

Preventing immediate-onset food allergy in infants, children and adults: Systematic review protocol

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Abstract

Background: More than 17 million people across Europe have allergies to food and the burden of food allergies is increasing. In 2014, the European Academy of Allergy and Clinical Immunology (EAACI) published guidelines for preventing food allergy. Important research has been published since then and it is essential to ensure the guidelines reflect the latest evidence. A systematic review will be undertaken to help prepare new guidelines due to be published in 2020.

Methods: Eleven bibliographic databases will be searched from inception to 31 October 2019 for randomized controlled trials about any intervention designed to prevent the development of new cases of immediate-type/IgE-mediated food allergy in infants, children and adults. There are few randomized controlled trials about the impact of breastfeeding on food allergy so prospective cohort studies about breastfeeding with at least 1000 participants at general risk or 200 at high risk of food allergy will also be eligible. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach will be used to assess the certainty of the evidence and tabulate summary data. The risk of bias in individual trials will be assessed using the Cochrane risk of bias tool. All data extraction and quality appraisal will be undertaken independently by two reviewers in partnership with a taskforce of EAACI members.

Conclusions: Preventing food allergy has the potential to improve personal well-being and reduce societal healthcare costs. It is important that forthcoming European guidelines take the latest research into account. Past reviews have tended to focus on single interventions or combined food allergy with other outcomes, making it difficult to draw robust conclusions about potential impacts for policy and practice.

KEYWORDS

adults, children, food allergy, IgE-mediated, infants, prevention

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1 | INTRODUCTION

1.1 | Rationale

About 17 million people in Europe have an allergy to foods such as cow's milk, hen's egg or peanut.¹ The prevalence of food allergy is increasing. In Western countries, challenge-diagnosed food allergy has been reported to be as high as 10%, with the highest prevalence amongst infants and young children.² There is also evidence of increasing prevalence in developing countries.²

Food allergy can affect people's well-being and result in costly medical visits and treatments. Food is an integral part of daily living so food allergy can have a substantial impact on the quality of life of those affected and their families.³ It also has a financial burden. A study in Europe found that the annual household cost of food allergy was €3961 per affected child, including direct and indirect costs.⁴ This is broadly equivalent to estimated direct and indirect costs of \$4184 per affected child per year in the United States.⁵

In 2014, the European Academy of Allergy and Clinical Immunology (EAACI) released guidelines to help countries, clinicians and families consider the practical things that could be done to prevent food allergy and areas where more evidence was needed.⁶ Since that time, additional research has been published, including studies focused on preventing food allergy by introducing allergenic foods early into infants' diets.⁷⁻¹⁰ It is important that European countries benefit from new guidelines, based on the latest evidence.

A number of recent systematic reviews are available and provide useful insights.¹¹⁻¹⁴ However, these reviews tend to combine food

Key Message

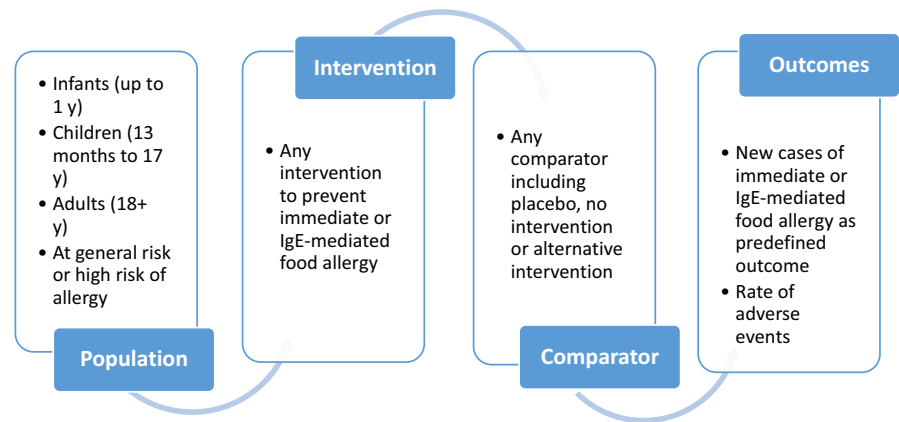
Food allergy affects the lives of millions of people throughout Europe and there has been much research published recently about attempts to prevent it. This evidence is of varying quality. Supported by a systematic review and expert insight, the European Academy of Allergy and Clinical Immunology's (EAACI) forthcoming guidelines will help countries, regions and individual clinicians make appropriate recommendations about the most effective and safe strategies to help prevent the individual and societal issues associated with food allergy. This article describes the methodology of a systematic review to support updating guidelines that were published in 2014.

