TITLE

Systematic Reviews: Understanding the Best Evidence For Clinical Decision-Making in Health Care: Pros and Cons

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ABSTRACT

In the era of evidence-based decision-making, systematic reviews are being widely used in many health care policies, government programs, and academic disciplines. Systematic reviews are detailed and comprehensive literature review of a specific research topic with a view to identifying, appraising and synthesising the research findings from various relevant primary studies. A systematic review therefore extracts the relevant summary information from the selected studies without bias by strictly adhering to the review procedures and protocols. This paper presents all underlying concepts, stages, steps and procedures in conducting and publishing systematic reviews. Unlike, the findings of narrative reviews, the synthesised results of any systematic reviews are reproducible, not subjective and bias free. However, there are a number of issues related to systematic reviews that directly impact on the quality of the end results. If the selected studies are of high quality, the criteria of the systematic reviews are fully satisfied, and the results constitute the highest level of evidence. It is therefore essential that the end users of systematic reviews are aware of the weaknesses and strengths of the underlying processes and techniques so that they could assess the results in the correct perspective within the context of the research question.

1. INTRODUCTION

Detailed, comprehensive, objective, bias free and high-quality evidence on the effectiveness of health care intervention is increasingly becoming important for decision-making in health sciences and healthcare policies. As stated by Jahan et al (1) systematic reviews (SRs) have immense importance in the research methodology and provide the highest level of evidence on the effectiveness of healthcare intervention. SR is therefore an essential tool for gathering, summarising and refining the most relevant available evidence from carefully designed healthcare studies to determine the most effective intervention that have a positive impact. A scrupulously conducted SR helps researchers to determine what is already known about a proposed research topic, appraise the quality of the research evidence, synthesise the research evidence from studies of the highest

quality, identify research gaps, prioritise availability of new evidence to fill these gaps, avoid unnecessarily duplication of research, and shape future research projects. SRs involve statistical techniques to synthesise the data from several research studies into a single quantitative estimate to determine the outcome which is largely dependent on the quality and level of the evidence which have been analysed. Drawing on the results of several high-quality studies is much more informative than relying on any single study. However, different studies and their data usually varies in assumptions, methods, sample size and design. SRs can help address such variabilities, offering a structured format of gathering and integrating results from these wider range of studies. The summary effect size becomes increasing important when dealing with a large number of scientific studies on similar research questions often with conflicting results.

The purpose of this article is to introduce the processes and requirements of SRs to minimise selection bias; achieve consistency and maintain high quality in assessing the studies with uniform standard. A number of rigorous systems with specific selection criteria have been developed to improve SR process to achieve its repeatability or reproducibility. In many SRs, statistical meta-analysis plays the key role to synthesise quantitative summary data from independent studies to estimate the common effect size (2). However, while the SRs are routinely used in many evidence-based decision-making processes and offer many advantages, they are not without criticism. Conclusions based on reviews might be subject to bias and error if there are flaws in the design of studies being reviewed and/or the way in which the SR is being conducted, particularly if it fails to follow the recommended criteria or if the evidence is not assessed, analysed and summarised appropriately. This paper critically investigates various aspects of systematic review process and highlights their weaknesses and strengths. The aim is to help the producers and end-users of the evidence to understand how they should assess the outcomes of SRs within the context of their own expertise in the relevant discipline and health care topics. However, it is always essential to make clear distinctions between primary studies and SRs (Table 1).

2. AN OVERVIEW OF SYSTEMATIC REVIEW

Research on any specific clinical topic differs depending on researchers' interest and the use of different analytical tools employed to analyse and summarise the findings. Furthermore, studies on the same topic may be underpinned by different theoretical concepts and assumptions, and the focus of analysis and findings may also represent the specific views of the researchers or funders. Reviews therefore play an important role in summarising existing evidence. These are usually of two types of reviews; narrative reviews (NRs) and SRs (3). Table 2 provides a summary of the differences between these two types of reviews.

