The transitivity assumption

Cochrane Airways has recently published our first network meta-analysis (NMA) (Kew 2014) and there is a growing interest in these kinds of reviews. NMA is a statistical tool used to rank three or more different treatments for a particular condition such as COPD. Below, Chris Cates explains transitivity from the point of view of multi-arm RCT, before explaining how the transitivity assumption applies in a NMA.

**Participants in RCTs have the same baseline characteristics (on average)**

In RCTs, there are usually two treatments tested and participants and randomised to receive one or the other. Sometimes trials can have more than two treatments. This results in a set of “pair-wise” randomised comparisons between the treatment options, but there are rarely trials comparing every treatment option to every other.

An example of a trial that compared 4 treatment options, randomised people to receive one of four options is the TORCH study. Participants were randomised to receive either placebo, salmeterol alone (LABA), fluticasone alone (ICS) or a combination of fluticasone and salmeterol (LABA/ICS) for their COPD.

This can be pictured as a network of treatments, as shown in the figure below. For this network from the TORCH study there is one pair of trial arms that compares each of the treatments above, and this is illustrated by the number one in brackets and the fact that the lines are all of the same thickness.

Since all the treatment options were randomised in the same group of patients in the same trial this network meets the “Transitivity Assumption”. The transitivity assumptions can be thought of in simple terms: whether it was equally likely that any patient in the network could have been given any of the treatments in the network.
We can compare the benefit of LABA and ICS both directly and indirectly from this network. The **direct** (randomised) estimate of the treatment difference is made using the diagonal line between LABA and ICS (shown in blue as a pair-wise comparison).

However, the treatment difference between LABA and ICS in the TORCH study can be calculated indirectly by comparing the estimated effect of LABA v placebo to the estimated effect of ICS versus placebo (difference between the purple lines which can be used to assess indirectly the dotted blue line).

*Making direct and indirect comparison between trials*
In NMAs, we construct a network with all the different treatments we want to consider and combine the direct (solid blue line) and indirect (dotted blue line) estimates of the treatment difference using data from different RCTs. By combining the estimates, we then have to assume that the true treatment effect of each of the treatments in the network is comparable across trials that contribute to the network.

Things can get quite complicated especially when different doses are taken into account—in Kew 2014; the following network diagram was constructed.

**Potential issues with NMA**

Although it is routine to compare the indirect and direct comparisons for “consistency” in a NMA, the power of this test to pick up inconsistency is low (especially if there is not much direct evidence), so we cannot rely on doing this alone.

In practice, the indirect comparisons are not protected by randomisation and may be confounded by differences between the trials, so we have to check that all the trials in a NMA were conducted in a similar way and recruited participants that were on average similar in any of their characteristics that might modify the treatment effect (to see if the transitivity assumption is justified). This could include age, disease severity, concomitant treatments in both arms, and duration of the treatment (and so on).

If these effect modifiers are clearly different between the trials, then a NMA should not be attempted.
Confounding by difference in the distribution of effect modifiers also needs to be considered when carrying out sub-group comparisons between trials, which we commonly do in our systematic reviews.

**What can we learn from this?**

- Target the PICO question for the protocol on a real decision that has to be made in clinical practice (as this will help with the practical application of the results of the systematic review).
- Identify (where possible) the likely important treatment effect modifiers that may vary across the trials, and make a plan for how you will assess transitivity before conducting the Network Meta-analysis.
- Consider whether measurements taken at different time points should be combined in the review or network.
- Add a caution about confounding by effect modifiers to any consideration of sub-group analysis or other indirect comparisons.
- Add a table of trial characteristics in reviews that includes important possible effect modifiers to assist the reader in understanding and applying the results of the review. It is useful to organise the table by direct pair-wise comparison to check if trials making a particular pair-wise comparison (e.g. LABA vs. placebo) are similar to trials making other pair-wise comparisons (e.g. ICS vs. placebo or LABA vs. ICS). Clarify the above characteristics in any application of the results (especially in the conclusions in the abstract).
- Report sub-group comparisons cautiously in the text, and do not generally report sub-groups in the abstract (as this perhaps gives them too much emphasis).

**References**


**Further reading**


Cates C. Maintenance treatment for adults with chronic asthma, BMJ 2014;348:g3148