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Review

# Outcomes for clinical trials of food allergy treatments

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**Key Messages**

- Increasing numbers of clinical trials are being undertaken to support the development of new food allergy treatments.
- There is still great heterogeneity in both what and how outcomes are measured in food immunotherapy trials.
- Previous food allergy treatment trials have focused on outcomes which are important to investigators and investors but may not be important to patients.
- Future trials should include patient-relevant outcomes and reports of the experiences of trial participants and their parents or caregivers.
- There is a pressing need for patients' and caregivers' voices to be heard to help identify core outcomes for food allergy. This will ensure that research is directed toward and translated into real life beneficial effects for people with food allergy.

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ABSTRACT

**Objective:** Food allergy is a common condition that can have a significant impact on the quality of life of affected individuals and their caregivers. Recent years have witnessed an increased effort to identify new treatments for food allergy. Here, we review the need to identify core outcomes for measurement in clinical trials of food allergy treatments.

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**Data Sources:** We reviewed the literature regarding core outcome set development, the important role that these play in prioritizing patient-relevant outcomes, and the potential for core outcomes to accelerate the path to product marketing by allowing prompt and reliable evidence synthesis after trial publication.
**Study Selection:** We reviewed recent clinical trials of food allergy treatments to understand which outcomes have previously been measured, and also reviewed available core outcome set initiatives for other allergic conditions to understand which other outcomes might be explored in future trials.
**Results:** Clinical trials of food allergy treatments have largely focused on outcomes that are relevant to investigators and commercial investors, especially the threshold of reactivity and immunologic changes. Future trials should consider addressing patient-important outcomes and should report the experiences of both adult and child participants and their caregivers.
**Conclusion:** There is a pressing need for core outcome set development for food allergy treatment trials.
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## Introduction

Immunoglobulin E (IgE)–mediated food allergy (FA) is a worldwide public health concern with a reported prevalence of up to 10% in Western countries.[1] FA carries a high economic burden to health services, patients, and their families.[2] FA affects the quality of life through the dietary and social restrictions imposed by allergen avoidance and the emotional and social burden of the risk of unpredictable, potentially severe allergic reactions.[3] Allergen avoidance, dietetic support, and medications for the management of acute reactions are the current standard of treatment for FA; however, accidental ingestion is common, causing frequent, unpredictable, and occasionally life-threatening reactions. Increased presentations at emergency departments and hospital admissions have been used as surrogate evidence of an increased prevalence of FA in Western countries; however, there is no associated rise in fatalities. Thus, there is an ongoing debate whether this perceived increase in FA is real.[4,5]

A new generation of treatments is emerging for IgE-mediated FA, using diverse approaches, and the United States Food and Drug Administration (US FDA) recently approved the first drug for the treatment of peanut allergy in children.[6] The most frequently evaluated treatments targeted at the underlying immunology are the following: (1) oral (OIT), sublingual, and epicutaneous allergen-specific immunotherapy; (2) monoclonal antibodies; and (3) specific nutritional supplements, such as probiotics and prebiotics.[7-14] Other interventions aim to address the social and emotional consequences of FA rather than the underlying immunologic reactivity.[15] Currently, however, these trials are being undertaken without a consensus on how best to measure clinical effectiveness. In this article, we review the concept of core outcome set (COS) development because it might apply to this emerging field of FA therapeutics. We first review what COS is, identify allergic conditions in which COS already exists, and explore the importance of specific COS development for FA. We then review outcomes already reported in FA treatment trials, highlighting neglected outcomes, and discuss the methodoloCgy for COS development, which is currently being applied within the European Core Outcome Measures for FA and in projects of the Clinical Outcomes of Efficacy in Food Allergen Immunotherapy trials. In this article, we do not specifically address issues pertaining to non–IgE-mediated FA.

## Core Outcome Sets

Outcome assessment plays a crucial role both in routine clinical practice and research. In clinical trials, outcomes are used as a measurement of the studied interventions' safety and effectiveness.[16] Researchers usually choose primary and secondary outcomes within the scope of a clinical trial based on their personal experience, previously published data, patient, colleague, or commercially-focused industry partners' views. The use of inappropriate or irrelevant outcomes carries 2 risks.[17] First, it means that readers of the trial publication are uncertain of the impact of the intervention on patients. This may potentially have the effect of slowing or halting product development and marketing owing to the uncertainty about the effectiveness or safety of the intervention. Second, when evidence synthesis is undertaken, for example, as part of a comprehensive health technology assessment, the heterogeneity in outcomes assessed and the measurement tools used results in the inability to pool data in a meta-analysis, leading to further uncertainty.[18] This may have an effect of slowing the development of the evidence base, clinical practice guidelines, and reimbursement approvals.

