Food allergy in children: treatment challenges and outcome standardization

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Summary

Relevance. Food allergy (FA) is an important public health concern, particularly among children, with an increasing prevalence. It is associated with a significant decrease in the quality of life for patients and their families due to the need to avoid allergens and the risk of severe allergic reactions, such as anaphylaxis. Despite active research, the primary treatment remains elimination diets, which limit patients' options and highlight the need for new therapeutic solutions.

Aim of the review. This review aims to summarize the current treatment methods for food allergy, discuss the challenges in evaluating the effectiveness of interventions, and highlight the importance of standardizing outcomes in clinical trials to improve comparability and practical relevance.

Content. The review discusses modern therapeutic approaches for food allergy, such as oral, epicutaneous, and sublingual immunotherapies, which have shown positive results in achieving tolerance to allergens. Special attention is given to safety concerns, particularly for children, emphasizing the need for further research. The potential use of biological agents, such as omalizumab, in food allergy treatment is also explored. The review addresses challenges in choosing and standardizing endpoints in clinical trials, where most focus on desensitization and immunological markers, while patient-centered outcomes, such as quality of life, remain under-researched. The implementation of "core outcome sets" is highlighted as an important step toward improving data comparability and forming a more objective basis for clinical recommendations.

Conclusions. The review emphasizes significant progress in food allergy treatment but notes the need for further research to ensure the safety of new therapies, particularly for children. Standardizing outcomes in clinical trials plays a key role in improving the quality and comparability of research, which will, in turn, help develop more effective clinical guidelines and improve patients' quality of life.

Keywords: harmonization, food allergy, clinical trials, treatment, core outcome sets

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Пищевая аллергия у детей: вызовы терапии и стандартизация исходов

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Резюме

Актуальность. Пищевая аллергия (ПА) является серьезной проблемой здравоохранения, особенно среди детей, с возрастающей распространенностью. Она оказывает значительное влияние на качество жизни пациентов и их семей из-за необходимости избегать аллергенов и рисков тяжелых аллергических реакций, таких как анафилаксия. Несмотря на активные исследования, основное лечение по-прежнему заключается в элиминационной диете, что ограничивает возможности пациентов и требует поиска новых терапевтических решений.

Цель обзора. Настоящий обзор направлен на обобщение современных методов лечения пищевой аллергии, рассмотрение актуальных проблем при оценке эффективности интервенций и обсуждение важности стандартизации исходов клинических исследований для улучшения их сопоставимости и практической значимости.

Содержание. Обзор включает обсуждение современных терапевтических подходов к лечению пищевой аллергии, таких как оральная, эпикутанная и сублингвальная иммунотерапии, которые демонстрируют положительные результаты в достижении толерантности к аллергенам. Особое внимание уделяется проблемам безопасности этих методов, особенно у детей, что подчеркивает необходимость дальнейших исследований. Кроме того, рассматриваются перспективы использования биологических препаратов, таких как омализумаб, в терапии пищевой аллергии. Также обсуждаются сложности в выборе и стандартизации конечных точек в клинических исследованиях, где большинство фокусируется на десенсибилизации и иммунологических показателях, тогда как такие пациент-ориентированные исходы, как качество жизни, остаются недостаточно изученными. Внедрение «наборов основных исходов» представляет важный шаг для улучшения сопоставимости данных и формирования более объективной базы для клинических рекомендаций.

Выводы. Обзор подчеркивает значительный прогресс в лечении пищевой аллергии, однако отмечает необходимость дальнейших исследований для обеспечения безопасности новых терапий, особенно для детей. Стандартизация исходов в клинических испытаниях играет ключевую роль для улучшения качества и сопоставимости исследований, что, в свою очередь, будет способствовать разработке более эффективных клинических рекомендаций и улучшению качества жизни пациентов.

Ключевые слова: гармонизация, пищевая аллергия, клинические исследования, лечение, набор ключевых исходов

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INTRODUCTION

Food allergy (FA) is a significant and growing public health problem worldwide. FA is an immunologically mediated body reaction to certain foods that can range from mild skin reactions to severe and life-threatening conditions such as anaphylaxis.

The prevalence of FA, especially among children, has increased significantly over the past decades, making it a subject of intense scrutiny by researchers and clinicians [1].

Despite the development of diagnostic and treatment methods, allergen elimination remains the main

List of abbreviations/ Список сокращений:

CI:	confidence interval
OIT:	oral immunotherapy
FA:	food allergy
RCT:	randomized clinical trial
EoE:	eosinophilic esophagitis
CDLQI:	children's dermatology life quality index
COMFA:	core outcome measures for food allergy
COS:	core outcome set
DLQI:	dermatology life quality index
EASI:	eczema area and severity index
EPIT:	epicutaneous immunotherapy
EREFS:	endoscopic reference evaluation scale of EoE
FLG:	filaggrin
FAQLQ:	quality of life questionnaire in patients with food allergy
HLA:	human leukocyte antigen
HOME:	harmonization of "outcome measures for eczema" initiative
IDQoL:	infant dermatology quality of life index
IL:	interleukin
POEM:	patient-oriented eczema measure
PROMs:	patient-reported outcome measures
RR:	relative risk
sIgE:	specific immunoglobulin E
SCIT:	subcutaneous immunotherapy
SLIT:	sublingual immunotherapy
SPINK5:	serine protease inhibitor type 5
SPIRIT:	standard protocol items: recommendations for interventional trials
SPT:	prick test
Th:	T-helpers
Tregs:	T regulatory cells

method of managing FA at the moment, which significantly limits the quality of patients' life and their families [2]. This is especially true for children whose social activity and psychological state are directly associated with dietary restrictions and the risk of accidental contact with allergens [3]. Modern interventional techniques, such as immunotherapy, aim at improving allergen tolerance and potentially achieving remission, but challenges remain regarding the safety and efficacy of these approaches.

