Network meta-analysis of biological response modifiers in rheumatoid arthritis including multiple outcomes at multiple time points

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Background

- **GetReal** is a three-year project of the Innovative Medicines Initiative (IMI), a EU public-private consortium consisting of pharmaceutical companies, academia, HTA agencies and regulators patient organisations

- **GetReal** aims to investigate how robust new methods of Real World Evidence (RWE) collection and synthesis could be adopted earlier in pharmaceutical R&D and the healthcare decision making process

- A case study in Rheumatoid Arthritis (RA) looking at how to utilise ALL available evidence in order to produce a framework for maximising the evidence base from multiple sources
Methods

• Systematic review & Network Meta-Analysis (NMA) undertaken for biologics as monotherapy or in combination with methotrexate (MTX)
• Binary outcome of interests were ACR50 and DAS28 remission
• NMA of licenced dose at 6 months
• All dose NMA at 6 months
• Bivariate NMA (1) at 6 months and multivariate NMA for each outcome across multiple time points
• Modelling profile of treatment effect over time using linear and polynomial models

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All dose network (ACR50 at 6 months)

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NMA – Standard

• Let \( \delta_{i(bk)} \) represent the study specific log-odds ratio (LOR) of the treatment in arm \( k \) of study \( i \)

• Assuming the treatment effect is normally distributed,

\[
y_{ik} \sim \text{Normal}(\theta_{ik}, S^2_{ik})
\]

\[
\theta_{ik} = \begin{cases} 
\mu_{ib} & \text{if } k = b \\
\mu_{ib} + \delta_{i(bk)} & \text{if } k \neq b 
\end{cases}
\]

\( b = A, B, C \)

\[
\delta_{i(bk)} \sim \text{normal}(d_{bk} = d_{Ak} - d_{Ab}, \tau^2_{bk})
\]

• \( y_{ik} \) is the log odds of remission in arm \( k \) of study \( i \)

• \( \mu_{ib} \) is the study specific baseline effect

• \( \delta_{i(bk)} \) is the study specific log odds ratio for treatment \( k \) relative to treatment \( b \)

• Hence, \( d_{bk} \) is the pooled effect of treatment \( k \) relative to treatment \( b \) and \( \tau^2_{bk} \) is the between study variance (heterogeneity parameter)
## Results of ACR50 at 6 months

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Licenced dose NMA</th>
<th>All dose NMA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LOR</td>
<td>LCI</td>
</tr>
<tr>
<td>Abatacept + MTX</td>
<td>1.09</td>
<td>-0.15</td>
</tr>
<tr>
<td>Adalimumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab + MTX</td>
<td>1.24</td>
<td>0.01</td>
</tr>
<tr>
<td>CTZ + MTX</td>
<td>2.27</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Etanercept</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab + MTX</td>
<td>0.91</td>
<td>-0.73</td>
</tr>
<tr>
<td>Placebo</td>
<td>-18.68</td>
<td>-149.00</td>
</tr>
<tr>
<td>Abatacept</td>
<td>-16.80</td>
<td>-147.00</td>
</tr>
<tr>
<td>Rituximab + MTX</td>
<td>1.58</td>
<td>0.30</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>1.22</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Tocilizumab + MTX</strong></td>
<td>1.61</td>
<td>0.28</td>
</tr>
</tbody>
</table>

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Multivariate model

- Data at **many time points** are often collected in clinical trials and more than one outcome is usually reported
- On average an outcome is reported at two time points in RA
- Real world evidence can provide longer term follow up
- This extra evidence that is not normally utilised but may **provide valuable information** to decision makers
- One method to **utilise** this extended evidence base is to use a **multivariate approach** by modelling **separate outcomes simultaneously** using the **correlation** to borrow information across;
  - Multiple outcomes
  - Multiple time points
Multivariate model (within study)

- For each arm \( k \) of study \( i \) let \( Y_{ikm} \) be the observed log-odds of an event for outcome \( m \) \((m=1,\ldots,M)\) jointly following a multivariate normal distribution, then,

\[
\begin{pmatrix}
Y_{ik1} \\
\vdots \\
Y_{ikM}
\end{pmatrix}
\sim \text{Normal}
\begin{pmatrix}
\theta_{ik1} \\
\vdots \\
\theta_{ikM}
\end{pmatrix},
\begin{pmatrix}
S^2_{ik1} & \cdots & r^{1M}_{ik}S_{ik1}S_{ikM} \\
\vdots & \ddots & \vdots \\
S^2_{ikM} & \cdots & S^2_{ikM}
\end{pmatrix}
\]

