Chapter 11: Undertaking network meta-analyses

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Key Points

- Network meta-analysis is a technique for comparing three or more interventions simultaneously in a single analysis by combining both direct and indirect evidence across a network of studies.
- Network meta-analysis allows for estimating the relative effects between any pairs of interventions in the network and usually yields more precise estimates than a single direct or indirect estimate. It also allows for the estimation of the ranking and hierarchy of interventions.
- A valid network meta-analysis relies on the assumption that the different sets of studies included in the analysis are similar, on average, in all important factors that may affect the relative effects.
- Incoherence (also called inconsistency) occurs when different sources of information (e.g. direct and indirect) for a relative effect disagree.
- Grading the confidence in the evidence in a network meta-analysis begins by evaluating each risk of bias domain for each direct comparison. Then the domain-specified assessments are combined to determine the overall confidence in the evidence.

11.1 Introduction

11.1.1 Overviews versus intervention reviews

Most Cochrane Reviews present pairwise comparisons between interventions for a specific condition and in a specific population or setting. However, it is usually the case that several, perhaps even numerous, competing interventions are available for some reviews. In these cases, people who need to decide between these interventions would benefit from a single review that includes all relevant interventions, and presents their comparative effectiveness

and potential for harm. Cochrane offers two different approaches that authors can use to produce such a review: an Overview or an Intervention Review that employs a network meta-analysis.

These two review types are quite different in their approaches and aims, and the *Cochrane Comparing Multiple Interventions Methods Group* has provided a decision chart (available from http://methods.cochrane.org/cmi/comparing-multiple-interventions-cochrane-reviews) designed to help authors and editors determine which format would best meet their needs. A key difference is that overviews present a synthesis of existing **systematic reviews**, while intervention reviews with a network meta-analysis provide a new synthesis of data from **individual randomized trials**. This leads to important distinctions in the methods employed, particularly for the search strategy and analysis plan, and also in the types of conclusions that can be drawn (Table 11.1.a).

Overviews are designed to compile evidence from multiple systematic reviews on a set of closely related interventions, populations, outcomes, or conditions into one accessible and usable document. A central aim is to serve as a 'friendly front end' to the CDSR allowing the reader an oversight (and an exhaustive list) of Cochrane Intervention Reviews relevant to a specific decision.

In contrast, an Intervention Review that includes a network meta-analysis undertakes a new set of statistical analyses using data from individual randomized trials in order to make inferences about the comparative effectiveness or harms of the interventions being compared. Inferences of this sort are rarely appropriate in Overviews.

Detailed guidance for authors who choose one of these two methods is provided in two separate chapters in the Handbook. The remainder of this chapter deals with Intervention Reviews that include a network meta-analysis. Guidance for Overviews is presented in Chapter V.

Table 11.1.a. Differences between an overview and an intervention review with network meta-analysis.

Review type	Overview	Intervention Review with network meta-analysis
Aim	Collate multiple systematic reviews about the effectiveness of interventions for the same condition to extract and	Re-analyse data from randomized trials of multiple interventions for the same condition to make inferences

	analyse their results across important outcomes. [Overviews may also be used for other purposes. These are described in Chapter V]	about their comparative effectiveness or safety
Focus of search strategy	Reviews of primary studies	Primary studies
Focus of statistical synthesis	Review data	Study data
Focus of data collection	Summary estimates based on existing meta-analyses from the included reviews	Estimates from individual randomized trials

11.1.2 Outline of the chapter

This chapter aims to provide an overview of the concepts, assumptions and methods that relate to indirect comparisons and network meta-analyses. More specifically, Section 11.2 first describes what an indirect comparison is and how it can be conducted. It then introduces the notion of **transitivity** as the core assumption underlying the validity of an indirect comparison. Examples are provided where this assumption is likely to be held or violated. An introduction to the ideas of network meta-analysis and the assumption of **coherence** follows. Section 11.3 provides guidance on the design of a Cochrane Intervention Review with multiple interventions and the appropriate definition of the research question with respect to selecting studies, outcomes and interventions. Section 11.4 briefly describes the available statistical methods for synthesizing the data, estimating the relative ranking and assessing incoherence in a network of interventions. Finally, the last two Sections 11.5 and 11.6 provide approaches for evaluating the confidence in the evidence and presenting the evidence base and the results form a network meta-analysis. Note that the present chapter only provides an introduction to the statistical aspects of network meta-analysis; authors will need a knowledgeable statistician to plan and execute these methods.

11.2 Important concepts

11.2.1 Direct and indirect comparisons

At the heart of network meta-analysis methodology is the concept of indirect comparison. Indirect comparisons are necessary when there are no studies that have directly compared two interventions.

11.2.1.1 What is an indirect comparison?

Indirect comparisons can be performed if studies in a systematic review provide information on three or more competing interventions. For example, suppose there are randomized trials directly comparing 'dietitian' (A) with 'doctor' (B) in providing dietary advice, and randomized trials comparing 'dietitian' (A) with 'nurse' (C). Suppose further that these randomized trials have been combined in standard, pairwise meta-analyses separately to derive **direct estimates** of AB and AC intervention effects, measured as mean difference (MD) in weight reduction (see Chapter 9, Sections 9.6.2, 9.6.3). We can derive an **indirect estimate** of the relative effect of *B versus C* by combining the two summary estimates *A versus B* and *A versus C* (see Figure 11.2.a).

When four or more competing interventions are available, indirect estimates can be derived via multiple routes (Hughes 2010). The only requirement is that two interventions are 'connected' and not necessarily via a single common comparator. An example of this situation is provided in Figure 11.2.b, where 'doctor' (B) and 'pharmacist' (D) do not have a common comparator, but we can compare them indirectly via the route 'doctor' (B) – 'dietitian' (A) – 'nurse' (C) – 'pharmacist (D).

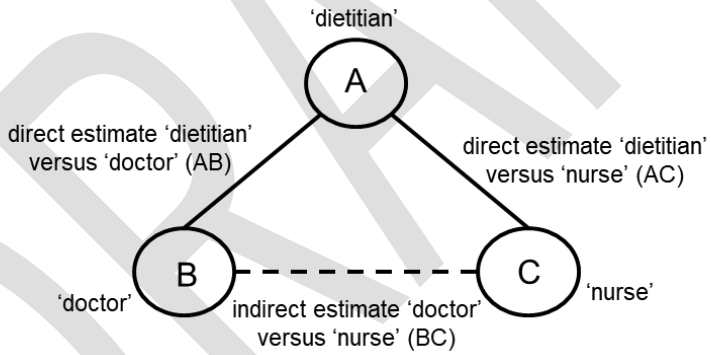


Figure 11.2.a. Example of deriving indirect estimate that compares the effectiveness of 'doctor' (B) and 'nurse' (C) in providing dietary advice through a common comparator 'dietitian' (A).

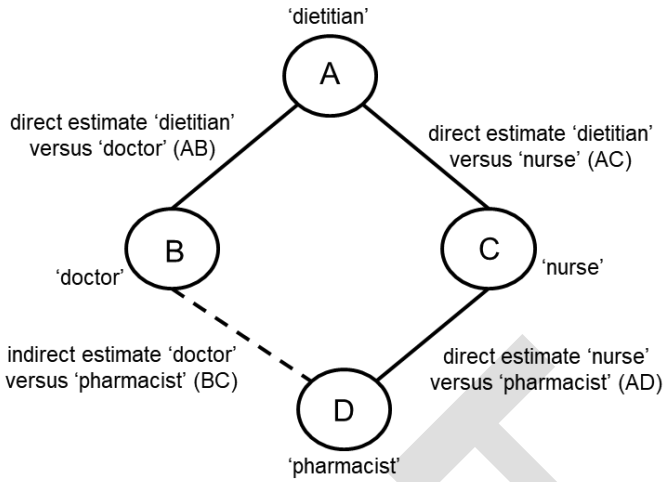


Figure 11.2.b. Example of deriving indirect estimate that compares the effectiveness of 'doctor' (B) and 'pharmacist' (D) in providing dietary advice through a connected loop.

11.2.1.2 Undertaking indirect comparisons

One simple approach to undertaking an indirect comparison is to think of a comparison *B versus C*, representing the benefit of B over C, as the sum of the benefit of B over A and the benefit of A over C. Thus, for example, the indirect comparison describing any benefit of 'doctor' over 'nurse' may be thought of as the benefit of 'doctor' over 'dietitian' plus the benefit of 'dietitian' over 'nurse' (these 'benefits' may be positive or negative; we do not intend to imply any particular superiority among these three types of people offering dietary advice). This is represented graphically in Figure 11.2.c. Mathematically, the sum can be written:

$$indirect\ MD(BvsC) = direct\ MD(BvsA) + direct\ MD(AvsC)$$

We usually write this in the form of subtraction:

$$indirect\ MD(BvsC) = direct\ MD(AvsC) - direct\ MD(AvsB)$$

such that the difference between the summary statistics of the intervention effect in the direct *A versus B* and *A versus C* meta-analyses provides an indirect estimate of the *B versus C* intervention effect. For the case where we have two direct comparisons (three interventions) the analysis can be conducted by performing subgroup analyses using standard meta-analysis routines (including RevMan): studies addressing either of the two relevant direct comparisons (i.e. *A versus B* and *A versus C*) can be treated as two subgroups in the meta-analysis. Subtracting the summary effect from each subgroup gives an estimate for the indirect comparison.

Most software will provide a P value for the statistical significance of the difference between the subgroups based on the estimated variance of the indirect relative effect (Bucher et al 1997):

$$variance[indirect\ MD(BvsC)] = variance[direct\ MD(AvsC)] + variance[direct\ MD(AvsB)]$$

where $variance[direct\ MD(AvsC)]$ and $variance[direct\ MD(AvsB)]$ are the variances of the respective direct estimates (from the two subgroup analyses).

A 95% confidence interval for the indirect summary effect is constructed by the formula:

$$\left[indirect\ MD(BvsC) \pm 1.96 \times \sqrt{variance[indirect\ MD(BvsC)]}\right]$$

This method uses the relative intervention effects from each group of randomized trials and therefore preserves within-trial randomization. Violation of within-trial randomization occurs by pooling single arms across the studies and then performing a direct comparison between them (i.e. treating the data as if they came from a single large randomized trial) (Li and Dickersin 2013). This approach should not be used. In general, any type of informal, non-statistical indirect comparison or judgment that does not follow the principles presented in this chapter should be avoided because the uncertainty and biases around the comparisons are not properly considered (Glenny et al 2005, Nikolakopoulou et al 2014).

