Bias adjustment methods for combining RCTs with NRS: Building Trust in HTA acceptance

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Conflicts of interest

I have no actual or potential conflicts of interest in relation to this presentation.

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Evidence synthesis in HTA

- Most HTAs will involve a meta-analysis of studies comparing the interventions of interest for the decision problem
- Often *multiple treatments* are of interest
- Network meta-analysis (NMA) is an extension of standard meta-analysis to incorporate direct and indirect evidence on multiple treatment comparisons in a coherent way
  - NMA methods now well established
  - Respects randomisation
  - Increases precision and robustness of results as multiple sources of evidence are used to estimate the same relative treatment effect.
What is Network Meta-analysis?

Indirect Comparisons

(a) B C (b) A B D

Network meta-analysis

- The existence of “evidence loops” means that there is both direct evidence and indirect evidence on the same contrast.
- More data → estimates more precise, more robust (less sensitive to any one source of data).
- Possible to estimate additional parameters.
Use of NRS to strengthen inferences based on RCTs

- NMAs informed mainly by RCTs but data on some comparisons may be sparse and results imprecise
  - NRS can be used to strengthen evidence in such cases
- Need to balance the desired increase in precision with the potential for introducing bias
- Different models have been proposed
  - Different assumptions (some unsuitable for decision making)
Possible Models

- Separate synthesis model
  - RCT and NRS evidence are synthesised separately (no information sharing).
- Lumped Model (shared parameter model)
  - Share heterogeneity and treatment effect parameters: no difference assumed in effects estimated by RCT and NRS evidence
    - Useful as a comparison model, but not suitable for inference
- Multi-level/ Hierarchical Models
  - Assumes both types of studies are estimating a parameter from a common distribution (exchangeability)
  - does not account for potential bias in NRS evidence and does not specifically downweight it compared to RCT evidence.
- Bias Models
  - Proposed to incorporate RCT evidence at risk of bias with evidence not at risk → extend to NRS
- Prior-based Models
  - Allow for explicit down-weighting of NRS evidence
Example Dataset

In-stent Restenosis (Efthimiou et al. 2017)

- Outcome: Need for target-lesion revascularisation (binary, odds ratio)
- Aggregate data from
  - 28 RCTs (N=5917, each study had between 17-259 patients)
  - 6 NRSs (N=1019 patients, each study had between 26-165 patients)
- Comparison of 8 different treatments for the treatment of coronary in-stent restenosis

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RCTs

RCT+ Observational Combined

Codes for interventions:
1= balloon angioplasty
2= sirolimus-eluting stents
3= drug-coated balloons
4= everolimus-eluting stents
5= paclitaxel-eluting stents
6= rotablation
7= bare metal stents
8=vascular brachytherapy.

NRS = non-randomised study
General Approach

- NMA with RCT data only
- Check robustness/precision of treatment effect estimates
  - Look at 95% CrI, threshold analysis (Phillippo et al. 2019 https://doi.org/10.7326/M18-3542)
  - Some comparisons of interest are sensitive to potential small changes in the evidence and imprecise
- NRS evidence available
  - Assumed of sufficient quality and relevance to incorporate in synthesis
  - Provides additional evidence on key comparisons
Hierarchical Model

- Assumes exchangeability between parameters informed by RCT and NRS
- Obtain estimate of overall relative treatment effects across both types of evidence
  - Also obtain model-based estimate of relative treatment effect for RCT evidence, accounting for the NRS evidence under the model assumptions (shrunken estimate)
- Which of these estimates to choose?
  - Can argue that RCT-specific estimate more meaningful
Comparing Treatment Effects

- NRS data added evidence to comparisons of treatments 2,3,4,5 to treatment 1 (creating new loops)
  - Lumped model results similar to RCT only
    - except for comparison of treatment 4 to 1
    - conflict in the RCT and NRS data
  - Shrunken estimates for RCT data more precise than RCT alone (using information from NRS, under modelling assumptions)
Bias Model

- Assumes NRS data are at risk of bias and RCT data are not at risk of bias
- True relative treatment effect for treatment Y compared to X
  - Unbiased studies (RCT) $\rightarrow \delta_{XY}$
  - Biased studies (NRS) $\rightarrow \delta_{XY} + \beta$
    - Assume $\beta \sim \text{Normal}(b, \kappa)$
- Estimate bias and adjust for it
- NRS evidence is automatically adjusted and down-weighted by the bias term
  - in a Bayesian framework the additional uncertainty is propagated to all the estimates automatically
- Where does information on $\beta$ come from?
Bias Model: info on $\beta$ from...

- **External sources**
  - Guess
  - Formal elicitation (Turner *et al* JRSS A, 2009)
  - Evidence-based: compare RCT and NRS evidence in similar meta-analyses to inform $\beta$ (Welton *et al* JRSS A, 2009)

- **Internal sources** (Dias *et al* JRSS A, 2010)
  - Evidence-based
  - Estimate bias due to type of study *within* same set of trials and adjust for it

- External evidence on bias can also be included in the form of prior distributions for $\beta$ (e.g. from meta-epidemiological data or expert opinion) which can be updated by the data
Comparing Treatment Effects

- Bias model tends to be similar to RCT estimates but “corrects” for assumed bias in NRS
- Most results similar to hierarchical model RCT estimates but increased “correction” for conflict in comparison with treatment 4
- Bias estimated as 0.53 (-0.48, 1.73) on a log-scale
## Between-study heterogeneity

<table>
<thead>
<tr>
<th>Data source</th>
<th>Split Model</th>
<th>Bias Model</th>
<th>Hierarchical Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>0.44 (0.15, 0.80)</td>
<td></td>
<td>0.44 (0.15, 0.81)</td>
</tr>
<tr>
<td>NRS</td>
<td>0.41 (0.02, 1.66)</td>
<td></td>
<td>0.46 (0.02, 1.65)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.91 (0.10, 1.86)</td>
</tr>
<tr>
<td>RCT + NRS</td>
<td></td>
<td>0.47 (0.17, 0.83)</td>
<td></td>
</tr>
</tbody>
</table>

**Split Model**
- RCT
- NRS

**Bias Model**
- Overall

**Hierarchical Model**
- RCT
- NRS

**SD**
- 0.0
- 0.5
- 1.0
- 1.5
- 2.0
- 2.5

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**Data source**
- RCT
- NRS
- Overall
- RCT + NRS
It is possible to estimate and adjust for the additional bias present in NRS

- In networks of moderate size where NRS add new evidence to several comparisons

- Assumed RCTs **not at risk** of bias and NRS all at the **same risk** of bias

  - But NRS can vary in quality and expected risk of bias (as can the RCTs...)
  - Model can be extended to have different types of bias within study type, according to study quality assessment (requires multiple studies of each type)
  - In the Bayesian implementation this can be supplemented by external prior information
  - Other proposed methods that adjust for the bias, require it to be estimated externally or “guessed”

- Hierarchical model did not improve precision and added heterogeneity, contributing to overall uncertainty

  - Argue that RCT specific estimate (accounting for the NRS data through the model) can be useful

- In NMA, performance of models can vary with network structure.

  - Increase in precision and ability to estimate key parameters may be limited in sparse networks (few comparisons, few studies)
  - Simulation work needed to see when different models can be useful.
Thank you

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