Bégin *et al.*
Allergy Asthma Clin Immunol (2020) 16:20
https://doi.org/10.1186/s13223-020-0413-7

Allergy, Asthma & Clinical Immunology

REVIEW

Open Access

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

P. Bégin[1,2,3*], E. S. Chan[4], H. Kim[5,6], M. Wagner[7], M. S. Cellier[3], C. Favron-Godbout[8], E. M. Abrams[9], M. Ben-Shoshan[10], S. B. Cameron[4,11], S. Carr[12], D. Fischer[5], A. Haynes[13], S. Kapur[14], M. N. Primeau[15], J. Upton[16], T. K. Vander Leek[12] and M. M. Goetghebeur[7]

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 dieticians, 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.

*Correspondence: philippe.begin@umontreal.ca
[1] Division of Clinical Immunology, Rheumatology and Allergy, Department of Pediatrics, Sainte-Justine University Hospital Centre, Montreal, QC, Canada
Full list of author information is available at the end of the article

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 dieticians, 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.

DIMENSIONS	Criteria
SOCIOPOLITICIAL *Promotion of conditions conducive to common good*	C1 - Historical, political, cultural context
	C2 - Stakeholder visions
POPULATIONAL *Promotion of equity*	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 *Promotion of health and well-being (outcomes of the intervention)*	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
	C12 - Impact of the intervention on quality of life and health as perceived by the user
ORGANIZATIONAL *Promotion of integrated care*	C13 - Alignment of the intervention with the mandate of the healthcare system
	C14 - System capacity and appropriate use of intervention
ECONOMIC *Promotion of sustainability*	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

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.

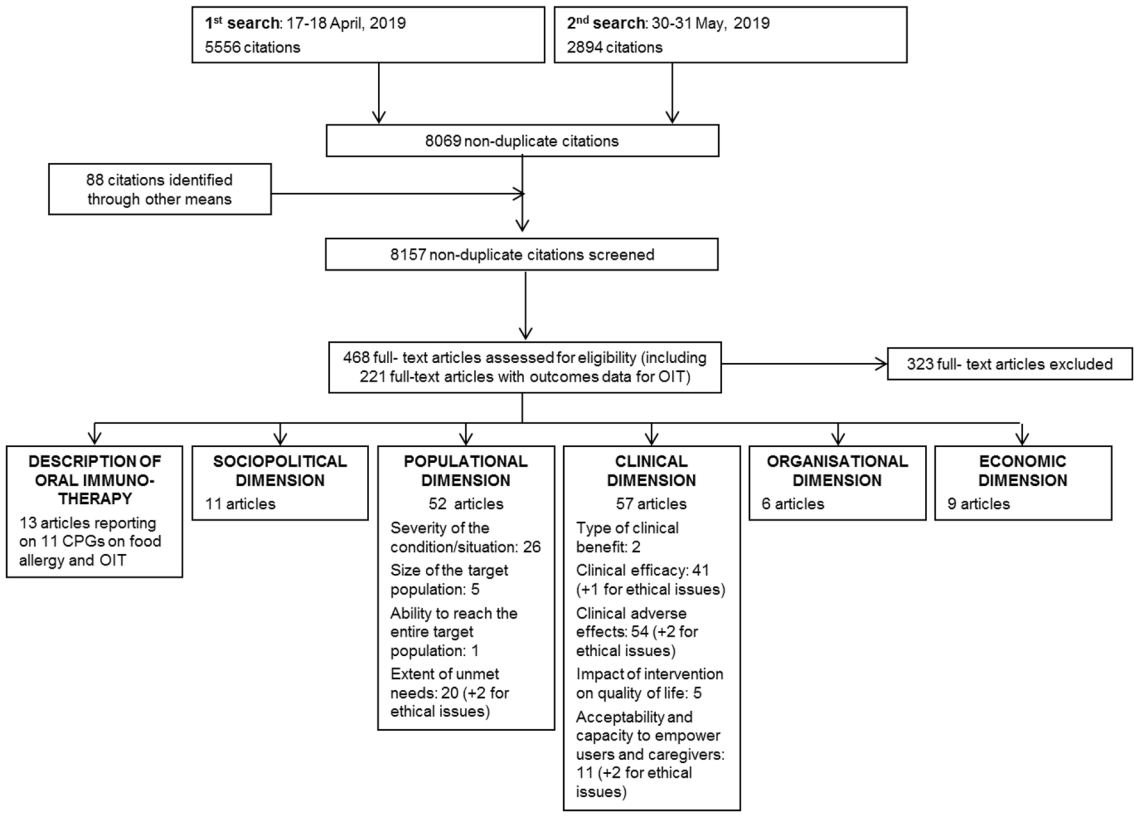


Fig. 2 PRISMA diagram

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.

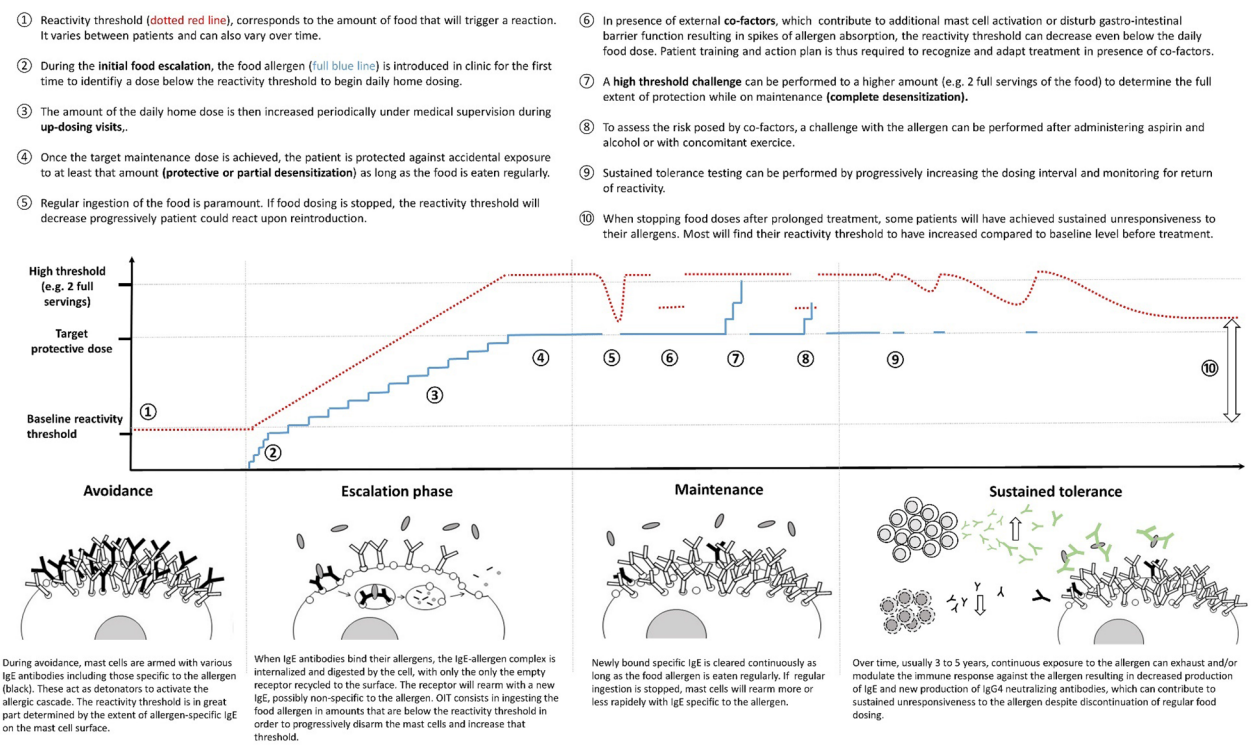


Fig. 3 Key concepts and definitions pertaining to OIT

Box 1: Recommendations for a sociopolitical context for optimized food allergy management	**Ethical imperative, data or other considerations in support of the recommendation**
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	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
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	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
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	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
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	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
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	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.

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

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	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.
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	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*
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	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*
OIT may be recommended to achieve sustained unresponsiveness, but data is limited and variable	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 *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	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*. 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)	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*
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	This recommendation is based on the principle of *nonmaleficence* It is supported by data from consultations with stakeholders
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 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* 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
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	
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 dieticians 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 dieticians 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 dieticians, 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 *reducing social inequalities in health* 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 *sustainability* and a *fair and efficient allocation* 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

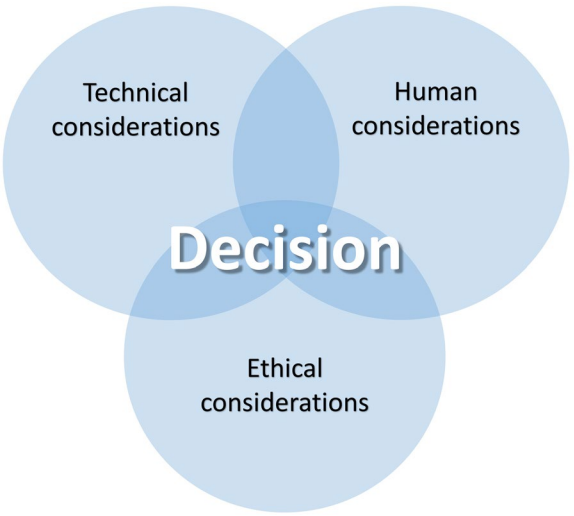


Fig. 4 Considerations for balanced decision-making in medicine

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 meting 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 EEACI 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)*
SOCIOPOLITICIAL DIMENSION AND PROMOTION OF CONDITIONS CONDUCIVE 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 Columbia[76]) 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 families[77] (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 dollars[79]), 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 AImmune.[80] The FDA granted a fast track process and breakthrough therapy designation to this product (Palforzia®) 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, 2018[78]) 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 84-86] 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 (RCT[74]). 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 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 reticent 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 dieticians, 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)

<table>
<tr><th>DIMENSION
Criteria</th><th>Data collected from the literature, milieu and consultations (in italics)</th></tr>
<tr><td></td><td>Pushing for OIT are: a portion of allergists, healthcare providers, patients and caregivers; pushing against: another portion of allergists, pharmaceutical companies, government officials.

