

PART 1: Cochrane reviews

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1 Introduction

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Key Points

- Systematic reviews seek to collate all evidence that fits pre-specified eligibility criteria in order to address a specific research question.
- Systematic reviews aim to minimize bias by using explicit, systematic methods.
- The Cochrane Collaboration prepares, maintains and promotes systematic reviews to inform healthcare decisions (Cochrane reviews).
- Cochrane reviews are published in the *Cochrane Database of Systematic Reviews* in *The Cochrane Library*.
- The *Cochrane Handbook for Systematic Reviews of Interventions* contains methodological guidance for the preparation and maintenance of Cochrane Intervention reviews and Cochrane Overviews of reviews.

1.1 The Cochrane Collaboration

1.1.1 Introduction

The Cochrane Collaboration (www.cochrane.org) is an international organization whose primary aim is to help people make well-informed decisions about health care by preparing, maintaining and promoting the accessibility of systematic reviews of the evidence that underpins them. By providing a reliable synthesis of the available evidence on a given topic, systematic reviews adhere to the principle that science is cumulative and facilitate decisions considering all the evidence on the effect of an intervention. Since it was founded in 1993, The Cochrane Collaboration has grown to

include over 15,000 contributors from more than 100 countries, easily making it the largest organization involved in this kind of work (Allen 2006, Allen 2007). The international Collaboration was launched one year after the establishment of the Cochrane Centre in Oxford (now the UK Cochrane Centre) founded by Sir Iain Chalmers and colleagues, and named after British epidemiologist Archie Cochrane. The Cochrane Collaboration is now an internationally renowned initiative (Clarke 2005, Green 2005).

The work of The Cochrane Collaboration is underpinned by a set of 10 key principles, listed in Box 1.1.a.

Box 1.1.a The principles of The Cochrane Collaboration

1. Collaboration, by internally and externally fostering good communications, open decision-making and teamwork.
2. Building on the enthusiasm of individuals, by involving and supporting people of different skills and backgrounds.
3. Avoiding duplication by good management and co-ordination to maximize economy of effort.
4. Minimizing bias, through a variety of approaches such as scientific rigour, ensuring broad participation, and avoiding conflicts of interest.
5. Keeping up to date, by a commitment to ensure that Cochrane reviews are maintained through identification and incorporation of new evidence.
6. Striving for relevance, by promoting the assessment of healthcare interventions using outcomes that matter to people making choices in health care.
7. Promoting access, by wide dissemination of the outputs of the Collaboration, taking advantage of strategic alliances, and by promoting appropriate prices, content and media to meet the needs of users worldwide.
8. Ensuring quality, by being open and responsive to criticism, applying advances in methodology, and developing systems for quality improvement.
9. Continuity, by ensuring that responsibility for reviews, editorial processes and key functions is maintained and renewed.
10. Enabling wide participation in the work of the Collaboration by reducing barriers to contributing and by encouraging diversity.

1.1.2 Structure of The Cochrane Collaboration

The work of The Cochrane Collaboration revolves around 52 Cochrane Review Groups (CRGs), responsible for preparing and maintaining reviews within specific areas of health care. The members of these groups include researchers, healthcare professionals and people using healthcare services (consumers), all of whom share a common enthusiasm for generating reliable, up-to-date evidence relevant to the prevention and treatment of specific health problems or groups of problems.

Cochrane Review Groups are supported in review preparation by Methods Groups, Centres and Fields. Cochrane Methods Groups provide a forum for methodologists to discuss development, evaluation and application of methods used to prepare Cochrane reviews. They play a major role in the production of the *Cochrane Handbook for Systematic Reviews of Interventions* (the *Handbook*) and, where appropriate, chapters contain information about the relevant Methods Group. Cochrane Centres are located in different countries and together they represent all regions and provide training and support for review authors and CRGs in addition to advocacy and promotion of access to Cochrane reviews. Cochrane Fields focus on broad dimensions of health care, such as the setting of care (e.g. primary care), the type of consumer (e.g. children), or the type of intervention (e.g. vaccines). People associated with Fields help to ensure that priorities and perspectives in their sphere of interest are reflected in the work of CRGs.