COS development overcomes these issues by identifying domains and outcomes within those domains that are important to all relevant stakeholders, most importantly patients and caregivers, and should, therefore, be measured in all treatment trials. COS development does not mean that other outcomes cannot be measured, but suggests that the identified core outcomes are evaluated in all trials.[19] Some COS developers also identify outcome measurement instruments with the best performance characteristics or develop new instruments when a suitable one is not available.

For many chronic diseases, COS has been developed and is routinely measured in clinical trials, bringing clarity to patients, health care providers and regulators, and the industry and their investors. Consequently, these groups can determine the value of new treatments for conditions such as rheumatoid arthritis (Outcome Measures in Rheumatology initiative) or eczema (Harmonizing Outcome Measures for Eczema [HOME] initiative).

Previous COS initiatives in other diseases have clearly found that without undertaking COS development, certain domains or outcomes are inadvertently omitted. For example, fatigue was not identified as an important outcome for clinical trials of rheumatoid arthritis until COS work was undertaken.[20] In the absence of a COS, the information generated by clinical trials can be unreliable or of limited relevance to those affected by the disease.[20]

## Core Outcome Sets in Allergic Conditions: Current Status

The current status of COS development for allergic conditions is summarized in Figure 1. A COS has been developed for eczema, but COS is yet to be established for other allergic conditions, including asthma, allergic rhinitis, anaphylaxis, drug allergy, venom allergy, and FA.[18]

### *Core Outcome Set for Respiratory Allergy*

Some initiatives were undertaken to assess respiratory allergy outcome assessment, but the selection of relevant outcomes lacked robust validity for all stakeholders. Among these initiatives, a task force from the World Allergy Organization published recommendations for standardization of clinical trials with allergen-specific immunotherapy for respiratory allergy.[21] A

combined symptom-medication score was suggested as a primary outcome for trials involving allergen-specific immunotherapy. This recommendation was based largely on expert opinion, rather than a formal COS development process, and did not include the patient or caregiver perspective or assessment of instrument validity. Thus, the value and comprehensiveness of the outcomes identified for patient improvement are uncertain.

In 2009, a task force from the American Thoracic Society and European Respiratory Society published joint recommendations for the outcomes of asthma control, severity, and exacerbations in clinical trials and clinical practice.[22] The minimum set of measures as recommended by the task force consisted of symptom-free days, reliever use, pre- and postbronchodilator forced expiratory volume in 1 second, composite scores, exacerbations (previous 1-4 weeks), quality of life, and treatment adverse effects. The task force recommendations were based on literature review and semistructured discussions. From 2010 to 2011, the National Institutes of Health and the Agency for Healthcare Research and Quality convened a workshop to propose core asthma outcomes for clinical research studies using literature reviews and stakeholder opinion.[23] Ongoing work includes a project from the Pediatric Emergency Research Network, which is developing a COS for randomized controlled trials in children with acute severe exacerbations of asthma, and coreASTHMA, which is developing COS for quality of life and symptom burden in late phase asthma trials.[24] We are not aware of ongoing any COS work on asthma outcomes for clinical settings, as opposed to clinical trial settings; currently, there is not a widely-accepted set of COSs for respiratory allergic diseases.