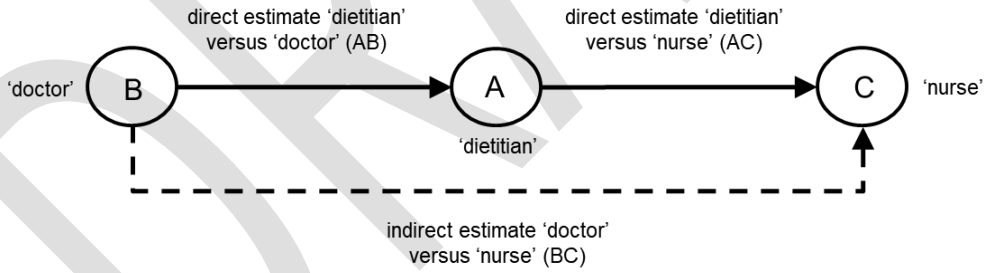


Figure 11.2.c. Graphical representation of the indirect comparison 'doctor' (B) versus 'nurse' (C) via 'dietitian' (A).

11.2.2 Transitivity

11.2.2.1 What is transitivity

Following the description in Section 11.2.1.2 it should be noted that indirect comparisons are observational evidence across randomized trials and may suffer the biases of observational studies, such as confounding (see Chapter 9, Section 9.6.6). The validity of an indirect comparison relies on the assumption that the different sets of randomized trials are similar,

on average, in all important factors other than the intervention comparison being made (Song et al 2003, Glenny et al 2005, Donegan et al 2010, Salanti 2012). Studies that compare different interventions may differ across a wide range of characteristics. Sometimes these characteristics are associated with the outcome of interest, in the sense that different levels of a particular characteristic may influence the effect of an intervention. If the *A versus B* and *A versus C* randomized trials differ with respect to such characteristics, also called 'effect modifiers', then it would not be appropriate to make an indirect comparison.

The underlying assumption of indirect comparisons is that the common comparator intervention A allows a **transitive** relationship between the *A versus B* and *A versus C* effects. This transitive relationship can be written mathematically as:

$$effect\ of\ B\ versus\ C\ =\ (effect\ of\ A\ versus\ B)\ -\ (effect\ of\ A\ versus\ C)$$

In words, this means that we can compare interventions B and C via intervention A (Figure 11.2.a).

Transitivity requires that intervention A is similar when it appears in *A versus B* studies and *A versus C* studies with respect to characteristics that may affect the two relative effects (Salanti et al 2009). For example, in the dietary advice network the common comparator 'dietitian' might differ between randomized trials that compare dietitian with doctor (*A versus B*) or with nurse (*A versus C*) with respect to the frequency of sessions with the participants; if the participants visit the dietitian once a week in AB studies and once a month in AC studies, transitivity may be violated. Similarly, any other effect modifiers should not differ between AB and AC studies.

Transitivity requires all competing interventions of a systematic review to be 'jointly randomizable'. That is, we can imagine all interventions being compared simultaneously in a single multi-arm randomized trial. Another way of viewing this is that the 'missing' interventions (those not included in the identified studies) may be considered to be missing for reasons unrelated to their relative effects (Caldwell et al 2005, Salanti 2012).

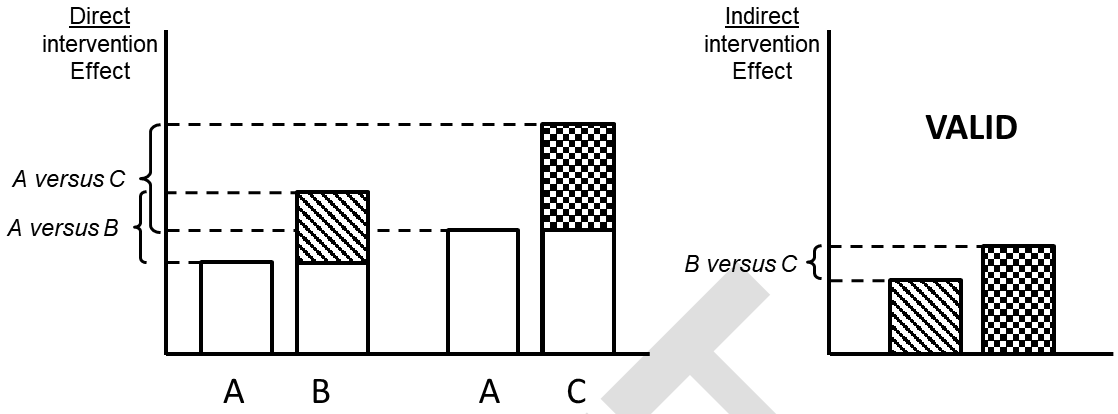
11.2.2.2 Assessing transitivity

Clinical and methodological differences are inevitable between studies in a systematic review. Researchers undertaking indirect comparisons should assess whether such differences are sufficiently large to cause **intransitivity**. In practice, transitivity can be evaluated by comparing the distribution of effect modifiers across the different comparisons (Salanti 2012, Cipriani et al 2013, Jansen and Naci 2013). Imbalanced distributions would threaten the plausibility of the transitivity assumption and thus the validity of indirect comparison. Extended guidance on the considerations about the potential effect modifiers and their impact on the evidence base is provided in Chapter 9, Section 9.5). For example, we may believe that age is a potential effect modifier so that the effect of the interventions differs between younger and older populations. If the average age in *A versus B* randomized trials is

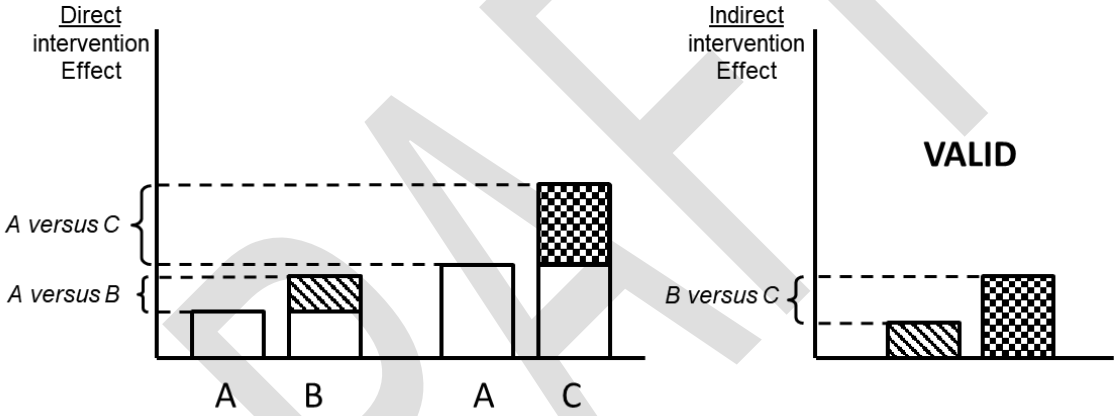
substantially older or younger than in *A versus C* randomized trials, transitivity may be implausible, and an indirect comparison *B versus C* may be invalid.

Figure 11.2.d shows examples of valid and invalid indirect comparisons for the studies of the dietary advice example. The severity of the disease (i.e. obesity measured by the BMI score) is considered as the only potential effect modifier. Assume that we have AB and AC studies in moderate and then severe disease populations as shown in the first two rows of the figure. The two subgroups of randomized trials with moderate or severe populations are analysed separately and each subgroup gives a valid indirect estimate *B versus C* that pertains to the respective population. Then, imagine all AB randomized trials are conducted only in moderately obese populations and all AC randomized trials are conducted only in severely obese populations as seen in the last row of the figure. In this situation, the distribution of effect modifiers is different in the two direct comparisons and the indirect effect for the entire population is invalid (due to intransitivity). In real datasets, differences in effect modifiers are usually less extreme than this hypothetical scenario; for example, AB randomized trials may have 80% moderately obese population and 20% severely obese, and AC randomized trials may have 20% moderately obese and 80% severely obese population but intransitivity still would invalidate the indirect estimate *B versus C*.

Population with moderate disease



Population with severe disease



Population with moderate obesity for A versus B
Population with severe obesity for A versus C

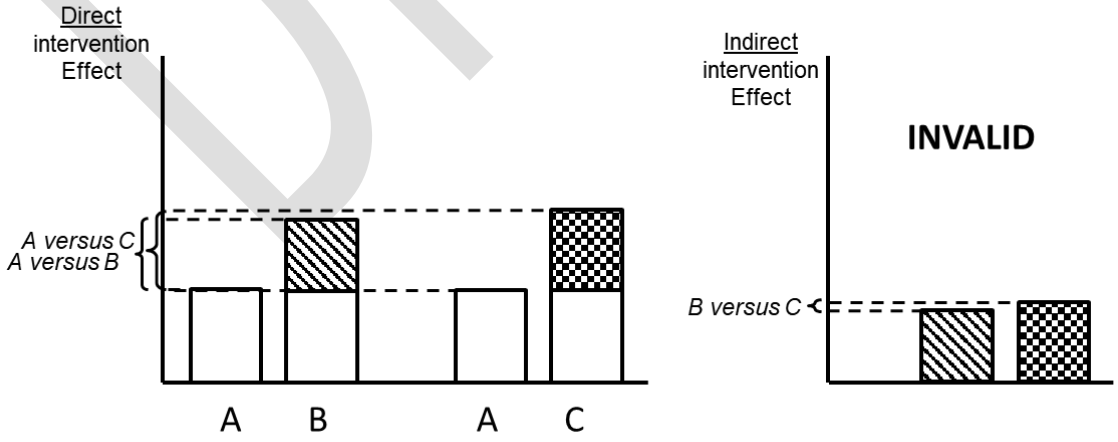


Figure 11.2.d. Example of valid and invalid indirect comparisons when the severity of disease acts as effect modifier and its distribution differs across the two direct comparisons. The shaded boxes represent the treatment effect estimates from each source of evidence (striped box for *A versus B* and checked box for *A versus C*). In the first row, randomized trials of *A versus B* and of *A versus C* are all conducted in severely obese populations; in the second row randomized trials are all conducted in moderately obese populations. In both of these the indirect comparisons of the treatment effect estimates would be valid. In the last row, the *A versus B* and *A versus C* randomized trials are conducted in different populations. As severity is an effect modifier, the indirect comparison based on these would not be valid (Jansen et al 2014).