1.1.3 Publication of Cochrane reviews

Cochrane reviews are published in full online in the *Cochrane Database of Systematic Reviews (CDSR)*, which is a core component of *The Cochrane Library*. *The Cochrane Library* is published by Wiley-Blackwell on the internet (www.thecochranelibrary.com) and on CD-ROM, and is available free at the point of use in some countries thanks to national licences and free access provided by Wiley-Blackwell in the most resource-poor settings. Elsewhere it is subscription based, or pay-per-view. In addition to *CDSR*, *The Cochrane Library* contains several other sources of knowledge, listed in Box 1.1.b.

Box 1.1.b Databases published in *The Cochrane Library*

- The *Cochrane Database of Systematic Reviews (CDSR)* contains the full text (including methods, results and conclusions) for Cochrane reviews and protocols.
- The *Database of Abstracts of Reviews of Effects (DARE)*, assembled and maintained by the Centre for Reviews and Dissemination in York, UK, contains critical assessments and structured abstracts of other systematic reviews, conforming to explicit quality criteria.
- The *Cochrane Central Register of Controlled Trials (CENTRAL)* contains bibliographic information on hundreds of thousands of studies, including those published in conference proceedings and many other sources not currently listed in other bibliographic databases.
- The *Cochrane Methodology Register (CMR)* contains bibliographic information on articles and books on the science of reviewing research, and a prospective register of methodological studies.
- The Cochrane Collaboration section contains contact details and other information about CRGs and the other contributing groups within The Cochrane Collaboration.

CDSR is published four times a year, each time with new reviews and updates of existing reviews. Issue 1, 2008 of *CDSR* contained more than 3000 Cochrane reviews and over 1700 protocols for reviews in progress.

1.2 Systematic reviews

1.2.1 The need for systematic reviews

Healthcare providers, consumers, researchers, and policy makers are inundated with unmanageable amounts of information, including evidence from healthcare research. It is unlikely that all will have the time, skills and resources to find, appraise and interpret this evidence and to incorporate it into healthcare decisions. Cochrane reviews respond to this challenge by identifying, appraising and synthesizing research-based evidence and presenting it in an accessible format (Mulrow 1994).

1.2.2 What is a systematic review?

A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question. It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made (Antman 1992, Oxman 1993). The key characteristics of a systematic review are:

- a clearly stated set of objectives with pre-defined eligibility criteria for studies;
- an explicit, reproducible methodology;
- a systematic search that attempts to identify all studies that would meet the eligibility criteria;
- an assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias; and
- a systematic presentation, and synthesis, of the characteristics and findings of the included studies;

Many systematic reviews contain meta-analyses. Meta-analysis is the use of statistical methods to summarize the results of independent studies (Glass 1976). By combining information from all relevant studies, meta-analyses can provide more precise estimates of the effects of health care than those derived from the individual studies included within a review (see Chapter 9, Section 9.1.3). They also facilitate investigations of the consistency of evidence across studies, and the exploration of differences across studies.

1.3 About this *Handbook*

The science of research synthesis is rapidly evolving; hence the methods employed in the conduct of Cochrane reviews have developed over time. The aim of the *Cochrane Handbook for Systematic Reviews of Interventions* (the *Handbook*) is to help Cochrane review authors make appropriate decisions about the methods they use, rather than to dictate arbitrary standards. Wherever possible, recommendations are informed by empirical evidence. The guidance provided here is intended to help review authors to be systematic, informed and explicit (but not mechanistic) about the questions they pose and how they derive answers to those questions. Interpretation and implementation of this guidance requires judgement and should be done in conjunction with editorial bases of CRGs.

This *Handbook* focuses on systematic reviews of the effects of interventions. Most of the advice contained within it is oriented to the synthesis of clinical trials, and of randomized trials in particular because they provide more reliable evidence than other study designs on the relative effects of healthcare interventions (Kunz 2007). Some chapters, however, provide advice on including other types of evidence, particularly in forms of care where randomized trials may not be possible or appropriate and in considerations of safety or adverse effects. In 2003, The Cochrane Collaboration expanded its scope to include Cochrane Diagnostic test accuracy reviews. Guidance for the conduct of these reviews is contained in a separate document: the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy*.