allergy with other outcomes^{15,16} or to focus on one specific intervention, such as infant formula or prebiotics.¹⁷ It is difficult to compare interventions because the inclusion criteria and measurement approaches vary across reviews. Some reviews, including a previous review by EAACI, have drawn conclusions based on studies of widely differing quality.¹⁸

1.2 | Objective

This paper sets out the protocol for a systematic review to support updating the EAACI food allergy guidelines, which are due

FIGURE 1 Populations, interventions, comparators and outcomes of interest



for release in 2020. The protocol is constructed in line with the PRISMA-P checklist.^{19,20} It has been developed by a taskforce made up of EAACI members, which includes allergy, gastroenterology, primary care, dietetics clinicians, immunologists and other researchers, patient representatives and information specialists (all authors).

The aim of the systematic review is to assess the effectiveness and safety of any approach (interventions) for preventing the development of immediate-type or IgE-mediated food allergy (outcome) in infants, children and adults (population) compared to any other intervention or placebo (comparator).

Figure 1 provides a population, intervention, comparison and outcomes (PICO) statement.

The review protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO): registration number CRD42019127457. Any updates to the protocol will be made via PROSPERO.

2 | METHODS

2.1 | Eligibility criteria

Studies will be eligible for inclusion in the review if they meet the following criteria:

- **Population:** infants (defined as up to 1 year old), children (13 months to 17 years) and/or adults (18+ years) with or without an increased risk for developing allergic disease and with or without any sensitization or atopic manifestations. For the purposes of the review, "increased risk" will be defined as having a risk factor such as eczema or asthma or having immediate relatives with a history of food allergy, asthma, hayfever or other allergies.²¹
- **Intervention:** any intervention to prevent the development of new cases of immediate-onset or IgE-mediated food allergy. This includes dietary initiatives and skin barrier initiatives.
- **Comparator:** any comparator, including placebo, no intervention or any other intervention or combination of interventions.

- **Outcomes:** studies that include the measurement of new cases of food allergy.
- **Timeframe:** published from database inception to 31 October 2019.

There will be no language or geographical restrictions. Where repeated reports of the same study are identified, the most up-to-date publication with food allergy as an outcome will be included unless there is a good clinical reason to use data from an earlier publication.

Randomized controlled trials will be eligible for inclusion in the review.

In addition, for research related to breastfeeding, prospective cohort studies with at least 1,000 participants at undifferentiated risk or at least 200 participants at increased risk of food allergy will be eligible. This is because previous reviews^{16,18} have shown that there is a lack of randomized controlled trials in this area and ethical issues preclude randomization of infants to be breastfed or not. These sample size numbers have been selected as cut-off points as a proxy for studies large enough to provide credible trends given the expected proportions in populations who may develop food allergy. Food allergy affects around 2% of the general population, so to be sufficiently powered to detect even moderate effect sizes or association, studies need to be reasonably large.²² The sample size requirements will only be applied to prospective cohort studies of breastfeeding.

Studies will be excluded if they:

- focus exclusively on non-IgE-mediated food allergy
- focus on reactions to food that have been referred to as "food intolerance" or non-immune food hypersensitivity
- include "sensitivity," "hypersensitivity" or similar as an outcome rather than "food allergy" or specific food allergies
- aim to prevent potential manifestations of food allergy such as eczema but do not include an explicit diagnosis of food allergy. It is recognized that food allergy may have many different manifestations but these may also have other causes
- are systematic or non-systematic reviews, discussion papers, non-research letters and editorials, case studies, observational studies apart from those listed above regarding breastfeeding,

animal studies, abstracts, studies not available in full form or unpublished material

These inclusion and exclusion criteria will be used at abstract and full-text stages.

