TECHNICAL REPORT

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Draft protocol for a systematic review on health outcomes related to the age of introduction of complementary food for the scientific assessment of the appropriate age of introduction of complementary feeding into an infant's diet

European Food Safety Authority

Abstract

In 2016, the European Food Safety Authority (EFSA) received a mandate from the European Commission to update its 2009 opinion on the appropriate age for introduction of complementary feeding of infants. In order to retrieve data on health outcomes related to the age of introduction of complementary food, a systematic literature review will be conducted in line with the EFSA guidance on the application of systematic review methodology to food and feed safety assessments to support decision making. These data will be considered together with data on the nutritional adequacy of exclusive breast-feeding or formula feeding at different ages and with data on neuromuscular, gastrointestinal and renal development which may affect the capacity of the infant to introduce non-milk foods in the diet as the basis for the scientific assessment. EFSA wishes to seek advice from stakeholders on the draft protocol for the systematic literature review aiming to retrieve data on health outcomes related to the age of introduction of complementary food. To this end, the NDA Panel endorsed the draft protocol for public consultation on 1 February 2017. The consultation is open from 16 February to 23 March 2017 (five weeks).

Key words: infants, breastfeeding, formula feeding, complementary feeding, age of introduction, protocol, systematic review

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1. Introduction

1.1. Background

In 2016, the European Food Safety Authority (EFSA) received a mandate from the European Commission to update its opinion on the appropriate age for introduction of complementary feeding of infants (EFSA NDA Panel, 2009).

In its 2009 opinion (EFSA NDA Panel, 2009), the Panel considered that the appropriate age for starting complementary feeding is determined by the nutritional adequacy of exclusive breast-feeding at different ages, by potential health benefits (or hazards) related to continued exclusive breast-feeding or formula feeding, including effects on development of motor, cognitive and social functions, and by the impact of early feeding on the risk of diseases in later life, particularly obesity, cardiovascular disease, diabetes mellitus, etc.

In order to retrieve data on health outcomes related to the age of introduction of complementary food, a systematic literature review will be conducted in line with the EFSA guidance on the "Application of systematic review methodology to food and feed safety assessments to support decision making" (EFSA, 2010). These data will be considered together with data on the nutritional adequacy of exclusive breast-feeding or formula feeding at different ages and with data on neuromuscular, gastrointestinal and renal development which may affect the capacity of the infant to introduce non-milk foods in the diet as the basis for the scientific assessment. These aspects will be addressed in a narrative way through comprehensive literature searches.

This document presents the draft protocol developed in relation to this systematic review, which in line with EFSA's Strategic Objective 1 (Prioritise public and stakeholder engagement in the process of scientific assessment), is subject to public consultation.

Section 2 has been developed by an external contractor (i.e. consortium of Pallas health research and consultancy and Wageningen University and Research) in the framework of a procurement procedure, who will also perform the systematic literature search up to (including) the stage of full text screening as part of the outsourcing project. Sections 3 to 5 have been developed by the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) and its Working Group (WG) on Infant Nutrition who, together with EFSA staff members, will be responsible for carrying out the remaining steps of the systematic literature review.

1.2. Objectives of the systematic literature review

The objectives of the systematic literature review are to identify, select, appraise and synthesise the evidence from human studies in healthy term infants and pre-term infants (both intervention and observational studies), or systematic reviews and/or meta-analyses thereof, which investigated the effect of the age at which complementary foods (solid or liquid foods consumed in addition to breast-milk or infant formula) are introduced into an infant's diet. Pertinent studies are those in which the groups which are compared are alike in terms of the type of milk-feeding (breast-milk or infant formula), and in which the only important difference is the time at which complementary food is introduced into the diet of the infant. Studies which investigate the effects of breast-feeding vs. formula-feeding or the timing at which infant formula is introduced to an infant's diet are not pertinent for the task.

The health outcomes which will be considered, at least, are the following:

- Overweight and obesity
- Diabetes mellitus types 1 and 2
- Risk factors for cardiovascular disease (e.g. blood pressure, blood cholesterol)
- Coeliac disease
- Allergy
- Dental health
- Renal function

- Gastrointestinal infections (search to be limited to countries with infection rates in the target population similar to those in EU Member States)
- Respiratory tract infections and otitis media (search to be limited to countries with infection rates in the target population similar to those in EU Member States)
- Neuromuscular development, cognitive development and cognitive function
- Growth
- Body composition
- Food patterns, food preferences and feeding disorders
- Indicators of nutrient status

In case during the literature search additional health outcomes are identified which have been investigated in conjunction with the age of introduction of complementary feeding, these will be added to the list.

2. Identification of relevant studies

In order to meet the objectives of the systematic literature review, as outlined in 1.2, a systematic and extensive literature search (ELS) will be performed according to Cochrane (Higgins and Green, 2011) and PRISMA (Moher et al. 2009) guidelines, and following EFSA guidelines (EFSA 2010).

A consortium of Pallas health research and consultancy and Wageningen University and Research (WUR) developed literature search strategies, the selection strategy, including criteria for the selection of literature based on title and abstracts, and for the selection of full-text articles and thus pertinent references. The contractor will conduct the literature search and the selection of pertinent studies after finalisation of the protocol.

2.1. Performing the literature search

Literature databases

According to the defined scope of the systematic review, the following literature databases are selected to be searched:

- PubMed
- Web of Science Core Collection
- Cochrane Library

Search strings and limits

Three search strings were composed, which can be combined for a literature database search for the research objectives:

A: Terms for infants

B: Terms for complementary feeding

C: Terms for introduction of complementary feeding

D: Terms for age of introduction of complementary feeding

E: Terms for relevant study designs

To exclude developing countries, animal studies and non-relevant publication types such as editorials and case-series, specific search strings for human studies and study designs will be applied:

F: Terms for non-EU low income and low-middle income countries according to the World Bank (used to exclude these)

G: Terms for study types and designs (used to exclude these)

H: Terms for animal studies (used to exclude these)

The search strings will be combined as (A AND B AND C AND D AND E NOT (F OR G OR H)), with no additional language limits.

The PubMed limit "human studies" will not be used as previous experiences have indicated that these limits may exclude relevant articles. This has been confirmed by information specialists. Animal studies, studies performed in low income countries or non-pertinent study designs that still result from the database search will be excluded during the literature selection (see Section 2.2).

As living standards in the EU/EEA have increased in the past decades, the focus has shifted from deficiency diseases to chronic diseases and diseases of affluence. The search will be limited to studies published since 1990 (last 27 years). This time limit has been chosen because the majority of studies have been performed after this period (Qasem et al., 2015; Pearce et al., 2013), and because relevant studies possibly published before that date will be retrieved by hand searching (see section 2.3).

The search strings are presented in Appendix A.

Output from the searched databases, including all indexed fields per hit (e.g. title, authors, abstract), will be exported into separate folders of Endnote™ version X7.4, allowing a count of the individual hits per database. Thereafter, duplicate articles will be removed by keeping PubMed as the main database and only adding additional new articles from Web of Science and Cochrane Library to the file. For each reference, the database of origin will be stated. The library without duplicates will be used for the selection procedure in EndNote™ (see section 2.2.1).

2.2. Eligibility criteria for study selection

Inclusion and exclusion criteria to be applied during the selection phase are listed in Table 1.

