Systematic reviews and meta–analysis – a stepwise approach

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As per Cochrane definition (2013), a systematic literature review (SR) attempts "to identify, appraise and synthesize all the empirical evidence that meets pre-specified eligibility criteria to answer a given research question" [1]. A meta-analysis (MA) is a statistical assessment of the data provided by multiple studies that attempt to ask / answer the same question. SR involves formulated questions, identifies relevant studies, appraises their quality, and summarises the evidence by use of explicit methodology.

Systematic reviews are different from narrative reviews, which are more descriptive, focusing typically on a subset of studies in an area of interest. In this article, we will focus on a stepwise approach to SR writing.

Step 1: Research question and objectives

This is the most important aspect of SR / MA. The research question should be novel, interesting, feasible, ethical, and relevant. However, there are two important aspects – firstly, the problem to be addressed should be clear, unambiguous, and structured, and secondly, a thorough search should be completed to be aware of any similar SR / MA published in recent times. Once ready, the question posed can be structured in PICO format – Population, Intervention, Comparison, and Outcome (Table 1).

Step 2: Literature search

Once the research question has been finalised, there is a need for a robust literature search. The easiest approach is to get help from your library. Most libraries can provide literature searches using their available software to search in different databases (like PubMed, Medline / OvidSP (includes EMBase), Web-of-Science, and BIOSIS, etc.). The library requires an online form completion which usually ask for information about the research question, timeline, inclusion and exclusion criteria, and a few appropriate references. Most libraries do an extensive literature search and provide results in various formats and often links with full access. The libraries provide a search strategy as well. This is a useful supplementary document for submission.

Alternatively, a literature search can be performed by authors on their own. After finalising the search question, appropriate keywords / MeSH (Medical Subject Headings) should be identified for each theme. Following this, appropriate Boolean operators, which are simple words including AND, OR, NOT, or AND NOT, are used as conjunctions to combine or exclude keywords in a search, resulting in more focused and productive results. This essentially saves the purpose of eliminating inappropriate hits. All possible electronic databases must be searched. For Cochrane review, a minimum of three databases need to be searched. Appropriate search filters such as duration, language, type of study (animal or human), etc. are required.

Step 3: Screening and selection of publications

Study screening and selection is a challenge, which can be made easy by using software like Rayyan [2], illustrated in Figure 1. It helps researchers to work remotely and collaborate within a distributed research team. The software requires literature searches from the library to be uploaded, and authors will need to ask the library to send the search results in a format compatible with the software. Once this has been uploaded authors can include or exclude studies based on inclusion and exclusion criteria. The full-text versions of studies should be sought out for inclusion in the review. Again, library services can be helpful, and if unavailable, direct polite communication with the original author can be helpful.

All essential collected data should be documented in an appropriate format that suits the author best. Most authors document data in Microsoft Excel and retain references in Mendeley software [3], which is displayed in Figure 2. Other reference managing software options are Zotero and Endnote.

This is the ideal time to complete your Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (2020) [4]. This should not be confused with the PRISMA checklist, which is usually completed towards the end and often uploaded as a supplementary document.

Step 4: Registration of research protocol

At this stage the study protocol should be registered with the different registry sites recommended by the Cochrane and Campbell collaborations. We recommend registering the research protocol with the International Prospective Register of Systematic Reviews (PROSPERO) [5]. A brief description of registration with the PROSPERO database is provided in Table 2.

Step 5: Interpreting data

We recommend following a two-stage approach. Firstly, tabulate all the studies

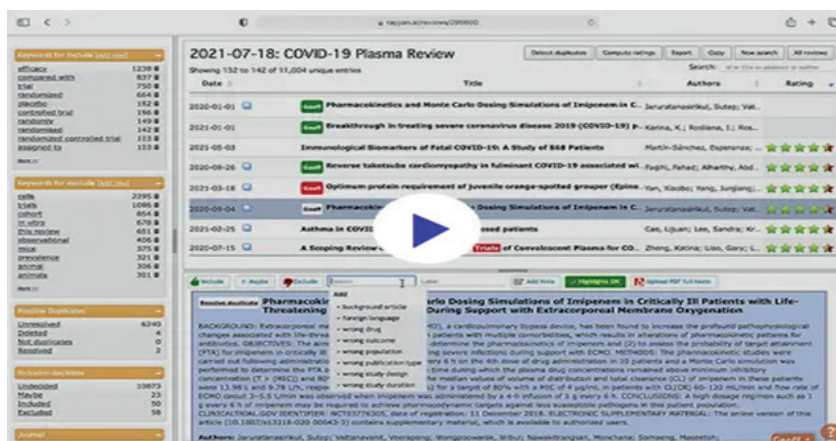| Table 1: PICO description			
P	**I**	**C**	**O**
Population Patient Problem	Intervention Or Exposure	Comparison	Outcome
Who are the patients? What is the problem?	What do we do to them? What are they exposed to?	What do we compare the intervention with?	What happens? What is the outcome?