11.2.3 From indirect comparisons to network meta-analysis

11.2.3.1 Combining direct and indirect evidence

Often there is direct evidence for a specific comparison of interventions as well as a possibility of making an indirect comparison of the interventions via one or more common comparators. If the key assumption of transitivity is considered reasonable, direct and indirect estimates should be considered jointly. When both direct and indirect intervention effects are available for a particular comparison, these can be synthesized into a single relative effect. This summary effect is sometimes called a **combined** or **mixed** estimate of the intervention effect. We will use the former term in this chapter. A combined estimate can be computed as an inverse variance weighted average (see Chapter 9, Section 9.4.2) of the direct and indirect summary estimates.

Since combined estimates incorporate indirect comparisons, they rely on the transitivity assumption. Violation of transitivity threatens the validity of both indirect and combined estimates. Of course, biased direct intervention effects for any of the comparisons also challenge the validity of a combined effect (Madan et al 2011).

11.2.3.2 Coherence or consistency

The key assumption of transitivity refers to potential clinical and methodological variation across the different comparisons. These differences may be reflected in the data in the form of disagreement in estimates between different sources of evidence. This is the statistical manifestation of transitivity and is typically called either **coherence** or **consistency**. We will use the former to distinguish the notion from inconsistency (or heterogeneity) within standard meta-analyses (e.g. as is measured using the I^2 statistic; see Chapter 9, Section 9.5.2). Coherence implies that the different sources of evidence (direct and indirect) agree with each other, and such a statistical assumption underlies any combined estimate (Ades 2004, Lu and Ades 2006). The coherence assumption is expressed mathematically by the **coherence equations**, which state that the true direct and indirect intervention effects for a specific comparison are identical:

$$'true'\ MD(BvsC) = 'true'\ MD(AvsC) - 'true'\ MD(AvsB)$$

The available methods for testing this assumption are presented in Section 11.4.3

11.2.3.3 Network meta-analysis

Any group of studies that links three or more interventions via direct comparisons forms a **network of interventions**. In a network of interventions there can be multiple indirect intervention effects for each comparison. Then, the combined estimates for any pairwise comparisons in a network may incorporate direct or several indirect estimates, or both. **Network meta-analysis** combines direct and indirect estimates across a network of interventions. Synonymous terms, less often used, are **mixed treatment comparison** or **multiple treatments meta-analysis**.

11.2.3.4 Network diagrams

A **network diagram** is a graphical depiction of the structure of the network (Chaimani et al 2013a). It consists of nodes representing the interventions in the network and lines showing the available direct comparisons between pairs of interventions. Distinct lines forming closed loops can be added in a network diagram to illustrate the presence of multi-arm studies. For example, a triangular loop would represent a three-arm study (see Figure 11.2.e). For large and complex networks this presentation of multi-arm studies may give complicated and unhelpful network diagrams. In this case it might be preferable to show multi-arm studies in a tabular format (see Section 11.6.1). Further discussion on network diagrams is available in Section 11.6.1.

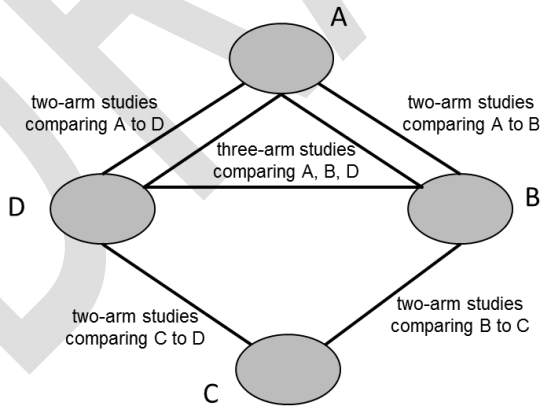


Figure 11.2.e. Example of network diagram with four competing interventions and information on the presence of multi-arm randomized trials.

11.2.3.5 Advantages of network meta-analysis

A network meta-analysis exploits all available direct and indirect evidence. Empirical studies have suggested it yields more precise estimates of the intervention effects in comparison with a single direct or indirect estimate (Cooper et al 2011, Caldwell et al 2015). In addition, network meta-analysis can provide information for comparisons between pairs of interventions that have never been evaluated within individual randomized trials. The simultaneous comparison of all interventions of interest in the same analysis enables the estimation of their relative ranking for a given outcome. More extensive discussion on the relative ranking of interventions is provided in Section 11.4.2.3.

11.2.3.6 Validity of network meta-analysis

The validity of network meta-analysis relies on the fulfilment of underlying assumptions. Both transitivity and coherence should hold in every loop of evidence within the network (see Section 11.4.3). Considerations about heterogeneity within each direct comparison in the network should follow the existing recommendations for standard pairwise meta-analysis (see Chapter 9, Section 9.5.3).

11.3 Planning a Cochrane Review to compare multiple interventions

11.3.1 Expertise required in the review team

Because of the complexity of network meta-analysis, it is important to establish a multidisciplinary review team that includes a statistician skilled in network meta-analysis methodology early and throughout. Close collaboration between the statistician and the content area expert is essential to ensure that the studies selected for a network meta-analysis are similar except for the interventions being compared (see Section 11.2.2.1). Because basic meta-analysis software such as RevMan does not support network meta-analysis, the statistician will have to rely on statistical software packages such as Stata, R, WinBUGS or OpenBUGS for analysis.

All other skills required for an Intervention Review are also needed for a review with network meta-analysis. Review authors should follow guidance on organizing the review team and seeking input from stakeholders outlined in Chapter 2, Section 2.3.4.

11.3.2 Building on existing reviews in the Cochrane context

Cochrane usually avoids publishing reviews whose scope overlaps with the scope of one or more existing reviews. For a Cochrane Review that uses a network meta-analysis to compare multiple interventions, such overlap is often inevitable, as many of the relevant randomized trials may have already been included, assessed, or even meta-analysed in reviews with a narrower scope. Access to trial-level data that have already been extracted will facilitate the production of the new review, although using existing data requires further discussion with authors of those reviews and with editorial staff.

Network meta-analysis authors should refer to any overlapping systematic reviews in their review. This could be achieved by describing existing relevant systematic reviews in the 'Why it is important to do this review?' section and discussing the findings in the 'Agreements and disagreements with other studies or reviews' section.

11.3.3 The importance of a well-defined research question

Defining the research question of a systematic review that intends to compare multiple interventions should follow the general guidelines described in Chapter 5 (Section 5.1) and should be stated in the 'Objectives' of the review. In this section, we summarize and highlight key issues that are pertinent to systematic review with a network meta-analysis.

Because network meta-analysis could be used to estimate the relative ranking of the included interventions (Salanti et al 2011, Chaimani et al 2013a), reviews that aim to rank the competing interventions should specify this in their 'Objectives' (Chaimani et al 2017). Review authors should consider obtaining an estimate of relative ranking as a secondary objective to supplement the relative effects. An extended discussion on the relative ranking of interventions is provided in Section 11.4.2.3.

11.3.3.1 Defining the population and choosing the interventions

Populations and interventions often need to be considered together given the potential for intransitivity (see Section 11.2.2). A driving principle is that any eligible participant should be eligible for randomization to any included intervention (Salanti 2012, Jansen and Naci 2013). Review authors should select their target population with this consideration in mind.

Detailed description of the populations, interventions and outcomes of interest in a Cochrane Review should be given as 'Criteria for considering studies for this review'. In the case of comparing multiple interventions, care is needed in the definition of the eligible interventions, as discussed in Chaimani et al (Chaimani et al 2017). For example, suppose a systematic review aims to compare four chemotherapy regimens for a specific cancer. Regimen (D) is appropriate for stage II patients exclusively and regimen (A) is appropriate for both stage I and stage II patients. The remaining two regimens (B) and (C) are appropriate for stage I patients exclusively. Now suppose A and D were compared in stage II patients, and A, B and C were compared in stage I patients (see Figure 11.3.a). The four interventions forming the network do not satisfy the transitivity assumption because regimen D cannot be given to the same patient population as regimens B and C. Thus, a four-arm randomized trial comparing all interventions (A, B, C and D) simultaneously is not a reasonable study to conduct.

Interventions of direct interest, referred to as the **decision set** of interventions, are those options among which patients and health professionals would be choosing in practice with respect to the outcomes under investigation. The choice of competing interventions to include in the decision set should ensure that the transitivity assumption is likely to hold (see also Section 11.2.2.1) (Salanti 2012).

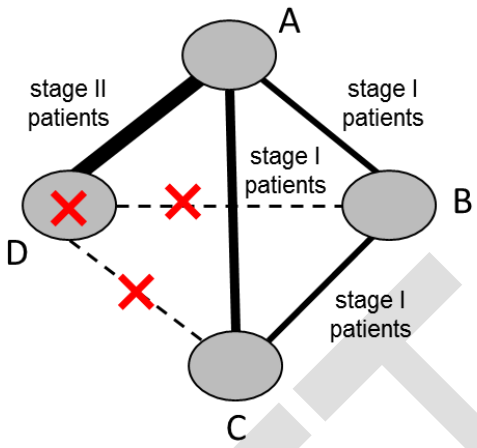


Figure 11.3.a. Example of a network comparing four chemotherapy regimens, where transitivity is violated due to incomparability between the interventions.

11.3.3.2 Adding further interventions to supplement the analysis

The ability of network meta-analysis to incorporate indirect evidence means that inclusion of interventions that are not of direct interest to the review authors might provide additional information in the network. For example, placebo is often included in network meta-analysis even when it is not a reasonable treatment option, because many studies have compared active interventions against placebo. In such cases, excluding placebo would result in ignoring a considerable amount of indirect evidence. Similar considerations apply to historical or legacy interventions.

We use the term **supplementary set** to refer to interventions, such as placebo, that are included in the network meta-analysis for the purpose of improving inference among interventions in the decision set. The full set of interventions, the decision set plus the supplementary set, has been called in the literature the **synthesis comparator set** (Ades et al 2013, Caldwell et al 2015).

When review authors decide to include a supplementary set of interventions in a network they need to be cautious regarding the plausibility of the transitivity assumption. In general, broadening the network challenges the transitivity assumption. Thus, supplementary interventions should be added when their value outweighs the risk of violating the transitivity assumption. The addition of supplementary interventions in the analysis might be considered more valuable for sparse networks that include only a few randomized trials per comparison. In these networks the benefit of improving the precision of estimates by incorporating supplementary indirect evidence may be quite important. There is limited empirical evidence to inform the decision of 'how far should we go in constructing the network evidence base'

(König et al 2013, Caldwell et al 2015). Inevitably it will require some judgment and the robustness of decisions can be evaluated in the sensitivity analysis and discussed in depth in the review.

