200; milk: 3600; egg: 6000			follow-up) who completed the FAQLQPF at mid up-dosing, a statistically significant improvement was seen between the start of OIT and mid-up-dosing for FA, SDL, and the total score but not for the EI domain:  Score (mean ± SE) Start Mid up-dosing Maintenance — EI — FA — SDL — Total Among the subset of patients whose FAQLQ-PF total score deteriorated (increased by > 0.5) from baseline to mid up-dosing (n=NR), FAQLQ-PF scores returned to near-baseline upon reaching maintenance. Mean FAQLQ-PF scores among 93 OIT patients with 6-months of maintenance (of 105, 88.6% follow-up) <table><tr><th></th><th>Baseline</th><th>Reaching maintenance</th><th>6 months of maintenance</th></tr><tr><td>Total score</td><td>3.55</td><td>3.23</td><td>2.55</td></tr><tr><td>EI</td><td>3.55</td><td>3.37</td><td>2.87</td></tr><tr><td>FA</td><td>3.78</td><td>3.32</td><td>2.55</td></tr><tr><td>SDL</td><td>3.33</td><td>2.99</td><td>2.28</td></tr></table> Significant differences were found for FA, SDL, and total score between start and maintenance and for all domains from maintenance to follow-up. The 14 patients reaching partial maintenance reported had worse FAQLQ-PF scores at baseline and reported significant improvement in the FA (P=.001) and SDL (P=.036) domain and the Total score (P=.015)		Baseline	Reaching maintenance	6 months of maintenance	Total score	3.55	3.23	2.55	EI	3.55	3.37	2.87	FA	3.78	3.32	2.55	SDL	3.33	2.99	2.28	SHTD (starting dose), reactions during treatment, duration of OIT. Borderline significant for EI and SDL: younger age Among the 158 patients who reached full desensitization, younger age predicted a greater improvement in the FAQLQ-PF scores. (EI, P=0.029, FA, P=n.s., SDL, P=0.021, total score, P=0.042)	*Not randomized: there may have been significant differences between controls and OIT groups *Only parent-reported QoL measures
	Baseline	Reaching maintenance	6 months of maintenance																							
Total score	3.55	3.23	2.55																							
EI	3.55	3.37	2.87																							
FA	3.78	3.32	2.55																							
SDL	3.33	2.99	2.28																							
Factor, 2012 ⁹² – peanut	Build-up target: 450 mg PP /d	At baseline and on achieving the maintenance dose: Parents	N=100	Significant improvement in QoL in all domains (AA, DR, RAE, EI, FA, and SDL) with the exception of the EI domain on the teens’ survey.	NA																					
Case series	Build-up interval: 2		Age: 5-18 (85 aged 5-12, 35 aged	QoL significantly improved (P<.02) on all 30 questions when parents assessed their children 5 to 12 years old.		<u>Limitations:</u> *No control group *No analysis																				

Study – food allergen	OIT protocol variables	PRO data collection	Number and age of patients enrolled	PRO Results (n: number of patients with valid responses)	Factors that influenced QoL outcomes	Main findings and study limitations						
Study design												
	weeks	of 5 to 12-year-old children: FAQLQ-PF 8-12-year-old children: FAQLQ-CF Teens (age 13-18): FAQLQ-TF	8-12, and 15 aged 13-18)	When children (8–12 years old) and teens assessed themselves, QoL improved (P<.05) on 22 of 24 questions and 12 of 18 questions, respectively. Percentage of responses than decreased by ≤ 1 point by domain: <table><tr><td>Parents (n=76)</td><td>FA: 65.7%, SDL: 64.4%; EI: 55.1%</td></tr><tr><td>Children (n=32)</td><td>DR: 69.7%, RAE: 65.2%; AA: 62.7%; EI: 56.5%</td></tr><tr><td>Teens (n=14)</td><td>AADR: 71.9%, RAE: 67.9%; EI: 49.4%</td></tr></table> See Figure below	Parents (n=76)	FA: 65.7%, SDL: 64.4%; EI: 55.1%	Children (n=32)	DR: 69.7%, RAE: 65.2%; AA: 62.7%; EI: 56.5%	Teens (n=14)	AADR: 71.9%, RAE: 67.9%; EI: 49.4%		
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n: number of patients with FAQLQ-PF data; N: number of patients enrolled; NA: not available; NR: not reported; T3: 3 months after build-up phase, T4: 12 months after build-up phase

FAIM: Food Allergy Independent Measure: FAIM total score is based on 4 main questions, with a response scale from 0 (no chance) to 6 (very great chance): FAIM-1: chance of accidental exposure, FAIM-2: chance of a severe reaction on food exposure, FAIM-3: the chance of dying from food exposure and FAIM-4: chance of a child effectively treating him/herself or receiving effective treatment, following a food allergic reaction. Additional questions 5 and 6 ask (respectively) how many foods are avoided because of FA (categorized as single, 2, multiple >2) and how much FA limits the type of activities that the child can take part in. A reduced FAIM score indicates an improvement in the parent's perception of the chance of an adverse outcome for their child with FA.