Besides, the question arises what outcomes and results are most relevant for evaluating the effectiveness of FA treatment [4]. Traditionally, many trials focus on outcomes such as desensitization and immunological changes, while patient-oriented outcomes such as quality of life and subjective perceptions of treatment are often overlooked. This highlights the need for standardization and harmonization of data in FA clinical trials [5].

The purpose of this article is to provide an overview of potential treatment approaches for food allergy, discuss key issues in assessing the effectiveness of interventions, and provide perspectives on standardizing outcomes in research and practice, given their importance to patients and clinical decisions.

FOOD ALLERGY EPIDEMIOLOGY

The increasing incidence of pediatric PA is a complex public health problem and is most likely caused by a combination of genetic, environmental, and dietary factors. FA has become a major threat in recent decades, especially in economically developed countries, where lifetime prevalence ranges from 4% to 7% [6]. In the United States, the incidence of pediatric FA increased by 50% between 1997 and 2011 [7]. This increase emphasizes the multifactorial nature of PA, which is affected by both hereditary factors, environmental exposures, and dietary changes.

A recently published systematic review summarizing data on the prevalence of FA in Europe [8], has demonstrated that the cumulative lifetime prevalence

of "self-reported" FA was 19.9% (95%; confidence interval (CI) 16.6- 23.3) and the point prevalence was 13.1% (95%; CI 11.3-14.8). The point prevalence of sensitization by specific immunoglobulin E (sIgE) was 16.6% (95%; CI 12.3-20.8), 5.7% (95%; CI 3.9-7.4) by prick tests (SPT), and 0.8% (95%; CI 0.5-0.9) by provocation tests. Although the lifetime prevalence of FA, as both "self-reported" and measured by positive provocation tests has changed insignificantly, the point prevalence of "self-reported" FA, sIgE, and SPT has increased compared to previous estimates. This may reflect both a real rise in FA cases and increased awareness, an expansion of the list of products evaluated, or an increase in the number of studies in countries with insufficient data in previous reviews.

The most common allergens causing reactions in children include cow's milk, chicken eggs, peanuts, peanuts, nuts, fish and seafood. According to a systematic review by Panesar et al. [9], cow's milk protein was responsible for 29% of pediatric PA cases, and chicken egg protein — for 25%. The proteins in these products often cause reactions in infants and young children. However, the prevalence of FA varies according to geographical and ethnic factors. For example, studies show that Asian children in Australia have a higher prevalence of atopic dermatitis and peanut allergy compared to children of other ethnic groups [10].

FA is often accompanied by other atopic diseases such as asthma and atopic dermatitis. For example, up to two thirds of children with atopic dermatitis may exhibit symptoms of FA despite the absence of sensitization to common environmental allergens [11]. The fact that FA is combined with other allergic diseases indicates the presence of common pathophysiologic mechanisms, which emphasizes the importance of searching for integrative treatment strategies aimed at alleviating the manifestations of several allergic diseases at once.

Genetic factors also play a key role in the development of FA. Suaini et al. identified specific genetic polymorphisms associated with FA in a systematic review that included data from 32 studies [12]. Associations have been identified for the FLG, HLA, IL10, and IL13 genes, and other variants including SPINK5, SERPINB, and C11orf30 have been identified. Nevertheless, genetic factors cannot fully explain the rapid increase in FA incidence. Environmental factors, especially those associated with diet and early allergen exposure, appear to play an important role in shaping the immune response. Studies show that early introduction of allergenic foods such as peanuts may reduce the risk of developing FA [13], which in recent years has influenced the revision of infant nutrition guidelines in many countries [14].

FA has a significant impact on the mental well-being of children and their families. Children with food allergies are more likely to experience anxiety disorders, depression and social isolation compared to their peers [15]. The constant need to avoid allergens and the fear of possible severe reactions create significant emotional stress for children and their parents. This emotional burden emphasizes the importance of incorporating psychological support into FA treatment plans, ensuring that both mental and physical health are given equal consideration.

APPROACHES TO TREATMENT OF FOOD ALLERGY

Despite active research into interventional therapies for FA, elimination of the causative allergen remains the mainstay of treatment [1]. Elimination is most commonly used in routine clinical practice and in the Russian Federation, in the absence of other alternatives. Although this approach reduces the risk of acute allergic conditions, long-term avoidance of "allergens" significantly affects the quality of life by restricting the child's diet and creating psychological difficulties for their families. In recent years, various

treatments have sought to overcome these limitations with the aim of active desensitization and the search for effective interventional strategies.

One of the most promising methods is oral immunotherapy (OIT), which involves the gradual introduction of allergenic foods under medical supervision to raise the "allergic response threshold." OIT has demonstrated its efficacy in improving the quality of life of children with food allergy. A study by Epstein-Rigbi et al. [16] showed that OIT has a positive effect on both children and their parents, reducing anxiety and improving daily life. However, the safety of OIT remains a matter of concern, as adverse reactions, including anaphylaxis, have been reported during therapy, which requires strict medical supervision.

Some experts believe that OIT can lead to "sustained insensitivity" in a significant proportion of children [17], which raises the hope that long-term remission can be developed in patients with FA. The mechanism of OIT effect is to switch from a Th2 response, which promotes IgE production and allergic reactions, to a more balanced Th1/Th2 response, which promotes tolerance formation [18]. This is supported by changes in cytokine profile and immune cell composition after OIT, including decreased levels of Th2-related cytokines and increased numbers of regulatory T cells [19]. However, the combination of OIT with adjuvants such as omalizumab (anti-IgE monoclonal antibody), has demonstrated efficacy in improving treatment outcomes, especially in children with multiple food allergies [20, 21], and this approach has yielded encouraging results in patients with more complex allergy profiles.

Epicutaneous immunotherapy (EPIT) offers a less invasive alternative by delivering "allergens" through the skin using special patches. This method has attracted attention due to the potentially lower risk of systemic reactions compared to OIT. Clinical trials have demonstrated the efficacy of EPIT for peanuts, resulting in an increase in the amount of peanut protein tolerated.

