

SECOND EDITION

Systematic reviews

TO SUPPORT EVIDENCE-
BASED MEDICINE

Khalid Khan, Regina Kunz,
Jos Kleijnen and Gerd Antes

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HOW TO REVIEW AND APPLY FINDINGS
OF HEALTHCARE RESEARCH

Khalid Khan, Regina Kunz,
Jos Kleijnen and Gerd Antes

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Professor Khan would like to dedicate this work to Heinke, Jani and Zarie.

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● Preface

Are you a health professional who wishes to improve the quality of your practice using systematic reviews? Are you embarking on a career in public health, epidemiology or health technology assessment? Are you a clinical teacher interested in discovering the likely educational effects of the courses you deliver? Are you interested in health from the social science perspective? Are you about to start your first review? If so, this book is for you.

The first edition of this book exceeded all expectations. It was commended in the Basis of Medicine category in the BMA Medical Book competition 2003. Commentators found it a clear, useful guide to a potentially off-putting topic that built the confidence of non-statisticians. The *British Journal of Surgery* called it a 'gem'. It recognized that it stood head and shoulders above other texts on account of its brevity and clarity of prose. It advised readers that if they ever read or wrote systematic reviews, they should read this book first. It was praised for conveying an enthusiasm that made the reader want to conduct a review of their own. Its well-organized materials, logical structured flow and useful worked examples led to a recommendation to all libraries of educational and research institutions concerned with health sciences. It was directed at novice reviewers, but it was cited over a hundred times, indicating that even seasoned researchers took quite an interest in its contents. With the passage of time a second edition became imperative. Like the first, this edition describes the main principles behind systematic reviews of healthcare research and provides guidance on how reviews can be appraised, conducted and applied in practice.

As our current healthcare practice and policy increasingly relies on clear and comprehensive summaries of information collated through systematic literature reviews, it is necessary for us to understand how reviews and practice guidelines are produced. You may not be trained in health research methods, but this book will enable you to grasp the principles behind reviewing literature. In this way you will be able to critically appraise published systematic reviews and guidelines, and evaluate their inferences and recommendations for application in your practice.

Published reviews and guidelines are not always adequate or sufficient for our needs. Have you ever wondered how you could conduct your own review? The resources required for undertaking reviews are increasingly becoming available in a clinical setting. The appointment of clinical librarians, internet access to many journals, ease of obtaining interlibrary loans and the availability of user-friendly software make it possible for systematic reviews to be conducted by healthcare practitioners. This book highlights the core information necessary for planning and preparing reviews. It focuses on a clinical readership and new reviewers,

not on experienced epidemiologists, social scientists, medical educationalists and statisticians. Using this book you will be able to initiate your own review.

What is new in this edition of the book? We have widened the scope to go beyond evaluation of effectiveness of interventions in healthcare. We demonstrate how reviews can be usefully applied to evaluate qualitative and educational research. We have thoroughly overhauled the section and examples on how to interpret the findings of a review, leading to judicious and credible recommendations for clinical practice. We have added a substantial number of new case studies, providing more worked illustration of key concepts.

For too many years there has been a mystery surrounding systematic reviews and reviewers. How did they select certain studies and reject others? What did they do to collate results? How did a bunch of insignificant findings suddenly become significant? You are about to embark on a journey that will demystify these intrigues. Enjoy reading.

KS Khan,
R Kunz,
J Kleijnen,
G Antes

● *About the authors*

Together we are veterans of over 250 systematic reviews. Over the years we have worked with healthcare commissioners, clinicians and other decision makers, producing reviews to inform policy and practice. We have collaborated with other epidemiologists and statisticians to advance methods for undertaking systematic reviews. Two of us work in an academic setting producing and promoting systematic reviews; two of us work in a clinical setting with patients, applying evidence from reviews to inform our practice.

Khalid S Khan is the Professor of Women's Health and Clinical Epidemiology at Bart and the London Medical School in Queen Mary, University of London. He is a clinician, trained in systematic reviews and evidence-based medicine (EBM). Qualified in medical education, he runs journal club and other EBM activities, including evidence-supported ward rounds and workshops on critical appraisal. As a clinical academic he leads a number of systematic review projects, teaches undergraduates and postgraduates, and provides peer review to several clinical journals.