<u>ETHICAL ISSUES:</u>
• 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.</td></tr>
<tr><td>C3-Severity of the condition / situation</td><td>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 departments[93]
• 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 hospitalization[96]) and 0.2% in adults.[97]
HEALTH-RELATED QUALITY OF LIFE (HRQOL):
• Fear of accidental exposure: uncertainty, anxiety and distress in parents, children[1-3] 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 10152, 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] hospitalizations[2]), multiple food allergies,[103 106] using[2] or carrying[103] an epinephrine auto-injector, a prolonged cow milk-free diet,[104] and older age of the child.[104-106]

<u>CONSULTATIONS</u>
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.

<u>ETHICAL ISSUES</u>:
• 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</td></tr>
</table>

Table 1 (continued)

DIMENSION Criteria	Data collected from the literature, milieu and *consultations (in italics)*
	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.
C4-Size of the target population	• **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.
C5–Ability to reach the entire target population (access)	• 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.
C6 - Extent of unmet needs	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 **children**[119] in and **their siblings**;[120] risk of **inadequate intake of certain nutrients**[121] (e.g., calcium with increased risk of osteoporosis[122]), 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

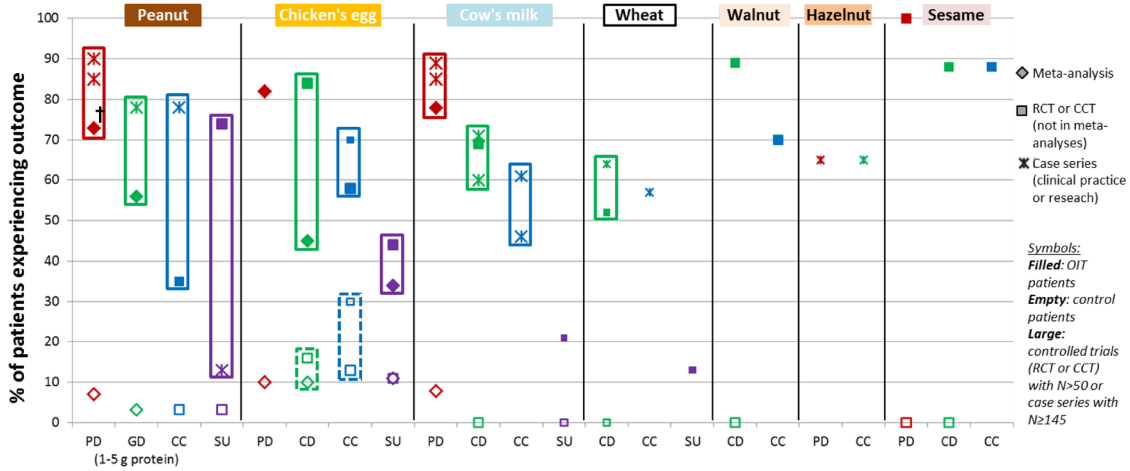
Table 1 (continued)

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 patients[130]). 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*".[77]
C7-Social priorities	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.
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 checklist [25] 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



Controlled trials	L	L	H	L	H	H	H	M	H	H	--	H	L	--	M	H	H	--	--	H	H	H	
Case series	M	M	M	H	--	--	--	--	M	M	M	--	L	L	--	--	--	H	H	--	--	--	
References	24 29 30	24 40	51 54	40 46	23	23 31	50 52	22 56	22 32 33	32 33 39	33 53	57	34 35	35	34	36	36	37	37	38	38	38	

† Note: This value is based on an additional analysis of 8 RCTs[43 44 46-48 61 64] (1 unpublished) included in the PACE meta-analyses: 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 egg[31])
- Across **three** reports of OIT clinical practice, **high specific IgE serum levels** (milk[33] peanut[40]) and **low tolerated dose of food allergen** (milk[32]) were **associated with failure to achieve full desensitization**; patients with a **history of anaphylactic** reactions were less likely to achieve desensitization according to one (milk[32]) 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 49 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).[54] (case series, N= 145 to 295)

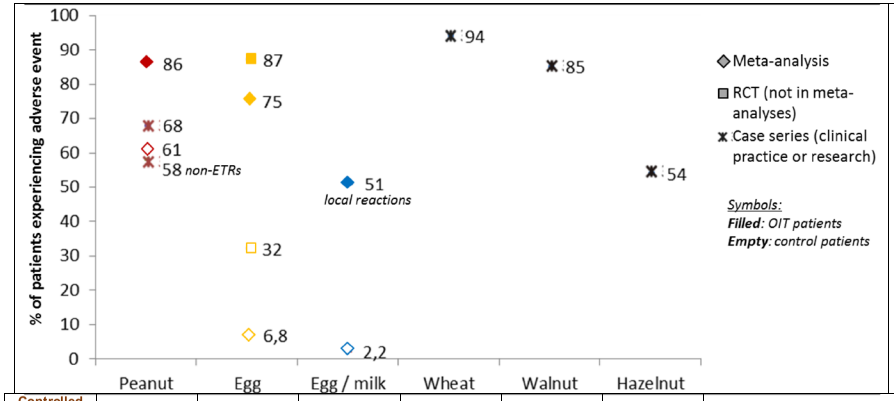
Data from studies in specific age groups:

- **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=37[58], N=270[30]); **90% desensitized to 200 mL milk** versus **23%** control (RCT[63], 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 trial[58]: N=37 OIT, 154 control) • **90%** continued to consume **200 mL milk** per day (RCT:[63] 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 controls[44]) • **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 study[44]: 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** (milk[72]) 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=145[54]) **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=280[32] peanut, N=111[54]) **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) (RCT:[31] 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%) (RCT:[34] 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). (RCT:[58] 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%) (RCT:[55] 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 (in italics)*
	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  ***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]

Controlled trials	L	H	M	L	H	--
Case series	L	--	--	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 (in italics)*

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** (integrated analysis of 2 double-blind RCTs[134])
- **17% peanut OIT** vs **45% placebo** (P=0.026) (double-blind RCT, N peanut OIT=30, placebo=31)[61]

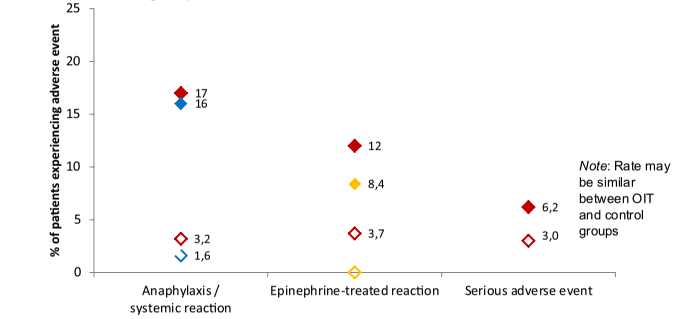
A3. SEVERE REACTIONS AND EPINEPHRINE USE

- **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: moderate[22])
- 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 high[23])
- 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.*



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*

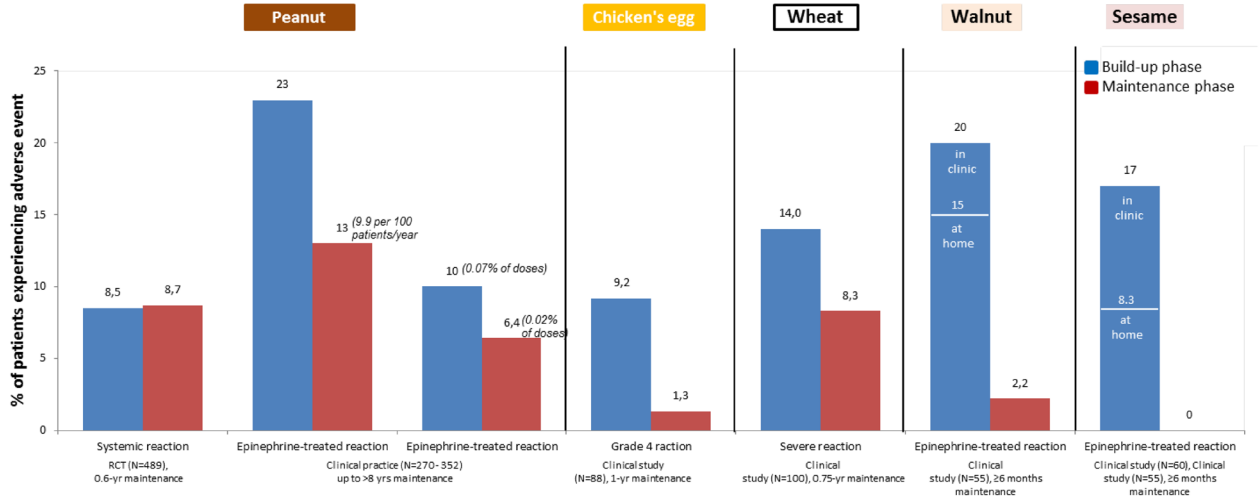
- **No** severe reaction (≥ grade 3) (CCT N=60 OIT, 15 control; high risk of bias)[38]

