Comparing Multiple Interventions in Cochrane Reviews

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This paper is the first of several products of a project funded by the Cochrane Methods Innovation Fund to further develop methods and recommendations for Cochrane authors wishing to include multiple interventions in their reviews:

- Pages 2-6 give some details about the history and rationale for the development of Cochrane Overviews.
- Pages 6-9 discuss some key issues for consideration when comparing interventions in either Overviews or Intervention Reviews.
- Pages 9-14 discuss the approaches taken by the first 10 Overviews published in CDSR
- Pages 14-16 outline six recommendations that were discussed by MARS, the Methods Executive and the Coordinating Editors' Board during the 2013 Mid-Year Meetings in Oxford.

Comparing Multiple Interventions in Cochrane Reviews

Introduction

Most Cochrane Reviews present pair-wise comparisons between interventions for a specific condition or in a specific population or setting. However, it is often the case that more than two competing interventions are available in a given situation. In these cases, it would be good to have a single review that includes all of the relevant interventions and allows readers to learn about their relative effectiveness or potential for harm. The question of how one might provide a Cochrane Review that compares multiple interventions has been the subject of increasing discussion in the Collaboration in recent years. The growing interest within the Collaboration was evident in a survey of Cochrane authors published in 2012 (Abdelhamid, 2012). Most of the activity has been in one of two distinct but overlapping areas – the development of the Overview format for Cochrane Reviews, and the development of increasingly sophisticated statistical methods for producing network meta-analyses (NMA) and related approaches that combine direct and indirect comparisons between a set of interventions. These two streams have now come together in the work of the Cochrane Comparing Multiple Interventions Methods Group (CMIMG). The CMIMG has been funded by the Cochrane Methods Innovation Fund to further develop these methods, to provide recommendations and produce a decision chart for Cochrane authors wishing to include multiple interventions in their reviews.

This paper briefly reviews the history of these discussions within the Collaboration, identifies some key issues for consideration in developing guidance for authors, and presents a set of recommendations for moving forward.

History

The Umbrella Reviews Working Group

The current handbook guidance on Cochrane Overviews was developed by the "Umbrella Review Working Group" (URWG) through a multi-year process that involved conference calls, consultation with the collaboration (occurring mainly during Colloquia) and shared drafts. The foundational idea was that each Overview of Reviews (OoR) would be "a systematic review of systematic reviews" – i.e. that the basic unit of search and of analysis in an overview would be systematic reviews. Thus, Overviews would be different from Intervention Reviews (IR), which search for and summarize trials.

Throughout the discussions of the URWG, two somewhat different concepts of an overview emerged, and both are reflected in the Handbook chapter. One view was that overviews should serve primarily as a "friendly front end" to the Cochrane Library - with the expectation that Overview readers would use them to discover the presence of a set of related reviews in the library, to get an idea of the contents of these reviews, but then to go to the individual reviews if they wished additional detail. A second view was that by reading an Overview, users would be able to learn about the relative effectiveness of different interventions, even when those interventions had never been directly compared with one another in a Cochrane Intervention Review. Users would then be able to make intelligent comparisons between an entire set of related interventions, even if the required analyses and data were spread throughout several Cochrane Reviews that each addressed only pairwise comparisons. These and other

potential uses for Overviews are summarized in chapter 22 of the Cochrane Handbook, which addresses Cochrane Overviews (Table 1).

Table 1: Reasons for overviewing reviews and their suitability for publication as a Cochrane Overview (reproduction of Table 22.1.a from Becker and Oxman (2008)).

Objective	**Selection criteria**	**Examples of overviews**	**Suitable for inclusion as a Cochrane Overview of reviews**	**Comments**
To summarize evidence from more than one systematic review of **different interventions** for the same condition or problem.	Cochrane Intervention reviews.	A Cochrane Overview of interventions for nocturnal enuresis (Russell 2006)	Yes.	This is the primary purpose of Cochrane Overviews (and should be referred to as an Overview of Cochrane reviews in the objectives section of the abstract and the text).
	Cochrane Intervention reviews and non-Cochrane systematic reviews.	Some *BMJ Clinical Evidence* chapters and an increasing number of health technology assessment (HTA) reports.	Possibly.	It may sometimes be appropriate to include non-Cochrane systematic reviews as well as Cochrane reviews, for example, if there are important interventions for which good quality systematic reviews have been published and a Cochrane review is not available. However, CRGs are encouraged to focus primarily on Overviews of Cochrane reviews as: searching for and including non-Cochrane reviews in Overviews entails additional work and challenges non-Cochrane reviews may not be accessible to users of *The Cochrane Library*. the primary aim of Cochrane Overviews is to summarize Cochrane reviews and to provide a user-friendly front end