To guarantee that the evidence reported in a SR is of highest quality, strict criteria has to be applied (a) to review literature comprehensively; (b) analyse the data objectively and (c) produce conclusions without any bias. Some biases, such as publication bias are difficult to eliminate due to its very nature. Publication bias means that studies which failed to find significant evidence or that contradict accepted believes (negative studies). These studies are less likely to be published than those showing statistically significant results (positive studies). Publication bias can lead to the overestimation of effect sizes and their significance. A funnel plot, where the study size is plotted against the effect estimates of the individual studies can be used to identify publication bias. Often quantitative publication bias is assessed by Egger test (4) and Begg test (5) . Therefore, researchers have been continuously trying to improve the processes, criteria and protocols of SRs to minimise errors due to various biases and design flaws to enhance the quality of the final product. Some protocols are specific to meta-analysis, where the results are quantitatively summarized using statistical methods and pooled effect estimates are calculated (6). Others are concerned with certain research designs such as Randomized Controlled Trials (RCTs), the most rigorous design of determining whether a cause-effect relation exists between intervention and outcome (7).

3. PROCESS OF SYSTEMATIC REVIEWS

A brief list of key protocols in conducting SRs and meta-analyses is provided below.

The Quality of Reporting of Meta-analyses (QUOROM) was proposed by Moher et al in 1999 (8) . This was superseded by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (9). PRISMA Protocols (7) was published in 2015 aiming to facilitate the development and reporting of SR . Consolidated Standards of Reporting Trials (CONSORT) (10) encompasses various initiatives developed by the CONSORT Group to deal with the problems arising from inadequate reporting of RCTs. The Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group (11) proposed a checklist for reporting of meta-analyses of observational studies.

SR must be comprehensive, exhaustive, and meet the expectation of reproducibility. Khan et al (12) suggest the following five steps:

(1) Framing the research or study questions for the intended review

(2) identifying all relevant work in the published and unpublished literature

(3) assessing the quality of studies

(4) summarizing the evidence and

(5) interpreting the findings

There are a number of a authors such as Bettany (13) , Yannascoli, et al (14) and Peters et al (15) who provided a comprehensive summary of conducting a good quality SR. In spite of some minor differences in the details, the key steps in conducting a systematic review literature largely remains the same.

3.1. Planning of systematic reviews

The first stage of any SR is the planning that includes creating a research team, identification of a research question, determining inclusion/exclusion criterias, preparation of data extraction form, organising a comprehensive literature search strategy and registration of study protocol.

3.1.1. Formation of a research team

Establishing a research team is the first step in conducting a SR once a research question is identified. The research team must agree on the review topic, strategy, approach and framework of their review. They require agreement on the list of tasks and any foreseeable problems should be addressed earlier on and during the planning stage. The team should agree on task distribution and timeframe to complete them. The successful implementation of the planning would require regular review of the progress and modification of the review process in the light of any new information.

3.1.2. Reason for the study

The aims and objectives for any chosen health care topic should be the driving force for a SR. The team must be fully aware of reasons behind the proposed review and why the study is important. It is essential to keep in mind the positive contribution of the review to the existing literature and the importance of its reproducibility along with its practical benefit such as (a) is the study going to answer a question proposed by the research team?; (b) how important is the health care topic in terms of benefit to the society?; (c) what is the overall advantage to the patient in terms of treatment? (d) is there a potential to save lives and or money?; (e) would it impact any future healthcare policy decisions? etc

3.1.3. Research question

This is the key driver in formulating a SR. This requires initial literature review to check if the research question has already been addressed by others and how recently, and if there is an

accessible and contemporary material to update it. All the planning and activities will be centred around the research question. Concepts within the review questions should be clearly defined to account for the gaps in the existing research. The review team must critically discuss the appropriateness and importance of the research question, and its associated concepts, and agree on an action plan guided by the resources available. The research questions should not be too broad or too narrow to ensure the review captures relevant evidence in-depth. At this stage, the team should agree on the theory or logic underpinning their research questions, particularly when complex interventions are synthesised.

Some helpful framework to decide research question are: Patient/Population/Problem, Intervention, Comparison, Outcome (PICO) for quantitative outcomes; and Setting, Perspective, Intervention, Comparison, Evaluation (SPICE) for qualitative outcomes. If the study has already been conducted by others or not can be check by visiting websites such as PROSPERO, Cochrane Database, JBI Database etc (see later).