Regina Kunz has recently been appointed Director of the Institute for Insurance Medicine at the University and University Hospital Basel, Switzerland. Nephrologist and clinical epidemiologist by training, she has comprehensive expertise in doing systematic reviews, meta-analyses and health technology assessments. Then, her clinical practice reminded her day by day how important it is to have high quality evidence syntheses at hand when advising patients and making management decisions. Today, the lack of high quality evidence synthesis in insurance medicine is a painful experience that urgently needs change. Her academic activities within the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group on guideline methodology and as a long-standing board member of the Guidelines International Network G-I-N corroborate the need for high quality reviews and meta-analyses in all areas of healthcare, to provide physicians, patients and decision makers with sound recommendations, and the difficulties of delivering convincing recommendations in the absence of such reviews. She is the founding member of the German Network EbM, editor of the German textbook Evidence-based Medicine in Clinic and Practice, and has a great deal of experience in running teaching courses on systematic reviews and meta-analyses, the GRADE-methodology and evidence-based medicine worldwide.

Jos Kleijnen is the Director of an independent company, Kleijnen Systematic Reviews Ltd and Professor of Systematic Reviews in Health Care at Maastricht University. Following his graduation from medical school, he pursued a career as a clinical epidemiologist and has a wealth of experience in

conducting and disseminating systematic reviews and other research. He is a member of various steering groups and advisory committees related to systematic reviews and health technology assessment. He was the founding Director of the Dutch Cochrane Centre, Professor and Director of the Centre for Reviews and Dissemination at the University of York, and is a member of several Methods Working Groups of the Cochrane Collaboration. He is an editor of the Cochrane Peripheral Vascular Diseases Review Group and also teaches on courses on systematic reviews and EBM in several countries. This includes a collaboration with the Horten Centre in Zurich and with the Vienna School of Clinical Research in Vienna.

Gerd Antes is the Director of the German Cochrane Centre, Freiburg. He is a medical statistician and has in-depth knowledge of the mathematics behind meta-analyses, heterogeneity, funnel plots, etc. As well as his interests in methodological work, statistical computing and medical informatics, he set up the German Cochrane initiative and spends considerable time supporting the progress of EBM and systematic reviews. He has been a founding member and previous president of the German EBM Network. He has also been a member of the Cochrane Collaboration Steering Group for several years. He is a member of the German Committee for Clinical Guidelines and of the German Commission for Vaccination. One of his activities includes teaching and training science journalists. He has also successfully contributed to the establishment of the German Register for Clinical Trials.

We have put this book together because we feel that health professionals have much to gain from reviews and guidelines and, at the same time, reviews and guidelines have much to gain from them. With this book we hope healthcare practitioners will feel empowered to use reviews effectively and to initiate their own reviews.

● *Acknowledgements*

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● *Abbreviations*

BEME	Best Evidence Medical Education Collaboration
CCTR	Cochrane Controlled Trials Register (this is now called CENTRAL)
CDSR	Cochrane Database of Systematic Reviews
CER	Control Event Rate
CI	Confidence Interval
DARE	Database of Abstracts of Reviews of Effects
EBM	Evidence-based Medicine
EER	Experimental Event Rate
ES	Effect Size (for continuous data)
GRADE	The Grading of Recommendations Assessment, Development and Evaluation working group
HTA	Health Technology Assessment
ITT	Intention-to-treat Analysis
LR	Likelihood Ratio (LR+, LR for positive test result; LR-, LR for negative test result)
MeSH	Medical Subject Heading
NNT	Number Needed to Treat
OR	Odds Ratio (<i>not to be confused with Boolean operator OR used in searching literature electronically</i>)
RCT	Randomized Controlled Trial
RD	Risk Difference (or ARR, absolute risk reduction)
RR	Relative Risk
SD	Standard Deviation
SE	Standard Error

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● Introduction

We hardly ever come across a healthcare journal that does not publish reviews. All disciplines related to medicine, including social science and medical education, rely heavily on reviews for guiding practice and scholarship. What makes them ubiquitous? Reviews provide summaries of evidence contained in a number of individual studies on a specific topic. Research that is relevant to our practice is scattered all over the literature and sometimes it is published in languages foreign to us. By going through a single review article in our own language we can get a quick overview of a wide range of evidence on a particular topic. Therefore, we like reviews. They provide us with a way of keeping up-to-date without the trouble of having to go through the individual studies relevant to our practice. With an ever-increasing number of things to do in our professional lives and not enough time to do them, who wouldn't find reviews handy? In all honesty, even if we had the time and means to identify and appraise relevant studies, many of us would still prefer reviews.