Objective	Selection criteria	Examples of overviews	Suitable for inclusion as a Cochrane Overview of reviews	Comments
To summarize evidence from more than one systematic review of the same intervention for the same condition or problem where **different outcomes** are addressed in different systematic reviews.	Cochrane Intervention reviews.	An overview of Cochrane reviews of hormone replacement therapy (HRT) for menopause where outcomes may include bone density, menopausal symptoms, cardiovascular risk/ events, cognitive function etc.	Occasionally.	As a rule, individual Cochrane reviews should include all outcomes that are important to people making decisions about an intervention. However, occasionally, as with HRT, different outcomes have to a large extent been considered in different systematic reviews.
	Cochrane Intervention reviews and non-Cochrane reviews.	Some *BMJ Clinical Evidence* chapters and some HTA reports.	Rarely.	The considerations for including non-Cochrane systematic reviews are the same as those noted above.
To summarize evidence from more than one systematic review of the same intervention for **different conditions, problems or populations**.	Cochrane Intervention reviews.	An overview of Cochrane reviews of vitamin A for different populations and conditions.	Occasionally.	The same or similar interventions may sometimes be used for different conditions or different studies and reviews may focus on different populations. While an overview of these reviews is unlikely to be of interest to clinicians and patients deciding how best to address a specific problem, an overview may be relevant to policy makers or to addressing questions that cut across the different reviews.
	Cochrane Intervention reviews and non-Cochrane reviews.		Rarely.	The considerations for including non-Cochrane systematic reviews are the same as those noted above.

Objective	Selection criteria	Examples of overviews	Suitable for inclusion as a Cochrane Overview of reviews	Comments
To summarize evidence about **adverse effects** of an intervention from more than one systematic review of use of the intervention for one or more conditions.	Cochrane Intervention reviews only or Cochrane Intervention reviews and non-Cochrane systematic reviews.	An overview of adverse effects of NSAIDs when used for osteoarthritis or rheumatoid arthritis or menorraghia.	Rarely.	While many Cochrane reviews report on adverse effects, few if any are designed primarily to assess rates of adverse effects. Many important adverse effects occur so rarely that their true prevalence cannot be accurately assessed from results of controlled trials. For these reasons, an overview based solely on Cochrane or other systematic reviews of controlled trials may not give an accurate picture of the adverse effect profile of a specific intervention - unless the systematic reviews it summarizes have been specifically designed to address the rates of adverse effects (see Chapter 14 for further information on the reporting of adverse effects in Cochrane reviews.
To provide a comprehensive overview of an area, including **studies not included in systematic reviews**.	Systematic reviews and studies not included in systematic reviews.	Some BMJ Clinical Evidence chapters, an increasing number of HTA reports or a synoptic review article for a journal.	No.	Including studies that have not previously been included in a systematic review may be appropriate in a number of circumstances, for example when undertaking a HTA report, developing a clinical practice guideline, or for resources such as *BMJ Clinical Evidence*. However, this is beyond the scope of what should be done in a Cochrane Overview. Authors of Cochrane Overviews should note when included reviews are out of date, particularly if new relevant studies have been published, and if there are relevant interventions for which a systematic review has not yet been published. However, they should not undertake an update of a systematic review or a new systematic review within the Overview.

Lumping/splitting

An additional motivation for the development of Overviews was the problem of lumping and splitting in Cochrane Reviews. It was anticipated that the availability of the Overview format might allow CRGs

to address synthesis of trials of a large number of competing interventions by splitting the pairwise analyses into a series of Intervention Reviews, and then producing an Overview that did the lumping. A series of Intervention Reviews each covering a relatively focused question is attractive to CRGs and review authors because such reviews require in general less effort in initiation, production, coordination, and updating.

Limited analysis detail

The discussions of the URWG and the resulting chapter did not deal with the issue of statistical analyses of multiple interventions to any great degree. Techniques for network meta-analyses were being developed, and the group felt that the methodology needed to be further distilled and summarized to be included in the Handbook. The Overviews chapter mentioned the availability of these methods and advised authors who considered using them in overviews to seek appropriate methodological and statistical support.