In a recent study, a positive outcome was reported in 67% of children in the intervention group compared with 33.5% in the placebo group (risk difference was 33.4 percentage points; 95% confidence interval 22.4-44.5; $p < 0.001$) [22]. The mechanism of action of EPIT involves activation of regulatory T cells (Tregs), including modulation of local immune responses in the skin, potentially causing the development of systemic tolerance [23]. The lower risk of severe side effects makes EPIT an attractive option for young children, who are at higher risk of serious allergic reactions [18].

Sublingual immunotherapy (SLIT) involves placing allergen extracts under the tongue for absorption through the oral mucosa. This technique is used extensively in the treatment of allergic rhinitis, but a number of studies have evaluated its efficacy in the treatment of FA. In two clinical trials comparing the efficacy of oral immunotherapy (OIT) and sublingual immunotherapy (SLIT) for peanut and cow's milk allergy, OIT was found to be more effective in inducing desensitization compared with SLIT [24, 25]. However, SLIT was also associated with a higher incidence of symptoms and moderate-to-severe reactions requiring epinephrine, as well as a higher number of discontinuations. Thus, the data suggest that SLIT may offer a higher safety profile, with fewer systemic reactions than OIT [26]. The immunologic mechanisms of SLIT are similar to OIT and include Tregs induction and switching of the immune response toward tolerance [18].

Subcutaneous immunotherapy (SCIT), traditionally used for pollen and house dust mite allergies, is also being studied as an alternative for the treatment of FA. SCIT involves administering allergen extracts by injection, which may cause desensitization over time. Although SCIT is effective for the treatment of allergies to "classical environmental allergens," its use in PA is limited due to the high risk of severe anaphylactic reactions [17].

In 2024, the U.S. Food and Drug Administration (FDA) in the USA approved omalizumab for the

treatment of children and adults with one or more food allergies. The decision was based primarily on the results of a randomized clinical trial (RCT) published in the New England Journal of Medicine [27]. Of the 118 participants receiving omalizumab, 67% met the primary endpoint (participants' ability to tolerate 600 mg or more of peanut protein), compared to 7% receiving placebo. In terms of safety, there were no significant differences between groups, with the exception of more frequent injection site reactions in the omalizumab group.

The study of interventional approaches for the treatment of pediatric PA continues to evolve rapidly, and techniques such as OIT, EPIT, SLIT and SCIT offer various benefits and challenges. Continued research is needed to optimize these techniques, improve safety, and increase understanding of the immunologic mechanisms underlying them. The consideration of psychosocial factors remains an important aspect, which will allow a more comprehensive and patient- oriented treatment approach to be developed.

EFFICACY EVALUATION IN CLINICAL TRIALS

RCTs aim to determine the efficacy of a particular treatment, but we most often do not think about the nuances of defining efficacy. The assessment of efficacy is closely linked to the selection of appropriate outcomes/endpoints that serve as key indicators of treatment success and patient benefit. Clearly defined and clinically relevant outcomes are essential for the proper interpretation of research results, allowing useful conclusions to be drawn for clinical practice. The importance of careful and thorough selection of primary endpoints is discussed in many areas of medicine, such as in studies related to neurocognitive outcomes in infant formula testing [28], where the clarity and relevance of endpoints are crucial for informative results. Experts point to the need for a clearer definition of indicators based on "evaluation of patient-reported outcomes" (PROMs), in oncology trials to accurately reflect the impact of treatment on patients' quality of life [29].

The measurement of PROMs, of which quality of life assessment is a classic example, is extremely important as it provides an opportunity to capture patients' own experience and perception of treatment, which helps to better understand its efficacy with no regard to the field of medicine in which the study is being conducted. D'Souza et al. demonstrated the value of PROMs in amyloidosis studies, where patient-centered outcomes provide important insights into the impact of treatment on daily life [30], and Taylor et al. recommend that aspects such as participation in activities of daily living be included as an additional indicator in chronic pain studies, which helps to further and better assess the impact of therapy on patients [31].

The high heterogeneity of definitions and methods for measuring outcomes across clinical trials presents a significant obstacle to meta-synthesizing data and conducting systematic reviews. As noted by Gianola et al. [32], inconsistencies in outcome reporting make it difficult to compare data between studies, making it difficult to build an evidence base for use in developing clinical guidelines and then making decisions in routine clinical practice. This issue is compounded by a lack of consensus on which outcomes are most appropriate for evaluating the efficacy of therapy for different diseases, which may lead to misunderstanding and misrepresentation of results [33].

Along with the choice of outcomes, the methodology of clinical trials plays a key role in ensuring the reliability and applicability of the results. The use of rigorous statistical methods and sufficient sample sizes are necessary for studies to be powerful enough to determine clinically meaningful differences. However, as has been repeatedly pointed out by experts, many studies do not meet these requirements, making their results less general or clinically meaningful [32]. It should also be remembered that statistical significance does not always correlate with clinical rele-

vance, which emphasizes the importance of cautious interpretation of RCT results.

In addition to the problems described above, the results of RCTs can be adversely affected by systematic errors in outcome reporting that occur when there are discrepancies between study protocols and published results. Kirkham et al. emphasize that such discrepancies reduce the accuracy of systematic reviews, making it necessary to document changes in outcomes more transparently [34]. Ioannidis et al. also express concern that covert modifications of outcomes may distort the true effectiveness of an intervention [35]. These errors can mislead clinicians and patients alike, ultimately leading to inappropriate decisions and negatively impacting medical care [36].

It is also important to remember that regulatory standards play a significant role in shaping the design of clinical trials. In the United States, regulatory approval of new medicines is based on a demonstration of clinical benefit supported by evidence from well-controlled trials [37]. This requires a thorough understanding of disease progression, the impact of treatment, and the use of various outcomes that reflect patients' multifaceted experience.