FAQL-PB: Food Allergy Quality of Life–Parental Burden: 7-point Likert scale (1 = not troubled, 7 = extremely troubled) for each question are summated, reporting the sum ranging from 17-119.

FAQLQ-PF: Food Allergy Quality of Life—Parent Form: for parents of children age 0-12 years: 7-point Scale (0- minimal impairment to 6 –maximal impairment), averaged over 3 areas with equal weighting: Emotional impact (EI), Food anxiety (FA), and Social and dietary limitations (SDL). The minimal clinically important difference (MCID) for FAQLQ-PF is 0.5.

FAQLQ-CF: Food Allergy Quality of Life—Child Form: for children age 8-12 years: 7-point Scale (1-not troubled to 7 –extremely troubled): 4 domains (24 items): Allergen avoidance (AA), Risk of accidental exposure (RAE), Emotional impact (EI), Dietary restrictions (DR). The minimal clinically important difference (MCID) for FAQLQ-CF is 0.5.

MCID: Minimally clinically important difference

PedsQL 4.0: Pediatric Quality of Life Inventory Version 4.0: 5-point Likert-scale (0=never, 4=almost always) for 8-18 year-olds, and a simplified 3-point scale for 5-7 year-olds. The 13 items are reverse-scored (0=100, 1=75, 2=50, 3=25, 4=0) reporting the mean sum of each item. The minimal clinically important difference (MCID) is ≥ 5.3 for child self-report and 5.5 for parental proxy report.

Perceived treatment burden: VAS-form: 3 domains: GI related AEs, taste and amount of daily peanut-dose, and time spent on OIT, range of VAS:0=no burden, 10=massive burden

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Appendix 4: Narrative summaries of the data that led to the recommendations

Recommendations on patient-centered care

Four studies in which parents completed the FAQLQ-PF questionnaire (a validated HRQoL instrument in food allergy) regarding the HRQoL of their allergic child both at baseline and after the build-up phase reported statistically and clinically significant improvements in the Total score,^{1,89,91,92} with the greatest improvements in the Food Anxiety domain.^{89,91} Two of them had randomized⁸⁹ or non-randomized⁹¹ control groups, in which HRQoL did not change significantly.^{89,91} The RCT observed that 77% of OIT patients reported clinically significant improvement in the Total score three months after completion of double-blind treatment compared to 34% of patients that had been randomized to placebo (P=significant),⁸⁹ with achieving sustained unresponsiveness significantly associated with larger QoL improvements.⁸⁹ FAQLQ-PF data for 66 patients from one Canadian OIT clinic also showed significant improvements upon completion of OIT (data on file). In contrast, in one double-blind peanut OIT RCT there were no statistically significant changes in FAQLQ-PF scores in the OIT arm, although there were numerical improvements.²

Two of the FAQLQ studies included self-reported data from a small number of children and teenagers (N=17 and 46);^{2,92} these reported significant improvements from baseline in the Total score and in most of its sub-domains.

One open-label RCT⁹⁰ used the generic Pediatric Quality of Life Inventory Version 4.0 questionnaire. The mean total score improved significantly from baseline to year 2 in the OIT group in both the children and their parents, with no significant changes in the control group; differences in the changes were statistically significant for the parents only.

In a longitudinal study following 175 children, the mean FAQLQ-PF scores improved from baseline through mid-up-dosing to reaching maintenance and further at 6 months into maintenance, with the greatest improvements seen during maintenance.⁹¹ In this cohort, a subset of patients reported deterioration in QoL during mid-up-dosing with a return to baseline levels upon reaching maintenance.⁹¹ Having a history of anaphylactic reactions and worse food-allergy related QoL at baseline was associated with larger QoL improvements.⁹¹ The type of food allergy treated (peanut, egg, milk) was not significant, but having multiple food allergies (in the context of single-food OIT) was associated with less positive QoL outcomes.⁹¹

Recommendations on eligible food allergens and clinical outcomes that can be achieved by OIT

