Toolkit of methodological resources to conduct systematic reviews [version 1; peer review: 2 approved with reservations]

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Abstract

Background: Systematic reviews (SR) can be classified by type depending on the research question they are based on. This work identifies and describes the most relevant methodological resources to conduct high-quality reviews that answer clinical questions regarding prevalence, prognosis, diagnostic accuracy and efficacy of interventions.

Methods: Methodological resources have been identified from literature searches and consulting guidelines from institutions that develop SRs. The selected resources are organized by type of SR, and stage of development of the review (formulation of the research question, development of the protocol, literature search, risk of bias assessment, synthesis of findings, assessment of the quality of evidence, and report of SR results and conclusions).

Results: Although the different types of SRs are developed following the same steps, each SR type requires specific methods, differing in characteristics and complexity. The extent of methodological development varies by type of SR, with more solid guidelines available for diagnostic accuracy and efficacy of interventions SRs. This methodological toolkit describes the most up-to-date risk of bias instruments: Quality in Prognostic Studies (QUIPS) tool and Prediction model study Risk Of Bias Assessment Tool (PROBAST) for prognostic SRs. Quality assessment of diagnostic accuracy studies tool (QUADAS-2) for diagnostic accuracy SRs, Cochrane risk of bias tool (ROB-2) and Risk of bias in non-randomised studies of interventions studies tool (ROBINS-I) for efficacy of interventions SRs, as well as the latest developments on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Conclusions: This structured compilation of the best methodological resources for each type of SR may prove to be a very useful tool for those researchers that wish to develop SRs or conduct methodological research works on SRs.
Keywords
Systematic reviews, prevalence, prognostic, diagnostic accuracy, efficacy of interventions

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Author roles: Roqué M: Conceptualization, Methodology, Project Administration, Writing – Original Draft Preparation, Writing – Review & Editing; Martinez-García L: Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; Solà I: Writing – Original Draft Preparation; Alonso-Coello P: Writing – Original Draft Preparation; Bonfill X: Writing – Original Draft Preparation; Zamora J: Conceptualization, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: Roqué M is supported by the Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP) as part of a Training Programme call for “Internal mobility: Internships in CIBERESP groups”, within the framework of the subprogramme 7.4 “Methodology, clinical records and scientific dissemination.” Martinez-García L has a Miguel Servet contract from the Institute of Health Carlos III [CP18/00007].

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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How to cite this article: Roqué M, Martinez-García L, Solà I et al. Toolkit of methodological resources to conduct systematic reviews [version 1; peer review: 2 approved with reservations] F1000Research 2020, 9:82 (https://doi.org/10.12688/f1000research.22032.1)

First published: 04 Feb 2020, 9:82 (https://doi.org/10.12688/f1000research.22032.1)
Introduction
Systematic reviews (SR) are studies that use a systematic and explicit method to identify, analyse and synthesize empirical evidence, and to answer a specific research question. Therefore, SRs are key tools to make informed health choices.

All SRs are based on a specific research question. Classic epidemiological research questions relate to the prevalence of a medical condition, the associated prognostic of the medical condition (including incidence or global prognosis, prognostic factors associated to the condition’s incidence or outcome, and risk profiles defined by prognostic models), diagnostic accuracy of tests that allow us to diagnose the medical condition, and efficacy of interventions to treat the medical condition. SRs can be classified by the type of research question they answer, as shown in Table 1.

The stages to develop an SR are common to all the types of SRs: 1) Formulating the research question, 2) development of the protocol that explicitly describes the methods to carry out each step of the SR, 3) literature search, 4) risk of bias assessment, 5) synthesis of findings, 6) assessment of the quality of evidence, and 7) report of SR results and conclusions. Although the different types of SRs share the same structure and follow a similar development process, their methods can be different and more or less complex depending on the type of SR.

Nowadays there are numerous methodological resources to conduct reviews, especially for intervention SRs and diagnostic SRs. However, the scattering of these resources and the lack of widely established manuals or recommendations are, in many situations, an obstacle to access them, especially for prevalence SRs and prognostic SRs. Therefore, the objective of this review is to identify and describe the methodological resources available to develop prevalence SRs, prognostic SRs, diagnostic accuracy SRs and efficacy of interventions SRs.

Methods
Information sources and search strategy
We consulted the guidelines from the main organizations that establish methods to conduct SRs (Cochrane, Joanna Briggs Institute, European Network for Health Technology Assessment (EUNETHTA), Enhancing the Quality and Transparency of Health Research (EQUATOR) network, Grading of Recommendations Assessment, Development and Evaluation (GRADE)) in order to identify their proposed resources.

Additionally, we performed a literature search in MEDLINE (accessed through PubMed) in November 2019 using the

Table 1. Research question by type of systematic review.

<table>
<thead>
<tr>
<th>Type of systematic review</th>
<th>Acronym for the research question</th>
<th>Example of research question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence review</td>
<td>CoCoPop-S (condition, context, population and study design)</td>
<td>What is the prevalence of frailty and prefrailty (condition) in community-dwelling older adults (population) living in low- and middle-income countries (context)?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>What is the worldwide (population) prevalence of insufficient physical activity (condition)?</td>
</tr>
<tr>
<td>Prognostic review - global prognosis</td>
<td>CoCoPop-S (condition, context, population and study design)</td>
<td>What is the incidence of dementia (condition) in individuals of at least 60 years of age (population) living in high-income countries (context)?</td>
</tr>
<tr>
<td>Prognostic review - prognostic factors</td>
<td>PICOT-S (population, intervention or factor, comparison, outcome, time and study design)</td>
<td>Is protease activity (prognostic factor) an independent prognostic factor for wound healing (outcome) at 24 weeks (timeframe) in people with venous leg ulcers (population)?</td>
</tr>
<tr>
<td></td>
<td>PFO-S (population, factor or model, outcome and study design)</td>
<td></td>
</tr>
<tr>
<td>Prognostic review - prognostic models</td>
<td>PICOT-S (population, intervention or factor, comparison, outcome, time and study design)</td>
<td>What is best prognostic model to predict overall or progression-free survival (outcome) in patients with chronic lymphocytic leukaemia (condition)?</td>
</tr>
<tr>
<td>Diag nostic accuracy review</td>
<td>PIRD-S (population, index test, reference test, diagnosis of interest and study design)</td>
<td>Do self-reported frailty to predict survival in adults with bacterial meningitis screening instruments (index test) accurately identify older people (population) at risk of frailty and prefrailty (condition of interest)?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Is PET 18F florbetapen (index test) useful in early diagnosing dementia (condition) in patients with mild cognitive impairment (population)?</td>
</tr>
<tr>
<td>Efficacy of intervention review</td>
<td>PICO-S (population, intervention, comparison, outcome of interest and study design)</td>
<td>What is the efficacy of ribavirin (intervention) in patients with Crimean Congo haemorrhagic fever to prevent death (outcome)?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Does comprehensive geriatric assessment (intervention) in older adults (population) reduce mortality (outcome)?</td>
</tr>
</tbody>
</table>