### *Core Outcome Set for Eczema*

Eczema is the only allergic condition with an established COS (HOME initiative, http://www.homeforeczema.org). The HOME initiative defined the following 4 core outcome domains for clinical trials: (1) clinical signs, (2) patient-reported symptoms, (3) long-term control, and (4) quality of life. For each of these domains, core outcome instruments were identified. The HOME initiative has also published a methodological framework to use when developing and implementing a COS.[16] In addition, and complementary to HOME, the international Treatment of Atopic Eczema Registry Taskforce established a COS containing 19 domains, with 69 domain items in eczema research registries that collect real-world data of children and adults on photo- and systemic immunomodulatory therapies.[25]

### *Core Outcome Set for Food Allergy*

There is no recognized COS for FA, perhaps owing to a lack of FA therapeutics until recently. FA immunotherapy products are, however, being tested in clinical trials, with promising results from trials of oral, sublingual and epicutaneous peanut protein immunotherapy, and ongoing trials of nutritional supplements such as probiotics. Furthermore, the use of biological agents, such as anti-IgE antibody in tandem with immunotherapy,[26,27] to mitigate the adverse effect profile is also under investigation. The expanding body of evidence indicating the effectiveness of food immunotherapy as an intervention to increase the threshold for reactivity is reflected in the recent European Academy of Allergy and Clinical Immunology food immunotherapy guidelines, which state that food immunotherapy for milk, egg, and peanut should be offered in recognized specialized centers[28] outside clinical trials. In the United States, a peanut powder product was recently approved by the US FDA for commercialization and epicutaneous peanut immunotherapy was given fast-track status by the US FDA, reflecting the perception that this treatment is necessary to "treat a serious condition and fill an unmet medical need."

To facilitate shared decision-making about FA treatments, we need to be able to compare clinical trial outcomes, which are measured using a standardized method. Unfortunately, there is a great heterogeneity in both "what" and "how" outcomes are measured in food immunotherapy trials. The most common outcome measures used in FA treatment trials rely on immunologic or clinical reactivity improvements and measures of the frequency and severity of adverse events.[12,14,29] Few trials of FA therapeutics have evaluated the disease-specific quality of life, patient or caregiver–reported global assessment or other patient-reported outcome measures.[6,12,30-32]

Despite the consequent poor understanding of OIT's real-life effectiveness from a patient's perspective, the treatment is being used in clinical practice in many regions,[33-36] in a significant number of centers and for a wide range of patients.

## Outcomes Evaluated in Previous Food Allergy Treatment Trials

### *Investigator-Reported Outcomes*

Peanut allergy has been the most frequently studied FA in clinical trials. Most trials use quantitative and investigator-driven measures of efficacy based on graded oral food challenge (OFC) at the end of treatment, sometimes compared with pretreatment OFC parameters. Limitations of this method of assessment include the following: (1) variability between study dosing regimens and OFC stopping criteria; (2) timing of OFC (ie, during maintenance treatment or weeks after treatment cessation); and (3) variations in the method of reporting OFC outcome, for example, highest vs cumulative dose ingested, or eliciting vs tolerated dose, during graded OFC. In addition, it is uncertain whether nonreactivity to a predefined dose of peanut protein during a stepwise OFC reflects real-life tolerance to the same dose, consumed in an uncontrolled setting, in which potential cofactors may alter reactivity threshold.[37,38] To date, there is little information available on outcomes from community ingestion of peanut after immunotherapy.[30,39,40] Real-world data can be difficult to capture because of the relatively low frequency of accidental reactions and issues with reporting reliability. Some investigators have tried to model the potential impact of changes in the threshold of reactivity at OFC on the risk of community reaction. They suggested that for subjects with a baseline eliciting dose of less than or equal to 300 mg of peanut protein or approximately 1 peanut kernel, an increase of up to 1000 mg peanut protein may provide more than 99% risk reduction.[41,42] These models, however, are only valid for foods containing peanut unintentionally, but not those containing peanut as an intentional ingredient, in which the quantity of peanut protein ingested is expected to be higher.

There is considerable variation in the peanut protein dose used in OFC studies, ranging from 992 mg[43] to 9996 mg,[44] partly influenced by the immunotherapy dosing regimen.[30,40] The timing of OFC also varies, rarely being undertaken after treatment has stopped; in these cases, the time interval between ceasing therapy and assessment varies from 2 weeks[45] to 12 months.[46] There is a lack of consensus on target threshold during OFC, or on the relative importance of desensitization (in which individuals can ingest the food without a clinical reaction so long as they continue eating it) vs sustained unresponsiveness (in which individuals remain clinically tolerant to the food after a period of strict avoidance). Studies quantifying risk reduction in real-life accidental exposures concerning target thresholds should inform of such discussions.[39,41]