A majority of patients undergoing OIT tolerate a higher amount of all food allergens at the end of the build-up phase (*at least partial desensitization*: peanut: 73-90% [³¹see note under Figure 1],^{9,56} chicken's egg: 82%,³⁰ cow's milk: 78-89%,^{14,15,29} hazelnut: 65%,²⁷ sesame: 100%²⁸), a significantly higher proportion compared to control patients in all controlled studies (Figure 1). (Note: For peanuts, an increase in the eliciting dose from less than 100 mg to 300 mg peanut protein was estimated to provide an at least 95% reduction of the risk of an allergic reaction stemming from exposure to traces of peanut in packaged foods.^{93,94}) Many patients can tolerate a full serving (*complete desensitization*: chicken's egg: 45-84%,^{20,30} cow's milk: 60-71%,¹³⁻¹⁵ wheat: 52-64%,^{24,25} walnut: 89%,²⁶ sesame: 88%²⁸) or a cumulative dose of at least 1 g peanut protein (4.2 peanuts) (56-78%) (Figure 1).^{8,31} A sizable proportion of patients continue consuming the food allergen regularly in the longer term (*continued consumption*: peanut: 35-78%,^{7,61} chicken's egg: 58-70%,^{60,62} wheat: 39%,²⁵ walnut: 70%²⁶, hazelnut: 65%,²⁷ sesame: 88%²⁸) and a variable proportion can maintain tolerance to the allergen after a period of food avoidance (*sustained*

unresponsiveness: peanut: 13-74%^{4,8} chicken's egg: 35-44%^{29,63} cow's milk: 21%,⁶⁷ wheat: 13%⁶⁷), but the amount of available data for this outcome is limited.

Patients undergoing OIT are more likely to experience allergic reactions related to consuming the OIT food allergen dose than patients who are avoiding the food. A majority of OIT patients have at least one allergic reaction, and, based on meta-analyses of milk, egg and peanut OIT trials, 16% to 17% of patients experience systemic or anaphylactic reactions (vs 1.6-2.6% of control patients),^{29,31} which require the use of epinephrine in 8.4% to 12% of patients (vs 0-3.7% of control patients).^{30,31} One meta-analysis estimated that peanut OIT approximately doubled the risk of serious adverse events (SAEs) (6.2% vs 3.0% control).³¹ Quality assessment of this analysis based on original source publications indicated misclassification of adverse events in some cases, suggesting that the rate of SAEs may be similar between OIT and control groups. Analyses of data from double-blind RCTs of peanut OIT indicate that adverse events related to accidental exposure to the food allergen occur in fewer patients undergoing OIT than in patients receiving placebo.^{2,95}

The average rate of discontinuation due to adverse events in peanut OIT RCTs has been estimated at 13% compared to 3.7% of control patients.³¹ Discontinuation rates due to adverse events ranged from 0 to 18% across egg^{12,17-19,21} and wheat²⁴ RCTs, sesame²⁸ and walnut²⁶ CCTs as well as in peanut⁸ and milk^{14,15} clinical practice. One exception is a wheat case series, in which an overall of 43% of patients discontinued OIT, 40% of them due to mild or moderate adverse events occurring during the 12-month maintenance.²⁵

Many studies across different designs and food allergens report that the occurrence or severity of allergic reactions declines as the treatment progresses from the build-up to the maintenance phase.^{2,3,8,9,13,20,25,26,28,32,56}

Recommendations on who could benefit from OIT (indications)

Most food OIT studies included children and adolescents across wide age ranges. Large case series of milk and peanut OIT, including patients starting from the age of four and up to 27 years, reported no significant association between age and safety outcomes and inconsistent observations regarding efficacy.^{7,14-16}

Three studies focused on toddlers and pre-school children (age 1-5 years) (2 peanut^{9,68} and 1 milk OIT¹¹); they indicate high efficacy (81-90% desensitization,^{9,11,68} 78% sustained unresponsiveness,⁶⁸ 90% continued consumption¹¹) and an excellent safety profile in this age group (0-0.4% had severe reactions). One peanut OIT RCT focused on adolescents (age 12-17 years); it reported a desensitization rate (400 mg peanut protein) of 81% compared to 11% for the placebo group. A second RCT, performing a sub-group analysis, reported that absolute differences in desensitization rates between OIT and placebo groups were comparable for adolescents and children aged 4 to 11 years (58% [95% CI 40 to 77%] and 66% [95% CI 54% to 78%] respectively).^{70,6} The same study also included adults (for a secondary end-point analysis), reporting a desensitization rate of 41% with OIT vs 14.3% with placebo, but the number of patients was small (41 in OIT and 14 in placebo group) and the difference was not statistically significant.^{6,70} One small case series of 23 adults receiving OIT reported significant increases in the amount of protein that patients were able to tolerate.⁷¹