11.3.3.3 Grouping variants of an intervention (defining 'nodes' in the network)

The definition of nodes needs careful consideration in situations where variants of one or more interventions are expected to appear in the eligible randomized trials. The appropriateness of merging, for example, different doses of the same drug or different drugs within a class depends to a large extent on the research question. Lumping and splitting the variants of the competing interventions might be interesting to both review authors and evidence users; in such a case this should be stated clearly in the 'Objectives' of the review and the potential for intransitivity should be evaluated in every network. A decision on how the nodes of an expanded network could be merged is not always straightforward and researchers should act based on pre-defined criteria where possible. These criteria should be formed in such a way that maximizes similarity of the interventions within a node and minimizes similarity across nodes.

The following example refers to a network that used two criteria to classify electronic interventions for smoking cessation into five categories:

"To be able to draw generalizable conclusions on the different types of electronic interventions, we developed a categorization system that brought similar interventions together in a limited number of categories. We sought advice from experts in smoking cessation on the key dimensions that would influence the effectiveness of smoking cessation programmes. Through this process, two dimensions for evaluating interventions were identified. The first dimension was related to whether the intervention offered generic advice or tailored its feedback to information provided by the user in some way. The second dimension related to whether the intervention used a single channel or multiple channels. From these dimensions, we developed a system with five categories… , ranging from interventions that provide generic information through a single channel, e.g. a static Web site or mass e-mail (category e1) to complex interventions with multiple channels delivering tailored information, e.g. an interactive Web site plus an interactive forum (category e5)."

(Madan et al 2014) p297

To date there is no empirical evidence on whether more or less expanded networks are more prone to present important intransitivity or incoherence. Extended discussion on how different dosages can be modelled in network meta-analysis has been published in the literature (Giovane et al 2013, Owen et al 2015, Mawdsley et al 2016).

11.3.3.4 Defining eligible comparisons of interventions (defining 'lines' in the network)

Once the 'nodes' of the network have been specified, every study that meets the eligibility criteria and compares any pair of the eligible interventions should be included in the review.

The exclusion of specific direct comparisons without a rationale may introduce selection bias in the analysis and should be avoided.

11.3.4 Selecting outcomes to examine

Guidelines on the selection and definition of the outcomes of interest in a Cochrane Review are available in Chapter 2 (Section 2.4). In the context of a network meta-analysis, outcomes should be specified a priori regardless of the number of interventions the review intends to compare or the number of studies the review is able to include. Review authors should be aware that some characteristics may be effect modifiers for some outcomes but not for other outcomes. This implies that sometimes the potential for intransitivity should be examined separately for each outcome before undertaking the analyses.

11.3.5 Study designs to include

Extended discussion on choice of study designs for inclusion in a systematic review is available in Chapter 2 (Section 2.5). In brief, randomized designs are generally preferable to non-randomized designs to ensure an increased level of validity of the summary estimates. Sometimes, however, observational data from non-randomized studies may form a useful source of evidence. In general, combining randomized with observational studies in a network meta-analysis is not recommended. In the case of sparse networks (i.e. networks with a few studies but many nodes), observational data might be used to supplement the analysis; for example, to form prior knowledge or provide information for baseline characteristics (Schmitz et al 2013, Soares et al 2013).

Randomized trials, when designed and conducted properly, provide the most valid evidence (see Chapter 8). Some design characteristics of randomized trials may affect the results of the network meta-analysis. A large meta-epidemiological study of networks of randomized trials found that the study variance was an important factor modifying effect estimates in network meta-analysis; studies with larger variance (usually smaller studies) tended to estimate larger treatment effects for the active or newer interventions when compared to inactive or older interventions than studies with smaller variance. This phenomenon is known as ‘small-study effects’. This finding should be considered alongside other meta-epidemiological findings for classical risk of bias items (Savović et al 2012, Chaimani et al 2013b).

11.4 Synthesis of results

Network meta-analysis can be performed using different approaches (Salanti et al 2008). Care is needed in defining the model parameters in a way that all relative effects can be estimated via the coherence equations. The comparisons that need to be estimated from the network meta-analysis model are often called **basic comparisons** (Lu and Ades 2006). The required number of basic comparisons equals the number of interventions minus one. For example, in a review of interventions for heavy menstrual bleeding (Figure 11.4.a) we may choose the following basic comparisons: ‘Hysterectomy versus first generation hysteroscopic

techniques', 'Mirena versus first generation hysteroscopic techniques' and 'second generation non-hysteroscopic techniques versus first generation hysteroscopic techniques'. All other (non-basic) comparisons in the network (e.g. 'Mirena versus hysterectomy', 'Mirena versus second generation non-hysteroscopic techniques', etc.) are called **functional comparisons**. The network meta-analysis model provides **network estimates** of the relative effects for all basic comparisons. We can obtain the estimates for the functional comparisons using the coherence equations (see Section 11.2.3.2).

11.4.1 Synthesizing direct and indirect evidence using meta-regression

Indirect comparisons were introduced in Section 11.2.1.2 in the context of subgroup analysis, where the subgroups are defined by the comparisons. Differences between subgroups of studies can also be investigated via meta-regression, without a full network meta-analysis (see Chapter 9, Section 9.6.4). When meta-regression is used to conduct this kind of analysis, each pair of interventions with a direct comparison is included in the analysis using 'dummy' variables (i.e. variables that do not have a true numerical value but are coded as 1 or 0 to indicate whether each study result comes from a study of that comparison or not).

For example, in the dietary advice network containing only three intervention nodes (see Section 11.2.1.1, Figure 11.2.a) one dummy variable is required to indicate the comparison 'dietitian versus nurse'. This variable takes the value 1 for a study that involves that corresponding comparison and 0 otherwise, and is included as a covariate in the meta-regression. In this way, the meta-regression model would have an intercept and a regression coefficient (slope). In this example the estimated intercept gives the meta-analytic direct summary effect for the comparison 'dietitian versus doctor' while the sum of the estimated regression coefficient and intercept gives the direct summary effect for the dietitian versus nurse'. Consequently, the estimated coefficient is the indirect summary effect for the comparison 'doctor versus nurse'.

Suppose now that in the dietary advice example studies that directly compare 'doctor versus nurse' are also available. A combined estimate for this comparison can be derived as a weighted average of direct and indirect estimates (see Section 11.2.3.1) or via meta-regression (Lumley 2002). This approach requires adding a second dummy variable to indicate the comparison 'dietitian versus doctor'. We do not require a third dummy variable because, under coherence, the comparison 'doctor versus nurse' can be expressed as the difference between the other two comparisons (see Section 11.2.3.2). This means that studies comparing 'doctor versus nurse' inform us about the difference between the other two comparisons and consequently we would assign values 1 and −1 to the dummies 'dietitian versus doctor' and 'dietitian versus nurse' respectively. Then, meta-regression should be fitted including both dummy variables without an intercept. The estimated regression coefficients that correspond to each dummy variable are the combined estimates for the respective comparisons. The difference between the two regression coefficients is the combined meta-analysis summary effect for 'doctor versus nurse'.

In the absence of multi-arm randomized trials, this approach may be performed using standard meta-regression routines such as the 'metareg' available in the Stata statistical software (Harbord and Higgins 2008). Otherwise, other methods are more appropriate.

11.4.2 Performing network meta-analysis

An overview of methodological developments in network meta-analysis can be found in (Efthimiou et al 2016). The main technical requirement for all approaches to network meta-analysis is that all treatments included in the analysis form a 'connected' network.

A popular approach to conducting network meta-analysis is via hierarchical models using random effects, commonly implemented within a Bayesian framework (Sobieraj et al 2013, Nikolakopoulou et al 2014, Petropoulou et al 2016), Chapter 16, Section 16.8. A detailed description of hierarchical models for network meta-analysis can be found in (Lu and Ades 2004, Salanti et al 2008, Dias et al 2018).

Multivariate meta-analysis methods, initially developed to synthesize multiple outcomes jointly (Jackson et al 2011, Mavridis and Salanti 2013), offer an alternative approach to conducting network meta-analysis. A multivariate meta-analysis approach starts by selecting a specific list of basic comparisons (e.g. each intervention against a common reference intervention) and treats these as analogous to different outcomes. A study can report on one or more of the basic comparisons; for example, there are two comparisons in a three-arm randomized trial. For studies that do not target any of the basic comparisons (e.g. a study that does not include the common reference intervention), a technique known as data augmentation can be used to allow the appropriate parameterization (White et al 2012). The method is implemented in 'network' available for the Stata statistical package (White 2015). A detailed description of the concepts and the implementation of this approach is available in (White et al 2012).

Methodology from electrical networks and graphic theory also can be used to fit network meta-analysis and is outlined in (Rucker 2012). This approach has been implemented in the R package 'netmeta' (Rucker and Schwarzer 2013).

11.4.2.1 Illustrating example

To illustrate the advantages of network meta-analysis, Figure 11.4.a presents a network of four interventions for heavy menstrual bleeding (Middleton et al 2010). Data are available for four out of six possible direct comparisons. Table 11.4.a presents the results from direct (pairwise) meta-analyses and a network meta-analysis using the meta-regression approach. Network meta-analysis provides evidence about the relative effectiveness for the comparisons 'Hysterectomy versus second generation non-hysteroscopic techniques' and 'Hysterectomy versus Mirena', for which no randomized trial has assessed these two comparisons directly. Also, the network meta-analysis results are more precise (narrower confidence intervals) than the pairwise meta-analyses results for two comparisons ('Mirena versus first generation hysteroscopic techniques' and 'Second generation non-hysteroscopic

techniques versus Mirena'). Note that precision is not gained for all comparisons; this is because for some comparisons (e.g. hysterectomy versus first generation hysteroscopic techniques), the network heterogeneity is larger compared with the heterogeneity within the direct comparison, and therefore some uncertainty is added in the network estimates (see Section 11.4.2.2).

