

## **Review Type & Methodological Considerations** **- Background Paper for the First Part of the Paris CMIMG<sup>1</sup> Discussion**

### **Part 1. Two formats possible for comparing multiple interventions**

#### **1.1. Overview or intervention review**

We now have two different review types available for authors who wish to compare multiple interventions. While overviews of reviews were developed with this application in mind, it is clearly also possible to use a standard Cochrane intervention review to compare three or more interventions for the same condition. As an example, one can look at the approaches that have been taken to comparing interventions for pain management for women in labor. A recent Cochrane overview on the subject provides a synthesis of 14 Cochrane reviews – each intervention review addressed a different class or type of intervention (acupuncture, opiates, transcutaneous electrical nerve stimulation, etc.) (Jones 2012). For one of these interventions (parenteral opioids) the intervention review also includes comparisons of multiple interventions (Ullman 2010). In that review, data from 57 studies are combined with meta-analyses for 29 different comparisons. Some of these compared an opioid with placebo, another compared opioids administered intramuscularly or intravenously, and one comparison involved opioids vs. transcutaneous electrical nerve stimulation. Although the authors intended to compare multiple interventions, network meta-analysis (NMA), a statistical method to combine both direct and indirect evidence, was not used (Higgins 1996, Lumley 2002, Lu 2004, Caldwell 2005, Salanti 2008, Li 2011). Direct evidence refers to evidence obtained through comparisons of interventions within randomized controlled trials (RCTs) and indirect evidence refers to evidence obtained through comparisons across trials based on a common comparator.

#### **1.2. Revisions to the definition of an overview proposed by the CMIMG**

In considering the choice of overview vs. intervention review, it is important to note the recent changes in definition and guidance for Cochrane overviews that arose from a special meeting organized by the CMIMG in Milan in March 2011. A key recommendation from that meeting was that *“Overviews 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.”*

#### **1.3. Synthesize rather than summarize**

The handbook currently lists “summarizing results” of existing Cochrane reviews as one of the potential aims for an overview. However, in the process of completing initial overviews it has become clear that simply listing results from related Cochrane reviews one after the other may be more confusing than helpful for readers, and that overview authors may need to synthesize results using their own approach. For example, the overview on financial incentives to change behavior of health care professionals found that some relevant systematic reviews focused on a specific type of provider, while others focused on a specific sort of incentive or type of outcome (Flodgren 2011). In order to provide a meaningful

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<sup>1</sup> Comparing Multiple Interventions Methods Group <http://cmimg.cochrane.org/>

synthesis, the overview authors constructed their own classifications of types of incentives and classes of outcomes and thus provided a synthesis that was unique to the overview.

Synthesis could also be quantitative, using indirect comparison and NMA techniques to draw inferences about the comparative effectiveness of multiple interventions simultaneously. The evidence provided by such analysis is valuable for clinical decision-making because it allows comparisons of interventions that may not have been directly compared in RCT setting. One example is the 12 new-generation antidepressants systematic review, published outside of *The Cochrane Library* (Cipriani 2009). The review was developed on the basis of several Cochrane intervention reviews, each focusing on a pair or a few interventions, and a NMA was conducted to facilitate simultaneous inference regarding all interventions of interest.

#### 1.4. Address a well-defined clinical question

The handbook currently indicates that Overviews are “intended primarily to overview multiple Cochrane Intervention reviews addressing the effects of two or more potential interventions for a single condition or health problem” and that the “primary audiences envisioned are decision makers (such as a clinicians, policy makers, or informed consumers) who are accessing *The Cochrane Library* for evidence on a specific problem.” However, the current guidance does not specify that a specific question should guide the overview, and also allows for the possibility of overviews that do not involve comparisons of potentially competing interventions. As a result, some overviews have been proposed with a very broad scope “Summarize reviews that address the prevention and treatment of ... (a specific condition)”. The recommendation in Milan was that broad-brush approaches such as this should be discouraged, and that overview authors be pressed to focus their efforts on a synthesis of the evidence to address a specific, focused question, relevant to policy or practice, that involves the comparison of two or more interventions.