Recommendations on contra-indications

A history of anaphylactic reactions to the targeted food allergen was generally not an exclusion criterion in OIT studies. Evidence from large case series on whether baseline history of anaphylaxis had an impact on OIT outcomes is inconsistent,^{7,8,14,16} but most patients with a history of anaphylaxis were able to achieve at least partial desensitization.^{8,14}

Across two reports of OIT clinical practice, there was no correlation between a patient's number of food allergies and the outcomes of single-food OIT.^{14 7} Studies of multi-food OIT targeting

patients with multiple food allergies raise no particular safety or efficacy issues in this patient demographic.^{22,23,96,97}

In many RCTs^{2-6,10,13,20} and reports of clinical practice,^{7,9,14} severe and/or poorly controlled or unstable asthma was an exclusion criterion for OIT. Baseline asthma was associated with an increased risk of adverse reactions in large case series,^{8,73,85,87} and asthma exacerbation was recorded as an adverse event in peanut and egg RCTs.^{6,20} Nevertheless, most patients with controlled asthma were able to achieve at least partial desensitization.^{7,8,15,73}

OIT requires patients (and/or their caregivers) to regularly attend visits, understand and follow instructions regarding administering the treatment at home, and be able to recognize and treat adverse events.^{59,98,99}

Recommendations on personalized protocols

Published OIT protocols vary in terms of food allergen product and preparation, initial dose escalation, build-up starting and target dose, up-dosing frequency, length of build-up phase and maintenance dose and frequency (see Table A1 in Appendix 2).

Most OIT clinical trials and all OIT clinical practice studies used non-pharmaceutical food-based products. There are no head-to-head comparisons between pharmaceutical and food-based products. Meta-analysis of peanut OIT RCTs found that both proprietary and non-proprietary OIT products led to desensitization versus placebo or usual care (non-proprietary: 67% [64/93] vs 7.5% ([4/53]; proprietary: 53% [256/481] vs 2.2% [5/231]).³¹

In terms of data directly comparing different OIT protocols, one egg OIT RCT indicated better efficacy outcomes when weekly up-dosing was combined with small daily dose increments than with weekly up-dosing only.²⁹ With respect to safety, this approach was associated with higher rates of mild and local reactions but lower rates of moderate to severe reactions.²⁹ Two small RCTs reported similar efficacy outcomes comparing different target or maintenance doses;^{24,68} however, in a clinical practice case series patients appeared to be more likely to continue peanut consumption when the maintenance dose was lowered.⁷ Consuming the maintenance dose daily versus every second day was associated with fewer reactions and better adherence in an egg OIT RCT,²¹ but in a milk OIT RCT there was no difference in the frequency of adverse events between daily and weekly consumption after one year of maintenance.¹⁰⁰

With respect to treating multiple food allergies, one non-randomized study (N=40) observed similar rates of reaction per dose with multiple-food OIT (targeting up to 5 foods simultaneously) as compared to single-food OIT, while time to reach 10-fold increase in desensitization threshold was only 3.2 months longer with multi-food OIT as compared to single-food OIT.²²

Recommendations for the safe provision of OIT

Clinical studies of OIT report that anaphylactic reactions or reactions requiring the use of epinephrine may occur in the clinic as well as during home dosing. Some studies reporting fewer reactions at home than in the clinic,^{9,14,26,28} while others report more reactions at home.^{8,13,56} Note that up-dosing, which is associated with a higher risk of reaction, occurs in the clinic, but the proportion of doses administered at home is usually higher and increases with the duration of treatment. These factors could contribute to the observed differences between studies.

EoE is more prevalent in children with food allergy compared to the general pediatric population (4.7% vs 0.04%) and is particularly associated with milk and egg allergy.¹⁰¹ Biopsy-confirmed EoE occurred in 0.4% (peanut) to 6.3% (milk) of patients undergoing OIT.^{2,5,6,55,66,78,81-83} Recurrent gastro-intestinal symptoms indicative of EoE were reported in 8.2 to 14% of OIT-treated children^{8,79} and 1.1%⁹ of pre-school children and were managed with dose adjustments.⁸⁰

Three RCTs compared OIT in the presence of omalizumab versus OIT with placebo.¹⁰² Omalizumab did not improve efficacy outcomes at 28 or 32 months when used for an extended time with a standard slow OIT schedule;¹⁰² however, a short course of omalizumab within an

accelerated OIT schedule significantly increased desensitization rates.^{97,103} Omalizumab use was also associated with a reduced rate of dosing reactions.^{97,102}

Appendix 5: Equipment required

The following tables on the minimal and additional safety requirements for the management of emergencies in allergy office are from the CSACI position paper on safety standards for the management of office emergencies (in redaction).