2.2 | Information sources

Eleven bibliographic databases will be searched by an information specialist for studies published from database inception to 31 October 2019:

- Cochrane Library (ISSN 1465-1858) comprising Cochrane Database of Systematic Reviews (CDSR), Database of Reviews of Effectiveness (DARE), CENTRAL (Trials), Methods Studies, Health Technology Assessments (HTA) and Economic Evaluations Database (EED)
- CINAHL (EBSCOhost, Cumulative Index to Nursing and Allied Health Literature)
- EMBASE (OVID)
- ISI Web of Science (Thomson Web of Knowledge)
- MEDLINE (OVID)
- WHOLIS (World Health Organization Library Information System)
- PAHO (Pan American Health Organization database)
- Science Citation Index and Social Sciences Citation Index
- TRIP Database (www.tripdatabase.com)
- WHO ICTRP (World Health Organization International Clinical Trials Registry Platform; www.who.int/ictrp)
- US National Institutes of Health Ongoing Trials Register (Clinicaltrials.gov, NIH web)

Unpublished research is not eligible for inclusion, but the trial registries in the list above will be searched to identify studies that may since have been published.

A search strategy has been devised on OVID MEDLINE and adapted for other databases (see Appendix S1 for the search terms). The search strategy was developed with input from methodologists and information specialists (DdS, CS) working in partnership with clinicians and patient representatives (all other authors). To retrieve randomized controlled trials, the Cochrane strategy for identifying trials in MEDLINE will be used: sensitivity- and precision-maximizing version.²³

Additional references will be located by searching the reference lists of systematic reviews and identified studies and through discussion with experts in the field who are part of a taskforce developed for this purpose.

2.3 | Selection process

Two reviewers (DdS and CS) will independently screen the titles and abstracts of potentially relevant studies to shortlist them for

full-text review. The reviewers have received training and have undertaken other systematic reviews.

Full-text copies of all studies identified as potentially relevant by either reviewer will be obtained and their eligibility for inclusion assessed independently by the two reviewers using a checklist containing the inclusion criteria. Studies that do not fulfil all of the inclusion criteria will be excluded. Any discrepancies will be resolved by consensus and, if necessary, arbitration by a third reviewer (GR). Inter-rater agreement will be calculated using percentage agreement levels. Data will be available to calculate Kappa if required.

Once a shortlist of studies for inclusion is generated, a summary of each study will be reviewed by the entire EAACI guidelines taskforce to ensure clinicians and patient representatives agree with methodologists about eligibility and so that the experts can suggest any additional studies for consideration that have not been identified by the bibliographic searches. Each taskforce member will then be assigned to a topic group and will review the full text of all studies about that topic. These taskforce groups will recommend studies eligible for meta-analysis based on whether appropriately similar populations, interventions and outcome measures have been used in the studies to allow clinically meaningful compilation.

2.4 | Data collection and management

Search results will be stored using Endnote X9 reference management software.

Data will be extracted from the selected studies including citation details, funder, country of study, study type, population type, sample number, food allergy risk status, intervention, comparator, outcome measures and study outcome data (in the format of estimates, confidence intervals and *P*-values where available). The primary outcome of interest is new cases of immediate-type/IgE-mediated food allergy. Data about adverse events will also be extracted where available. The rationale is that the effectiveness for prevention needs to be weighed against any safety issues or other adverse consequences. Given the variety of interventions that have been tested, studies are unlikely to have measured the same outcomes or used the same measurement approaches, so the review will extract the data in the form provided by individual studies.

Data will be independently extracted in duplicate into a customized data extraction form by two reviewers (CS and DdS) who have received training. The checklists used for screening and for data extraction will be piloted with a sample of studies, comparing results across two reviewers. A sample form is included in Appendix S1. Any data extraction discrepancies will be resolved by discussion, with arbitration by a third reviewer if consensus cannot be reached (GR). Agreed data will be stored in an Excel spreadsheet.

In addition, data extraction will be checked by the EAACI guidelines taskforce, divided into small groups. Taskforce members will only be part of topic review groups if they have no potential interests declared about a topic area. The purpose of clinicians and patients checking data extraction is to increase accuracy, ensure that clinically relevant outcomes have been extracted and ensure that the clinical and patient experts are aware of the study findings for interpretation.

2.5 | Risk of bias in individual studies

The risk of bias will be examined at outcome level (using the GRADE approach described below) and at the level of individual studies. Randomized controlled trials will be assessed using the Cochrane Effective Practice and Organisation of Care (EPOC) risk of bias tool.²⁴ Prospective cohort studies about breastfeeding will be assessed using the domains from the Strengthening the Reporting of Observational Studies in Epidemiology tool (STROBE).²⁵ These tools were used when creating previous EAACI guidelines⁶ and have been chosen to aid consistency of EAACI reviews over time. The EAACI Taskforce was aware of alternative tools such as ROB-2 and ROBINS-I but felt that it was important to be consistent with 2014 guidelines in the bias assessment. The domains in EPOC are similar to the newer ROB-2 tool. A member of a Cochrane Collaborative group will review the quality assessments to ensure alignment with latest good practice (RB).

