



Consensus on DEfinition of Food Allergy SEverity (DEFASE): Protocol for a systematic review

Stefania Arasi^{a,*}, Ulugbek Nurmatov^b, Paul J. Turner^{c,v}, Ignacio J. Ansotegui^d, Shahd Daher^f, Audrey Dunn-Galvin^e, Motohiro Ebisawa^g, Philippe Eigenmann^h, Montserrat Fernandez-Rivasⁱ, Ruchi Gupta^j, Anna Nowak-Węgrzyn^{k,w}, Stavros Petrou^f, Graham Roberts^{l,m,n}, Mario A. Sánchez Borges^o, Sayantani B. Sindhur^{p,q}, Luciana Kase Tanno^{r,x}, Marta Vazquez-Ortiz^s, Brian P. Vickery^t, Gary Wing-Kin Wong^u and Alessandro Fiocchi^a

ABSTRACT

Background and aims: The term “Food Allergy” refers to a complex global health problem with a wide spectrum of severity. However, a uniform definition of severe food allergy is currently missing. This systematic review is the preliminary step towards a state-of-the-art synopsis of the current evidence relating to the severity of IgE-mediated food allergy; it will inform attempts to develop a consensus to define food allergy severity by clinicians and other stakeholders.

Methods: We will undertake a systematic review, which will involve searching international biomedical databases for published studies. Studies will be independently screened against pre-defined eligibility criteria and critically appraised by established instruments. Data will be descriptively and, if possible and applicable, quantitatively synthesised.

Ethics and dissemination: This study does not require any specific ethical approval since it is a systematic review. We plan to report results from this systematic review in a peer reviewed journal. These results will be used to inform the development of an international consensus to define severe food allergy. Author's potential conflicts of interest are clearly stated.

PROSPERO registration number: CRD42020183103.

Keywords: Classification, Definition, Food allergy, Severity

BACKGROUND

Food allergy is emerging as a global health problem with an estimated prevalence of up to 10%.¹⁻³ It is responsible for remarkable morbidity and, in some cases, mortality.^{4,5} Epidemiological

studies suggest that the prevalence and severity of food allergy may be increasing, particularly in children.^{6,7} Food allergy has a significant adverse impact on health-related quality of life for both allergic individuals and their families, with a

^aPredictive and Preventive Medicine Research Unit, Multifactorial and Systemic Diseases Research Area, Pediatric Allergology Unit, Bambino Gesù Children's Hospital IRCCS, Rome, Italy

*Corresponding author. Pediatric Allergology Unit, Bambino Gesù Hospital (IRCCS), Piazza S. Onofrio, 00161, Rome, Italy: stefania.arasi@opbg.net
Full list of author information is available at the end of the article

<http://doi.org/10.1016/j.waojou.2020.100493>

Received 6 August 2020; Received in revised form 27 October 2020; Accepted 18 November 2020

Online publication date xxx

1939-4551/© 2020 Published by Elsevier Inc. on behalf of World Allergy Organization. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

noteworthy emotional, social, and financial burden.⁸ However, as for other diseases, including all allergic pathologies, there are different phenotypes of food allergy. Patients with milder forms, such as the oral allergic syndrome, are certainly worthy of diagnostic attention, but they may not require all the therapeutic and management resources that are necessary for the patient at higher risk of life-threatening food-induced anaphylaxis. However, in the absence of a reliable classification system, we incur the risk of treating all food allergy patients the same way. This crude one-size-fits-all approach very likely ignores clinically important variation that has been, to date, difficult to classify; and it is unhelpful to patients and caregivers and their providers. In the past, severity classifications have been carried out for both allergic rhinitis and asthma; however, food allergy, as such, is not recognized with a specific scoring of severity in the absence of a consensus on this point.^{9,10}

The concept of food allergy severity is important not only for clinicians in evaluating patients, but also for patients (and parents/families), patient advocacy groups, disease registries, research (clinical trials, epidemiologic, genetic, immunological, and mechanistic studies), food and drug industries, government agencies and regulators, as well as for legislative bodies. Notwithstanding, the terminology and definitions currently applied are not standardized, and often are misleading. Furthermore, different stakeholders perceive the concept of severity differently.¹¹ Therefore, a common approach is needed for an international consensus-based system to define food allergy severity.

