Study designs: Part 7 – Systematic reviews

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Abstract

In this series on research study designs, we have so far looked at different types of primary research designs which attempt to answer a specific question. In this segment, we discuss systematic review, which is a study design used to summarize the results of several primary research studies. Systematic reviews often also use meta-analysis, which is a statistical tool to mathematically collate the results of various research studies to obtain a pooled estimate of treatment effect; this will be discussed in the next article.

Keywords: Research design, review [publication type], systematic review [publication type]

In the previous six articles in this series on study designs, we have looked at different types of *primary* research study designs which are used to answer research questions. In this article, we describe the systematic review, a type of *secondary* research design that is used to summarize the results of prior primary research studies. Systematic reviews are considered the highest level of evidence for a particular research question.[1]

SYSTEMATIC REVIEWS

As defined in the *Cochrane Handbook for Systematic Reviews of Interventions*, "Systematic reviews seek to collate evidence that fits pre-specified eligibility criteria in order to answer a specific research question. They aim to minimize bias by using explicit, systematic methods documented in advance with a protocol."[2]

NARRATIVE VERSUS SYSTEMATIC REVIEWS

Review of available data has been done since times immemorial. However, the traditional narrative reviews ("expert reviews") do not involve a systematic search of the literature. Instead, the author of the review, usually an expert on the subject, used informal methods to identify (what he or she thinks are) the key studies on the topic. The final review thus is a summary of these "selected" studies. Since studies are chosen at will (haphazardly!) and without clearly defined criteria, such reviews preferentially include those studies that favor the author's views, leading to a potential for subjectivity or selection bias.

In contrast, systematic reviews involve a formal prespecified protocol with explicit, transparent criteria for the inclusion and exclusion of studies, thereby ensuring completeness of coverage of the available evidence, and providing a more objective, replicable, and comprehensive overview it.

META-ANALYSIS

Many systematic reviews use an additional tool, known as meta-analysis, which is a statistical technique for combining the results of multiple studies in a systematic review in a

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mathematically appropriate way, to create a single (pooled) and more precise estimate of treatment effect. The feasibility of performing a meta-analysis in a systematic review depends on the number of studies included in the final review and the degree of heterogeneity in the inclusion criteria as well as the results between the included studies. Meta-analysis will be discussed in detail in the next article in this series.

THE PROCESS OF A SYSTEMATIC REVIEW

The conduct of a systematic review involves several sequential key steps.[3,4] As in other research study designs, a clearly stated research question and a well-written research protocol are essential before commencing a systematic review.

Step 1: Stating the review question
Systematic reviews can be carried out in any field of medical research, e.g. efficacy or safety of interventions, diagnostics, screening or health economics. In this article, we focus on systematic reviews of studies looking at the efficacy of interventions. As for the other study designs, for a systematic review too, the question is best framed using the Population, Intervention, Comparator, and Outcome (PICO) format.

For example, Safi *et al.* carried out a systematic review on the effect of beta-blockers on the outcomes of patients with myocardial infarction.[5] In this review, the **Population** was patients with suspected or confirmed myocardial infarction, the **Intervention** was beta-blocker therapy, the **Comparator** was either placebo or no intervention, and the **Outcomes** were all-cause mortality and major adverse cardiovascular events. The review question was *"In patients with suspected or confirmed myocardial infarction, does the use of beta-blockers affect mortality or major adverse cardiovascular outcomes?"*

Step 2: Listing the eligibility criteria for studies to be included
It is essential to explicitly define *a priori* the criteria for selection of studies which will be included in the review. Besides the PICO components, some additional criteria used frequently for this purpose include language of publication (English versus non-English), publication status (published as full paper versus unpublished), study design (randomized versus quasi-experimental), age group (adults versus children), and publication year (e.g. in the last 5 years, or since a particular date). The PICO criteria used may not be very specific, e.g. it is possible to include studies that use one or the other drug belonging to the same group. For instance, the systematic review by Safi *et al.* included all randomized clinical trials, irrespective of setting, blinding, publication status, publication year, or language, and reported outcomes, that had used any beta-blocker and in a broad range of doses.[5]

Step 3: Comprehensive search for studies that meet the eligibility criteria
A thorough literature search is essential to identify all articles related to the research question and to ensure that no relevant article is left out. The search may include one or more electronic databases and trial registries; in addition, it is common to hand-search the cross-references in the articles identified through such searches. One could also plan to reach out to experts in the field to identify unpublished data, and to search the grey literature non-peer-reviewednon-peer-reviewed. This last option is particularly helpful non-pharmacologic (theses, conference abstracts, and non-peer-reviewed journals). These sources are particularly helpful when the intervention is relatively new, since data on these may not yet have been published as full papers and hence are unlikely to be found in literature databases. In the review by Safi *et al.*, the search strategy included not only several electronic databases (Cochrane, MEDLINE, EMBASE, LILACS, etc.) but also other resources (e.g. Google Scholar, WHO International Clinical Trial Registry Platform, and reference lists of identified studies).[5] It is not essential to include all the above databases in one's search. However, it is mandatory to define in advance which of these will be searched.