An important step towards improving the quality of RCTs is the development and implementation of Core Outcome Sets (COS), which standardize the measurement of outcomes across studies and are described in later sections of this article. The use of COS improves comparability of data and facilitates their synthesis in systematic reviews. Many experts advocate the implementation of COS in clinical trials, as recommended in the guidelines of the Standard Protocol Elements Recommendations for Interventional Trials (SPIRIT), to ensure that the endpoints assessed in trials are relevant to patients and to increase harmonization of their evaluation [38]. This is important and relevant also in allergology, where RCTs of FA treatment have mainly focused on outcomes, that are meaningful to researchers and commercial investors, such as "reactivity threshold" and "immunologic changes" [39].

ENDPOINTS IN RCT OF FOOD ALLERGY THERAPY

When discussing the problems of measuring outcomes in clinical trials of food allergy treatment, it is evident that the lack of standardization and focus on patient-centered outcomes significantly limits the ability to apply the results of studies in clinical practice [4]. First of all, most studies focus on objective indicators such as desensitization and remission, which, although useful from the point of view of the scientific community, does not always reflect the real needs and priorities of patients.

The most frequent outcome assessed in RCTs of FA therapy is desensitization (Table 1) [40]. Desensitization is usually understood as an increase in the patient's tolerance to the food allergen, but this tolerance is maintained only with continuous exposure to the allergen [41]. This outcome is usually demonstrated in a study by increasing the threshold of response to the allergen. In contrast, "remission" implies the absence of clinical response after discontinuation of therapy for a certain period of time [42]. Patients who have achieved desensitization are protected against allergic reactions in case of accidental exposure to the allergen, but they must continue daily treatment, e.g. immunotherapy, and strictly avoid contact with the causative allergen. In case of remission, however, patients can discontinue therapy and freely include the allergen in their diet without restrictions [4].

In RCTs, the increase in allergen tolerance is usually assessed using provocation tests, which are still not very widespread in the Russian Federation. However, attempts to introduce provocative tests into clinical practice are actively being made in various institutions. For example, the feasibility of using provocation testing as a method of diagnosing FA in children is currently being evaluated as part of the

Table 1. **Examples of clinical trials for the treatment of food allergy in children and the outcomes used to assess the effectiveness of therapy (author's table)**
Таблица 1. **Примеры клинических исследований по лечению пищевой аллергии у детей и исходов, используемых для оценки эффективности терапии (таблица автора)**

Author, year	Country	Sample size and age	Allergen	Intervention	Treatment duration	Main outcome	Outcome determination
Cohen et al, 2022 [53]	Canada	69 children, median age is 12 years (9–15)	Cow's milk	OIT Dose escalation from 4 ml to 200 ml (equivalent to 8000 mg of cow's milk protein)	Median 24 (17,7–33,4) weeks	Desensitization	Probability of achieving the maintenance dose of 200 mL of cow's milk, given factors such as sIgE levels to milk, accumulated dose at initiation, and adverse events
Maeda et al, 2021 [54]	Japan	28 children, 3–12 years	Cow's milk	OIT 3300 mg of cow's milk protein (100 ml a day)	1 year	Desensitization	Efficacy of OIT in achieving tolerance to 100 ml of milk, specific IgE levels, adverse events
Palosuo et al, 2021 [55]	Finland	50 children, 6–17 years	Chicken egg	OIT, dose up to 1 g of egg white	8 and 18 months	Desensitization	Tolerance of 1000 mg in 8/18 months, change in levels of specific antibodies (IgE, IgG4, IgA) to egg protein components (Gal d 1-4), adverse events
Fleischer et al, 2019 [56]	USA, Canada, Australia, Germany, Ireland	356 children, 4–11 years	Peanut	EPIT, 250 µg of peanut protein	12 months	Desensitization	Percentage of participants who were able to increase the peanut dose to ⩾300 mg or ⩾1000 mg or more, side effects such as skin reactions and anaphylactic reactions
Takaoka et al, 2019 [57]	Japan	33 children, median age is 6 years	Chicken egg	OIT with low-allergen cookies (79–110 mg of egg white)	4 months	Desensitization	Percentage of "well-responsive" patients (those who passed the food test without allergy to 2 g of cooked egg white), incidence of adverse events

ОИТ, оральная иммунотерапия; EPIT, эпикутанная иммунотерапия; sIgE, специфический иммуноглобулин Е.

study "Provocation tests for polyvalent allergy in the intensive care unit. It is implemented by a team of specialists on the basis of GBHI CSCH № 9 named after G. N. Speransky.

There is some evidence to suggest that OIT induces desensitization in many patients undergoing treatment, and some may experience remission of their allergies.

However, the long-term sustainability of remission remains uncertain and varies from patient to patient. Despite the effectiveness of OIT in increasing allergen tolerance, the impact on patient- oriented outcomes such as quality of life remains poorly understood. It is still not fully understood whether OIT improves the life quality of patients receiving therapy.

In a meta-analysis of 12 RCTs published in The Lancet, it was noted that although OIT given to patients with peanut allergy effectively increases the threshold of allergen response in a controlled clinical setting, it does not reduce the incidence of allergic reactions and anaphylaxis in real life [43]. On the contrary, the study demonstrated that OIT increases the relative risk of anaphylaxis (RR 3.12) and the use of adrenaline (RR 2.21) compared to allergen elimination or placebo. This highlights the contradiction between the desensitization achieved and the actual clinical results, such as the incidence of allergic reactions. In addition, the results of the study have shown that OIT does not improve the quality of patients' lives. This conclusion is based on the analysis of two RCTs that used the parent-child quality of life questionnaire (FAQLQ). The findings showed that there was no significant difference in the improvement of quality of life between patients receiving OIT and the control group who were on an elimination regimen.

Although there are a number of validated qualities of life assessment tools specifically designed for patients with FA, their use in RCTs remains inconsistent, and when they are used, it is not with the same rigor as for assessing clinical and intervention safety outcomes. In particular, several large studies only reported changes in quality of life in the active treatment group, without comparing these changes with the placebo group [44]. This aspect is important, as participation in RCTs may itself have significant benefits due to the so-called placebo effect.