Table 1: Inclusion and exclusion criteria to be applied

	Inclusion	Exclusion
Topic	- Studies that investigate the effect of the age of complementary foods introduction to infants in groups that are alike in terms of the type of milk-feeding (breast-milk or infant formula)	- Studies on the effects of breast-feeding vs. formula-feeding - Studies on the timing at which infant formula is introduced to an infant's diet - Studies on the nutritional content of breastmilk or infant formula
Study design	- Intervention, experimental studies - Longitudinal, prospective, observational, cohort studies - Nested case-control studies with prospective data collection - Meta-analyses or systematic reviews *(also for hand search)*	- Animal studies, *in vitro* studies - Case studies/case-series - Case-control studies with retrospective data collection - Comments, editorials, and letters to the editor, other not peer-reviewed publication types - Cross-sectional studies
Publication type	Peer-reviewed scientific articles	- PhD Theses (see grey literature) - Extended abstracts, conference proceedings (see grey literature)
Study characteristics	- Baseline data available e.g.: population characteristics including age, sex - Studies reporting on the age at which complementary foods are introduced - Clear outcome definitions used	- Studies not reporting on the age at which complementary foods are introduced - Missing a clear description of methodology, outcome definitions, exposure or outcome assessment
Population	- All population groups, males and females - Generally healthy term infants (a) - Pre-term infants - Infants not older than 12 months of age at introduction of complementary foods	- Studies in populations under clinical care - Specific subgroups of infants with diseases or disorders, medication use known to affect nutritional status - Studies in populations with very poor nutritional status, like refugees or mistreated or abused children - Other children not representative of children living in EU/EEA countries

	Inclusion	Exclusion
		- Animals
Setting	- Countries that are comparable with EU and EEA member states	- Studies conducted in EU/EEA countries but during exceptional period in time, e.g. during a famine or war - Studies conducted in regions geographically or culturally not comparable to EU/EEA countries (b)

(a): It should be noted that studies that include a large general population of children might have included some infants with diseases or disorders affecting nutritional status.

(b): Studies conducted in countries outside EU/EEA that have been categorized by the World Bank as low income countries in 2017 will be excluded. For studies in other countries outside EU/EEA, comparability of the study population with infants in EU/EEA will be assessed studying baseline characteristics such as proportion of children wasted or stunted, nutritional status and living conditions. A full list of countries and incomes can be downloaded at the website of the World Bank: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups

2.3. Study selection process

Pertinent references will be selected by a three-stage selection procedure by two reviewers independently from each other, using EndNote™. Inclusion and exclusion criteria applied in these steps are provided in Table 1.

Selection steps:

1. *Screening of title and abstract: this will yield the articles that will be assessed in full text.*

   The EndNote™ library with unique citations (i.e. without overlap from the different databases) will be used for the first selection step. Titles and abstracts will be screened for relevance according to the inclusion criteria. Articles that do not describe information in the title or abstract relevant to the research objectives will not be selected for full text assessment. In addition, if it is very obvious that the article does not meet one of the other inclusion criteria, it will be excluded. In case this cannot be determined based on the title or the abstract, the article will be assessed in more detail in full text during the second selection step.

   Articles that have been excluded during screening of title and abstract will be stored in an indexed folder in EndNote™. Non-pertinent articles are sorted in separate folders based on the criterion of exclusion (see Table 1).

2. *Screening of full article: in this selection step the full text articles will be assessed.*

   Articles will be included if the reported information is relevant based on the same inclusion and exclusion criteria as used for selection step 1. In this stage, a checklist will be used to evaluate the relevance of the full articles. The checklist comprises the specific inclusion and exclusion criteria that have been formulated for this review (see Table 1).

   When a full article is excluded from the review, the criterion based on which it has been excluded will be documented and presented in an exclusion table. In this way, the selection procedure is transparent, will assure reproducibility, and provides a tool to the EFSA NDA Panel to assess the selection procedure. A separate Endnote™ library will be made containing the excluded articles together with the reasons for exclusion and information from which database/source the article was retrieved.

3. *Screening during data-extraction phase*

   Further scrutiny of the article during the data-extraction phase might lead to exclusion. For example:

   - From articles presenting similar results from identical datasets, only one will be included. Usually this will be the most recently published article, except when this article presents too limited information.
   - Meta-analysis or good quality systematic reviews will be indexed in a separate Endnote folder. The reference lists will be checked for relevant articles that may have been missed with our search. If this is the case, these original articles will be included (see also under "Hand search").

The screening and selection of full text articles with also be recorded using EndNote™. In this way, transparency will be maintained at all phases and a tool will be provided for the EFSA NDA Panel to retrospectively assess the selection procedure. First, a preliminary Endnote file will be provided to EFSA for reviewing. After discussing and adapting this where needed, a final Endnote™ file will be delivered.

A final list of exclusion criteria applied in all steps of the selection procedure will be reported in the final report. Furthermore, the contractor will report the exclusion reasons per reference for papers excluded during all selection steps.

The results of the different selection steps will be represented in a flow-chart in the final report. In Figure 1, an example of this schematic representation of the selection procedure is shown, with an estimated number of hits and included articles for each selection step.

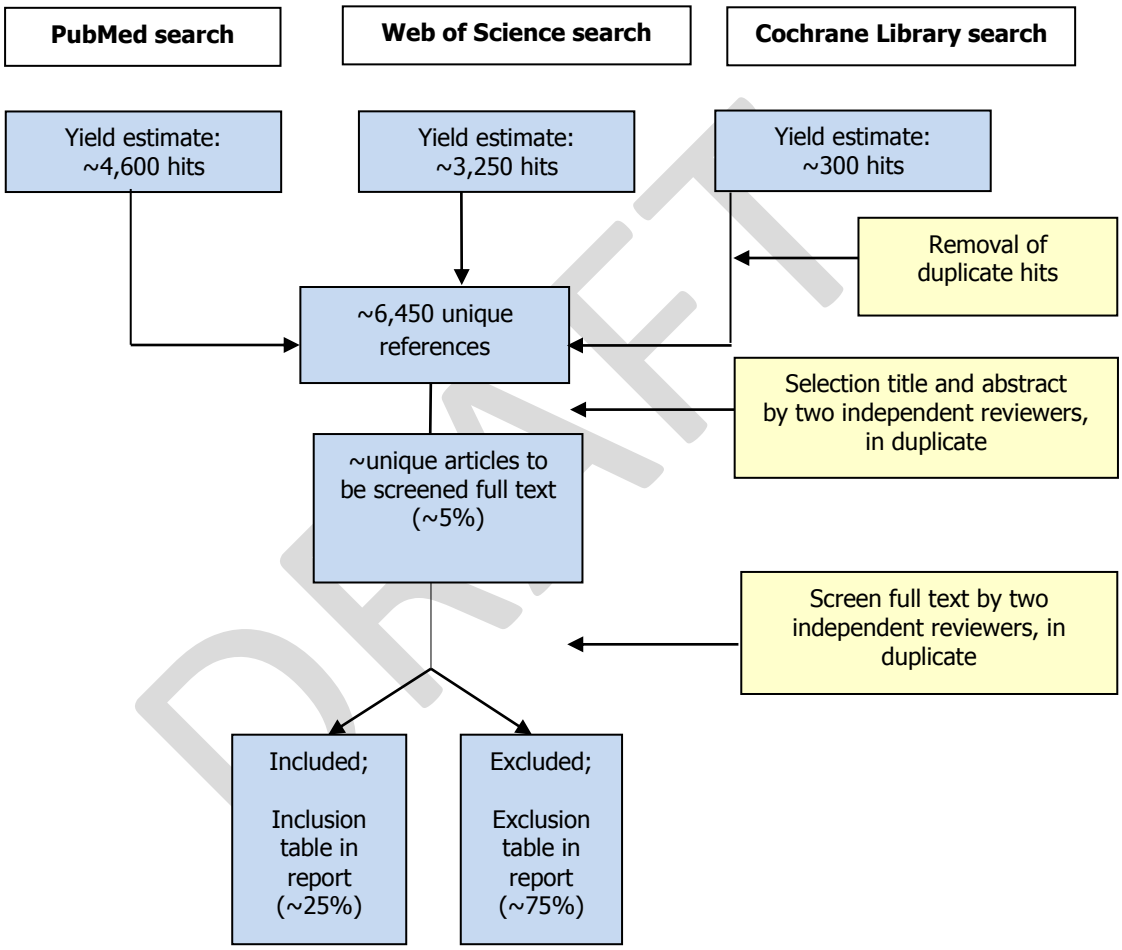

Figure 1: Selection procedure of papers based on number of hits in PubMed, Web of Science and the Cochrane Library

Hand search

During full text selection, the reference lists of relevant review articles and included studies will be checked for potentially relevant primary articles. With this, the contractor will update key references possibly missed by the search in the above-mentioned bibliographic databases. Articles included via hand search will be added to the Endnote™ file in a separate folder.