We also performed ad hoc scientific literature searches to find other resources for each type of SR in relation to the research question structure, the literature search strategy, the risk of bias assessment and the statistical analysis.

Eligibility criteria
We included the resources available to design prevalence SRs, prognostic SRs, diagnostic SRs and intervention SRs.

We excluded the methodological resources to develop other types of SRs (methodological, economic evaluation and qualitative research SRs).

Data selection and extraction
The authors are members of CIBERESP (Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública - Biomedical Research Center Network of Epidemiology and Public Health) and experts in different fields of knowledge (statistics, development of Cochrane reviews, research methodology, information retrieval, development of clinical guidelines). They evaluated the search results, selected the most relevant and accurate resources, and summarized the most relevant information by development stage and type of SR.

The resources were organised in 7 sections, following the development stages of an SR: 1) Formulating the research question, 2) development of the protocol and review registration, 3) search strategy, 4) risk of bias assessment, 5) statistical synthesis of findings, 6) quality of evidence assessment, and 7) results report and presentation. The resources are presented by type of SR in each section, and an example of their use is included.

Results
We identified several manuals as a result of the bibliographic searches. Joanna Briggs Institute has a specific section in their methodological manual dedicated to the development of prevalence and global prognosis SRs, and another one dedicated to prognostic factor SRs14-16. Other specific publications offer guidelines to develop prognostic factor and aetiology SRs17-18. During the performed search, we did not identify specific methodological manuals to develop prognostic model SRs. Instead, methodological information can be found in the series of publications from the PROGRESS project, in the resource compilation from Cochrane’s Prognosis Methods Group and in specific publications9.

For diagnostic accuracy SRs and efficacy of interventions SRs, the methodological manuals developed by Cochrane Collaboration are available19,20. The recommendations drawn from these are complemented with specific resources that refer to each one of them, as we will see in the following sections.

Formulating the research question
The type of SR is determined by the research question, which must be formulated in a structured manner as shown in Table 1. Careful development of the research question is vital, since the SR inclusion criteria will stem from it.

Prevalence review. Prevalence SRs aim to answer the question “How common is a health problem in a specific population?” Prevalence SRs focus on existing cases at a given time, measure the global burden of a health problem, and describe the characteristics of the affected population, the geographical distribution of that problem and its variation among subgroups. The structure of the research question must include the elements of condition, context, population and study design (CoCoPop-S)21, as shown in Table 1. The most adequate study designs to estimate the prevalence would be population registers or cross-sectional studies that include population-representative samples. For instance, Guthold et al. (2018) considers studies based on population surveys as a reliable source of information to obtain global prevalence estimators of insufficient physical activity.

Prognostic review. SRs of prognosis are mainly based on three types of research questions: 1) “What is the risk of an specific population to have a health problem?”, descriptive question (review of global prognosis) that focuses in new cases occurring within a period of time (incidence), 2) “what factors are associated with or determine a specific outcome?”, an explanatory question (review of prognostic factors), and 3) “are there risk profiles that have higher probability of presenting specific outcomes?” a result prediction question (review of prognostic models or risk prediction). We have excluded from the aim of this project a 4th type of prognostic question, known as stratified medicine, and that alludes to the use of prognostic information to individualise therapeutic choices in a group of people with similar characteristics.

Structured questions about global prognosis must specify population, outcome, condition to be predicted, context and time frame to determine the incidence (CoCoPop-S). The study designs that provide more reliable incidence estimates are prospective cohort studies with representative samples19,22. Structured questions regarding either prognostic factors or models must include population; exposure in terms of the prognostic factor or model of interest, including how it is measured, the intensity and the exposure time; outcome, condition to be predicted; follow-up time; and context (PICOT-S or PFO-S)9,21. The best study designs to evaluate prognostic factors or models are also prospective cohort studies. For instance, Westby et al. (2018) published a prognostic factor SR that gives priority to the inclusion of cohort studies and, if none is found, it resorts to including case-control studies, which also explore the association of prognostic factors with the outcome of interest, although with less reliability.

Diagnostic accuracy review. Diagnostic SRs aim to answer the question “How good is a test to identify or dismiss the presence of a condition or health problem in a particular population, in comparison with a reference test?” The research question can be posed with the elements of population, index test, reference test, diagnosis of interest and study design (PIRD-S)21. The SR approach will depend on the role of the index test in
the clinical diagnostic pathway: if it replaces another test, if it will be used in addition to another test to refine the diagnosis, or if it is a triage test previous to other tests. Diagnostic SRs preferentially include cross-sectional studies, where the participants are evaluated using the index test and/or the reference test to determine if they have the condition of interest. Case-control designs are subject to risk of bias and their inclusion in diagnostic SRs is not recommended. For instance, Ambagtsheer et al. (2017) include in their SR cross-sectional studies where one or more self-reported frailty screening scales have been compared with one of three reference standards: frailty phenotype, frailty index or comprehensive geriatric assessment.