The Handbook did, however, encourage authors to present summary data from related reviews in juxtaposition to one another so that readers could make their own comparisons. Concerns about the potential problems in such informal indirect comparisons were not addressed in the Handbook chapter. The format in Table 2 was suggested (with the various rows to be taken from different reviews):

Table 2. Template for an 'Overview of reviews' table (reproduction of Figure 22.3.b from Becker and Oxman (2008)).

Interventions for [Condition] in [Population]							
Outcome	**Intervention and Comparison intervention**	Illustrative comparative risks (95% CI)		**Relative effect (95% CI)**	**Number of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
		Assumed risk	Corresponding risk				
		With comparator	**With intervention**				
Outcome #1							
	Intervention/Comparison #1						
	Intervention/Comparison #2						
	Etc…						
Outcome #2							
	Intervention/Comparison #1						
	Intervention/Comparison #2						

	Etc…						
Outcome #3							
	Intervention/Comparison #1						
	Intervention/Comparison #2						
	Etc…						

Development of NMA methods and formation of the CMIMG

The statistical methodology for comparison of multiple interventions in systematic reviews was advancing very quickly during the time the URWG was in operation and those advances have continued at an increasing pace since the publication of the Overviews chapter in the Handbook. The CMIMG was formed in 2010. Core functions of the Methods Group include developing and maintaining guidance for use of these increasingly powerful statistical methods in Cochrane Reviews as well as ongoing responsibility for guidance on Overviews of reviews. The CMIMG quickly recognized that there were areas of conflict or potential conflict between the guidance provided for authors in Chapter 22 and the principles being enunciated for NMA, and began a program designed to explore these potential conflicts and find ways to resolve them.

A core underlying issue in all of the identified concerns was the fact that NMA methods were developed with the assumption that individual trials would be examined for inclusion and that data from individual trials would be used in NMA analyses, while Overview guidance recommended that systematic reviews rather than individual trials be used for these purposes.

Indirect comparisons using summary statistics of the reviews

Chapter 22 suggested the possibility that Overview authors might perform indirect comparisons using summary statistics from the included reviews. Caldwell *et al* (2010) has demonstrated that this approach is feasible using Cochrane Reviews of interventions for enuresis. However, the enuresis reviews primarily used the same two key outcomes. Most of the reviews included in other Cochrane Overviews have not demonstrated the same consistency in their outcome selection (Wang et al, 2012), so this shortcut of using review summary statistics for indirect comparisons is rarely available. Even if the same outcome measures are used in the reviews, appropriate use of NMA requires that authors ensure that the key underlying assumptions of the method (particularly the transitivity assumption required for indirect comparisons) have been met. This is best achieved by examining the relevant trials in detail.

Importance of the transitivity assumption

The transitivity assumption states that two or more interventions can validly be compared using trials that did not compare them directly but which compared one or other of them against a common comparator. Mathematically, the assumption states that if A > C and C > B, then A > B. A strong form of the assumption is used in indirect comparisons, by assuming that (A – B) = (A – C) + (C – B), or equivalently, (A – B) = (A – C) – (B – C). In other words, the effect size for A versus B can be obtained by taking the difference between the effect size for A versus C and the effect size for B versus C. The transitivity assumption is likely to hold across a network of interventions only when all trial participants could reasonably be expected to receive any of the interventions. One way to consider this is that the

interventions being compared in a network meta-analysis are "jointly randomizable", i.e. when "…it is possible to imagine that a single randomized trial could have been designed to compare all these treatments" (Salanti 2012). An example of a situation in which this would not hold is when intervention A is clinically indicated only for previously untreated patients and intervention B is clinically indicated only when all other treatments have failed. In such a case, interventions A and B are not indicated for the same patients and would not be considered jointly randomizable. A second example would be the situation in which intervention A is only indicated for primary prevention while intervention B is only indicated for secondary prevention.

The relevance and importance of the transitivity assumption is not limited to reviews that use formal statistical techniques to perform indirect comparisons. Presentation of a table that includes results of pairwise comparisons taken from different systematic reviews (as in the example from the Handbook chapter cited above) encourages readers to make their own informal indirect comparisons. This has been shown to lead to erroneous conclusions if the trials summarized in the various rows of the table are not comparable or the interventions not jointly randomizable (Caldwell et al, 2010).