2.4. Grey literature

Grey literature is defined as information produced on all levels of government, academia, business and industry in electronic and print formats not controlled by commercial publishing i.e. 'where publishing

is not the primary activity of the producing body'. A search in grey literature can be useful for example when data from peer-reviewed articles are inconsistent or lacking. In addition to the peer-reviewed literature search, the contractor will therefore also perform a grey literature search in data sources that are not peer-reviewed to find relevant information to the research objectives.

The consortium will search in three databases for grey literature:

- www.ntis.gov: The National Technical Information Service (NTIS) provides access to the results of both US and non-US government-sponsored research and can provide the full text of the technical report for most of the results retrieved.
- www.opengrey.eu: System for Information on Grey Literature in Europe, open access to 700.000 bibliographical references of grey literature (paper) produced in Europe.
- Biosis Previews: a database containing also non-journal coverage, such as meeting abstracts, conferences, book chapters, notes, letters, and selected reports on health related subjects.
- Open Access Theses and Dissertations, https://oatd.org/: a database for finding open access graduate theses and dissertations published around the world.

The search will be based on the following key-words: complementary feeding, infant diet, infant nutrition. Date and time of the search will be recorded.

From the above mentioned databases, the following sources relevant for collecting data will be listed:

- Scientific reports (e.g. reports from the European Commission, national Health Ministries, UNICEF or World Health Organisation)
- Conference abstracts or posters or dissertations published since 2011
- Non-peer reviewed reports (e.g. reports from national health institutes, governmental documents and statistics)
- Evidence-based guidelines (see below)

For conference abstracts, posters or dissertations, a time limit will be put into place because good quality and relevant scientific data acquired before 2011 should have been published in peer-reviewed literature.

In the collected grey literature, references will also be checked for relevant peer-reviewed articles that may have been missed via the systematic literature search in bibliographic databases.

Evidence-based guidelines

An additional search will be conducted in Google to find international and national evidence-based guidelines on infant nutrition. The search for guidelines will at least include the website of the US National Guideline Clearinghouse. This website contains guidelines developed by organisations such as NICE and SIGN. Also, guidelines may be available from international organisations such as The European Paediatric Association (EPA), The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), American Academy of Pediatrics (AAP), UNICEF, WHO. The search terms complementary feeding, infant diet, and infant nutrition will be used to find potentially relevant guidelines. Date and time of the search will be recorded.

The AGREE II tool[1] will be used for the quality assessment of guidelines found via the search. Inclusion or exclusion of a guideline will be based on a stepwise approach. In a first step, guidelines will be included or excluded primarily based on three main criteria from the AGREE II tool, i.e.:

1. The overall objective(s) of the guideline is (are) specifically described.

[1] http://www.agreetrust.org/

2. Systematic methods were used to search for scientific evidence, and clearly described.
3. The recommendations are specific and unambiguous.

In case of doubt on the quality of a guideline, a guideline will be assessed on all 23 criteria from the AGREE II tool and thereafter included or excluded.

Recommendations presented in the guidelines can be evidence-based (EB), practice-based (PB), or a combination of both. EB recommendations are exclusively based on the scientific literature and not on good clinical practices or expert opinions. PB recommendations are not based on scientific evidence and reflect expert opinion or information derived from good clinical practices. For this project, EB-guidelines and recommendations that are a combination of EB and PB will be included. If more than one version of a guideline is available, the most comprehensive up-to-date version will be included.

A list will be prepared with relevant evidence-based guidelines, focussing on infants representative of infants living in EU/EEA countries. Guidelines for malnourished or vulnerable infants will not be selected.

2.5. Quality control during selection

The following quality control measures will be put in place:

- Selection of title and abstract will be executed by two reviewers independently from each other; all references will be screened in duplicate. After the first 20%, the results will be compared and discussed and in case of persistent disagreements, references will always be included for full text assessment. In case of doubts on references covering the scope of the review, the contractor will contact EFSA for agreement.
- Screening and critical appraisal of full text articles will be executed by two independent reviewers from Pallas; all full texts will be screened in duplicate. After the first 20%, the results will be compared and discussed, and this will be repeated after every 20% of screened articles during the screening process. Any disagreements will be adjudicated by a third (senior) reviewer if necessary. In case of persistent doubts, the eligibility of the article will be discussed with an advisory expert of WUR and EFSA.

3. Assessment of the reliability of included studies

Each study will be assessed with respect to its risk of bias at the outcome level and by considering specific features of the study design. The assessment of individual bias domains will rely on the criteria proposed by the Cochrane Collaboration risk of bias tools for randomised controlled trials (RCTs) (i.e. individually randomized and cluster randomized parallel group trials)[2], and for non-randomised studies of interventions and observational studies (Sterne et al., 2016)[2].

A summary of the items that will be considered when assessing the risk of bias in RCTs and non-randomised studies of interventions studies are given in Appendix B.

In this context it should be mentioned that, in RCTs conducted to assess the impact of the timing of introduction of complementary feeding into an infant's diet on a particular outcome, the intervention cannot be blinded to caregivers, so that blinding would be limited to the outcome assessors. Therefore, the item referring to the blinding of the intervention to study participants and caregivers in the risk of bias tool to be used for RCTs will not be assessed in this context and will be labelled as not being applicable in the evaluation of the risk of bias for individual studies. The impact of caregivers not being blinded to the intervention on the risk of bias, however, will be considered and discussed at the level of the body of evidence.

[2] Available at: https://sites.google.com/site/riskofbiastool/

Systematic reviews and meta-analyses will be assessed using the ROBIS tool without further modifications (Whiting et al., 2016).

The information included in the publication which supports the conclusions of the reviewers on each of the items in the risk of bias assessment will be documented and will be published alongside the assessment as part of the overall scientific evaluation.

For each of the domains assessed for an outcome in RCTs, the response options will be the following:

	Low risk of bias
	Some concerns
	High risk of bias

For each outcome of interest assessed in RCTs, the overall risk of bias judgment will be performed as follows:

	Overall risk of bias judgement	**Criteria**
	Low risk of bias	The study is judged to be at low risk of bias for all domains for this outcome.
	Some concerns	The study is judged to be at some concerns in at least one domain for this outcome.
	High risk of bias	The study is judged to be at high risk of bias in at least one domain for this outcome. Or The study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the outcome.

For each of the domains assessed for an outcome in non-randomised studies of interventions and observational studies, the response options will be the following:

	Low risk of bias	The study is comparable to a well-performed randomized trial with regard to this domain
	Moderate risk of bias	The study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial
	Serious risk of bias	The study has some important problems in this domain
	Critical risk of bias	The study is too problematic in this domain to provide any useful evidence on the effects of intervention
	No information	No information on which to base a judgement about risk of bias for this domain

For each outcome of interest assessed in non-randomised studies of interventions and observational studies, the overall risk of bias judgment will be performed as follows:

	Overall risk of bias judgement	**Criteria**
	Low risk of bias	The study is judged to be at low risk of bias for all domains for this outcome
	Moderate risk of bias	The study is judged to be at low or moderate risk of bias for all domains for this outcome.