There is a high degree of heterogeneity in outcome measures used across studies. In Table 1, we summarize outcome assessments from 2 recent trials of peanut immunotherapy, the PALISADE (peanut allergy oral immunotherapy study of AR101 for desensitization in children and adults), and PEPITES (efficacy and safety of viaskin peanut in children with immunoglobulin E (IgE)-mediated peanut allergy) trials[6,47] (Table 1). These illustrate a focus on

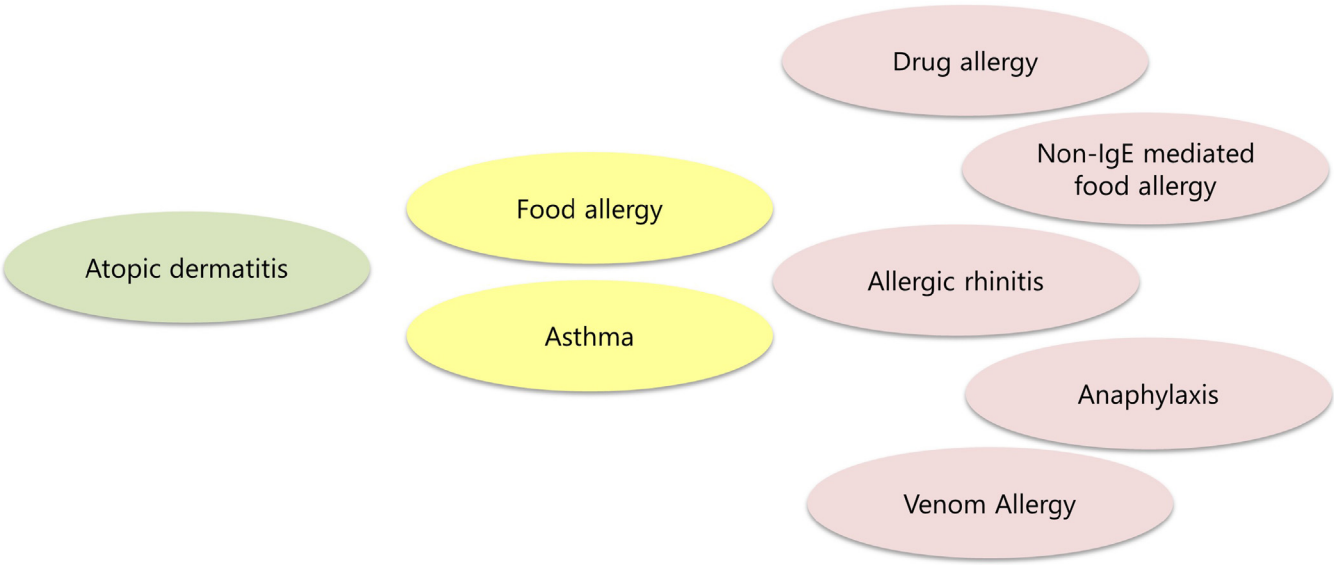


**Figure 1.** Current status of the core outcome set development for allergic diseases. Conditions in green have established consensus-based core outcome domains and preferred core outcome measurement instruments. Conditions in yellow represent ongoing core outcome set development projects. For conditions in red, we were unable to identify core outcome set development projects in progress or the published literature.

investigator-assessed outcomes and a lack of consistency in how these are measured. Variation among trials in methods of outcome assessment can hamper attempts at evidence synthesis and comparative effectiveness evaluations. Not every patient will have the same objectives when treated with food immunotherapy. In the work by Dunlop et al,[48] overall motivations of patients and motivations for starting food immunotherapy were surveyed. Only 9% of 123 patients aimed to incorporate the food into their diet, whereas 62% and 11% aimed to reduce the risk of a fatal reaction or the inconvenience of strict avoidance, respectively. Core outcomes for immunotherapy trials in FA need to consider these varied aims and perspectives.