3.1.4. Determine inclusion and exclusion criteria

The determination of research question and well-defined relevant concepts help determine the types of studies to be included. Inclusion criteria may also determine the countries, year and language of studies to be included in the review. Clear specification of criteria is essential to avoid personal or selection bias during the literature search process. The specific conditions and protocols to select studies in the proposed review should be explicitly stated under this section. There are many considerations that could potentially impact on the inclusion/exclusion criteria but the most relevant ones (e,g. study period, study type/design, RCTs, language, outcome measures) must be clearly stated and implemented throughout the searching process.

3.1.5. Preparation of data extraction form

Data extraction form in a SR is similar to the questionnaire in a survey. It must clearly specify what data from the selected records will be extracted and how. Since independent search of databases is a requirement for a SR, the data extraction form makes the collected data consistent and in the same format.

3.1.6. Registration of protocol

Before starting a SR, the team requires to register the study protocol on an online professional platform dedicated for such studies. This would inform the global research community of the upcoming research by a specific team ensuring that the study is not duplicated by another team. One of the sites based in the UK is the International prospective register of systematic reviews accessible via https://www.crd.york.ac.uk/prospero/. Another option is Cochrane Database of Systematic Reviews as at (16) or JBI Database of Systematic Reviews and Implementation Reports at (17). Helpful guidance on development of protocol is found in the JBI Reviewers Manual at JBI database (18).

3.2. Search strategy and data extraction

The second stage of systematic review involves the actual search of all relevant databases, review of search outcomes, collection of relevant studies, selection of records based on inclusion criteria, extraction of research data using data extraction form and comparison of records of different team members.

3.2.1. Database search strategy

Extensive and comprehensive search of all the relevant literature on a research topic are undertaken to identify and collect all materials pertaining to the review. Search should be inclusive of all published and unpublished studies in any language and from any country. Before embarking on the

search, the team must prepare a search strategy, list the relevant databases and appropriate search engines and if needs be, create accounts for various databases for the entire team to access. Because research questions do not always precisely match existing academic disciplines and databases may not be comprehensive, it is essential to search all relevant electronic databases methodically from different disciplines to capture all evidences to address the same research question . The choice of bibliographic databases is critical in determining the thoroughness of one's search. Study time period should be specified for the search to reflect that only the studies conducted within the relevant period are considered for the review. During the search, all different combinations of the key/technical words, phrases and terms related to the topic of interest must be included using all available search engines. The search should be extended to all major languages to make sure that the publications in non-English languages are fully covered, however, this will depend on the resources available and the expertise of the research team. It is important to record the search date and note the cut-off date up to which the review entries are included from a particular database. Accurate details of every search history including search log, search terms/phrases, date/time of search, name of database etc. is imperative.

3.2.2. Review of search outcomes

At least two members of the review team should conduct independent searches in all relevant databases taking into account both the electronic and paper version of the materials, and then reconcile the information gathered from the identified studies. If needed, a third reviewer may be engaged to reach an agreement on the selection of any disputed studies. Any limitations or weaknesses of the search should be included in the review report. In case of disputes/discrepancies between two members of the search team on inclusion of any study, an independent opinion of another expert will be used.

3.2.3. Collection of studies

During the first stage, the selection of studies is based on the checking the title of the articles by the independent reviewers. The studies selected in the first stage are then critically analysed based on the abstracts and full text articles are subsequently obtained. In the final stage, the selection of studies which will be included in the SR is undertaken. The list of citations or bibliographies of the full text articles should be reviewed to identify any additional studies on the topic of interest. The same criteria of inclusion/exclusion should be applied to these additional studies.

3.2.4. Selection of records based on inclusion criteria

Once the individual members of the team have independently identified the articles to be included in the SR, all the relevant documents, including full-text article, must be collected and listed for review and record. A well-documented summary of key information in each study may help conduct the review in a systematic and orderly manner. The analytical and critical review of these documents would lead to the review report to address the research question. The selected records then be verified against the predetermined inclusion and exclusion criteria to determine for the final research synthesis. Referencing software such as EndNote or Rayyan should be used to keep an accurate record of the selected studies. Any studies excluded during the full-text review should be recorded and reasons explained.

