16.6 Indirect comparisons and multiple-treatments meta-analysis

16.6.1 Introduction

Head-to-head comparisons of alternative interventions may be the focus of a Cochrane Intervention review, a secondary aim of a Cochrane Intervention review, or a key feature of a Cochrane Overview of reviews. Cochrane Overviews summarize multiple Cochrane Intervention reviews, typically of different interventions for the same condition (see Chapter 22). Ideally, direct head-to-head comparisons of alternative interventions would be made within randomized studies, but such studies are often not available. Indirect comparisons are comparisons that are made between competing interventions that have not been compared directly with each other: see Section 16.6.2. Multiple-treatments meta-analysis (MTM) is an extension to indirect comparisons that allows the combination of direct with indirect comparisons, and also the simultaneous analysis of the comparative effects of many interventions: see Section 16.6.3.

16.6.2 Indirect comparisons

Indirect comparisons are made between interventions in the absence of head-to-head randomized studies. For example, suppose that some trials have compared the effectiveness of 'dietician versus doctor' in providing dietary advice, and others have compared the effectiveness of 'dietician versus nurse', but no trials have compared the effectiveness of 'doctor versus nurse'. We might then wish to learn about the relative effectiveness of 'doctor versus nurse' by making indirect comparisons. In fact, doctors and nurses can be compared indirectly by contrasting trials of 'dietician versus doctor' with trials of 'dietician versus nurse'.

One approach that should never be used is the direct comparison of the relevant single arms of the trials. For example, patients receiving advice from a nurse (in the 'dietician versus nurse' trials) should not be compared directly with patients receiving advice from a doctor (in the 'dietician versus doctor' trials). This comparison ignores the potential benefits of randomization and suffers from the same (usually extreme) biases as a comparison of independent cohort studies.

More appropriate methods for indirect comparisons are available, but the assumptions underlying the methods need to be considered carefully. A relatively simple method is to perform subgroup analyses, the different subgroups being defined by the different comparisons being made. For the particular case of two subgroups (two comparisons; three interventions) the difference between the subgroups can be estimated, and the statistical significance determined, using a simple procedure described by Bucher (Bucher 1997). In the previous example, one subgroup would be the 'dietician versus doctor' trials, and the other subgroup the 'dietician versus nurse' trials. The difference between the summary effects in the two subgroups will provide an estimate of the desired comparison, 'doctor versus nurse'. The test can be performed using the test for differences between subgroups, as implemented in RevMan (see Chapter 9, Section 9.6.3.1). The validity of an indirect comparison relies on the different subgroups of trials being similar, on average, in all other factors that may affect outcome. More extensive discussions of indirect comparisons are available (Song 2003, Glenny 2005).

Indirect comparisons are not randomized comparisons, and cannot be interpreted as such. They are essentially observational findings across trials, and may suffer the biases of observational studies, for example due to confounding (see Chapter 9, Section 9.6.6). In situations when both direct and indirect comparisons are available in a review, then unless there are design flaws in the head-to-head trials, the two approaches should be considered separately and the direct comparisons should take precedence as a basis for forming conclusions.

16.6.3 Multiple-treatments meta-analysis

Methods are available for analysing, simultaneously, three or more different interventions in one meta-analysis. These are usually referred to as 'multiple-treatments meta-analysis' ('MTM'), 'network meta-analysis', or 'mixed treatment comparisons' ('MTC') meta-analysis. Multiple-treatments meta-analyses can be used to analyse studies with multiple intervention groups, and to synthesize studies making different comparisons of interventions. Caldwell et al. provide a readable introduction (Caldwell 2005); a more comprehensive discussion is provided by Salanti et al. (Salanti 2008). Note that multiple-treatments meta-analyses retain the identity of each intervention, allowing multiple intervention comparisons to be made. This is in contrast to the methods for dealing with a single study with multiple intervention groups that are described in Section 16.5, which focus on reducing the multiple groups to a single pair-wise comparison.

The simplest example of a multiple-treatments meta-analysis is the indirect comparison described in Section 16.6.2. With three interventions (e.g. advice from dietician, advice from doctor, advice from nurse), any two can be compared indirectly through comparisons with the third. For example, doctors and nurses can be compared indirectly by contrasting trials of 'dietician versus doctor' with trials of 'dietician versus nurse'. This analysis may be extended in various ways. For example, if there are also trials of the direct comparison 'doctor versus nurse', then these might be combined with the results of the indirect comparison. If there are more than three interventions, then there will be several direct and indirect comparisons, and it will be more convenient to analyse them simultaneously.

If each study compares exactly two interventions, then multiple-treatments meta-analysis can be performed using subgroup analyses, and the test for subgroup differences used as described in Chapter 9 (Section 9.6.3.1). However, it is preferable to use a random-effects model to allow for heterogeneity within each subgroup, and this can be achieved by using meta-regression instead (see Chapter 9, Section 9.6.4). When some studies include more than two intervention groups, the synthesis requires multivariate meta-analysis methods. Standard subgroup analysis and meta-regression methods can no longer be used, although the analysis can be performed in a Bayesian framework using WinBUGS: see Section 16.8.1. A particular advantage of using a Bayesian framework is that all interventions in the analysis can be ranked, using probabilistic, rather than crude, methods.

Multiple treatment meta-analyses are particularly suited to problems addressed by Overviews of reviews (Chapter 22). However, they rely on a strong assumption that studies of different comparisons are similar in all ways other than the interventions being compared. The indirect comparisons involved are not randomized comparisons, and may suffer the biases of observational studies, for example due to confounding (see Chapter 9, Section 9.6.6). In situations when both direct and indirect comparisons are available in a review, any use of multiple-treatments meta-analyses should be to supplement, rather than to replace, the direct comparisons. Expert statistical support, as well as subject expertise, is required for a multiple-treatments meta-analysis.