Table S5.1: Minimal Safety Medications, Equipment and Supplies

Category	
Vital sign assessment	- Stethoscope - Sphygmomanometer and blood pressure cuffs - Oxygen saturation monitor - Personal protective equipment (gloves, mask, eye shield) - Watch or clock
Medications	- Intramuscular epinephrine (3 doses) - Glucagon or vasopressin for adults on beta blocker - Salbutamol (with MDI and spacer or nebulizer) - Second generation antihistamine
Airway	- Oropharyngeal airway (adult and pediatric)
Breathing	- Self inflating bag-valve-mask (adult and pediatric) - Disposable face masks (adult and pediatric) - Oxygen tank - Oxygen extension tubing - Oxygen nasal cannula - Non rebreather mask (adult and pediatric)
Circulation	- Tourniquet - Tape - Alcohol swabs - Drip chamber - Syringe with needles - T-connector - Extension tubing - Intravenous 0.9 normal saline (two 1 liter bags) A method to establish parenteral access which could include any of: - Intravenous butterfly needles - Indwelling catheters - Intraosseous devices
Other	- Written anaphylaxis management protocol - Flow chart for recording times and events - 911 script for office staff to use

Table S5.2: Additional equipment and medications to consider, depending on provider experience, skill and location

Category	
Vital sign assessment	- Automated BP cuff, HR, and O2 sat monitor - 5 minute timer
Airway	- Portable suction - Nasal airway - Laryngeal airway masks (LMA) with lubrication - Laryngoscope with blades, ET tubes, stylet and CO2 detector, tape and suction, and Magill forceps

	- Alternative airway devices (eg: King Airway)
Breathing	- Nebulizer mask
Circulation	- Pediatric Armboard - Set up for 3 way stopcock for pediatric fluid bolus - Intraosseous devices - AED
Medications for treatment of allergic conditions	- Ipratropium bromide (spacer with MDI or nebulizer) - Diphenhydramine IV - Corticosteroid for injection
Medications for treatment of non allergic conditions	- Nitroglycerine spray - ASA - Naloxone - Lorazepam or diazepam - Glucose gel

Appendix 6: Sample protocols

The following sample protocols are based on the protein content for the allergen(s) included in the OIT treatment. The actual amount of food given will therefore depend on the protein content of the allergen.

The following equivalency table provides protein content for foods frequently used for OIT, based on the USDA food database. Because variations in protein content are to be expected according to brand or nut size, patients should be advised to use the same product at home as the one used in clinic during the up-dosing phase. Ideally, new products are introduced during up-dosing visits. Once maintenance has been achieved and is well tolerated, patients can usually experiment with new food alternatives safely, provided they understand the concept of food equivalency. Consultation with registered dietitians experienced in OIT and teaching tools to that effect can be very helpful to assist patients with equivalent food alternatives.

For food containing heat-labile allergens, such as milk or egg, special consideration should be given to the product used in OIT. Where desensitization with raw forms will protect against cooked forms, the reverse may not be true. In practice, patient objectives regarding heat-labile and heat-resistant allergens are often not the same. Where patients often wish to achieve complete desensitization to cooked forms to allow their introduction in diet and reduce limitations, most only wish to achieve partial desensitization against raw forms to protect against accidental contamination. The choice of products should reflect those objectives, which can change during therapy as patients discover their love or dislike of the food they had been avoiding. For example, a target daily maintenance dose for milk allergy could be 15mL of fresh milk (0.5g protein) and 1 whole portion of string cheese (6g protein).

Measurement of daily doses

Whole units: With larger dose amounts, easily measurable food units can be used (e.g. $\frac{1}{4}$ peanut snack stick, 1 cm of string cheese).

Weight: With smaller amounts, individual doses can be measured precisely with scale in soufflé cups or capsules. Usual practice aims for a level of precision of $\pm 10\%$. If this task is delegated, proper training is essential to avoid dosing errors and cross-contamination and ensure traceability.

Volume: A practical alternative to weighing individual doses consists in using syringes or measuring spoons for patient to calculate daily dose for liquid food or suspension.

The suspension media must be adapted to the food. For example, defatted peanut or sesame flour are best suspended in simple syrup suspension. Nut meals, on the other hand, tend to float in simple syrup because of their oil content. Suspension vehicles with suspending and anti-foam agents (e.g. oral-blend or oral mix) are therefore better suited for nut meals.

