Flexible generic framework for evidence synthesis in health technology assessment

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Goal

Randomised Controlled Trials (RCT)  Non-Randomised Studies (NRS)

Individual Participant Data (IPD)  Aggregated Data (AD)
**Flowchart of IPD-AD-RCT-NRS NMA**

1. Records identified through PubMed database searching ($n = 1421$)
   - Titles screened ($n = 1422$)
   - Abstracts assessed for eligibility ($n = 66$)
   - Full-text articles assessed for eligibility ($n = 32$)
   - Articles discuss methods to combine IPD and AD ($n = 25$)

2. Additional records identified through other sources (Twitter) ($n = 1$)
   - Records excluded (titles clearly suggest an application) ($n = 1362$)
   - Records excluded, not methodological papers ($n = 30$)
   - Studies excluded for irrelevant methodology ($n = 18$)

3. Articles discuss methods to combine RCT and NRS ($n = 7$)
   - Studies in the NMA review ($n = 6$)
   - Studies in the MA review ($n = 1$)
   - Studies included in the NMA review ($n = 6$)
   - Studies included in the NMA review ($n = 5$)

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**Models to combine IPD and AD NMR**

1. Three-level hierarchical NMR model (3LH-NMR) ([Saramago 2012, Leahy 2012, Donegan 2012](#))
2. Multilevel network meta-regression (ML-NMR) ([Leahy 2012, Phillippo 2020](#))
3. Matching-adjusted indirect comparisons (MAIC) ([Signorovitch 2010](#))
4. Simulated treatment comparisons (STC) ([Caro 2010](#))

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**Models to combine RCT and NRS NMR**

1. Naïve approach
2. Using NRS as an informative prior
3. Design-adjusted model
### Models to combine IPD and AD NMR

1. **Three-level hierarchical NMR model (3LH-NMR)** (Saramago 2012, Leahy 2012, Donegan 2012)
2. **Multilevel network meta-regression (ML-NMR)** (Leahy 2012, Phillippo 2020)
3. **Matching-adjusted indirect comparisons (MAIC)**
   - simple indirect comparison
   - MAIC perform poorly in simulations
4. **Simulated treatment comparisons (STC)** (Caro 2010)

### Models to combine RCT and NRS NMR

1. **Naïve approach**
2. **Using NRS as an informative prior**
3. **Design-adjusted model**
   - several study designs and several studies within each design

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### IPD-AD network meta-regression: 3LH-NMR

#### 1. IPD studies
For i individual in j study with k treatment

\[
y_{ijk} \sim Bernoulli (p_{ijk})
\]

\[
\text{logit} (p_{ijk}) =
\]

\[
u_j + \beta_1 x_{ijk} + \beta_{2,k} (x_{ijk} - x_{jk}) + \beta_{2,k} x_{jk} + \delta_{jbk}
\]

#### 2. AD studies
For j study with k treatment

\[
y_{jk} \sim Binomial (p_{jk})
\]

\[
\text{logit} (p_{jk}) =
\]

\[
u_j + \beta_{2,k} x_{jk} + \delta_{jbk}
\]

#### 3. Exchangeable effects:

\[
\delta_{jbk} \sim N(d_k - d_b, \tau^2), \beta_{2,k}^B \sim N(B_k^B - B_b^B, \sigma_B^2) \text{ and } \beta_{2,k}^W \sim N(B_k^W - B_b^W, \sigma_W^2)
\]
1. IPD studies
For RCT and NRS

\[ y_{ijk} \sim \text{Bernoulli}(p_{ijk}) \]
\[ \text{logit}(p_{ijk}) = u_j + \beta_1 x_{ijk} + \beta_{2,k}(x_{ijk} - x_{jk}) + \beta_{2,k}x_{jk} + \delta_{jbk} \]

2. AD studies
For RCT and NRS

\[ y_{jk} \sim \text{Binomial}(p_{jk}) \]
\[ \text{logit}(p_{jk}) = u_j + \beta_{2,k}x_{jk} + \delta_{jbk} \]

3. Exchangeable effects:
\[ \delta_{jbk} \sim N(d_k - d_b, \tau^2), \beta_{2,k}^B \sim N(B_k^B - B_b^B, \sigma_B^2) \] and \[ \beta_{2,k}^W \sim N(B_k^W - B_b^W, \sigma_W^2) \]

We introduce \( R_j \) which reflects the risk of bias in study \( j \)

