



WAO consensus on DEfinition of Food Allergy SEverity (DEFASE)

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ABSTRACT

Background: While several scoring systems for the severity of anaphylactic reactions have been developed, there is a lack of consensus on definition and categorisation of severity of food allergy disease as a whole.

Aim: To develop an international consensus on the severity of food allergy (DEfinition of Food Allergy Severity, DEFASE) scoring system, to be used globally.

Methods: Phase 1: We conducted a mixed-method systematic review (SR) of 11 databases for published and unpublished literature on severity of food allergy management and set up a panel of international experts.

Phase 2: Based on our findings in Phase 1, we drafted statements for a two-round modified electronic Delphi (e-Delphi) survey. A purposefully selected multidisciplinary international expert panel on food allergy (n = 60) was identified and sent a structured questionnaire, including a set of statements on different domains of food allergy severity related to symptoms, health-related quality of life, and economic impact. Participants were asked to score their agreement on each statement on a 5-point Likert scale ranging from "strongly agree" to "strongly disagree". Median scores and percentage agreements were calculated. Consensus was defined *a priori* as being

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achieved if 70% or more of panel members rated a statement as “strongly agree” to “agree” after the second round. Based on feedback, 2 additional online voting rounds were conducted.

Results: We received responses from 92% of Delphi panel members in round 1 and 85% in round 2. Consensus was achieved on the overall score and in all of the 5 specific key domains as essential components of the DEFASE score.

Conclusions: The DEFASE score is the first comprehensive grading of food allergy severity that considers not only the severity of a single reaction, but the whole disease spectrum. An international consensus has been achieved regarding a scoring system for food allergy disease. It offers an evaluation grid, which may help to rate the severity of food allergy. Phase 3 will involve validating the scoring system in research settings, and implementing it in clinical practice.

Keywords: Consensus, Definition, Food allergy, Severity, e-Delphi study

INTRODUCTION

Food allergy (FA) is a growing public health challenge with an estimated prevalence of up to 10% of the general population.¹⁻⁴ This potentially life-threatening condition can result in a substantial emotional, social, and financial burden for individuals with allergic disease and their families, with consequences for health systems and broader societies.⁵ FA refers to a broad spectrum of phenotypes and severity degrees reflected by variability in food-triggered clinical manifestations and eliciting doses.⁶

FA diagnostics is complex. The most commonly used tests are skin prick testing (SPT) and food allergen-specific immunoglobulin E (sIgE), but oral food challenge (OFC) remains the gold standard, although with some limitations (eg, risk of severe reactions, costs, reproducibility). As sensitization tests do not correlate with the severity of reaction observed during OFC, reliable biomarkers able to predict the risk of allergen-specific reactions and their respective severity are under investigation.⁷

To this end, many definitions and scores are presently in use, which are not comparable across studies and among different stakeholders.^{8,9} On the other hand, a comprehensive definition of FA as a whole disease is missing. This impairs our ability to efficiently allocate finite resources in this area, in effect applying a one-size-fits-all approach that is of limited utility to patients, their families, and their providers. A standardized classification of FA severity would help provide

substantial benefits for patients, health professionals, and other stakeholders involved, including patient advocacy groups, disease registries, research investigators, food and drug industries, government agencies and regulators, and legislative bodies. Therefore, the World Allergy Organization (WAO) initiated this project for the development of an international definition and classification system of severity associated with food allergy (“**DE**finition of **F**ood **A**llergy **SE**verity”, DEFASE). To the best of our knowledge, there is currently no previously reported specific scoring system for classifying severity of FA^{11,12} and DEFASE represents a unique international consensus-based system to define severity of FA. The preliminary step in the formulation of a uniform definition and classification of FA severity included a systematic review (SR)¹⁰ to provide a state-of-the-art synopsis of the current evidence. The systematic review focused exclusively on IgE-mediated food allergy (i.e. acute allergic reactions manifesting as a broad spectrum of signs/symptoms ranging from urticaria to vomiting and wheezing, up to fatal or near-fatal anaphylaxis.¹¹ Building on these data, we aimed to develop a comprehensive scoring system to be used in research settings with the aim of measuring the severity of a clinical situation of food allergy.

METHODS

Developing the DEFASE score

In Phase 1, we conducted a mixed-method SR of the primary studies dealing with the definition

and/or assessment of food allergy severity. Eleven databases were searched to identify published and unpublished quantitative and/or qualitative evidence on the severity of FA. We categorised FA severity as either symptom-related or non-symptom-related severity scores.¹⁰ A panel of experts participated to ensure comprehensiveness. We followed these online meetings of the experts, aimed to identify the core domains and proposed components of DEFASE score for the definition of food allergy severity.

the e-Delphi technique,¹²⁻¹⁷ a validated method for evaluating and refining group opinion, as shown in Fig. 1. The technique employs several iterative rounds of questioning, with an independent facilitator providing an anonymized summary of the results after each round. Typically, a group would come to consensus/agreement through repeated rounds of survey.^{12,13,15} The anonymity of an e-Delphi survey is crucial because it allows for opinions to evolve over time while still being inclusive.

Overview of the Delphi process

Based on our findings in Phase 1, we proceeded with the Phase 2 survey to reach a consensus on the severity score. We employed an adaptation of

Panel selection

We compiled a database of 60 international experts from Europe, North and South America, Asia, Africa, and Australia who had published on FA management, served on FA review and

