

Evolution of Cochrane Intervention Reviews and Overviews of Reviews to better accommodate comparisons among multiple interventions

Report from a meeting of the Cochrane Comparing Multiple Interventions Methods Groups, Milan, March 2011.

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1. Introduction

The Cochrane Comparing Multiple Interventions Methods Group (CMIMG) was established in September 2010. Among its objectives are to consider how the aims, methods and processes for Cochrane Overviews of Reviews (OoRs) might evolve over time, and to explore the role of multiple treatments meta-analysis (MTM, also known as network meta-analysis or mixed treatment comparisons meta-analysis) in both OoRs and Intervention Reviews (IRs). In order to start addressing these objectives, a meeting was held in Milan in March 2011, hosted by the Italian Cochrane Centre. In addition to methodologists with an interest in comparing multiple interventions, participants included five Co-ordinating Editors, a recent Managing Editor, a Trials Search Coordinator, a Field Convener, a Centre Director, authors of OoRs and IRs, and the Editor in Chief. This report summarizes the outputs of the meeting, providing a new proposed strategy for ensuring that comparisons among multiple interventions are provided in a sound and meaningful manner within the *Cochrane Database of Systematic Reviews (CDSR)*. The report includes a series of recommendations, emphasized in bold type face and summarized in a box at the end.

2. Addressing multiple interventions in Cochrane Intervention Reviews

The starting point for any Cochrane review is the formulation of clinical question (or series of questions). The meeting noted substantial variation in the breadth of questions in relation to the inclusion of multiple interventions in IRs. At one extreme, some reviews include a single specific pair-wise comparison (e.g. a single drug versus placebo). At the other extreme, many reviews address all interventions for a particular clinical condition. Many IRs therefore compare multiple interventions, but this intention is largely implicit rather than explicit. Consequently, the use of formal methods (such as indirect comparisons and MTM) is uncommon.

The meeting decided that the Methods Group should not seek to dictate the breadth of interventions included in any particular IR, since these should be guided by clinical and practical judgements.

The large majority of IRs that involve many interventions present meta-analyses of a series of pair-wise comparisons without a specific plan to integrate the various pieces of evidence. Statistical synthesis using MTM could be performed in many cases, provided that the assumptions of this

approach are fulfilled. **CRGs should be encouraged to identify existing IRs that compare multiple interventions and consider the feasibility of indirect comparisons and MTM.** Further guidance is required to support these considerations. At minimum, authors will need to ensure that the interventions have the same indication, or, in other words, that all interventions could reasonably be randomized against each other in a single trial.

Consideration of these statistical methods applies also to new titles and protocols. **When a new IR seeks to compare multiple interventions (i.e. to determine a preferential ordering of three or more competing interventions for a particular outcome), this should be made explicit in the protocol, and appropriate methods should be planned and implemented.** Support may be sought from the CMIMG (see Section 7).

The more interventions that are included in a MTM, the greater the potential gain in precision and the greater the ability to establish whether various sources of evidence ‘agree’ with each other. Therefore, it may sometimes be useful to include interventions that are not current candidates for clinical practice, such as placebo or no treatment, or interventions that are no longer recommended or available (‘legacy treatments’). Guidance is also required on such issues.

3. Addressing multiple interventions in Cochrane Overviews of Reviews

The meeting decided to recommend a change in the emphasis of an Overview. **OoRs should be re-defined as reviews that *integrate or synthesize* (rather than summarize) evidence from existing systematic reviews, and should address a well-defined clinical question.** This would involve a change to *Handbook* guidance, which currently allows OoR to be driven by the question ‘What is in the Library?’, leading to a simple summary of existing reviews without an attempt to integrate their findings. One particular approach to integrating evidence is the use of statistical synthesis across evidence in the included reviews. **Authors of OoRs should be encouraged to consider the implementation of indirect comparisons and MTM.** Nevertheless, some OoRs will involve no statistical analysis and findings will be presented in a narrative format.