**Efficacy of interventions review** Interventions SRs aim to answer the question “What effect does a specific intervention have on the relevant outcomes in people with a particular health problem, in comparison with a reference intervention?” The research question is posed with the elements of population, intervention, comparator, outcomes of interest and study design (PICO-S). The randomised clinical trial (RCT) is the most appropriate study design to evaluate the efficacy of an intervention, as it is the design with less risk of bias and that best helps to establish causality. In cases where it is not possible to conduct randomised trials for ethical or organizational reasons, non-randomised trials, before-after studies, time series, cohort studies or case-control studies can be considered for their inclusion in the SR. For instance, the SR by Johnson et al. (2018) regarding ribavirin for treating Crimean Congo haemorrhagic fever included both RCTs and non-randomised trials to use the available data, given the previous lack of preparedness for experimental research therapeutics in outbreak situations, but concludes that estimates of effect based on the existing literature are highly uncertain due to confounding in non-randomised studies.

**Development of the protocol and review registration** Writing the SR protocol is a fundamental step that must be done before designing an SR. Herein, the stages and methods to be applied during the development of the SR can be pre-specified. Similarly to the requirement of clinical trial registration, the SR should also be registered in order to avoid redundancies and, more importantly, to avoid reporting bias, therefore guaranteeing transparency and rigor during the development of the SR. Prospective registration of an SR protocol is recommended by the PRISMA guidelines and is associated with higher SR methodological quality and is published in Cochrane Library and automatically registered in PROSPERO.

**Search strategy** Designing a comprehensive research study for an SR is vital in order to reduce bias when identifying studies, and it is important to describe it in the relevant section within the protocol in a transparent and thorough manner to facilitate its evaluation by third parties and its reproducibility. Methodological reference standards to design comprehensive searches have been published. In addition, methodological manuals to develop SRs provide guidelines for diagnostic and efficacy of interventions SRs.

The design of the search strategies does not differ by type of SR, but rather their differences are due to the elements of the research question and the design of studies to be identified. In general terms, electronic searches are designed to identify bibliographic references that use a language similar to the elements of the review’s clinical question. To this effect, the strategies are built based on the elements of the structured clinical question. Search algorithms use a combination of natural language and the appropriate controlled vocabulary for each bibliographic database. Validated filters can be applied to these strategies to determine specific study designs that can be useful to identify, among others, clinical trials, or prognostic studies. However, the use of filters is controversial in diagnostic accuracy studies.

Search performance will vary depending on the type of studies that are included in the SR. Thus, in intervention SRs, the search results for RCTs are more precise (they have a higher proportion of relevant references among all the references that the search has identified), due to better indexation of this type of studies in bibliographic databases. On the contrary, in SRs that include observational studies, like prognostic SRs, identifying studies is more complex given the variability of designs to be included and its poorer indexation in databases, which results in less specific literature searches that lead to a longer and more complex study selection process.

Searches must be designed to optimise their sensitivity (the ability to retrieve as many relevant study references as possible), which is a feature that tends to be a detriment to precision, which in SRs ranges on an average of 3%. To obtain an efficient search with adequate sensitivity, performing searches in MEDLINE and EMBASE is sufficient, as they are the two most frequently used bibliographic databases, and they are enough to identify most relevant studies for a specific SR.

Searching in bibliographic databases can be completed with additional strategies, such as checking public trial registers, searching in the reference list of relevant studies, or cross-searching citations. Searching grey literature, understood as any document that is not published in biomedical or scientific journals, has a limited impact in efficacy of interventions SRs, but offers good results in other types of SRs, such as qualitative evaluation SRs.
If we take into consideration the methodological and technical challenges that the design and implementation of search strategies pose, involving a medical librarian can be convenient to improve the search quality.\textsuperscript{17–49}

Risk of bias assessment

Assessing the risk of bias is a key element in any SR. It helps evaluate and interpret the included studies results, and it is a determinant of the evidence quality of the SR results. The current tools to assess risk of bias are organised by domains, which roughly correspond to the classic epidemiological biases related to each type of research question. The identified tools to assess risk of bias are presented in Table 2, organised by type of SR and by domain of epidemiological bias assessed.

Each of the domains of these tools includes a number of index questions related to specific aspects of study design or development that can lead to a bias in that domain. The tools can be adapted \textit{a priori} to each review, modifying or deleting questions, or adding new questions specific to the considered research question. The process to assess risk of bias is similar in all the current scales. Firstly, they identify the risk of bias in each domain based on the answers to the questions, and secondly, they integrate these risks in a risk of bias assessment for each health problem, prognostic factor, diagnosed condition or outcome of interest assessed, depending on the type of SR.

Prevalence review. The tool to assess risk of bias by Hoy \textit{et al.} (2012) is available for prevalence SRs. It assesses internal and external validity aspects in the prevalence study.\textsuperscript{60} The tool comprises 10 questions where a judgement of high or low risk of bias is made. Based on the answers, the researcher makes a subjective assessment of the study’s overall risk of bias as low, moderate or high.\textsuperscript{60}

Prognostic review. There is no scale available to assess the risk of bias in global prognostic studies, although a series of criteria has been proposed to assess risk of bias. These are classified in 1) definition and representativeness of the population, 2) completeness of follow-up, and 3) objective and unbiased measurement of outcome of interest.\textsuperscript{52} However, some authors like Roerh \textit{et al.} (2018) use a version of the scale to assess risk of bias designed by Hoy \textit{et al.} (2012), adapted to the assessment of incidence studies considering the duration of the incidence period.\textsuperscript{5}