Limitations of searching only for systematic reviews

The Handbook recommends that Overview authors "Typically search for only relevant Cochrane Intervention reviews" but "May occasionally search for non-Cochrane systematic reviews." However, it is very likely that some trials that are very relevant to a NMA would be missed by such a search – either because the systematic reviews have not been updated, or because some of the interventions or comparisons of interest in the NMA have not been relevant to the scope of any of the systematic reviews identified.

In addition, some of the trials included in the systematic reviews may be considered outside the scope of the NMA. This could include trials with intervention groups that are of little clinical relevance currently (e.g., legacy treatment). For example, pilocarpine, a drug used for more than 100 years in glaucoma patients is no longer prescribed as the first, second, or even third-line drug, but is included in some Cochrane glaucoma reviews. Authors of a network meta-analysis comparing modern drugs for glaucoma may choose to exclude trials of pilocarpine against a more recent drug. On the other hand, the more interventions that are included in a NMA, 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. There is little empirical evidence on the implications of specifying broad or narrow inclusion criteria for a NMA. In any case, the criteria should be specified by the NMA authors rather than be based on the (sometimes conflicting) decisions made by individual teams of systematic review authors.

Even when up-to-date reviews are available that cover all of the interventions of interest, if both Cochrane and non-Cochrane reviews are included in the Overview there may be multiple reviews on the same or closely related topics. The methods for choosing between reviews in this situation have not been developed. Inclusion of all such reviews is likely to lead to double counting of some trials.

Assessing risk of bias

Although the Handbook asks Overview authors to assess the methodological quality of included reviews, there is no agreement on which tool or instrument should be used to carry out these assessments. In addition, the quality of the reviews included in an Overview does not necessarily

provide an indication of the risk of bias in the various trials included in each review (although this information may be provided within the review).

Milan meeting (March 2011) – plans for a new direction

In order to start addressing these issues, the CMIMG organized a meeting in Milan in March 2011, hosted by the Italian Cochrane Centre and supported by the Cochrane Discretionary Fund. 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.

The decision at this meeting (reflected in the document that evolved from it - http://cmimg.cochrane.org/Milan-report) was to attempt to broaden the definition of an Overview to make it possible to include valid NMAs within Cochrane Reviews of this type. The report suggested that *"Broadening the search in an OoR to include individual studies may be appropriate in some cases"* and also that *"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."*

It was decided that authors would be encouraged to consider the implementation of indirect comparisons and the use of NMA within their Overviews and to expand their search to include individual trials and/or use results from individual trials in their analyses if necessary.

These decisions were communicated to the Collaboration via Cochrane.org and by publication of the full report on the CMIMG website. In addition, the CMIMG presented a workshop at the Madrid Colloquium on the topic, and included the recommendations in their comments when asked to provide peer review on Overview protocols or reviews.

Paris meeting (April 2012) – reconsideration of previous proposals

In 2011, the CMIMG received funding from the Cochrane Methods Innovation Fund to set up three working groups to address specific issues related to comparisons of multiple interventions. The first activity funded by this grant was a meeting in Paris in April 2012. The 26 participants included authors, CRG staff and others who had experience in the authorship of Overviews, and who were aware of the guidance available in the Handbook and in the report of the Milan meeting.

It was clear at this meeting that authors and CRGs found the Overview guidance quite confusing and that the attempt following the Milan meeting to extend the definition and methods of Overviews had increased rather than decreased the confusion. The participants encouraged the CMIMG to return to the earlier definition of an Overview as a "review of reviews." There was also a clear preference among participants for the CMIMG to base future guidance for indirect comparisons and NMA on the assumption that authors would develop a search strategy for individual trials and would use individual trial data in their analyses.

Approaches taken with Cochrane Overviews published to date

The authors of the 10 Cochrane Overviews that have been published in CDSR have taken a variety of approaches to both the search and the synthesis of results for their reviews.

Three Overviews have included formal statistical indirect comparisons:

- Biologics for rheumatoid arthritis: an overview of Cochrane reviews (Singh et al, 2009);
- Adverse effects of biologics: a network meta-analysis and Cochrane overview (Singh et al, 2011); and
- Safety of regular formoterol or salmeterol in children with asthma: an overview of Cochrane reviews (Cates et al, 2012)

All three used data extracted by the Overview authors from individual studies in their analyses. The first of these three overviews searched only for published Cochrane Reviews, and used trials included in those reviews in their analyses. The other two Overviews started with reviews, but then performed additional searches for trials or other relevant studies.

