

CME Article

# Systematic reviews and meta-analysis

S Green

## ABSTRACT

**Systematic reviews form a potential method for overcoming the barriers faced by clinicians when trying to access and interpret evidence to inform their practice. This fourth article in the Evidence-Based Medicine and Healthcare series of the Singapore Medical Journal introduces readers to systematic reviews, outlining why they are important, describing their methods and providing readers with the skills to recognise and understand a reliable review.**

**Keywords: evidence-based medicine, meta-analysis, systematic reviews**

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## INTRODUCTION

This important series published by the Singapore Medical Journal has introduced readers to the need for, and concepts of, evidence-based healthcare. To date, papers in this series have outlined the process of evidence-based healthcare, the steps of identifying evidence through searching the literature, and appraisal of research<sup>(1-3)</sup>.

Evidence-based healthcare is the integration of best research evidence with clinical expertise and patient values<sup>(4)</sup>. Using evidence from reliable research to inform healthcare decisions has the potential to ensure best practice and reduce variation in healthcare delivery. However, incorporating research into practice is time consuming, and so we need methods of facilitating easy access to evidence for busy clinicians. Systematic reviews aim to inform and facilitate this process through research synthesis of multiple studies, enabling increased and efficient access to evidence. As Susan Bidwell outlines in her contribution to this series on finding the evidence<sup>(2)</sup>, the first step to take when an information need arises is to find out whether someone else has already asked the same question and produced a reliable and systematic review. Because no study, regardless of its type, should be interpreted in isolation, a systematic review is generally the best form of evidence<sup>(5)</sup>.

This article aims to introduce readers to:

- the rationale for systematic reviews
- the reasons for undertaking and using a systematic review
- the steps in undertaking a systematic review, and
- the concept of meta-analysis.

## What is a systematic review?

A systematic review is a scientific tool that can be used to appraise, summarise, and communicate the results and implications of otherwise unmanageable quantities of research. In this way, healthcare providers can evaluate existing or new technologies and practices efficiently and consider the totality of available evidence. Systematic reviews are of particular value in bringing together a number of separately conducted studies, sometimes with conflicting findings, and synthesising their results. To this end, systematic reviews may or may not include a statistical synthesis called meta-analysis, depending on whether the studies are similar enough so that combining their results is meaningful<sup>(6)</sup>.

Systematic reviews are often called overviews. The evidence-based practitioner, David Sackett, makes a distinction between a review, an overview and a meta-analysis, defining each as follows:

- Review: the general term for all attempts to synthesise the results and conclusions of two or more publications on a given topic.
- Overview: when a review strives to comprehensively identify and track down all the literature on a given topic (also called “systematic literature review”).
- Meta-analysis: a specific statistical strategy for assembling the results of several studies into a single estimate<sup>(4)</sup>.

Although many people use the term meta-analysis interchangeably with systematic review, strictly speaking a meta-analysis is an optional component of a systematic review. This paper uses the term systematic review for the whole process of finding, selecting, appraising, synthesising and reporting

Monash Institute of  
Health Services  
Research  
Locked Bag 29  
Clayton  
Victoria 3168  
Australia

S Green, PhD  
Associate Professor  
and Director,  
Australasian  
Cochrane Centre

**Correspondence to:**  
Dr Sally Green  
Tel: (61) 3 9594 7531  
Fax: (61) 3 9594 7554  
Email: sally.green@  
med.monash.edu.au

evidence, and meta-analysis for the specific statistical technique of combining the data from individual studies.

### What are Cochrane reviews?

Cochrane reviews are systematic reviews undertaken by members of The Cochrane Collaboration<sup>(7)</sup>, adhering to a specific methodology. The Cochrane Collaboration is an international organisation that aims to help people make well-informed decisions about healthcare by preparing, maintaining and promoting the accessibility of systematic reviews of the effects of healthcare interventions. Completed Cochrane reviews are published in The Cochrane Library, which is available on subscription<sup>(8)</sup>. *The Cochrane Library* is published four times a year. Each issue contains all existing Cochrane reviews plus an increasingly wider range of new and updated reviews. It is published and distributed by Wiley InterScience and by Issue 1, 2005, *The Cochrane Library* contained 2,249 completed reviews, and 1,539 protocols for reviews in progress.