3.2.5. Extraction of summary data

Data extraction on the items of interest (variables) should be entered independently by at least two team members on a spreadsheet in a predetermined format. The format should allow sufficient flexibility to accommodate reporting of data in different format or scale or unit. It may be a good idea to pilot the data extraction sheet with a subset of the studies to make sure that the format is robust enough to deal with the diversities, if any. The data entry of individual team member for each variable should be compared and consensus should be achieved before embarking on the analyses

of the data. In case of any dispute a third reviewer or an expert in the field should be consulted in the decision-making process. In case of any missing or confusing data, the authors of the relevant articles should be contacted for clarification or obtaining the missing information. Excel or any other spreadsheet program should be used to gather qualitative and quantitative information. The summary of numerical data may be used for meta-analysis to synthesise quantitative results of independent primary studies.

3.3. Research data synthesis and reporting

The third stage of any SR deals with the synthesis of the data, interpretation of findings and reporting of results for publication.

3.3.1. Synthesis of research data

Research data from all selected primary studies should be presented in a tabular form so that different characteristics and summary statistics are on a single document. The synthesis of numerical data is obtained by using meta-analysis which calculates estimate of the common effect size of relevant intervention along with 95% confidence interval (19).

3.3.2. Interpretation of findings

The results produced by SRs should be interpreted accurately in the context of the study based on the research synthesis. This will be the most important piece of information for readers and users, including policy makers, indicating the implications of the final finding. The synthesis may reveal new evidence that may have future research and policy implications.

3.3.3. Reporting the study outcomes

Reporting of findings of SRs may have different form and/or outlet. This may include technical report, journal article, updating previous report etc. The style and content of the report may vary

but the final outcome of the review must be the same and reproducible. A flow chart (Figure 1) of the number of studies starting from an initial search stage to the final selection of records is essential for the reporting of any SR (20). Forest plot (Figure 2) also is an essential part of the report if meta-analysis is included in the synthesis (21).

4. STUDY QUALITY AND LEVEL OF EVIDENCE

Not every SR would produce results of good quality with high level of evidence. These depend on the quality of the individual studies included in the synthesis as well as the level of evidence they provide (Table 3).

4.1. Assessing quality of studies

The quality of the included studies directly impacts on the quality of evidence. In fact, the quality of the SR is no better than the study with the worst quality included in the review. Thus, quality analysis of the included studies is a crucial part of any systematic reviews.

One key aspect of any systematic review is to check the internal and external validity of the selected studies (21). The internal validity is threatened by the methodological errors and varieties of biases such as selection, measurement, analytical, and interpretation bias. The introduction of any kind of bias invalidates the reproducibility of the studies. Studies do not meet the criteria of external validity disqualify to be included in the analysis as the results based on the data from such studies should not be generalised to the wider population.

There are several measures of study quality in the literature. One measure to assess the quality of randomised controlled trials in meta-analysis is Jadad Score (22). This score is also known as the Oxford Quality Scoring System which ranges from zero to five, zero being the lowest quality and five being the highest achievable quality based on reporting of randomization, blinding, and withdrawals

316 reported during the study period. The most recent one is a revised Cochrane Risk-of-Bias (RoB 2)
317 tool for RCTs (23). The Newcastle-Ottawa Scale (NOS) is used for assessing the quality of
318 nonrandomised studies in meta-analyses. Wells et al (24) have developed this scale to assess the
319 quality of nonrandomised studies. The other method to address the study bias is the Risk Of Bias In
320 Non-randomised Studies of Interventions (ROBINS-I) proposed by Sterne et al (6) . It is a new tool
321 for evaluating risk of bias in estimates of the comparative effectiveness (harm or benefit) of
322 interventions from studies that did not use randomisation to allocate units (individuals or clusters of
323 individuals) to comparison groups. The tool is particularly useful to those undertaking systematic
324 reviews that include non-randomised studies.
325
326 ***4.2. Level of evidence***
327 Not every study provides the same level of evidence because it depends on the design of the
328 primary study (Table 3). There are two different sources of evidence – primary and secondary. The
329 primary source provides the original data and analysis from the research studies. No outside
330 evaluation or interpretation is provided. An example of a primary literature source is a peer-
331 reviewed research article. Other primary sources include preprints, theses, reports and conference
332 proceedings.
333 The level of evidence from primary source are broadly categorised based on the study design as
334 follows (highest to lowest):
335 • Experimental: Randomised Controlled Trials (RCTs), known as the 'Gold Standard'
336 • Quasi-experimental studies (such as Non-randomised control studies, Before-and-after
337 study, Interrupted time series)
338 • Observational studies (eg Cohort study, Case-control study, Cross-sectional studies).
339 The secondary source includes analysis, synthesis, interpretation and evaluation of primary works.
340 These include commentaries on and discussions of evidence. Table 3 provided a More detailed rating

