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Systematic Reviews and Meta-Analysis: Scientific Rationale and Interpretation

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ABSTRACT

Systematic reviews represent a specific type of medical research in which the units of analysis are the original primary studies. They are essential tools in synthesizing available scientific information, increasing the validity of the conclusions of primary studies, and identifying areas for future research. They are also indispensable for the practice of evidence-based medicine and the medical decision-making process. However, conducting high quality systematic reviews is not easy and they can sometimes be difficult to interpret. This special article presents the rationale for carrying out and interpreting systematic reviews and uses a hypothetical example to draw attention to key-points.

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Revisiones sistemáticas y metaanálisis: bases conceptuales e interpretación

Palabras clave:
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Metaanálisis
Medicina basada en la evidencia

RESUMEN

Las revisiones sistemáticas son investigaciones científicas en las cuales la unidad de análisis son los estudios originales primarios. Constituyen una herramienta esencial para sintetizar la información científica disponible, incrementar la validez de las conclusiones de estudios individuales e identificar áreas de incertidumbre donde sea necesario realizar investigación. Además, son imprescindibles para la práctica de una medicina basada en la evidencia y una herramienta fundamental en la toma de decisiones médicas. Sin embargo, la realización de una revisión sistemática de calidad no es una tarea sencilla, como en ocasiones tampoco lo es su interpretación. En este artículo especial se presentan las bases conceptuales para la realización y la interpretación de revisiones sistemáticas, poniendo especial énfasis en los puntos clave durante su ejecución mediante un ejemplo hipotético.

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Abbreviations

MA: meta-analysis
RCT: randomized clinical trial
SR: systematic review

INTRODUCTION

It has been a tiring week. You sit down to look back calmly on the decisions you've made. These included requesting an operation for a patient with three-vessel disease, deciding whether to treat an 82 year old patient with inferior infarction of 70 min duration with fibrinolytic therapy or move her to your center for primary angioplasty, and deciding on anticoagulation treatment for an outpatient with atrial fibrillation.

Although you are reasonably sure your decisions were based on the best available evidence, you have some lingering doubts. Perhaps studies have been published which could lead your decisions to be questioned? Or perhaps different studies of the same intervention have produced different results? It's true that you have not had much time for reading over the past few months. To quickly clear up your doubts, you realize you need a concise, current, and rigorous summary of the best available evidence regarding the decisions you had to take. In other words, you need a systematic review (SR).[1]

SRs are considered to be the most reliable source in informing medical decision-making,[2] which may explain their increasing popularity and the large rise in the number of SRs published in recent years.[2] However, performing a high-quality SR is not easy. There are rules governing the way they should be carried out and, as with other designs, recommendations on how results should be presented. These quality control guidelines have been developed by international, multidisciplinary groups of experts which include authors of SRs, methodologists, clinicians, and editors.[2–4] This article presents the underlying rationale for performing and interpreting SRs and uses a hypothetical example to highlight key-points in their execution.

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CONCEPT AND NOMENCLATURE

SRs are scientific investigations in which the unit of analysis is the original primary studies. These are used to answer a clearly formulated question of interest using a systematic and explicit process. For that reason, SRs are considered to be secondary research ("research-based research"). On the other hand, reviews which do not follow a systematic process (narrative reviews) cannot be considered to constitute a formal research process, but are simply a type of scientific literature based primarily on opinion.

From a formal point of view, SRs summarize the results of primary research using strategies to limit bias and random error.[5] These strategies include:

- Systematic and exhaustive searching for all potentially relevant articles.
- The use of explicit and reproducible criteria to select articles which are eventually included in the review.[1]
- Describing the design and implementation of the original studies, synthesizing the data, and interpreting the results.

Although SRs are a tool for synthesizing information, it is not always possible to present the results of the primary studies briefly. When results are not combined statistically, the SR is called a qualitative review. In contrast, a quantitative SR, or meta-analysis (MA) is an SR which uses statistical methods to combine the results of two or more studies.[1]

An SR should not to be confused with an MA. The first is always possible, while the second is only sometimes possible. However, when conditions allow, MAs provide very useful, manageable information regarding the effect of a treatment or intervention, both in general and in specific patient groups. In addition, MAs make it possible to estimate the effect of an intervention more precisely and to detect moderate but clinically important effects that may have gone undetected in the primary studies. Typically, MAs combine aggregate data from published studies, but sometimes individual data from patients in different studies can be combined. This is called individual patient data meta-analysis and is considered the gold standard in SR.[6]

It should be noted that, in contrast to narrative reviews, SRs use a systematic method to search for all potentially relevant studies and apply explicit, reproducible, previously defined criteria to select the articles included in the final review. It is these features which give SRs their scientific character, in contrast to narrative reviews. Table 1 shows the difference between the two types of review.

As in clinical trials, a protocol should be developed prior to carrying out an SR.[7] This will help the researchers to give due consideration to the most appropriate methods for use in the review and will also prevent decisions being taken *a posteriori* based on the results. The first international register of protocols for systematic reviews, apart from the Cochrane SRs, was recently published under the name of PROSPERO (http://www.crd.york.ac.uk/prospero/).

STAGES IN A SYSTEMATIC REVIEW

Briefly, a SR consists of the following steps:

- Definition of the clinical question of interest and the inclusion and exclusion criteria for studies.
- Identification and selection of relevant studies.
- Extraction of data from primary studies.
- Analysis and presentation of results.
- Interpretation of results.

Definition of the Clinical Question of Interest

The first step is to correctly formulate the clinical question of interest. In general, this should be explicit and structured so as to include the following key components:[8]

- The specific population and context. For example, elderly patients (over 75 years) admitted for acute myocardial infarction with ST elevation.
- The exposure of interest. This could be a risk factor, a prognostic factor, an intervention or treatment, or a diagnostic test. In the case of an intervention, treatment or diagnostic test a control exposure is usually defined at the same time. For example, primary angioplasty (intervention) versus fibrinolysis (control).
- Events of interest. For example, total mortality, cardiovascular mortality, readmission for acute coronary syndrome, revascularizations, etc.

From these elements, you might frame the question as follows: compared with fibrinolysis, does primary angioplasty reduce mortality and myocardial infarction in patients over 75 years of age? Once the question of interest has been defined and circumscribed, it is easier to establish the inclusion and exclusion criteria for primary studies. An ill-defined research question, on the other hand, leads to confused decision-making about which studies may be relevant in answering the question.

In many cases not easy to decide what the specific research question should be. It is however clear that it should be clinically relevant. If questions are too vague (e.g. is primary angioplasty useful in acute myocardial infarction?), they will be of little help to the clinician when making a decision about a particular patient. Exposures or patient characteristics which may affect the event of interest should also be taken into account. For example, it is not uncommon for patients over 75 years of age to be treated with oral anticoagulation, which could affect the expected event of interest. The study population could therefore be restricted to patients who are not receiving oral anticoagulation. However, overly specific inclusion criteria may limit the applicability of the results. Another

Table 1
Differences Between Systematic and Narrative Reviews.

Characteristic	Narrative review	Systematic review
Question of interest	Not structured, not specific	Structured question, well-defined clinical problem
Article search and sources	Not detailed and not systematic	Structured and explicit search
Selection of articles of interest	Not detailed and not reproducible	Selection based on explicit criteria uniformly applied to all articles
Assessing the quality of the information	Absent	Structured and explicit
Synthesis	Often a qualitative summary	Qualitative and quantitative summary
Inferences	Sometimes evidence-based	Normally evidence-based

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