Now a word of warning – the manner in which traditional reviews search for studies, collate evidence and generate inferences is often suspect. In the worst cases, personal interests of the author may drive the whole of the review process and its conclusions. After all, many of the reviews we read are invited commentaries; they are not properly conducted pieces of research. So, how can we be certain that reviews are not misleading us? This is why systematic reviews have come to replace traditional reviews.

Robust systematic reviews of healthcare literature are proper pieces of research. They identify relevant studies, appraise their quality and summarize their results using scientific methodology. In this way they differ from traditional reviews and off-the-cuff commentaries produced by 'experts'. More importantly, the recommendations of systematic reviews, instead of reflecting personal views of 'experts', are based on balanced inferences generated from the collated evidence.

This book describes the principles behind systematically reviewing the literature on healthcare and related subjects. Using this book, readers should be able to confidently appraise a review for its quality, as well as initiate one of their own.

Critically appraising systematic reviews

More and more healthcare policy is being based on clear and comprehensive summaries of information collated through systematic reviews of the relevant literature. So, in the current day and age, evidence-based practice requires more than just critical

A **systematic review** is a research article that identifies relevant studies, appraises their quality and summarizes their results using a scientific methodology.

The term **meta-analysis** is not synonymous with a **systematic review**. It is only a part of the **review**. It is a statistical technique for combining the results of a number of individual studies to produce a summary result. Some publications called meta-analysis are not systematic reviews.

From here onwards, whenever this book uses the term **review**, it will mean a **systematic review**, using these terms interchangeably. Reviews should never be done in any other way.

Meta-synthesis is the synthesis of existing qualitative research findings on a specific research question. This does not involve meta-analysis.

Evidence-based medicine (EBM) is the judicious use of current best evidence in making decisions about healthcare. Systematic reviews provide strong evidence to underpin EBM.

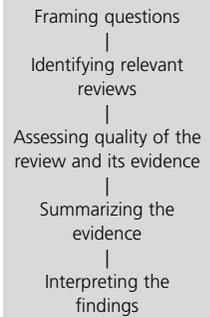
appraisal of individual studies. Practice guidelines are a prime example of how systematic reviews have come to occupy a pivotal role in our professional lives.

Systematic reviews may represent a quantum leap in review methodology. However, we should not have blind faith. Reviews and guidelines, just like individual studies, can be of a variable quality. There are numerous examples of poor reviews published in top healthcare journals and of inferior guidelines produced by professional bodies. Hence, there is a potential for misleading inferences even among apparently robust reviews and guidelines. Therefore, it is necessary for us, as healthcare practitioners, to acquire a deeper understanding of the principles behind systematic reviews. Although we may only have a basic knowledge in health research methods and consider the task of appraising reviews onerous, with this book, readers will be able to grasp the process and pitfalls of systematically reviewing literature, and discriminate between robust and not-so-robust reviews and guidelines more easily.

We can identify existing reviews to support our practice by searching the resources shown in Box 0.1. Once relevant reviews have been identified, the quality of their methods should be appraised, their evidence should be examined and their findings should be assessed for application in practice. Examples of how to use findings from existing reviews are shown in the case studies in Section B of this book. When drawing on reviews to support our practice, we will occasionally become painfully aware that relevant reviews either do not exist or they supply inadequate information. When you can't find a review that meets your needs, why not initiate a new one?

Guidelines are systematically developed statements to assist practitioners and patients in making decisions about specific clinical situations. They often, but not always, use evidence from systematic reviews.

What is involved in the identification, appraisal and application of evidence summarized in reviews?