Example of Recipe for 60 mL of peanut suspension at 250mg protein per 5mL (50mg/mL):

In a sterile specimen cup, add 6g of defatted peanut flour (or 7.2g of powdered peanut butter). Add simple syrup up to the 50mL line. Mix thoroughly with spoon. Complete with simple syrup up to the 60 mL line. Shake. Keep refrigerated.

On the label, make sure to indicate:

- Patient name
- Content and concentration (e.g. peanut 250mg/5mL)
- Date of production
- Peanut flour lot
- Peanut flour expiry date

Equivalency table: protein content per type of allergen

Protein content is based on the USDA database. Exact allergen content may vary according to brand. Food escalations in clinic should therefore be performed with the same product that will be used at home.

Allergen		Amount of protein
Chicken's egg	1 mg of powdered-egg whites	1.25 mg
	1 whole egg	5000 mg
	1 ml raw egg* mixed	100 mg
	Note: Raw egg is not recommended under 1 year old unless pasteurized due to risk of bacterial contamination	
Peanut	1 peanut	250 mg
	1 ml Peanut butter (Kraft®)	200 mg
	2.4 mg of powdered peanut butter (PB2®)	1 mg
	2 mg of defatted peanut flour	1 mg
	0.1 mL of peanut flour suspension (50mg/mL)	5 mg
	1 peanut stick snack (Bamba®)	80 mg
Cow's milk	1 ml milk (any percent of fat)	35 mg
	2.8 mg of powdered milk	1 mg
	1 cm of string cheese stick (6g protein for 12cm stick)	500 mg
Mustard	1 ml yellow mustard	40 mg
Hazelnut	1 table spoon of Nutella ®	300 mg
	1 hazelnut	180 mg
	Hazelnut meal	1 mg
Almond	1 almond	275 mg
	4.6 mg of almond meal/flour, non-defatted	1 mg
	2.6 mg of powdered almond butter (PB2®)	1 mg
Cashew	1 cashew	275 mg
	5.6 mg of cashew meal	1 mg
Pecan	1 pecan half	150 mg
	10 mg of pecan meal	1 mg
Pistachio	1 pistachio	150 mg
	4.6 mg of pistachio meal	1 mg
Walnut	1 walnut half	360 mg
	6 mg of walnut meal	1 mg
Salmon	5 mg of smoked or raw salmon	1 mg
Sesame	1 ml tahini	167 mg
	2.5 mg of defatted sesame flour	1 mg
	DO NOT USE whole sesame seeds unless crushed to allow release of the allergen contained in the seed.	
Shrimps	1 small shrimp (2.5g)	450 mg
Soy	1 ml soy milk (7g/250 ml)	28 mg
Oat	7.5 mg of oat flour	1 mg
Barley	9.3 mg of barley baby cereal	1 mg
Rye	7.5 mg of rye flour	1 mg
Buckweat	7.5 mg of buckwheat flour	1 mg
Wheat	1 slice of whole wheat bread (32g)	4380 mg
	10 mg of white all-purpose flour	1 mg
	1 macaroni (elbow)	35 mg

Sample dosing schedules

Note: all schedules are meant as guidance and should be adapted to patient response and personal objectives. These are provided as examples to guide implementation of OIT and have not been shown superior to other published schedules.

CoFAR schedule

This protocol, published by Burks et al in 2012,³² consists in an initial food escalation up to a dose of 6 to 50 mg of food protein. Followed by daily dosing with the highest tolerated dose and up-dosing every other week.

Food doses are initially doubled (+100%) at each step up to a dose of 50 mg protein. Percentage increments are then progressively decreased to increments of +25%.

Step	Protein amount	% increase
1	0.1 mg	-
2	0.2 mg	100%
3	0.4 mg	100%
4	0.8 mg	100%
5	1.5 mg	100%
6	3 mg	100%
7	6 mg	100%
8	12 mg	100%
9	25 mg	100%
10	50 mg	100%
11	75 mg	50%
12	100 mg	33%
13	125 mg	25%
14	156 mg	25%
15	195 mg	25%
16	245 mg	25%
17	306 mg	25%
18	383 mg	25%
19	479 mg	25%
20	599 mg	25%
21	749 mg	25%
22	936 mg	25%
23	1170 mg	25%
24	1463 mg	25%
25	1829 mg	25%
26	2286 mg	25%
27	2858 mg	25%
28	3572 mg	25%
29	4465 mg	25%
30	5582 mg	25%
31	7000 mg	25%

Omalizumab-enabled accelerated schedule

Adapted from Begin et al., 2014²³

This up-dosing schedule follows the same structure as CoFAR schedule, but faster. The first steps for the initial escalation triple the amount of food (+200%) and latter up-doses consist in doubling the dose (+100%). This accelerated protocol was developed for patients having received omalizumab for at least 2 months prior to initiating OIT, which contributes to increase their reactivity threshold (off-label indication).