Three Overviews included only results from direct comparisons:

- Open, small-incision, or laparoscopic cholecystectomy for patients with symptomatic cholecystolithiasis. An overview of Cochrane Hepato-Biliary Group reviews (Keus et al, 2010);
- Single dose oral analgesics for acute postoperative pain in adults (Moore et al, 2011); and
- Efficacy and safety of pharmacological interventions for the treatment of the Alcohol Withdrawal Syndrome (Amato et al, 2011).

All three restricted their search to published Cochrane Reviews. The first of these three Overviews compared three surgical interventions for cholelithiasis. The authors found three Cochrane Reviews, each of which synthesized the evidence for a comparison between two of the three competing interventions. The overview tables included results of the pairwise comparisons taken from the three included reviews. The other two Overviews in this group used results from Reviews that had compared the various interventions of interest with placebo controls. Both Overviews used tables or figures to present summary statistics from the included Cochrane Reviews in juxtaposition to one another, as suggested in the Handbook chapter (Figures 1 and 2).

Figure 1: Results from an Overview of single dose oral analgesics for acute postoperative pain in adults (from Moore et al, 2011)

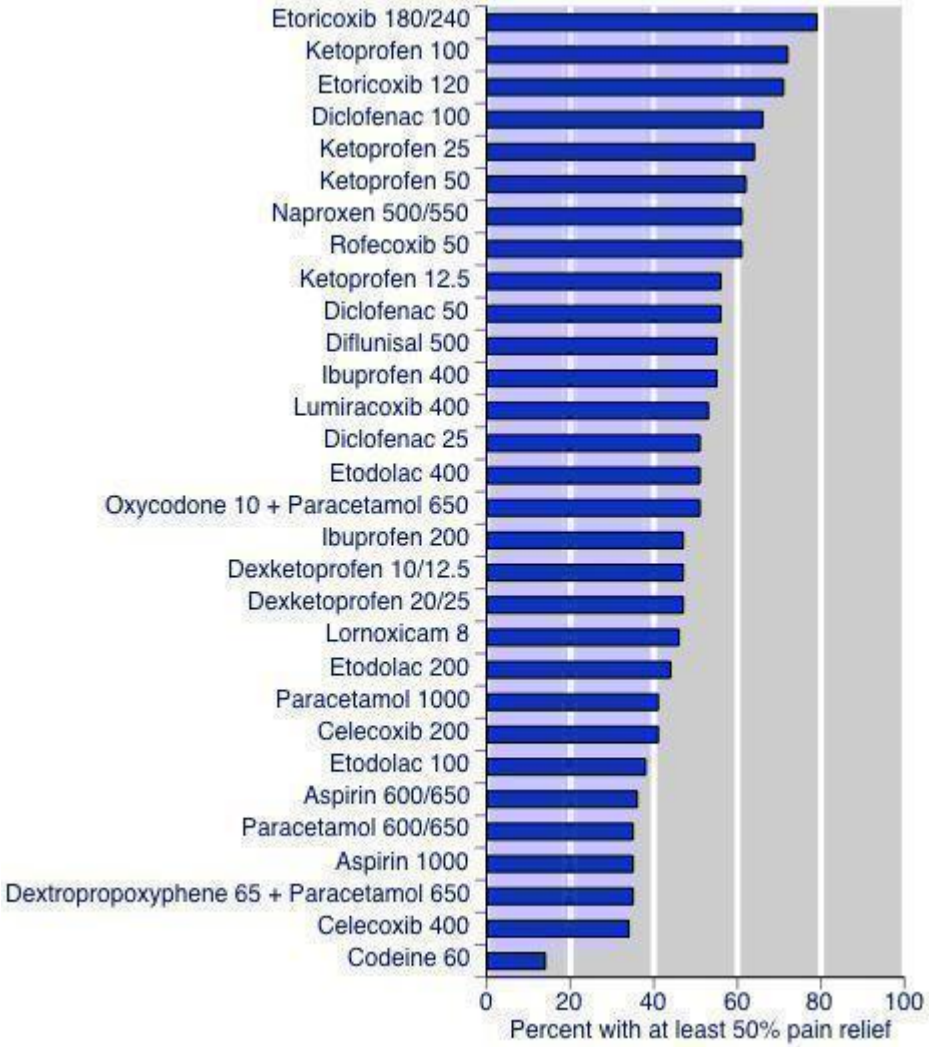
Etoricoxib 180/240
Ketoprofen 100
Etoricoxib 120
Diclofenac 100
Ketoprofen 25
Ketoprofen 50
Naproxen 500/550
Rofecoxib 50
Ketoprofen 12.5
Diclofenac 50
Diflunisal 500
Ibuprofen 400
Lumiracoxib 400
Diclofenac 25
Etodolac 400
Oxycodone 10 + Paracetamol 650
Ibuprofen 200
Dexketoprofen 10/12.5
Dexketoprofen 20/25
Lornoxicam 8
Etodolac 200
Paracetamol 1000
Celecoxib 200
Etodolac 100
Aspirin 600/650
Paracetamol 600/650
Aspirin 1000
Dextropropoxyphene 65 + Paracetamol 650
Celecoxib 400
Codeine 60
0
20
40
60
80
100
Percent with at least 50% pain relief