*Safety Outcomes*

Safety is clearly a fundamental outcome of OIT trials owing to the risk of anaphylaxis or fatal anaphylaxis. Outcome measures such as adrenaline use, serious adverse events, and allergic reactions during treatment are often recorded. However, there is variation in what constitutes a severe adverse event other than the regulatory definition. In one study,[45] this was defined as any symptom that prevents daily activities and might require therapeutic intervention; this resulted in a high rate of severe adverse events in both the active and placebo arms. A recent expert review on food oral immunotherapy trials has established a pressing need for an international consensus to be reached on the reporting of safety data from such trials.[49] The recent meta-analysis by Chu et al[50] has found that maintenance of peanut OIT is associated with a nearly 3-fold increased risk of an allergic reaction including measures of a severe allergic reaction, such as the use of adrenaline, or reactions defined as anaphylaxis.[51] Fatal anaphylaxis has been reported during a clinical trial of subcutaneous FA immunotherapy, in which a patient in the

**Table 1**
Outcome Measures Measured in the Recent PALISADE and PEPITES Trials

| | PALISADE oral immunotherapy trial | PEPITES epicutaneous immunotherapy trial |
|---|---|---|
| Primary outcome | Proportion of participants tolerating a cumulative dose of at least 1043 mg peanut protein with no more than mild symptoms in a supervised double-blind, placebo-controlled food challenge (exit challenge) | Proportion of participants with an eliciting dose of ≥300 mg peanut protein (for participants with baseline eliciting dose ≤10 mg) or ≥1000 mg peanut protein (for participants with baseline eliciting dose >10 mg) |
| Secondary outcomes | Proportion of participants tolerating a cumulative dose of at least 443 mg peanut protein with no more than mild symptoms at the exit challenge<br>Proportion of participants tolerating a cumulative dose of at least 2043 mg peanut protein with no more than mild symptoms at the exit challenge<br>Maximum severity of symptoms during the exit food challenge<br>Use of epinephrine as a rescue medication at the exit challenge<br>Maximum dose ingested during exit challenge with no more than mild symptoms<br>Changes in peanut-specific IgE and IgG4 levels<br>Changes in mean peanut skin prick test wheal diameter<br>Quality of life assessment using FAIM<br>Safety outcomes including adverse events, Serious adverse events, accidental ingestion of peanut and other allergenic foods, allergic reactions, anaphylaxis, epinephrine use, and asthma control using ACT | Change in eliciting dose from baseline to end of study assessment (12 mo)<br>Change in cumulative eliciting dose from baseline to end of study assessment<br>Changes in peanut-specific IgE and IgG4 levels from baseline to end of study assessment<br>Proportion of participants with treatment-related adverse events.<br>Peak expiratory flow rate<br>Composite measure of laboratory values: hematology and biochemistry<br>Composite measure of vital signs<br>Composite measure of physical examinations |

Abbreviations: ACT, asthma control test; FAIM, food allergy independent measure; IgE; immunoglobulin E; IgG4, immunoglobulin G4; PALISADE, peanut allergy oral immunotherapy study of AR101 for desensitization in children and adults; PEPITES, efficacy and safety of viaskin peanut in children with immunoglobulin E (IgE)-mediated peanut allergy.