To date, only a very small number of randomized placebo-controlled trials have provided data comparing post-treatment quality of life measures between active and placebo groups [45]. At the same time, there is increasing evidence that clinical conditions (directly native FA, desensitization without remission and remission) as well as the ability to freely consume the allergen without restrictions are closely associated with quality of life in food allergy [46].

It has also been found that the amount and frequency of allergen consumption may affect quality of life measures. In the PPOIT-003 peanut OIT clinical trial, children who were in remission and able to freely consume peanuts showed a significant improvement in quality of life 12 months after completion of treatment compared to those who were desensitized but had to continue daily intake of a fixed allergen dose [46].

HARMONIZING OUTCOMES IN FOOD ALLERGY STUDIES

COS are standardized sets of outcomes that should be measured and reported in all clinical trials for a particular disease or condition [5]. These sets include the most important and relevant outcomes that are meaningful to both researchers and patients. COSs play a key role in ensuring comparability and consistency of data between different studies, which ultimately improves the quality of medical decisions and clinical practice.

The need to develop and implement COSs is driven by several important factors. First of all, they allow researchers to compare and pool data from different studies, since all studies use the same key outcomes. This is particularly important for meta-analyses and systematic reviews that form the basis for clinical guidelines. Without a standardized set of outcomes, results from individual studies can be hard to compare, making it difficult to build a robust evidence base.

In addition, COSs help prevent publication bias, where researchers may choose to publish only those outcomes that are statistically significant or interesting, ignoring other important data [34]. COS also helps to ensure that all key outcomes are measured

and reported, which improves the quality of reporting and reduces the risk of distorted information.

Another important reason to implement COS is patient- orientedness

Another important reason to implement COS is patient-centeredness and the inclusion of the patient in the decision-making process. COSs are usually designed involving not only researchers, but also patients, clinicians and other parties concerned. This ensures that studies include outcomes that matter most to patients, such as quality of life, functional ability, and other aspects that directly affect people's well-being. The inclusion of patient-centered indicators helps to better understand how treatment affects patients' daily life [47].

The development of COS for RCTs of allergic diseases is actively pursued. Atopic dermatitis is probably the most developed nosology. The development of COS for eczema, or atopic dermatitis, was undertaken as part of the international Harmonization of Outcome Measures for Eczema (HOME) initiative launched in 2010. The goal of this initiative was to create a standardized set of outcomes that could be used in all clinical trials for atopic dermatitis. The COS for atopic dermatitis includes key outcomes that should be measured and recommends specific tools to assess these outcomes [48].

In the first stages, the COS developers focused on determining which aspects of the disease should be measured in the RCT. The primary outcomes chosen were: clinical symptoms (e.g. itching and sleep loss), clinical signs (skin inflammation), quality of life, and long-term disease control. An important feature of the process was patient participation, which made COS more patient-oriented, taking into account not only medical but also psychological and social aspects of the disease [48].

For each of the main outcomes, appropriate measurement tools were selected. For example, the Patient-Oriented Eczema Evaluation Measure (POEM) scale, which has proven valid and reliable in various studies, was chosen to assess symptoms. The Eczema Area and Severity Index (EASI) was recommended to assess clinical features, and the Dermatology Quality of Life Index (DLQI) and its pediatric and infant versions were recommended to measure quality of life (CDLQI и IDQoL).

These tools allow to standardize the results of clinical trials, improving the possibility of data comparison and subsequent analysis [49, 50].

COS development processes for FA research have been initiated relatively recently. For example, the results of the eosinophilic esophagitis (EoE) project were published in 2022. The creation of COS was a necessary step due to the significant heterogeneity in the assessment of study outcomes and the lack of harmonized measures that could be used to compare the efficacy of different therapy approaches. COS for EoE, called COREOS, was developed in collaboration with international experts including gastro-enterologists, allergists, pathomorphologists, nutritionists and patients.

During the development of COS for EoE, four key outcome domains were identified that should be considered in every study: histopathology, endoscopy, patient-reported symptoms, and EoE-specific quality of life. These outcomes were selected as the most important for assessing treatment efficacy. For example, histologic changes, such as the number of eosinophils in esophageal tissue, and endoscopic parameters, such as the Endoscopic EoE Reference Evaluation Scale (EREFS) score, play an important role in determining disease activity. Simultaneously, subjective data such as improvement in dysphagia symptoms and improved quality of life have also been found to be critical for patients, highlighting the need to consider not only biomarkers but also patient- oriented outcomes in clinical trials [51].

Table 2. **Outcomes and their definitions used in the Core Outcomes for Food Allergy (COMFA) consensus process [52]**
Таблица 2. **Исходы и их определения, использовавшиеся в рамках консенсусного процесса основные меры оценки исходов для пищевой аллергии (COMFA) [52]**