For the prognostic factor studies, the tools QUIPS and “RoB instrument for NRS of exposures” were identified.\textsuperscript{11–16} The QUIPS tool helps assess the risk of bias using 31 questions divided in 6 domains. For each domain, a judgement of high, low or unclear risk of bias is made. Before using the tool, one must carefully consider the potential confounders that can lead to bias. Clinical experts in the specific topic of the SR should participate. The tool “RoB instrument for NRS of exposures” evaluates the risk of bias using 32 questions divided in 7 domains, including a key domain regarding confounders and a domain regarding departures from intended exposures. For each domain, a judgement of critical, serious, moderate or low risk of bias is made. An example of the use of the QUIPS scale can be seen in the review by Westby \textit{et al.} (2018). The authors defined \textit{a priori} two key confounders (age and infection), which the experts and the literature described as prognostic factors for their condition of interest (venous leg ulcers), and which were simultaneously associated with the prognostic factor of interest in the SR (protease activity biomarker). These two confounders were included in the QUIPS scale in the section of control by confounders.\textsuperscript{8}

We identified the Prediction model Risk Of Bias ASsessment Tool (PROBAST) for the prognostic model SRs.\textsuperscript{64} This tool assesses the risk of bias using 20 questions divided in 4 domains (participants, predictors, outcome and analysis). For each domain, a judgement of high, low or unclear risk of bias is made. The questions vary according to the aim of the study (development, validation, or development and validation of the prognostic model).

Diagnostic accuracy review. The tool QUADAS-2, which evaluates 11 questions divided in 4 domains, is available to assess the risk of bias in diagnostic accuracy studies.\textsuperscript{5} For each domain, a judgement of high, low or unclear risk of bias is made. In addition, the external validity or study applicability in relation to the SR is assessed in each domain.

Diagnostic SRs mainly include observational studies, which are more subject to risk of bias, and therefore adapting the QUADAS-2 tool, modifying or adding specific questions to the SR topic, is virtually a requirement during the protocol stage. For instance, the SR by Martínez \textit{et al.} (2017) studied the diagnostic accuracy of an imaging test (amyloid PET) that requires complex visual interpretation. For this reason, a question was included in the QUADAS scale to assess whether the test interpretation was performed by trained readers.\textsuperscript{11}

Efficacy of interventions review. For intervention SRs, the Risk of Bias (RoB) 2.0 tool is available to assess the potential bias in randomised clinical trials, and the Risk Of Bias In Non-randomised Studies - of Interventions (RoBiNS-I) tool in non-randomised clinical trials.\textsuperscript{66,67} The RoB 2.0 tool includes 16 questions divided in 5 domains, including a specific domain for randomisation and a domain for deviations from intended interventions.\textsuperscript{66} For each domain, a judgement is made: high or low risk of bias, or some concerns. For instance, in their SR, Ellis \textit{et al.} (2017) assessed the risk of bias in the evaluation of results separately for the objective outcomes (such as living at home or death) and for the subjective outcomes, showing a lower risk of bias in the evaluation of the objective outcomes.\textsuperscript{13}

The RoBiNS-I tool assesses the biases that the non-randomised study has when compared with an ideal, pragmatic, unbiased randomised trial, which answers the clinical question of interest (even if this ideal trial may not be feasible or ethical).\textsuperscript{15} RoBiNS-I has 34 questions divided in 7 domains, including a key domain regarding confounders and a domain for deviations from intended interventions. As in the case of prognostic
<table>
<thead>
<tr>
<th>Scale (n items)</th>
<th>Prevalence review</th>
<th>Prognostic review - prognostic factors</th>
<th>Prognostic review - prognostic models</th>
<th>Diagnostic accuracy review</th>
<th>Efficacy of intervention review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoy 2012 (10)†</td>
<td>- Representativeness of population sample (1)</td>
<td>- Sample and recruitment (3)</td>
<td>- Selection of participants (5)</td>
<td>- Selection of participants (3)</td>
<td>- Selection of participants (6)</td>
</tr>
<tr>
<td>ROB 1 (20)†‡</td>
<td>- Sample and recruitment (2)</td>
<td>- Confounders definition and measurement (6)</td>
<td>- Deviations from intended exposure (4)</td>
<td>- Confounders definition and measurement (3)</td>
<td>- Confounders definition and measurement (4)</td>
</tr>
<tr>
<td>QUIPS (31)†</td>
<td>- Study participation (3)</td>
<td>- Prognostic factors definition and measurement (6)</td>
<td>- Index test interpretation (1)</td>
<td>- Deviation from intended intervention (2)</td>
<td>- Classification of intervention (3)</td>
</tr>
<tr>
<td>PROBAST (20)†</td>
<td>- Design of study and selection of participants (2)</td>
<td>- Deviations from intended exposure (5)</td>
<td>- Threshold specification for index test (1)</td>
<td>- Deviation from intended intervention (2)</td>
<td>- Selection of participants (6)</td>
</tr>
<tr>
<td>QUADAS-2 (11)†</td>
<td>- Selection of participants (3)</td>
<td>- Exposures definition and measurement (5)</td>
<td>- Adequacy and interpretation of reference test (2)</td>
<td>- Deviation from intended intervention (2)</td>
<td>- Selection of participants (6)</td>
</tr>
</tbody>
</table>

No risk of bias tool has been identified for global prognosis systematic reviews.
SRs, there should be an a priori careful consideration of the potential confounders that must be included in the tool to assess individual studies. A judgement of critical, serious, moderate or low risk of bias is made for each domain. A low risk of bias implies that the non-randomised study is comparable to a well-performed randomised trial. For instance, Johnson et al. (2018) excluded from their analyses the non-randomised studies that showed a critical risk of bias according to RoBiNS-I, rejecting 18 out of the 22 included studies.

Statistical synthesis of findings
SRs may include a section with a quantitative statistical synthesis or meta-analysis, where a combined estimator of the parameter of interest is obtained from the estimators of the individual studies. Table 3 shows the main characteristics of the meta-analysis methods and the main software commands for each type of SR.

A necessary previous step to any meta-analysis is the evaluation of the existing clinical and statistical heterogeneity in the set of studies, which will inform us 1) if it is reasonable to perform a quantitative synthesis of findings, 2) what meta-analysis model we should apply, and 3) if additional investigation of the causes of heterogeneity is required, for example, subgroup and sensitivity analyses, or meta-regressions.