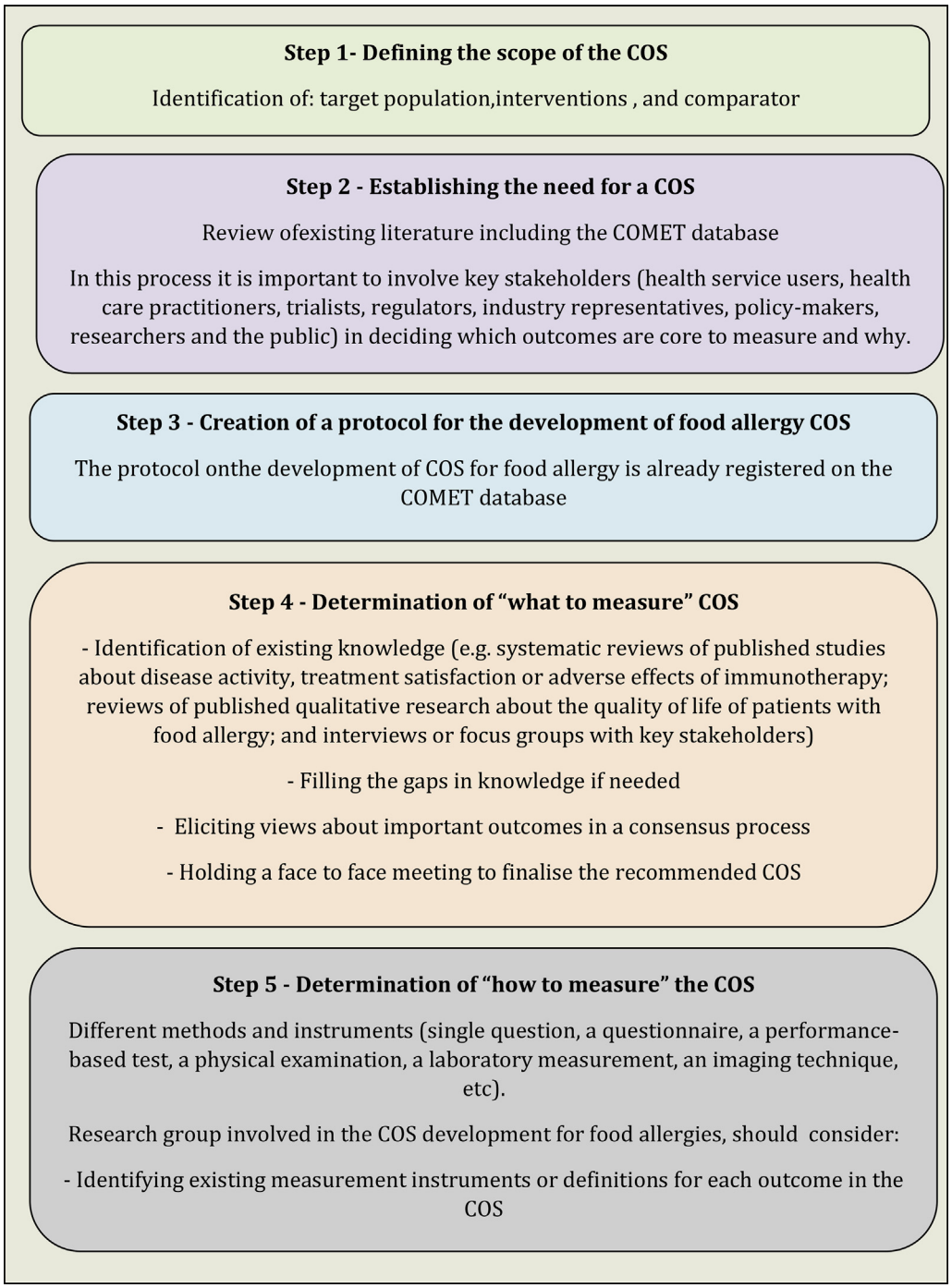


**Figure 2.** Flowchart illustrating the potential process of the core outcome set development for food allergies. COS, core outcome set.

placebo group received an active dose of subcutaneous peanut immunotherapy because of a formulation error and during OFC for threshold determination before OIT outside of a clinical trial.[52,53] It is unclear what proportion of reactions during FA immunotherapy trials are unpredictable community reactions vs reactions to known doses administered in a controlled setting, and participants may vary in their interpretation of the risk depending on their sense of control. Important safety outcome measures that should be considered are whether the reduced frequency of reactions, or reduced severity of reactions, or indeed both, are the goals for participants.

*Patient and Caregiver-Reported Symptoms*

Patient-reported outcomes are crucial outcomes in COS for most chronic conditions. In the case of FA, these might include a wide spectrum of objective and subjective symptoms affecting the respiratory, gastrointestinal, and cutaneous systems. These symptoms may lead to withdrawal from studies[49]; indeed, persisting problems with these adverse effects have driven the use of biological agents, such as anti-IgE antibodies, to reduce the symptom profile associated with OIT. In older children and adults, measuring these outcomes may be straightforward, but in the youngest

