Network Meta-Analysis using Individual Participant Data
When do benefits arise?

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IMI GETREAL
Background

Network meta-analysis
Synthesize results from studies that compare multiple competing interventions for the same condition
Background

• Network meta-analysis (NMA) often based on aggregate data (AD)
• Concerns regarding validity of indirect comparisons
• About 1/8 of AD-NMA suffer from network inconsistency
• Heterogeneity may also degrade usefulness of NMA
• NMA framework used for inclusion non-randomized studies

What can we gain by obtaining Individual Participant Data (IPD)?
The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115303], resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.

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Network meta-analysis of 18 anti-depressant trials

CASE STUDY
Case study

• 18 anti-depressant trials
  – Adults diagnosed with major depressive disorder
  – Follow-up of 2 – 6 weeks

• Comparison of 3 types of treatment
  – Tricyclic antidepressants
  – Tetracyclic antidepressants
  – Placebo

• Evaluation of Hamilton Depression score (HAMD)
  – Rating scale of 17 items
  – Score ranges between 0 (no depression) and 54 (severe depression)
No access to IPD

SCENARIO 1
Scenario 1: no access to IPD

- **Aim**
  - Investigate the relative change in HAMD score between TeCA and TCA after 6 weeks
  - Explore heterogeneity & network inconsistency

- **Common methods for meta-analysis of aggregate data**
  - Pairwise meta-analysis
  - Network meta-analysis
  - Network meta-regression (Tx: baseline HAMD score)
Problem: drop-out

Available response data

Generator data according to:

- Complete case analysis (CCA)
- Last observation carried forward (LOCF)
- Multivariate linear regression (MVR)
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IPD available for all trials

SCENARIO 2
**Option 2:** Standard one-stage pairwise meta-analysis (PMA)

\[ H_{ijk6} \sim N(\mu_{ijk}, \sigma_{i6}^2) \]

\[ \mu_{ijk6} = \begin{cases} 
\alpha_i & : j = b \\
\alpha_i + \delta_i & : j \neq b 
\end{cases} \]

\[ \delta_i \sim N(d_{iib_i}, \tau_{iib_i}^2) \]

Missing HAMD responses are considered ignorable!
**Option 2:** Standard one-stage network meta-analysis (NMA)

\[ H_{ijk6} \sim \mathcal{N}(\mu_{ijk}, \sigma^2_{i6}) \]

\[ \mu_{ijk6} = \begin{cases} 
\alpha_i & : j = b \\
\alpha_i + \delta_i & : j \neq b 
\end{cases} \]

\[ \delta_i \sim \mathcal{N}(d_{ti} - d_{bi}, \tau^2) \quad \text{with} \quad d_1 = 0 \]

Consistency equations

Missing HAMD responses are considered ignorable!
Option 3: Adjust for confounders/prognostic factors (NMA-PF)

\[ H_{ijk6} \sim \mathcal{N}(\mu_{ijk}, \sigma^2_{i6}) \]

\[
\mu_{ijk6} = \begin{cases} 
\alpha_i + \gamma_i x_{ijk} & : j = b \\
\alpha_i + \gamma_i x_{ijk} + \delta_i & : j \neq b
\end{cases}
\]

\[ \delta_i \sim \mathcal{N}(d_{t_i} - d_{b_i}, \tau^2) \quad \text{with} \quad d_1 = 0 \]

Missing HAMD responses are considered ignorable!
Option 4: Adjust for effect modifiers (NMA-TX)

\[
H_{ijk6} \sim N\left(\mu_{ijk}, \sigma^2_{ij6}\right)
\]
\[
\mu_{ijk6} = \begin{cases} 
\alpha_i + \gamma_i x_{ijk} & : j = b \\
\alpha_i + \gamma_i x_{ijk} + \theta_i x_{ijk} + \delta_i & : j \neq b 
\end{cases}
\]
\[
\delta_i \sim N\left(d_i - d_{bi}, \tau^2\right) \quad \text{with} \quad d_1 = 0
\]

Notes:
- Missing HAMD responses are considered ignorable
- Ideally $\theta_i$ should ideally be separated to distinguish between within- and across-trial interaction
Option 5: Multivariate network meta-analysis (MNMA)

Model distribution of within-study covariance matrices to allow imputation of studies with incomplete follow-up

Auto-regressive heterogeneity matrix
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Conclusions

• AD-NMA leads to excessive network inconsistency and/or heterogeneity
• IPD-NMA models achieved higher precision
• IPD-NMA models achieved improved consistency and less heterogeneity
  – By modelling longitudinal outcomes with informative drop-out
  – By allowing for participant-level treatment-covariate interaction

Our findings confirm the recommendations from the literature, and indicate that access to IPD may be helpful to improve the validity and usefulness of summary estimates of relative treatment effect.
Recommendations

Prioritization of IPD retrieval

• Presence of network inconsistency
• Presence of heterogeneity
• Publications with inappropriate summary statistics
Overview of statistical methods & source code

An overview of methods for network meta-analysis using individual participant data: when do benefits arise?

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