- The \( S^2_{ik} \) matrix is the associated **within-study** covariance matrix

- If \( r^{1M}_{ik} = 0 \) then the problem reduces to \( M \) independent outcomes/NMAs

\[
\begin{pmatrix}
\theta_{ik1} \\
\vdots \\
\theta_{ikM}
\end{pmatrix}
= \begin{cases}
\begin{pmatrix}
\mu_{ib1} \\
\vdots \\
\mu_{ibM}
\end{pmatrix}, & \text{if } k = b \\
\mu_{ib1} + \delta_i(bk1) & \text{if } k \neq b \\
\vdots \\
\mu_{ibM} + \delta_i(bkM)
\end{cases}
\]

\text{for } b = A, B, C, \ldots
Multivariate model (between study)

• Then,

\[
\begin{pmatrix}
\delta_{i(bk)1} \\
\vdots \\
\delta_{i(bk)M}
\end{pmatrix}
\sim \text{Normal}
\begin{pmatrix}
d_{(bk)1} = d_{(Ak)1} - d_{(Ab)1} \\
\vdots \\
d_{(bk)M} = d_{(Ak)M} - d_{(Ab)M}
\end{pmatrix}
\begin{pmatrix}
\tau^2_{(bk)1} & \ldots & \rho^{1M}_{bk} \\
\vdots & \ddots & \vdots \\
\vdots & \ldots & \tau^2_{(bk)M}
\end{pmatrix}
\]

• Where \(\tau^2_{(bk)}\) is the covariance matrix containing terms for the \textit{between study} variances \((\tau^2_{(bk)m})\) with \(\rho^{mn}_{bk}\) being the between-study correlations between effects measured by outcome \(m\) and \(n\) \((m \neq n)\) specific to each \(k\) versus \(b\) comparison.

• Multiple arms and treatments were adjusted for in all models

• Bivariate case for ACR50 and DAS28

• Trivariate case using ACR50 at 3, 6 and 12 months
## Multivariate results for ACR50 at 6 months

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Full NMA at 6 months</th>
<th>Bivariate ACR50 + DAS28</th>
<th>Trivariate case ACR50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LOR</td>
<td>LCI</td>
<td>UCI</td>
</tr>
<tr>
<td>Abatacept + MTX</td>
<td>1.09</td>
<td>-0.22</td>
<td>2.41</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>1.04</td>
<td>-1.69</td>
<td>3.84</td>
</tr>
<tr>
<td>Adalimumab + MTX</td>
<td>1.25</td>
<td>-0.09</td>
<td>2.59</td>
</tr>
<tr>
<td>CTZ + MTX</td>
<td>2.31</td>
<td>0.91</td>
<td>3.71</td>
</tr>
<tr>
<td><strong>Etanercept</strong></td>
<td><strong>1.71</strong></td>
<td><strong>-1.45</strong></td>
<td><strong>4.90</strong></td>
</tr>
<tr>
<td>Infliximab + MTX</td>
<td>0.89</td>
<td>-0.85</td>
<td>2.65</td>
</tr>
<tr>
<td>Placebo</td>
<td>-0.82</td>
<td>-3.17</td>
<td>1.56</td>
</tr>
<tr>
<td>Abatacept</td>
<td>1.05</td>
<td>-2.06</td>
<td>4.19</td>
</tr>
<tr>
<td>Rituximab + MTX</td>
<td>1.57</td>
<td>0.20</td>
<td>2.93</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>1.76</td>
<td>0.31</td>
<td>3.25</td>
</tr>
<tr>
<td><strong>Tocilizumab + MTX</strong></td>
<td><strong>1.72</strong></td>
<td><strong>0.72</strong></td>
<td><strong>2.72</strong></td>
</tr>
</tbody>
</table>