Outcome	Outcome determination
Adherence	The degree to which the individual is following agreed upon treatment for food allergies (e.g., taking medication, following a diet and/or adhering to/changing lifestyle).
Concomitant allergic diseases	Occurrence of new concomitant allergic diseases or change in the degree of control of current concomitant allergic diseases such as eosinophilic esophagitis, eczema, asthma, allergic rhinitis, etc., with or without exposure to food containing the causative allergen.
Allergic symptoms	Onset and incidence of allergic symptoms (tingling and itching; raised itchy blisters (urticaria); swelling of the face, lips (angioedema), throat and other parts of the body; difficulty swallowing; wheezing or shortness of breath; hoarse voice; sensation of dizziness, confusion, nausea or vomiting, dysphagia; abdominal pain or diarrhea; anaphylaxis; manifestations of allergic rhinitis such as runny nose (rhinitis), itchy eyes (allergic conjunctivitis) associated with intentional or unintentional consumption of food containing the causative allergen.
Desensitization	The ability to consume (as a result of the intervention) a predetermined amount of food containing a trigger allergen without allergic symptoms that bother a person with food allergies. *(This outcome can be assessed either at a specific point in time or at multiple points in time, continuously.)*
Economic impact	Financial consequences associated with medication, food and non-health related expenses due to food allergies. Frequency of visits to health care professionals (e.g., physician, psychotherapist, psychologist), emergency medications, hospital visits or emergency medical calls, including alternative medicine (e.g., acupuncturists, naturopaths); indirect costs (lost time, lost productivity and additional costs due to food allergies); health care system costs.
Behavior as part of food allergy treatment	Degree of confidence, motivation and current knowledge of being able to help manage food allergies (ability to talk about allergies in restaurants, carry emergency medications (such as epinephrine, antihistamines, inhaled steroids)).
Psychological distress associated with food allergies	Anxiety (including phobias), fear associated with food allergies.
Personal and family aspects	Including, but not limited to food intake, preparing meals together, including impact on people who live with the person with food allergies; effect on friends, maintaining and being able to make new acquaintances, build romantic and personal relationships, participate in community life. The impact of food allergies on people who live with the person with food allergies; relationships within the family and with friends.
Remission/sustained non-response	The ability to safely consume (without restriction) foods containing the causative allergen.
Work, study and leisure	The impact of food allergies on work, school, attendance, participation and engagement in various activities.
Satisfaction with the intervention (treatment)	The extent to which the intervention (meaning any type of treatment) has met the expectations of the person with food allergies and their caregivers, family members.
Stigma	Fears or experience of discrimination, bullying, exclusion from any activity, being ignored by employer/school/kindergarten/university, healthcare professional, social group, family/friends/neighbors and others.
Achieving the initial expectations of the intervention (treatment)	The extent to which expectations (beliefs) of the health system intervention (treatment) or interventions will be achieved.
Quality of life	A person's perception of their position in life in the cultural context and in relation to the value system in which they live and in relation to their goals, expectations, standards and concerns. It is a generalized term covering at least physical, mental and social health.

The development of COS for FA research was initiated within the framework of the international study "Core Outcome Measures for Food Allergy" (COMFA). The main objective of this project was to standardize outcomes for clinical trials and observational studies aimed at evaluating interventional tactics for IgE-mediated FA. The study was a Delphi consensus study, involving a variety of participants: patients with FA and their family members, members of the medical community, and researchers.

This has led to the development of a uniform set of key outcomes that should be measured and reported in every FA study [52].

The development process began with a systematic literature review that produced an initial version of the list of outcomes, which was then reduced to 14 outcomes submitted for voting in a consensus process (Table 2). Allergic symptoms and quality of life were considered key for inclusion as endpoints in all FA studies because they reflect the direct impact of allergy on the patient and their daily life.

Other important outcomes, such as desensitization and remission, did not meet the threshold of agreement for inclusion in the core set, but were considered significant and recommended for consideration in separate trials. It is important to note that the results of the COMFA study also emphasize the need for mandatory consideration of adverse events, such as side effects and anaphylaxis, in clinical trials.

CONCLUSION

FA remains a major public health problem, especially in the pediatric population. The mainstay of treatment to date is allergen elimination, but this approach has a significant impact on the quality of patients' and their families' lives. Therefore, current treatment strategies such as oral, epicutaneous and sublingual immunotherapies offer promising alternatives, although they require further development to improve safety and efficacy. The introduction of new techniques, such as the use of monoclonal antibodies (e.g., omalizumab), also opens new horizons in FA therapy.

Standardization of outcomes is an essential step to improve the quality of ongoing clinical trials on the treatment of FA. The use of COS not only improves the quality of studies, but also makes their results more comparable and applicable in practice. COSs facilitate the inclusion of critical outcomes, including allergy symptoms, patient quality of life, and side effects of therapy, which is particularly important in the context of diverse treatments and heterogeneous clinical data.

Further progress in the treatment of FA requires additional research to improve existing therapies as well as to develop new approaches that address both the clinical and psychosocial aspects of the disease. Particular attention should be paid to those outcomes that have been identified as critical by the COS processes that have been implemented.

REFERENCES

1. Sicherer S.H., Sampson H.A. Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J Allergy Clin Immunol. 2018; 141 (1): 41–58.
2. Muraro A., de Silva D., Halken S., et al. Managing food allergy: GA(2)LEN guideline 2022. World Allergy Organ J. 2022; 15 (9): 100687.
3. Yamamoto-Hanada K., Pak K., Iwamoto S., Konishi M., Saito-Abe M., Sato M., Miyaji Y., Mezawa H., Nishizato M., Yang L., Kumasaka N., Ohya Y.; Japan Environment and Children's Study (JECS) Group. Parental stress and food allergy phenotypes in young children: A National Birth Cohort (JECS). Allergy. 2024 Jul;79(7):1881-1892. https://doi.org/10.1111/all.16035.
4. Lloyd M., Patel N., Munblit D., Tang M.L.K. Endpoints and Outcomes After Immunotherapy for Food Allergy: What Is Meaningful for Patients? J Allergy Clin Immunol Pract. 2023; 11 (4): 998–1007.
5. Williamson P.R., Altman D.G., Bagley H., et al. The COMET Handbook: version 1.0. Trials. 2017; 18 (Suppl 3): 280.
6. Kim J.F., McCleary N., Nwaru B.I., Stoddart A., Sheikh A. Diagnostic Accuracy, Risk Assessment, and Cost-effectiveness of Component-resolved Diagnostics for Food Allergy: A Systematic Review. Allergy. 2018; 73 (8): 1609–1621.
7. Contributors W., Joint Task Force on Practice Parameters R. Anaphylaxis — a 2020 Practice Parameter Update, Systematic Review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Analysis. Journal of Allergy and Clinical Immunology. 2020; 145 (4): 1082–1123.
8. Spolidoro G.C.I., Amera Y.T., Ali M.M., et al. Frequency of food allergy in Europe: An updated systematic review and meta-analysis. Allergy. 2023; 78 (2): 351–368.
9. Panesar S.S., Javad S., Silva Dd, et al. The Epidemiology of Anaphylaxis in Europe: A Systematic Review. Allergy. 2013; 68 (11): 1353–1361.