	Serious risk of bias	The study is judged to be at serious risk of bias in at least one domain for this outcome, but not at critical risk of bias in any domain.
	Critical risk of bias	The study is judged to be at critical risk of bias in at least one domain for this outcome.
	No information	There is no clear indication that the study is at serious or critical risk of bias for this outcome and there is a lack of information in one or more key domains of bias.

For each outcome variable, studies classified into the category of being at high risk of bias will not be excluded *a priori* from scientific evaluation as they may provide supportive evidence. Whether or not these studies can be further used in the scientific assessment process will be decided on a case-by-case basis by the NDA Panel and its WG on Infant Nutrition depending on the type of bias and/or the type and amount of data available for the outcome.

The assessment of the risk of bias of the studies/systematic reviews/meta-analyses will be done independently by two expert reviewers (i.e. WG members and EFSA senior scientific staff). If a discrepancy in the assessment occurs and cannot be resolved through discussion among the two reviewers, a third expert reviewer will be involved to facilitate decisions. In case no decision can be reached, the more conservative assessment will be taken over. In case additional expert judgment is needed to conclude on the assessment of a specific item (e.g. on the appropriateness of the methods used to measure/assess a certain outcome), expert reviewers may consult experts in the field in order to reach a conclusion.

MS Excel or Distiller SR will be used to document the ratings for each individual study.

The assessment of the precision of a study will not be part of the risk of bias assessment, but will rather be considered in the overall scientific assessment process.

4. Data extraction from relevant studies

As it is not planned to perform any quantitative data synthesis during the scientific assessment process, the data extraction will serve the only purpose of summarising the results of the studies considered pertinent in order not to overload the core of the scientific opinion with detail.

The step of extracting data from relevant studies will only be conducted after the studies have been assessed for their reliability and a decision has been made on which ones are to be included in the scientific assessment.

For studies with multiple arms, only information pertaining to the relevant study arms will be extracted. In case more than two study arms are relevant, the data sheets will be adapted accordingly for the particular study in order to accommodate the information. Data will be extracted in the original units and units will be indicated in the data sheets. In case recalculation will be necessary in order to make the data more comparable, a separate line will be included in the data sheets in order to allow the reporting of both the original and the transformed data.

Data extraction from each article will be carried out by two reviewers (members of the WG on Infant nutrition and EFSA staff members), one extracting the data and the other checking for accuracy and completeness (i.e. sequential review). If non-resolvable discrepancies occur between the two reviewers, a third reviewer will be asked for an opinion. In order to have a common understanding on the information to be extracted, the data extraction exercise will be piloted on a subset of the data and the outcome will be discussed by all reviewers (NTP, 2015).

It is not planned to gather **missing data** from the authors of publications on a systematic basis, unless it relates to key information on a pivotal study for the assessment.

The **elements which are proposed to be extracted** from each publication are listed in Table 2. In case it appears necessary during the assessment process that amendments are made to that list, the additional information will be extracted for all studies. Such a change in protocol will be reported as protocol deviation in the final opinion, and the type of change will be outlined.

The data will be extracted into an MS Excel file or by using Distiller SR.

402 **Table 2:** Information included in the data extraction sheets

Study		
	Study group	**Comparison group**
Endpoint		
Age at which the endpoint was assessed		
Method by which the endpoint was assessed		
Study design		
Population		
Location		
N		
Inclusion criteria		
Exclusion criteria		
Type of milk feed		
Breast-feeding ever/never		
Breast-feeding duration		
Timing of introduction of complementary foods		
Type of food		
Data collection tool		
Length of follow-up		
N lost to follow-up		
Handling of missing data		
Statistical analysis		
Power calculation		
Confounders for which the analysis was adjusted for		
Point estimate of the index (adjusted model(s))		
Measure of spread (adjusted model(s))		
p-value, if appropriate		

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404 If systematic reviews and meta-analyses of sufficient quality clearly address the same research
405 question as the present systematic review and report on all items relevant for the subsequent
406 scientific assessment (and thus can be used in the assessment as such), data from the individual
407 studies included in these publications will not be extracted, but reference will be made to the
408 systematic review and meta-analysis in question.

409 5. Plans for updating the literature search

410 The literature search will be updated once before the release of the Scientific Opinion of the NDA
411 Panel for public consultation, and once before the final adoption of the Opinion. The timeframe will be
412 chosen so that both the WG on Infant Nutrition and the NDA Panel have sufficient time to review and
413 assess the additional evidence. This will be done by EFSA staff. Databases and keywords will be those
414 of the original search. Date limits will be defined based on the cut-off date of the preceding search. All
415 other steps described in the present protocol will then be applied to the retrieved studies/systematic
416 reviews/meta-analyses.

417

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456 # Abbreviations

AGREE	Appraisal of Guidelines for Research and Evaluation
APP	American Academy of Pediatrics
Distiller SR	Distiller software for systematic reviews
EB	Evidence based
EEA	European Economic Area
EFSA	European Food Safety Authority
ELS	Extensive literature search
EPA	European Paediatric Association
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
EU	European Union
IYCF	Infant and Young Child Formula
MS Excel	Microsoft Excel
NDA Panel	EFSA's expert panel on Dietetic Products, Nutrition and Allergies
NICE	National Institute for Health and Care Excellence
NTIS	National Technical Information Service
PB	Practice based
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised controlled trial
ROBIS	Risk of Bias in Systematic Reviews
SIGN	Scottish Intercollegiate Guidelines Network
UNICEF	United Nations Children's Fund (formerly United Nations International Children's Emergency Fund)
US	United States
WG	Working group
WHO	World Health Organisation
WUR	Wageningen University and Research

457

Appendix A – Search strings

458

459 **PubMed search strings**

460 Search strings will be combined as: (#1 AND #2 AND #3 AND #4) NOT (#5 OR #6 OR #7), with time
461 limit 1990-current

462 **#1 Search string infants**

463 "Infant"[mh:noexp] OR infan*[tiab] OR young child*[tiab] OR baby[tiab] OR babies[tiab] OR early
464 childhood[tiab] OR weanling*[tiab]

465 **AND**

466 **#2 Search string complementary feeding**

467 "Infant Nutritional Physiological Phenomena"[Mesh:NoExp] OR "Infant Food"[Mesh:NoExp] OR
468 "Weaning"[Mesh] OR wean*[tiab] OR diet[tiab] OR nutrition*[tiab] OR food*[tiab] OR feeding[tiab]
469 OR beikost[tiab] OR "partial breast-feeding"[tiab] OR "partial breastfeeding"[tiab] OR "non-exclusive
470 breast-feeding"[tiab] OR "non-exclusive breastfeeding"[tiab] OR "mixed breast-feeding"[tiab] OR
471 "mixed breastfeeding"[tiab] OR fruit*[tiab] OR vegetable*[tiab] OR cereal*[tiab] OR wheat[tiab] OR
472 egg*[tiab] OR peanut*[tiab] OR fish[tiab] OR shellfish[tiab] OR porridge[tiab] OR rice[tiab] OR
473 meat[tiab] OR bread[tiab] OR juice[tiab] OR corn[tiab] OR IYCF[tiab]

474 **AND**

475 **#3 Search string introduction**

476 introduction[tiab] OR introduce*[tiab] OR introducing[tiab] OR start*[tiab] OR beginning[tiab]

477 **AND**

478 **#4 Search string age of introduction**

479 time[tiab] OR timing[tiab] OR moment[tiab] OR duration[tiab] OR age[tiab] OR month[tiab] OR
480 months[tiab] OR early[tiab] OR week[tiab] OR weeks[tiab] OR year[tiab] OR years[tiab] OR day[tiab]
481 OR days[tiab]

482 **NOT**

483 **#5 Search string excluding letters, editorials, comments, case reports (combine with**
484 **NOT)**

