

Cochrane systematic reviews of health care interventions

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Introduction

As a chiropractor, you want the best for your patients. In order to make well-informed clinical decisions you and your patients require high-quality, up-to-date, trustworthy healthcare information. Such information is available in

The Cochrane Library of systematic reviews of healthcare interventions.

The Cochrane Collaboration, The Canadian Cochrane Network and Center and *The Cochrane Library* were described in the first article in this series.¹ This is the

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second article and it is specifically about Cochrane systematic reviews; what they are; how they are prepared and updated; how you can become a Cochrane reviewer; and, how The Cochrane Collaboration provides healthcare information for patients and the public.

Evidence-based practice

It bears repeating that evidence-based practice is “the conscientious, explicit, and judicious use of the current best evidence in making decisions about the care of individual patients”.² While research reports from single studies may provide clinically relevant, useful information, the knowledge derived from systematic reviews of multiple studies is better, in part because reviews provide a more precise estimate of the treatment effect size.

Individual studies may not detect differences in the effects of two therapies.³ The number of patients included in any one study may be inadequate to provide a definitive conclusion.

Systematic reviews efficiently integrate data drawn from critically appraised primary studies. They determine where the effects of certain interventions are consistent and research findings can be applied across different populations, settings and variations in treatment such as methods of manipulation.⁴ They also identify where effects may vary significantly. The use of explicit, systematic review methods, described below, limits the possibility of bias and reduces the occurrence of chance effects. This means that systematic reviews provide more reliable results upon which conclusions can be drawn and upon which you can confidently base your clinical decisions.

Systematic reviews

In general terms, systematic reviews are critical summaries of the results of several single studies of the effectiveness of a particular clinical intervention.⁵ Other terms used to describe this methodology are “research syntheses” and “overviews”. In more technical terms, systematic reviews are reviews that begin with “a clearly formulated question and then use systematic and explicit methods to identify, select and critically appraise relevant research and to collect and analyze data from the studies included in the review”.⁵

Another important and related term is “meta-analysis”. Meta-analysis is a subcategory, or type, of systematic review.⁶ A meta-analysis is not the same as a systematic

review. Meta-analysis is a specific methodological and statistical technique for combining quantitative data from primary studies assessed to meet the necessary criteria for the pooling of data.⁵ Other definitions of the terms systematic review and meta-analysis are provided in Table 1.

Systematic reviews are not new. The history of research synthesis and systematic reviews is documented by Chalmers et al.⁸ They cite 18th century examples of research synthesis. Systematic reviews are by no means unique to health care. They have been used to summarize research results from primary studies in education, astronomy, physics, agriculture, psychology and business.⁸ According to Chalmers et al., healthcare researchers were “relative latecomers” to research synthesis.⁸ However, over the past three decades the number of systematic reviews in health care has been rapidly accumulating. In Issue 4, 2002 of *The Cochrane Library*, there are 1519 completed reviews and 1136 protocols – reviews in the process of being prepared.⁹

Table 1 Definitions

Systematic Review: The application of strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic. Meta-analysis may be, but is not necessarily, used as part of this process. (pp 176–177)

Meta-analysis: The statistical synthesis of the data from separate but similar, i.e. comparable studies, leading to a quantitative summary of the pooled results. (p. 114)

Quoted from Last’s (2001) *Dictionary of Epidemiology*.⁷

Preparation of Cochrane Reviews

Cochrane systematic reviews are prepared and maintained by teams of volunteer reviewers working with 49 different Collaborative Reviews Groups (CRGs). Table 2 presents a complete list of the CRGs in 2002. The ones of particular interest to chiropractors are the Cochrane Back Review Group, the Cochrane Movement Disorders Review Group, the Cochrane Multiple Sclerosis Review Group, the

Cochrane Musculoskeletal Review Group, the Cochrane Musculoskeletal Injuries Review Group, the Cochrane Neuromuscular Disease Review Group, the Cochrane Pain, Palliative Care and Supportive Care Review Group, and the Cochrane Stroke Review Group. Two of these Review Groups are based in Canada. The Back Review Group is located at the Institute for Work & Health in Toronto with Dr. Claire Bombardier as the Co-ordinating Editor (<http://www.cochrane.iwh.on.ca/>). In Ottawa at the Institute of Population Health, Dr. Peter Tugwell is the Co-ordinating Editor of the Musculoskeletal Review Group (<http://www.cochranemsk.org/>).