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]



References	47	40	29	31	35	36	38

Additional studies report as well that the occurrence or severity of allergic reactions declines as the treatment progresses (not in figure).[30 39 49 60 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 walnut[36] or wheat[34] 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 symptoms[144]

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<0.01[53]); *wheat*: **59%** (N=17);[145] *egg*: **28%** (N=61).[145] Patient-reported precipitating factors included exercise,[33 53 145] fatigue[145] 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 analysis[30]), **history of anaphylactic reactions** (2 analyses [53 54]) and **low tolerated dose of food allergen** (1 analysis[32]) 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**,[94] **low tolerated dose of food allergen**[53] 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 egg[31]). Percentages of patients experiencing following adverse events in these studies:

	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:[64] **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 arrest[31]	• **8.0%** OIT vs Control: NR[31]
Milk	• 6.7% of patients visited emergency departments during home dosing[41]	• hospital rush phase: **13%** OIT vs **0** control; home-dosing: **3.3%** OIT vs **0** control[41]

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 enrolment from age [29 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) undergoing **milk OIT** 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=37[58], N=270;[30] milk: RCT:[63] 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 study[44]: 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=194[72]; peanut, N=270[40]), **moderate to severe adverse reactions** during the hospital-based rush phase (milk, N=192[146]), **eosinophilic esophagitis-like OIT- related syndrome** (peanut, N=270[40]), and **adverse events** during maintenance (peanut, N=104[147]); however, one study found no association between asthma and reactions during home-dosing (milk, N=132[148]). • 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 (RCT[150], 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 v*alue not reported* (RCT:[55] 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=25) and **single-food OIT** (N=15) (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)[71] **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.
C10 -Type of clinical benefit offered by the intervention	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.*
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)*

	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[40])
	  • **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=295[33])
	
	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]

C12-Impact of the intervention on quality of life and health as perceived by the user	**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 placebo[160]), 1 prospective cohort study[161] (peanut, egg, sesame, tree nuts; N=175 OIT, 48 control), 1 case series[162] (peanut, N=100), 1 open-label cross-over RCT[64] (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 10 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 instrument [163] (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 adolescents[162]) 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 RCT[164]) 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)

<table>
<tr><th>DIMENSION
Criteria</th><th>Data collected from the literature, milieu and consultations (in italics)</th></tr>
<tr><td></td><td>
GENERIC QUALITY OF LIFE OUTCOMES (Pediatric Quality of Life Inventory Version 4.0 (PedsQL 4.0, not validated in food allergy; 1 peanut RCT[164] (N= OIT: 39, Control 20)
• Child QoL: OIT: significant improvement (P<.0001) 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<.0001) 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></th><th>Data source</th><th>Factor</th><th>Significant association?</th></tr>
<tr><td rowspan="6">Baseline characteristics</td><td rowspan="6">Prospective cohort study of 191 children with various food allergies[161]</td><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</td><td>No</td></tr>
<tr><td>asthma status</td><td>No</td></tr>
<tr><td rowspan="3">Treatment outcomes</td><td>RCT of 62 children with peanut allergy[160]</td><td>achieving sustained unresponsiveness</td><td>✓</td></tr>
<tr><td rowspan="2">Prospective cohort study of 191 children with various food allergies[161]</td><td>duration of up-dosing</td><td>No</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

<u>CONSULTATIONS</u>
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 supress 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.
<u>ETHICAL ISSUES</u>: Not applicable
</td></tr>
<tr><td colspan="2">ORGANIZATIONNAL DIMENSION AND PROMOTION OF INTEGRATED CARE</td></tr>
<tr><td>C13–Alignment of the intervention with the mandate of the healthcare system</td><td>
• OIT is aligned with the mandate of the healthcare system.
• The Canada Health Care Acts 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)

<u>CONSULTATIONS</u>
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.
<u>ETHICAL ISSUES</u>: Not applicable
</td></tr>
<tr><td>C14-System</td><td>• 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]</td></tr>
</table>

Table 1 (continued)

<table>
<tr><th>DIMENSION
Criteria</th><th>Data collected from the literature, milieu and consultations (in italics)</th></tr>
<tr><td>capacity and appropriate use of intervention</td><td>

In hospital, resources for food allergy are devoted to avoidance.
Implementation of OIT requires consideration of several factors explored below:

<table>
<tr><th></th><th>Recommendations or reported practices for OIT in clinical practice</th><th>Reference</th></tr>
<tr><td>Expertise / training requirements</td><td>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</td><td>FAST, 2018[78] – USA
EAACI, 2018[8] - Europe</td></tr>
<tr><td>Equipment and medications required</td><td>Stethoscope, 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</td><td>EAACI, 2018[8] - Europe</td></tr>
<tr><td>Logistics of patient education, communication and shared decision-making</td><td>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?)</td><td>FAST, 2018[78] - USA
Blaiss, 2019[81] - USA
Nachshon, 2015[166] - Israel
SEICAP, 2017a[9] - Spain
EAACI, 2018[8] - Europe</td></tr>
<tr><td>Logistics of food allergen dose administration</td><td>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)</td><td>Blaiss et al, 2019[81] - USA
EAACI, 2018[8] - Europe
SEICAP, 2017a[9] - Spain</td></tr>
<tr><td>Logistics of food allergen dose preparation and storage</td><td>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</td><td>FAST, 2018[78] - USA
Blaiss, 2019[81] - USA</td></tr>
</table>
<u>CONSULTATIONS</u>
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 dieticians 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 thing with people other than their parents. Some issues might come out more effectively this way, amongst people sharing their experiences, which would help address 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.

<u>ETHICAL ISSUES</u>: Not applicable
</td></tr>
</table>

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 dose**[167] (data from 1 Canadian OIT clinic) **Commercial approach:** • **Acquisition cost of commercialized peanut product** (estimate): **US$3600 to US$4800** per year (ICER, 2019[6]); 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 weeks[69])* **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 dieticians 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.* **ETHICAL ISSUES**: Not applicable
C17-Costs for the user / caregiver	**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)

<table>
<tr><th>DIMENSION
Criteria</th><th>Data collected from the literature, milieu and consultations (in italics)</th></tr>
<tr><td></td><td>
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]

<u>CONSULTATIONS</u>
Patients: 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.
Allergists: Not applicable
Other healthcare professionals: 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.

<u>ETHICAL ISSUES</u>: 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.
</td></tr>
<tr><td>C18 - Societal costs</td><td>
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.

<u>CONSULTATIONS</u>
Patients: 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.
Allergists: Not applicable
Other healthcare professionals: If all patients used OIT, there would be savings to schools or workplaces, but otherwise, measures might be reduced but would have to remain.

<u>ETHICAL ISSUES</u>: Not applicable
</td></tr>
<tr><td>C19-Environmental impact</td><td>
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.
</td></tr>
<tr><td>C20-Cost-effectiveness</td><td>
Cost-effectiveness model of the Institute for Clinical And Economic Review of commercially developed OIT (AR101) for peanut allergy[6]

Base case results: 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)
<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 rowspan="2">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>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 colspan="3">Incremental cost per QALY (incremental cost-effectiveness ratio, ICER)</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)

<u>ETHICAL ISSUES</u>: Not applicable
</td></tr>
</table>

Table 1 (continued)

DIMENSION Criteria	Data collected from the literature, milieu and *consultations (in italics)*
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 administrating 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
C22- Opportunity cost regarding the resources of the patient / caregiver / user and financial affordability	***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.

Acknowledgements

We would like to acknowledge the other members of the deliberative committee. The deliberative committee was composed of members of the working group as well as A Boisvert, Peer supporter, Montréal, QC; MJ Cadieux, BPharm, Pharmacist and Peer supporter, University of Montreal, QC; B Francoeur, MD Family physician, Trois-Rivières, QC; J Garnavos; L Lavallée, RN, Allergy nurse, CHU Ste-Justine, Montréal, QC; G Parizeault MD, Pediatrician, Chicoutimi, QC; S Pernice, MSc, Nutritionist, CHU Ste-Justine, Montréal, QC; M Stasiuk; C Vaillancourt, MD, Family physician, St-John, NB.