Two reviewers will independently assess the risk of bias for each study. This will then be checked with the EAACI taskforce topic review groups to make sure that clinical and patient representative views are included. Any discrepancies will be resolved by consensus and, if necessary, arbitration by the senior reviewer (GR). The risk of bias information will be used when analysing the overall certainty of evidence for particular interventions.

2.6 | Data synthesis

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist will be used to guide the reporting of the systematic review.²⁶

The overall certainty of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.²⁷ GRADE is a framework for developing and presenting summaries of evidence to support clinical practice recommendations. A bespoke summary of findings table and evidence profile will be constructed for the primary outcome of new cases of food allergy. The Appendix S1 provides the planned templates.

In addition, GRADE provides a framework for examining meta-biases such as the risk of publication bias. A funnel plot will be used to explore potential publication bias if six or more studies are available about any intervention, and tested by Egger's regression test and Begg's rank correlation test. The EAACI Taskforce will review the body of evidence about each intervention to develop a consensus about potential meta-bias.

If there were both observational studies and randomized controlled trials available about breastfeeding, then the results of randomized and non-randomized studies would be presented separately, with narrative about the risk of bias.

Due to the heterogeneous nature of interventions and populations, the reviewers expect to undertake a narrative synthesis of all topics, summarizing the results descriptively and drawing attention to any differences in outcome based on age or risk profile. The reviewers will examine whether interventions have been found to be more or less effective for groups at general or increased risk of food allergy because past research has found different effects or magnitude of effects (including safety outcomes) dependent on familial risk of allergy.²⁸

For some topics, such as hydrolysed infant formula or the early introduction of egg or peanut into infant diets, meta-analyses have already been conducted.^{11,13,15} The reviewers will draw on these in the review narrative rather than replicating existing work.

If the following criteria are met, additional random-effects meta-analysis will be undertaken: four or more studies about a topic are available; studies provide sufficiently detailed quantitative data to allow compilation; the data available are measured in a similar manner; the populations have a similar demographic and risk profile, and no other relevant meta-analysis has been published. Random-effects modelling has been selected to avoid overweighting studies with the largest sample sizes.

A statistician will be part of the review team (see Acknowledgements) and if appropriate will conduct the meta-analysis with the Comprehensive Meta-Analysis (version 3) software developed by Biostat. Odds ratios with 95% confidence intervals will be reported as a measure of overall effect size. The Comprehensive Meta-analysis program weights studies by inverse variance rather than by sample size. This is a method of aggregating random variables where each variable is weighted in inverse proportion to its variance in order to minimize the variance of the weighted average. The inverse variance is roughly proportional to sample size, but is a more nuanced measure. The pooled mean effect size will be calculated using the random-effects model. The Q_{within} -statistic will be used to assess the heterogeneity of studies and quantified with the I^2 statistic. Probability value $< .1$ will be used to suggest statistically significant heterogeneity. Heterogeneity will be considered low, moderate and high when the values are below 25%, between 25% and 75%, and above 75%, respectively. Subgroup analysis by age and food allergy risk profile will be undertaken if supported by the data.

The review will be published and an appendix will contain summary information about each included study as well as tables summarizing the outcomes associated with each intervention.

3 | DISCUSSION

Preventing food allergy is important given its high societal and healthcare costs. However, available evidence needs to be carefully evaluated to reach conclusions about which preventative strategies should be routinely implemented.

The food allergy prevention guidelines released by EAACI in 2014⁶ have helped countries adapt and strengthen their policies for the prevention of food allergy. Since the publication of the European guidelines, several other societies and national bodies have released their own guidelines or consensus statements.²⁹⁻³² However, further important research has emerged in this area so the European guidelines are being updated to take account of this.

This systematic review will not merely update a previous systematic review by EAACI,¹⁸ because a number of lessons have been learnt and built into this protocol. Firstly, consistent with other international guidelines, a GRADE approach will be used so that the focus is on a defined and comparable outcome and so meta-biases can be accounted for. This will allow clear links between the certainty of evidence and guideline recommendations.