Cochrane reviews have a standard, consistent, and predictable format. The basic contents include a cover sheet, a consumer synopsis, a structured abstract, the review text, tables and figures, and references. Table 3 lists the detailed structured outline of a Cochrane review.⁴ These

standard headings guide the reviewers when preparing their report and are helpful for the reader as well. This outline is provided in the custom computer software used to prepare a review. **Review Manager (RevMan)** was developed and is being updated by The Nordic Cochrane Centre for The Cochrane Collaboration. It can be viewed and downloaded from <http://www.cochrane.org/cochrane/revman.htm#DL>¹⁰

The following is a brief description of the seven major steps in the process of preparing and maintaining a Cochrane review. The mechanisms for ensuring the quality and reliability of these systematic reviews are also identified. This information has been taken from the **Cochrane Reviewers' Handbook**. The current version is 4.1.5 and was updated April 2002.⁴ It can be read and downloaded from The Cochrane Collaboration Web site at <http://www.cochrane.org/cochrane/hbook.htm>.

Table 2 List of Cochrane Collaborative Review Groups

Acute Respiratory Infections	Infectious Diseases
Airways	Inflammatory Bowel Disease
Anaesthesia	Injuries
Back	Lung Cancer
Breast Cancer	Menstrual Disorders and Subfertility
Colorectal Cancer	Metabolic and Endocrine Disorders
Consumers and Communication	Movement Disorders
Cystic Fibrosis and Genetic Disorders	Multiple Sclerosis
Dementia and Cognitive Impairment	Musculoskeletal (Subgroups)
Depression, Anxiety and Neurosis	Musculoskeletal Injuries
Developmental, Psychosocial and Learning Problems	Neonatal
Drug and Alcohol	Neuromuscular Disease
Ear, Nose and Throat Disorders	Oral Health
Effective Practice and Organisation of Care	Pain, Palliative and Supportive Care
Epilepsy	Peripheral Vascular Diseases
Eyes and Vision	Pregnancy and Childbirth
Fertility Regulation	Prostatic and Urologic Cancers
Gynaecological Cancer	Renal
Haematological Malignancies	Schizophrenia
Heart	Sexually Transmitted Diseases
Hepato-Biliary	Skin
HIV/AIDS	Stroke
Hypertension	Tobacco Addiction
Incontinence	Upper Gastrointestinal & Pancreatic Diseases
	Wounds

Step one: formulating the problem

The primary purpose of a Cochrane systematic review is to summarize and help people understand the evidence related to a particular healthcare problem or question. The critical first step in preparing a review is to clearly define the problem of interest in the review and express it in a specific question. A well-formulated question guides the subsequent steps in the process of preparing a review: locating and selecting studies; critically appraising the relevance and validity of studies according to predetermined criteria; abstracting data from the studies; and, analyzing the results. The review question serves to help readers determine the relevance of the review for their practice and clinical decision-making.

A clearly defined question specifies the following predetermined components: types of people (patients); types of interventions (treatments); types of comparisons; and,

types of outcomes. An example of a question for a review of interest to chiropractors is “What are the effects of multi-disciplinary bio-psycho-social rehabilitation on adults with disabling low back pain of more than three months duration?”¹¹

The disease or health problem of interest (e.g., low back pain) influences the specification of the types of patients. Pertinent characteristics of the population (e.g., age, sex, socio-economic status) and the setting (e.g., community, hospital, nursing home) are also specified in the question. The second key component of the review question is the particular intervention or treatment of interest (e.g., multi-disciplinary bio-psycho-social rehabilitation) and the intervention(s) or placebo against which it is compared (e.g., non-multidisciplinary control intervention). Finally, the question should specify the important outcomes of interest – both positive and negative – and how they are

Table 3 Detailed Outline of a Cochrane Review

<p>Cover sheet: Title Reviewers Sources of support</p> <p>Text of review: Consumer synopsis Structured abstract Background Objectives Search strategy Selection criteria Data collection and analysis Main results Reviewers' conclusions Background Objectives Criteria for selecting studies Types of studies Types of participants Types of interventions Types of outcome measures Search strategy for identification of studies Methods of the review Description of studies</p>	<p>Methodological quality Results Discussion Reviewers' conclusions Implications for practice Implications for research Acknowledgements Conflicts of interest</p> <p>References: References to studies Included studies Excluded studies Studies awaiting assessment Ongoing studies Other references Additional references Other published versions of this review</p> <p>Tables and figures: Characteristics of included studies Characteristics of excluded studies Characteristics of ongoing studies Comparisons, data and graphs Additional tables</p>
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measured (e.g., pain, function, quality of life, employment status, and global improvement).