**Table 2**
Potential Food Allergy Core Outcome Domains and Methods of Measurement

| What to measure? | How to measure? |
|---|---|
| Patient and caregiver-reported outcomes | |
| Symptoms | • Through severity and frequency of allergic reactions to the culprit food in daily life |
| Quality of life, the emotional burden | • Using food allergy quality of life questionnaires FAQLQ-AF, FAQLQ-TF, and FAQLQ-CF; STAI; FAQL-PB; and FASE-P<br>• Using SPS-FA |
| Patient satisfaction with treatment | • Using ESPIA |
| Safety outcomes | |
| Treatment-related adverse events | • For immunotherapy, this might include risk of anaphylaxis or epinephrine use, risk of less severe adverse effects, and measures of psychological or emotional health |
| Investigator-reported outcomes | |
| Change in threshold | • The threshold of reactivity at a supervised, graded oral food challenge |
| Severity of a reaction | • Classification of the outcome of a food challenge reaction, immunotherapy dosing reaction, or community reaction according to a validated severity scoring system |
| Sustained unresponsiveness | • Lack of clinical reactivity after cessation of treatment and continued food allergen avoidance for a period of time (typically 2-12 wk) |
| Desensitization | • Reduced clinical reactivity during treatment, established either during ad libitum ingestion or during a supervised oral food challenge |
| Biomarkers | |
| Proxy outcomes for reactivity[a] | • Specific IgE levels, IgG4 level, regulatory T cells, skin prick test reactivity, basophil activation test, mast cell activation test |
| Health resource utilization | |
| Direct medical costs | • Questionnaire on the household, individual cost of living, health, and illness |
| Indirect medical costs | • Questionnaire on the household, individual cost of living, health, and illness (eg, EuroPrevall project questionnaire) |

Abbreviations: EuroPrevall, the prevalence cost and basis of food allergy across Europe; ESPIA, satisfaction scale for patients receiving allergen immunotherapy; FAQL-PB, food allergy quality of life parental burden index; FAQLQ-AF, food allergy quality of life questionnaire—adult form; FAQLQ-CF, food allergy quality of life questionnaire—child form; FAQLQ-TF, food allergy quality of life questionnaire—teenage form; FASE-P, food allergy self-efficacy scale for parents; IgE, immunoglobulin E; IgG4, immunoglobulin G4; SPS-FA, the scale for psychosocial factors in food allergy; STAI, state-trait anxiety inventory.
[a]In general, these proxy outcomes have not yet been found to be reliable biomarkers of clinical reactivity.

participants[54] who cannot verbalize, recording symptoms is more difficult. In conditions such as eosinophilic esophagitis, symptoms may be subtle, and the incidence, therefore, underrepresented.[55] There is a paucity of data relating to the quality of life in the studies published so far. The meta-analysis by Chu et al[50] found no evidence that OIT improves the quality of life. Understanding the effects of OIT on quality of life needs to incorporate the burden of treatment. For example, some OIT regimens mandate no exercise, showering, or bathing within 3 hours of doses, or no dose within 2 hours of bedtime[6] or when excessively tired.[40] The burden of adhering to this advice may adversely impact the quality of life. Although daily dosing is likely to place a significant burden on patients, there is so far little work describing the burden of OIT treatment. Additional tools that may be used for quality of life assessment and patient/caregiver outcomes in COS development are the FA Self-Efficacy Scale for Parents and the Scale for Psychosocial Factors in FA.[56,57] In young patients, quality of life data can be hard to evaluate. The FA Quality of Life Questionnaire—Parent Form[58] is a useful measure of parent report but is only a surrogate for direct child-reported outcomes. There are validated FA quality of life questionnaires for children aged more than 6 years but evaluating QOL in younger children is difficult because of communication issues, and in some studies, parents underestimated the impact of food allergies compared with their children.[59] Nevertheless, despite this challenge, it is clearly important to include outcome measures that adequately characterize the views of younger children.

## Beyond Food Allergy Immunotherapy Trials

FA causes a significant psychological and emotional burden, which can be comparable with that caused by other chronic diseases such as type 1 diabetes, asthma, or epilepsy.[60] A lack of confidence in food choices can lead to social isolation, with events such as birthday parties, sleepovers, and holidays being associated with anxiety and stress. There is a financial impact on families who have to purchase special foods, and extra time required to do routine tasks such as grocery shopping and food preparation.[2,61] Much of this impact may be mitigated by education, increased public awareness, and better management of FA by key community stakeholders, including the food industry.[62,63] Avoidance of foods with precautionary labels leads to a significant increase in the number of foods that an individual avoids, some of which may not be necessary. Food labeling initiatives[64] aim to set standards for the food industry as to when labeling is required in relation to the amount of allergen present in the food product, and have the potential to safely liberalize diets for individuals with food allergies, and restore confidence in precautionary labeling. Very few clinical trials to date have addressed any aspects of FA aside from the induction of immunologic tolerance, such as the use of cognitive-behavioral therapy or educational interventions for empowering people with FA and their caregivers.[15]