Figure 2: Results from an Overview of pharmacological interventions for the treatment of the alcohol withdrawal syndrome (from Amato et al, 2011)

Treatments versus Placebo for alcohol withdrawal

Patient or population: patients with alcohol withdrawal
Settings: inpatient and outpatient
Intervention: Treatments versus Placebo

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Treatments versus Placebo	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Alcohol withdrawal seizures - Benzodiazepine objective Follow-up: mean 10 days	**Study population**		RR 0.16 (0.04 to 0.69)	324 (3 studies)	⊟⊟⊟⊟ **moderate**[1]	
	80 per 1000	13 per 1000 (3 to 55)				
	Medium risk population					
	69 per 1000	11 per 1000 (3 to 48)				
Alcohol withdrawal seizures - Anticonvulsants objective Follow-up: mean 10 days	**Study population**		RR 0.52 (0.25 to 1.07)	1108 (10 studies)	⊟⊟⊟⊟ **moderate**[2]	
	101 per 1000	53 per 1000 (25 to 108)				
	Medium risk population					
	150 per 1000	78 per 1000 (38 to 161)				
Adverse events - Benzodiazepine subjective Follow-up: mean 10 days	**Study population**		RR 3.28 (0.31 to 34.52)	71 (2 studies)	⊟⊟⊟⊟ **moderate**[3]	
	28 per 1000	92 per 1000 (9 to 967)				
	Medium risk population					
	46 per 1000	151 per 1000 (14 to 1000)				
Adverse events - Anticonvulsant subjective Follow-up: mean 10 days	**Study population**		RR 1.56 (0.74 to 3.31)	663 (7 studies)	⊟⊟⊟⊟ **moderate**[4]	
	50 per 1000	78 per 1000 (37 to 165)				
	Medium risk population					
	34 per 1000	53 per 1000 (25 to 113)				
Adverse events - GHB subjective Follow-up: mean 10 days	**Study population**		RR 16.25 (1.04 to 254.98)	23 (1 study)	⊟⊟⊟⊟ **low**[5]	
	0 per 1000	0 per 1000 (0 to 0)				
	Medium risk population					
	0 per 1000	0 per 1000 (0 to 0)				
Dropouts - Benzodiazepine objective Follow-up: mean 10 days	**Study population**		RR 0.64 (0.37 to 1.12)	375 (5 studies)	⊟⊟⊟⊟ **moderate**[6]	
	164 per 1000	105 per 1000 (61 to 184)				
	Medium risk population					
	143 per 1000	92 per 1000 (53 to 160)				
Dropouts - Anticonvulsant objective Follow-up: mean 10 days	**Study population**		RR 0.82 (0.5 to 1.34)	801 (11 studies)	⊟⊟⊟⊟ **moderate**[7]	
	89 per 1000	73 per 1000 (44 to 119)				
	Medium risk population					
	21 per 1000	17 per 1000 (10 to 28)				
Dropouts - GHB objective Follow-up: mean 10 days	See comment	See comment	Not estimable	23 (1 study)	See comment	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Allocation concealment unclear in all the three studies
[2] Allocation concealment unclear in the majotity of studies
[3] Small sample size, wide confidence interval
[4] allocation concealment: 3/7 unclear, 1/7 no; 1/7 no blinding
[5] only one study, wide confidence interval, few participants
[6] allocation concealment unclear in 3/5 studies, blinding unclear in 1/
[7] allocation concealment: 7/11 unclear and 1/11 no; blinding no in 1 study and unclear in 1 study; sequence generation inadequate in 1 study