Because Cochrane systematic reviews primarily address questions about the effectiveness of healthcare interventions, the “best available evidence” is sought in randomized controlled trials (RCTs). RCTs are considered the “gold standard” because they minimize bias (systematic deviation from the truth) caused by unknown and uncontrolled factors. In RCTs, participants are randomly allocated to intervention(s) and the control group, thereby ensuring that the groups are similar.¹² The allocation of patients is concealed (blinded) so that the researcher and/or clinician cannot influence the assignment and bias the results. While RCTs are preferred, many Cochrane reviews include other study designs. They do this in instances where RCTs are not appropriate or not available.

Once a team of reviewers has formulated their review question, they are ready to register the title of their review with the appropriate review group. The titles of Cochrane reviews are distributed throughout the Collaboration to ensure that there is no duplication or overlap of reviews. The title of the review being cited as an example in this article is “Multidisciplinary bio-psycho-social rehabilitation for chronic low back pain”.¹¹

Step two: locating and selecting studies

When a clearly defined question has specified the key components of a review (types of people, types of interventions, types of comparisons, and types of outcomes), the next step in the review process is to locate and select all the primary studies that meet the inclusion selection criteria.¹³ A comprehensive, unbiased search of the literature is a defining characteristic of a systematic review.

Cochrane reviewers are expected to search not only the various electronic databases such as MEDLINE and EMBASE, but also they are directed in the Reviewers’ Handbook to search for non-English publications and unpublished, “gray” literature including technical reports, dissertations, and conference proceedings. A complete literature search entails a review of reference lists of publications as well as correspondence with individuals and companies with pertinent expertise.

The Cochrane Collaboration provides assistance with this phase of review preparation. In *The Cochrane Library* there is the Cochrane Central Register of Controlled Trials

that currently includes 329,117 registered trials. This is the first source reviewers should search for relevant primary studies. In addition, each Collaborative Review Group (CRG) has specialized search strategies and a specialized trials register that the CRG staff will help reviewers use.

There are several sources of bias to be avoided when searching the literature for relevant studies. For example, a review can be distorted by publication bias (the preferential reporting of studies with positive results).⁴ To protect against this particular source of bias, it is essential that reviewers search systematically and thoroughly for all pertinent studies that report negative as well as positive results.

Not only is it important how the search of the literature is conducted, but also it is important how it is reported in the abstract and the text of the review. Proper documentation of the search specifies the dates the searches were conducted, the search strategy, and the key sources used, including handsearched journals, Internet sites and manufacturers.

Next, the reviewers must examine all the identified studies and select those that will be included in the review.¹⁴ It is considered best practice in the preparation of a review to engage two or more independent reviewers in the selection process.

Reviews in the process of being prepared are published in *The Cochrane Library* in the form of protocols. Protocols include the cover sheet, background, objectives, selection criteria, search strategy, methodology, acknowledgements, conflict of interest, additional references, and additional tables.

Step three: assessing the quality of the studies

This step in preparing a systematic review is documented in detail in the protocol. The Handbook guides reviewers to prepare and test a standardized appraisal form that includes all the aspects of quality to be evaluated whether the primary studies are randomized controlled trials or other research designs.

The primary studies are appraised from three basic perspectives:

- 1 the validity of each study;
- 2 the design characteristics that affect the interpretation of the results;

3 the applicability, or generalizability, of the findings to clinical practice.¹⁴

The validity of the studies is determined by the extent to which the design, conduct and analysis of the studies minimize the potential for bias. Because of inadequacies in the reporting of the primary studies, methodological features can be difficult to assess. On occasion it will be necessary to contact the author(s) of the primary studies to obtain additional information or clarify points of uncertainty.

The common sources of bias are clearly described and discussed in the Reviewers' Handbook (selection bias, performance bias, attrition bias, detection bias). Non-randomized studies, unconcealed allocation and unblinded studies have all been found to overestimate the effectiveness of interventions.¹⁴

Cochrane reviewers are advised to have two or more investigators to independently evaluate the studies. The process for identifying and resolving disagreements should be defined in advance and documented in the protocol.

Step four: collecting data

Extracting the pertinent data from the primary studies is a detailed and precise process guided by a planned, pre-tested and standardized approach and form. The forms provide a record of decisions made throughout the process of identifying and selecting the data to be entered into the review using the RevMan software. The sections of the form reflect and are consistent with the key components of the review question and the planned analysis. The process of extracting the data provides an important opportunity to verify the eligibility of the studies for inclusion in the review.

Section 7 of the Reviewers' Handbook provides explicit directions on how to design data extraction forms. As a potential Cochrane reviewer you would be interested in this section. As an informed reader of systematic reviews it is sufficient to know that the data upon which a review is based are carefully collected and recorded by two or more trained investigators. For those who have access to the full Cochrane systematic reviews, and not just the abstracts, these data are found in the Table of Included Studies. The structured abstracts provide only a summary of the data collection and analysis methods.