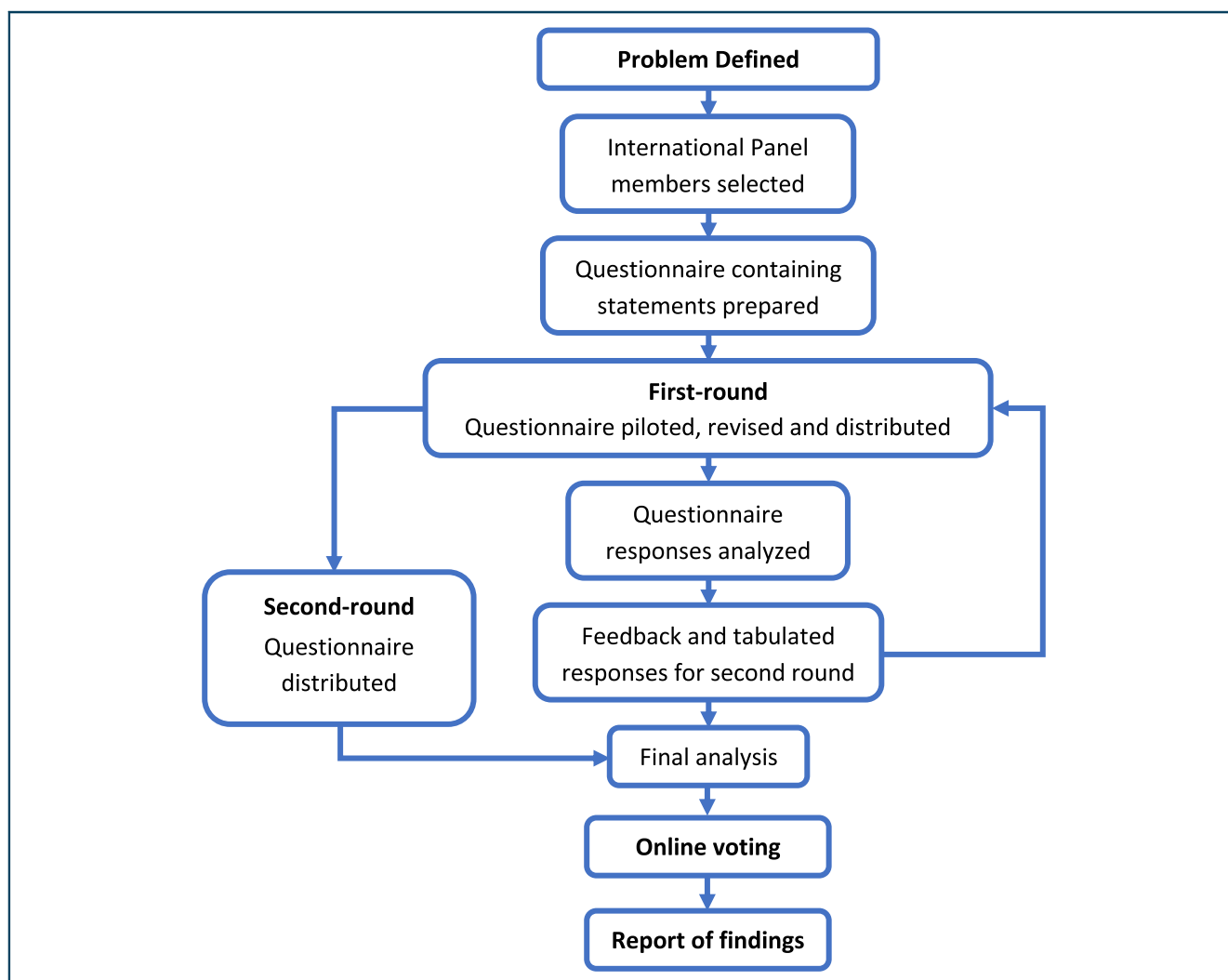


Fig. 1 Flow chart of eDelphi process

reference groups, FA patients' representatives, advisory groups, and/or contributed to the development of scores for clinical use. Representatives from patient advisory groups were also included to ensure that practitioners and other stakeholders in a variety of disciplines involved in FA management with a wide spectrum of experience were included. To get the most complete and representative panel possible, some representatives were included after the first round as per e-Delphi methodology¹⁸ (Fig. 2 and Table S1).

Questionnaire development and piloting

The e-Delphi questionnaire was designed by identifying key potential domains and components in the severe food allergy management, informed by findings from the mixed-methods SR, encompassing both emergency and long-term management. The issues were categorised into 5 domains [(A) symptoms/signs with previous reactions; (B) minimum therapy to treat the most severe previous reaction; (C) individual eliciting dose; (D) current food allergy-related quality of life; and (E) economic impact of food allergy severity] (Tables 1A and 1B). The key elements of these 5 domains were assessed using 14 questions. For the economic impact of FA, in order to understand average expenditures related to FA across the world, we conducted a pilot online survey of country representatives. The findings of this survey helped us to refine the DEFASE economic impact score. The questionnaire was

piloted with eight professionals in the field of FA diagnosis and management.

Data collection and analysis

International panellists who agreed to participate (Fig. 2 and Table S1) were asked to rate each statement on a 5-point Likert scale ranging from "strongly disagree" to "strongly agree". To capture the diversity and nuance, free-text comments were invited, collected, and content analysis was undertaken. The percentage agreement for each item was assessed after each round. The second round-questionnaire included revised tables that reflect strongly expressed views from a number of panel members in the first round on various domains/components of the DEFASE score.

Additional online votings

Guided by recent advanced publications and guidelines¹⁹⁻²³ in this field, we additionally conducted online voting on two domains to improve the wording of the DEFASE final score. For domain (B) (ie, minimum therapy to treat the most severe previous reaction, such as number of I.M. epinephrine doses), we asked participants to vote for one of the two following options.

- OPTION 1: cut off ≥ 1 dose of epinephrine for moderate reaction and ≥ 2 doses of epinephrine for severe reaction,

