

# What is a network meta-analysis and how can we use it to inform clinical practice?

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**What is a network meta-analysis?** For many diseases or conditions, clinicians face a choice amongst several treatment options. Optimal decision making requires structured summaries of evidence from studies evaluating the alternatives.<sup>1</sup> If available, systematic reviews (SRs) of well-designed and conducted randomized controlled trials (RCTs) provide the best evidence supporting treatment decisions.<sup>2</sup> SRs have traditionally focused on pair-wise comparisons of 2 treatments (A vs. B), which can make it difficult to establish the relative merits of 3 or more alternatives.<sup>3</sup>

The need for a more comprehensive evaluation of the available evidence regarding the complete range of alternative management strategies has motivated the development of a new methodology that allows the comparison of multiple interventions in a single SR: “network meta-analysis” (NMA), also known as multiple-treatment meta-analysis or mixed-treatment comparisons. NMA is a statistical method that combines both the direct and indirect evidence from all RCTs of interventions for treating a particular health problem.<sup>4</sup>

NMAs have gained popularity in recent years. A search of NMAs in Pubmed shows 17 articles—including both NMAs and associated methodological papers—published during 2004 to more than 400 published during 2014 with a total of more than 1600 to date. The increasing use of NMAs necessitates that clinicians become familiar with this method.

The NMA combines direct and indirect estimates of effect to calculate the relative effectiveness of 3 or more alternatives. In other words, if an NMA is addressing treatments A, B, and C, for the A–B comparison, the direct estimates will come from all RCTs that compare A vs. B, and the indirect estimates will come from RCTs comparing A vs. C and B vs. C, which allow to make an inference of the estimate of A vs. B, through C (FIGURE).

## Strengths and challenges of a network meta-analysis

The advantages of NMAs include their ability to address all treatments for a specific problem in the same model, the ability to compare interventions even in situations where there are no head-to-head comparisons, and the potential for increasing certainty of the evidence by pooling direct and indirect evidence to generate overall pooled estimates.<sup>4-7</sup> The NMA also presents many dangers to the unwary, particularly if investigators combine results from studies that are too heterogeneous in population, intervention, control, or outcome.

## Assessing the trustworthiness of network meta-analyses

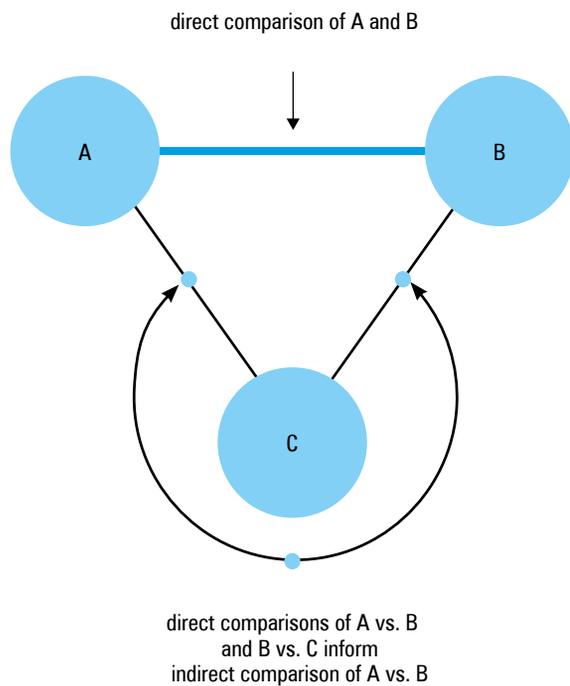
Recent publications have addressed how to use NMAs, and to assess the confidence in treatment effects, in order to inform clinical practice and assist clinicians wanting to apply the results to their patients.<sup>8,9</sup> The main 2 aspects to consider when assessing the trustworthiness of an NMA are whether the SR was well done and what was the evidence available to the reviewers.

When assessing whether the SR was well done, the key aspects to consider are the extent to which the review explicitly addressed a sensible clinical question, the search for relevant studies was exhaustive, the selection and assessments of studies were reproducible, the results were presented ready for clinical application, and the assessment of the confidence in effect estimates. All these issues are the same as those clinicians can apply when assessing the trustworthiness of a conventional meta-analysis.

One aspect particular to the NMA is whether the study characteristics of direct comparisons used to calculate an indirect estimate are the same among studies. For example, consider if the indirect estimate we are interested in is A vs. B and we wish to make inferences through an indirect comparison with C. The indirect comparison will

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**FIGURE** Direct and indirect comparisons in a network meta-analysis. If head-to-head trials have compared treatment A vs. treatment B, both direct evidence (head-to-head trials) and indirect evidence (comparison of A vs. B through a common comparator C, that is, comparison of A vs. C and B vs. C trials) inform the comparison A vs. B.

only be valid to the extent to which study characteristics such as patient characteristics, interventions characteristics (ie, dose or mode of administration), comparators, cointerventions and outcome measurement are sufficiently similar between the RCTs comparing A vs. C and B vs. C. If some characteristics differ, the indirect estimate of A vs. B may be biased. This phenomenon—differences in patients, interventions, and outcomes that could bias comparisons—is known as “intransitivity”.<sup>9</sup>

If the review process is rigorous, then we can assess how trustworthy the results are on the basis of the evidence. The confidence in the estimates of effects (also known as quality of the evidence) reflects the extent to which we think the estimates of effects obtained in the SR process are correct.<sup>10</sup> In an NMA, our confidence in the estimates of effects will vary across comparisons. Therefore, the assessment of the confidence in the estimates of effects needs to be done for each paired comparison.<sup>9</sup>

Our confidence in the estimates of effects will decrease if there is high risk of bias in the included studies; the confidence intervals around the pooled estimates are excessively wide (imprecision); the populations, interventions, comparisons, and outcomes are not entirely applicable to practice (indirectness); the trials included do not show similar estimates of treatment effects (inconsistency); and there is a suspicion of publication bias.<sup>8,10</sup> The GRADE working group has provided guidelines on how to do these assessments for an NMA,<sup>9</sup> and an example of how issues

around these aspects arise have been previously addressed in this journal.<sup>11</sup>

The possibility of ranking treatments has been proposed as one of the main advantages of the NMA.<sup>3,5,6</sup> Even though seductive, rankings can be misleading. They only provide an estimate of the probability of a treatment being the best; however, they do not say anything about the effect size of this difference. In other words, even if treatment A is ranked above treatment B, the relative risk reduction with A over B may be both trivial (ie, a relative risk reduction of 5%) and uncertain. Moreover, there may be substantially higher confidence in the estimates of effect for B vs. other treatments (such as placebo); considering these issues, B may be a better choice than A despite its lower rank.

In summary, using an SR that reports an NMA involves the consideration of aspects that are relevant to all SRs, and aspects that are particular to the NMA. Clinicians will often find apparently valuable information in an article that reports an NMA; however, if the authors do not provide an assessment of the confidence for each paired comparison, it will be hard to establish the relative merit of the interventions, and thus how to use the results.

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