Regarding methodological contributions, we are indebted to the ethics support of I Ganache, PhD, ethicist, Unit Methods, ethics and participation, INESSS, National Institute for excellence in health and social services, Montreal, QC, as well as to the contribution of S Nairn, PhD Department of Sociology, McGill University, Montreal QC, to patient consultation and literature review. We also would like to acknowledge V Berretta, PhD, Pavia University, Italy for setting up the multicriteria software interface (CITAVI), P Bush, PhD, INESSS, for clinical data extraction, P Dodin, librarian, Information Unit services, CHU Sainte-Justine, Montreal, QC, for the search strategy, A Maurice, Research center of the university hospital center Sainte-Justine, Montréal QC for IT support and L Tremblay, CSACI Executive Director, Canadian Society of Allergy and Clinical Immunology, Ottawa, ON, for administrative support.

Finally, we wish to acknowledge all the other participants to the consultations including C Avril; MJ Bettez, Peer supporter at Déjouez les allergies, Quebec, QC; G Briand; S Beugnot, PhD Psychologist, Montreal, QC; A Boisvert, Peer supporter, Montréal, QC; V Brousseau; P Chainé; L Couture; N Ford; J Gerdts, Food Allergy Canada; J Gomis, RN, Nurse, CHU Sherbrooke, QC; J Huang, Food Allergy Canada; L Lavallée, RN, Nurse, CHU Ste Justine, Montréal, QC; C Marcoux; H Matharu, MD, Family Physician, Toronto, ON; O Nazarko; S Pietrzykowski; S Sissons; MA Therrien; J Trudel MD, Pediatrician, Shawiningan, QC; W Toma, MD, Pediatrician Vancouver, BC; G Van Herck, Social worker & psychotherapist, Montreal, QC; G Zheng.

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.

Funding

CSACI.

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. Begin 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 recherché 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.

Fischer reports speaker and/or advisor fees from ALK, AstraZeneca, Aralez, Bausch Health, Merck, Mylan, Pfizer, Novartis, Pediapharm, Sanofi and Teva outside the submitted work. A. Haynes reports advisor fees from Sanofi outside the submitted work. S. Kapur reports speaker and/or advisor fees from Pediapharm and has been a member of advisory boards for, Bausch, Kaleo, Mylan, Novartis, Pediapharm, Pfizer, and Sanofi outside the submitted work. He also holds shares in ABK Biomedical, who are not involved in the field of allergy. H. Kim reports speaker and/or advisor fees for ALK-Abelló, Aralez, Astra Zeneca, CSL Behring, Shire, Novartis, Pediapharm, Stallergenes, Kaleo, Sanofi, Pfizer, and Mylan outside the submitted work. M. N. Primeau reports speaker and/or advisor fees from ALK, Allergie Québec, Aralez, Bausch Health, Food Allergy Canada, Mead Johnson, Mylan, Novartis, Nutricia, Pediapharm and Pfizer outside the submitted work. J. Upton reports advisor fees from Food Allergy Canada, ALK-Abelló, Kaleo, as well as research grant support from Toronto SickKids Foundation, DBV technologies and Regeneron outside the submitted work. T. K. Vander Leek reports speaker and/or advisor fees from Pediapharm, Pfizer and Aralez outside the submitted work. Other authors and members of the deliberative committee declared no financial conflicts of interest.

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. Begin 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 as 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.

Author details
[1] Division of Clinical Immunology, Rheumatology and Allergy, Department of Pediatrics, Sainte-Justine University Hospital Centre, Montreal, QC, Canada. [2] Division of Allergy and Clinical Immunology, Department of Medicine, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada. [3] Research Center of the Sainte-Justine University Hospital Center, Montreal, QC, Canada. [4] Division of Allergy & Immunology, Department of Pediatrics, University of British Columbia, BC Children's Hospital, Vancouver, BC, Canada. [5] Division of Clinical Immunology and Allergy, Department of Medicine, Western University, London, ON, Canada. [6] Division of Clinical Immunology and Allergy, Department of Medicine, McMaster University, Hamilton, ON, Canada. [7] Unit Methods, Ethics and Participation, INESSS, National Institute for Excellence in Health and Social Services, Montreal, QC, Canada. [8] Department of Bioethics, School of Public Health of the University of Montreal, Montreal, Canada. [9] Section of Allergy and Clinical Immunology, Department of Pediatrics, University of Manitoba, Winnipeg, MB, Canada. [10] Division of Allergy Immunology and Dermatology, Department of Pediatrics, Montreal Children's Hospital, Montreal, QC, Canada. [11] Community Allergy Clinic, Victoria, BC, Canada. [12] Department of Pediatrics, University of Alberta, Edmonton, AB, Canada. [13] Discipline of Pediatrics, Memorial University of Newfoundland, St. John's, NL, Canada. [14] Department of Pediatrics, Dalhousie University, Halifax, NS, Canada. [15] Division of Allergy and Clinical Immunology, Department of Medicine, CISSS Laval, Laval, QC, Canada. [16] Division of Immunology and Allergy, Department of Pediatrics, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada.

Received: 28 December 2019 Accepted: 14 February 2020
Published online: 18 March 2020

References

1. Moen OL, Opheim E, Trollvik A. Parents experiences raising a child with food allergy; a qualitative review. J Pediatr Nurs. 2019;46:e52–63. https://doi.org/10.1016/j.pedn.2019.02.036.
2. Chow C, Pincus DB, Comer JS. Pediatric food allergies and psychosocial functioning: examining the potential moderating roles of maternal distress and overprotection. J Pediatr Psychol. 2015;40(10):1065–74. https://doi.org/10.1093/jpepsy/jsv058.
3. Cortes A, Castillo A, Sciaraffia A. Food allergy: children's symptom levels are associated with mothers' psycho-socio-economic variables. J Psychosom Res. 2018;104:48–54. https://doi.org/10.1016/j.jpsychores.2017.11.009.
4. Johnson SF, Woodgate RL. Qualitative research in teen experiences living with food-induced anaphylaxis: a meta-aggregation. J Adv Nurs. 2017;73(11):2534–46. https://doi.org/10.1111/jan.13325.
5. Protudjer JL, Jansson SA, Middelveld R, et al. Impaired health-related quality of life in adolescents with allergy to staple foods. Clin Transl Allergy. 2016;6:37. https://doi.org/10.1186/s13601-016-0128-5.
6. Institute for Clinical and Economic Review. Oral immunotherapy and Viaskin® peanut for peanut allergy: effectiveness and value: Institute for Clinical and Economic Review. 2019.
7. Schofield AT. A case of egg poisoning. Lancet. 1908;171(4410):716. https://doi.org/10.1016/S0140-6736(00)67313-0.
8. Pajno GB, Fernandez-Rivas M, Arasi S, et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. Allergy. 2018;73(4):799–815. https://doi.org/10.1111/all.13319.
9. Martorell A, Alonso E, Echeverria L, et al. Oral immunotherapy for food allergy: a Spanish guideline. Immunotherapy egg and milk Spanish guide (ITEMS guide). Part I: cow milk and egg oral immunotherapy: introduction, methodology, rationale, current state, indications, contraindications, and oral immunotherapy build-up phase. J Investig Allergol Clin Immunol. 2017;27(4):225–37. https://doi.org/10.18176/jiaci.0177.
10. Martorell A, Alonso E, Echeverria L, et al. Oral Immunotherapy for food allergy: a Spanish guideline. egg and milk immunotherapy Spanish guide (ITEMS GUIDE). Part II: maintenance phase of cow milk (CM) and egg oral immunotherapy (OIT), special treatment dosing schedules. Models of dosing schedules of OIT with CM and egg. J Investig Allergol Clin Immunol. 2017;27(5):279–90. https://doi.org/10.18176/jiaci.0178.