The Overview of single dose analgesics addressed transitivity issues in some detail in its Discussion section. The authors pointed out that "The trials used in these reviews have a high level of clinical and methodological homogeneity, having, for more than 50 years, used consistent validated methods of measuring pain in patients with established pain of at least moderate severity, over at least four to six hours, and with placebo as a common comparator." They identified case mix as the primary source of clinical heterogeneity in the trials and presented results separately for trials of dental procedures and for surgery of other sorts.

The remaining four Overviews:

- **Consumer-oriented interventions for evidence-based prescribing and medicines use: an overview of systematic reviews (Ryan et al, 2011);**
- **Pain management for women in labour: an overview of systematic reviews (Jones et al, 2012);**
- **An overview of reviews evaluating the effectiveness of financial incentives in changing healthcare professional behaviours and patient outcomes (Flodgren et al, 2011);** and
- **Interventions for fatigue and weight loss in adults with advanced progressive illness (Payne et al, 2012)**

did not provide either direct or indirect comparisons between differing interventions, but instead used the results of the included reviews to provide a map of the existing evidence. Two of the reviews provided their own taxonomies of interventions and of outcomes.

When review results were reported in these Overviews, they were usually reported on a review by review basis so that only the results from a single review appeared in any given table. The overview of financial incentives presented evidence from individual trials, using a vote-counting technique to investigate how the trial results mapped onto the various cells in the authors' intervention/outcomes taxonomy (Table 3).

Table 3: Results from an Overview of financial incentives in changing healthcare professional behaviours and patient outcomes (from Flodgren et al, 2011).

Table 6. Vote counting results

Outcome	Consultation/ Visit rates	Processes of care	Referrals/ Admissions	Compliance with guidelines	Prescribing costs	Overall effect within intervention
Intervention						
Payment for working for a specified time period	3/ 9 outcomes from 1 study reported in 1 review favoured the intervention			0/2 outcomes from 1 study reported in 1 review favoured the intervention		3/11 (27%) 1 study 1 review
Payment for each service/ episode/visit	3/ 3 outcomes from 1 study reported in 2 reviews favoured the intervention	4/6 outcomes from 4 studies reported in 1 review favoured the intervention	0/ 1 outcomes from 1 study reported in 1 review favoured the intervention			7/10 (70%) 5 studies 3 reviews
Payment for providing care for a patient or a specific population		17/30 outcomes from 8 studies reported in 1 review favoured the intervention	3/ 5 outcomes from three 3 studies reported in 2 reviews favoured the intervention		28/34 outcomes from 10 studies reported in 1 review favoured the intervention	48/69 (70%) 13 studies 2 reviews
Payment for providing a prespecified level or providing a change in activity or quality		16/16 outcomes from 5 studies reported in 2 reviews favoured the intervention	1/2 outcomes from three studies reported in 1 review favoured the intervention	0/2 outcomes from 2 studies reported in 1 review favoured the intervention		17/20 (85%) 10 studies 2 reviews
Mixed or other systems	4/5 outcomes from 2 studies (1 outcome unclear) reported in 2 reviews favoured the intervention	4/5 outcomes from 3 studies reported in 2 reviews favoured the intervention	7/8 outcomes from 5 studies reported in 2 reviews favoured the intervention	5/13 outcomes from 2 studies reported in 1 review favoured the intervention		20/31 (65%) 7 studies 3 reviews

Moving forward - CMIMG recommendations for Overviews and for comparing multiple interventions

1 - Define Overviews as reviews of reviews

The attempt following the Milan meeting to broaden the definition of an Overview was seen as confusing, and should therefore be abandoned. We should return to the guidance outlined in the Handbook, which indicates that Overviews should search for reviews and provide their synthesis at the review level.

2 - Cochrane authors who wish to include indirect comparisons or network meta-analysis in their reviews should examine individual trial reports and use individual trial data in their analyses

The primary reason for this recommendation is that it may be very difficult to be certain that the assumptions for indirect comparison and network meta-analysis have been satisfied using only information provided in reviews.