Step 4: Identifying and selecting relevant studies
Once the search strategy defined in the previous step has been run to identify potentially relevant studies, a two-step process is followed. First, the titles and abstracts of the identified studies are processed to exclude any duplicates and to discard obviously irrelevant studies. In the next step, full-text papers of the remaining articles are retrieved and closely reviewed to identify studies that meet the eligibility criteria. To minimize bias, these selection steps are usually performed independently by at least two reviewers, who also assign a reason for non-selection to each discarded study. Any discrepancies are then resolved either by an independent reviewer or by mutual consensus of the original reviewers. In the Cochrane review on beta-blockers referred to above, two review authors independently screened the titles for inclusion, and then, four review authors independently reviewed the screen-positive studies to identify the trials to be included in the final review.[5] Disagreements were resolved by discussion or by taking the opinion of a separate reviewer. A summary of this selection process, showing the degree of agreement between reviewers, and a flow diagram that depicts the

numbers of screened, included and excluded (with reason for exclusion) studies are often included in the final review.

Step 5: Data extraction

In this step, from each selected study, relevant data are extracted. This should be done by at least two reviewers independently, and the data then compared to identify any errors in extraction. Standard data extraction forms help in objective data extraction. The data extracted usually contain the name of the author, the year of publication, details of intervention and control treatments, and the number of participants and outcome data in each group. In the review by Safi *et al.*, four review authors independently extracted data and resolved any differences by discussion.[5]

Handling missing data

Some of the studies included in the review may not report outcomes in accordance with the review methodology. Such missing data can be handled in two ways – by contacting authors of the original study to obtain the necessary data and by using data imputation techniques. Safi *et al.* used both these approaches – they tried to get data from the trial authors; however, where that failed, they analyzed the primary outcome (mortality) using the best case (i.e. presuming that all the participants in the experimental arm with missing data had survived and those in the control arm with missing mortality data had died – representing the maximum beneficial effect of the intervention) and the worst case (all the participants with missing data in the experimental arm assumed to have died and those in the control arm to have survived – representing the least beneficial effect of the intervention) scenarios.

Evaluating the quality (or risk of bias) in the included studies

The overall quality of a systematic review depends on the quality of each of the included studies. Quality of a study is inversely proportional to the potential for bias in its design. In our previous articles on interventional study design in this series, we discussed various methods to reduce bias – such as randomization, allocation concealment, participant and assessor blinding, using objective endpoints, minimizing missing data, the use of intention-to-treat analysis, and complete reporting of all outcomes.[6,7] These features form the basis of the Cochrane Risk of Bias Tool (RoB 2), which is a commonly used instrument to assess the risk of bias in the studies included in a systematic review.[8] Based on this tool, one can classify each study in a review as having low risk of bias, having some concerns regarding bias, or at high risk of bias. Safi *et al.* used this tool to classify the included studies as having low or high risk of bias and presented these data in both tabular and graphical formats.[5]

In some reviews, the authors decide to summarize only studies with a low risk of bias and to exclude those with a high risk of bias. Alternatively, some authors undertake a separate analysis of studies with low risk of bias, besides an analysis of all the studies taken together. The conclusions from such analyses of only high-quality studies may be more robust.

Step 6: Synthesis of results

The data extracted from various studies are pooled quantitatively (known as a meta-analysis) or qualitatively (if pooling of results is not considered feasible). For qualitative reviews, data are usually presented in the tabular format, showing the characteristics of each included study, to allow for easier interpretation.

Sensitivity analyses

Sensitivity analyses are used to test the robustness of the results of a systematic review by examining the impact of excluding or including studies with certain characteristics. As referred to above, this can be based on the risk of bias (methodological quality), studies with a specific study design, studies with a certain dosage or schedule, or sample size. If results of these different analyses are more-or-less the same, one can be more certain of the validity of the findings of the review. Furthermore, such analyses can help identify whether the effect of the intervention could vary across different levels of another factor. In the beta-blocker review, sensitivity analysis was performed depending on the risk of bias of included studies.[5]

IMPORTANT RESOURCES FOR CARRYING OUT SYSTEMATIC REVIEWS AND META-ANALYSES

Cochrane

Cochrane is an organization that works to produce good-quality, updated systematic reviews related to human healthcare and policy, which are accessible to people across the world.[9] There are more than 7000 Cochrane reviews on various topics. One of its main resources is the Cochrane Library (available at https://www.cochranelibrary.com/), which incorporates several databases with different types of high-quality evidence to inform healthcare decisions, including the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Clinical Answers.

The Cochrane Handbook for Systematic Reviews of Interventions

The Cochrane handbook is an official guide, prepared by the Cochrane Collaboration, to the process of preparing and maintaining Cochrane systematic reviews.[10]

Review Manager software

Review Manager (RevMan) is a software developed by Cochrane to support the preparation and maintenance of systematic reviews, including tools for performing meta-analysis.[11] It is freely available in both online (RevMan Web) and offline (RevMan 5.3) versions.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement is an evidence-based minimum set of items for reporting of systematic reviews and meta-analyses of randomized trials.[12] It can be used both by authors of such studies to improve the completeness of reporting and by reviewers and readers to critically appraise a systematic review. There are several extensions to the PRISMA statement for specific types of reviews. An update is currently underway.

Meta-analysis of Observational Studies in Epidemiology statement

The Meta-analysis of Observational Studies in Epidemiology statement summarizes the recommendations for reporting of meta-analyses in epidemiology.[13]

PROSPERO

PROSPERO is an international database for prospective registration of protocols for systematic reviews in healthcare.[14] It aims to avoid duplication of and to improve transparency in reporting of results of such reviews.

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