10. Wang Y., Allen K.J., Suaini N.H.A., McWilliam V., Peters R.L. The Global Incidence and Prevalence of Anaphylaxis in Children in the General Population: A Systematic Review. Allergy. 2019; 74 (6): 1063–1080.
11. Tsakok T., Marrs T., Mohsin M., et al. Does Atopic Dermatitis Cause Food Allergy? A systematic Review. Journal of Allergy and Clinical Immunology. 2016; 137 (4): 1071–1078.
12. Suaini N.H.A., Wang Y., Soriano V.X., et al. Genetic Determinants of Paediatric Food Allergy: A Systematic Review. Allergy. 2019; 74 (9): 1631–1648.
13. Skjerven H.O., Lie A., Vettukattil R., et al. Early food intervention and skin emollients to prevent food allergy in young children (PreventADALL): a factorial, multicentre, cluster-randomised trial. Lancet. 2022; 399 (10344): 2398–2411.
14. Silva Dd, Geromi M., Halken S., et al. Primary Prevention of Food Allergy in Children and Adults: Systematic Review. Allergy. 2014; 69 (5): 581–589.
15. Vazquez-Ortiz M., Angier E., Blümchen K., et al. Understanding the Challenges Faced by Adolescents and Young Adults With Allergic Conditions: A Systematic Review. Allergy. 2020; 75 (8): 1850–1880.
16. Epstein-Rigbi N., Goldberg M.R., Levy M.B., Nachshon L., Elizur A. Quality of Life of Children Aged 8-12 Years Undergoing Food Allergy Oral Immunotherapy: Child and Parent Perspective. Allergy. 2020; 75 (10): 2623–2632.
17. Scurlock A.M., Jones S.M. Advances in the Approach to the Patient With Food Allergy. Journal of Allergy and Clinical Immunology. 2018; 141 (6): 2002–2014.
18. Muraro A., Agache I., Clark A., et al. EAACI Food Allergy and Anaphylaxis Guidelines: Managing Patients With Food Allergy in the Community. Allergy. 2014; 69 (8): 1046–1057.
19. Crestani E., Harb H., Charbonnier L.-M., et al. Untargeted Metabolomic Profiling Identifies Disease-Specific Signatures in Food Allergy and Asthma. Journal of Allergy and Clinical Immunology. 2020; 145 (3): 897–906.
20. Mortz C.G. A Randomized, Double-blind Placebo-controlled Study on the Efficacy of Omalizumab on Food Allergy Threshold in Children With Severe Food Allergy. Allergy. 2024; 79 (4): 964–976.
21. Sampath V., Sindher S., Alvarez-Pinzon A.M., Nadeau K. Can Food Allergy Be Cured? What Are the Future Prospects? Allergy. 2019; 75 (6): 1316–1326.
22. Greenhawt M., Sindher S.B., Wang J., et al. Phase 3 Trial of Epicutaneous Immunotherapy in Toddlers with Peanut Allergy. N Engl J Med. 2023; 388 (19): 1755–1766.
23. Leung D.Y., Guttman-Yassky E. Deciphering the Complexities of Atopic Dermatitis: Shifting Paradigms in Treatment Approaches. Journal of Allergy and Clinical Immunology. 2014; 134 (4): 769–779.
24. Narisety S.D., Frischmeyer-Guerrerio P.A., Keet C.A., 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.
25. Keet C.A., Frischmeyer-Guerrerio P.A., Thyagarajan A., et al. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. J Allergy Clin Immunol. 2012; 129 (2): 448–455, e1-5.
26. Togias A., Cooper S., Acebal M.L., et al. Addendum Guidelines for the Prevention of Peanut Allergy in the United States: Report of the National Institute of Allergy and Infectious Diseases — sponsored Expert Panel. Journal of Allergy and Clinical Immunology. 2017; 139 (1): 29–44.
27. Wood R.A., Togias A., Sicherer S.H., et al. Omalizumab for the Treatment of Multiple Food Allergies. N Engl J Med. 2024; 390 (10): 889–899.
28. Sun H., Como P., Downey L.C., Murphy D., Ariagno R.L., Rodriguez W.J. Infant Formula and Neurocognitive Outcomes: Impact of Study End-Point Selection. Journal of Perinatology. 2015; 35 (10): 867–874.
29. Coleman R.L., Beck J.T., Baranda J., et al. The Use of Patient-Reported Outcome Measures in Phase I Oncology Clinical Trials. Oncology. 2021; 99 (7): 444–453.
30. D'Souza A., Hari P., Pasquini M.C., Jacobsen K.K., Flynn K.E. Baseline Patient-Reported Outcomes in Light-Chain Amyloidosis Patients Enrolled on an Interventional Clinical Trial. Amyloid. 2019; 26 (sup1): 87–88.
31. Taylor A.M., Phillips K., Patel K.V., et al. Assessment of Physical Function and Participation in Chronic Pain Clinical Trials: IMMPACT/OMERACT Recommendations. Pain. 2016; 157 (9): 1836–1850.
32. Gianola S., Castellini G., Corbetta D., Moja L. Rehabilitation Interventions in Randomized Controlled Trials for Low Back Pain: Proof of Statistical Significance Often Is Not Relevant. Health and Quality of Life Outcomes. 2019; 17 (1).
33. Gorst S.L., Prinsen C.A., Salcher-Konrad M., Matvienko-Sikar K., Williamson P., Terwee C.B. Methods Used in the Selection of Instruments for Outcomes Included in Core Outcome Sets Have Improved Since the Publication of the COSMIN/COMET Guideline. Journal of Clinical Epidemiology. 2020; 125: 64–75.

