

Interpretation and understanding of network meta-analysis

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Title: Interpretation and understanding of network meta-analysis: a method to compare multiple treatments for the same indication

Running title: Interpretation and understanding of network meta-analysis

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Prerequisite Topics

Meta-analysis

Systematic review

Key words

Network meta-analysis; mixed treatment comparison; multiple treatment comparison; indirect comparison; evidence synthesis.

Interventions are best compared by randomised controlled trials (RCTs). Often numerous interventions are available for an indication and separate RCTs compare different pairs or sets of interventions. For example, some RCTs may compare dinoprostol vs Foley catheter, and others dinoprostol vs misoprostol, as interventions for cervical ripening (Chen et al, BJOG 2016,123(3):346-354). Conventional meta-analysis pools results from RCTs comparing the same two interventions to estimate their relative effectiveness and could separately synthesise the evidence on dinoprostol vs Foley catheter and dinoprostol vs misoprostol. But such 'direct' evidence is often unavailable for all pairs of treatments, e.g. if no trials compare Foley catheter to misoprostol. Even if RCTs are available, there is no clear way to determine which intervention is best from three pair-wise pooled estimates. A joint analysis of all evidence is required to determine the most effective intervention.

What is Network meta-analysis?

Network meta-analysis (NMA) sometimes called multiple or mixed treatment comparison (MTC) is a statistical method for estimating the comparative effects of all interventions of interest, using all RCTs that compare at least two of them (Caldwell et al, BMJ 2005,331). In the figure 1 example, as well as providing direct evidence for their respective comparisons, trials comparing dinoprostol vs Foley catheter, and dinoprostol vs misoprostol taken together also provide 'indirect' evidence for the comparison between Foley catheter and misoprostol. Furthermore, if trials comparing Foley catheter vs misoprostol do exist then the consistency (i.e. agreement) between the direct and indirect evidence can be statistically evaluated. Any number of interventions can be included provided they are all linked by within trial comparisons, forming a network of treatment comparisons (figure 1).

Assumptions and Bias

NMA is an extension of pair-wise meta-analyses and meta-analysis assumptions should hold across all included trials. Thus, in the presence of statistical or clinical heterogeneity, factors that can change relative treatment effects should be balanced across all comparisons and should, as in pair-wise meta-analysis, represent the population to be treated. Note that balance is not required across comparisons for all confounders, only those that can modify the treatment effect. This will help ensure clinical and statistical homogeneity across the network. For example, if dinoprostol was more effective in older women, the distribution of age across all included trials should be similar to the population for whom the treatment decision is being made. NMA is also subject to the same biases as pairwise meta-analyses (Price, BJOG in press). RCTs contributing to a NMA should be identified using a single protocol for all treatments and their risk of bias assessed.

Results from NMAs

Treatment effect estimates and confidence intervals can be calculated for all pairs of treatments in the network. The probability each treatment is the most effective, and the ranking of each

treatment with confidence intervals can be estimated. NMA can inform clinical decision-making and cost-effectiveness analyses, identify gaps in evidence and inform research decisions.

RESOURCES

Summaries of methods, software links, and references:

<http://methods.cochrane.org/cmi/network-meta-analysis-toolkit>.

[http://www.nicedsu.org.uk/Evidence-Synthesis-TSD-series\(2391675\).htm](http://www.nicedsu.org.uk/Evidence-Synthesis-TSD-series(2391675).htm)

LEARNING POINTS

Often multiple interventions are available for a health condition and numerous trials compare different sets of these.

Network meta-analysis (NMA) is a statistical method to synthesise this evidence to produce relative effect estimates and rank interventions by efficacy.

NMA requires the assumptions of meta-analysis to hold across all trials in the network. Where possible, agreement between direct and indirect evidence should be statistically evaluated.

Disclosure of Interests

None

Figure Legend

Figure 1. Example: Network meta-analysis comparing Foley Catheter, misoprostol, and dinoprostol for cervical ripening. Evidence of network formed by interventions and numbers of direct comparisons. Each node presents a specific treatment. The width of the line indicate the number of direct comparisons (also shown by the numbers on each line). Reproduced from (Chen et al, BJOG 2016,123(3):346-354).