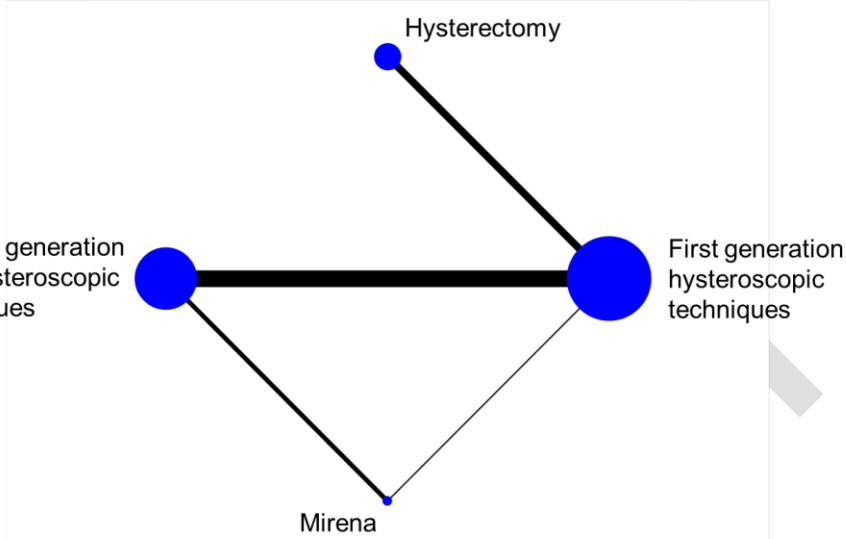


Figure 11.4.a. Network graph of four interventions for heavy menstrual bleeding (Middleton et al 2010). The size of the nodes is proportional to the number of participants assigned to the intervention and the thickness of the lines is proportional to the number of randomized trials that studied the respective direct comparison.

Table 11.4.a. Relative effectiveness, measured as odds ratios of patient dissatisfaction at 12 months of four interventions for heavy menstrual bleeding. Odds ratios lower than 1 favour the column-defining intervention for the network meta-analysis results (lower triangle) and the row-defining intervention for the pairwise meta-analysis results (upper triangle).

Pairwise meta-analysis			
Hysterectomy	-	-	0.38 (0.22 to 0.65)
0.45 (0.24 to 0.82)	**Second generation non-hysteroscopic techniques**	1.35 (0.45 to 4.08)	0.82 (0.60 to 1.12)
0.43 (0.18 to 1.06)	0.96 (0.48 to 1.91)	**Mirena**	2.84 (0.51 to 15.87)

0.38 (0.23 to 0.65)	0.85 (0.63 to 1.15)	0.88 (0.43 to 1.84)	First generation hysteroscopic techniques
Network meta-analysis			

11.4.2.2 Assumptions about heterogeneity

Heterogeneity reflects the underlying differences between the randomized trials that directly compare the same pair of interventions (see Chapter 9, Section 9.5). In a pairwise meta-analysis, the presence of important heterogeneity makes the interpretation of the summary effect challenging. Network estimates are a combination of the available direct estimates and therefore any comparison in the network is subject to the heterogeneity in all comparisons from which it is informed directly or indirectly.

It is important to specify assumptions about heterogeneity in the network meta-analysis model. Heterogeneity can be specific to each comparison or assumed to be common across all pairwise comparisons. The idea is similar to a subgroup analysis: the different subgroups could have a common heterogeneity or different heterogeneities, the latter can be estimated accurately only if enough studies per subgroup are available.

The assumption of a common heterogeneity across all pairwise comparisons is most frequently employed in network meta-analyses (Higgins and Whitehead 1996). This approach has two advantages compared with assuming comparison-specific heterogeneities. First, it borrows information from the other comparison and enables the estimation of heterogeneity that otherwise would not be estimable for comparisons with a few (one or two) studies. Likewise, for comparisons with many studies, heterogeneity is estimated more precisely because more data are incorporated, resulting usually in more precise estimates of relative effects. Second, assuming common heterogeneity makes model estimation computationally easier than assuming comparison-specific heterogeneity (Lu and Ades 2009).

The choice of heterogeneity assumption should be based on clinical and methodological understanding of the data, and assessment of the plausibility of the assumption, in addition to statistical properties.

11.4.2.3 Ranking interventions

One hallmark feature of network meta-analysis is that it can estimate relative rankings of the competing interventions for a particular outcome. **Ranking probability**, the probability that an intervention is at a specific rank (first, second, etc.) when compared with the other interventions in the network, is frequently used. Ranking probabilities may vary for different outcomes. As for any estimated quantity, ranking probabilities are estimated with some variability. Therefore, inference based solely on the probability of being ranked as the best, without accounting for the variability, is misleading and should be avoided.

Ranking measures such as the **mean ranks**, **median ranks**, and the **cumulative ranking probabilities** summarize the estimated probabilities for all possible ranks and accounts for the variability in relative ranking. For further details on ranking measures refer to (Salanti et al 2011, Chaimani et al 2013a, Tan et al 2014, Rücker and Schwarzer 2015).

The estimated ranking probabilities for the heavy menstrual bleeding network (see Section 11.4.2.2) are presented in Table 11.4.b. 'Hysterectomy' is the most effective intervention according to mean rank.

Table 11.4.b. Ranking probabilities and mean ranks for intervention effectiveness in heavy menstrual bleeding. Lower mean rank values indicate that the interventions are associated with less mortality.

	Rank	Hysterectomy	Second generation non-hysteroscopic techniques	Mirena	First generation hysteroscopic techniques
Probabilities	1	96%	1%	4%	0%
	2	4%	46%	40%	9%
	3	0%	46%	19%	35%
	4	0%	7%	37%	56%
Mean rank		1	3	3	4

11.4.3 Disagreement between evidence sources (incoherence)

11.4.3.1 What is incoherence?

Incoherence refers to the violation of the coherence assumption in a network of interventions (see Section 11.2.3.2). Incoherence occurs when different sources of information for a particular relative effect are in disagreement (Song et al 2003, Lu and Ades 2006, Salanti 2012). In much of the literature on network meta-analysis, the term **inconsistency** has been used, rather than incoherence.

The amount of incoherence in a closed loop of evidence can be measured as the absolute difference between the direct and indirect summary estimates for any of the pairwise comparisons in the loop (Bucher et al 1997, Song et al 2011, Veroniki et al 2013). We refer to this method of detecting incoherence as the 'loop-specific approach'. The obtained statistic is

usually called **incoherence factor** or **inconsistency factor** (IF). For example, in the dietary advice network the incoherence factor would be estimated as:

$$IF = |direct\ MD(BvsC) - indirect\ MD(BvsC)|$$

IF measures the level of disagreement between the direct and indirect effect estimates.

The standard error of the incoherence factor is obtained from

$$variance[IF] = variance[direct\ MD(BvsC)]\ + variance[indirect\ MD(BvsC)]$$

and can be used to construct a 95% confidence interval for the IF:

$$[IF \pm 1.96 \times SE(IF)]$$

Several approaches have been suggested for evaluating incoherence in a network of interventions with many loops (Donegan et al 2013, Veroniki et al 2013), broadly categorized as **local** and **global** approaches. Local approaches evaluate regions of network separately to detect possible 'incoherence spots', whereas global approaches evaluate coherence in the entire network.

11.4.3.2 Approaches to evaluating local incoherence

A local approach, that we term SIDE (Separating Indirect from Direct Evidence) evaluates the IF for every pairwise comparison in a network by contrasting a direct estimate (when available) with an indirect estimate; the latter being estimated from the entire network once the direct evidence has been removed. The method was first introduced by (Dias et al 2010) under the name 'node-splitting'. The SIDE approach has been implemented in the 'network' macro for the Stata statistical package (White 2015) and the 'netmeta' command in R (Schwarzer et al 2015). For example, Table 11.4.c presents the incoherence results of a network that compares the effectiveness of four active interventions and placebo in preventing serious vascular events after transient ischaemic attack or stroke (Thijs et al 2008). Data are available for seven out of ten possible direct comparisons and none of them was found to be statistically significant in terms of incoherence.

In the special case where direct and several independent indirect estimates are available, the 'composite Chi^2 statistic' can be used instead (Caldwell et al 2010).

The loop-specific approach described in Section 11.4.3.1 can be extended to networks with many interventions by evaluating incoherence separately in each closed loop of evidence. The approach can be performed using the 'ifplot' macro available for the Stata statistical package (Chaimani and Salanti 2015). However, unlike the SIDE approach, this method does not incorporate the information from the entire network when estimating the indirect evidence.

Tests for incoherence have low power and therefore may fail to detect incoherence as statistically significant even when it is present (Song et al 2012, Veroniki et al 2014). This means that the absence of statistically significant incoherence is not evidence for the absence of incoherence. More preferably, review authors should consider the confidence interval of incoherence factors and decide whether the confidence interval includes values that are sufficiently large to suggest clinically important discrepancies between direct and indirect evidence. It should be noted that statistical incoherence can be assessed only for parts of the network with available direct evidence. Considerations upon the presence of incoherence are discussed in Section 11.4.3.4

Table 11.4.c. Results based on the SIDE approach to evaluating local incoherence. P values less than 0.05 suggest statistically significant incoherence.

Comparison	Direct		Indirect		Incoherence factor		
	Estimate	Standard error	Estimate	Standard error	Estimate	Standard error	*P value*
A versus C	-0.15	0.05	-0.21	0.10	0.07	0.12	*0.56*
A versus D	-0.45	0.07	-0.32	0.11	-0.14	0.13	*0.28*
A versus E	-0.26	0.14	-0.23	0.07	-0.03	0.16	*0.85*
B versus C	0.18	0.11	0.13	0.08	0.05	0.14	*0.70*
B versus E	0.07	0.07	0.12	0.12	-0.05	0.14	*0.70*
C versus D	-0.23	0.06	-0.35	0.12	0.12	0.13	*0.38*
C versus E	-0.06	0.05	-0.11	0.10	0.05	0.11	*0.66*

11.4.3.3 Approaches to evaluating global incoherence

Global incoherence in a network can be evaluated and detected via **incoherence models**. These models differ from the **coherence models** described in Section 11.4.2.1 by relaxing the coherence equations (see Section 11.2.3.2) and allowing intervention effects to vary when estimated directly and indirectly (Lu and Ades 2006). The models add additional terms, equivalent to the incoherence factors (IFs) defined in Section 11.4.3.1, to the coherence equations. For example, in the dietary advice network the coherence equation given in Section 11.2.3.2 would be modified to:

$$'true'indirect\ MD(BvsC) =' true'direct\ MD(AvsC) -'true'direct\ MD(AvsB) + IF_{ABC}$$

The quantity IF_{ABC} measures incoherence in the evidence loop 'dietitian-doctor-nurse'. Obviously, complex networks will have several IFs. For a network to be coherent, all IF need to be close to zero. This can be formally tested via a Chi^2 statistic test which is available in Stata in the 'network' macro (White 2015). An extension of this model has been suggested where incoherence measures the disagreement when an effect size is measured in studies that involve different sets of interventions (termed 'design incoherence') (Higgins et al 2012).