Box 0.1 Selected sources of systematic reviews and guidelines

The Cochrane Library* (www.thecochranelibrary.com) has several databases of published and ongoing systematic reviews:

- **The Cochrane Database of Systematic Reviews (CDSR)**
Contains the full text of regularly updated systematic reviews of healthcare interventions carried out by the Cochrane Collaboration, plus protocols for reviews currently in preparation.
- **Database of Abstracts of Reviews of Effects (DARE)+**
Critical appraisals of systematic reviews found in sources other than CDSR. These reviews are identified by regular searching of bibliographic databases, hand searching of key major medical journals, and scanning grey literature.
- **Health Technology Assessment (HTA) Database+**
Abstracts of completed technology assessments and ongoing projects being conducted by members of the International Network of Agencies for Health Technology Assessment (INAHTA) and other healthcare technology agencies. Most of these include systematic reviews.

- **Collaborative Review Groups (CRGs)**

Found under 'about the Cochrane Collaboration' in the Cochrane Library. It contains a list of the total output of each one of 95 CRGs and provides an alternative method of searching the Cochrane Library.

There are more systematic reviews around than one might think. For example, in the 2nd issue of the 2011 Cochrane Library alone there were 6671 complete reviews and protocols combined in April 2011, 14602 abstracts of quality assessed reviews in DARE and 9965 abstracts of technology assessments in the HTA database.

General electronic databases: (*also see Box 2.3*)

- MEDLINE – PubMed Clinical Queries using the Systematic Reviews feature available at www.ncbi.nlm.nih.gov/entrez/query/static/clinical.html. At the time of writing there were 126 190 citations included in the PubMed Systematic Reviews subset strategy.
- CINAHL, EMBASE, PsycLIT and others may be searched for reviews by adapting one of the search filters (a combination of text words, indexing terms and subject headings that captures relevant articles) available from the Centre for Reviews and Dissemination search strategies available at http://www.york.ac.uk/inst/crd/identifying_research_evidence.htm

Selected internet sites:

- CMA Infobase – Clinical Practice Guidelines – www.mdm.ca/cpgsnew/cpgs/index.asp
- Guidelines and Guidelines in Practice – www.eguidelines.co.uk
- GIN Guidelines International Network – www.g-i-n.org:
- HTA Programme of the National Institute for Health Research (NIHR) – www.nchta.org/project/htapubs.asp
- NHS Evidence – <http://www.evidence.nhs.uk/nhs-evidence-content/journals-and-databases>
- National Institute for Health and Clinical Excellence (NICE) – www.nice.org.uk/
- OMNI – www.omni.ac.uk (use advanced search and specify Practice Guidelines in Resource Type)
- International Prospective Register of Systematic Reviews (PROSPERO) <http://www.crd.york.ac.uk/PROSPERO/>
- SchHARR-Lock's Guide to the evidence – www.shef.ac.uk/uni/academic/R-Z/scharr/ir/sceb.html
- SIGN guidelines – <http://www.sign.ac.uk/index.html>
- Turning Research Into Practice (TRIP) – www.tripdatabase.com

Selected print publications:

- Clinical Evidence – www.clinicalevidence.org

**See Case study 1 for an example search of the Cochrane Library*

+Also available free at <http://www.york.ac.uk/inst/crd>

Web sites are constantly changing. The internet addresses provided in this book were obtained from searches in June 2011.

Conducting a systematic review

Internet access to literature searching, the ability to obtain articles either electronically or through interlibrary loans, user-friendly software for meta-analysis, etc. all make this kind of reviewing possible. As these resources are increasingly available in a clinical setting, undertaking systematic reviews has become a realistic option for healthcare practitioners. But why should practitioners undertake reviews?

There is no shortage of reasons for undertaking one's own review. One may wish to conduct reviews for supporting evidence-based practice, personal professional development, informing clinical policy, publishing in a peer-reviewed journal, writing an introduction to a research thesis, or preparing a presentation at a conference, a technical report or an invited commentary.

However, there should be no need to reinvent the wheel. Existing reviews and guidelines should be used to their full potential. Up-to-date good quality reviews may already contain all the information we need.

When reviews and guidelines on a specific topic do not exist, are not up-to-date or are of a poor quality, our options are:

- ask 'experts' for advice
- appraise available primary studies
- conduct a systematic review.