When it is reasonable to perform a statistical synthesis, there are two main models to conduct a meta-analysis: fixed effects model and random effects model. For practical purposes, the chosen model determines how the studies included in the meta-analysis will be numerically weighed. Both models are based on different assumptions, and they differ in their application and interpretation.

Finally, there is a variety of resources to conduct meta-analyses, from specific programs to perform meta-analyses (free or paid) to user-defined routines using general statistics packages (SAS, Stata, SPSS), as well as Excel utilities or R libraries. An archive with software and utilities is available from SR Tool Box.

Due to the complexity of the statistical techniques to synthesise results, and the difficulty to standardise methods and decisions to be made during the analysis, it is vital to involve a statistician in the planning and conduct stages of the meta-analysis, especially for prognostic and diagnostic SRs.

Table 3. Methodological characteristics of meta-analysis by type of systematic review

<table>
<thead>
<tr>
<th>Measures to combine</th>
<th>Assessment of heterogeneity</th>
<th>Model</th>
<th>Method</th>
<th>Command (package)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence review</td>
<td>- Proportion (prevalence)</td>
<td>- Qualitative</td>
<td>- Fixed/Random effects</td>
<td>- Metaprop (Stata)</td>
</tr>
<tr>
<td>Prognostic review - global prognosis</td>
<td>- Cumulative incidence</td>
<td>- Meta-regression</td>
<td>- Fixed/Random effects</td>
<td>- Metan (Stata)</td>
</tr>
<tr>
<td>Prognostic review - prognostic factors</td>
<td>- Hazard Ratio</td>
<td>- Meta-regression</td>
<td>- Random effects</td>
<td>- Metafor (R)</td>
</tr>
<tr>
<td>Prognostic review - prognostic models</td>
<td>- Calibration</td>
<td>- Meta-regression</td>
<td>- Random effects</td>
<td>- Metamisc (R)</td>
</tr>
<tr>
<td>Diagnostic accuracy review</td>
<td>- Sensitivity</td>
<td>- Meta-regression</td>
<td>- Random effects</td>
<td>- Metadas (SAS)</td>
</tr>
<tr>
<td>Efficacy of intervention review</td>
<td>- Mean difference</td>
<td>- Meta-regression</td>
<td>- Fixed/Random effects</td>
<td>- Metafor (R)</td>
</tr>
<tr>
<td></td>
<td>- Risk difference</td>
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<tr>
<td></td>
<td>- Standardised mean difference</td>
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<tr>
<td></td>
<td>- Hazard Ratio</td>
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<tr>
<td></td>
<td>- Incidence rate ratio</td>
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<tr>
<td></td>
<td>- Odds Ratio</td>
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<td></td>
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<tr>
<td></td>
<td>- Risk ratio</td>
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</tr>
</tbody>
</table>

\(^a\) Tukey-Freeman or logit transformation. \(^b\) Transformation for the cumulative incidence. \(^c\) Hierarchical summary receiver operating characteristic (HSROC) method allows estimation of a Receiver operating characteristic (ROC) curve or sensitivity and specificity indexes.
while in prognostic factor SRs, the meta-analysis combines odds ratios or hazard ratios, which can be presented in individual studies as raw estimates or as covariate-adjusted estimations derived from logistic or Cox regression models. If combining adjusted estimates, all of them should be adjusted by a minimum set of common factors. In prognostic model SRs, the meta-analysis combines estimates of model discrimination and calibration. These indicators can be synthesised separately or jointly using multivariate models.

Prognostic studies usually show significant variability in terms of design, sample case-mix, measurement instruments, analysis methods and presentation of results. Therefore, in prognostic factor and model SRs, it is recommended to perform the meta-analysis using the random effects model, and even to use multivariate meta-analysis methods adjusting for relevant factors. For instance, the SR by Westby et al. (2018) describes how the authors dismissed performing a meta-analysis due to the high risk of bias and the extreme heterogeneity across the included studies in terms of population, measurement of the prognostic factor (cut-off points and analytical methods) and outcome measurement.

**Diagnostic accuracy review.** In diagnostic SRs, the meta-analysis combines estimates of sensitivity and specificity of the index test. The meta-analysis in diagnostic SRs shows a higher degree of complexity because the studies may have used different thresholds, both implicit and explicit, to define a positive result in the evaluated test. This leads to a correlation between the sensitivity and specificity indexes, which must be modelled jointly using multivariate methods. The most common available statistical methods are the bivariate hierarchical model and the HSROC model (Hierarchical summary receiver-operating characteristic). Diagnostic SRs tend to combine studies with very heterogeneous results, and it is recommended to use the random effects model by default and perform a comprehensive examination of the sources of heterogeneity using meta-regression. For instance, the protocol of the SR by Ambagtsheer et al. (2017) expects to estimate an average sensitivity and specificity for the frailty scales, when the included studies have applied the same explicit cut-off points to the considered scales. However, given that they are subjective, self-reported scales, the studies could share the same explicit cut-off point, and yet that cut-off point could correspond to different levels of frailty in the studies (implicit thresholds), which will advise against calculating pooled estimates of diagnostic accuracy.

**Efficacy of interventions review.** In intervention SRs, the meta-analysis combines different measures, depending on the type of outcome: odds ratio or hazard ratio for binary outcomes, mean difference or standardised mean difference for continuous outcomes, hazard ratio for time-to-event outcomes, and incidence rate ratios for outcomes that count number of events.

In intervention SRs, the I² estimator has been proposed to assess statistical heterogeneity as a supplement to the assessment of clinical and methodological heterogeneity. This indicator is defined as the percentage of the overall variability that cannot be explained by chance, and has values ranging from 0% to 100%; with higher values indicating higher statistical heterogeneity. For instance, in the SR by Ellis et al. (2017), the authors established a 70% heterogeneity limit for I², beyond which a meta-analysis combining the results would not be performed. Despite its popularity and ease of interpretation, the use of this indicator is not exempt of controversy due to its dependence on the number of studies and sample size; thus, a small statistical heterogeneity could seem substantial only by the effect of a large sample size of the included studies.

