Combining Observational & Clinical Trial Evidence for Health Technology Assessment (HTA)

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Introduction & Outline

• Issues with RWE & Network Meta-Analysis (NMA)
• IMI GetReal Project
• NMA incl. Real World Evidence (RWE)
• Allowing for both rigour & relevance in RWE
• Use of RWE in Multivariate MA
• Discussion & Current/Future Areas of Research
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Use of RCTs & RWE in estimating RE

(Relative) Clinical Effectiveness – RCTs

\[ \text{RCT}_1 (A \text{ v} P) \quad \text{RCT}_2 (B \text{ v} P) \quad \text{RCT}_3 (C \text{ v} P) \]

Real World Evidence

Registry/Obs \( (A \text{ v} B \text{ v} C \text{ v} P) \)

- Adjusting for case-mix/confounding
- IPD available – Propensity score/IV methods

Common comparator + variable follow-up
Early thrombolysis for AMI (Caldwell & Higgins *BMJ* 2005):

NMA considers the network of *all* relevant evidence to a decision problem.

NMA methods allow comparison/effect estimates for all interventions & associated uncertainty.

### Table 3 Percentage mortality at 35 days and the probability that each treatment is best (lowest mortality) in multiple treatment comparison analysis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Fixed effect model 35 day Mortality %</th>
<th>Random effects model 35 day Mortality %</th>
<th>Probability best</th>
<th>Probability best</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptokinase</td>
<td>6.7</td>
<td>6.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alteplase</td>
<td>6.7</td>
<td>6.5</td>
<td>0</td>
<td>0.003</td>
</tr>
<tr>
<td>Accelerated alteplase</td>
<td>5.8</td>
<td>5.8</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>Streptokinase + alteplase</td>
<td>6.5</td>
<td>6.6</td>
<td>0</td>
<td>0.002</td>
</tr>
<tr>
<td>Reteplase</td>
<td>6.1</td>
<td>6.0</td>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td>Tenecteplase</td>
<td>5.8</td>
<td>5.8</td>
<td>0.004</td>
<td>0.03</td>
</tr>
<tr>
<td>Percutaneous transluminal coronary angioplasty</td>
<td>4.4</td>
<td>4.3</td>
<td>0.995</td>
<td>0.95</td>
</tr>
</tbody>
</table>

![Network diagram](#)
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• Europe's largest public-private initiative
• Joint undertaking between European Union and European pharmaceutical industry association EFPIA.
• GetReal project
• Understanding how real-world data can contribute to decision-making in drug development
  – October 2013 to December 2016 (39 months)
  – 29 partners
  – Total budget: €18 million
    • 50% staff from the 15 participating pharma companies
    • 50% cash contribution from the EU to fund ‘public’ sector
Focus of GetReal

RWE intensifying across product lifecycle, but **RCTs are getting shorter** with conditional licencing by FDA & EMA -> HTA/reimbursement agencies face *challenge* of making decisions with **less RCT evidence**
WP1
Frameworks
Processes
Policies

WP2
Understanding the efficacy-effectiveness gap
simulation of trials to improve design

WP3
Overcoming practical barriers to the design of real-world studies

WP4
Identifying best practice and creating new methods for evidence synthesis and predictive modelling

- Standardising terminology
- Interviews to understand and the perspectives and policies of different stakeholders
- Designing a framework for decision-making during development

- 5 Case studies using drugs that had difficulty at regulation and HTA
  - 360 degree reviews
  - Re-designing development pathways to include real-world data
  - Simulation
  - Ascertaining impact on decision makers
WP1 – Case Studies

- **Multiple Sclerosis (MS)** – RWE in NMA (UoL, NICE & Novartis)
- **Rheumatoid Arthritis (RA)** – Lines of therapy & NMA including RWE (UoL, UoBern, Amgen & Roche)
- **NSCLC** – Generalisability of RCTs (UoL & Lilly)
- **Malignant Melanoma (MM)** – extrapolation using RWE (UoL, ZIN & BMS)
- **COPD** – Pragmatic RCTs (NICE & GSK)
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Adding **RWE** to NMA of RCTs

- Allow for heterogeneity using study-level covariates
- Adjust for potential biases in RWE (power transform prior & hierarchical modelling approaches)
Power Transform Prior Approach

- RWE is weighted by term $\gamma$, i.e. likelihood is raised to the power of $\gamma$ (Ibrahim & Chen, 2000);

$$P(\theta|RCT, Obs) = L(\theta|RCT)[L(\theta|Obs)^\gamma P(\theta)]$$

- $0 \leq \gamma \leq 1$ is degree of weighting
- $\gamma = 0 \implies$ total discounting of NRSs
- $\gamma = 1 \implies$ accept at NRSs ‘face value’
- Evaluate for a range of values of $\gamma$