Step five: analyzing and presenting results

Both the protocol and final review will include a plan for analysis in the Methods sections. The plan will clearly specify the comparisons that will be made. The comparisons relate directly to the question formulated in Step One. Next, the data from the primary studies are summarized in tables. RevMan provides tables for dichotomous data (outcomes expressed in either/or terms such as alive or dead), continuous data (variables measured on scales such as weight and blood pressure), individual patient data, and 'other' types of data that don't fit in the previous categories.

The aim of most Cochrane reviews is "to provide a reliable estimate of the effects of an intervention, based on a weighted average of the results of all the available relevant studies".⁴ A critical decision is whether the nature of the studies and the data permit the combination (pooling) of the results. Pooled results can increase statistical power and lead to more precise estimates of the treatment effect.⁴

Where it is possible to combine the results of the selected studies, a meta-analysis (quantitative synthesis) can be conducted using various summary statistics. Dichotomous data can be summarized using measures of treatment effect such as the relative risk (risk ratio), the odds ratio and the risk difference.^{4,15} The weighted mean difference or the standardized mean difference is used to summarize continuous data. Interested readers are referred to the article by Lau et al, the Reviewers Handbook (Section 8) and the Open Learning Materials (Modules 10 to 15) for detailed discussions of the application of these and other methods of statistical analysis.^{4,15,16}

If there are differences in the types of patients, interventions or outcomes, then subgroup analyses may be required. These should be planned in advance to avoid the bias introduced by the knowledge of the actual results. Sensitivity analyses should also be predetermined and carried out to evaluate the effect of different statistical approaches.⁴

The results of meta-analyses are presented in a graphic form that shows the point estimates and their confidence intervals (CIs). Different statistics may be used to analyze the effects while others may be used to present the results because they are more understandable. For example, the number needed to treat (NNT) provides the number of people who would need to be treated with the experimental

intervention (compared with the control) to prevent one event (e.g., death). The NNT is merely the inverse of the risk difference but it is more readily understood.¹⁶

The Cochrane Collaboration provides many sources of statistical support and assistance for reviewers: the policies and staff of their Collaborative Review Group; the references in the Cochrane Review Methodology Database in *The Cochrane Library*; the RevMan User Guide; the Frequently Asked Questions (FAQ) list for RevMan; The Canadian Cochrane Network and Centre and its Statistical Consultant; and the Reviewers' Handbook with its various reference lists as well as the new Open Learning Materials.

Step six: interpreting results

Since many people read the conclusions and discussion sections of a review first, this is an important step in the preparation process. Cochrane reviews are intended to present a summary of the evidence for diverse international audiences, and not to provide advice for individual decision-making. It is the reader's role and responsibility to apply the evidence in individual situations where there are specific contextual factors to be considered such as patient and family values, preferences, costs and resources.

Systematic reviews are a form of research. Like all research reports, they need to identify and discuss the important methodological limitations of the included primary studies, the methods used in the review and the implications for the reported results.⁴ Module 16 of the Open Learning Materials outlines several factors, internal and external to a review, that need to be considered when formulating conclusions about the strength of the evidence concerning the effectiveness of the intervention in question.¹⁶ For example, the number of primary studies in the review and the number of participants in each study are important internal factors as are the size, precision and consistency of the treatment effects.

The discussion of the strength of the evidence presented in the review should also include the relationship of the results of the review to other existing pertinent evidence not part of the review. These external factors include relevant biological, psychological and social evidence, the results of excluded study designs, and agreement with other related systematic reviews.¹⁶

While the ultimate responsibility for determining the

applicability of the results rests with the reader, Cochrane reviewers are instructed to discuss known differences with respect to biological and cultural variation, predictable differences in compliance, and variation in baseline risk.^{4,16} They are also guided to identify and discuss all possible outcomes of the intervention of interest, not only the positive, beneficial effects but also the negative or adverse, harmful effects.

Where there is insufficient information about specific outcomes, reviewers conventionally make recommendations for future research. The inability to draw firm conclusions due to the lack of evidence is not a weakness of a systematic review but rather a service to health researchers by identifying gaps in knowledge that need to be filled.

Step seven: improving and updating reviews

The Cochrane Collaboration continuously strives to improve the methods and standards of Cochrane systematic reviews. There are ten Methods Groups that work to develop policies, provide advice and conduct methodological research to enhance the quality of Cochrane reviews.