11. Pattani R, Straus SE. What is EBM? 2019. https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-ebm/. Accessed 22 Nov 2019.
12. Schunemann HJ, Al-Ansary LA, Forland F, et al. Guidelines International Network: principles for disclosure of interests and management of conflicts in guidelines. Ann Intern Med. 2015;163(7):548–53. https://doi.org/10.7326/M14-1885.
13. Deal CL, Tony M, Hoybye C, et al. GrowthHormone Research Society workshop summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. J Clin Endocrinol Metab. 2013;98(6):E1072–87. https://doi.org/10.1210/jc.2012-3888.
14. Goetghebeur M, Castro-Jaramillo H, Baltussen R, et al. The art of priority setting. Lancet. 2017;389(10087):2368–9. https://doi.org/10.1016/S0140-6736(17)31573-8.
15. Goetghebeur M, Wagner M. Identifying value(s): a reflection on the ethical aspects of MCDA in healthcare decisionmaking. In: Marsh K, Goetghebeur M, Thokala P, et al., editors. Multi-criteria decision analysis to support healthcare decisions. Cham: Spinger Nature; 2017. p. 29–46.
16. Goetghebeur MM, Cellier MS. Can reflective multicriteria be the new paradigm for healthcare decision-making? The EVIDEM journey. Cost Eff Resour Alloc. 2018;16(Suppl 1):54. https://doi.org/10.1186/s12962-018-0116-9.
17. The EVIDEM framework. 2019. http://www.evidem.org/evidem-framework/. Accessed 22 Nov 2019.
18. Daniels N, Sabin J. Limits to health care: fair procedures, democratic deliberation, and the legitimacy problem for insurers. Philos Public Aff. 1997;26(4):303–50.
19. Berwick DM, Nolan TW, Whittington J. The triple aim: care, health, and cost. Health Aff. 2008;27(3):759–69. https://doi.org/10.1377/hlthaff.27.3.759.
20. Horwitz RI, Hayes-Conroy A, Caricchio R, et al. From evidence based medicine to medicine based evidence. Am J Med. 2017;130(11):1246–50. https://doi.org/10.1016/j.amjmed.2017.06.012.
21. Higgins JPT, Green S (eds). Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011. https://handbook-5-1.cochrane.org/.
22. Nurmatov U, Dhami S, Arasi S, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. Allergy. 2017;72(8):1133–47. https://doi.org/10.1111/all.13124.
23. Romantsik O, Tosca MA, Zappettini S, et al. Oral and sublingual immunotherapy for egg allergy. Cochrane Database Syst Rev. 2018;4:CD010638. https://doi.org/10.1002/14651858.CD010638.pub3.
24. Chu DK, Wood RA, French S, et al. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. Lancet. 2019. https://doi.org/10.1016/S0140-6736(19)30420-9.
25. Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist, 2014.
26. Chatham House The Royal Institute of International Affairs. Chatham House Rule: Chatham House; 2019. https://www.chathamhouse.org/chatham-house-rule#. Accessed 13 Dec 2019.
27. Centre for Evidence-based Medicine. Oxford Centre for evidence-based medicine—Levels of Evidence (March 2009). 2009. https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/.
28. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383–94. https://doi.org/10.1016/j.jclinepi.2010.04.026.
29. Wasserman RL, Factor JM, Baker JW, et al. Oral immunotherapy for peanut allergy: multipractice experience with epinephrine-treated reactions. J Allergy Clin Immunol Pract. 2014;2(1):91–6. https://doi.org/10.1016/j.jaip.2013.10.001.
30. Soller L, Abrams EM, Carr S, et al. First real-world safety analysis of preschool peanut oral immunotherapy. J Allergy Clin Immunol Pract. 2019. https://doi.org/10.1016/j.jaip.2019.04.010.
31. Martin-Munoz MF, Belver MT, Alonso Lebrero E, et al. Egg oral immunotherapy in children (SEICAP I): daily or weekly desensitization pattern. Pediatr Allergy Immunol. 2019;30(1):81–92. https://doi.org/10.1111/pai.12974.
32. Levy MB, Elizur A, Goldberg MR, et al. Clinical predictors for favorable outcomes in an oral immunotherapy program for IgE-mediated cow's milk allergy. Ann Allergy Asthma Immunol. 2014;112(1):58–63.e1. https://doi.org/10.1016/j.anai.2013.10.001.
33. Kauppila TK, Paassilta M, Kukkonen AK, et al. Outcome of oral immunotherapy for persistent cow's milk allergy from 11 years of experience in Finland. Pediatr Allergy Immunol. 2019. https://doi.org/10.1111/pai.13025.
34. Nowak-Wegrzyn A, Wood RA, Nadeau KC, et al. Multicenter, randomized, double-blind, placebo-controlled clinical trial of vital wheat gluten oral immunotherapy. J Allergy Clin Immunol. 2019;143(2):651–661.e9. https://doi.org/10.1016/j.jaci.2018.08.041.
35. Kulmala P, Pelkonen AS, Kuitunen M, et al. Wheat oral immunotherapy was moderately successful but was associated with very frequent adverse events in children aged 6–18 years. Acta Paediatr. 2018;107(5):861–70. https://doi.org/10.1111/apa.14226.
36. Elizur A, Appel MY, Nachshon L, et al. Walnut oral immunotherapy for desensitisation of walnut and additional tree nut allergies (Nut CRACKER): a single-centre, prospective cohort study. Lancet Child Adolesc Health. 2019;3(5):312–21. https://doi.org/10.1016/s2352-4642(19)30029-x.
37. Barni S, Mori F, Piccorossi A, et al. Low-dose oral food challenge with hazelnut: efficacy and tolerability in children. Int Arch Allergy Immunol. 2019;178(1):97–100. https://doi.org/10.1159/000493019.
38. Nachshon L, Goldberg MR, Levy MB, et al. Efficacy and safety of sesame oral immunotherapy—a real-world, single-center study. J Allergy Clin Immunol Pract. 2019. https://doi.org/10.1016/j.jaip.2019.05.031.
39. De Schryver S, Mazer B, Clarke AE, et al. Adverse events in oral immunotherapy for the desensitization of cow's milk allergy in children: a randomized controlled trial. J Allergy Clin Immunol Pract. 2019. https://doi.org/10.1016/j.jaip.2019.02.007.
40. Wasserman RL, Hague AR, Pence DM, et al. Real-world experience with peanut oral immunotherapy: lessons learned from 270 patients. J Allergy Clin Immunol Pract. 2019;7(2):418–426.e4. https://doi.org/10.1016/j.jaip.2018.05.023.
41. Longo G, Barbi E, Berti I, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. J Allergy Clin Immunol. 2008;121(2):343–7. https://doi.org/10.1016/j.jaci.2007.10.029.
42. Pajno GB, Caminiti L, Ruggeri P, et al. Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study. Ann Allergy Asthma Immunol. 2010;105(5):376–81. https://doi.org/10.1016/j.anai.2010.03.015.
43. Bird JA, Spergel JM, Jones SM, et al. Efficacy and safety of AR101 in oral immunotherapy for peanut allergy: results of ARC001, a randomized, double-blind, placebo-controlled phase 2 clinical trial. J Allergy Clin Immunol Pract. 2018;6(2):476–85.e3. https://doi.org/10.1016/j.jaip.2017.09.016.
44. Fauquert JL, Michaud E, Pereira B, et al. Peanut gastrointestinal delivery oral immunotherapy in adolescents: results of the build-up phase of a randomized, double-blind, placebo-controlled trial (PITA study). Clin Exp Allergy. 2018;48(7):862–74. https://doi.org/10.1111/cea.13148.
45. Narisety SD, Frischmeyer-Guerrerio PA, Keet CA, et al. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. J Allergy Clin Immunol. 2015;135(5):1275–1282.e1–6. https://doi.org/10.1016/j.jaci.2014.11.005.
46. Tang ML, Ponsonby AL, Orsini F, et al. Administration of a probiotic with peanut oral immunotherapy: a randomized trial. J Allergy Clin Immunol. 2015;135(3):737–744.e8. https://doi.org/10.1016/j.jaci.2014.11.034.
47. Vickery BP, Vereda A, Casale TB, et al. AR101 oral immunotherapy for peanut allergy. N Engl J Med. 2018;379(21):1991–2001. https://doi.org/10.1056/NEJMoa1812856.
48. Varshney P, Jones SM, Scurlock AM, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. J Allergy Clin Immunol. 2011;127(3):654–60. https://doi.org/10.1016/j.jaci.2010.12.1111.
49. Burks AW, Jones SM, Wood RA, et al. Oral immunotherapy for treatment of egg allergy in children. N Engl J Med. 2012;367(3):233–43. https://doi.org/10.1056/NEJMoa1200435.
50. Jones SM, Burks AW, Keet C, et al. Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy. J Allergy Clin Immunol. 2016;137(4):1117–27.e10. https://doi.org/10.1016/j.jaci.2015.12.1316.