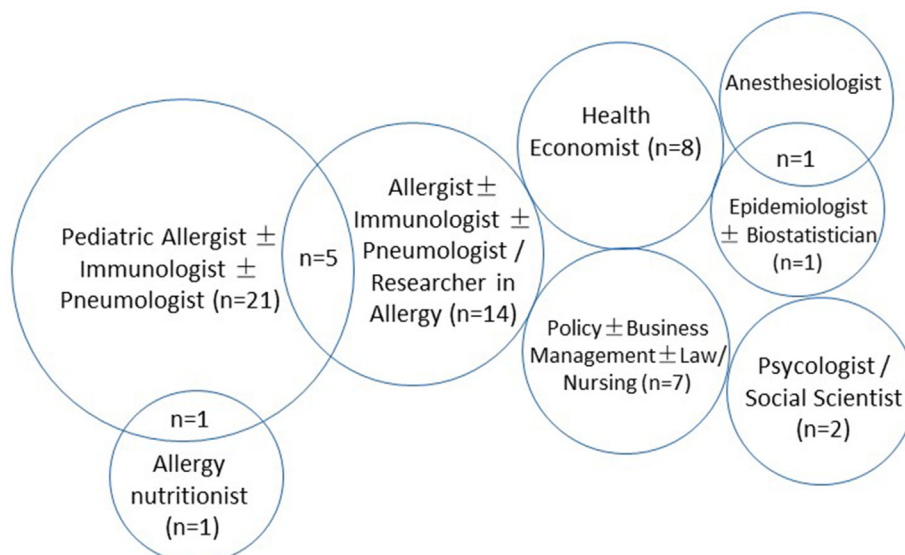


Fig. 2 Professional characteristics of Global Delphi expert panel

Domains	Mild (1 point for each domain)	Moderate (2 points for each domain)	Severe (3 points for each domain)
<p>(A) Symptoms/signs with the most severe previous reaction^{a,b} adapted from Brown 2004 (25), Cardona 2020 (WAO) (26), Fernandez-Rivas 2022 (FASS) (27), Muraro 2018 (EAACI) (28), Muraro 2022 (EAACI) (29), Niggemann 2016 (30), Sampson 2003 (31), and expert consultation</p>	<ul style="list-style-type: none"> Only cutaneous (e.g. generalized pruritus, flushing, urticaria, angioedema) and/or mild gastrointestinal (e.g. oral pruritus, oral tingling, mild lip swelling, nausea or 1-3 vomiting, mild abdominal pain) and/or rhinoconjunctivitis symptoms 	<ul style="list-style-type: none"> Lower respiratory and/or laryngeal and/or gastrointestinal (e.g. persistent crampy, abdominal pain, ≥ 4 vomiting and/or diarrhoea) and/or cardiovascular symptoms or signs 	<ul style="list-style-type: none"> Respiratory and/or circulatory failure
<p>(B) Minimum therapy to treat the most severe previous reaction^a</p>	<ul style="list-style-type: none"> No previous <i>need</i> for adrenaline (epinephrine)*. Only symptomatic therapy (e.g. local and systemic antihistamines) 	<ul style="list-style-type: none"> Reaction(s) have always visibly responded to a maximum of two doses of i.m. adrenaline (epinephrine)* 	At least one of the following therapies was administered to treat a previous reaction: <ul style="list-style-type: none"> More than 2 doses of i.m. adrenaline (epinephrine) <i>needed</i>* Intensive care treatment (e.g. positive pressure ventilation, intubation, intravenous vasopressors, extracorporeal membrane oxygenation)*
<p>(C) Individual minimal eliciting dose^a Based on datasets reviewed and used by WHO/ United Nations FAO Codex Expert Panel</p>	<ul style="list-style-type: none"> $> ED_{20}$ exposure 	<ul style="list-style-type: none"> $ED_{05} < \text{exposure} \leq ED_{20}$ 	<ul style="list-style-type: none"> $\leq ED_{05}$ exposure
<p>(D) Current food allergy -related - quality of life (FA-QoL) Items from FAQLQ^b: Allergen avoidance and dietary restrictions; Emotional impact; Risk of accidental exposure; Food allergy-related health; Social and dietary limitations.</p>	<ul style="list-style-type: none"> No/minimal impact on FAQoL [e.g. FAQLQ, average across age groups, using the interval scale value, on a scale of 0-6 (6-0/3) = 2, 0-1.99 = no - minimal impact 	<ul style="list-style-type: none"> Moderate impact on FAQoL [e.g. FAQLQ, average across age groups, using the interval scale value, on a scale of 0-6 (6-0/3) = 2, 2-3.99 = moderate impact 	<ul style="list-style-type: none"> Severe impact on FAQoL [e.g. FAQLQ, average across age groups, using the interval scale value, on a scale of 0-6 (6-0/3) = 2, ≥ 4: severe impact

(continued)

Domains	Mild (1 point for each domain)	Moderate (2 points for each domain)	Severe (3 points for each domain)
(E) Current health-economic impact Items: direct medical costs, direct costs to other sectors of the economy, and indirect costs (see DEFASE – ES, DEFASE economic score at table 1B.	<ul style="list-style-type: none"> No or minimal impact (ES ≤ 30) 	<ul style="list-style-type: none"> Moderate impact (ES: 31 to 60) 	<ul style="list-style-type: none"> Severe impact (ES ≥ 61)

Table 1A. (Continued) DEFASE score. *BEFORE* assessing severity of food allergy, *exclude difficult to manage issues*: a. Failure to define triggering food allergens. b. Failure of self-management support for patient, parent or family (i.e. the provision of education and supportive interventions by health care staff to increase patients' skills and confidence in managing their allergic condition, including regular assessment of progress and problems, goal setting, and problem-solving support). c. Failure of self-management - failure to be prepared to manage reactions (e.g. no management plan or therapy), failure to avoid the triggering allergen(s), failure to properly treat a reaction. Failure by the patient/parent/family to effectively manage allergic disease, including symptoms, treatment (of reactions), physical and social consequences, and lifestyle changes (e.g. allergen avoidance, reading labels, adrenaline carriage etc.). When none of the above features are present, a patients' food allergy severity can be differentiated into mild, moderate or severe on the basis of the following DEFASE scoring system. In contrast, if any of these features are present, food allergy severity can be defined only after having addressed the above-mentioned issue(s). Patients who experienced at least a near-fatal reaction requiring ICU treatment(s) are considered to have lifetime severe food allergy. **List of abbreviations:** ED05 and ED20 values, eliciting dose values predicting to elicit objective allergic symptoms in 5% and 20%, respectively, of the allergic population; ES, economic score; FAQoL, Food allergy-related quality of life; FAQLQ, Food Allergy Quality of Life Questionnaires. **DEFASE score = symptoms/signs with the most severe previous reaction + therapy to treat the most severe previous reaction + individual eliciting dose + current food allergy-related quality of life + current health-economic impact. Score: ≤6 mild; 7-12 moderate; ≥13 severe food allergy. Increasing score is associated with more severe food allergy.**^aThe Food Allergy Quality of Life Questionnaires (FAQLQ). There are five different forms of the FAQLQ. Three forms are completed by the patients themselves (Child Form, FAQLQ-CF; Teenager Form, FAQLQ-TF; and Adult Form, FAQLQ-AF), and two forms are completed by parents of food-allergic children (Parent Form; FAQLQ-PF) and teenagers (Parent Form Teenager; FAQLQ-PFT). ^bItems evaluated on the average of the last 3 years with food allergy (less if shorter food allergy history). ^cFor patients with multiple symptoms, reaction severity is based on the most severe symptom; symptoms that constitute more severe grades always supersede symptoms from less severe grades. The grading system can be used to assign reaction severity after the reactions. ^dData related food-induced anaphylaxis.

- OPTION 2: cut off ≥2 doses of epinephrine for moderate reaction and ≥3 dose of epinephrine for severe reaction.

For domain (C) (i.e. individual minimal eliciting dose), participants were invited to vote for one of the following.

- OPTION 1, MILD: ≥25% of an age-appropriate portion of food²⁴; MODERATE: 24 to 5% of an age appropriate portion of food; SEVERE: minimal dose (<5% of an age appropriate portion of food);
- OPTION 2, MILD: > ED20 exposure; MODERATE: ED05 < exposure ≤ ED20; SEVERE: ≤ ED05 exposure, and
- OPTION 3, based on datasets reviewed and used by WHO/United Nations FAO Codex Expert Panel, MILD: > ED50 exposure; MODERATE: ED20 < exposure ≤ ED50; SEVERE: ≤ ED20 exposure.

Defining consensus

After the second round, a minimum of 70% or more of the panel members ranked the statement

as “strongly agree” or “agree,” indicating that consensus had been reached (Tables 2A and 2B). Members of the panel were encouraged to write comments in response to each statement if they so desired.

Ethical considerations

Although formal ethics approval was not required, we conducted this study with adherence to relevant and accepted ethical principles.^{12,13,15}

The DEFASE SCORE: overview, calculation, and application

The DEFASE score for the definition of IgE-mediated food allergy severity covers the most relevant aspects across different clinical scenarios. We arbitrarily indicated that a DEFASE Score ≤6 indicates a mild form of food allergy; 7-12 signifies moderate; and ≥13 signifies severe food allergy. A higher score signifies increasing severity.

The expert panel agreed that, before assessing the severity of food allergy at an individual level, the following difficult to manage issues must be excluded.