**Quality of evidence**

The quality (also confidence or certainty) of evidence in an SR is the degree of confidence that is held against the fact that an estimate of effect or association is close to the actual value of interest. Certainty of evidence is evaluated for each one of the key SR outcomes or factors. Certainty in the obtained estimates is classified as high, moderate, low or very low. A level of certainty of evidence is first established from the design of the studies that form the evidence body, which might or might not have an optimal design for the type of considered question. This initial confidence in the evidence body can then decrease in one or two levels if the following is detected: 1) design or execution limitations, 2) inconsistency, 3) indirect evidence, 4) imprecision in estimates, or 5) publication bias.

The certainty of evidence is a key element to interpret and communicate results, and as such, it should be included in the sections of results, discussion, conclusion and abstract, using semi-standardised statements. Additionally, it can be included in a Summary of Findings table, where for each comparison, the key information regarding relative effect and absolute effect magnitude, quantity of available evidence and its certainty is presented.

We will now highlight the specific aspects in which the GRADE system adapts to each type of SR.

**Prevalence review.** There are no formal adaptations of the GRADE system for prevalence SRs, but there is a proposal to assess the quality of the evidence based on this system. High initial certainty is awarded to survey or cross-sectional study designs with population representativeness that have been properly designed and conducted, while studies with no population representativeness will have lower initial quality.

**Prognostic review.** There is a GRADE proposal for global prognostic SRs and an adaptation for prognostic factor SR. Guidelines for prognostic model SR are still under development.

In global prognostic SRs, the study designs that have high initial certainty are longitudinal cohort studies and pragmatic randomised controlled trials with representative samples. Other observational designs would offer low initial certainty.
**prognostic factor** SRs, explanatory and confirmatory longitudinal designs offer high initial certainty, while exploratory studies are considered to be of moderate quality⁶³.

In prognostic SRs, the assessment of the limitations follows the general procedure already described, with two particularities: 1) qualitative assessment of inconsistency, because of low reliability of I² estimator in the prognostic field²⁶,⁷⁷, and 2) possibility of increased certainty in the studies that do not show limitations in the quality of evidence, if (i) the estimated effect magnitude is substantial, or (ii) there is an exposure-response gradient⁶⁷. For instance, the prognostic factor SR by Westby et al. (2018) considered the possibility of increasing the certainty of evidence in the studies presenting no limitations. Due to the exploratory nature of the included studies and their high risk of bias, the certainty was not increased in any case and the evidence obtained in the review was of very low quality³.

**Diagnostic accuracy review.** The methods to assess quality of evidence in diagnostic SRs are still under development⁹⁴. The study designs that start with the highest degree of evidence are RCTs and cohort or cross-sectional studies where the index test and the reference standard have been directly compared in all participants⁸⁴. If the SR included case-control studies, these would offer low-quality initial evidence⁵¹.

There is uncertainty regarding how to assess inconsistency, because heterogeneity is common and hard to quantify in diagnostic SRs, and it often cannot be explained even if multivariate models are adjusted. It is also unclear how to assess inaccuracy when the SR has estimated the SROC curve, or when the role of the test in the clinical pathway gives different weight to the sensitivity and specificity estimates. With regard to the criteria to increase the level of evidence, it is unclear whether they should be applied and how to do it in diagnostic SRs⁵³,⁶⁶. The uncertainty surrounding the process of assessing the quality of evidence in diagnostic SRs explains why it is not a requirement in Cochrane SRs. For instance, the SR by Martínez et al. (2017) only included a Summary of Findings table with numerical results and an estimation of the absolute effect that the test would have on a hypothetical cohort of individuals³.

**Efficacy of interventions review.** The GRADE system for assessing the quality of evidence was initially developed for intervention SRs, and it is the indication for which clearer and widely agreed guidelines are available⁹¹. In terms of study design, RCTs are initially classified as having high certainty, while all non-randomised or observational studies are classified as having low certainty.

The assessment of the certainty limitations is well-defined in intervention SRs. Inconsistency can be assessed using the I² estimator⁹⁴. Imprecision is assessed taking into account whether the review meets the optimal information size, and whether the confidence interval of the effect estimate allows reaching a conclusion, because either it only includes values consistent with a relevant intervention effect, or it completely dismisses it⁹⁴. In observational studies that do not have limitations in the quality of evidence, three criteria are considered to increase certainty: 1) the estimated effect magnitude is important or very important, 2) there is dose-response gradient, and 3) all possible biases that could reduce the observed effect confirm the obtained conclusions.

For instance, the SR by Ellis et al. (2017) applied the GRADE system to the included randomised trials, and it concluded that there was high certainty of the effect of the comprehensive geriatric assessment on the efficacy outcomes based on a high number of studies and participants, with a globally low risk of bias, and results consistent among studies. However, the certainty of evidence obtained in cost-effectiveness was low, due to imprecision and inconsistency of results⁸⁶.

**Results report**

It is vital to inform about the methods, results and conclusions of the SRs in a transparent and thorough manner so that their users can interpret, evaluate and apply them. The EQUATOR initiative has developed, and keeps up-to-date, a library with guidelines to communicate the different types of research studies. The PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) has been proposed in the SR field⁹⁸. This statement consists of a checklist comprised of 27 items and a flow diagram to present the number of studies considered in the SR. In addition, several extensions focusing on reporting specific aspects of SRs have been developed, such as PRISMA-P for reporting SR protocols⁹⁹, PRISMA-AbsAbstracts for reporting abstracts⁹¹, and PRISMA-Harms for reporting harms outcomes in SRs⁹².

Although the PRISMA statement and the cited extensions are focused on intervention SRs, a specific PRISMA extension has also been developed for diagnostic SRs⁹³. On the contrary, no tools have been identified to communicate prevalence or prognostic SRs. In recent years, clarity and transparency in study communications has improved thanks to the development of checklists for scientific paper publication, although there is still room for improvement⁷⁴–⁷⁶.