3 - The Overview format should only be used to do indirect comparisons when the Overview authors have evaluated the assumption of transitivity for all of the trials included in those comparisons

This follows as a logical conclusion from #1 and #2. This may be possible in some cases. For example, when the overview authors are also authors of all of the included reviews they will have already examined all of the trials and may feel that they are able to address the transitivity issues using the Overview format. If the included reviews are all up to date and have taken a consistent approach to trial inclusion criteria, selection of outcomes, and approach to potential sources of heterogeneity, then it may be possible to use summary statistics from the included reviews in indirect comparisons and network meta-analyses. However the situations in which all of these conditions apply are likely to be rare.

4 – Overviews that facilitate "informal" indirect comparison by readers must address transitivity issues

As noted above, the transitivity assumption is not only an issue for reviews that include a network meta-analysis or other formal statistical approaches to indirect comparisons. Overview authors who choose to juxtapose data from different systematic reviews in a single table or figure (as in the examples above) are inviting readers to do their own informal indirect comparisons. A table or figure of this sort should only be used if the Overview authors are confident that the trials included in these reviews could have been "jointly randomizable" (Such an argument was presented by the authors in the Single Dose Analgesic Overview cited above). If there is a good possibility that the various included reviews contain data from trials that were not sufficiently similar to one another, Overview authors should present results of the included reviews on a review-by-review basis.

5 – The Collaboration should re-examine the issue of "overlapping" reviews, and find an approach that allows both reviews that include a NMA and reviews that examine a more restricted subset of the available interventions to be published in The Cochrane Library.

[NB – This recommendation was discussed by the Coordinating Editors Board, the Methods Executive and by MARS at the Oxford 2013 mid-year meeting. There was strong agreement with the principle that "overlapping" reviews should be allowed in The Cochrane Library when one of the reviews was a review that compared multiple interventions with the intent of finding the interventions likely to have the highest efficacy or fewest adverse effects. The preferred mechanism for doing this was to define a new review type that would compare 3 or more interventions, would use data from individual trials, and would use formal methods to assess their relative effectiveness or potential for harm.]

One logical conclusion from recommendations 1-3 above would be that NMAs should be performed in Cochrane Intervention Reviews rather than in Overviews. There is a potential problem with this, however because of the desire within the Collaboration to minimize overlap between reviews. If an intervention including a NMA is proposed when CDSR already includes a series of Intervention reviews with a more narrow scope, many of the trials to be included in this network meta-analysis will be included in the 'simple' intervention reviews. There could be some overlap in the analyses as well, since specific direct comparisons would be included in the NMA review as well as in the reviews with a narrower scope.

One way to resolve this problem would be for the authors of the reviews with a more restricted scope to withdraw them once the NMA review is published. This may work if the author team for the NMA has considerable involvement by the authors of the 'simpler' intervention reviews, but could lead to significant difficulty and dispute in some cases. In addition, these more narrowly focused reviews may have taken a broader approach to their review, and included some outcomes, comparisons or subgroup analyses that do not appear in the NMA. Thus withdrawing the component reviews could do a disservice to their authors and remove valuable information from readers of CDSR.

Another possibility would be to define yet another type of Cochrane Review that is different from both an Intervention Review and an Overview. This would allow the principle of minimizing overlap among *Intervention reviews* to be upheld, while allowing NMA reviews to be produced.

We would recommend a third approach, which would involve an agreement across the Collaboration that overlapping Intervention Reviews would be allowed in this specific case – i.e. when one Intervention Review containing an NMA overlaps with one or more other Intervention Reviews.

6 - The Collaboration should develop mechanisms to facilitate the production of Reviews that include NMAs

Because of recent methodological developments in this area, the number of reviews that include a statistical approach to indirect comparisons has been growing. Unfortunately, relatively few of these reviews have been published in the Cochrane Database of Systematic Reviews. In theory, Cochrane authors should have a head start in producing a review with indirect comparisons, because much of the trial data needed for these comparisons will have already been extracted for direct comparisons in other Cochrane Reviews. Unfortunately, there is currently no way to pull already extracted study characteristics or data from one Cochrane Review for use in another. Developing methods to do this would facilitate the production of Cochrane Reviews that provide rigorous comparisons of multiple interventions and should lead to the inclusion of more such reviews in CDSR.

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