### Why are systematic reviews important?

For busy healthcare providers and decision makers, systematic reviews are important as they summarise the overwhelming amount of research-based healthcare information that is available to be read and synthesised<sup>(6)</sup>. They also overcome some of the bias associated with small single trials where results may not be robust against chance variation if the

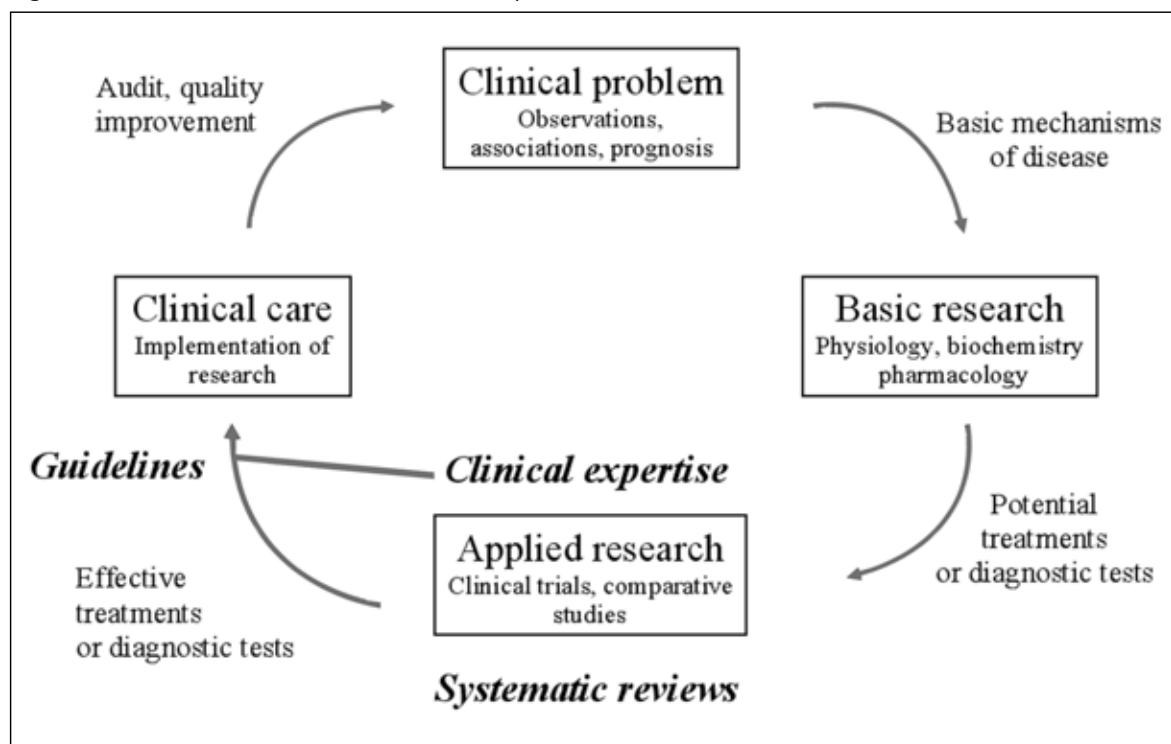
effects being investigated are small. Finally, systematic reviews may overcome the lack of generalisability inherent in studies conducted in one particular type of population by including many trials conducted in varying populations.

While a traditional or narrative review may be no more than a subjective assessment by an expert using a select group of studies to support their conclusion, a systematic review attempts to be systematic in the identification and evaluation of research, objective in its interpretation and reproducible in its conclusions. As systematic reviews attempt to consider all studies published on a given clinical question, conclusions are drawn based on all the available evidence, and a thorough overview of the body of knowledge can be presented.

### How do systematic reviews contribute to evidence-based healthcare?

Systematic reviews contribute to the use of evidence to solve clinical problems, but they are not all that we need. A framework for the use of evidence to solve clinical problems is outlined in Fig. 1. Systematic reviews are a form of applied research and fit into this framework both by synthesising and interpreting primary research and, in conjunction with clinical expertise, informing clinical care. Systematic reviews do not replace the need for basic research and observational studies to identify appropriate clinical questions and formulate promising hypotheses. Nor

Fig. 1 Framework for the use of evidence to solve clinical problems<sup>(9)</sup>.



are systematic reviews fulfilling the same function as evidence-based clinical practice guidelines, which interpret and apply the results of systematic reviews in local clinical settings.