Each of the eighty-three entities that make up The Cochrane Collaboration actively recruit dedicated volunteers to become reviewers. Preparing and maintaining a Cochrane review is a major commitment. Different groups of entities assume responsibility for training and supporting these volunteers. The Cochrane Collaboration has a Code of Conduct for Avoiding Potential Financial Conflict of Interest to ensure the integrity of Cochrane reviews.⁴ Reviewers and members of the editorial teams must disclose any potential conflict of interest.

Prior to publication, all reviews must be refereed by at least two people external to the Review Group Editors. Referees will have methodological or content expertise. Consumers are also included in the peer review process to evaluate the relevance of the review and the readability of the consumer summary, the structured abstract as well as the full review.

In addition, The Cochrane Collaboration has developed a Criticism Management System by which readers of Cochrane reviews are encouraged to submit comments and suggested improvements on reviews. Every CRG has a Criticism Editor who screens and summarizes any feedback and forwards them to the reviewers for response. Comments are also posted on the public Web

site of Update Software, the current publisher of *The Cochrane Library*, at <http://www.update-software.com/comcritusers/>. One of the unique features of The Cochrane Collaboration is its commitment to maintaining the reviews it produces. The Collaboration has a policy that each review should be updated within two years or that a commentary is added to explain why it will be done less frequently. The Collaboration is also working toward the goal of converting all protocols into full reviews within two years. As the number of systematic reviews increases with each issue of *The Cochrane Library*, the challenge of updating protocols and reviews increases as well.

Becoming a Cochrane Reviewer

This article was intended to inform you about systematic reviews and how they are prepared so that you have an appreciation of the process involved in producing a review and keeping it up-to-date. It was designed to outline the quality control mechanisms that ensure Cochrane reviews are reliable and continuously being improved. Table 4 summarizes the various ways in which the quality of Cochrane systematic reviews is ensured.

Volunteer clinicians, researchers and consumers prepare the Cochrane reviews. If you are interested in becoming a Cochrane reviewer, there are various support systems in place to help you. Each year, The Canadian Cochrane Network and Centre (CCN/C) provides reviewer training workshops to assist reviewers with the preparation of a protocol, the use of RevMan, and the process involved in completing a review for publication in *The Cochrane Library*. Information about these workshops is posted on the CCN/C Web site at <http://cochrane.mcmaster.ca/workshops.asp>.

For those who would prefer to learn on their own at home, The Cochrane Collaboration has a Reviewers' Handbook that describes in detail the process of creating Cochrane systematic reviews. It is revised frequently to ensure that it remains up-to-date. The current version is 4.1.5 and was updated April 2002. It can be read and downloaded from The Cochrane Collaboration Web site at <http://www.cochrane.org/cochrane/hbook.htm>.

The Collaboration has new distance learning materials that complement the Reviewers' Handbook. These modules are available from the CCN/C in paper format or on CD ROM. They are also available on the Web at <http://www.cochrane-net.org/openlearning/>. The Coch-

Table 4 Quality Control Mechanisms

Pre-determined review question and process
Comprehensive, unbiased search
Explicit inclusion and exclusion criteria
Independent selection of primary studies by two or more reviewers
Use of pre-tested, standardized selection, appraisal and data extraction forms and protocols
Independent appraisal of primary studies by two or more reviewers
Use of appropriate statistical techniques to synthesize results
Sensitivity analyses of different statistical approaches
Judicious use of subgroup analyses
Cautious interpretation of results and formulation of conclusions
Full reporting of the materials and methods used in the review
Internal peer review
External peer review
Comments and criticism process
Code of conduct re conflict of interest

rane software, RevMan, can be accessed free and downloaded from <http://www.cochrane-net.org/revman/>.

If you have further questions about the review preparation process or require assistance identifying and contacting a Collaborative Review Group related to your interests, please contact the CCN/C staff at cochrane@mcmaster.ca.

Health care information for patients and the public

Effective clinician-patient relationships are based upon trust, mutual respect and well-informed decision-making on the part of the patient as well as the clinician. The Cochrane Collaboration has been committed to patient/consumer involvement in all aspects of healthcare decision-making including patients' personal care. In addition to the Cochrane systematic reviews and the structured abstracts, The Cochrane Collaboration prepares short, plain-language consumer summaries (synopses). These are freely available on the Internet at <http://www.cochraneconsumer.com/>. They are written or ap-

proved by the authors of the systematic reviews and in most cases they have been prepared with input from consumers involved in the Collaborative Review Group or the Consumer Network. The Consumer Network is based in Australia but has active members throughout the world.

Next article

The third, and final, article in this series will be about evaluating systematic reviews and using them in chiropractic clinical practice.

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