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Multivariate results

• Broadly similar results to the standard NMA models
• Less extreme results are to be found in the multivariate analysis
• Reduction in uncertainty around effectiveness estimates
  – Larger reduction with stronger correlation between outcomes
• Borrows information to ‘strengthen’ results
• Predicts missing values based on correlation
  – If there is a missing treatment effect for an outcome, it can be predicted
Polynomial models for Outcomes over time

- Further to the previous models, polynomial models including multivariate normal distribution allowing for borrowing of strength across time points can be applied (2)
- 1\textsuperscript{st} (linear) and 2\textsuperscript{nd} order polynomial models were applied for ACR50 at 3, 6 & 12 months
- Correlation between ACR50 at multiple time points from the same study was incorporated using a multivariate approach
- Deviance Information Criterion (DIC) was used to assess the ‘goodness of fit’ of the models and to choose the final model

Polynomial model

• The polynomial model for the log odds at time $t$ for treatment $k$ of study $i$, is as follows,

$$y_{ikt} \sim \text{Normal}(\theta_{ikt}, S^2_{ikt}) \quad \theta_{ikt} = \beta_{0ik} + \sum_{m=1}^{M} \beta_{mik} t^{p_m}$$

$$\begin{pmatrix}
\beta_{0ik} \\
\vdots \\
\beta_{Mik}
\end{pmatrix} = \begin{pmatrix}
\mu_{0ib} \\
\vdots \\
\mu_{Mib}
\end{pmatrix} + \begin{pmatrix}
\mu_{0ik} \\
\vdots \\
\mu_{Mik}
\end{pmatrix} + \begin{pmatrix}
\delta_{0ibk} \\
\vdots \\
\delta_{Mibk}
\end{pmatrix} \quad \text{if } k \neq b$$

• Where $\theta_{ikt}$ reflect the log odds of treatment $k$ at time $t$ for study $i$
Polynomial model

• The vectors \( \left( \mu_{0ib} \right) \vdots \left( \mu_{Mib} \right) \) and \( \left( \delta_{0ibk} \right) \vdots \left( \delta_{Mibk} \right) \) are trial specific and represent the parameters \( \beta_0, \beta_1, \ldots, \beta_M \) for the ‘baseline’ treatment \( b \) and the difference in \( \beta_0, \beta_1, \ldots, \beta_M \) for treatment \( k \) relative to \( b \), respectively.

• As in the previous multivariate model, \( \delta \) then follows a multivariate normal distribution to account for study correlation

\[
\left( \begin{array}{c}
\delta_{0ibk} \\
\vdots \\
\delta_{Mibk}
\end{array} \right) \sim \text{Normal} \left( \begin{array}{c}
d_{0(bk)} = d_{0(Ak)} - d_{0(Ab)} \\
\vdots \\
d_{M(bk)} = d_{M(Ak)} - d_{M(Ab)}
\end{array} \right), \tau^2
\]

• Where \( \tau^2 \) is the between study covariance matrix.
Polynomial results

- On the left are the results from the 1\textsuperscript{st} order (linear) polynomial model
- On the right are the results from the 2\textsuperscript{nd} order polynomial model and the lowest DIC
1\textsuperscript{st} vs 2\textsuperscript{nd} order polynomial of ACR50

- The blue and red lines represent the credible intervals (dashed) and mean log odds obtained from the 1\textsuperscript{st} and 2\textsuperscript{nd} order model for tocilizumab + MTX vs MTX, respectively.
Conclusions

• Licenced and full NMA
  – Routinely used in decision making
  – Full NMA provides more information and comparisons for decision makers with potentially reduced uncertainty

• Multivariate model
  – Allows more information to be utilised
  – Can reduce uncertainty by borrowing strength across outcomes
  – Predicts outcomes when information is missing for various treatments

• Polynomial models
  – Estimates treatment effect *profiles* over time
  – Allows for more information to be utilised
Further Work

- Including Real World Evidence (RWE)
  - RWE could be included directly in NMA with appropriate bias adjustment
  - RWE could be used to inform the correlation structure, i.e. between outcomes, as a prior distribution for correlation parameters in multivariate NMA models
  - RWE could be used to extend and support estimation of the treatment profile over time, i.e. having longer follow-up, but appropriate bias adjustment is required.
THANK YOU FOR LISTENING!