The term “food allergy” includes both IgE-mediated food allergies (ie, 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), and non-IgE-mediated food allergy (ie, delayed reactions to the culprit food).¹² The World Allergy Organization (WAO) is in the process of developing an international definition and classification of the severity addressed to food allergy (“**D**efinition of **F**ood **A**llergy **S**everity”, DEFASE).

As a preliminary step, this systematic review aims to provide a state-of-the-art synopsis of the current evidence in relation to the concept of severity in food allergy. The results will be used to inform the formulation of a uniform definition and classification of food allergy severity for clinicians and different stakeholders. The systematic review will focus exclusively on IgE-mediated food allergy. To our knowledge, this will be the first systematic review of the literature on current severity classifications used for food allergy.

METHODS

Approach

For the purpose of this review, we will categorize severity as either symptom-related or non-symptom related, as shown in Fig. 1.

We will undertake a combined search to inform the following questions:

A) SYMPTOM-BASED DEFINITIONS

- i. Review of existing grading systems for IgE-mediated food allergy: data will then be extracted relating to the origins and development of the grading system, and the symptoms constituting the most severe grade prior to “*death or cardiovascular/respiratory collapse/arrest*” noted as reflected symptom severity. For recording purposes, we will also note symptoms at one grade level prior to this (“*moderate grade*”) for evaluation, as severity is not a binary event but rather a spectrum of symptoms which are perceived differently by different stakeholders.
- ii. Review of definitions of anaphylaxis: to assess whether there are any further symptoms not identified by (i) which might be considered by experts to reflect severity and should therefore be considered at later evaluation.
- iii. We will further assess whether there are any definitions in the literature referring to concepts such as “*refractory*” anaphylaxis, and how these are defined.

Food Allergy Severity

Symptom - specific

- Which symptoms are defined as severe by existing grading system?
- Which symptoms are associated with increased healthcare utilisation?

Non Symptom - specific

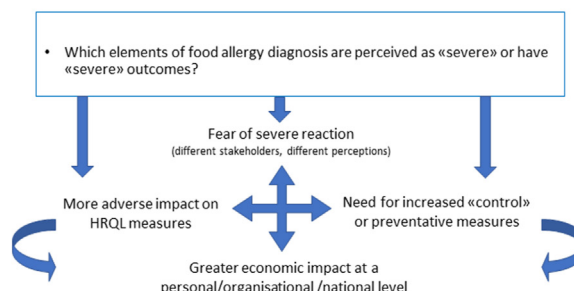


Fig. 1 Approach to food allergy severity categorization

- iv. Finally, we will also extract any symptoms which are reported by the identified reports as leading to increased healthcare utilization.

These 4 "lists" will then be reviewed by healthcare experts and other relevant stakeholders using a DELPHI approach to refine a set of proposed symptoms which might be considered to constitute severity.

B) NON-SYMPTOM BASED DEFINITIONS

We will further review the literature identified to assess for other definitions of severity, based on impact on HRQL, economic implications (eg, food recalls, increased shopping costs, or healthcare costs), markers of control (eg, frequency of prior reactions) or excessive avoidance measures.

Inclusion criteria

Patient characteristics

This systematic review will focus on studies conducted on patients of any age with a physician confirmed diagnosis of IgE-mediated food allergy to eggs, milk, peanuts, tree nuts, and/or other foods. We will evaluate if the allergic status is confirmed by positive history and positive skin prick tests, specific-IgE and/or food challenge tests. We will perform a sensitivity analysis based on with or without food challenge test. We will also evaluate validated scoring system for food allergy quality of life (FAQL) and how FAQL and/or food allergy independent measure (FAIM) is impacted

by "severity" of food allergic reactions in patients with physician - confirmed food allergy.