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.

www.imi.europa.eu
Power prior - results

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www.imi.europa.eu
Power prior - results

Abrams KR et al. Multiple Sclerosis Case Study report. IMI GetReal www.imi-getreal.eu
Benefits & Limitations

• Benefits:
  – Adjustment of IPD RWE can allow for *known* confounders
  – Further adjustment can allow for potential *unknown* confounders
  – Provides a sensitivity analysis for Decision Makers
  – Can provide revised inputs into cost-effectiveness models

• Limitations:
  – Does not give a specific answer
  – Some methods rely on meta-epidemiology to provide an estimate of bias

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• Numerous methods are available for inclusion of RWE in R+D/regulatory/HTA process/pathway, BUT ...
  – They make various **assumptions** which may be untestable/subjective
  – Rely on **availability** of RWE(!)
  – There may be differing levels of **acceptance** by different HTA bodies
  – Need for assessment of impact on **cost-effectiveness**

• **Therefore** ...
  – Further **case studies** are required & elicitation of **stakeholder views**
  – More **research on methods** for inclusion *and* adjustment of RWE (especially in form of IPD & AD)
  – Greater use of **simulation** to evaluate different methods
  – Support for initiatives to **share RWE IPD** or at least relevant **summary AD**, e.g. Conditional covariate distributions, subgroup estimates, etc.
  – **MRC/NICE**-funded Methods Project (Bristol, Leicester & York)
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Background

• Key question – How could decision makers proceed faced with both RCTs and Non-randomised [comparative] evidence in order to make decisions for their target population or future trial?

• Useful to think of both rigour and relevance

• **Rigour** – quality and risk of bias of studies – here consider mainly rigour with respect to NRS

• **Relevance** – how closely do studies match (or are aligned with) the target population?

• How can we consider importance of both dimensions when assessing and appraising an evidence base which contains both RCTs and NRS to help make decisions for a target population?
Motivating Example – Statin Therapy & Diabetes

- Sattar *et al* (2010) reported 13 RCTs which had reported on incident cases of diabetes.
- Casula *et al* (2017) reported 18 cohort studies which had reported on incident cases of diabetes.
- 17 out of the 18 cohort studies assessed quality/bias using Newcastle-Ottawa Scale (NOS).
- All studies had study-level covariate information on mean age, length of follow-up and percentage of non-diabetics at baseline.

NRS: 1.48 (1.29 to 1.69)
RCTS: 1.10 (1.03 to 1.17)
ALL: 1.30 (1.17 to 1.43)
Standard/Univariate Power Prior – Results

NRS totally discounted: 1.09 (1.01 to 1.18)
NRS at ‘face value’: 1.13 (1.06 to 1.22)
NRS totally discounted: 1.18 (1.09 to 1.32)
Univariate *supra* Power Prior – Methods

- Univariate power prior assumes that all NRSs get downweighted by *same* degree/factor/power $\gamma$

- Assume for each study a measure of *quality/bias/rigour* had been obtained (Newcastle-Ottawa Scale etc) and this was converted to 0-1 scale and denoted $W_{Bi}$ (*Rigour weights*) [1 indicating the highest weight, i.e. least bias, most rigour]

\[
P(\theta | RCT, Obs) = \prod_{i=1}^{n} L(\theta | RCT_i) \prod_{j=1}^{m} L(\theta | OBS_j)^{\alpha^*_j} P(\theta)
\]

- Where $\alpha^*_j = W_{Bj}^\alpha$ and so $\alpha$ gives an overall measure of the *importance of rigour* (again $0 \leq \alpha \leq 1$)

- In statins-diabetes example, all RCTs are assumed to have rigour weight of 1, i.e. perfect quality.
Univariate \textit{supra} Power Prior – Results

Rigour of \textit{minimal importance} (all at ‘face value’):
- 1.48 (1.28 to 1.72)
- 1.47 (1.27 to 1.71)
- 1.46 (1.27 to 1.71)

Rigour of \textit{maximal importance} (fully quality weighting):
- 1.48 (1.28 to 1.72)
NRS – Meta-Regression for Quality (NOS)

Slope: 
-0.31 (1.25 to 0.64) 
P=0.52
Bivariate \textit{supra} Power Prior – Methods

- Assume that there are 3 covariates which can be used to define \textit{relevance}, $X_1, X_2, X_3$ such that the \textit{target population} is defined by $X_1^*, X_2^*, X_3^*$ (in example, age=55, follow-up=5 years & non-diabetic=100%)