ITEMS*	Unit value	Number of events	Final value
N° of outpatient visit(s) to the allergy specialist(s) in the last year	2.5		
N° of other outpatient visits due to FA in the last year (eg. dietician, psychologist [non-MD])	1		
N° of community visits due to FA in the last year (eg. GPs, general pediatrician)	1.2		
N° of serum test panels (extracts) in the last year	1.5		
N° of molecular diagnostic tests in the last year	3		
N° of cutaneous tests in the last year	1		
N° of in vivo tests (oral food challenges) in the last year	6.5		
N° emergency department visit(s) in the last year because of FA	8.5		
N° emergency department admission(s) in the last year because of FA	20		
N° emergency ambulance call(s) because of FA in the last year	5		
N° day(s) spent in ICU because of FA in the entire patient's life	33		
N° adrenaline (/epinephrine) auto-injector prescription in the last year because of FA	2.5		

Table 1B. DEFASE score on economic impact of food allergy severity (DEFASE - ES, DEFASE economic score). **List of abbreviations:** FA, food allergy; GP, general practitioner; ICU, intensive care unit. The DEFASE economic score (DEFASE - ES) is calculated on an individual basis by summing up the expenses in the last year. Therefore, the value of each item has to be multiplied by the respective number of times applied in the previous year. Costs for each item are then summed. For instance, a patient who underwent 2 outpatient visit(s) to the allergy specialist(s) in the last year, had a cost of 5 unit ($2 \times 2.5 = 5$) for this item. The sum of values for all of the items will represent the final value of the DEFASE-ES. The sum of items will be scored as following: **DEFASE - ES, DEFASE economic score: ≤ 30 mild; 30-60 moderate; ≥ 60 severe food allergy**

- a. Failure to define triggering food allergens;
 - b. Failure of self-management support for patient, parent or family (ie, the provision of education and supportive interventions by health care staff to increase patients' skills and confidence in managing their allergic condition, including regular assessment of progress and problems, goal setting, and problem-solving support).
 - c. Failure of self-management - failure to be prepared to manage reactions (eg, no management plan or therapy), failure to avoid the triggering allergen(s), failure to properly treat a reaction. Failure by the patient/parent/family to effectively manage allergic disease, including symptoms, treatment (of reactions), physical and social consequences, and lifestyle changes (eg, allergen avoidance, reading labels, adrenaline carriage, etc.).
 - If any of a the above are present, food allergy severity can be defined only after they have been addressed.
 - If none of the above features are present, a patient's FA severity can be differentiated into mild, moderate or severe FA on the basis of the DEFASE scoring system (Table 1A).
 - Note that individuals who experienced at least a near-fatal food triggered allergic reaction requiring intensive care unit (ICU) treatments are considered to have lifetime severe food allergy, unless the specific food allergy has resolved.
- The DEFASE economic score (DEFASE - ES) was developed by the health economists in the group, and submitted to the whole group for their two-round evaluation.

RESULTS

Fifty-four of 60 international experts approached consented to take part (Fig. 2 & Table S1). Round One had a 92% (48/52)

No	Statements	Agreement rate after First Round
1	The overall DEFASE score includes all relevant domains for the appropriate classification of food allergy severity in the context of the management of food allergy. [Do you agree?] 88% (strongly agree and agree).	81%
2	About MILD severity domain referred to symptoms/signs with the most severe previous reaction (Table 1): [do you think the following statement "Only cutaneous (e.g. sudden itching of eyes and nose, generalized pruritus, flushing, urticaria, angioedema) and/or mild gastrointestinal (e.g. oral pruritus, oral tingling, mild lip swelling, nausea or 1-3 emesis, mild abdominal pain) and/or rhinoconjunctivitis symptoms" is efficient to describe this spectrum of severity?]	79%
3	About MODERATE severity domain referred to symptoms/signs with the most severe previous reaction (Table 1): [do you think the following statement "Lower respiratory and/or laryngeal and/or gastrointestinal (e.g. persistent crampy abdominal pain, recurrent vomiting and/or diarrhoea) and/or cardiovascular symptoms or signs ("i.e. anaphylaxis")" is efficient to describe this spectrum of severity?]	67%*
4	About SEVERE severity domain referred to symptoms/signs with the most severe previous reaction (Table 1): [do you think the following statement "Anaphylaxis causing respiratory and/or circulatory failure" is efficient to describe this spectrum of severity?]	73%
5	About MILD severity domain referred to minimum therapy to treat the most severe previous reaction (Table 1): [do you think the following statement "No indication for adrenaline (/epinephrine). Only symptomatic therapy (e.g. local and systemic antihistamines and/or steroids)" is efficient to describe this spectrum of severity?]	71%
6	About MODERATE severity domain referred to minimum therapy to treat the most severe previous reaction (Table 1): [do you think the following statement "Reaction(s) have always visibly responded to maximum 1 dose of i.m. adrenaline (/epinephrine)" is efficient to describe this spectrum of severity?]	65%*
7	About SEVERE severity domain referred to minimum therapy to treat the most severe previous reaction (Table 1): [do you think the following statement "At least one of the following therapies was administered to treat a previous reaction: a) two or more doses of i.m. adrenaline (/epinephrine); b) intensive care treatment (e.g. positive pressure ventilation, intubation, intravenous vasopressors, extracorporeal membrane oxygenation) "is efficient to describe this spectrum of severity?]	65%*
8	About MILD severity domain referred to individual eliciting dose (Table 1): [do you think the following statement "100%-25% of an age-appropriate portion of food" is efficient to describe this spectrum of severity?]	56%*
9	About MODERATE severity domain referred to individual eliciting dose (Table 1): [do you think the following statement "24 to 5% of an age-appropriate portion of food" is efficient to describe this spectrum of severity?]	50%*

(continued)

No	Statements	Agreement rate after First Round
10	About SEVERE severity domain referred to individual eliciting dose (Table 1): [do you think the following statement "minimal dose (<5% of an age-appropriate portion of food)" is efficient to describe this spectrum of severity?]	60%*
11	About MILD severity domain referred to current food allergy-related - Quality of Life (Table 1): [do you think the following statement "no/minimal impact on QoL" is efficient to describe this spectrum of severity?]	88%
12	About MODERATE severity domain referred to current food allergy-related - Quality of Life (Table 1): [do you think the following statement "moderate impact on QoL" is efficient to describe this spectrum of severity?]	85%
13	About SEVERE severity domain referred to current food allergy-related - Quality of Life (Table 1): [do you think the following statement "substantial impact on QoL" is efficient to describe this spectrum of severity?]	83%
14	About Table 2 on current health economic impact: [do you think the items and the respective scale of impact (minimal, moderate, and severe) are efficient to describe the economic spectrum of severity?]	71%

TABLE 2A. (Continued) Agreement rates on DEFASE score at the first round.

response rate, while round two had an 85% (50/59) response rate. After Round Two, there was over 70% agreement on 13 of the 14 statements, which included the following domains.

- A. symptoms/signs of the most severe previous reaction (mild, moderate, severe), adapted from Brown 2004,²⁵ Cardona 2020 (WAO),²⁶ Fernandez-Rivas 2021 (FASS),²⁷ Muraro 2018 (EAACI),²⁸ Muraro 2021 (EAACI),²⁹ Niggemann 2016,³⁰ Sampson 2003 (31), and expert consultation;
- B. minimum therapy to treat the most severe previous reaction (mild, severe);
- C. individual eliciting dose (mild, moderate, severe);
- D. current food-allergy related quality of life (mild, moderate, severe);
- E. current health-economic impact of the severity of food allergy.