485 Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Clinical Conference[ptyp] OR pubmed
486 books[filter] OR Comment[sb] OR "Cross-Sectional Studies"[Mesh] OR "Retrospective studies"[Mesh]
487 OR "retrospective cohort"[tiab] OR "retrospective analysis"[tiab]

488 **#6 Search string animals (combine with NOT)**

489 Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh])

490 **#7 Search string to exclude non-EU low income and low-middle income countries**
491 **according to World Bank (combine with NOT)**

(Afghanistan*[tiab] OR Benin*[tiab] OR Burkina Faso[tiab] OR Burund*[tiab] OR Central African Republic[tiab] OR Republique Centrafricaine[tiab] OR Chad*[tiab] OR Comoros[tiab] OR Congo*[tiab] OR Eritrea[tiab] OR Ethiopi*[tiab] OR Gambia[tiab] OR Guinea[tiab] OR Guinean[tiab] OR Guinée[tiab] OR Guinea-Bissau[tiab] OR Guinea Bissau[tiab] OR Guinée Bissau[tiab] OR Haiti*[tiab] OR Korea*[tiab] OR Liberia*[tiab] OR Madagascar*[tiab] OR Malawi*[tiab] OR Mali[tiab] OR Malian[tiab] OR Mozambiqu*[tiab] OR Nepal[tiab] OR Niger[tiab] OR Rwand*[tiab] OR Senegal*[tiab] OR "Sierra Leone"[tiab] OR Somali*[tiab] OR Sudan*[tiab] OR Tanzani*[tiab] OR Togo[tiab] OR Togolese[tiab] OR Ugand*[tiab] OR Zimbabw*[tiab] OR Armenia*[tiab] OR Banglades*[tiab] OR Bhutan[tiab] OR Bolivia[tiab] OR "Cabo Verde"[tiab] OR "Cape Verde"[tiab] OR Cambodia*[tiab] OR Cameroon*[tiab] OR Congo[tiab] OR "Cote D'Ivoire"[tiab] OR "Ivory Coast"[tiab] OR Djibout*[tiab] OR Egypt*[tiab] OR "El Salvador"[tiab] OR Ghana*[tiab] OR Guatemala[tiab] OR Honduras[tiab] OR India*[tiab] OR Indonesia*[tiab] OR Keny*[tiab] OR Kiribati[tiab] OR Kyrgyzstan*[tiab] OR "Kyrgyz Republic"[tiab] OR Lao*[tiab] OR Lesotho*[tiab] OR Mauritania*[tiab] OR Mauritius[tiab] OR Mauritian*[tiab] OR Micronesi*[tiab] OR Mongolia*[tiab] OR Morocc*[tiab] OR Burma[tiab] OR Myanmar[tiab] OR Nicaragua*[tiab] OR Nigeria*[tiab] OR Pakistan*[tiab] OR "Papua New Guinea"[tiab] OR Philippine*[tiab] OR Samoa[tiab] OR "São Tomé and Principe"[tiab] OR "São Tomé e Príncipe"[tiab] OR Solomon Island*[tiab] OR Sri Lanka[tiab] OR Sudan*[tiab] OR Swazi*[tiab] OR Syria*[tiab] OR Tajikistan*[tiab] OR Timor-Leste[tiab] OR Tonga[tiab] OR Tunisia*[tiab] OR Uzbekistan*[tiab] OR Vanuatu*[tiab] OR Vietnam*[tiab] OR "West Bank"[tiab] OR Gaza[tiab] OR Yemen*[tiab] OR Zambia*[tiab]) NOT ((Afghanistan*[tiab] OR Benin*[tiab] OR Burkina Faso[tiab] OR Burund*[tiab] OR Central African Republic[tiab] OR Republique Centrafricaine[tiab] OR Chad*[tiab] OR Comoros[tiab] OR Congo*[tiab] OR Eritrea[tiab] OR Ethiopi*[tiab] OR Gambia[tiab] OR Guinea[tiab] OR Guinean[tiab] OR Guinée[tiab] OR Guinea-Bissau[tiab] OR Guinea Bissau[tiab] OR Guinée Bissau[tiab] OR Haiti*[tiab] OR Korea*[tiab] OR Liberia*[tiab] OR Madagascar*[tiab] OR Malawi*[tiab] OR Mali[tiab] OR Malian[tiab] OR Mozambiqu*[tiab] OR Nepal[tiab] OR Niger[tiab] OR Rwand*[tiab] OR Senegal*[tiab] OR "Sierra Leone"[tiab] OR Somali*[tiab] OR Sudan*[tiab] OR Tanzani*[tiab] OR Togo[tiab] OR Togolese[tiab] OR Ugand*[tiab] OR Zimbabw*[tiab] OR Armenia*[tiab] OR Banglades*[tiab] OR Bhutan[tiab] OR Bolivia[tiab] OR "Cabo Verde"[tiab] OR "Cape Verde"[tiab] OR Cambodia*[tiab] OR Cameroon*[tiab] OR Congo[tiab] OR "Cote D'Ivoire"[tiab] OR "Ivory Coast"[tiab] OR Djibout*[tiab] OR Egypt*[tiab] OR "El Salvador"[tiab] OR Ghana*[tiab] OR Guatemala[tiab] OR Honduras[tiab] OR India*[tiab] OR Indonesia*[tiab] OR Keny*[tiab] OR Kiribati[tiab] OR Kyrgyzstan*[tiab] OR "Kyrgyz Republic"[tiab] OR Lao*[tiab] OR Lesotho*[tiab] OR Mauritania*[tiab] OR Mauritius[tiab] OR Mauritian*[tiab] OR Micronesi*[tiab] OR Mongolia*[tiab] OR Morocc*[tiab] OR Burma[tiab] OR Myanmar[tiab] OR Nicaragua*[tiab] OR Nigeria*[tiab] OR Pakistan*[tiab] OR "Papua New Guinea"[tiab] OR Philippine*[tiab] OR Samoa[tiab] OR "São Tomé and Principe"[tiab] OR "São Tomé e Príncipe"[tiab] OR Solomon Island*[tiab] OR Sri Lanka[tiab] OR Sudan*[tiab] OR Swazi*[tiab] OR Syria*[tiab] OR Tajikistan*[tiab] OR Timor-Leste[tiab] OR Tonga[tiab] OR Tunisia*[tiab] OR Uzbekistan*[tiab] OR Vanuatu*[tiab] OR Vietnam*[tiab] OR "West Bank"[tiab] OR Gaza[tiab] OR Yemen*[tiab] OR Zambia*[tiab]) AND (Europe[MeSH] OR Europe*[tw] OR Scandinavia* [tw] OR Mediterranean[tw] OR Baltic[tw] OR Andorra*[tw] OR Azerbaijan*[tw] OR Albania*[tw] OR Armenia*[tw] OR Austria*[tw] OR Belarus*[tw] OR Byelarus*[tw] OR Bosni*[tw] OR Herzegovin*[tw] OR Croat*[tw] OR Cyprus[tw] OR Cypriot*[tw] OR Czech[tw] OR Belgi*[tw] OR Bulgaria*[tw] OR Denmark[tw] OR Danish[tw] OR Estonia*[tw] OR Finland[tw] OR Finnish[tw] OR France*[tw] OR French*[tw] OR Georgia*[tw] OR German*[tw] OR Greece[tw] OR Greek[tw] OR Hungar*[tw] OR Iceland*[tw] OR Ital*[tw] OR Sicil*[tw] OR Sardinia*[tw] OR Latvi*[tw] OR Liechtenstein*[tw] OR Lithuania*[tw] OR Luxembourg*[tw] OR Macedonia*[tw] OR Malta[tw] OR Maltese[tw] OR Moldova*[tw] OR Monaco[tw] OR Montenegr*[tw] OR Netherlands[tw] OR Dutch[tw] OR Norway[tw] OR Norwegian*[tw] or Svalbard*[tw] OR Poland*[tw] OR Polish*[tw] OR Portugal[tw] OR Portuguese[tw] OR Romania*[tw] OR Roumania*[tw] OR Rumania*[tw] OR San Marino[tw] OR Serb*[tw] OR Slovak*[tw] OR Slovenia*[tw] OR Spain*[tw] OR Spanish*[tw] OR Sweden[tw] OR