Step	Protein amount	% increase
1	5 mg	-
2	15 mg	+200%
3	50 mg	+233%
4	150 mg	+200%
5	300 mg	+100%
6	600 mg	+100%
7	1200 mg	+100%
8	2400 mg	+100%
9	4800 mg	+100%
10	9600 mg	+100%

Pre-school peanut schedule

This protocol was published in a cohort study of toddlers and pre-schoolers undergoing peanut OIT⁹ but can be used for any patient with high baseline reactivity threshold to their food. It can be initiated with an initial escalation or directly at a dose that is expected to be below the patient's reactivity threshold (given in clinic). For convenience, the up-dosing steps were developed based on easily measurable portions of the Bamba peanut snack. The schedule should be adapted to the food used to remain convenient.

Step	Protein amount		% increase
1	10 mg	1/8 sticks	-
2	20 mg	1/4 sticks	100%
3	40 mg	1/2 sticks	100%
4	80 mg	1 sticks	100%
5	120 mg	1 1/2 sticks	50%
6	160 mg	2 sticks	33%
7	240 mg	3 sticks	50%
8	320 mg	4 sticks	33%

Individualized symptom-driven up-dosing

This approach consists of individualizing up-dosing speed according to patient tolerance. There is no predetermined schedule. Home dosing is started at the highest tolerated dose from an initial escalation customized based on patient's baseline allergy profile (i.e. allergy testing, previous challenges or clinical reactions) and personal tolerance to the risk of reacting on that first introduction.

Intervals between dosing visits

The approach generally assumes constant intervals between up-dosing visits (2 weeks to 3 months). In some patients, longer intervals may improve chances of tolerating a given escalation but the extent to which length of interval between up-dosing visits contributes to preparedness for next escalation is unknown and most likely varies between patients. At a minimum, new symptoms from the previous escalation should have abated before proceeding with the next escalation. Greater intervals between intervals can also contribute to decreasing the logistical burden of therapy for patients and providers.

First up-dosing visit:

When the starting dose was well tolerated, both in clinic and at home, the first up-dosing visit will usually consist of an attempt to double the dose (+100%). An additional +100% can be added 30 minutes later during the same visit if it was well tolerated, for a total +200% escalation. A more conservative initial increment of +50% can also be considered based on specific context and shared-decision making.

Example A: First up-dosing after starting OIT at a daily dose of 10mg.

Step	Amount	% of current dose	Cumulative
1	20 mg	+100%	20 mg
	10 mg	+100%	30 mg

If the escalation is not tolerated in clinic: Patient should remain on the current dose and rescheduled for an attempt to escalate with half the failed % increment (+50% in the example above, 15 mg). Alternatively, in absence of systemic symptoms to the failed escalation, the patient could also attempt to increase to half the failed % increment at home.

Following visits:

If the dose was well tolerated at home since the last escalation: The subsequent escalation should use the same percent increment.

Example A: Escalation to 30 mg (+200%) was well tolerated in clinic and at home.

Step	Amount	% of current dose
2	90	+200%
3	270	+200%
4	2 hazelnuts	

If the escalation was not well tolerated at home after the last escalation: The subsequent escalation should use half of the % increment

Example B: Escalation to 20mg (+100%) was tolerated in clinic but patient was bothered by moderate symptoms during the first week of home dosing at that dose.

Step	Amount	% of current dose	Outcome
2	30	+50%	Moderate symptoms at home
3	38	+25%	No symptoms

4	48	+25%	No symptoms
5	60	+25%	No symptoms

If following escalations are completely symptom-free: Re-attempting higher percent increments can be considered. Assessment of dosing tolerance should take into account whether or not pre-medication is used prior to food dosing. Transient mild symptoms with home dosing are frequent in the first week following an escalation and are an indication that treatment speed is most likely optimal.

Example B (cont'd)

Step	Amount	% of current dose	Outcome
6	90	+50%	Oral pruritus for 4 days
7	135	+50%	No symptoms*
8	200	+50%	No symptoms*
9	300	+50%	No symptoms*
10	2 hazelnuts		No symptoms

*Patient advised to take cetirizine 60 minute before dose for the first 4 days after an escalation.

When patients are using pre-medication before taking food dose at home, the same medication should be used prior to the up-dosing. When patients are symptom-free with medication, ability to tolerate the dose without the pre-medication should be assessed before considering further increasing the up-dosing speed.