Measures like the Q-test and the I^2 statistic, which are commonly used for the evaluation of heterogeneity in a pairwise meta-analysis (see Chapter 9, Section 9.5.2), have been developed recently for the assessment of heterogeneity and incoherence in network meta-analysis. For a description of these measures see (Krahn et al 2013, Rucker and Schwarzer 2013, Jackson et al 2014). These have been implemented in the package 'netmeta' in R (Schwarzer et al 2015).

11.4.3.4 Forming conclusions about incoherence

We suggest review authors use both local and global approaches and consider their results jointly before making inferences about incoherence. The approaches presented in Sections 11.4.3.2 and 11.4.3.3 for evaluating incoherence have limitations. As for tests for statistical heterogeneity in a standard pairwise meta-analysis (see Chapter 9, Section 9.5.2), tests for detecting incoherence often lack power to detect incoherence when it is present, as shown in simulations and empirical studies (Song et al 2012, Veroniki et al 2014). Also, different assumptions and different methods in the estimation of heterogeneity may impact on the findings about incoherence. Extended discussion on this issue is available in (Veroniki et al 2013, Veroniki et al 2014). Empirical evidence suggests that review authors sometimes assess the presence of incoherence, if at all, using inappropriate methods (Veroniki et al 2013, Nikolakopoulou et al 2014, Petropoulou et al 2016).

Conclusions should be drawn not just from consideration of statistical significance but by interpreting the range of values included in confidence intervals of the incoherence factors. Researchers should remember that the absence of statistically significant incoherence does not ensure transitivity in the network, which should always be assessed before undertaking the analysis (see Section 11.2.2.2).

Once incoherence is detected, possible explanations should be sought. Errors in data collection, broad eligibility criteria, and imbalanced distributions of effect modifiers may have introduced incoherence. Possible analytical strategies in the presence of incoherence are presented in (Salanti 2012, Jansen and Naci 2013).

11.5 Evaluating confidence in the results of a network meta-analysis

The GRADE approach is recommended for use in Cochrane Reviews to assess the confidence of the evidence for each pairwise comparison of interventions (see Chapter 12, Section 12.2.1). The approach starts by assuming high confidence in the evidence for randomized

trials of a specific pairwise comparison and then downgrades the evidence for considerations of five issues: study limitations, indirectness, inconsistency, imprecision and publication bias.

Study limitations include possible flaws in the design of the studies, such as lack of blinding or allocation sequence concealment. Indirectness refers to differences between the characteristics of the studies (i.e., populations, interventions, and outcomes) included in the systematic reviews and the characteristics of the target population to which the inference is made. Inconsistency considers the presence of important between-study variance (i.e. heterogeneity). Imprecision refers to the width of the confidence intervals of the summary statistic. Publication bias examines the likelihood of existing studies that remain unpublished.

Rating the confidence in the evidence from a network of interventions is more challenging than pairwise meta-analysis (Dumville et al 2012). To date, two frameworks have been suggested in the literature to extend the GRADE system to indirect comparisons and network meta-analyses: Salanti and colleagues (Salanti et al 2014) and Puhan and colleagues(Puhan et al 2014). Section 11.5.1 describes the principles of each approach, noting similarities and differences.

11.5.1 Available approaches for evaluating confidence in the evidence

The two available approaches to evaluating confidence in evidence from a network meta-analysis acknowledge that the confidence in each combined comparison depends on the confidence in the direct and indirect comparisons that contribute to it, and that the confidence in each indirect comparison in turn depends on the confidence in the pieces of direct evidence that contribute to it. Therefore, all GRADE assessments are built to some extent on applying GRADE ideas for direct evidence. The two approaches diverge in the way they combine the considerations when thinking about an indirect or combined comparison.

More specifically, since indirect and combined comparisons are estimated by combining the information on two or more direct comparisons (See Sections 11.2 and 11.4), the confidence in each direct piece of evidence involved may be used to rate the confidence in the indirect evidence for this comparison. Then, they can be integrated to rate an indirect comparison following two possible ways which are illustrated in Table 11.5.a using the dietary advice example.

At the time of writing, no formal comparison has been performed to evaluate the degree of agreement between these two methods. Thus, at this point we do not prescribe using one approach or the other. However, when indirect comparisons are built on existing pairwise meta-analyses, which have already been rated with respect to their confidence, it may be reasonable to follow the Puhan and colleagues approach. On the other hand, when the body of evidence is built from scratch, or when a large number of interventions are involved, it may be preferable to consider the Salanti and colleagues approach whose application is facilitated via the online tool CINeMA (Confidence in Network Meta-Analysis, http://cinema.ispm.ch/).

The framework by Salanti and colleagues is driven by the ability to express each estimated intervention effect from a network meta-analysis as a weighted sum of all the available direct *comparisons* (see Section 11.4) (Lu et al 2011, König et al 2013, Krahn et al 2013). The weight is determined, under certain assumption, by the **contribution matrix,** which has been implemented in the 'netweight' macro (Chaimani and Salanti 2015) available for the Stata statistical package and programmed in CINeMA. The matrix contains the percentage of information attributable to each direct *comparison* and can be interpreted as the **contributions** of the direct *comparisons*. Then, the confidence in an indirect or combined comparison is estimated by combining the confidence assessment for the available direct comparisons with their contribution to the combined (or network) *comparison*. This approach is similar to the process of evaluating the likely impact of a high risk of bias study by looking at its weight in a pairwise meta-analysis to decide whether to downgrade or not in a standard GRADE assessment.

For example, in the dietary advice network (Figure 11.2.a) suppose that the direct comparison 'dietitian versus doctor' has been judged at low risk of bias and contributes 80% of the information in the indirect comparison 'doctor versus nurse', whereas the comparison 'dietitian versus nurse' (with 20% contribution) has been judged at high risk of bias (step 1). In this situation, in step 2 it seems reasonable to assess the indirect comparison as having low or at least moderate risk of bias but not high. This approach might be preferable when there are indirect or mixed comparisons informed by many loops within a network, and for a specific comparison these loops lead to different risk of bias assessments. The contributions of the direct comparisons and the risk of bias assessments may be presented jointly in a bar graph with bars proportional to the contributions of direct comparisons and different colours representing the different judgments. The bar graph for the heavy menstrual bleeding example is available in Figure 11.5.a, which suggests that there are two comparisons (first generation hysteroscopic techniques versus Mirena and second generation non-hysteroscopic techniques versus Mirena) for which a substantial amount of information comes from studies at high risk of bias.

JPTH comment: NO! I don't agree. The indirect comparison still depends heavily on high risk of bias studies.

Regardless of whether a review contains a network meta-analysis or a simple indirect comparison, Puhan and colleagues propose to focus on so-called 'most influential' loops only. These are the connections between a pair of interventions of interest that involve exactly one common comparator. This implies that the assessment for the indirect *comparison* is dependent only on confidence in the two other direct comparisons in this loop. To illustrate, consider the dietary advice network described in Section 11.2 (Figure 11.2.a), where we are interested in confidence in the evidence for the indirect comparison 'doctor versus nurse'. According to Puhan and colleagues, the lower confidence rating between the two direct comparisons 'dietitian versus doctor' and 'dietitian versus nurse' would be chosen to inform the confidence rating for the indirect comparison. If there are also studies directly comparing doctor versus nurse, the confidence in the combined comparison would be the higher rated source between the direct evidence and the indirect evidence. The main rationale for this is that, in general, the higher rated *comparison* is expected to be the more

precise (and thus the dominating) body of evidence. Also, in the absence of important incoherence, the lower rated evidence is only supportive of the higher rated evidence; thus it is not very likely to reduce the confidence in the estimated intervention effects. One disadvantage of this approach is that investigators need to identify the most influential loop; this loop might be relatively uninfluential when there are many loops in a network, which is often the case when there are many interventions. In large networks, many loops with comparable influence may exist and it is not clear how many of those equally influential loops should be considered under this approach. For further detail on this approach see (Puhan et al 2014).

Since network meta-analysis produces estimates for several intervention effects, the confidence in the evidence should be assessed for each intervention effect that is reported in the results. In addition, network meta-analysis may also provide information on the relative ranking of interventions and any concerns about confidence in the evidence also pertain to this output. Consequently, confidence in the evidence should also be considered in interpreting the relative ranking results when these are reported. Salanti and colleagues addressed this based on the contributions of the direct comparisons to the *entire* network as well as on the use of measures and graphs that aim to assess the different GRADE domains in the network together (e.g. measures of global incoherence (see Section 11.4.3).

The two approaches modify the standard GRADE domains to fit network meta-analysis to varying degrees. These modifications are briefly described in Box 11.5.1.a; more details and examples are available in the original articles (Puhan et al 2014, Salanti et al 2014).

Table 11.5.a. Steps to obtain the overall confidence ratings (across all GRADE domains) for every combined comparison of the dietary advice example. A ✓ or × indicates whether a particular step is needed in order to proceed to the next step.