Study designs

We will include observational studies (ie, cohort; case-control; case series involving 40 or more participants, cross-sectional, assessments of economic consequences by food allergy severity) and interventional studies (ie, randomized controlled trials, RCTs; quasi- RCTs; controlled clinical trials, CCT; interrupted time series, ITS; and controlled before after studies, economic evaluations). We will consider studies whose primary or secondary aim is to define or identify severity classifications of IgE-mediated food allergy in humans. We will also evaluate reviews, systematic reviews, guidelines, position and consensus papers, editorials, and rostrums. Any feature used to identify severity scores will be included: either static or dynamic parameters of the study populations; clinical (eg, type and numbers of reactions to the culprit food; comorbidities; cofactors; disease related - quality of life impairment), genetic, immunological characteristics (eg, pattern of sensitization to allergenic molecules, IgE specific activities) will be all considered.

Exclusion criteria

The following exclusion criteria will be applied:

- Studies of non-IgE mediated food allergy
- Primary data from studies in patients undergoing allergen immunotherapy

- Non-research letters, case reports, case-series with less than 40 participants and in-progress phenotyping studies (abstracts) as they are unlikely to provide sufficient detail on the definitions of food allergy severity score
- Animal studies
- Studies that examined food allergy as a predictor of a separate outcome (eg, asthma development)

Information sources

Search strategy

We will search the following databases:

- CAB
- AMED
- CINAHL (Ebscohost)
- Cochrane Library including the:
 - CENTRAL (Trials)
 - Methods Studies
 - Health Technology Assessments (HTA)
 - Economic Evaluations Database (EED)
- EconLit
- Embase (OVID)
- Global Health
- Google Scholar
- ISI Web of Science (Thomson Web of Knowledge)
- MEDLINE (OVID)
- TRIP Database (www.tripdatabase.com)

The search strategy has been developed on OVID MEDLINE and then adapted for the other databases (see [Appendix 1](#)). In all cases, the databases will be searched from inception to December 2019. Additional references will be located through searching the references cited by the identified studies. We will invite experts who are active in the field from a range of disciplines and regions to add to the list of included studies by identifying any additional published papers. We will include only English language publications.

Study records

Data management

Literature search results will be uploaded into an EndNote Master database and undergo initial deduplication. The consecutive stages of the review process will include, in order: title, abstract, and full-text screening; data extraction, and risk of bias assessment.

Selection process

Two reviewers will independently check all study titles according to the above selection criteria and categorize them as: "included", "not included" or "unsure". Calibration will be undertaken after the first 30 screens to review any discrepancies between reviewers. For those papers in the unsure category, we will retrieve the abstract and re-categorize as above. Any disagreement will be resolved through discussion and, if necessary, a third reviewer will be consulted. Full text copies of potentially relevant studies will be obtained and their eligibility for inclusion independently assessed. Studies that do not fulfil all of the inclusion criteria will be excluded.

Data extraction process

For those papers fulfilling the inclusion criteria, data from the full texts will be independently extracted by 2 reviewers using a predesigned data extraction form and any discrepancy will be resolved by discussion among investigators or, if agreement cannot be reached, by arbitration by a third reviewer.

Data items

Study data

We will extract the following items concerning the study: design; year(s) conducted; country/countries conducted in; setting conducted in (eg, population-based; specialist); inclusion/exclusion criteria; number of participants; age range of participants; gender balance of participants; and allergic comorbidities.

Disease data

We will extract the following items concerning food allergy: definition criteria, severity definition,

prevalence and/or incidence of moderate or severe food allergy (if relevant) and any other relevant data.

Outcomes

The outcomes for this review are food allergy severity classifications, respective criteria and features; most of which are expected to be qualitative (ie, non-numeric) data. Primary outcomes are: (a) food allergy severity classification reported in published papers; (b) the features used to define them (ie, variables); and (c) the characteristics statistically significantly associated (in subsequent analyses) with each severity category. Our secondary outcomes include a brief summary of the methodological approaches used to derive definition of food allergy severity, the effectiveness and cost-effectiveness of interventions in this area and estimates of economic consequences by food allergy severity.

We will not proactively seek particular values of the outcomes described above; we will collect any and all outcomes reported in the publications.