Swedish[tw] OR Switzerland[tw] OR Swiss[tw] OR Great Britain*[tw] OR British*[tw] OR Channel Islands*[tw] OR Guerns*[tw] OR England*[tw] OR English*[tw] OR Hebrid*[tw] OR Ireland*[tw] OR Irish*[tw] OR Scotland*[tw] OR Scotch*[tw] OR Scottish*[tw] OR Wales*[tw] OR Welsh*[tw] OR United Kingdom*[tw] OR UK[tw] OR Gibraltar[tw] OR Ukrain*[tw] OR Vatican[tw] OR Yugoslavia*[tw]))

Web of Science search strings

#1 Search string children

TOPIC: (infan* OR "young child*" OR baby OR babies OR "early childhood" OR weanling*)

AND

#2 Search string complementary feeding

TOPIC: (diet OR nutrition OR food* OR wean* OR feeding OR IYCF OR "partial breast-feeding" OR "partial breastfeeding" OR "non-exclusive breast-feeding" OR "non-exclusive breastfeeding" OR "mixed breast-feeding" OR "mixed breastfeeding" OR fruit* OR vegetable* OR cereal* OR wheat OR egg* OR peanut* OR shellfish OR porridge OR rice OR meat OR bread OR juice OR corn)

AND

#3 Search string timing complementary feeding

TOPIC: (introduction OR introduce* OR introducing OR start OR beginning)

NEAR

#4 Search string age of introduction

TOPIC: (time OR timing OR moment OR duration OR age OR month OR months OR early OR week OR weeks OR year OR years OR day OR days)

NOT

Limits for Document Types (include these Types): Article OR Correction OR Database Review OR Proceedings Paper OR Reprint OR Review

#5 Search string to exclude non-EU low income and low-middle income countries according to World Bank (combine with NOT)

TOPIC: ((Afghanistan* OR Benin* OR Burkina Faso OR Burund* OR Central African Republic OR Republique Centrafricaine OR Chad* OR Comoros OR Congo* OR Eritrea OR Ethiopi* OR Gambia* OR Guinea OR Guinée OR Guinea-Bissau OR Guinea Bissau OR Guinée Bissau OR Haiti* OR Korea* OR Liberia* OR Madagascar* OR Malawi* OR Mali OR Malian OR Mozambiqu* OR Nepal* OR Niger OR Rwand* OR Senegal* OR "Sierra Leone" OR Somali* OR Sudan* OR Tanzani* OR Togo OR Togolese OR Ugand* OR Zimbabw*) OR (Armenia* OR Banglades* OR Bhutan OR Bolivia OR "Cabo Verde" OR "Cape Verde" OR Cambodia* OR Cameroon* OR Congo OR "Cote D'Ivoire" OR "Ivory Coast" OR Djibout* OR Egypt* OR "El Salvador" OR Ghana* OR Guatemala OR Honduras OR India* OR Indonesia* OR Keny* OR Kiribati OR Kyrgyzstan* OR "Kyrgyz Republic" OR Lao* OR Lesotho* OR Mauritania* OR Mauritius OR Mauritian* OR Micronesi* OR Mongolia* OR Morocc* OR Burma OR Myanmar OR Nicaragua* OR Nigeria* OR Pakistan* OR "Papua New Guinea" OR Philippine* OR Samoa OR "São Tomé and Principe" OR "São Tomé e Príncipe" OR Solomon Island* OR Sri Lanka OR Sudan* OR Swazi* OR Syria* OR Tajikistan* OR Timor-Leste OR Tonga OR Tunisia* OR Uzbekistan* OR Vanuatu* OR Vietnam* OR "West Bank" OR Gaza OR Yemen* OR Zambia*) NOT ((Afghanistan* OR Benin* OR Burkina Faso OR Burund* OR Central African Republic OR Republique Centrafricaine OR Chad* OR Comoros OR Congo* OR Eritrea OR Ethiopi* OR Gambia* OR Guinea OR Guinée OR Guinea-Bissau OR Guinea Bissau OR Guinée Bissau OR Haiti* OR Korea* OR Liberia* OR Madagascar* OR Malawi* OR Mali OR Malian OR Mozambiqu* OR Nepal* OR Niger OR Rwand* OR Senegal* OR

"Sierra Leone" OR Somali* OR Sudan* OR Tanzani* OR Togo OR Togolese OR Ugand* OR Zimbabw*) OR (Armenia* OR Banglades* OR Bhutan OR Bolivia OR "Cabo Verde" OR "Cape Verde" OR Cambodia* OR Cameroon* OR Congo OR "Cote D'Ivoire" OR "Ivory Coast" OR Djibout* OR Egypt* OR "El Salvador" OR Ghana* OR Guatemala OR Honduras OR India* OR Indonesia* OR Keny* OR Kiribati OR Kyrgyzstan* OR "Kyrgyz Republic" OR Lao* OR Lesotho* OR Mauritania* OR Mauritius OR Mauritian* OR Micronesi* OR Mongolia* OR Morocc* OR Burma OR Myanmar OR Nicaragua* OR Nigeria* OR Pakistan* OR "Papua New Guinea" OR Philippine* OR Samoa OR "São Tomé and Principe" OR "São Tomé e Príncipe" OR Solomon Island* OR Sri Lanka OR Sudan* OR Swazi* OR Syria* OR Tajikistan* OR Timor-Leste OR Tonga OR Tunisia* OR Uzbekistan* OR Vanuatu* OR Vietnam* OR "West Bank" OR Gaza OR Yemen* OR Zambia*) AND (Europe* OR Scandinavia* OR Mediterranean OR Baltic OR Andorra* OR Azerbaijan* OR Albania* OR Armenia* OR Austria* OR Belarus* OR Byelarus* OR Bosni* OR Herzegovin* OR Croat* OR Cyprus OR Cypriot* OR Czech OR Belgi* OR Bulgaria* OR Denmark OR Danish OR Estonia* OR Finland OR Finnish OR France* OR French* OR Georgia* OR German* OR Greece OR Greek OR Hungar* OR Iceland* OR Ital* OR Sicil* OR Sardinia* OR Latvi* OR Liechtenstein* OR Lithuania* OR Luxembourg* OR Macedonia* OR Malta OR Maltese OR Moldova* OR Monaco OR Montenegr* OR Netherlands OR Dutch OR Norway OR Norwegian* or Svalbard* OR Poland* OR Polish* OR Portugal OR Portuguese OR Romania* OR Roumania* OR Rumania* OR San Marino OR Serb* OR Slovak* OR Slovenia* OR Spain* OR Spanish* OR Sweden OR Swedish OR Switzerland OR Swiss OR Great Britain* OR British* OR Channel Islands* OR Guerns* OR England* OR English* OR Hebrid* OR Ireland* OR Irish* OR Scotland* OR Scotch* OR Scottish* OR Wales* OR Welsh* OR United Kingdom* OR UK OR Gibraltar OR Ukrain* OR Vatican OR Yugoslavia*)))

Cochrane library search strings

Search strings will be combined as: (#1 AND #2 AND (#3 NEAR #4) NOT (#5), with limit for document types and time limit 1990-current

#1 Search string children

"Infant"[mh:noexp] OR infan*:ti,ab OR young child*:ti,ab OR baby:ti,ab OR babies:ti,ab OR early childhood:ti,ab OR weanling*:ti,ab