### **How are systematic reviews conducted? Key points in the appraisal of systematic reviews**

In order to reduce bias in systematic reviews, a formal, rigorous methodology has been developed. This is comprehensively outlined by the Cochrane Collaboration in their Cochrane Handbook for Systematic Reviews of Interventions<sup>(10)</sup>. Developing an understanding of the methodology of conducting systematic reviews and the attempts review authors make to minimise bias in their reviews can help in the appraisal of published reviews.

Developing a systematic review requires a number of discrete steps<sup>(10)</sup>:

#### 1. Defining an appropriate question.

Defining the question for a systematic review requires a clear statement of the intervention of interest, relevant patient groups and appropriate outcomes. Repeatedly asking “why is this clinical question important to answer?” is helpful in framing the question correctly. When appraising a systematic review, you should look to see if the question the review addresses is clearly stated, and if it includes description of the intervention, population and outcomes of interest to you. The objectives of the review should follow logically from the question and be clearly stated.

#### 2. Searching the literature.

The published and unpublished literature should be carefully searched for all reports of appropriate and relevant studies. In systematic reviews of treatment and preventive interventions, randomised comparative trials are generally used, as they are likely to be subject to the least amount of bias. The search must include accessing a number of electronic databases and non-English sources. When appraising a systematic review, you should note whether the search strategy used by the review author was comprehensive enough for you to be confident that relevant studies were not overlooked.

#### 3. Selecting the studies for inclusion in the review.

Once a clear question for a systematic review has been developed, the components of the question (type of intervention, population, and outcome) are used to create a set of inclusion criteria for studies in the review. The studies identified by the search strategy are then assessed against

these criteria to determine if they should be included in the review. To avoid study selection that is biased by preconceived ideas, it is important to use a systematic and standardised approach to the appraisal of studies. Ideally, selection of studies should be made by two people working independently. When appraising a systematic review, it is helpful to ask yourself whether or not the method of selecting studies for inclusion in the review is clearly stated and objective.

#### 4. Assessing and reporting the quality of included studies.

Once all possible relevant studies have been identified and each study is assessed for eligibility for inclusion in the review, study quality or validity of the included studies is commented on. This should be presented clearly and allow you to determine the validity of the studies which provide the data to the review. A good quality systematic review will comment on all the important study appraisal criteria outlined in the checklist for study appraisal provided in the earlier paper in this series: “How to read a paper”<sup>(3)</sup>.

#### 5. Combining the results.

If appropriate, the findings from the individual included studies can then be aggregated to produce a summary estimate of the overall effect of the intervention. Sometimes this aggregation is qualitative (i.e., individual descriptions of the included studies), but more usually it is a quantitative assessment using meta-analysis. Meta-analysis should only be performed when the studies are similar with respect to population, outcome and intervention.

A meta-analysis is a two-stage process. The first stage is the extraction of data from each individual study and the calculation of a result for each individual study (the “point estimate” or “summary statistic”) with an estimate of the chance variation we would expect with studies like that (the “confidence interval”). The second stage involves deciding whether it is appropriate to calculate a pooled average result across studies and, if so, calculating and presenting such a result. Part of this process is to give greater weight to the results from studies that give us more information, because these are likely to be closer to the truth we are trying to estimate.

The usual way of displaying data from a meta-analysis is by pictorial representation (sometimes known as a forest plot) and a summary measure

of effect size with a confidence interval, shown at the bottom of the plot (Fig. 2).

#### 6. Placing the findings in context.

A systematic review should attempt to place the findings from meta-analysis of a minimally-biased selection of studies in context. This discussion should address such issues as the quality and heterogeneity (variation between studies in the effect of treatment) of the included studies, the likely impact of bias and chance, and the applicability of the findings.

In summary, the key characteristics of a systematic review are:

- Clearly stated title and objective for the review.
- Comprehensive strategy to search for studies that address the objectives of the review (relevant studies) that include published and unpublished studies.
- Explicit and justified criteria for the inclusion and exclusion of any study.
- Comprehensive list of all studies identified.
- Comprehensive list of all studies excluded and justification for exclusion.
- Clear presentation of the characteristics of each study included and an analysis of methodological quality.
- Clear analysis of the results of the eligible studies using statistical synthesis of data (meta-analysis) if appropriate and possible.
- Structured report of the review clearly stating the aims, describing the methods and materials and reporting the results.