Pre-medication

Note: The following protocol on the use of pre-medication is meant as an example to help support implementation of OIT and has not been shown superior to other clinical approaches to pre-medication in OIT. Recourse to and choice of medication should be individualized based on patient specific symptoms and context and should be adapted to patient response and personal objectives. Apart from disodium cromoglycate which is specifically indicated for the prevention of gastro-intestinal IgE-mediated symptoms, the uses described below constitute off-label uses.

For oral pruritus:

- Consider a trial of non-sedating oral H1 antagonists one hour before taking the food dose.

For immediate gastro-intestinal symptoms (<30 minutes):

- Consider taking the food dose with along with a bulky meal or snack
- Consider a trial of oral H2 antagonists and/or non-sedating oral H1 antagonists one hour before taking the dose.

For delayed gastro-intestinal symptoms (>45 minutes):

- Consider taking dose in the morning, as sleep cycle/deprivation can contribute to decreased dose tolerance.
- Consider a trial of oral montelukast, one hour before taking the doses¹⁰⁴.
- Consider taking misoprostol before the dose, once a day. Finding optimal dosage of misoprostol can be challenging as it can cause confusing symptoms of intestinal cramping and diarrhea. Determining the right therapeutic index in the context of OIT requires close follow-up with patient and adjustments. It is usually reserved for patients where delayed symptoms appear to progress rather than abate over time following a food dose increase, presumably from the local cumulative amplifying effect of prostaglandins, and mast cell stabilizers are insufficient or not covered.

For either immediate or delayed gastro-intestinal symptoms, or both:

- Consider a trial of disodium cromoglycate no more than 15 minutes before taking the dose (once a day, unless food dose is taken multiple times).

In the context of an unavoidable co-factor (e.g. NSAIDs following dental procedure), to decrease the risk of systemic reactions to the dose:

- Consider a transient decrease in the daily dose
- Consider transiently adding disodium cromoglycate, taken once a day, no more than 15 minutes before the food dose. In mice models, disodium cromoglycate prevents the loss of barrier functions resulting from mast cell activation in the gastro-intestinal tract that is exacerbated by co-factors such as NSAIDs, which in turn protected against co-factor induced systemic reactions to the food dose.¹⁰⁵

To prevent the occurrence of isolated bronchospasms following food dosing:

- The presentation of isolated bronchospasm without other systemic manifestation of anaphylaxis following food dosing suggests localized increased sensitivity of mast cells in bronchial tissue.
- If known asthma, reassess control and need to increase inhaled corticosteroids.
- If no asthma, consider diagnosis and consider a trial of inhaled corticosteroids.
- Assess and address potential contribution of environmental allergens.
- Consider performing FeNO. The objective measure of a local inflammatory process with FeNO is particularly useful to confirm the presence of underlying “sub-clinical” asthma when patient has no manifestation of asthma other than with food dosing. It can be

helpful to demonstrate the concept to the patient and to monitor response to therapy in this particular context.

For gastro-intestinal symptoms which timing is not related to food dosing:

- Consider the possibility of a cellular-mediated allergic reaction to the food allergen. This can be difficult to differentiate from delayed type IgE-mediated reactions. Response to trials with the above-mentioned medications can help distinguish the underlying process.
- Consider adding a proton-pump inhibitor.
- Consider transiently or permanently decreasing the food dose.
- Consider performing endoscopy. In the context of OIT, the presence of eosinophils on endoscopy can result from either recurrent delayed type IgE-mediated reactions or from a cellular-mediated reaction and should therefore not be the sole basis on which to orient management.
- Consider performing an atopy patch test (APT) with the food allergens. Where many patients with IgE-mediated food allergy can present mild infiltrate on APT, a strong reaction to one or more specific food is unusual and can be useful to guide management.
- *For patient with symptoms compatible with eosinophilic oesophagitis (EoE),*
 - o Discuss the options of discontinuing or continuing OIT with patient. In a previous cohort of patients with cellular-mediated symptoms with OIT, those with symptoms compatible with EoE were generally able to continue treatment.
 - o Consider a trial of swallowed topical corticosteroid after discussing.
- *For patients with symptoms compatible with eosinophilic gastro-intestinal disease (EGID),*
 - o Consider discontinuing OIT. In a previous cohort of patients with cellular-mediated symptoms with OIT, those with symptoms compatible with EGID were unable to complete treatment.
 - o For patients already receiving another biologic therapy indicated for their asthma, consider switching to dupilumab, which could contribute to a better control of cellular-mediated allergic response in the gastro-intestinal tract¹⁰⁶.