51. Hsiao KC, Ponsonby AL, Axelrad C, et al. Long-term clinical and immunological effects of probiotic and peanut oral immunotherapy after treatment cessation: 4-year follow-up of a randomised, double-blind, placebo-controlled trial. Lancet Child Adolesc Health. 2017;1(2):97–105. https://doi.org/10.1016/s2352-4642(17)30041-x.
52. Meglio P, Giampietro PG, Carello R, et al. Oral immunotherapy in children with IgE-mediated hen's egg allergy: follow-ups at 25 and 7 years. Allergy Rhinol. 2017;8(3):157–69. https://doi.org/10.2500/ar.2017.8.0211.
53. Elizur A, Appel MY, Goldberg MR, et al. Clinical and laboratory 2-year outcome of oral immunotherapy in patients with cow's milk allergy. Allergy. 2016;71(2):275–8. https://doi.org/10.1111/all.12794.
54. Nachshon L, Goldberg MR, Katz Y, et al. Long-term outcome of peanut oral immunotherapy-real-life experience. Pediatr Allergy Immunol. 2018;29(5):519–26. https://doi.org/10.1111/pai.12914.
55. Martin-Munoz MF, Alonso Lebrero E, Zapatero L, et al. Egg OIT in clinical practice (SEICAP II): maintenance patterns and desensitization state after normalizing the diet. Pediatr Allergy Immunol. 2019;30(2):214–24. https://doi.org/10.1111/pai.13002.
56. Sampson HA, Leung DYM, Jones SM, et al. Egg oral immunotherapy (OIT) induces more rapid desensitization and sustained unresponsiveness (SU) in egg-allergic, baked-egg tolerant children than the addition of daily baked-egg products. J Allergy Clin Immunol. 2019;143(2):AB255. https://doi.org/10.1016/j.jaci.2018.12.779.
57. Takahashi M, Taniuchi S, Soejima K, et al. Two-weeks-sustained unresponsiveness by oral immunotherapy using microwave heated cow's milk for children with cow's milk allergy. Allergy Asthma Clin Immunol. 2016;12(1):44. https://doi.org/10.1186/s13223-016-0150-0.
58. Vickery BP, Berglund JP, Burk CM, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. J Allergy Clin Immunol. 2017;139(1):173–81.e8. https://doi.org/10.1016/j.jaci.2016.05.027.
59. Escudero C, Rodriguez Del Rio P, Sanchez-Garcia S, et al. Early sustained unresponsiveness after short-course egg oral immunotherapy: a randomized controlled study in egg-allergic children. Clin Exp Allergy. 2015;45(12):1833–43. https://doi.org/10.1111/cea.12604.
60. Reier-Nilsen T, Michelsen MM, Lodrup Carlsen KC, et al. Feasibility of desensitizing children highly allergic to peanut by high-dose oral immunotherapy. Allergy. 2019;74(2):337–48. https://doi.org/10.1111/all.13604.
61. Blumchen K, Trendelenburg V, Ahrens F, et al. Efficacy, safety, and quality of life in a multicenter, randomized, placebo-controlled trial of low-dose peanut oral immunotherapy in children with peanut allergy. J Allergy Clin Immunol Pract. 2019;7(2):479–91.e10. https://doi.org/10.1016/j.jaip.2018.10.048.
62. Morisset M, Moneret-Vautrin DA, Guenard L, et al. Oral desensitization in children with milk and egg allergies obtains recovery in a significant proportion of cases A randomized study in 60 children with cow's milk allergy and 90 children with egg allergy. Eur Ann Allergy Clin Immunol. 2007;39(1):12–9.
63. Martorell A, De la Hoz B, Ibanez MD, et al. Oral desensitization as a useful treatment in 2-year-old children with cow's milk allergy. Clin Exp Allergy. 2011;41(9):1297–304. https://doi.org/10.1111/j.1365-2222.2011.03749.x.
64. Anagnostou K, Islam S, King Y, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. Lancet. 2014;383(9925):1297–304. https://doi.org/10.1016/s0140-6736(13)62301-6.
65. Fuentes-Aparicio V, Alvarez-Perea A, Infante S, et al. Specific oral tolerance induction in paediatric patients with persistent egg allergy. Allergol Immunopathol. 2013;41(3):143–50. https://doi.org/10.1016/j.aller.2012.02.007.
66. Caminiti L, Pajno GB, Crisafulli G, et al. Oral immunotherapy for egg allergy: a double-blind placebo-controlled study, with postdesensitization follow-up. J Allergy Clin Immunol Pract. 2015;3(4):532–9. https://doi.org/10.1016/j.jaip.2015.01.017.
67. Burks A, Casale T, Beyer K, et al. Age-related findings from the peanut allergy oral immunotherapy study of Ar101 for desensitization (Palisade) study. Ann Allergy Asthma Immunol. 2018;121(5 Supplement):S4.
68. Begin P, Winterroth LC, Dominguez T, et al. Safety and feasibility of oral immunotherapy to multiple allergens for food allergy. Allergy Asthma Clin Immunol. 2014;10(1):1. https://doi.org/10.1186/1710-1492-10-1.
69. Begin P, Dominguez T, Wilson SP, et al. Phase 1 results of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using Omalizumab. Allergy Asthma Clin Immunol. 2014;10(1):7. https://doi.org/10.1186/1710-1492-10-7.
70. Eapen AA, Lavery WJ, Siddiqui JS, et al. Oral Immunotherapy for multiple foods in a pediatric allergy clinic setting. Ann Allergy Asthma Immunol. 2019. https://doi.org/10.1016/j.anai.2019.08.463.
71. Andorf S, Purington N, Block WM, et al. Anti-IgE treatment with oral immunotherapy in multifood allergic participants: a double-blind, randomised, controlled trial. Lancet Gastroenterol Hepatol. 2018;3(2):85–94. https://doi.org/10.1016/S2468-1253(17)30392-8.
72. Elizur A, Goldberg MR, Levy MB, et al. Oral immunotherapy in cow's milk allergic patients: course and long-term outcome according to asthma status. Ann Allergy Asthma Immunol. 2015;114(3):240–44.e1. https://doi.org/10.1016/j.anai.2014.12.006.
73. MacGinnitie AJ, Rachid R, Gragg H, et al. Omalizumab facilitates rapid oral desensitization for peanut allergy. J Allergy Clin Immunol. 2017;139(3):873–881.e8. https://doi.org/10.1016/j.jaci.2016.08.010.
74. Howe LC, Leibowitz KA, Perry MA, et al. Changing patient mindsets about non-life-threatening symptoms during oral immunotherapy: a randomized clinical trial. J Allergy Clin Immunol Pract. 2019. https://doi.org/10.1016/j.jaip.2019.01.022.
75. Wb C. Informal sociology, a casual introduction to sociological thinking. New York: Random House; 1963. p. 13.
76. HealthLink BC. Reducing risk of food allergy in your baby British Columbia: HealthLink BC; 2018. https://www.healthlinkbc.ca/healthy-eating/reducing-baby-food-allergy-risk. Accessed 10 Oct 2019.
77. Haeusermann T. I can't eat that: the sociology behind the rise in food allergies and intolerances. Curr Sociol. 2015;63(3):369–86. https://doi.org/10.1177/0011392114559847.
78. Wasserman RL, Jones DH, Windom HH. Oral immunotherapy for food allergy: the FAST perspective. Ann Allergy Asthma Immunol. 2018;121(3):272–5. https://doi.org/10.1016/j.anai.2018.06.011.
79. Perkin MR. Oral desensitization to peanuts. N Engl J Med. 2018;379(21):2074–5. https://doi.org/10.1056/NEJMe1813314.
80. Hamblin J. The U.S. health-care system found a way to make peanuts cost $4,200. The Atlantic, 2019.
81. Blaiss MS, Tilles S, Petroni D, et al. Current management and use of oral immunotherapy in the United States for patients with peanut allergy. Allergy Asthma Proc. 2019. https://doi.org/10.2500/aap.2019.40.4228.
82. Arasi S, Corsello G, Villani A, et al. The future outlook on allergen immunotherapy in children: 2018 and beyond. Ital J Pediatr. 2018;44(1):80. https://doi.org/10.1186/s13052-018-0519-4.
83. Greenhawt MJ, Vickery BP. Allergist-reported trends in the practice of food allergen oral immunotherapy. J Allergy Clin Immunol Pract. 2015;3(1):33–8. https://doi.org/10.1016/j.jaip.2014.06.023.
84. Soller L, Abrams EM, Chan ES. An update on the controversy around offering oral immunotherapy to peanut-allergic children outside of research. Ann Allergy Asthma Immunol. 2019. https://doi.org/10.1016/j.anai.2019.02.011.
85. Greenhawt M, Hourihane JO. Looking into the seeds of time: are home-based OIT programs the shape of things to come for selected patients? Ann Allergy Asthma Immunol. 2018;120(5):453–4. https://doi.org/10.1016/j.anai.2017.11.004.
86. Mansfield LE. Oral immunotherapy for peanut allergy in clinical practice is ready. Allergy Asthma Proc. 2013;34(3):205–9. https://doi.org/10.2500/aap.2013.34.3666.
87. Umasunthar T, Leonardi-Bee J, Hodes M, et al. Incidence of fatal food anaphylaxis in people with food allergy: a systematic review and meta-analysis. Clin Exp Allergy. 2013;43(12):1333–41. https://doi.org/10.1111/cea.12211.
88. Shaker MS, Schwartz J, Ferguson M. An update on the impact of food allergy on anxiety and quality of life. Curr Opin Pediatr. 2017;29(4):497–502. https://doi.org/10.1097/mop.0000000000000509.
89. Xu YS, Kastner M, Harada L, et al. Anaphylaxis-related deaths in Ontario: a retrospective review of cases from 1986 to 2011. Allergy Asthma Clin Immunol. 2014;10(1):38. https://doi.org/10.1186/1710-1492-10-38.