		Step 1				Step 2		Step 3	
		Domain-specific ratings for direct comparisons		*Overall rating across domains for direct comparisons*		*Domain-specific ratings for combined comparisons*		*Overall rating across domains for combined comparisons*	
Direct comparisons	**GRADE domains**	**Salanti et al**	**Puhan et al**	**Salanti et al**	**Puhan et al**	**Salanti et al**	**Puhan et al**	**Salanti et al**	**Puhan et al**
Dietitian vs nurse	Study limitations	✓	✓	×	✓	✓	×	✓	✓
	Indirectness	✓	✓			✓	×		
	Inconsistency	✓	✓			✓	×		
	Imprecision	-	-			✓	×		
	Publication bias	✓	✓			✓	×		
Dietitian vs doctor	Study limitations	✓	✓	×	✓	✓	×	✓	✓
	Indirectness	✓	✓			✓	×		
	Inconsistency	✓	✓			✓	×		
	Imprecision	-	-			✓	×		

	Publication bias	✓	✓			✓	×		
Nurse vs doctor	Study limitations	✓	✓	×	✓	✓	×	✓	✓
	Indirectness	✓	✓			✓	×		
	Inconsistency	✓	✓			✓	×		
	Imprecision	-	-			✓	×		
	Publication bias	✓	✓			✓	×		

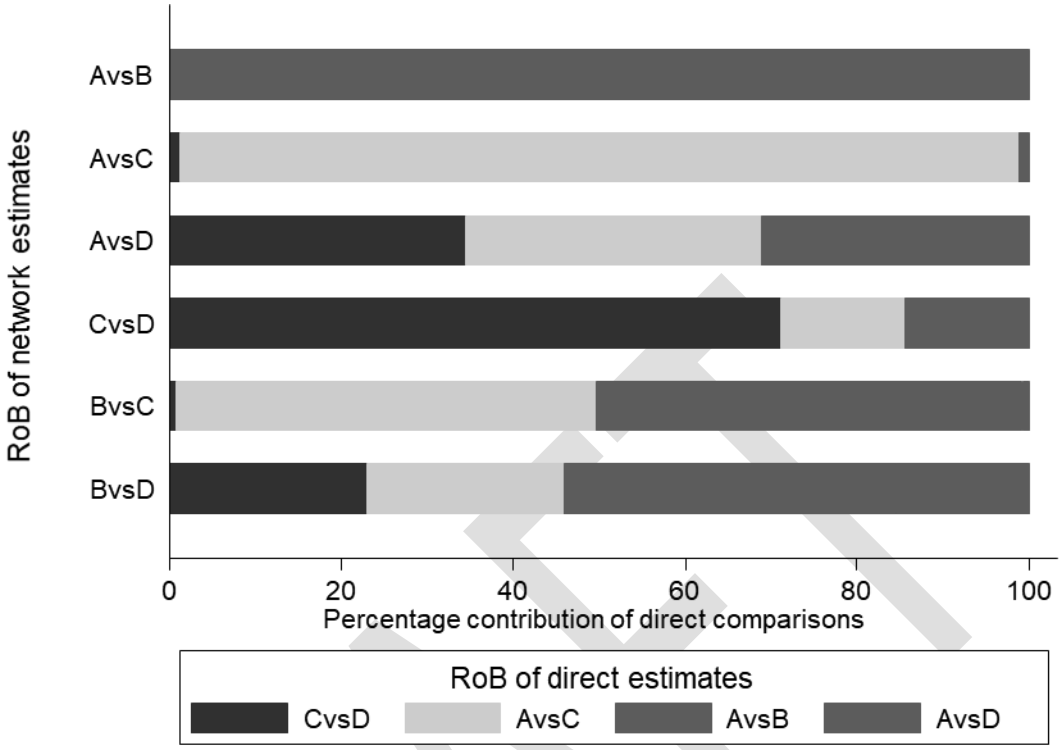


Figure 11.5.a. Bar graph illustrating the percentage of information for every comparison that comes from low (dark grey), moderate (light grey), or high (black) risk of bias studies with respect to both randomization and compliance to treatment for the heavy menstrual bleeding network (Middleton et al 2010). The risk of bias of the direct comparisons was defined based on Appendix 3 of the original paper. The intervention labels are A: first generation hysteroscopic techniques, B: hysterectomy, C: second generation non-hysteroscopic techniques, D: Mirena.

Box 11.5.1.a. Modifications to the five domains of the standard GRADE system to fit network meta-analysis.

Study limitations (i.e. classical risk of bias items): Salanti and colleagues suggest a bar graph with bars proportional to the contributions of direct comparisons and different colours representing the different confidence ratings (e.g. green, yellow, red for low, moderate or high risk of bias) with respect to study limitations (Figure 11.5.a). The decision about downgrading or not is then formed by interpreting this graph. Such a graph can be used to rate the confidence of evidence for each combined *comparison* and for the relative ranking.

Indirectness: The assessment of indirectness in the context of network meta-analysis should consider two components: the similarity of the studies in the analysis to the target question (PICO); and the similarity of the studies in the analysis to each other. The first addresses the extent to which the evidence at hand relates to the population, intervention(s), comparators and outcomes of interest and the second relates to the evaluation of the transitivity assumption. A common view of the two approaches is that they do not support the idea of downgrading indirect evidence by default. They suggest that indirectness should be considered in conjunction with the risk of intransitivity.

Inconsistency: Salanti and colleagues propose to create a common domain to consider jointly both types of inconsistency that may occur: heterogeneity within direct comparisons and incoherence. More specifically, they evaluate separately the presence of the two types of variation and then consider them jointly to infer whether downgrading for inconsistency is appropriate or not. It is usual in network meta-analysis to assume a common heterogeneity variance. They propose the use of prediction intervals to facilitate the assessment of heterogeneity for each combined comparison. Prediction intervals are the intervals expected to include the true intervention effects in future studies (Higgins et al 2009, Riley et al 2011) and they incorporate the extent of between-study variation; in the presence of important heterogeneity they are wide enough to include intervention effects with different implications for practice. The potential for incoherence for a particular comparison can be assessed using existing approaches for evaluating local and global incoherence (see Section 11.5). We may downgrade for one or two levels due to the presence of heterogeneity or incoherence, or both. The judgment for the relative ranking is based on the magnitude of the common heterogeneity as well as the use of global incoherence tests (see Section 11.4).

Imprecision: Both approaches suggest that imprecision of the combined comparisons can be judged based on their 95% confidence intervals. Imprecision for relative treatment ranking is the variability in the relative order of the interventions. This is reflected by the overlap in the distributions of the ranking probabilities; i.e. when all or some of the interventions have similar probabilities of being at a particular rank.

Publication bias: The potential for publication bias in a network meta-analysis can be difficult to judge. If a natural common comparator exists, a 'comparison-adjusted funnel plot' can be employed to identify possible small-study effects in a network meta-analysis (Chaimani and Salanti 2012, Chaimani et al 2013a). This is a modified funnel plot that allows putting together all the studies of the network irrespective of the interventions they compare. However, the primary considerations for both the combined comparisons and relative ranking should be non-statistical. Review authors should consider whether there might be unpublished studies for every possible pairwise comparison in the network.

11.6 Presenting network meta-analyses

The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions should be considered when reporting the results from network meta-analysis (Hutton et al 2015). Key graphical and numerical summaries include the network plot (e.g. Figure 11.4.a), a league table of the relative effects between all treatments with associated uncertainty (e.g. Table 11.4.a), and measures of heterogeneity and incoherence.

11.6.1 Presenting the evidence base of a network meta-analysis

Network diagrams provide a convenient way to describe the structure of the network (see Section 11.2.3.4). They may be modified to incorporate information on study-level or comparison-level characteristics. For instance, the thickness of the lines might reflect the number of studies or patients included in each direct comparison (e.g. Figure 11.4.a), or the comparison-specific average of a potential effect modifier. Using the latter device, network diagrams can be considered as a first step for the evaluation of transitivity in a network. In the example of Figure 11.6.a the age of the participants has been considered as a potential effect modifier. The thickness of the line implies that the average age within comparisons *A versus D* and *C versus D* seems quite different to the other three direct comparisons.

The inclusion of studies with design limitations in a network (e.g. lack of blinding, inadequate allocation sequence concealment) often threatens the validity of findings. The use of coloured lines in a network of interventions can reveal the presence of such studies in specific direct comparisons. Further discussion on issues related to confidence in the evidence is available in Section 11.5.

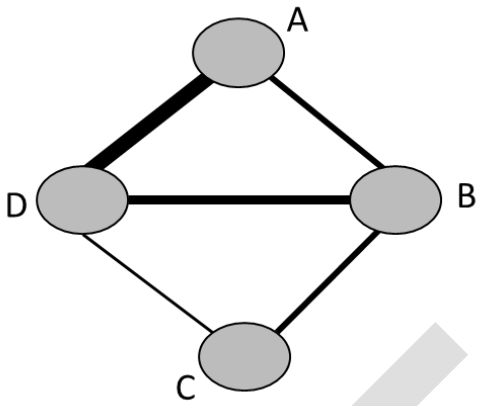


Figure 11.6.a. Example of network diagram with lines weighted according to the average age within each pairwise comparison. Thicker lines correspond to greater average age within the respective comparison.

11.6.2 Tabular presentation of the network structure

For networks including many competing interventions and multiple different study designs, network diagrams might be the most appropriate tool for presenting the data. An alternative way to present the structure of the network is to use a table, in which the columns represent the competing interventions and the rows represent the different study designs in terms of interventions being compared (Table 11.6.a) (Lu and Ades 2006). Additional information, such as the number of participants in each arm, may be presented in the non-empty cells.

Table 11.6.a. Example of table presenting a network that compares seven interventions and placebo for controlling exacerbation of episodes in chronic obstructive pulmonary disease (Baker et al 2009).

No. of studies	Placebo	Fluticasone	Budesonide	Salmeterol	Formoterol	Tiotropium	Fluticasone+ Salmeterol	Budesonide+ Formoterol
4	x	x		x			x	
4	x	x						
2	x		x		x			x
2	x			x		x		
2	x			x			x	
8	x			x				
2	x				x			
10	x					x		
1	x						x	
1				x		x		
1				x			x	
1					x	x		
1						x	x	

11.6.3 Presenting the flow of evidence in a network

Another way to map the evidence in a network of interventions is to consider how much each of the included direct comparisons contributes to the final combined effect estimates. The percentage information that direct evidence contributes to each relative effect estimated in a network meta-analysis can be presented in the contribution matrix (see Section 11.4), and could help investigators understand the flow of information in the network (Chaimani et al 2013a, Chaimani and Salanti 2015).

Figure 11.6.b presents the contribution matrix for the example of the network of interventions for heavy menstrual bleeding (obtained from the 'netweight' macro in Stata). The indirect treatment effect 'second generation non-hysteroscopic techniques' versus 'Hysterectomy' (*B versus C*) can be estimated using information from the four direct relative treatment effects; these contribute information in different proportions depending on the precision of the direct treatment effects and the structure of the network. Evidence from the direct comparison of first generation hysteroscopic techniques versus hysterectomy (*A versus B*) has the largest contribution to the indirect comparisons hysterectomy versus second generation non-hysteroscopic techniques (*B versus C*) (49.6%) and hysterectomy versus Mirena (*B versus D*) (38.5%), for both of which no direct evidence exists.