This assumes NRS and RCTs of high risk bias contributes the same (according to their precision) with low risk of bias RCTs.
1. IPD studies
For RCT and NRS
\[ y_{ijk} \sim \text{Bernoulli}(p_{ijk}) \]
\[
\logit(p_{ijk}) = u_j + \beta_1 x_{ijk} + \beta_{2,k}(x_{ijk} - x_{jk}) + \beta_{2,k} x_{j,k} + \delta_{jbk} + \gamma_j R_j
\]

2. AD studies
For RCT and NRS
\[ y_{jk} \sim \text{Binomial}(p_{jk}) \]
\[
\logit(p_{jk}) = u_j + x_{jk} \beta_{2,k} + \delta_{jbk} + \gamma_j R_j
\]

3. Exchangeable effects:
\[ \delta_{jbk} \sim N(d_k - d_b, \tau^2) \beta_{2,k}^B \sim N(B_{k}^B - B_{b}^B, \sigma_B^2) \text{ and } \beta_{2,k}^W \sim N(B_{k}^W - B_{b}^W, \sigma_W^2) \]

4. Bias assumptions
\[ \gamma_j \sim N(g, \sigma_g^2), R_j \sim \text{Bern}(\pi_j) \]
\[ R_j = \begin{cases} 
\pi_{\text{low}} \sim \text{beta}(1,20) \\
\pi_{\text{unclear}} \sim \text{beta}(1,1) \\
\pi_{\text{high}} \sim \text{beta}(20,1)
\end{cases} \]

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1. IPD –NMR
For RCT
\[ y_{ijk} \sim \text{Bernoulli}(p_{ijk}) \]
\[
\logit(p_{ijk}) = u_j + \beta_1 x_{ijk} + \beta_{2,k}(x_{ijk} - x_{jk}) + \beta_{2,k} x_{j,k} + \delta_{jbk}
\]

2. AD –NMR
For RCT
\[ y_{jk} \sim \text{Binomial}(p_{jk}) \]
\[
\logit(p_{jk}) = u_j + x_{jk} \beta_{2,k} + \delta_{jbk}
\]

3. Exchangeable effects:
\[ \delta_{jbk} \sim N(d_k - d_b, \tau^2) \beta_{2,k}^B \sim N(B_{k}^B - B_{b}^B, \sigma_B^2) \text{ and } \beta_{2,k}^W \sim N(B_{k}^W - B_{b}^W, \sigma_W^2) \]

4. Priors
\[ u_j, B_{k}^W, B_{k}^B \sim N(0, 10^4), \tau, \sigma_B, \sigma_W \sim \text{Unif}(0,10) \]
\[ d_k \sim N(d_k^{\text{NRS}}, V_{\text{NRS}}) \]
**Case study**

- Relapsing remitting multiple sclerosis (RRMS)
- Binary outcome: relapse in 2 years (0/1)
- Covariate = age (reference to the mean age 37 yrs) – between and within–study interaction are the same

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of data</th>
<th>Design/RoB</th>
<th>Probability of risk</th>
<th>Treatment compared</th>
<th>Sample size</th>
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<tr>
<td>DEFINE</td>
<td>IPD</td>
<td>RCT/high risk</td>
<td>Beta(3,1)</td>
<td>Dimethyl fumarate Placebo</td>
<td>1234</td>
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<td>CONFIRM</td>
<td>IPD</td>
<td>RCT/high risk</td>
<td>Beta(3,1)</td>
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<td>IPD</td>
<td>RCT/low risk</td>
<td>Beta(1,20)</td>
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<tr>
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<td>RCT/unclear risk</td>
<td>Beta(1,1)</td>
<td>Glatiramer acetate Placebo</td>
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<td>Swiss cohort</td>
<td>IPD</td>
<td>NRS/high risk</td>
<td>Beta(30,1)</td>
<td>All</td>
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</tr>
</tbody>
</table>

**Network diagram**

- Natalizumab
- Placebo
- Glatiramer acetate
- Dimethyl fumarate

- IPD-RCT
- AD-RCT
- NRS
Results (response active vs placebo for 37 yrs)

- CrI of $\gamma$ (bias parameter):
  - 0.2
  - 1.1
  - 2.7

Results (OR vs age in design-adjusted model)
Summary

- Introduce 3 generic framework approaches
- Adding the observational evidence increase the precision
- We have to acknowledge the differences between RCT and NRS

Further development

- Extend ML-NMR with design-adjustment
- Include single-arm trials
- Implement the model in larger network
- Sensitivity analysis especially for bias parameters