Figure 1: Screenshot of Rayyan software.

Figure 2: Screenshot of Mendeley desktop.

describing the authors, primary aim, type of study (prospective, retrospective), methodologies used, results, and conclusions in a summarised manner. This table needs to be written in author's words to make it relevant to SR and avoid plagiarism. This table does go into the final paper. Secondly, author's should make a master table (preferably Excel or Word) and extract as much information as possible. Even if, in some studies, you feel you do not need additional data, we recommend extracting it as well. This is the most critical part of SR and authors need to be careful and vigilant in interpreting data, as this forms the essential source of information for SR. You can keep modifying the data table as the studies included may have presented data in different ways. Once this master table is ready, author's should start collating data in new tables as per the aims and objectives of the SR.

Step 6: Risk of bias assessment

Systematic reviews are also susceptible to bias that arise in primary studies, each of which needs to be critically appraised. The Cochrane manual defines risk of bias as "a systematic error, or deviation from the truth, in results." It further states that "biases can lead to under-estimation or over-estimation of the true intervention effect and can vary

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Table 2: PROSPERO database information

Background
PROSPERO is an international database of prospectively registered systematic reviews in health and social care. It has been developed and is managed by the Centre for Reviews and Dissemination (CRD) at the University of York and is funded by the UK's National Institute for Health Research (NIHR).

Purpose
The aim is to provide a comprehensive listing of systematic reviews registered at inception, to help avoid unplanned duplication.

When to register your review
Do not register too early. Your systematic review protocol should be complete before you submit your registration request.

Requirements for registration
• A full protocol should be ready before registering with PROSPERO.
• Submissions must be made before data extraction commences.
• Registration forms must be complete.
• Submissions must be in English (search strategies and protocols attached to a record may be in any language).

PROSPERO accepts
Systematic review protocols assessing:
• Interventions (including qualitative and individual participant data reviews)
• Diagnostic accuracy
• Prognostic factors
• Prevention
• Epidemiological reviews relevant to health and social care
• Public health
• Service delivery in health and social care
• Methodological.

PROSPERO does not accept:
• Systematic reviews without an outcome of clear relevance to the health of humans
• Scoping reviews
• Literature reviews that use a systematic search
• Systematic reviews assessing sports performance as an outcome
• Methodological reviews that assess ONLY the quality of reporting.

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in magnitude: some are small (and trivial compared with the observed effect) and some are substantial (where an apparent finding may be due entirely to bias)."

Popular risk of bias assessment tools

1. Modified Downs and Black Checklist
Provides both an overall score for study quality and a numeric score out of a possible 30 points. It has five sections. Administration of the tool can be either within the systematic review process or as a quality assessment tool for individual articles.

2. Newcastle-Ottawa Quality Assessment Scale
A tool used to assess the quality of non-randomised studies. It allocates a maximum of nine stars for the quality of selection, comparability, exposure, and outcome of study participants [6].

3. Cochrane Risk of Bias Tool (RoB 2)
Tool used to assess the risk of bias for randomised controlled trials. Required for all Cochrane group systematic reviews.

4. Cochrane Risk of Bias in Non-Randomised Studies of Interventions (ROBINS-I Tool)
The ROBINS-I is a tool developed to assess the risk of bias in the results of non-randomised studies that compare the health effects of two or more interventions.

5. MMAT (Mixed Methods Appraisal Tool)
The MMAT is intended to be used as a checklist for concomitantly appraising and / or describing studies included in systematic mixed studies reviews (reviews including original qualitative, quantitative, and mixed methods studies) when the SR includes data from animal research, the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE)'s risk of bias tool [7] should be used.