Specifically, consensus was not reached (62%) for the statement on the moderate severity in domain (B) (ie, minimum therapy to treat the most severe previous reaction) (Tables 2A and 2B). After the second round of eDelphi, we conducted an

expert consultation with 51 specialists in the field of food allergy and patient representatives with a response rate of 80% (41/51). Of the 41 responses we received, 2 were abstaining. At this online voting, we reached an agreement (78%) for the question on domain (C) (ie, on individual eliciting dose during the previous reactions). Indeed, we reached consensus for the question of domain (B) (75%) only at the further online-voting, attended by 44/51 (response rate of 86%) experts in the field of FA and patient representatives with 5 abstaining. The exact wording of domain (B) was debated in the two rounds of e-Delphi study and at the first online expert consultation. In terms of the domain (B), after the second round of the e-Delphi study there was an internal inconsistency on consensus rates between grades of allergic reactions (mild 74%), (moderate 62%) and severe (78%). To address this issue, the experts suggested to conduct an additional online voting. The first online voting did not reach a consensus either (59%). Furthermore, the experts recommended to conduct a second (final) online voting on this domain (B). The rationale for this final voting was the existing evidence that evolving in this field of research and practice. The second, final online voting revealed agreement between the

No	Statements	Agreement rate after Second Round
1	The overall DEFASE score includes all relevant domains for the appropriate classification of food allergy severity in the context of the management of food allergy. [Do you agree?]	88%
2	About MILD severity domain referred to symptoms/signs with the most severe previous reaction (Table 1): [do you think the following statement "Only cutaneous (e.g. generalized pruritus, flushing, urticaria, angioedema) and/or mild gastrointestinal (e.g. oral pruritus, oral tingling, mild lip swelling, nausea or 1-3 emesis, mild abdominal pain) and/or rhinoconjunctivitis symptoms" is efficient to describe this spectrum of severity?]	78%
3	About MODERATE severity domain referred to symptoms/signs with the most severe previous reaction (Table 1): [do you think the following statement "Lower respiratory and/or laryngeal and/or gastrointestinal (e.g. persistent crampy abdominal pain, ≥ 4 vomiting and/or diarrhoea) and/or cardiovascular symptoms or signs" is efficient to describe this spectrum of severity?]	78%
4	About SEVERE severity domain referred to symptoms/signs with the most severe previous reaction (Table 1): [do you think the following statement "Respiratory and/or circulatory failure" is efficient to describe this spectrum of severity?]	86%
5	About MILD severity domain referred to minimum therapy to treat the most severe previous reaction (Table 1): [do you think the following statement "No indication for adrenaline (/epinephrine). Only symptomatic therapy (e.g. local and systemic antihistamines)" is efficient to describe this spectrum of severity?]	74%
6	About MODERATE severity domain referred to minimum therapy to treat the most severe previous reaction (Table 1): [do you think the following statement "Reaction(s) have always visibly responded to maximum 1 dose of i.m. adrenaline (/epinephrine)" is efficient to describe this spectrum of severity?]	62%*
7	About SEVERE severity domain referred to minimum therapy to treat the most severe previous reaction (Table 1): [do you think the following statement "At least one of the following therapies was administered to treat a previous reaction: a) two or more doses of i.m. adrenaline (/epinephrine); b) intensive care treatment (e.g. positive pressure ventilation, intubation, intravenous vasopressors, extracorporeal membrane oxygenation) "is efficient to describe this spectrum of severity?]	78%
8	About MILD severity domain referred to individual eliciting dose (Table 1): [do you think the following statement " $\geq 25\%$ of an age-appropriate portion of food ²⁴ " is efficient to describe this spectrum of severity?]	74%
9	About MODERATE severity domain referred to individual eliciting dose (Table 1): [do you think the following statement " 24 to 5% of an age-appropriate portion of food ²⁴ " is efficient to describe this spectrum of severity?]	72%
10	About SEVERE severity domain referred to individual eliciting dose (Table 1): [do you think the following statement "minimal dose (<5% of	76%

(continued)

No	Statements	Agreement rate after Second Round
	an age-appropriate portion of food) ²⁴ is efficient to describe this spectrum of severity?]	
11	About MILD severity domain referred to current food allergy-related - Quality of Life (Table 1): [do you think the following statement "no/minimal impact on QoL" is efficient to describe this spectrum of severity?]	86%
12	About MODERATE severity domain referred to current food allergy-related - Quality of Life (Table 1): [do you think the following statement "moderate impact on QoL" is efficient to describe this spectrum of severity?]	90%
13	About SEVERE severity domain referred to current food allergy-related - Quality of Life (Table 1): [do you think the following statement "substantial impact on QoL" is efficient to describe this spectrum of severity?]	86%
14	About Table 2 on current health economic impact: [do you think the items and the respective scale of impact (minimal, moderate, and severe) are efficient to describe the economic spectrum of severity?]	74%

TABLE 2B. Agreement rates on DEFASE score at the second round of e-Delphi. *Agreement has not been reached

research team and a consensus was reached (75%) on the domain (B) (Tables 2A and 2B).

In general, a substantial support was shown for all domains in the process of building the consensus for the DEFASE score. Panel members' free text comments provided nuance to the quantitative responses thereby helping to clarify the ratings provided, and highlighting a number of important points in the development of the DEFASE score for the management of severe food allergy in children and adults.

The development of the "economic impact" domain of food allergy severity

As part of the DEFASE e-Delphi project, we conducted a pilot survey of professionals from 15 countries (Argentina, Canada, Chile, China, Costa Rica, Egypt, Hong Kong, Italy, Japan, Poland, Russia, Spain, Switzerland, United Kingdom, and United States) to refine the economic impact domain of the DEFASE score. The aim of this pilot online survey was to gather information on the average expenditures related to food allergies across the world. We asked the participants about the healthcare systems in their countries, currency used, and expenditures related to the management of food allergy: honoraria for allergy

specialists, dieticians, psychologists; costs of general practitioners; costs of diagnostic tests for food allergy; OFC expenses; emergency department visits or admissions; emergency ambulance calls; time spent in ICUs because of food allergy; adrenaline/epinephrine autoinjector use. Furthermore, we enquired about school days/work days lost by individuals and/or caregivers and/or broader members of the household, negative impacts of food allergy such as the need to select more expensive food shops/restaurants/schools/holidays/private additional health insurance, as well as any adverse impacts on, for example, job choice, restricted career, job change, restricted social life, restriction in sport, hobbies, delay in having children, and expanding family.

The findings of the pilot study varied across participating countries, particularly on the average costs attributable to food allergies. For example, in Egypt the cost for 1 outpatient visit to the allergy specialist was reported between € 0.27-0.54 at a University Hospital, whilst in the United States the average reported direct cost was around € 510 (September 2021). The large variations in the average costs attributable to food allergy depend, in part, on across country differences in health care and broader systems, on the relative prices of resource inputs, and on the level of economic

development based on Gross National Income per capita: high, upper-middle, lower-middle, and low-income countries, among other factors.