Secondly, the review will include only primary studies rather than systematic reviews so that data about the outcome of interest can be appropriately extracted and so that the quality and outcomes of studies can be compared. Other systematic reviews are available and will be drawn on as a source of citations and for meta-analyses where appropriate, but previous reviews do not cover the entire range of interventions of interest or focus exclusively on food allergy.

Thirdly, the review will focus only on randomized controlled trials rather than including a wide range of study designs as previously. This will ensure that it is more appropriate to combine data and make robust recommendations than when study designs are heterogeneous and when quality varies substantially.

Fourthly, patient representatives and clinicians will be involved at all stages, from developing the protocol through to extracting data, assessing quality and synthesizing the results. An international taskforce has been set up to support this. Drawing on lessons from other reviews, taskforce members will only be involved in analysing and discussing research about topics where they have no declared interests.

Finally, a statistician will be part of the taskforce to ensure appropriate expertise to combine data quantitatively if the data warrants this.

Implementing guidelines can be challenging,³³ and there has been considerable debate about how prevention interventions should be put into practice.³⁴ One of the key issues supporting the implementation of guidelines may be their credibility from a scientific and reputational perspective. Strengthening the rigour and consistency of the methodology used to compile evidence in this review will support up-to-date and well-considered recommendations to guide national policy and individual practice. The review will supplement the clinical expertise and experience that is key in considering what will be most appropriate for infants, children and adults in different parts of Europe.

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CONFLICT OF INTERESTS

The authors declared no conflict of interest in preparing a protocol for a systematic review. Some of the authors have professional affiliations related to the content of the review to be conducted as set out below. During the conduct of the review itself, these authors will not be involved in decisions about study selection, data extraction or analysis of studies in fields where they have a declared interest. CS, DdS, EA, HA, SA and VV declared no potential interests. AM has received research grants from Aimmune and served as a speaker for DVB, Aimmune, Mylan, ALK and Nestle. AH has served as a speaker for Nestle, Bristol-Myers and ALK. CV has received research grants from ThermoFisher and served as a speaker for Danone, Abbott, Nestle and Mead Johnson. CJ is an employee of Allergy UK and this organization has received funding from Abbott, Aimmune, Allergy Therapeutics, DBV, Danone, Nutricia, Mead Johnson, Sanofi-Genzyme. GdT has received research grants from Aimmune, DBV, NIH (LEAP study), Action Medical (EAT study) and education grants from Allergy Academy. GL has received research grants from NIH (LEAP study), Action Medical (EAT study); has been a consultant for DBV, Aravex, Aimmune, ALK, Novartis and Sanofi-Genzyme; and a shareholder of DBV and Mission Mighty Me. GR has received research grants from NIH (LEAP study), Action Medical (EAT study); has been a consultant for Nutricia; and is Editor in Chief of Clinical & Experimental Allergy. HS received research grants from Aria, BioGaia, Winclove; has been a consultant for Bayer, Biogaia, Biocodex, Danone, Nestle and Nutricia; served as a speaker for Bayer, Biogaia, Biocodex, Danone, Nestle, Nutricia and Merck; and was editor of the Journal of Pediatric Gastroenterology and Nutrition. KB received research grants from Aimmune, ALK, Berliner Sparkasson Stiftng, Danone, DBV, DST Diagnostic, Good Mills, Hipp, Hycor, Infectopharm, ThermoFisher, VDI, EU, German Research Foundation and BMBF and has been a consultant for Aimmune, ALK, Allergopharma, Bausch & Lomb, Bencard, Danone, Hycor, Di-Text, Hammer und Rall Media, Infectopharm, Mabyon, Meda Pharma, Mylan, Nestle, Unilever. KG has been a consultant for Nutricia, Abbott, Mead Johnson and Reacta Biotech; RB has been a consultant for Dairy Goat Cooperative, Cochrane Children and Families. PE received research grants from LETI, Nestle and ThermoFisher; has been a consultant for Danone, Novartis, ALK, DBV, Stallergens and Abbott; and is Editor in Chief of PAI. SH has been a consultant for ALK and received research grants from ALK.