#### 1.5. Proposal and discussion

##### *Factors in the decision to begin an overview vs. an intervention review*

This redefinition would make overviews more comparable to intervention reviews, which also aim to provide a synthesis and to address a carefully designed question or set of questions. The difference is that overview relies on at least one existing Cochrane intervention review, which cover (at least some) interventions to be assessed in the overview. How does one then decide when it is better to embark on an overview or an intervention review? There is no firm set of rules here, but the aim of this session is to explore some of the factors that might push an author team toward doing their review in one format or the other, and to discuss the differences in methodology or approach that would follow on from that decision.

The selection of one approach over another depends on (1) the scope of the question and the resources available to the author team, and (2) the availability of a set of intervention reviews. The same

considerations apply to methodological issues that we will discuss later, for example, whether to conduct a new literature search or rely on existing searches in individual reviews.

In some cases, it may be appropriate to consider conducting both an overview and an intervention review. Both types of reviews may be approached simultaneously, but in many cases this will be a sequential process with a review of one type suggesting the need for the other. An overview may reveal important gaps that could be filled by one or several intervention reviews on related sub topics. Or the authors of a set of related intervention reviews may see an overview as an effective way to provide a broader synthesis.

The scope of the clinical question may be an issue, with broader questions lending themselves better to overviews. The pain management in labor overview provides an example. The process began with the series of intervention reviews which each addressed a focused subset of the potential pain management strategies. The overview drew on the results of the intervention reviews and provided a synthesis that included all possible strategies. This model could profitably be used on other situations when there are a number of different potential classes of interventions (which could be summarized in an overview) and many different interventions to be compared within each class (potentially by an intervention review). Coordinated planning of such a suite of intervention reviews and overviews could allow the analyses to be presented with minimal overlap – i.e. with the intra-class comparisons handled primarily in the intervention reviews, while the inter-class comparisons were explored in more detail in the overview.

Cochrane Review Groups (CRGs) may find overviews a useful approach to synthesis of an existing body of related intervention reviews. The 14 Cochrane reviews on the topic of pain management for women in labor all followed the same generic protocol and used a set of core outcomes developed in collaboration with members of the Pregnancy and Childbirth consumers' group. In this situation an overview and NMA seem like an ideal mechanism for synthesis. In other cases, there may not be reviews that cover all of the interventions of interest, or those available may not have been recently updated, an intervention review may be more appropriate.

## Part 2. Methodological considerations

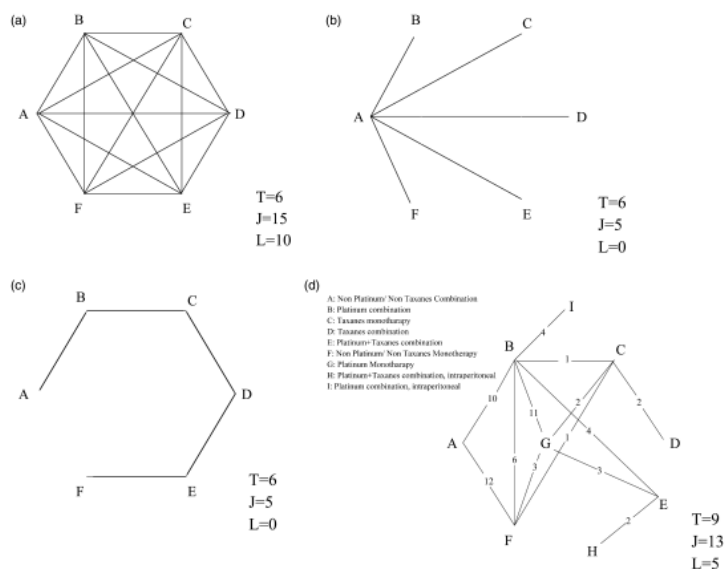
### 2.1. Defining eligibility criteria and its implications

#### 2.1.1. Interventions to be compared and network map

The decision about which interventions to include in the comparison depends primarily on the review question and in part on the envisioned approach for analysis. This is because different specifications of eligibility criteria have implications for the structure and extent of an evidence network and may lead to discrepant findings (Li 2011). In some cases, it would be reasonable to include only interventions that are currently available and in use. However, if a NMA is planned, the addition of data from placebo groups of trials or from groups receiving interventions no longer in use (i.e., legacy treatments) may seem to be unrelated but may provide important indirect information for the target comparison of interest. Including a placebo group is also important in establishing the efficacy of an active intervention, that is, whether the active intervention works at all.