The basic unit of the search strategy for an OoR is the review (Cochrane Reviews and optionally non-Cochrane systematic reviews). As a further evolution in guidance for Overviews, the meeting decided that this may not be sufficient to provide a suitable answer to the clinical question. **Broadening the search in an OoR to include individual studies may be appropriate in some cases.**

For some OoRs it will be possible to extract all of the required data from the included reviews. Estimated intervention effects from pair-wise meta-analyses may be used to generate indirect comparisons (possibly combined additionally with direct comparisons). Study-specific data, as reported in the individual reviews, may be copied and used to perform MTM. However, in many cases OoR authors will find that there is insufficient information in the published reviews (for example, if the reviews were undertaken before the Cochrane risk of bias tool was in widespread use). **An OoR may need to examine the original reports from individual studies and collect data not available in the existing reviews in order to perform an adequate synthesis.**

In some cases, the authors of an OoR may decide that the question of interest cannot be adequately answered using the methods designed for OoRs, and decide that an IR is needed. In these cases, the preparation of the OoR will have served an important ‘scoping’ function, and will allow detailed exploration of a number of important issues for the IR, such as the specific framing of the question, considerations of interventions and outcomes to be included and identification of a number of key trials in the area. Strategies for moving from an OoR to an IR are discussed in Section 6.

With the change in emphasis of OoR, the meeting considered future possibilities for providing a ‘friendly front end’ to the *CDSR*, which is part of the role that OoR have played until now. It was suggested that simple summaries of the contents of existing Cochrane Reviews are best provided in the form of editorials and annotated collections of reviews, as currently prepared by the Cochrane Editorial Unit.

4. Clarification of the distinction between Intervention Reviews and Overviews of Reviews

The main characteristic that distinguishes IRs from OoRs is the focus of the search. IRs perform a comprehensive search for all relevant primary studies, while OoRs find studies by searching for Cochrane Reviews or other systematic reviews. Consequently, the data extracted for IR are always study-specific data. Currently, pair-wise meta-analyses are used in IRs to compare interventions, but statistical synthesis using MTM could also be done in many cases, provided that the assumptions of this approach are fulfilled. The following table attempts to clarify the differences between IRs and OoRs.

Review type	Focus of search strategy	Focus of data collection	Focus of statistical synthesis	Comment
Intervention Review (IR)	Trials	Original trial reports	Trial data	A new review may be planned around a MTM (or indirect comparisons)
Overview of Reviews (OoR)	Reviews	Review reports (meta-analysis summary estimates or trial data); or possibly original trial data	Meta-analysis summary estimates or trial data	Synthesis may involve indirect comparisons based on meta-analysis results, or re-analysis of trial data from either review reports or trial reports

5. Implications of Overviews for authors and editors of Intervention Reviews

A new requirement that OoRs provide a question-based synthesis rather than simply reporting on 'What is in the Library?' has important implications for CRGs and for authors of IRs. To meet this requirement, OoR authors will need to find up-to-date IRs that address all of the key interventions and have taken similar approaches to issues such as study inclusion criteria and selection of outcomes. Thus harmonization of protocols across IRs that address the same participant group but involve different interventions is highly desirable. Authorship issues for OoRs will also need careful ongoing consideration. The meeting deemed it desirable to involve authors of IRs included in a OoR in one of several possible ways: as OoR authors, as peer reviewers, or simply through a process of communication to facilitate speedy update of IRs and correction of any mistakes or omission identified. It may be helpful to formalize feedback of certain issues from OoRs to IR authors. For example, an automated process for populating the 'Studies awaiting assessment' section when OoR authors identify studies that have not been included in a relevant IR could be developed.

It was agreed that tagging of reviews that compare multiple interventions will be useful for a number of purposes. The CMIMG decided to tag reviews to create a list of reviews according to the methodology employed for research purposes (e.g. indirect comparisons, or MTM). It was agreed that CRGs could facilitate the 'merging' of IR that address the same question by tagging reviews focusing on the same participant groups. Furthermore, a mechanism to link IRs included in particular OoRs would facilitate feedback and update.

6. A sequential approach for undertaking reviews that compare multiple-interventions

OoRs can be completed more quickly and require fewer resources than IRs, but may not give a complete answer to the question of interest, due to the restrictions on the search strategy and availability of data (as these are extracted from IRs). To make the best use of available resources while preparing reviews of high quality and of relevance to the medical decision-making the following process has been suggested and could be included in the protocol when a comparison of multiple interventions is being planned.