Quality assessment strategy

Quality assessments will be carried out on each study by 2 independent reviewers using the relevant quality assessment tools. The quality of included RCTs will be assessed using the Cochrane eight domain-based evaluation for RCTs and quasi-randomized trials (see Table 8.5a in the Cochrane Handbook).¹³ Each domain and overall score will be rated as: low risk of bias, unclear risk of bias, or high risk of bias.

We will assess the quality of observational studies following the Effective Public Health Practice Project (EPHPP).¹⁴ We will focus on the following domains to assess the quality of included studies: selection bias; study design; confounders; blinding; data collection method; withdrawals and dropouts; and final global rating. Each component-specific parameter (ie, suitability of the study design for the research question; risk of selection bias; exposure measurement; outcome assessment; and generalizability of findings) will be given a judgment: "strong"; "moderate"; and "weak". At the end of critical appraisal, we also will provide the overall grading for each study.

Health economic evaluations will be assessed using the relevant Critical Appraisal Skills Programme (CASP) tool¹⁵ and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist for reporting quality.¹⁶ Any discrepancies will be resolved by discussion or, if agreement cannot be reached, a third reviewer will arbitrate.

Data synthesis

A brief description with summary data tables will be produced to reassess the literature. We will conduct meta-analysis only if there will be a sufficient number of homogeneous studies.

Meta-biases

Meta-bias could derive from any absence of studies looking at important indicators of food allergy severity as well as any missing publication of study results or any selective reporting of outcomes. Furthermore, for qualitative outcomes, an objective measurement will not be feasible. We will engage premiere experts in the field to determine whether these are likely to be important limiting factors in our results interpretation and how best to address the potential metabias.

Patient and public involvement

The research questions have been developed in consultation with Dr. Ruchi Gupta, which includes patient representation.

REGISTRATION, ETHICS, AND REPORTING

This review has been (registration number is: CRD42020183103) registered with the International Prospective Register of Systematic Reviews (PROSPERO): <http://www.crd.york.ac.uk/prospero/>. Any amendment to the protocol will be documented on the PROSPERO site simultaneously, and a full explanation of any change will be provided. We plan to report results from this systematic review in a peer reviewed journal. These results will be used to inform the development of an international consensus on a uniform definition of severe food allergy.

Ethical approval is not required for this study, as it is a systematic review. However, author's potential conflicts of interest is disclosed from the

beginning. We plan to submit a report of our findings for publication in a peer-reviewed journal. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist will be used to guide the reporting of the systematic review: <http://www.prisma-statement.org/>.

CONCLUSION

This review will involve systematically identifying, critiquing, and synthesizing the evidence on the current classifications of food allergy severity and respective features. It will build on earlier reviews in this area. The findings from this review will be used to inform the development of an international consensus on the definition of severe food allergy.

Abbreviations

CASP: Critical Appraisal Skills Programme; CBA: controlled before after studies; CCT: controlled clinical trials; CHEERS: Consolidated Health Economic Evaluation Reporting Standards; CI: confidential interval; FAQL: food allergy quality of life; FAIM: food allergy independent measure; FARE: Food Allergy Research & Education; GRADE: Grading of Recommendations Assessment, Development and Evaluation; ITS: interrupted time series; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO: Prospective Register of Systematic Reviews; RCT: randomized controlled trials; WAO: World Allergy Organization

Acknowledgements

This is a project of the World Allergy Organization (WAO), supported by a grant from Novartis, as well as Abbott Laboratories and Food Allergy Research & Education (FARE). WAO will fund the systematic review to support the development of the international consensus on the definition of severe food allergy. The funder and supporters had no role in the development of the protocol nor will they have any role in the conduct of the systematic review or its publication.

Authors contribution

This protocol was drafted by SA. The document was first revised by AF and UN and then revised 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 a systematic review. However, author's potential conflicts of interest is disclosed from the beginning.

Declaration of competing interest

The following authors declared no potential interests: Ignacio J Ansotegui; Stefania Arasi; Shahd Daher; Alessandro Fiocchi; Ulugbek Nurmatov; Stavros Petrou; Graham Roberts; Mario Sánchez-Borges; Luciana Kase Tanno; Marta Vazquez Ortiz; Gary Wing-Kin Wong.