Construction of a network map is an important early step in planning a review that compares multiple interventions. In a network map, a node represents an intervention, narrowly or broadly defined. When two interventions have been compared directly against each other in RCTs, a line is drawn to connect the two interventions (Salanti 2008).

Networks can have a variety of different geometries (see Figure below). If the authors were to plan from scratch, it would be difficult to know the exact shape of the network graph. If a set of intervention reviews already exists, the authors may populate the network map using information already available to them.



**Figure 2** Different geometries for a network: (a) full connected polygon, (b) radiating star, (c) linear structure, and (d) mixed example from real data.<sup>9</sup> For the last panel, each line connecting two treatments also shows the number of available direct comparisons between the two treatments.

Salanti G, Higgins J, Ades A, Ioannidis J. Evaluation of networks of randomized trials. *Statistical Methods In Medical Research*. 2008;17(3):279-301.

### 2.1.2. Characteristics of the participants in included trials

As above, the research question and analysis plan will be an important consideration. For a NMA it is important that the groups receiving the interventions be highly comparable. However, if only a narrative synthesis is planned, greater heterogeneity is acceptable, so long as appropriate caveats are offered and potential impacts of the discrepant populations on the observed differences in outcome is discussed.

### 2.1.3. Types of outcomes

Regardless of whether comparison of multiple interventions is intended or not, a systematic review should examine all outcomes that are meaningful and important to patients, doctors, and other evidence users. The authors could refer to the recommendations described in the *Cochrane Handbook for Systematic Reviews for Interventions* for general guidance. If an overview is planned and a NMA is intended, then harmonizing the protocol for each component review and developing a set of core outcomes will help to streamline the process and should be considered by the author team.

### 2.1.4. Proposal and discussion

The authors should consider including a network map in an intervention review or an overview when the goal is to draw inference about the comparative effectiveness of multiple interventions simultaneously in a single analysis. The authors must pre-specify and justify eligibility criteria for including trials into the review. Considerations should be given to whether the interventions assessed in the review are indeed suitable for the patient population of interest (e.g., if a new trial was conducted, whether it is legitimate to randomize patients with characteristics outlined in the eligibility criteria to each intervention group specified) and whether populations are comparable in terms of prognostic factors for outcomes. The author teams should consider harmonizing the protocol for component intervention reviews by defining and including core outcomes that are meaningful and important to patients, doctors, and other evidence users.

## 2.2. Searching for and selecting studies

### 2.2.1. Approaches for identifying trials

As it is the case with a conventional pair-wise meta-analysis, the validity of findings from a comparison of multiple interventions depends upon whether all eligible trials were identified and included in the analysis (Higgins 2011). Including a non-random or selective subset of all eligible trials in the analysis may introduce selection bias in estimating treatment effects.

The traditional approach to identification of trials for a Cochrane intervention review is to conduct a new, comprehensive literature search. This *de novo* approach would be a duplication of effort and waste valuable resources if high quality systematic reviews with comprehensive searches for the relevant questions already exist. The comparable strategy for Overviews, as initially envisaged, would involve searching for systematic reviews instead of trials, and combining results from those reviews. However, it has become clear that overview authors may need to supplement a search of this sort with searches for specific trials in areas of interest not covered in the identified reviews.

This mixed search strategy has been used in the literature. As an example, to assess the inhaled drugs to reduce exacerbations in patients with chronic obstructive pulmonary disease, Puhan et al. (Puhan 2009) searched the Cochrane Library for existing systematic reviews (Cochrane and non-Cochrane) and included trials from relevant reviews. The authors noted “We based our searches on existing systematic reviews in order to avoid unnecessary duplication of previous work. The existing systematic reviews used extensive search strategies that included several databases such as Medline, EMBASE, CINAHL and LILACS as well as websites of regulatory bodies. In addition, drug companies were approached for unpublished trials.” To supplement these searches, the authors also entered all included trials into the ‘related articles’ function in PubMed to identify additional inclusions.

### 2.2.2. Proposal and discussion

#### *Factors in the decision to begin an overview vs. an intervention review*

How can an author team decide whether to search *de novo* for all relevant studies or consider using data identified through existing high quality systematic reviews of relevant pair-wise treatment comparisons? What are the factors that would suggest the use of one approach versus another, or a hybrid or sequential approach?