Building on this information, an Economic Impact Food Allergy Severity score was elaborated and agreed. It can be calculated on an individual basis by summing up economic values over the last year (Table 1B). By consensus, the value of each item has to be multiplied by the respective number of times applied in the previous year. The total costs for each item are then summed in a compound manner. For example, a patient who underwent two outpatient visit(s) to the allergy specialist(s) in the last year generated a total outpatient visit cost of 5 units ($2 \times 2.5 = 5$) for this item. The sum of cost values for all of the items represent the total economic value within the DEFASE-ES. The sum of items is then categorised as follows: a DEFASE economic score: ≤ 30 represents mild impact; 30-60 represents moderate impact; and ≥ 60 represents severe impact. An increasing score therefore represents increasingly severe food allergy-related economic impact.

DISCUSSION

This study represents a collective reflection of the global food allergy community about the definition of its severity. Studies performed so far have generated individual reaction severity assessment tables,¹⁰ that have also been validated,²⁷ but not a general assessment table about the severity of the condition. Yet, punctual severity assessments in allergic diseases have been in use for many years for asthma,³² allergic rhinitis³³ and atopic dermatitis.³⁴ In carrying out this research, our group considered that in addition to assessing the risk indices for severe anaphylactic-type reactions, it was necessary to reconcile assessments of the influence that the disease exerts on the quality of life and on the financial commitment for each patient. To the best of our knowledge, the possibility of evaluation offered by Table 1 is unprecedented.

Strengths and limitations of this work

A strength of this consensus is that it is based on the e-Delphi method. This has been used widely in healthcare research to find agreement at national

or international levels on a particular research question.^{15,35} It involves circulating a set of statements, assumptions, solutions, or options to be anonymously scored by international panel of members in an iterative fashion. The Delphi technique helps to minimize the risk of actual or perceived peer pressure that may bias responses.^{12,13,15} The e-Delphi method also allowed us to engage with a geographically dispersed international expert panel in an efficient and cost-effective way. In this particular case, we were able to apply the method starting from a previous rigorous up-to-date systematically collated evidence base, led by independent methodologists with no conflicts of interest.¹⁰ This score is one of the first to incorporate patient perspectives from leaders of FA patient-focused organizations. The evidence base was interpreted and applied to real-world settings by an international, multidisciplinary group including patient representatives, clinicians, academicians, researchers, psychologists, world-leading health economists and other stakeholders. Furthermore, response rates were overall high and consensus reached for a high number of statements. This modified e-Delphi study also included a pilot survey of professionals on the economic costs of FA and online voting of experts to finalise the wording and score. The tools of the quality of life domain are validated measures. In addition, based on our findings, research gaps in evidence synthesis and prioritization of gaps were identified. Most of data presented covered food-induced anaphylaxis. The information presented here intends to be helpful to the clinical and academic community but represents a course of evolving knowledge in the field, which may be updated with the implemented understanding of FA.

However, several limitations should be considered and judged with caution.

Due to the paucity and heterogeneity of existing knowledge, we moved on unexplored terrain in which some aspects could be underestimated and others overestimated.

The choice of panellists was based on a literature search, but our ambition to produce a document of global interest may have been frustrated by a limited representation of regions as Australia, Africa, and Asia.

Symptom domain

Clinical history is one of the milestones for the assessment of FA severity.²⁹ However, it has some limitations. In particular, current data show that prior anaphylaxis is not a good predictor for the risk of future fatal or near-fatal reaction.⁸ In the largest reported series of food-related fatal anaphylaxis, most of the cases occurred in subjects with only previous mild reaction(s).³⁶ Several factors may impact severity, such as the level of allergen exposure and the presence/absence of co-factors (eg, physical exercise, sleep deprivation, use of NSAIDs, intercurrent infections). The role of comorbidities (eg, asthma, mastocytosis) and their degree of control is still debated.^{36,37} Furthermore, several scores have been applied to grade the severity of allergic reactions (including those triggered by foods)¹⁰ as well as the severity of anaphylaxis. The DEFASE symptom score has been designed on the basis of existing grading systems,²⁵⁻³¹ and adapted from the perspective of patient representatives, in order to keep it as simple and user-friendly as possible for lay audience. DEFASE recommends one estimate of disease severity at a single time point and may not be predictive of future severity of food allergy for an individual patient.

Minimum therapy to treat the most severe reaction domain

This has been a highly debated issue. This topic has also been discussed in two online votings and agreement was reached only at the fourth eDelphi process. This criterion will be difficult to apply where epinephrine auto-injectors are not available. Up-to-date guidelines provide evidence-based recommendations on the proper management of allergic reactions.^{29,38} However, in real-life, interventions can be variable based on both patient and provider experiences as well as different local jurisdictions.³⁹

There are patients who are not treated with epinephrine even though wheezing is present and some others are treated with several medications including i. v. hydration by the emergency room but not treated with epinephrine when it is indicated. However, the number of epinephrine doses has been considered in more than one guideline as a marker of severity²⁹ and a potential higher risk

for biphasic reactions in children.⁴⁰⁻⁴² Furthermore, a recent meta-analysis shows that around 10% of severe reactions are treated with multiple doses of epinephrine.¹⁹ Aligned with this, panellists agreed to classify severe anaphylactic reactions as needing more than two doses of adrenaline or ICU admission.

Eliciting dose

The relationship between dose of exposure and severity of the resulting reaction is unclear. A single study evaluated the severity of reactions in a small cohort of peanut allergic children (n = 27) during oral challenge without interrupting the diagnostic procedure at onset of objective symptoms.⁴³ The majority (78%, 21/27) of challenge-proven peanut-allergic children had anaphylaxis (i.e. multi-organ system reaction - involvement of ≥ 2 systems) when given a sufficient amount of allergen but not as initial type of reaction. Therefore, a previous lack of anaphylaxis (at least in children with peanut allergy) may reflect insufficient allergen exposure rather than an inherently low risk of anaphylaxis.¹¹

In the online voting, we asked participants to vote on the basis of two main approaches, both built on OFC data. One approach referred to age-appropriate portion of food.²⁴ The second approach referred to eliciting doses based on TNO-FARRP datasets reviewed and used by WHO/United Nations FAO Codex Expert Panel in 2020-22.^{22,23} A strong majority was in favour of the latter.

However, the setting may play a role. In the oral food challenge, severity may be affected by both *ad hoc* controlled conditions (eg, absence of co-factors) and dose restrictions, so these data may not be applicable to accidental reactions in the community. In addition, in this context, it can be difficult to know how much allergen is in a serving portion, especially of a composite food.

Current food allergy-related - quality of life

The FAQoL domain plays a key role in the assessment of FA severity. It embraces different aspects of the disease, which are not otherwise covered by the DEFASE score. In particular, due to the paucity of evidence⁷ and heterogeneities among populations, and for making the score

user-friendly, we did not include as separated the following variables: number of culprit foods, type of foods, comorbidities, and cofactors. These items are covered by the quality of life domains. Subjects that have allergies to staple foods in their diet (eg, milk or egg) are more likely to have more severely impacted FAQoL than others with more easily avoidable food allergens.⁴⁴ In addition, the number of food allergies can be related to the severity of FAQoL. This depends of course on many factors including the relative cultural importance and most common preparations of the eliciting food allergen. Those who are asthmatic may suffer because of concomitant disease. Other cofactors may play a role (eg, exercise, menses, and use of NSAIDs), especially in some sensitivity pattern (e.g. allergy to lipid transfer proteins). Patients may need to avoid exercise close to the meal with a negative impact on their QoL.