### CONCLUSION

Systematic reviews appear at the top of the hierarchy of evidence. This reflects the fact that, when rigorously conducted, they should give us the best possible estimate of any true effect. However, caution must be exercised before accepting the findings of any systematic review without first appraising it. Like any piece of research, a systematic review may be done poorly. Not all systematic reviews are rigorous and unbiased. Little attention may have been paid to the intervention, the patient selection group or the search strategy; or the systematic review may have combined studies in meta-analysis which should not have been pooled because they differ in terms of intervention used or participants included. Therefore, it is important that users of systematic reviews become familiar with the steps involved



Fig. 2 The Cochrane Collaboration's logo incorporates a forest plot.

in undertaking a review (as described previously) and routinely appraise the methods used by review authors to minimise bias on the findings.

In order to base their clinical practice on evidence, healthcare providers need access to reliable and relevant evidence. Systematic reviews that provide a synthesis of available research are likely to be an efficient method of accessing evidence. By understanding the rationale for systematic reviews and the steps that should be followed in their conduct, clinicians are better empowered to recognise and implement reliable evidence into their clinical practice.

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## SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME

### Multiple Choice Questions (Code SMJ 200506B)

True    False

**Question 1.** A systematic review is:

- |   |                          |                          |
|---|--------------------------|--------------------------|
| (a) A subjective assessment of a group of studies selected to support a conclusion. | <input type="checkbox"/> | <input type="checkbox"/> |
| (b) Ideally performed by one person, so as not to be biased by external views.      | <input type="checkbox"/> | <input type="checkbox"/> |
| (c) Another name for a meta-analysis.   | <input type="checkbox"/> | <input type="checkbox"/> |
| (d) Useful in bringing separate studies together and synthesising their results.    | <input type="checkbox"/> | <input type="checkbox"/> |

**Question 2.** The steps in conducting a systematic review always include:

- |  |                          |                          |
|--|--------------------------|--------------------------|
| (a) Being clear about the objective of the review by defining an appropriate question. | <input type="checkbox"/> | <input type="checkbox"/> |
| (b) Searching only for relevant, published studies in English.                         | <input type="checkbox"/> | <input type="checkbox"/> |
| (c) Critically appraising studies included in the review.                              | <input type="checkbox"/> | <input type="checkbox"/> |
| (d) Combining data from individual studies to get a summary statistic of effect.       | <input type="checkbox"/> | <input type="checkbox"/> |

**Question 3.** Systematic reviews:

- |   |                          |                          |
|---|--------------------------|--------------------------|
| (a) Are a form of scientific research.  | <input type="checkbox"/> | <input type="checkbox"/> |
| (b) May have a summary measure of effect size displayed in the form of a forest plot.               | <input type="checkbox"/> | <input type="checkbox"/> |
| (c) May be used as primary research in place of observational or experimental studies.              | <input type="checkbox"/> | <input type="checkbox"/> |
| (d) May improve generalisability because there may be many trials conducted in varying populations. | <input type="checkbox"/> | <input type="checkbox"/> |

**Question 4.** A well-reported systematic review will include:

- |  |                          |                          |
|--|--------------------------|--------------------------|
| (a) A clearly stated objective for the review.                         | <input type="checkbox"/> | <input type="checkbox"/> |
| (b) A description of the search strategy used to locate studies.       | <input type="checkbox"/> | <input type="checkbox"/> |
| (c) A description of inclusion and exclusion criteria for studies.     | <input type="checkbox"/> | <input type="checkbox"/> |
| (d) An analysis of the methodological quality of all included studies. | <input type="checkbox"/> | <input type="checkbox"/> |

**Question 5.** Which of the following statements are true?

- |  |                          |                          |
|--|--------------------------|--------------------------|
| (a) A systematic review is irrelevant when there is a single large randomised controlled trial providing evidence; smaller studies on the same issue can be ignored. | <input type="checkbox"/> | <input type="checkbox"/> |
| (b) Systematic reviews are not required in evidence-based clinical practice guidelines.  | <input type="checkbox"/> | <input type="checkbox"/> |
| (c) A systematic review is a powerful method to summarise the evidence because results from very different trials can always be combined through meta-analysis.      | <input type="checkbox"/> | <input type="checkbox"/> |
| (d) Well-conducted systematic reviews can help empower clinicians to implement reliable evidence into their clinical practice.                                       | <input type="checkbox"/> | <input type="checkbox"/> |

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4. The SMJ editorial office will submit the list of successful candidates to the Singapore Medical Council.