The selection of one approach over another depends on (1) the breadth of the topic and the resources available to the author team; (2) the availability and quality of existing systematic reviews; and (3) the comprehensiveness, completeness, and timeliness of searches employed in existing systematic reviews.

As described earlier, the research question addressed in a systematic review can be defined broadly or narrowly. A narrowly defined topic may refer to evaluating a subset of all available interventions for a given condition or for a subset of population. In this case, although simultaneous comparison of several interventions is intended, the resource requirement may be comparable to a conventional intervention review. In contrast, if the research question encompasses a full range of interventions then author

teams face greater resource constraints and they usually need to make the search more efficient without compromising on the quality.

The choice of approach to searching also depends on the availability and quality of existing reviews. The authors could use registries of systematic reviews for identifying existing reviews when they exist. For example, the Cochrane Eyes and Vision Group (CEVG) has created and maintained a registry of eyes and vision (Cochrane and non-Cochrane) systematic reviews (Li 2010, Straus 2010). The reviews in the CEVG register are classified by topic and include a methodological quality assessment for several topics (Li 2012, Yu 2012). Such registers can help authors with prioritizing systematic reviews that intend to compare multiple interventions and therefore, serve an important scoping role. We will discuss the quality of existing reviews later in this paper.

### *Recommendations*

If one were to identify trials for a review through existing reviews then it is important to evaluate the comprehensiveness, completeness, and timeliness of searches employed within the individual reviews. We suggest that the authors consider the following factors when choosing an approach to searching for studies in a network meta-analysis (MECIR 2012, IOM 2011):

- Comprehensiveness of existing searches
  - Number and type of bibliographic databases searched;
  - Use of both indexing terms specific for the bibliographic database and keywords;
  - Other sources searched: reference lists, contacting experts, unpublished studies, ongoing studies, and studies published in the hard-to-access literature.
- Comparability of existing searches
  - Consider the factors listed above and assess whether there are “gaps” in the existing search (e.g., none of the existing reviews searched ongoing studies or omitted major bibliographic databases).
- Timeliness of existing searches
  - Depends on the topic, but in general, consider if the literature search was done within two years (Moher 2008).

## 2.3. Including existing systematic reviews into an overview

### 2.3.1. Quality of included reviews

If the authors of an overview wish to use data already extracted for existing systematic reviews then they must carefully evaluate already extracted data and validity of findings in the reviews. Several instruments have been developed for assessing the methodological quality and reporting quality of systematic reviews (CASP <http://www.casp-uk.net/>, Shea 2007, Shea 2009, Liberati 2009, Moher 2009). These tools may be adapted to suit the authors' needs. For example, Li et al. has adapted 13 items from AMSTAR, PRISM, and GRADE to assess the methodological quality of 39 systematic reviews on glaucoma management (Li 2012).

### 2.3.2. Proposal and discussion

The author team should describe in the protocol for the overview how they would assess the methodological quality of existing reviews. This plan should include details on the instrument(s) to be used, criteria for deciding whether a review will be considered for the purpose of identifying trials or for other data about the trials. Although it has been shown consistently that Cochrane reviews are more likely to follow rigorous methodology than non-Cochrane reviews (Bhandari 2001, Delaney 2005, Glenny 2003, Li 2012, Lundh 2009, Shea 2002), the assessment of methodological quality of existing reviews should be conducted for both Cochrane and non-Cochrane reviews.

When both Cochrane and non-Cochrane reviews are considered appropriate for inclusion, there will sometimes be overlap in their clinical questions and inclusion criteria. Some trials will be included in more than one review and the findings from overlapping reviews may or may not agree with each other. The author team should pre-specify how they would address such issues. One approach would be to develop a priori criteria for choosing a single review for inclusion when multiple potential candidates are available. Another is to include all reviews, but specify how overlap reviews will be managed. For example, they may choose to use existing reviews as a source to identify trials and conduct their own data abstraction from trial reports, or they may use data already extracted in individual reviews. The author team should be extremely careful not to double-counting trials that were included in more than more review and have a procedure to check data quality as data abstraction and analyses errors are not uncommon in systematic reviews.

When only non-Cochrane reviews are available for certain interventions, the authors should pre-specified in the protocol how they would handle those reviews. Additional trial-level data abstraction is often needed, for example, to perform risk of bias assessment and for analysis of different outcomes. The authors may also choose to conduct a Cochrane intervention review to fill in the gaps before performing the overview.



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