1. State clearly the research question, which should be based on clinical need and not the availability of reviews or studies. Include interventions that could reasonably be randomized against each other.
2. Start with an OoR: search for Cochrane Reviews that meet the inclusion criteria.
3. If possible and useful, extract the study-level data from the Cochrane reviews.
4. If possible and useful, extend the search to non-Cochrane reviews
5. If possible and useful, extend the search to individual studies, either in order to add one or more interventions, or in order to update existing systematic reviews.
6. Determine if trials contain sufficient data to perform a MTM, and enough information to judge that the assumptions of MTM are plausible. If yes, do it.
7. If resources permit (funding, statistical support) and/or the topic is of priority for the CRG, extend the OoR to an IR for multiple interventions. This would involve a search for individual studies and extraction of all data at the study level (in some cases it may be

possible and appropriate to use the data extracted from reviews in step 2). If judged appropriate, do a MTM.

Depending on the nature of the research question, the available resources and the CRG priorities, reviewers could go directly to step 7.

7. Role of the Cochrane Comparing Multiple Interventions Methods Group

CRGs should be encouraged to consult the CMIMG when they start a review that aims explicitly to compare more than two interventions. The CMIMG may be able to provide methodological support and/or peer review. All review teams comparing multiple interventions should involve a statistician or methodologist with expertise in the techniques that are likely to be employed. When a review team works closely with a methodologist designated by the CMIMG, authorship should be offered if the amount of support is considered to be substantial. For this purpose the CMIMG is compiling a list of suitable individuals. In the longer term, a model similar to the one developed by the Diagnostic Test Accuracy Working Group will be explored. This would involve methodological peer review, dual sign-off of protocols and reviews, and the possibility of funded methodological support for teams unable to identify suitable individuals.

The meeting initiated three Working Groups to tackle some of the methodological, practical and editorial issues that arise when undertaking an OoR or IR that compare multiple interventions. These are described below. Training will be carried out as soon as the Working Groups come up with specific guidance. Links with the Training Working Group will be established.

8. Creation of Working Groups to tackle methodological and practical issues in comparing multiple interventions

Working Group 1: Fundamental considerations

This group will address fundamental issues associated with the initiation and logistics of undertaking, publishing and maintaining reviews that compare multiple interventions. More specifically, the group plans to address:

- When it is appropriate to compare multiple interventions?
- What are the methodological considerations associated with the selection of interventions to be included (including legacy treatments)?
- How might CRGs develop their strategy to deal with out-of-date reviews, authorship, and topics that overlap across CRGs?

The working group will also work on refining the sequential approach described in Section 6, and on issues associated with the inclusion of non-Cochrane reviews and individual studies in OoRs.

Working Group 2: Statistical issues

This group will concentrate on the statistical considerations. These include:

- When are indirect comparisons and MTM appropriate?
- What are the appropriate statistical methods for indirect comparisons and MTM?

- What is the assumption of ‘consistency’, how it can be evaluated and what should be done when substantial inconsistency is found?
- How should we present and interpret the results of a MTM?
- What software is suitable for each type of analysis?
- To what extent can RevMan support MTM?

Working Group 3: Summaries of findings and assessing risk of bias

This group will focus on the interpretation of the evidence included in a review that compares multiple interventions. Questions addressed by this group include:

- What is the role of RoB in indirect comparisons?
- Is direct evidence always preferable to the indirect evidence?
- What are the necessary adjustments in SoF tables so they can be used for CMIRs?

It was agreed that close links should be established with the GRADE Working Group, the Cochrane Applicability and Recommendations Methods Group and the Cochrane Bias Methods Group.

The three groups have some overlap in their scope and they will work in co-ordination to prepare specific guidance.

Summary of recommendations

1. Cochrane Review Groups should be encouraged to identify existing Intervention Reviews that compare multiple interventions and consider the feasibility of indirect comparisons and multiple treatments meta-analysis.
2. When a new Intervention Review seeks to compare multiple interventions (i.e. to determine a preferential ordering of three or more competing interventions for a particular outcome), this should be made explicit in the protocol, and appropriate methods should be planned and implemented.
3. Overviews of Reviews should be re-defined as reviews that *integrate* or *synthesize* (rather than summarize) evidence from existing systematic reviews, and should address a well-defined clinical question.
4. Authors of an Overviews of Review should be encouraged to consider the implementation of indirect comparisons and multiple treatments meta-analysis.
5. Broadening the search in an Overview of Reviews to include individual studies may be appropriate in some cases.
6. Cochrane Review Groups should be encouraged to consult the Cochrane Comparing Multiple Interventions Methods Group when they start a review that aims explicitly to compare more than two interventions.