In addition, QoL has some areas of overlaps with the economic domain.

Economic domain

We extrapolated the value for each contributing item by the mean of costs from several continents across the world. In economic evaluation, the crucial point is that costs to the health system and to patients always represent in some way foregone benefits. Therefore, it is important to know the total consequences of FA when estimating costs. In order to estimate the costs related to FA, at this stage the total costs were divided between direct and indirect costs. *Direct costs* are incurred by the health system in diagnosing, treating and living with FA. *Indirect costs* arise because.

- a. loss of employment or education because of FA;
- b. n° school/work days lost per year because of FA (patients and/or caregiver and/or household);
- c. Impact of FA on selecting more expensive food shops/restaurant/school/holidays/private-additional health insurance;
- d. Impact of FA on job choice/restricted career/job change/restricted social life/restriction in sport, hobbies/delay in having children/expanding family.

A further aspect of cost is the loss of well-being arising from pain, suffering and inconvenience, or other effects on quality of life, known as *intangible costs*. Intangible costs were not considered at this stage because they can be estimated through willingness-to-pay (WTP), using Contingent Valuation or Choice Modelling methodology which is not the objective of this study and presents some disadvantages such as overestimation of costs and bias in revealing an accurate WTP.

Notwithstanding, several limitations for this first pilot economic score should be considered, including the following ones: lacking of validated data on current costs; fluctuations on the costs for each item; heterogeneity in health care systems, availability of facilities, currency and per capita income.

The economic domain, as the whole DEFASE score, needs to be validated in the future. The direct and indirect cost structure will be adapted taking into account different features, including the following.

- Distinction between adults and children. In the children and adolescents' score table various items should be adapted for the daily activities relevant to them (i.e., loss of hours/days of school; loss of hours/days meeting friends and so on)
- In the Direct Cost Score table distinction between private and public costs could be envisaged according to the Healthcare System in each country.
- The persistence and temporal variability of effects of food allergies on the quality of life.
- Inter-individual variability in the estimated economic value of time.

RESEARCH GAPS

Food allergy severity is a complex matter embracing symptoms and non-symptom-related aspects, currently affected by several unmet needs (Table 3). Our ability to predict the risk of fatal and near-fatal reactions in patients with food allergy is currently limited. We lack reliable biomarkers to accurately predict who is at higher risk and this impair our ability to individualise avoidance advice and any specific therapeutic approach

Gaps	Suggested plan to address	Priority
<p>Symptom-related domains</p> <p>Standardised definitions of anaphylaxis, patient level and condition level severity to provide a basis for evaluating hospital resource use or to establish patient care guidelines.</p>	<p>Consensus discussion with patients, clinicians, and regulators. Development of patient and condition level metrics using novel methods including Active Learning (AL) techniques, to increase accuracy in expert labeling efforts.</p>	<p>High</p>
<p>Reliable predictors of clinical severity to estimate the probability of an outcome of interest (e.g., anaphylaxis, mortality) on the basis of known patient characteristics.</p>	<p>Longitudinal studies evaluating food induced allergic reactions and collecting data systematically. Case-control studies assessing risk factors for life-threatening reactions. Mechanistic studies to understand the biological process (es) involved and define predictors of severity. Combine multiple metrics and factors, along with their strength to predict symptom severity across diagnostically distinct patient groups</p>	<p>High</p>
<p>Strategies to minimize the risk of accidental reactions and their severity</p>	<p>Large randomized control trials to specifically evaluate the impact of meaningful intervention measures for individuals and carers managing food allergy (e.g. educational programs and tools, allergen labelling, nutrition consultation) A standardized measurement framework that incorporates patient-centred outcomes, together with agreed definitions of constructs, scales, outcomes and timeframes, would allow for the comparison of efficacy of strategies between samples, centres, trials, and/or settings.</p>	<p>Medium</p>
<p>Food Allergy-related - quality of life</p>		
<p>Promote consistent use FAQoL questionnaires as user-friendly tools in primary care</p>	<p>Adaptation of current validated questionnaires available as a simple to use mobile-health tool, supported by an online platform.</p>	<p>High</p>
<p>Determine the association and boundaries between symptom assessment, disease severity, and HRQL evaluation</p>	<p>Use of HRQL as an a priori endpoint in blinded randomized trials. Determine if interactions exist between clinical outcome, safety and HRQL, to better understand patient "benefit".</p>	<p>High</p>
<p>Develop a standardized measurement framework that incorporates patient-centred outcomes, together with agreed definitions of constructs, scales, application, and interpretation</p>	<p>Consensus discussion with patients, clinicians, and regulators Development of patient and condition level metrics using novel methods including Active Learning (AL) techniques. Develop online platform which wide access to all stakeholders.</p>	<p>High</p>
<p>Address gaps in measurement, interpretation and reporting of FAQoL</p>	<p>Use of translational science and methods to bridge gaps and to determine which</p>	<p>High</p>

(continued)

Gaps Symptom-related domains	Suggested plan to address	Priority
	implementation strategies work for whom, in what settings, and why.	
Establishing PROs as key outcome measures in food allergy	<p>Inclusion of PROs in food allergy clinical trials</p> <p>A standardized measurement framework that incorporates patient-centred outcomes, together with agreed definitions of constructs, scales and timeframes, would allow for the comparison of efficacy of food allergy treatments between centres, trials, and/or settings.</p> <p>Treatment success in trials should be defined not only by clinical outcome (desensitization, remission) and safety - but also by improved HRQL (and other relevant PROs, such as stress and anxiety).</p> <p>Comparison between food immunotherapy (active intervention) and placebo arms, and long term follow up of FAQoL in both arms. HRQL measured at multiple intervals during the trial and post-trial (systematic analysis and modelling of antecedent factors, mediators, and outcomes) to fully understand the benefits of treatment to determine if HRQL benefits are maintained, lost or increased, as participants adjust to their altered allergy status.</p> <p>Attention should be paid to screening for and addressing, patient and parent anxiety related to desensitization treatments.</p>	High
Integration of patient-centred psychoeducational activities in clinical practice	<p>Multidisciplinary integrated care that promotes: therapeutic relationships; emotional response; shared-decision making; exchanging information; enabling self-management (e.g. adrenaline autoinjectors training).</p> <p>The impact of chronic illness on pediatric patients and their families is multi-faceted and therefore needs a multi-faceted care response.</p> <p>Use of comprehensive health assessment batteries that reflect the experiences of patients</p> <p>Allergy services to work with hospital paediatric psychology services to develop, integrate and deliver psychological services (across levels of care) for children with allergy and their families.</p> <p>Future research needs to focus on the efficacy of psychological therapies, interventions, models of care and delivery in an allergy population (including the patient experience) - and which strategies work for whom, in what settings, and why.</p>	High