## How Are Core Outcome Sets Developed?

COS is developed through consensus-based methodology, aiming to derive a minimum set of outcomes to be assessed in clinical research or clinical care. An important distinction in COS development is between outcome domains (what to measure) and outcome measurement instruments (how to measure).[16] COS development is a stepwise process (Fig 2). The first step is to define COS scope[16,19] by defining the context (eg, clinical trials), the target population (eg, ages, disease phenotypes), the interventions (eg, OIT, epicutaneous immunotherapy), and comparators. The second step is establishing the need for a COS within the defined scope by reviewing the academic literature, including the online searchable database developed by the Core Outcome Measures in Effectiveness Trials initiative. The creation of a protocol for the development of the COS represents the third step of the process. The crucial parts of the development of COS for food allergies are the determination of what (step 4) and how to measure the COS (step 5)[19] (Table 2).

Step 4 focuses on identifying the outcome domains.[19,65] These should involve different aspects of food allergies, such as quality of life, symptoms, clinical signs, productivity loss, or disability in persons with food allergies. Outcome domains are determined by a synthesis of existing knowledge (eg, systematic reviews, qualitative

research, interviews) and filling in the gaps (eg, holding focus groups), then eliciting views on important outcomes using a consensus process (eg, the Delphi technique), agreement of the finalized COS, and reporting the work using the COS standards for reporting guidance.[66] After the consensus agreement on which outcome domains should be measured, step 5, the final stage of the process, is undertaken, which focuses on how the COS for food allergies should be defined and measured (ie, measurement method to be used, items to be included, and how to quantify the response). Factors that should be considered are the identification of existing measurement instruments and evaluation of the validity of these instruments. Some COS projects go one step further and develop new measurement instruments when there is no suitable instrument available for measuring outcomes within a specified domain.

## Conclusion

Despite the need for COS development for FA trials and clinical practice, no initiatives have been developed until recently, and this hampers the evaluation of treatments for FA. Harmonization of core outcomes in FA has been considered a top priority because very little research or exploratory work has been carried out in this area.[67] There is a need for more focused work, the extensive integration of knowledge and increased interdisciplinary and intersectoral collaboration, involving all stakeholders (health professionals, psychologists, researchers, industry, regulators, policymakers, and patient representatives). Recent systematic reviews highlighted pitfalls in existing approaches to OIT efficacy assessment and called for standardization and COS development.[50,68] Rodriguez del Rio et al[68] suggested that many trials have methodological limitations, which may lead to overestimation of treatment efficacy, whereas Chu et al[50] reported higher rates of anaphylactic reactions in trials of peanut OIT with no significant changes in health-related quality of life. Ignoring patient-reported outcomes and focusing on changes of reactivity thresholds at exit challenge as a primary outcome may represent an example of industry-related bias and an important reason to prioritize COS development to give clarity to the field.

Within the previous year, 2 initiatives aiming at the development of COS in FA were launched. The Core Outcome Measures for Food Allergy Consortium (https://www.cost.eu/actions/CA18227) is funded by the European Union Cooperation in Science and Technology program, which will facilitate COS development for FA and will bring stakeholders from European and non-European countries together to define the scope and applicability of FA COS, to develop COS and measurement tools for FA, and to reach a consensus on terminology and definitions of measurement properties for FA COS. A second project focused on immunotherapy trials was separately initiated by a group of experts within the European Academy of Allergy and Clinical Immunology. The Clinical Outcomes of Efficacy in Food Allergen Immunotherapy trials task force (https://www.eaaci.org/science/task-forces.html#category-anchor-1242) is looking to evaluate all clinical variables of efficacy used in food immunotherapy trials and develop recommendations on the convenience of using each of them. Both teams are working in close collaboration and aim to overcome the current lack of standardization by following a stepwise and comprehensive process of the systematic review and international consensus-building to identify core outcomes and instruments and ensure their harmonization for any future clinical trials. This will provide a transparent, credible evidence base for FA COS, ensuring widespread use and acceptance by stakeholders. Harmonization of core outcomes in FA, based both on existing and newly-generated bodies of evidence, is needed to lay the groundwork for trials of new food allergy therapeutics. The ultimate goal is to develop FA treatments, which impact important outcomes that can be reliably measured and thereby benefit people affected by FA.

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