Some of the authors have professional affiliations related to the content of the systematic review as set out below:

Audrey Dunn-Galvin: consultancy fee from Aimmune and DBV; Motohiro Ebisawa: lecture fees: DBV technologies and Mylan; Philippe Eigenmann: Research grants and support: Ulrich Muller Gierock Foundation, ThermoFisher Scientific; Consultant: DBV technologies, Nesté, Danone, Novartis, Abbott; Speaking engagements: ThermoFisher Scientific, ALK, Abbott; Stock options: DBV technologies; Montserrat Fernandez-Rivas: research grants from the Spanish Government (MINECO, ISCIII) for the proyectos SOLMILK, ARADyAL network and PI19/01095; consultancy fees from Aimmune, DBV, Novartis, SPRIM; lecture fees from ALK, Allergy Therapeutics, Diater, GSK, HAL Allergy, Thermofisher Scientific.

Ruchi Gupta: grants from The National Institute of Health (NIH) (R21 ID # AI135705, R01 ID# AI130348, U01 ID # AI138907), Rho Inc., Stanford Sean N. Parker Center for Allergy Research, UnitedHealth Group, Thermo Fisher Scientific, Genentech, and the National Confectioners Association (NCA); is employed by Ann & Robert H. Lurie Children's Hospital of Chicago; is a Professor of Pediatrics at Northwestern University; and serves as a medical consultant/advisor for Before Brands, Kaléo Inc., Genentech, ICER, FARE, Aimmune Therapeutics, Aimmune Therapeutics, and DBV Technologies; Anna Nowak-Węgrzyn: Grant/Research/Clinical Trial Support: DBV Technologies; ITN/NIAID; Astellas Pharmaceutical; Sanofi-Aventis [Future therapies for food allergy]. International FPIES Association [FPIES, unpaid advisor]. Consultant/Advisory Boards: Gerber Nutrition Institute; Merck. Speaking engagements: Nestle, Thermofisher Scientific; Sayantani B Sindher: supported by NIH grants. Involved in clinical trials with Regeneron, Aimmune Therapeutics, DBV Technologies, Adare Pharmaceuticals, Sanofi, Novartis; Paul J Turner: grants from UK Medical Research Council, NIHR/Imperial BRC, JM Charitable Foundation and UK Food Standards Agency; personal fees from UK Food Standards Agency, DBV Technologies, ILSI Europe and Allergenics, non-financial support from Aimmune Therapeutics; Brian P Vickery: Employment: Pediatric Institute of Emory University + Children's Healthcare of Atlanta; Consultant/Advisor: Aimmune Therapeutics; AllerGenis, LLC; Food Allergy Research and Education (FARE); Reacta

Biosciences; Grant support: Immune Tolerance Network; NIH-NIAID; FARE; Genentech; Clinical investigator: Aimmune; DBV Technologies; Regeneron.

Appendix A Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.waojou.2020.100493>.

Author details

^aPredictive and Preventive Medicine Research Unit, Multifactorial and Systemic Diseases Research Area, Pediatric Allergology Unit, Bambino Gesù Children's Hospital IRCCS, Rome, Italy. ^bDivision of Population Medicine, School of Medicine, Cardiff University, Wales, UK. ^cNational Heart & Lung Institute, Imperial College London, London, UK. ^dDept. Allergy and Immunology, Hospital Quironsalud Bizkaia, Bilbao, Spain. ^eApplied Psychology and Paediatrics and Child Health, University College Cork, Cork, Ireland. ^fNuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Observatory Quarter, England, UK. ^gClinical Research Center for Allergy and Rheumatology, Sagamiara National Hospital, Kanagawa, Japan. ^hPediatric Allergy Unit, Department of Women-Children-Teenagers Pediatrics, University Hospitals of Geneva, Geneva, Switzerland. ⁱServicio de Alergia, Hospital Clinico San Carlos, UCM, IdISSC, ARADyAL, Madrid, Spain. ^jCenter for Food Allergy and Asthma Research (CFAAR), Northwestern University Feinberg School of Medicine; Department of Pediatrics & Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, USA. ^kAllergy and Immunology, Department of Pediatrics, New York University School of Medicine, Langone Health, New York, NY, USA. ^lNIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK. ^mClinical and Experimental Sciences and Human Development in Health, Faculty of Medicine, University of Southampton, Southampton, UK. ⁿThe David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight, UK. ^oAllergy and Clinical Immunology Department, Centro Médico Docente La Trinidad, Caracas, Venezuela. ^pDivision of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Stanford University, Stanford, CA, USA. ^qSean N. Parker Center for Allergy and Asthma Research at Stanford University, Stanford University, Stanford, CA, USA. ^rHospital Sírio Libanês, São Paulo, Brazil. ^sDepartment of Paediatrics, Imperial College, London, United Kingdom. ^tDepartment of Pediatrics, Emory University, Atlanta, GA, USA. ^uDepartment of Paediatrics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, China. ^vDiscipline of Paediatrics and Child Health, School of Medicine, University of Sydney, Sydney, Australia. ^wDepartment of Pediatrics, Gastroenterology and Nutrition, Collegium Medicum, University of Warmia and Mazury, Olsztyn, Poland. ^xUniversity Hospital of Montpellier; Sorbonne Universités, Paris, Montpellier, France.