- Calculate the standardised Euclidean distance;

$$Z_i = \sqrt{(X_{1i} - X_1^*)^2 + (X_{2i} - X_2^*)^2 + (X_{3i} - X_3^*)^2}$$

$$Z_i^* = Z_i / \max(Z_i)$$

- Power Prior posterior distribution becomes;

$$P(\theta | RCTS, OBS) = \prod_{i=1}^{n} L(\theta | RCT)^{\beta_i^* \alpha_i^*} \prod_{j=1} {L(\theta | OBS)^{\beta_j^* \alpha_j^*}} P(\theta)$$

Where $\alpha_i^* = W_{Bi}^\alpha$ and $\beta_i^* = Z_i^\beta$
Bivariate \textit{supra} Power Prior – Results
Discussion of BSPP Approach

• Why not use Meta-Regression with the covariates?
  – Low power (Lambert et al, 2002)

• Meta-Regression + Bayesian Model Averaging (BMA)
  – Allows subjective assessment of importance of covariates

• Predicting effects in target populations?
  – Hierarchical model (accounting for sources of evidence)

• Other approaches …
  – Multi-Criteria Decision Analysis (MCDA)
  – Response surface approach
  – Extension to NMA

• Power prior approaches …
  – Allow decision makers to explore potential impact of non-randomised evidence on effect estimates & decisions for their target population
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Example: Rheumatoid Arthritis (RA)


• Meta-analyses of 3 outcomes of rheumatoid arthritis (RA):
  – American College of Rheumatology *(ACR)*
  – Disease Activity Score *(DAS)*
  – Health Assessment Questionnaire *(HAQ)*

• Showed benefit of anti-TNF- inhibitors when used sequentially.

• In economic models evaluating treatments in RA, *EQ-5D* is used and is usually *derived* from HAQ.
## Multiple Outcomes: RA, Lloyd *et al.*

<table>
<thead>
<tr>
<th>Study</th>
<th>HAQ</th>
<th>DAS28</th>
<th>ACR20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennet 2005</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Bingham 2009</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Bombardieri 2007</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Harouj 2004</td>
<td>✓</td>
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<tr>
<td>Hyric 2008</td>
<td>✓</td>
<td></td>
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<tr>
<td>Iannone 2009</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Navarro-Sarabia 2009</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Van der Bijl 2008</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Buch 2007</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cohen 2005</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Di Poi 2007</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Finckh 2007</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Hjardem 2007</td>
<td></td>
<td>✓</td>
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</tr>
<tr>
<td>Laas 2008</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Nikas 2006</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Wick 2005</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Karlsson 2008</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Buch 2005</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Van Vollenhoven 2003</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>
Multivariate MA Approach to RA (Bujkiewicz et al, 2013)

- **External Summary Data**
  - HAQ, DAS, ACR

- **“Lloyd” data** (summary data)
  - HAQ, DAS, ACR

- **Individual Patient Data**
  - haq, das, acr

Prior on the between-study correlation

Prior on the within-study correlation

Based on NICE Appraisal (RCTs)

British Rheumatoid Outcome Study Group (BROSG) Cohort
### Multivariate Model: Results

<table>
<thead>
<tr>
<th></th>
<th>URMA: HAQ</th>
<th>URMA: DAS-28</th>
<th>URMA: ACR20</th>
<th>BRMA</th>
<th>TRMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAQ</td>
<td>-0.25 (0.09)</td>
<td>[-0.43, -0.09]</td>
<td>-0.28 (0.07)</td>
<td>[-0.41, -0.14]</td>
<td>-0.28 (0.07)</td>
</tr>
<tr>
<td>DAS</td>
<td>-1.57 (0.13)</td>
<td>[-1.84, -1.31]</td>
<td>-1.51 (0.08)</td>
<td>[-1.67, -1.35]</td>
<td>-1.51 (0.09)</td>
</tr>
<tr>
<td>ACR</td>
<td>0.62 (0.05)</td>
<td>[0.53, 0.71]</td>
<td>0.61 (0.05)</td>
<td>[0.52, 0.71]</td>
<td></td>
</tr>
<tr>
<td>$\tau_H$</td>
<td>0.21 (0.09)</td>
<td>[0.08, 0.38]</td>
<td>0.21 (0.07)</td>
<td>[0.10, 0.35]</td>
<td>0.22 (0.07)</td>
</tr>
<tr>
<td>$\tau_D$</td>
<td>0.44 (0.11)</td>
<td>[0.25, 0.67]</td>
<td>0.44 (0.11)</td>
<td>[0.24, 0.67]</td>
<td>0.44 (0.11)</td>
</tr>
<tr>
<td>$\tau_A$</td>
<td>0.52 (0.19)</td>
<td>[0.20, 0.90]</td>
<td>0.53 (0.19)</td>
<td>[0.22, 0.91]</td>
<td></td>
</tr>
<tr>
<td>$\rho_b^{DH}$</td>
<td>0.89 (0.12)</td>
<td>[0.65, 0.994]</td>
<td>0.84 (0.18)</td>
<td>[0.46, 0.99]</td>
<td></td>
</tr>
<tr>
<td>$\rho_b^{AH}$</td>
<td></td>
<td></td>
<td>-0.14 (0.31)</td>
<td>[-0.64, 0.49]</td>
<td></td>
</tr>
</tbody>
</table>
### Mapping from HAQ to EQ-5D: Results