90. Versluis A, Knulst AC, Kruizinga AG, et al. Frequency, severity and causes of unexpected allergic reactions to food: a systematic literature review. Clin Exp Allergy. 2015;45(2):347–67. https://doi.org/10.1111/cea.12328.
91. Cherkaoui S, Ben-Shoshan M, Alizadehfar R, et al. Accidental exposures to peanut in a large cohort of Canadian children with peanut allergy. Clin Transl Allergy. 2015;5:16. https://doi.org/10.1186/s13601-015-0055-x.
92. Umasunthar T, Leonardi-Bee J, Turner PJ, et al. Incidence of food anaphylaxis in people with food allergy: a systematic review and meta-analysis. Clin Exp Allergy. 2015;45(11):1621–36. https://doi.org/10.1111/cea.12477.
93. O'Keefe A, Clarke A, St Pierre Y, et al. The risk of recurrent anaphylaxis. J Pediatr. 2017;180:217–21. https://doi.org/10.1016/j.jpeds.2016.09.028.
94. Kimchi N, Clarke A, Moisan J, et al. Anaphylaxis cases presenting to primary care paramedics in Quebec. Immun Inflamm Dis. 2015;3(4):406–10. https://doi.org/10.1002/iid3.78.
95. Hochstadter E, Clarke A, De Schryver S, et al. Increasing visits for anaphylaxis and the benefits of early epinephrine administration: a 4-year study at a pediatric emergency department in Montreal, Canada. J Allergy Clin Immunol. 2016;137(6):1888–1890.e4. https://doi.org/10.1016/j.jaci.2016.02.016.
96. Ben-Shoshan M, La Vieille S, Eisman H, et al. Anaphylaxis treated in a Canadian pediatric hospital: incidence, clinical characteristics, triggers, and management. J Allergy Clin Immunol. 2013;132(3):739–741.e3. https://doi.org/10.1016/j.jaci.2013.06.016.
97. Asai Y, Yanishevsky Y, Clarke A, et al. Rate, triggers, severity and management of anaphylaxis in adults treated in a Canadian emergency department. Int Arch Allergy Immunol. 2014;164(3):246–52. https://doi.org/10.1159/000365631.
98. Chooniedass R, Temple B, Martin D, et al. A qualitative study exploring parents' experiences with epinephrine use for their child's anaphylactic reaction 11 Medical and Health Sciences 1117 Public Health and Health Services. Clin Transl Allergy. 2018;8(1):1–9. https://doi.org/10.1186/s13601-018-0230-y.
99. Patel N, Herbert L, Green TD. The emotional, social, and financial burden of food allergies on children and their families. Allergy Asthma Proc. 2017;38(2):88–91. https://doi.org/10.2500/aap.2017.38.4028.
100. Fong AT, Katelaris CH, Wainstein B. Bullying and quality of life in children and adolescents with food allergy. J Paediatr Child Health. 2017;53(7):630–5. https://doi.org/10.1111/jpc.13570.
101. Dean J, Fenton NE, Shannon S, et al. Disclosing food allergy status in schools: health-related stigma among school children in Ontario. Health Soc Care Community. 2016;24(5):e43–52. https://doi.org/10.1111/hsc.12244.
102. Protudjer JL, Jansson SA, Heibert Arnlind M, et al. Household costs associated with objectively diagnosed allergy to staple foods in children and adolescents. J Allergy Clin Immunol Pract. 2015;3(1):68–75. https://doi.org/10.1016/j.jaip.2014.09.021.
103. Protudjer JL, Jansson SA, Ostblom E, et al. Health-related quality of life in children with objectively diagnosed staple food allergy assessed with a disease-specific questionnaire. Acta Paediatr. 2015;104(10):1047–54. https://doi.org/10.1111/apa.13044.
104. Indinnimeo L, Baldini L, De Vittori V, et al. Duration of a cow-milk exclusion diet worsens parents' perception of quality of life in children with food allergies. BMC Pediatr. 2013;13:7. https://doi.org/10.1186/1471-2431-13-203.
105. Soller L, Clarke AE, Lyttle A, et al. Comparing quality of life in Canadian children with peanut, sesame, and seafood allergy. J Allergy Clin Immunol Pract. 2019. https://doi.org/10.1016/j.jaip.2019.07.006.
106. Thornqvist V, Middelveld R, Wai HM, et al. Health-related quality of life worsens by school age amongst children with food allergy. Clin Transl Allergy. 2019;9:10. https://doi.org/10.1186/s13601-019-0244-0.
107. Soller L, Ben-Shoshan M, Harrington DW, et al. Adjusting for nonresponse bias corrects overestimates of food allergy prevalence. J Allergy Clin Immunol Pract. 2015;3(2):291–293.e2. https://doi.org/10.1016/j.jaip.2014.11.006.
108. CHU St-Justine, Université de Montréal. Clinique d'immunothérapie orale (CITO) - Coûts des phases 1 à 3 : du pilote au transfert de connaissances et à une offre de soins et services de réseau provincial. Montreal, 2016.
109. DunnGalvin A, Chang WC, Laubach S, et al. Profiling families enrolled in food allergy immunotherapy studies. Pediatrics. 2009;124(3):e503–9. https://doi.org/10.1542/peds.2008-3642.
110. Tackett AP, Farrow ML, McQuaid EL. Food security, utilization of food assistance programs, and caregiver perceptions of food-induced anaphylaxis risk in children with food allergies. Pediatr Allergy Immunol Pulmonol. 2018;31(2):91–6. https://doi.org/10.1089/ped.2017.0857.
111. Sharma HP, Herbert LJ. Food allergy: psychosocial impact and public policy implications. Chem Immunol Allergy. 2015;101:221–6. https://doi.org/10.1159/000373907.
112. Harrington DW, Elliott SJ, Clarke AE, et al. Exploring the determinants of the perceived risk of food allergies in Canada. Hum Ecol Risk Assess. 2012;18(6):1338–58. https://doi.org/10.1080/10807039.2012.722857.
113. Graham F, Begin P. L'immunothérapie orale pour le traitement des allergies alimentaires: L'Association des Allergologues et Immunologues du Québec, 2016.
114. Begin P, Paradis L, Paradis J, et al. Natural resolution of peanut allergy: a 12-year longitudinal follow-up study. J Allergy Clin Immunol Pract. 2013;1(5):528–530.e1–4. https://doi.org/10.1016/j.jaip.2013.05.008.
115. Abrams EM, Sicherer SH. Diagnosis and management of food allergy. Can Med Assoc J. 2016;188(15):1087–93. https://doi.org/10.1503/cmaj.160124.
116. Arasi S, Caminiti L, Crisafulli G, et al. A general strategy for de novo immunotherapy design: the active treatment of food allergy. Expert Rev Clin Immunol. 2018;14(8):665–71. https://doi.org/10.1080/1744666x.2018.1498784.
117. Remington BC, Baumert JL, Blom WM, et al. Unintended allergens in precautionary labelled and unlabelled products pose significant risks to UK allergic consumers. Allergy. 2015;70(7):813–9. https://doi.org/10.1111/all.12625.
118. Blom WM, Michelsen-Huisman AD, van Os-Medendorp H, et al. Accidental food allergy reactions: products and undeclared ingredients. J Allergy Clin Immunol. 2018;142(3):865–75. https://doi.org/10.1016/j.jaci.2018.04.041.
119. Prell C, Koletzko B. Restrictive diets risk of malnutrition and preventive options. Monschr Kinderheilkd. 2014;162(6):503–10. https://doi.org/10.1007/s00112-013-3070-9.
120. Lavine E, Clarke A, Joseph L, et al. Peanut avoidance and peanut allergy diagnosis in siblings of peanut allergic children. Clin Exp Allergy. 2015;45(1):249–54. https://doi.org/10.1111/cea.12403.
121. Venter C, Mazzocchi A, Maslin K, et al. Impact of elimination diets on nutrition and growth in children with multiple food allergies. Curr Opin Allergy Clin Immunol. 2017;17(3):220–6. https://doi.org/10.1097/ACI.0000000000000358.
122. Nachshon L, Goldberg MR, Schwartz N, et al. Decreased bone mineral density in young adult IgE-mediated cow's milk-allergic patients. J Allergy Clin Immunol. 2014;134(5):1108–1113.e3. https://doi.org/10.1016/j.jaci.2014.06.026.
123. Shanahan L, Zucker N, Copeland WE, et al. Are children and adolescents with food allergies at increased risk for psychopathology? J Psychosom Res. 2014;77(6):468–73. https://doi.org/10.1016/j.jpsychores.2014.10.005.
124. Cannon HE. The economic impact of peanut allergies. Am J Manag Care. 2018;24(19 Suppl):S428–33.
125. Marchisotto MJ, Harada L, Kamdar O, et al. Food allergen labeling and purchasing habits in the United States and Canada. J Allergy Clin Immunol Pract. 2017;5(2):345–351.e2. https://doi.org/10.1016/j.jaip.2016.09.020.
126. Tilles SA, Petroni D. FDA-approved peanut allergy treatment: the first wave is about to crest. Ann Allergy Asthma Immunol. 2018;121(2):145–9. https://doi.org/10.1016/j.anai.2018.06.005.
127. Fleischer DM, Greenhawt M, Sussman G, et al. Effect of epicutaneous immunotherapy vs placebo on reaction to peanut protein ingestion among children with peanut allergy: the PEPITES randomized clinical trial. JAMA. 2019. https://doi.org/10.1001/jama.2019.1113.
128. Scurlock AM. Oral and sublingual immunotherapy for treatment of IgE-mediated food allergy. Clin Rev Allergy Immunol. 2018;55(2):139–52. https://doi.org/10.1007/s12016-018-8677-0.
129. Kim EH, Yang L, Ye P, et al. Long-term sublingual immunotherapy for peanut allergy in children: clinical and immunologic evidence of desensitization. J Allergy Clin Immunol. 2019. https://doi.org/10.1016/j.jaci.2019.07.030.