We realize that 'expert' opinions may not be evidence-based and they may be unacceptable to others – for every 'expert' there is an equal and opposite 'expert'. We know that appraisal of individual studies will not provide information on the complete picture. Isn't this the point where we want to start a new review? Many Cochrane reviews commence in this way and when they are published everyone can benefit from them. Conducting a new systematic review will take a lot of effort, but not everything that is worthwhile is easy.

When undertaking research projects, advanced courses or educational assignments, we (or at least our supervisors) should be aware that non-systematic reviews are increasingly less acceptable. Where do we go next? We should do our own systematic review. As academics in the health professions (without advanced epidemiology and statistics training), we may be used to publishing editorials, opinions and commentaries. We are now under pressure from journal editors to be more systematic in our approach. Why not try a systematic review for the next commentary? We may feel inhibited as the knowledge or skills required for initiating such reviews may not be within our grasp. Help is in our hands. This book provides the core information necessary for planning and initiating reviews of healthcare literature.

This book focuses primarily on a clinical readership and first-time reviewers, not on epidemiologists, social scientists, educationalists and statisticians. This book will enable readers

The **Cochrane Collaboration**, established in 1993, is an international network of people helping healthcare providers, policy makers, patients, their advocates and carers, make well-informed decisions about human health care by preparing, updating and promoting the accessibility of **Cochrane Reviews**

Cochrane Reviews are systematic reviews of primary research in human health care and health policy. They investigate the effects of interventions (literally meaning to intervene to modify an outcome) for prevention, treatment and rehabilitation. They also assess the accuracy of a diagnostic test for a given condition in a specific patient group and setting.

to initiate reviews without relying on professional reviewers and will also give advice about further reading and how to seek professional input in difficult areas. Considering the nature of work involved in the various Steps of a review, it is advisable to find one or more other reviewers to join in. First-time reviewers might want to attend a local workshop or course on systematic reviews. The Cochrane Collaboration organizes many of these – why not ask the local Cochrane Centre about their next training event?

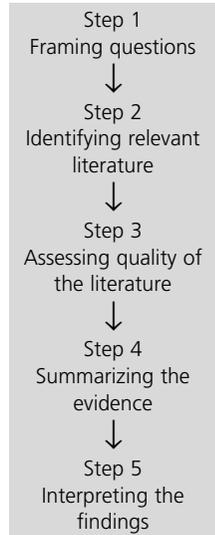
How this book is structured

This book will help readers to understand the principles of systematic reviews. In the discourse that follows there is a step-by-step explanation of the review process. There are just five steps. This book provides guidance for each step of a review with examples from published reviews. Many examples are followed through the different steps so that we will be able to see the link between the steps. In addition, application of the theory is illustrated through case studies. Each case consists of a scenario requiring evidence from reviews, a demonstration of some review methods and a proposed resolution of the scenario. Insight into critical appraisal and conducting a systematic review can be gained by working through the various Steps, examples and case studies.

If we have made up our mind to initiate a review, we should first produce a brief outline (or a protocol) of the project, giving some background information and a specification of the problem to be addressed along with the methodology to be used in the review. Throughout the review work, the protocol will remind us where we are coming from and what direction we want to go in, avoiding distractions and keeping us on track. It will also provide a document that could be peer reviewed before the review work is commenced. Some people suggest that a review protocol should be posted on a website to facilitate a wide peer review, but input from visitors to the site may be variable. Realistically, we have a much better chance of getting a professional to comment on the protocol if we ask a colleague experienced in reviewing or if we register our review with a relevant Review Group of the Cochrane or the Best Evidence Medical Education (BEME) Collaboration.

This book will be a useful companion in protocol development as well as throughout the five steps in the review process:

- First, the problems to be addressed have to be specified in the form of well-structured questions (Step 1). This is a key step, as all other aspects of the review follow directly from the questions.
- Second, thorough literature searches have to be conducted to identify potentially relevant studies which can shed light on the questions (Step 2). This is an essential feature that makes a review systematic.
- Third, the quality of the selected studies is assessed (Step 3).



The **Best Evidence in Medical Education (BEME)**

Collaboration is committed to the promotion of BEME through the dissemination and production of systematic reviews of medical education. An additional objective is the creation of a culture of BEME amongst teachers, institutions and national bodies.