AND

#2 Search string complementary feeding

Infant Nutritional Physiological Phenomena"[Mesh:NoExp] OR "Infant Food"[Mesh:NoExp] "Weaning"[Mesh] OR diet:ti,ab OR nutrition:ti,ab OR food*:ti,ab OR feeding:ti,ab OR wean*:ti,ab OR "partial breast-feeding":ti,ab OR "partial breastfeeding":ti,ab OR "non-exclusive breast-feeding":ti,ab OR "non-exclusive breastfeeding":ti,ab OR "mixed breast-feeding":ti,ab OR "mixed breastfeeding":ti,ab OR fruit*:ti,ab OR vegetable*:ti,ab OR cereal*:ti,ab OR wheat:ti,ab OR egg*:ti,ab OR peanut*:ti,ab OR shellfish:ti,ab OR porridge:ti,ab OR rice:ti,ab OR meat:ti,ab OR bread:ti,ab OR juice:ti,ab OR corn:ti,ab OR IYCF:ti,ab OR "young child feeding":ti,ab

AND

#3 Search string timing complementary feeding

introduction:ti,ab OR introduce*:ti,ab OR introducing:ti,ab OR start:ti,ab OR beginning:ti,ab

NEAR

#4 Search string age of introduction

time:ti,ab OR timing:ti,ab OR moment:ti,ab OR duration:ti,ab OR age:ti,ab OR month:ti,ab OR months:ti,ab OR early:ti,ab OR week:ti,ab OR weeks:ti,ab OR year:ti,ab OR years:ti,ab OR day:ti,ab OR days:ti,ab

NOT

#5 Search string to exclude non-EU low income and low-middle income countries according to World Bank

(Afghanistan*:ti,ab OR Benin*:ti,ab OR Burkina Faso:ti,ab OR Burund*:ti,ab OR Central African Republic:ti,ab OR Republique Centrafricaine:ti,ab OR Chad*:ti,ab OR Comoros:ti,ab OR Congo*:ti,ab OR Eritrea:ti,ab OR Ethiopi*:ti,ab OR Gambia:ti,ab OR Guinea:ti,ab OR Guinean:ti,ab OR Guinée:ti,ab OR Guinea-Bissau:ti,ab OR Guinea Bissau:ti,ab OR Guinée Bissau:ti,ab OR Haiti*:ti,ab OR Korea*:ti,ab OR Liberia*:ti,ab OR Madagascar*:ti,ab OR Malawi*:ti,ab OR Mali:ti,ab OR Malian:ti,ab OR Mozambiqu*:ti,ab OR Nepal:ti,ab OR Niger:ti,ab OR Rwand*:ti,ab OR Senegal*:ti,ab OR "Sierra Leone":ti,ab OR Somali*:ti,ab OR Sudan*:ti,ab OR Tanzani*:ti,ab OR Togo:ti,ab OR Togolese:ti,ab OR Ugand*:ti,ab OR Zimbabw*:ti,ab OR Armenia*:ti,ab OR Banglades*:ti,ab OR Bhutan:ti,ab OR Bolivia:ti,ab OR "Cabo Verde":ti,ab OR "Cape Verde":ti,ab OR Cambodia*:ti,ab OR Cameroon*:ti,ab OR Congo:ti,ab OR "Cote D'Ivoire":ti,ab OR "Ivory Coast":ti,ab OR Djibout*:ti,ab OR Egypt*:ti,ab OR "El Salvador":ti,ab OR Ghana*:ti,ab OR Guatemala:ti,ab OR Honduras:ti,ab OR India*:ti,ab OR Indonesia*:ti,ab OR Keny*:ti,ab OR Kiribati:ti,ab OR Kyrgyzstan*:ti,ab OR "Kyrgyz Republic":ti,ab OR Lao*:ti,ab OR Lesotho*:ti,ab OR Mauritania*:ti,ab OR Mauritius:ti,ab OR Mauritian*:ti,ab OR Micronesi*:ti,ab OR Mongolia*:ti,ab OR Morocc*:ti,ab OR Burma:ti,ab OR Myanmar:ti,ab OR Nicaragua*:ti,ab OR Nigeria*:ti,ab OR Pakistan*:ti,ab OR "Papua New Guinea":ti,ab OR Philippine*:ti,ab OR Samoa:ti,ab OR "São Tomé and Principe":ti,ab OR "São Tomé e Príncipe":ti,ab OR Solomon Island*:ti,ab OR Sri Lanka:ti,ab OR Sudan*:ti,ab OR Swazi*:ti,ab OR Syria*:ti,ab OR Tajikistan*:ti,ab OR Timor-Leste:ti,ab OR Tonga:ti,ab OR Tunisia*:ti,ab OR Uzbekistan*:ti,ab OR Vanuatu*:ti,ab OR Vietnam*:ti,ab OR "West Bank":ti,ab OR Gaza:ti,ab OR Yemen*:ti,ab OR Zambia*:ti,ab) NOT ((Afghanistan*:ti,ab OR Benin*:ti,ab OR Burkina Faso:ti,ab OR Burund*:ti,ab OR Central African Republic:ti,ab OR Republique Centrafricaine:ti,ab OR Chad*:ti,ab OR Comoros:ti,ab OR Congo*:ti,ab OR Eritrea:ti,ab OR Ethiopi*:ti,ab OR Gambia:ti,ab OR Guinea:ti,ab OR Guinean:ti,ab OR Guinée:ti,ab OR Guinea-Bissau:ti,ab OR Guinea Bissau:ti,ab OR Guinée Bissau:ti,ab OR Haiti*:ti,ab OR Korea*:ti,ab OR Liberia*:ti,ab OR Madagascar*:ti,ab OR Malawi*:ti,ab OR Mali:ti,ab OR Malian:ti,ab OR Mozambiqu*:ti,ab OR Nepal:ti,ab OR Niger:ti,ab OR Rwand*:ti,ab OR Senegal*:ti,ab OR "Sierra Leone":ti,ab OR Somali*:ti,ab OR Sudan*:ti,ab OR Tanzani*:ti,ab OR Togo:ti,ab OR Togolese:ti,ab OR Ugand*:ti,ab OR Zimbabw*:ti,ab OR Armenia*:ti,ab OR Banglades*:ti,ab OR Bhutan:ti,ab OR Bolivia:ti,ab OR "Cabo Verde":ti,ab OR "Cape Verde":ti,ab OR Cambodia*:ti,ab OR Cameroon*:ti,ab OR Congo:ti,ab OR "Cote D'Ivoire":ti,ab OR "Ivory Coast":ti,ab OR Djibout*:ti,ab OR Egypt*:ti,ab OR "El Salvador":ti,ab OR Ghana*:ti,ab OR Guatemala:ti,ab OR Honduras:ti,ab OR India*:ti,ab OR Indonesia*:ti,ab OR Keny*:ti,ab OR Kiribati:ti,ab OR Kyrgyzstan*:ti,ab OR "Kyrgyz Republic":ti,ab OR Lao*:ti,ab OR Lesotho*:ti,ab OR Mauritania*:ti,ab OR Mauritius:ti,ab OR Mauritian*:ti,ab OR Micronesi*:ti,ab OR Mongolia*:ti,ab OR Morocc*:ti,ab OR Burma:ti,ab OR Myanmar:ti,ab OR Nicaragua*:ti,ab OR Nigeria*:ti,ab OR Pakistan*:ti,ab OR "Papua New Guinea":ti,ab OR Philippine*:ti,ab OR Samoa:ti,ab OR "São Tomé and Principe":ti,ab OR "São Tomé e Príncipe":ti,ab OR Solomon Island*:ti,ab OR Sri Lanka:ti,ab OR Sudan*:ti,ab OR Swazi*:ti,ab OR Syria*:ti,ab OR Tajikistan*:ti,ab OR Timor-Leste:ti,ab OR Tonga:ti,ab OR Tunisia*:ti,ab OR Uzbekistan*:ti,ab OR Vanuatu*:ti,ab OR Vietnam*:ti,ab OR "West Bank":ti,ab OR Gaza:ti,ab OR Yemen*:ti,ab OR Zambia*:ti,ab) AND (Europe*:ti,ab,kw OR Scandinavia* :ti,ab,kw OR Mediterranean:ti,ab,kw OR Baltic:ti,ab,kw OR Andorra*:ti,ab,kw OR Azerbaijan*:ti,ab,kw OR Albania*:ti,ab,kw OR Armenia*:ti,ab,kw OR Austria*:ti,ab,kw OR Belarus*:ti,ab,kw OR Byelarus*:ti,ab,kw OR Bosni*:ti,ab,kw OR Herzegovin*:ti,ab,kw OR Croat*:ti,ab,kw OR