REFERENCES

1. Nwaru BI, Hickstein L, Panesar SS, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. *Allergy*. 2014;69(1):62-75.
2. Gupta RS, Warren CM, Smith BM, et al. Prevalence and severity of food allergies among US adults. *JAMA Netw Open*. 2019;2(1), e185630.
3. Gupta RS, Warren CM, Smith BM, et al. The public health impact of parent-reported childhood food allergies in the United States. *Pediatrics*. 2018;142(6).
4. Turner PJ, Jerschow E, Umasunthar T, Lin R, Campbell DE, Boyle RJ. Fatal anaphylaxis: mortality rate and risk factors. *J Allergy Clin Immunol Pract*. 2017;5(5):1169-1178.
5. Umasunthar T, Leonardi-Bee J, Hodes M, et al. Incidence of fatal food anaphylaxis in people with food allergy: a systematic review and meta-analysis. *Clin Exp Allergy*. 2013;43(12):1333-1341.
6. Prescott S, Allen KJ. Food allergy: riding the second wave of the allergy epidemic. *Pediatr Allergy Immunol*. 2011;22(2):155-160.
7. Prescott SL, Pawankar R, Allen KJ, et al. A global survey of changing patterns of food allergy burden in children. *World Allergy Organ J*. 2013;6(1):21.
8. Patel N, Herbert L, Green TD. The emotional, social, and financial burden of food allergies on children and their families. *Allergy Asthma Proc*. 2017;38(2):88-91.
9. Fiocchi A, Ebisawa M. Severe food allergies: can they be considered rare diseases? *Curr Opin Allergy Clin Immunol*. 2017;17(3):201-203.
10. Muraro A, Fernandez-Rivas M, Beyer K, et al. The urgent need for a harmonized severity scoring system for acute allergic reactions. *Allergy*. 2018;73(9):1792-1800.
11. Turner PJ, Baumert JL, Beyer K, et al. Can we identify patients at risk of life-threatening allergic reactions to food? *Allergy*. 2016;71(9):1241-1255.
12. Tanno LK, Calderon MA, Smith HE, et al. Dissemination of definitions and concepts of allergic and hypersensitivity conditions. *World Allergy Organ J*. 2016;9:24.
13. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions vol. 6 (Updated 22 August 2019). Cochrane Collaboration. Available: <https://training.cochrane.org/handbook/current> (last access 8 April 2020).
14. The Effective Public Health Practice Project (EPHPP). Quality assessment tool for quantitative studies. Available from: <http://www.ephpp.ca/tools.html> (last access 28 March 2020).
15. CASP. checklist for Economic evaluations http://media.wix.com/ugd/dded87_3b2bd5743feb4b1aac6ebdd68771d3f.pdf (last access 28 March 2020).
16. Husereau D, Drummond M, Petrou S, et al, CHEERS Task Force. Consolidated health economic evaluation reporting Standards (CHEERS) statement. *BMJ*. 2013;346:f1049.