130. Upton J, Nowak-Wegrzyn A. The impact of baked egg and baked milk diets on IgE- and non-IgE-mediated allergy. Clin Rev Allergy Immunol. 2018;55(2):118–38. https://doi.org/10.1007/s12016-018-8669-0.
131. Amat F, Kouche C, Gaspard W, et al. Is a slow-progression baked milk protocol of oral immunotherapy always a safe option for children with cow's milk allergy? A randomized controlled trial. Clin Exp Allergy. 2017;47(11):1491–6. https://doi.org/10.1111/cea.13022.
132. Murdoch B, Adams EM, Caulfield T. The law of food allergy and accommodation in Canadian schools. Allerg Asthma Clin Immunol. 2018;14:8. https://doi.org/10.1186/s13223-018-0273-6.
133. Wood RA, Kim JS, Lindblad R, et al. A randomized, double-blind, placebo-controlled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. J Allergy Clin Immunol. 2016;137(4):1103–1110.e11. https://doi.org/10.1016/j.jaci.2015.10.005.
134. Aimmune Therapeutics. Allergenic Products Advisory Committee Meeting (APAC) briefing document—peanut, arachis hypogaea, allergen powder for oral administration (Proposed Trade Name: Palforzia), 2019.
135. Cox L, Larenas-Linnemann D, Lockey RF, et al. Speaking the same language: the world allergy organization subcutaneous immunotherapy systemic reaction grading system. J Allergy Clin Immunol. 2010;125(3):569–574.e1–e7. https://doi.org/10.1016/j.jaci.2009.10.060.
136. Sampson HA. Anaphylaxis and emergency treatment. Pediatrics. 2003;111(6 Pt 3):1601–8.
137. Burks AW, Jones SM, Plaut M. Oral immunotherapy for egg allergy in children REPLY. N Engl J Med. 2012;367(15):1472–3.
138. Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. Ann Allergy Asthma Immunol. 2014;113(6):624–9. https://doi.org/10.1016/j.anai.2014.08.004.
139. Echeverria-Zudaire LA, Fernandez-Fernandez S, Rayo-Fernandez A, et al. Primary eosinophilic gastrointestinal disorders in children who have received food oral immunotherapy. Allergol Immunopathol. 2016;44(6):531–6. https://doi.org/10.1016/j.aller.2016.05.002.
140. Gomez Torrijos E, Mendez Diaz Y, Moreno Lozano L, et al. Frequency and course of eosinophilic esophagitis during oral immunotherapy for cow's milk allergy in a series of 57 children. J Investig Allergol Clin Immunol. 2017;27(2):132–3. https://doi.org/10.18176/jiaci.0130.
141. Rodriguez CG, Torrijos EG, De la Pinzon FR, et al. Dysphagia in a boy treated with oral immunotherapy for cow's milk allergy. J Investig Allergol Clin Immunol. 2014;24(5):363–5.
142. Hill DA, Dudley JW, Spergel JM. The prevalence of eosinophilic esophagitis in pediatric patients with IgE-mediated food allergy. J Allergy Clin Immunol Pract. 2017;5(2):369–75. https://doi.org/10.1016/j.jaip.2016.11.020.
143. Goldberg MR, Elizur A, Nachshon L, et al. Oral immunotherapy-induced gastrointestinal symptoms and peripheral blood eosinophil responses. J Allergy Clin Immunol. 2017;139(4):1388–1390.e4. https://doi.org/10.1016/j.jaci.2016.09.053.
144. Goldberg MR, Nachshon L, Levy MB, et al. Risk factors and treatment outcomes for oral immunotherapy-induced gastrointestinal symptoms and eosinophilic responses (OITIGER). J Allergy Clin Immunol Pract. 2019. https://doi.org/10.1016/j.jaip.2019.07.034.
145. Manabe T, Sato S, Yanagida N, et al. Long-term outcomes after sustained unresponsiveness in patients who underwent oral immunotherapy for egg, cow's milk, or wheat allergy. Allergol Int. 2019. https://doi.org/10.1016/j.alit.2019.02.012.
146. Barbi E, Longo G, Berti I, et al. Adverse effects during specific oral tolerance induction: in-hospital "rush" phase. Eur Ann Allergy Clin Immunol. 2012;44(1):18–25.
147. Virkud YV, Burks AW, Steele PH, et al. Novel baseline predictors of adverse events during oral immunotherapy in children with peanut allergy. J Allergy Clin Immunol. 2017;139(3):882–88.e5. https://doi.org/10.1016/j.jaci.2016.07.030.
148. Barbi E, Longo G, Berti I, et al. Adverse effects during specific oral tolerance induction: in home phase. Allergol Immunopathol. 2012;40(1):41–50. https://doi.org/10.1016/j.aller.2011.05.004.
149. Vazquez-Ortiz M, Alvaro M, Piquer M, et al. Life-threatening anaphylaxis to egg and milk oral immunotherapy in asthmatic teenagers. Ann Allergy Asthma Immunol. 2014;113(4):482–4. https://doi.org/10.1016/j.anai.2014.07.010.
150. Pajno GB, Caminiti L, Salzano G, et al. Comparison between two maintenance feeding regimens after successful cow's milk oral desensitization. Pediatr Allergy Immunol. 2013;24(4):376–81. https://doi.org/10.1111/pai.12077.
151. Sampson HA. Peanut oral immunotherapy: is it ready for clinical practice? J Allergy Clin Immunol Pract. 2013;1(1):15–21. https://doi.org/10.1016/j.jaip.2012.10.009.
152. Sato S, Yanagida N, Ebisawa M. Recent trends in the management of food allergy. Curr Allergy Clin Immunol. 2018;31(3):138–41.
153. Remington BC, Krone T, Koppelman SJ. Quantitative risk reduction through peanut immunotherapy: safety benefits of an increased threshold in Europe. Pediatr Allergy Immunol. 2018;29(7):762–72. https://doi.org/10.1111/pai.12961.
154. Baumert JL, Taylor SL, Koppelman SJ. Quantitative assessment of the safety benefits associated with increasing clinical peanut thresholds through immunotherapy. J Allergy Clin Immunol Pract. 2018;6(2):457–65.e4. https://doi.org/10.1016/j.jaip.2017.05.006.
155. Kao LM, Greenhawt MJ, Warren CM, et al. Parental and parent-perceived child interest in clinical trials for food allergen immunotherapy. Ann Allergy Asthma Immunol. 2018;120(3):331–33.e1. https://doi.org/10.1016/j.anai.2017.12.012.
156. Greenhawt M, Marsh R, Gilbert H, et al. Understanding caregiver goals, benefits, and acceptable risks of peanut allergy therapies. Ann Allergy Asthma Immunol. 2018;121(5):575–9. https://doi.org/10.1016/j.anai.2018.06.018.
157. Dunlop JH, Keet CA. Goals and motivations of families pursuing oral immunotherapy for food allergy. J Allergy Clin Immunol Pract. 2019;7(2):662–63.e18. https://doi.org/10.1016/j.jaip.2018.05.035.
158. Sato S, Sugizaki C, Yanagida N, et al. Nationwide questionnaire-based survey of oral immunotherapy in Japan. Allergol Int. 2018;67(3):399–404. https://doi.org/10.1016/j.alit.2018.02.006.
159. Traister RS, Green TD, Mitchell L, et al. Community opinions regarding oral immunotherapy for food allergies. Ann Allergy Asthma Immunol. 2012;109(5):319–23. https://doi.org/10.1016/j.anai.2012.08.012.
160. Dunn Galvin A, McMahon S, Ponsonby AL, et al. The longitudinal impact of probiotic and peanut oral immunotherapy on health-related quality of life. Allergy. 2018;73(3):560–8. https://doi.org/10.1111/all.13330.
161. Epstein-Rigbi N, Goldberg MR, Levy MB, et al. Quality of life of food-allergic patients before, during, and after oral immunotherapy. J Allergy Clin Immunol Pract. 2019;7(2):429–436.e2. https://doi.org/10.1016/j.jaip.2018.06.016.
162. Factor JM, Mendelson L, Lee J, et al. Effect of oral immunotherapy to peanut on food-specific quality of life. Ann Allergy Asthma Immunol. 2012;109(5):348–52.e2. https://doi.org/10.1016/j.anai.2012.08.015.
163. Dufresne E, Poder TG, Lacombe-Barrios J, et al. Quality-adjusted life-year gain with oral immunotherapy: preliminary results from a real-life cohort. Montreal: CSACI Annual Scientific Meeting; 2019.
164. Reier-Nilsen T, Carlsen KCL, Michelsen MM, et al. Parent and child perception of quality of life in a randomized controlled peanut oral immunotherapy trial. Pediatr Allergy Immunol. 2019. https://doi.org/10.1111/pai.13066.
165. Danchin M, De Bono N, Allen K, et al. Managing simple food allergy in community settings: a pilot study investigating a new model of care. J Paediatr Child Health. 2016;52(3):315–20. https://doi.org/10.1111/jpc.13026.
166. Nachshon L, Goldberg MR, Elizur A, et al. A Web site-based reporting system for monitoring home treatment during oral immunotherapy for food allergy. Ann Allergy Asthma Immunol. 2015;114(6):510–5. https://doi.org/10.1016/j.anai.2015.04.007.
167. Leroux H, Langlois A, Dion C, et al. Efficiency of peanut suspension with simple syrup compared to individual pre-weighted flour doses for oral immunotherapy. Montreal: CSACI Annual Scientific Meeting; 2019.
168. Minaker LM, Elliott SJ, Clarke A. Exploring low-income families' financial barriers to food allergy management and treatment. J Allergy. 2014;2014:160363. https://doi.org/10.1155/2014/160363.
169. Gupta R, Holdford D, Bilaver L, et al. The economic impact of childhood food allergy in the United States. JAMA Pediatr. 2013;167(11):1026–31. https://doi.org/10.1001/jamapediatrics.2013.2376.

Publisher's Note