678 Cyprus:ti,ab,kw OR Cypriot*:ti,ab,kw OR Czech:ti,ab,kw OR Belgi*:ti,ab,kw OR Bulgaria*:ti,ab,kw OR
679 Denmark:ti,ab,kw OR Danish:ti,ab,kw OR Estonia*:ti,ab,kw OR Finland:ti,ab,kw OR Finnish:ti,ab,kw
680 OR France*:ti,ab,kw OR French*:ti,ab,kw OR Georgia*:ti,ab,kw OR German*:ti,ab,kw OR
681 Greece:ti,ab,kw OR Greek:ti,ab,kw OR Hungar*:ti,ab,kw OR Iceland*:ti,ab,kw OR Ital*:ti,ab,kw OR
682 Sicil*:ti,ab,kw OR Sardinia*:ti,ab,kw OR Latvi*:ti,ab,kw OR Liechtenstein*:ti,ab,kw OR
683 Lithuania*:ti,ab,kw OR Luxembourg*:ti,ab,kw OR Macedonia*:ti,ab,kw OR Malta:ti,ab,kw OR
684 Maltese:ti,ab,kw OR Moldova*:ti,ab,kw OR Monaco:ti,ab,kw OR Montenegr*:ti,ab,kw OR
685 Netherlands:ti,ab,kw OR Dutch:ti,ab,kw OR Norway:ti,ab,kw OR Norwegian*:ti,ab,kw or
686 Svalbard*:ti,ab,kw OR Poland*:ti,ab,kw OR Polish*:ti,ab,kw OR Portugal:ti,ab,kw OR
687 Portuguese:ti,ab,kw OR Romania*:ti,ab,kw OR Roumania*:ti,ab,kw OR Rumania*:ti,ab,kw OR San
688 Marino:ti,ab,kw OR Serb*:ti,ab,kw OR Slovak*:ti,ab,kw OR Slovenia*:ti,ab,kw OR Spain*:ti,ab,kw OR
689 Spanish*:ti,ab,kw OR Sweden:ti,ab,kw OR Swedish:ti,ab,kw OR Switzerland:ti,ab,kw OR
690 Swiss:ti,ab,kw OR Great Britain*:ti,ab,kw OR British*:ti,ab,kw OR Channel Islands*:ti,ab,kw OR
691 Guerns*:ti,ab,kw OR England*:ti,ab,kw OR English*:ti,ab,kw OR Hebrid*:ti,ab,kw OR
692 Ireland*:ti,ab,kw OR Irish*:ti,ab,kw OR Scotland*:ti,ab,kw OR Scotch*:ti,ab,kw OR Scottish*:ti,ab,kw
693 OR Wales*:ti,ab,kw OR Welsh*:ti,ab,kw OR United Kingdom*:ti,ab,kw OR UK:ti,ab,kw OR
694 Gibraltar:ti,ab,kw OR Ukrain*:ti,ab,kw OR Vatican:ti,ab,kw OR Yugoslavia*:ti,ab,kw))

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Appendix B – Bias domains and examples of signalling questions to assess the risk of bias for RCTs and non-randomised studies of interventions

Please note that some signalling questions will be/will not be addressed depending on the answers given to previous signalling questions, to which these are conditional. The full risk of bias assessment tools can be found at: https://sites.google.com/site/riskofbiastool/

RCTs (individually randomized and cluster randomized parallel group trials)	**Non-randomised studies of interventions**
	Bias due to confounding
	Is there potential for confounding of the effect of intervention in this study?
	Was the analysis based on splitting participants' follow up time according to intervention received?
	Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?
	Did the authors use an appropriate analysis method that controlled for all the important confounding domains?
	Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?
	Did the authors control for any post-intervention variables that could have been affected by the intervention?
	Did the authors use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding?
	Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?
Bias arising from the randomization process	**Bias in selection of participants into the study**
Was the allocation sequence random?	Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?
Was the allocation sequence concealed until participants were recruited and assigned to interventions?	Do start of follow-up and start of intervention coincide for most participants?
Were there baseline imbalances that suggest a problem with the randomization process?	Were adjustment techniques used that are likely to correct for the presence of selection biases?
Bias arising from the timing of identification and recruitment of individual participants in relation to timing of randomization (for cluster randomized, parallel group trials)	**Bias in classification of interventions**
Were all the individual participants identified before randomization of clusters (and if the trial specifically recruited patients were they all recruited before randomisation of clusters)?	Were intervention groups clearly defined?
Is it likely that selection of individual participants was affected by knowledge of the intervention?	Was the information used to define intervention groups recorded at the start of the intervention?
Were there baseline imbalances that suggest differential identification or recruitment of individual participants between arms?	Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?
Bias due to deviations from intended interventions	**Bias due to deviations from intended interventions**
Were participants aware of their assigned intervention during the trial? – NOT APPLICABLE	
Were carers and trial personnel aware of participants' assigned intervention during the trial? - NOT APPLICABLE	
Were there deviations from the intended interventions beyond what would be expected in usual practice?	Were there deviations from the intended intervention beyond what would be expected in usual practice?
Were these deviations from intended interventions unbalanced between the two interventions and likely to have affected the outcome?	Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?

Was the intervention implemented successfully?	Were important co-interventions balanced across intervention groups?
Did study participants adhere to the assigned intervention regimen?	Was the intervention implemented successfully for most participants?
Were any participants/clusters analysed in a group different from the one to which they were assigned?	Did study participants adhere to the assigned intervention regimen?
Was there potential for a substantial impact (on the estimated effect of intervention) of analysing participants in the wrong group?	Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?
Bias due to missing outcome data	**Bias due to missing data**
Were outcome data available for all, or nearly all, participants/clusters randomized (and participants within clusters)?	Were outcome data available for all, or nearly all, participants?
Are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?	Were participants excluded due to missing data on intervention status?
Is there evidence that results were robust to the presence of missing outcome data?	Were participants excluded due to missing data on other variables needed for the analysis?
	Are the proportion of participants and reasons for missing data similar across interventions?
	Is there evidence that results were robust to the presence of missing data?
Bias in measurement of the outcome	**Bias in measurement of outcomes**
Were outcome assessors aware of the intervention received by study participants?	Could the outcome measure have been influenced by knowledge of the intervention received?
Was the assessment of the outcome likely to be influenced by knowledge of the intervention received?	Were outcome assessors aware of the intervention received by study participants?
	Were the methods of outcome assessment comparable across intervention groups?
	Were any systematic errors in measurement of the outcome related to intervention received?
Key question: Was the method used to assess the outcome appropriate?	**Key question:** Was the method used to assess the outcome appropriate?
Bias in selection of the reported result	**Bias in selection of the reported results**
Are the reported outcome data likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain or from multiple analyses of the data?	Are the reported outcome data likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain, from multiple analyses of the data or from different subgroups?

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