This *Handbook* has 22 chapters organized into three parts. Part 1 introduces Cochrane reviews, covering their planning and preparation, and their maintenance and updating, and ends with a guide to the contents of a Cochrane review or protocol. Part 2 provides general methodological guidance relevant to all Cochrane reviews, covering question development, eligibility criteria, searching, collecting data, within-study bias, analysing data, reporting bias, presenting and interpreting results. Part 3 addresses special topics that will be relevant to some, but not all, Cochrane reviews, including particular considerations in addressing adverse effects, meta-analysis with non-standard study designs and using individual patient data. This part has chapters on incorporating economic evaluations, non-randomized studies, qualitative research, patient-reported outcomes in reviews, prospective meta-analysis and reviews in health promotion and public health. A final chapter describes the new review type, Overviews of reviews.

Each chapter contains a list of key points to summarize the information and draw out the main messages for review authors.

The *Handbook* is largely prepared by The Cochrane Collaboration's Methods Groups, whose members conduct much of the methodological and empirical research that informs the guidance.

Although the main intended audience for the *Handbook* is authors of Cochrane Intervention reviews, many of the principles and methods are applicable to systematic reviews applied to other types of research and to systematic reviews of interventions undertaken by others (Moher 2007).

1.4 Contributors to the *Handbook*

“If I have seen further, it is by standing on the shoulders of Giants”

– Isaac Newton

This *Cochrane Handbook for Systematic Reviews of Interventions* (Version 5) is a major revision of a document that has evolved over time since the early days of The Cochrane Collaboration. Many chapters build on previous versions of the *Handbook*, and others are newly authored for Version 5. It is a truly collaborative effort, reflecting the principles of The Cochrane Collaboration. Many people have contributed directly to this revision, as chapter authors, chapter editors, peer reviewers, members of the Cochrane Handbook Advisory Group, and in numerous other ways. The *Handbook* also reflects the invaluable contributions of previous editors, past and present members of Cochrane Methods Groups, review authors, Cochrane Review Groups, the RevMan Advisory Group, Cochrane Centres and Cochrane Fields.

The initial methodological guidance for Cochrane review authors was developed by Andy Oxman, Iain Chalmers, Mike Clarke, Murray Enkin, Ken Schulz, Mark Starr, Kay Dickersin, Andrew Herxheimer and Chris Silagy, with administrative support from Sally Hunt. It was published in March 1994 as *Section VI: Preparing and maintaining systematic reviews* (*The Cochrane Collaboration Tool Kit*) of a comprehensive handbook for the Collaboration. It described the original structured format of a Cochrane review, which was developed by Mike Clarke, Murray Enkin, Chris Silagy and Mark Starr, with input from many others. The guidance became a stand-alone document in October 1996 as the *Cochrane Collaboration Handbook* (Version 3), under the editorship of Andy Oxman and Cynthia Mulrow, supported by the newly formed Handbook Advisory Group. Version 4, named the *Cochrane Reviewers' Handbook*, was released in 1999 to coincide with the launch of RevMan 4 and was edited by Mike Clarke and Andy Oxman from 1999 until December 2003, when Phil Alderson, Julian Higgins and Sally Green became editors (from Version 4.2.1). The introduction of Cochrane Diagnostic test accuracy reviews and the need for a new handbook specific to those reviews prompted, from Version 4.2.4 in March 2005, the change in title to the *Cochrane Handbook for Systematic Reviews of Interventions*, edited by Julian Higgins and Sally Green.

The current *Handbook* editors are supported by advice from the Handbook Advisory Group. The current membership of the Handbook Advisory Group is: Lisa Askie, Chris Cates, Jon Deeks, Matthias Egger, Davina Gherzi, Donna Gillies, Paul Glasziou, Sally Green (Co-Convenor), Andrew Herxheimer, Julian Higgins (Co-Convenor), Jane Lane (Administration), Carol Lefebvre, Harriet MacLehose, Philippa Middleton, Ruth Mitchell, David Moher, Miranda Mugford, Jane Noyes, Donald Patrick, Jennie Popay, Barney Reeves, Jacob Riis, Ian Shemilt, Jonathan Sterne, Lesley Stewart, Jessica Thomas, Jayne Tierney and Danielle Wheeler.

In addition to the previous editors, named above, the following have made substantial contributions to previous versions of the *Handbook*: Christina Aguilar, Doug Altman, Bob Badgett, Hilda Bastian, Lisa Bero, Michael Brand, Joe Cavellero, Mildred Cho, Kay Dickersin, Lelia Duley, Frances Fairman, Jeremy Grimshaw, Gord Guyatt, Peter Gøtzsche, Jeph Herrin, Nicki Jackson, Monica Kjeldstrøm, Jos Kleijnen,

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1.5 Chapter information

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