(highest to lowest) of level of evidence for quantitative questions is suggested in the health care literature (25) . Further information can be found in Canberra University Library (26)

5. STRENGTHS AND WEAKNESSES OF SYSTEMATIC REVIEWS

The strengths and limitations of SRs are briefly summarised below. These remarks should only be taken within the context of the specific SR, assuming that all relevant conditions are met.

5.1. Strengths

SRs are based on a clearly formulated questions of all the relevant high quality studies summarising the evidence using an explicit methodology. These reviews provide objective appraisal of evidence as the underlying procedures and protocols minimise the bias and errors from difference sources and make the final outcomes reproducible. Furthermore, SRs are peer-reviewed at different stages which helps minimise errors and reduce researcher bias. Unlike NR, SRs could use the quantitative data of individual studies to combine them for providing much stronger evidence. Meta-analyses can be an integral part of SRs if the studies contain summary statistics on quantitative outcome variables. All information about the method and extent of searches, collection and selection of studies, extraction of data, any resolution of disagreements or missing information etc are fully recorded by the research team in any SR making the outcomes more transparent and open. Properly conducted SRs may help set up relatively objective baseline or benchmark to assess future research and evidence on specific topic. SRs could identify research gap during the process of searches and investigations enabling to evolve new research questions for further investigations in the areas where disagreement or lack of sufficient evidence is present. The strength of a SR lies in the transparency at each phase of the synthesis process, allowing the reader to focus on the merits of each decision made in compiling the information.

5.2. Weaknesses

Even though the SRs provide more reliable, objective and accurate evidence than the NRs, it has its own potential weaknesses if the procedures and protocols are not strictly followed. Flaw or non-compliance in any step or stage of SR will seriously undermine the quality of evidence. SRs can be inconclusive if there are conflicting evidences from different studies or trials. This may suggest the need for further investigations. SRs are subject to different kind of biases including description bias, selection bias, measurement bias, analytical bias an interpretation bias (27).

6. CONCLUSIONS

It is inevitable that rigorous focus on generating evidence-based guidelines, researchers and organisations in the health care sector are increasing adapting the practice of SRs and meta-analysis. It is essential that everyone involved in the evidence-based decision-making process must have an in-depth knowledge of various stages of undertaking these complex reviews from its inception to the end. The quality of the results produced by any SR will never be better than the quality of the study design reported in the individual trials. However, a properly conducted SR could provide much needed high quality evidence for making appropriate decisions if the underlying processes, protocols and methods are properly and strictly observed. Nonetheless, every step in a SR must be scrutinized for potential bias, from the formulation of the research question to the interpretation and discussion of the results, to ensure the quality and value of the final product. The research team must be well-skilled to decide on what should and should not be included strictly following the agreed procedure and criteria as well as meeting the underlying assumptions and satisfying the technical requirements. In case of disagreement, expert opinion, past experience and discipline knowledge may be the useful guide for the research team. Some of the key benefits of using an evidence based approach for policy-making include (a) ensuring that policies are responding to the real needs of the community; (b) highlighting the urgency of an issue or problem which requires immediate attention; (c) sharing of information amongst other members of the health care sector; (d) potentially reducing

393 the government expenditure which may otherwise be directed into ineffective policies or programs
394 which is likely to produce an acceptable return on the financial investment allocated toward various
395 public programs and (f) enhancing consultative decisions that are characterised by transparency and
396 accountability.
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