(continued)

Gaps Symptom-related domains	Suggested plan to address	Priority
Transition of care	<p>Implementation of current guidelines^{45,46}; multidisciplinary integrated care, engaging living environment & community (e.g. motivated patients associations; school; work; public areas; regulatory authorities; food labelling)</p> <p>A multidisciplinary approach to food allergy management with an integrated psychological service can help paediatric and young adult patients successfully navigate the complex world of managing a chronic illness – and will ultimately reduce and mitigate the risk of short-term and long-term health and mental health complications in a vulnerable patient population.</p> <p>Future research should focus on establishing and promoting practices for the safe transition of care from caregiver to patient; understanding the impact of transition of allergy-related care on a family unit; efficacy of strategies to support the family unit.</p>	Moderate
Age and developmental factors	<p>Bio-psychosocial development during the life-course means that dimensions relevant to FAQoL, change rapidly with age and may impact the outcome of interest - independently of the treatment or interventions received.</p> <p>In light of the lack of consensus or guidelines around when and at what age self-report and proxy-report administrations should be used, where feasible, both self- and caregiver proxy-reported HRQL should be collected and presented, to provide a more holistic view of impact and outcome.</p> <p>Research specifically on age related impacts and outcomes.</p> <p>Implementation of current guidelines^{45,46}; multidisciplinary integrated care, engaging living environment & community (e.g. motivated patients associations; school; work; public areas; regulatory authorities; food labelling)</p>	Medium
Develop consensus or guidelines around when and at what age self-report and proxy-report	<p>Use of developmental science from chronic condition research on PROs, together with novel studies on allergy specific measures to determine whether transition from the FAQLQ-Child to FAQLQ-Teenager to FAQLQ-Adult forms, when administered to a single participant, can support valid comparison of HRQL over time.</p>	High

Health-economic impact

(continued)

Gaps	Suggested plan to address	Priority
Symptom-related domains		
Taxation and health regulations policy	Assessment of the impacts of health and tax policies on low- and middle-income patients for each study country	Medium
Exchange rates of general price levels, particularly for food	Estimation of how the exchange rate of food items, particularly for countries that import products specifically for those with food allergies changes from country to country.	High
Cost-effectiveness analyses to also be driven primarily by PROs.	While efficacy and safety outcomes are crucial -without PROs and real-world follow up - it is difficult to determine the true value of an intervention and the patients who are most likely to benefit across a range of outcomes including economic.	High

Table 3. (Continued) Gaps in the evidence. *List of abbreviations:* FAQoL, Food allergy-related quality of life; PROs, patient reported outcomes

to minimize the impairment on quality of life and a proper cost/effectiveness analysis.

Consideration of quality of life, together with other metrics (number, frequency and severity of allergic reactions, symptoms, epinephrine use, self-management), ensures a more patient centred perspective is taken on severity, particularly given the limitations of current diagnostics. However, consensus is also needed on core outcome sets for patient reported outcome measures (PROMs). A full understanding of physiological and psychosocial patient factors impacting severity (and their interaction), is also needed.

In addition, a number of factors may affect the economic impact of allergies on patients across different countries. The factors that influence the cost analysis are: different level of taxation and health regulations policy; exchange rates and/or general price levels, particularly for food; fairness or equity in policy for public health and wealth and the distribution of costs and benefits across various sections of society. These factors are to be considered when we want to make a comparison between different countries that have different fiscal policies and regulation. Therefore, at this early stage of the study, we lack data on current costs of food products all over the world, heterogeneity in health care systems, availability of facilities, currency and per capita income.

A proper education and shared decision-making for individuals suffering from FA and

their families is crucial to support a correct management of FA at individual and societal level.

CONCLUSIONS

This consensus sets up the first attempt for the definition of the severity of FA in children and adults including symptoms and non-symptoms related domains. Despite the limitations inherent to the complexity of the matter, the coining of the definition will be useful for dictating the levels of diagnostic, management and therapeutic commitment for the disease in the various geographical contexts.

The score is based on current evidence including a systematic review¹⁰ and expert opinion from a multidisciplinary panel of experts including the different stakeholders involved. We offer the score as a base of common language for the definition of FA burden. It may not automatically translate in an indication of specific diagnostic and therapeutic behaviours; we rather suggest that, considering the contexts, regulators may decide to apply greater diagnostic or therapeutic efforts to scores not necessarily coinciding with our definition of severity. Further research is necessary to identify candidates for specific therapeutic/management approaches.

The validation of this first severity scoring system for FA could allow a standardised patient monitoring and also a proper eligibility of allocating patients for clinical studies and therapeutic

approaches. Future research should focus on external validation of scoring systems, tailoring of these models to different food allergenic sources, populations, and settings. In addition, as a gold standard, a standardised, harmonised, consensus-based severity scoring system for food allergy needs to be tested for reliability and validity in a range of settings and populations. Standardised and validated definitions and measurement approaches, alongside shared decision-making with patients and families, will allow for more targeted supports and guidance and help to minimize the substantial burden of FA.

IMPORTANCE TO STAKEHOLDERS AND IMPLEMENTATION

The concept of FA severity plays a key role for patients and their family members, healthcare professionals, food and drug industries, research, government agencies and regulators, and policy makers. The current terminology and definitions are not standardized, and often misleading. Furthermore, the perception of the concept of severity differs among the stakeholders involved. Consequently, a shared approach is needed for an international consensus-based system to define food allergy severity and provide a proper management of FA according to the specific patient's needs.

FUTURE RESEARCH

In the near future, further effort will be required to validate this first international consensus on the definition of FA severity in children and adults. Well-designed clinical impact studies using large clinical databases are needed to test the reliability and validity of severity scoring systems for FA. Then, well-conducted large randomized controlled trials will be needed to assess the proper use of consensus-based definitions of FA severity, effectiveness and cost-effectiveness of interventions in order to reduce the burden of FA.

Abbreviations

DEFASE, DEfinition of Food Allergy Severity; e-Delphi, electronic Delphi; EE, Economic Evaluation; FA, Food Allergy; FA-QoL, Food Allergy-related Quality of Life; FAQLQ, Food Allergy-related Quality of Life Questionnaire; OFC, Oral Food Challenge; sIgE, food allergen-specific

Immunoglobulin E; SR, Systematic Review; WAO, World Allergy Organization.

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Availability of data and materials

Primary anonymised data that support the findings of this study are available from the corresponding author, [SA], upon reasonable request.

Author contributions

SA & AF conceived the study. SA designed the manuscript. This manuscript was drafted by SA, UN, ADG, PT, AF. The document was reviewed by all co-authors. All authors read, provided feedback and approved the final manuscript.

Ethics approval

Ethical approval is not required for this study as it is an eDelphi not involving any sensitive data. However, author's potential conflicts of interest are disclosed from the beginning.

Authors' consent for publication

All authors have approved the submission of this manuscript.

Declaration of competing interest

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Appendix A. Supplementary data

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