**Discussion**

**Key results**

This review identifies and describes the most relevant methodological resources to conduct prevalence, prognostic, diagnostic accuracy and efficacy of interventions SRs. This review offers a general and comparative perspective of the methodological resources by SR stage, highlighting the differential elements of each type of SR.

**Current context**

This paper corroborates that developing a rigorous SR is a complex and resource-intensive task⁷⁷,⁷⁹. In order to tackle the increasing complexity of SRs and ensure the adoption of rigorous methodology, it is necessary that the reviews are made by **multidisciplinary work groups** with knowledge and experience in methodology (such as statistical analysis and information retrieval)⁸⁰–⁸⁲. In addition, it is important to consider the increasing availability of artificial-intelligence-based **technological tools**, which make it possible to semi-automate the different steps of the SR development, and thus reduce the time and human resources required to conduct the review⁹³.
Once the rigorous SR has been developed, ensuring the conveyance of the generated knowledge is essential. In this sense, new formats for synthesis and presentation of SR results are being explored nowadays to help their dissemination and the adoption of their conclusions in clinical practice and healthcare decision-making. For instance, new formats for result presentation and Summary of Findings tables are being proposed, adapted to the profile of their potential users.32,33

Limitations and strengths

The four types of SRs considered in this paper are fundamental to define preventive activities and public health policies, as well as to make health decisions. However, this research has not considered other types of SRs, such as methodological, economic evaluation and qualitative research SRs, for which it would be convenient to perform similar methodological compilations. Another limitation of this research is the need to keep it up to date, given the speed at which the methods and methodological resources to develop SRs are updated.

On the other hand, the main strengths of this paper are its transversal approach for the different types of reviews, and the identification of resources for all the stages in the development of an SR. There are few previous publications that offer a transversal perspective of the different types of systematic reviews, and these are focused on a specific stage of the review or on a particular topic. For instance, the work carried out by Munn et al. (2018) defined a typology for SRs, characterised from 10 different types of research questions, and diving into the format of each type of question.31 Pollock et al. (2017) review the steps of an SR for 5 types of question, specifically focusing on the particularities of the reviews on stroke rehabilitation.34 Muka et al. (2019) offer a structured compilation of resources for each SR stage, but without delving into the specificities of the different types of SRs.35 Finally, organising the resources to assess the risk of bias by type of review is a strength and a novelty compared with previous works, which compile the quality assessing tools by type of study design but without linking them to the aim of the study nor the type of systematic review.36,37

Conclusions

SRs are a key research tool to make decisions in healthcare, public health and medical research. There are methods and resources to develop high-quality reviews to answer most types of clinical questions. This review offers a complete resource guide for prevalence, prognostic, diagnostic and intervention reviews, and is a very useful tool for those researchers that wish to develop SRs or conduct methodological research works in that field.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Acknowledgements

Marta Roqué i Figuls is presently working on her PhD with the PhD Programme in Biomedical Research Methodology and Public Health from the Autonomous University of Barcelona.

References


Open Peer Review

Current Peer Review Status:  

Version 1

Reviewer Report 28 February 2020

https://doi.org/10.5256/f1000research.24297.r59540

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I have a few suggestions which may be helpful to the authors:

1. When discussing research methods, it may be worth just mentioning the efficacy/effectiveness issue.

2. I think that this "To obtain an efficient search with adequate sensitivity, performing searches in MEDLINE and EMBASE is sufficient, as they are the two most frequently used bibliographic databases\(^{99}\), and they are enough to identify most relevant studies for a specific SR\(^{40*}\) might be a bit of a sweeping statement - are the two databases always sufficient? I think it would be helpful to mention some others as well - unless the authors really do believe that these are enough.

3. "involving a medical librarian can be convenient to improve the search quality\(^{47–49}\). I am not sure that convenient is quite the right word.

4. Be clear to differentiate risk of bias at the study level from RoB at the review level. For example RoB2 is study-level, ROBIS is review level.

5. "For instance, in the SR by Ellis \textit{et al.} (2017), the authors established a 70% heterogeneity limit for I \(^2\), beyond which a meta-analysis combining the results would not be performed\(^{13*}\) - why 70%? This does not sound like a sensible decision making process anyway. Either the authors thought it was worth doing a MA in which case the heterogeneity form parts of the results, or it is not worth doing in which case this would not be a consideration. Also not doing a MA may have the effect of hiding this heterogeneity. There are also ways of investigating heterogeneity that can be illuminating.

6. Mention ROBIS and AMSAR2 as review-level tools.

Is the work clearly and accurately presented and does it cite the current literature?  
Yes
Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Paediatrics, infection control, systematic review.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 14 February 2020
https://doi.org/10.5256/f1000research.24297.r59538

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The authors have summarised the current literature around methods for conducting systematic reviews, encompassing reviews of prevalence, prognosis, diagnosis and intervention effectiveness. In a field of methodology where some guidance is collated in well-known handbooks, but other areas are scattered among the methods literature, and where development of new methods is relatively fast-moving, this map of available guidance and methods studies is likely to be very useful to researchers new to systematic reviews or branching out into different review types. The authors are experienced experts in this field, and the review is well-written and clear.

In my understanding, this paper aims to fulfil two roles: (1) a toolkit that enables authors of systematic reviews to navigate out to key methods resources, and (2) a brief summary of methods guidance for each review type. It may be helpful throughout the paper, including in the abstract and conclusions, to separate out these two roles more clearly. I have some suggestions to improve the transparency and usability of the paper from each of these perspectives.
Major recommendations

As a review and toolkit of methodological resources, I would make the following suggestions:

- **Methods:** The authors could provide more transparent detail on the selection process for included documents, including specifying which organisational websites were searched, how many resources were identified, and if any were excluded. Although this is intended as a mapping, rather than systematic review, some additional detail would help readers to understand how the guidance documents were selected, and why perhaps some resources they may have used before are not listed.

- Importantly, more detail could be presented on how the authors selected the most “relevant” or “best” resources, especially where there may have been multiple candidate documents. For example, were they most recent, most comprehensive, those endorsed by a credible organisation, most introductory, most rigorous methods? The role of the authors’ expert judgement in these decisions should be stated explicitly. Note that I am not suggesting that a different process should have been used, just suggesting a more detailed description of the judgement process.