34. Kirkham J.J., Altman D.G., Chan A.W., Gamble C., Dwan K., Williamson P. Outcome Reporting Bias in Trials: A Methodological Approach for Assessment and Adjustment in Systematic Reviews. BMJ. 2018: k3802.
35. Ioannidis J.P.A., Caplan A.L., Dal-Ré R. Outcome Reporting Bias in Clinical Trials: Why Monitoring Matters. BMJ. 2017: j408.
36. Schilsky R.L. Moving From Evaluation to Value in Cancer Care. Clinical Cancer Research. 2015; 21 (5): 947–949.
37. Clair C.O.S, Papadopoulos E.J. Considerations in the Assessment of Clinical Benefit With a Focus on Pain: A Regulatory Perspective. Neurotherapeutics. 2020; 17 (3): 770–773.
38. Gargon E., Gurung B., Medley N., et al. Choosing Important Health Outcomes for Comparative Effectiveness Research: A Systematic Review. Plos One. 2014; 9 (6): e99111.
39. Sim K., Mijakoski D., Stoleski S., et al. Outcomes for clinical trials of food allergy treatments. Ann Allergy Asthma Immunol. 2020; 125 (5): 535–542.
40. Rodriguez Del Rio P., Alvaro-Lozano M., Arasi S., et al. Evaluation of clinical outcomes of efficacy in food allergen immunotherapy trials, COFAITH EAACI task force. Allergy. 2024; 79 (4): 793–822.
41. Burks A.W., Sampson H.A., Plaut M., Lack G., Akdis C.A. Treatment for food allergy. J Allergy Clin Immunol. 2018; 141 (1): 1–9.
42. Plaut M., Sawyer R.T., Fenton M.J. Summary of the 2008 National Institute of Allergy and Infectious Diseases — US Food and Drug Administration Workshop on Food Allergy Clinical Trial Design. J Allergy Clin Immunol. 2009; 124 (4): 671–678 e1.
43. Chu D.K., Wood R.A., French S., et al. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. Lancet. 2019; 393 (10187): 2222–2232.
44. Dunn Galvin A., Fleischer D.M., Campbell D.E., et al. Improvements in Quality of Life in Children Following Epicutaneous Immunotherapy (EPIT) for Peanut Allergy in the PEPITES and PEOPLE Studies. J Allergy Clin Immunol Pract. 2021; 9 (1): 216–224 e1.
45. Dunn Galvin A., Lloyd M., Hsiao K.C., Tang M.L.K., PPOIT-001 study team. Long-term benefit of probiotic peanut oral immunotherapy on quality of life in a randomized trial. J Allergy Clin Immunol Pract. 2021; 9 (12): 4493–4495 e1.
46. Loke P., Orsini F., Lozinsky A.C., et al. Probiotic peanut oral immunotherapy versus oral immunotherapy and placebo in children with peanut allergy in Australia (PPOIT-003): a multicentre, randomised, phase 2b trial. Lancet Child Adolesc Health. 2022; 6 (3): 171–184.
47. Schmitt J., Apfelbacher C., Spuls P.I., et al. The Harmonizing Outcome Measures for Eczema (HOME) roadmap: a methodological framework to develop core sets of outcome measurements in dermatology. J Invest Dermatol. 2015; 135 (1): 24–30.
48. Williams H.C., Schmitt J., Thomas K.S., et al. The HOME Core outcome set for clinical trials of atopic dermatitis. J Allergy Clin Immunol. 2022; 149 (6): 1899–1911.
49. Schmitt J., Langan S., Deckert S., et al. Assessment of clinical signs of atopic dermatitis: a systematic review and recommendation. J Allergy Clin Immunol. 2013; 132 (6): 1337–1347.
50. Chalmers J.R., Simpson E., Apfelbacher C.J., et al. Report from the fourth international consensus meeting to harmonize core outcome measures for atopic eczema/dermatitis clinical trials (HOME initiative). Br J Dermatol. 2016; 175 (1): 69–79.
51. Collaborators C., Ma C., Schoepfer A.M., et al. Development of a core outcome set for therapeutic studies in eosinophilic esophagitis (COREOS). J Allergy Clin Immunol. 2022; 149 (2): 659–670.
52. Demidova A., Drewitz K.P., Kimkool P., et al. Core Outcome Set for IgE-mediated food allergy clinical trials and observational studies of interventions: International Delphi consensus study 'COMFA'. Allergy. 2024; 79 (4): 977–989.
53. Cohen C.G., Zhao W.W., Ke D., et al. Elevated Cow's Milk-Specific IgE Levels Prior to Oral Immunotherapy Decrease the Likelihood of Reaching the Maintenance Dose. J Allergy Clin Immunol Pract. 2022; 10(1): 215–221 e2.
54. Maeda M., Imai T., Ishikawa R., et al. Effect of oral immunotherapy in children with milk allergy: The ORIMA study. Allergol Int. 2021; 70 (2): 223–228.
55. Palosuo K., Karisola P., Savinko T., Fyhrquist N., Alenius H., Makela M.J. A Randomized, Open-Label Trial of Hen's Egg Oral Immunotherapy: Efficacy and Humoral Immune Responses in 50 Children. J Allergy Clin Immunol Pract. 2021; 9 (5): 1892–1901 e1.
56. Fleischer D.M., 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; 321 (10): 946–955.
57. Takaoka Y., Maeta A., Takahashi K., et al. Effectiveness and Safety of Double-Blind, Placebo-Controlled, Low-Dose Oral Immunotherapy with Low Allergen Egg-Containing Cookies for Severe Hen's Egg Allergy: A Single-Center Analysis. Int Arch Allergy Immunol. 2019; 180 (4): 244–249.

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Daniil B. Munblit — concept development, idea formation; formulation and development of key goals and objectives, preparation and creation, text evaluation and editing, taking responsibility for all aspects of the work, ensuring the integrity of all parts of the article and its final version, approval of the final version of the article.

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