Step 7: Analytic choices in case of meta-analysis

Meta-analysis is a quantitative, formal, epidemiological study design used to systematically assess previous research studies to derive conclusions about that body of research. The benefits of meta-analysis include a consolidated and quantitative review of a large, and often complex, sometimes apparently conflicting, body of literature.

Four meta-analytical methods are primarily used in contemporary management research which allow the investigation of different types of research questions:
- **a.** Univariate meta-analysis
- **b.** Meta-regression
- **c.** Meta-analytic structural equation modelling
- **d.** Qualitative meta-analysis.

Software solutions to perform meta-analyses range from built-in functions or additional packages of statistical software to those that are purely focused on meta-analyses. These may be commercial or open-source solutions. However, in addition to personal preferences, the choice of the most suitable software depends on the complexity of the methods used and the dataset itself. Analysts therefore must carefully check if their preferred software is capable of performing the intended analysis.

Table 3: Stepwise approach to writing a paper	
Title page	Author details; affiliations; correspondence author.
Abstract	Write as per the journal recommendations.
Key words	Use search terms / MeSH words if used in the search.
Running title	Usually shorter version of the title appears at top or bottom of page.
Introduction	Two to three paragraphs, the last paragraph should mention the primary and secondary aims of SR.
Material and methods	• Protocol and registration • Evidence acquisition (inclusion and exclusion criteria, use PICO) • Outcome measures (primary and secondary) • Search methods (mention PRISMA checklist and search strategy) • Study selection (include details of software used) • Data extraction • Quality assessment (mention tool used) • Statistical analysis (if performing MA).
Results	• Study selection results (PRISMA flow diagram) • Quality assessment results • Study characteristics • Study results • Statistical results.
Discussion	• Compare results from previous research with this SR • Mention the pros and cons of source studies.
Conclusion	• Conclusion should be specific and easy to understand.
Acknowledgments	• Mention library services if used or any specific person who has helped in SR.
Supplementary materials	• If any available.
Funding statement	• Declaration statement.
Author contribution	• Follow journal guidelines.
Conflicts of interest	• Mention same.
References	• Follow journal guidelines • Online software available.

FEATURE

Among commercial software providers, Stata (from version 16 onwards) offers built-in functions to perform various meta-analytical analyses or to produce various plots. Researchers using the open-source software R, provide an overview of 63 meta-analysis packages and their functionalities. For new users, they recommend the package *metafor,* which includes the most necessary functions. In addition to packages and macros for statistical software, templates for Microsoft Excel has also been developed to conduct simple meta-analyses such as meta-essentials. Finally, programs purely dedicated to meta-analysis also exist, such as Comprehensive Meta-Analysis or RevMan by The Cochrane Collaboration (2020).

Sometimes due to the nature of data, a network meta-analysis becomes essential to arrive at conclusions. Network meta-analysis is a technique for comparing three or more interventions simultaneously in a single analysis by combining both direct and indirect evidence across a network of studies.

In the end, if the authors find it difficult to perform a statistical analysis due to complex data or lack of knowledge, it is recommended to get help from a professional statistician.

Step 8: Drafting the paper

Once all this is ready, it is time to write the initial draft. The paper should be written either by keeping in focus on a particular journal or being flexible in terms of which journal it would be submitted to for publication. If authors consider a particular journal, it may be worth contacting the editorial team first as some journals entertain only invited reviews. Table 3 is a useful guide to writing the paper. At this stage, the PRISMA checklist should be completed.

Step 9: Article submission

There are a few things to consider before submitting a paper and which must be completed before, including:

a. Author details, affiliations, preferably ORCID numbers
b. Author contribution (check the journal requirements)
c. Acknowledgements (if any)
d. Running title
e. Keyword list
f. Conflict of interest statement
g. Copyright form (specific for each journal)
h. Cover letter.

References

1. https://www.cochranelibrary.com/cdsr
2. https://www.rayyan.ai
3. https://www.mendeley.com
4. http://prisma-statement.org/prismastatement/flowdiagram.aspx
5. https://www.crd.york.ac.uk/prospero
6. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
7. Hooijmans CR, Rovers MM, de Vries RB, et al. SYRCLE's risk of bias tool for animal studies. *BMC Med Res Methodol* 2014;**14**:43.

All links last accessed April 2024.

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