- **Results:** As a navigation guide, I found that citing the resources within the text did not tell me everything I wanted to know. Also, the key resources are mixed in the reference list with exemplar reviews and other citations. A table outlining the recommended resources by category with hyperlinks to each resource would be helpful.

- As a reader, I would find it helpful for the authors to draw the distinction between the different types of resources cited. For example, some were synthesised, ‘best practice’ guidance intended for use by authors (such as the Cochrane or JBI Handbooks). Some were reporting guidelines (which often list good practice but are not intended to provide detailed guidance on the conduct of reviews). Some were primary methods studies (e.g. measuring the prevalence or impact of a method, which may describe or evaluate possible methods options but are not intended as guidance on the ‘best’ available methods for authors. All may be useful in different ways.

As a brief summary of methods guidance, I would make the following suggestions:

- **Methods:** It would be helpful to include a brief description of your role in selecting and writing this summary of guidance, for example, stating briefly that key areas of methods were summarised, and how the methods to be highlighted were selected, especially where multiple and potentially conflicting sources were available (e.g. major methods applicable to all reviews, key differences between review types, expert opinion about interesting or important advice).

- It might be helpful to note that the summary of guidance presented is just that, a brief summary, and that authors who are new to systematic reviews should consult the more detailed documents for complete guidance.

- **Results:** It might be particularly helpful to note where there is disagreement in the literature in relation to particular areas of guidance. For example, comments that searching the grey literature is not useful for effectiveness reviews, or that risk of bias tools should be adapted for each review, which may be in disagreement with some of the major guidance handbooks and reporting guidelines. I’m not arguing about these specific items, just noting that some methods choices have been made by the authors, and it may be helpful to make this transparent.

Minor recommendations

- **Title and abstract:** It would be helpful to briefly define the scope of this review, especially in the context of a journal such as F1000Research, which publishes in a wide range of scientific fields.
For example, using a term such as ‘systematic reviews in health care’, and noting that the review looks at prevalence, prognosis, diagnosis and health interventions (and not other areas relevant to health such as environmental exposure).

- **Competing interests**: The authors could note any roles with Cochrane and the GRADE Working Group. These are not necessarily financial conflicts, but may be relevant to the authors’ decision to recommend guidance from these sources (which of course I agree with!).

- **Results**: In the first two paragraphs, you discuss some specific points in relation to resources available for diagnostic and prognosis reviews. As all review types appeared to cite both guidance handbooks and additional primary methods studies, I wasn’t clear on the point you were trying to make in this section.

- There were some key guidance documents that I would have expected to see, although there may be good reasons not to include them, such as:
  - General guidance on systematic reviews from the US Institute of Medicine and the Centre for Reviews and Dissemination at the University of York (both are older documents, so this may be the reason).
  - Tools to assess the risk of bias in reviews, such as ROBIS or AMSTAR, which may enable reflection by authors on their choice of methods, in a similar manner to reporting guidelines.
  - Resources on the development of protocols (as distinct from study registration), such as Chapter 1 of the Cochrane Handbook.
  - Guidance on synthesis in the absence of meta-analysis, such as Chapter 12 in the Cochrane Handbook and papers by (Campbell, McKenzie et al. (2020)\(^1\)) and (Popay, Roberts et al. (2006)\(^2\)). This may be relevant to synthesis, assessment of heterogeneity and GRADE.
  - Guidance on network meta-analysis, such as Chapter 11 of the Cochrane Handbook and multiple journal articles, as well GRADE guidance and CINEMA.
  - Two papers from the GRADE Working Group (published this week!) on the use of GRADE for diagnostic test accuracy studies published this week.

- In the text on risk of bias and Table 2, is it worth noting that the number of items in RoB 2 varies depending on the effect of interest and the included study designs?

- In Table 3, as there are more variations on the measures to combine (e.g. Ratio of Means), and statistical methods for meta-analysis of efficacy of interventions (including the inverse-variance method, which is mentioned for other types), could it be helpful to note in the table somewhere that these are common characteristics, not an exhaustive list?

- When discussing fixed effect and random effects models, it may be helpful to note that they differ in relation to assumptions and heterogeneity, as you mention something briefly about analysis using random-effects models later in the paper that relies on understanding this.

- On page 9, under “Efficacy of intervention reviews”, I think hazard ratios are listed in error against binary outcomes as well as time-to-event outcomes. Perhaps you meant risk ratios?

- In the section on assessing certainty of the evidence, it would be helpful to describe the GRADE approach in the first paragraph (it is currently named without description in the third paragraph).
**Discussion:** I would also acknowledge under limitations of this review that the selection of resources and summary of guidance were informed by expert opinion, and that others may have selected different resources or made different recommendations.

**References:** 1: I think there may be an error – should this be a reference to the 2019 edition of the Cochrane Handbook, rather than an older paper by Higgins in *Cochrane Methods* on RoB 2? I assume this based on its use in the Introduction as a general reference about review methods, and also on the availability of general Handbooks in para 2 of the Results.

20: could be based on the references to individual chapters, i.e. Deeks JJ, Bossuyt PM, Gatsonis C (editors), *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy*.

63: It’s great to see the Spanish Manual GRADE cited. If I am correct, this is a translation of the 2013 GRADE Handbook (apologies if I am wrong). Would it be helpful to cite some of the more recent GRADE papers as well, as they reflect the most up to date guidance? I note you also cite the paper on using standard language to express GRADE, as well as the recent Cochrane Handbook Chapter, so perhaps this is sufficient.

**References**

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
No

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?
Yes

**Competing Interests:** I am an Associate Editor of the Cochrane Handbook for Systematic Reviews, and an Editor with Cochrane Public Health.
Reviewer Expertise: In presenting my comments, I acknowledge that my own experience focuses on methods around systematic reviews of the effects of interventions, and so I cannot comment with expertise on the details of methods described for other review types.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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