		Direct comparisons in the network (% contribution)			
		A-B	A-C	A-D	C-D
Network meta-analysis estimates	Mixed estimates				
	A-B	100.0			
	A-C		97.8	1.1	1.1
	A-D		34.5	31.1	34.5
	C-D		14.4	14.4	71.2
	Indirect estimates				
	B-C	49.6	48.9	0.7	0.7
	B-D	38.5	23.0	15.5	23.0
Entire network		31.4	36.4	10.5	21.7
Included studies		5	11	1	3

Figure 11.6.b. Contribution matrix for the network on interventions for heavy menstrual bleeding presented in Figure 11.4.a. Four direct comparisons in the network are presented in the columns, and their contributions to the combined treatment effect are presented in the rows. The entries of the matrix are the percentage weights attributed to each direct comparison. The intervention labels are A: first generation hysteroscopic techniques, B: hysterectomy, C: second generation non-hysteroscopic techniques, D: Mirena.

11.6.4 Presentation of results

Unlike pairwise meta-analysis, the results from network meta-analysis cannot be easily summarized in a single figure, such as a standard forest plot. Especially for networks with many competing interventions that involve many comparisons, presentation of findings in a concise and comprehensible way might be challenging.

Summary statistics of the intervention effects for all pairs of interventions are the most important output from network meta-analysis. Results from a subset of comparisons is sometimes presented due to space limitations and the choice of the findings to be reported is based on the research question and the target audience (Tan et al 2013). In such cases, the use of additional figures and tables to present all results in detail is necessary. Additionally, review authors might wish to report the relative ranking of interventions (see Section 11.4.2.3) as a supplementary output, which provides a concise summary of the findings and might facilitate decision making. For this purpose, joint presentation of both relative effects and relative ranking is recommended (see Figure 11.6.c or Table 11.4.a of Section 11.4.2.1).

In the presence of many competing interventions, the results across different outcomes (e.g. efficacy and acceptability) might be contradicting with respect to which interventions work best. To avoid drawing misleading conclusions, review authors may consider the simultaneous presentation of results for outcomes in these two categories.

Interpretation of the findings from network meta-analysis should always be considered with the evidence characteristics: risk of bias in included studies, heterogeneity, incoherence, and selection bias. Reporting results with respect to the evaluation of incoherence and heterogeneity (such as I^2 statistic for incoherence) is important for drawing meaningful conclusions.

11.6.4.1 Presentation of intervention effects and ranking

A table presenting direct, indirect, and network summary relative effects along with their confidence ratings is a helpful format (Puhan et al 2014). In addition, various graphical tools have been suggested for the presentation of results from network meta-analyses (Salanti et al 2011, Chaimani et al 2013a, Tan et al 2014). Summary relative effects for pairwise comparisons with their confidence intervals can be presented in a forest plot. For example,

Figure 11.6.c shows the summary relative effects for each intervention versus a common reference intervention for the 'heavy menstrual bleeding' network.

Ranking probabilities for all possible ranks may be presented by drawing probability lines, which are known as 'rankograms', and show the distribution of ranking probabilities for each intervention (Salanti et al 2011). The rankograms for the 'heavy menstrual bleeding' network example are shown in Figure 11.6.d. The graph suggests that 'Hysterectomy' has the highest probability of being the best intervention, 'First generation hysteroscopic techniques' have the highest probability of being worst followed by 'Mirena' and 'Second generation non-hysteroscopic techniques' have equal chances of being second or third.

The relative ranking for two (competing) outcomes can be presented jointly in a two-dimensional scatterplot (Chaimani et al 2013a). An extended discussion on different ways to present jointly relative effects and relative ranking from network meta-analysis is available in (Tan et al 2013).

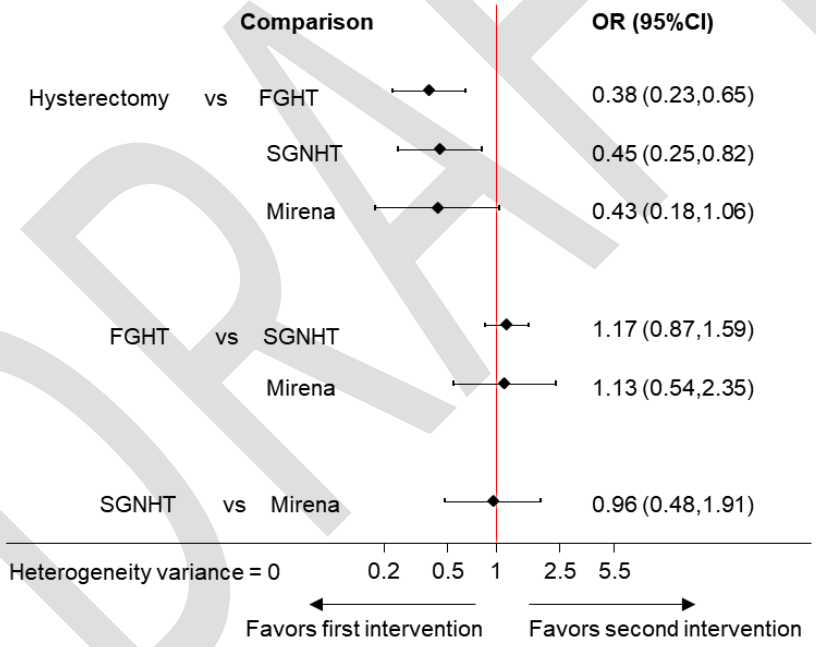


Figure 11.6.c. Forest plot for effectiveness in heavy menstrual bleeding between four interventions. FGHT: first generation hysteroscopic techniques, SGNHT: second generation non-hysteroscopic techniques.

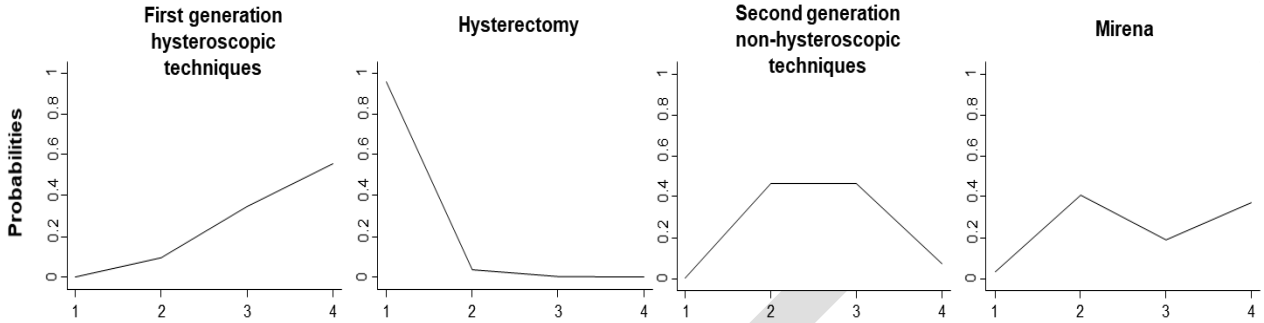


Figure 11.6.d. Ranking probabilities (rankograms) for the effectiveness of interventions in heavy menstrual bleeding. The horizontal axis shows the possible ranks and the vertical axis the ranking probabilities. Each line connects the estimated probabilities of being at a particular rank for every intervention.

11.6.4.2 Presentation of heterogeneity and incoherence

The level of heterogeneity in a network of interventions can be expressed via the magnitude of the between-study variance Tau^2, typically assumed to be common in all comparisons in the network. A judgment on whether the estimated Tau^2 suggests the presence of important heterogeneity depends on the clinical outcome and the type of interventions being compared. More extended discussion on the expected values of tau-squared specific to a certain clinical setting is available (Turner et al 2012, Nikolakopoulou et al 2014).

Forest plots that present all the estimated incoherence factors in the network and their uncertainty may be employed for the presentation of local incoherence (Salanti et al 2009, Chaimani et al 2013a). The results from evaluating global incoherence can be summarized in the P value of the Chi^2 statistic incoherence test and the I^2 statistic for incoherence (see Chapter 9, Section 9.5.2).

11.6.5 'Summary of findings' tables

The purpose of 'Summary of findings' tables in Cochrane Reviews is to provide concisely the key information in terms of available data, confidence in the evidence and intervention effects (see Chapter 11, Section 11.5). Providing such a table is more challenging in reviews that compare multiple interventions simultaneously, which very often involve a large number of comparisons between pairs of interventions. A general principle is that the comparison of multiple interventions is the main feature of a network meta-analysis, so is likely to drive the structure of the 'Summary of findings' table. This is in contrast to the 'Summary of findings' table for a pairwise comparison, whose main strength is to facilitate comparison of effects on different outcomes. Nevertheless, it remains important to be able to compare network meta-analysis results across different outcomes. This provides presentational challenges that are

almost impossible to resolve in two dimensions. One potential solution is an interactive electronic display such that the user can choose whether to emphasize the comparisons across interventions or the comparisons across outcomes.

For small networks of interventions (perhaps including up to five competing interventions) a separate 'Summary of findings' table might be produced for each main outcome. However, in the presence of many (more than five) competing interventions, researchers would typically need to select and report a reduced number of pairwise comparisons. Review authors should provide a clear rationale for the choice of the comparisons they report in the 'Summary of findings' tables. For example, they may consider including only pairwise comparisons that correspond to the **decision set** of interventions; that is the group of interventions of direct interest for drawing conclusions (see Section 11.3.3.1). The distinction between the decision set and the wider **synthesis comparator set** (all interventions included in the analysis) should be made in the protocol of the review. If the decision set is still too large, researchers may be able to select the comparisons for the 'Summary of findings' table based on the most important information for clinical practice. For example, reporting the comparisons between the three or four most effective interventions with the most commonly used intervention as a comparator.

11.7 Concluding remarks

Network meta-analysis is a method that can inform comparative effectiveness of multiple interventions, but care needs to be taken using this method because it is more statistically complex than a standard meta-analysis. In addition, as network meta-analyses generally ask broader research questions, they usually involve more studies at each step of systematic review, from screening to analysis, than standard meta-analysis. It is therefore important to anticipate the expertise, time, and resource required before embarking on one.

A valid indirect comparison and network meta-analysis requires a coherent evidence base. When formulating the research question and deciding the eligibility criteria, populations and interventions in relation to the assumption of transitivity need to be considered. Network meta-analysis is only valid when studies comparing different sets of interventions are similar enough to be combined. When conducted properly, it provides more precise estimates of relative effect than a single direct or indirect estimate. Network meta-analysis can yield estimates between any pairs of interventions, including those that have never been compared directly against each other. Network meta-analysis also allows the estimation of the ranking and hierarchy of interventions. Much care should be taken when interpreting the results and drawing conclusions from network meta-analysis, especially in the presence of incoherence or other potential biases.

11.8 Chapter information

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