<table>
<thead>
<tr>
<th>Model</th>
<th>Number of cohorts/studies</th>
<th>ΔHAQ</th>
<th>ΔDAS - 28</th>
<th>ACR20</th>
<th>ΔEQ - 5D</th>
</tr>
</thead>
<tbody>
<tr>
<td>URMA</td>
<td>8/8</td>
<td>-0.25</td>
<td>-</td>
<td>-</td>
<td>0.08 (0.025, 0.141)</td>
</tr>
<tr>
<td></td>
<td>( -0.43, -0.09 )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRMA</td>
<td>18/16</td>
<td>-0.28</td>
<td>-1.51</td>
<td>-</td>
<td>0.09 (0.041, 0.138)</td>
</tr>
<tr>
<td></td>
<td>( -0.41, -0.14 )</td>
<td></td>
<td>(-1.67, -1.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRMA</td>
<td>21/19</td>
<td>-0.28</td>
<td>-1.51</td>
<td>61%</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>( -0.42, -0.13 )</td>
<td></td>
<td>(-1.70, -1.33)</td>
<td>(52%, 71%)</td>
<td>(0.042, 0.139)</td>
</tr>
</tbody>
</table>

#### Diagrams

- **ΔHAQ**
  - URMA: HAQ: -0.25 ( -0.428, -0.076 )
  - BRMA: HAQ & DAS-28: -0.28 ( -0.416, -0.133 )
  - TRMA: HAQ, DAS-28 & ACR20: -0.28 ( -0.423, -0.129 )

- **ΔEQ-5D**
  - URMA: HAQ: 0.08 (0.025, 0.142)
  - BRMA: HAQ & DAS-28: 0.09 (0.044, 0.139)
  - TRMA: HAQ, DAS-28 & ACR20: 0.09 (0.042, 0.141)
Benefits & Limitations

• Benefits:
  – Potential increase in precision/reduction in uncertainty
  – External/RWE is not necessarily used directly
  – Useful when RCTs only report limited HTA-relevant endpoints, e.g. EQ-5D

• Limitations:
  – Relies on external/RWE especially for correlations between outcomes
  – Not always transparent and can increase methodological uncertainty
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Discussion

• Use of RWE will increase – because of changing nature of RCTs & availability of RWE e.g. (linked) EHRs

• Formal use of RWE presents challenges (rigour) & opportunities (relevance) – other approaches not discussed …

• AI/ML applied to RWE …
  – Confounding and selection effects
  – Understanding of “data generation mechanism”
  – Informative observations e.g. BP in primary care

• Other situations in which ES & RWE can help …
  – Choosing comparator in future RCT
  – Estimating effects in other settings, e.g. 1L/2L
  – Helping design RCTs in other populations e.g. multimorbidity – HDR UK
Developing & Evaluating Methods for Harnessing EHRs to Generalise RCT Findings to Multimorbid Populations & Design of Future RCTs

Existing RCTs
- Networks of RCT Evidence in Single Conditions

Existing Cohort(s)
- COPD
- HF

EHR Platform
- COPD + HF
- RCT (possibly adaptive & in sub-population) on EHR Platform in Multimorbid Population

WP1
- COPD
- HF

WP2
- COPD + HF

WP3
- RCT (possibly adaptive & in sub-population) on EHR Platform in Multimorbid Population

WP4 – Stakeholders Workshops
Thank you
&
What Questions do you have?
Backup Slides
Extension to Network Meta-Analysis (NMA)

Mapping from HAQ to EQ-5D

\[ EQ - 5D = a + b \times HAQ, \]

where \( a \sim N(\mu_a, s^2_a) \) and \( b \sim N(\mu_b, s^2_b) \), and \( \mu_a = 0.628 \), \( \mu_b = -0.327 \), \( s_a = 0.034 \), \( s_b = 0.021 \).

This relationship can be assumed to remain the same at any time point, hence the relationship between the change from baseline of EQ-5D and the change from baseline of HAQ can be modelled as

\[ \Delta EQ - 5D = b \times \Delta HAQ. \]
Augmenting NMAs with RWE when estimating treatment sequences