AUTHOR CONTRIBUTIONS

All authors jointly developed the content for this article. CS and DdS developed an initial draft for refinement by GR, SH and AM. All other authors contributed further refinements and quality-assured the material in writing and verbally. GR acted as the final decision-maker and guarantor. All authors have made substantial contributions to conception and design of this paper, been involved in drafting the manuscript or revising it critically for important intellectual content, given final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: de Silva D, Halken S, Singh C, et al. Preventing immediate-onset food allergy in infants, children and adults: Systematic review protocol. *Pediatr Allergy Immunol*. 2019;00:1-7. <https://doi.org/10.1111/pai.13177>

Additional material

Example search strategy for Ovid MEDLINE

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to 2019 October 31>

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1      exp food hypersensitivity/
2      (food* adj3 (allerg* or hypersensitiv* or reaction* or atop* or hyperallerg*
3      or acute sensitiv* or anaphyla*)).ti,ab.
4      ((allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute
5      sensitiv* or anaphyla*) adj3 prevent* adj3 (milk or egg* or peanut* or nut*
6      or tree nut* or wheat or soy* or shellfish or fish or seafood* or kiwi fruit* or
7      banana* or prevent* or diet* or nutrient or milk or meat or cow or chicken
8      or corn or fruit or vege* or breastfe* or complementary food or solid or
9      probiotic or prebiotic or symbiotic or formula or microbial or fish oil or
10     PUFA or omega or fatty acids or micronutrient or vitamin or skin barrier or
11     high risk)).ti,ab.
12     food allerg*.mp.
13     allergy, food.mp.
14     or/1-5
15     randomized controlled trial.pt.
16     controlled clinical trial.pt.
17     randomized.ab.
18     placebo.ab.
19     clinical trials as topic.sh.
20     randomly.ab.
21     trial.ti.
22     or/7-13
23     exp animals/ not humans.sh.
24     14 not 15
25     cohort studies.pt.
26     cohort$.tw.
27     breastfe$.ab.
28     6 and 16
29     19 and 17
30     19 and 18
31     21 and 22
32     20 and 23
```

Example data extraction sheet

Study ID

IDs of other reports of this study

General Information

1. Date form completed	
2. Reviewer name	
3. Study citation	
4. Publication type (e.g. full paper, abstract, letter)	
5. Notes:	

Eligibility

Study characteristics	Review inclusion criteria	Yes / No / Unclear	Location in text (page)
6. Type of study	Randomised controlled trial		
	For breastfeeding only, prospective cohort study with at least 1000 general risk of 200 high risk participants		
7. Outcome measure	Immediate type / IgE-mediated food allergy as pre-defined outcome		
8. Intervention	Intervention to prevent new cases of food allergy, with any comparator		
9. Decision:	Include / exclude / uncertain		
10. Reason for exclusion			

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

Data extraction

	Description	Location in text (<i>page</i>)
11. Country / region		
12. Funding source		
13. Study type		
14. Population type / age (infants, children, adults)		
15. Risk status (general / high)		
16. Sample number	Include numbers in each group and follow up	
17. Intervention	Include intervention description, timing, dose	
18. Comparator	Include comparator description, timing, dose	
19. Food allergy outcome measure		
20. Food allergy outcome data	Include time points measured, point estimate, confidence interval and p-value	
21. Safety / adverse event outcome data		
22. Notes		

Information for Risk of Bias assessment

Domain	Risk of bias <i>Low / Medium / High / Unclear</i>	Notes	Location in text (<i>page</i>)
23. Random sequence generation			
24. Allocation concealment			
25. Blinding of participants and personnel			
26. Blinding of outcome assessment			
27. Incomplete outcome data			
28. Selective outcome reporting			
29. Other bias			
30. Notes:			

Example display tables

Example risk of bias summary table format

First author	Design	Adequate sequence generation	Allocation concealment	Blinding / patient-related outcomes	Incomplete outcome data addressed	Free of selected reporting	Free of other bias	Other method notes	Overall quality assessment
	RCT	✗	✓	✓	✓	✓	✗		
	RCT	✓	✓	✓	✓	✓	✗		

Example of GRADE evidence profile format

Intervention	Population	Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall GRADE
Avoidance of dietary food allergens	Pregnant women at general risk							
	Pregnant women at high risk							

Example of adapted GRADE summary of findings table

Intervention	Population	Key findings	Studies	GRADE of evidence
Interventions in pregnancy				
Dietary avoidance of food allergens in pregnant women	General risk			
	High risk			