Bayesian modelling of resource use alongside multinational randomised clinical trials

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## Multinational RCT to conduct economic evaluations

### Data Quality
- Protocol driven HCRU
- Design (length of follow-up, comparators)
- Single source of information
- Number of patients by country

### Minimises Selection Bias
- Country-specific data

### Single Source of Information
- Number of patients by country

### Country-specific Data
- Protocol driven HCRU
- Design (length of follow-up, comparators)
- Single source of information
- Number of patients by country

### Table:

<table>
<thead>
<tr>
<th>Visit</th>
<th>V1</th>
<th>V2</th>
<th>V3</th>
<th>V4</th>
<th>V5</th>
<th>V6</th>
<th>V7</th>
<th>V8</th>
<th>V9</th>
<th>V10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week</td>
<td>-2</td>
<td>0</td>
<td>2</td>
<td>8</td>
<td>16</td>
<td>24</td>
<td>32</td>
<td>40</td>
<td>48</td>
<td>51</td>
</tr>
<tr>
<td>HCRU</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
1. Country of interest: \( i \)

2. Unit costs for country \( i \):
   - GP visit: \( UC_{\text{GPV}}_i \)
   - Specialist visit: \( UC_{\text{SPEV}}_i \)
   - Hospital day: \( UC_{\text{HSPD}}_i \)

3. Cost estimation

<table>
<thead>
<tr>
<th>Pat</th>
<th>Country</th>
<th>( Nb_{\text{GPV}} )</th>
<th>( Nb_{\text{SPEV}} )</th>
<th>( Nb_{\text{HSPD}} )</th>
<th>Total Cost ( C_{i,j} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>4</td>
<td>6</td>
<td>12</td>
<td>( C_{1,i} )</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>( C_{2,i} )</td>
</tr>
<tr>
<td>3</td>
<td>b</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>( C_{3,i} )</td>
</tr>
<tr>
<td>...</td>
<td>..</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-2</td>
<td>i</td>
<td>10</td>
<td>1</td>
<td>0</td>
<td>( C_{N-2,i} )</td>
</tr>
<tr>
<td>N-1</td>
<td>i</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>( C_{N-1,i} )</td>
</tr>
<tr>
<td>N</td>
<td>( j )</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>( C_{N,i} )</td>
</tr>
</tbody>
</table>

4. Cost analysis
Classical approach: issue

Relative price differences may affect HCRU consumption

Confound Price effect with country effect
Study objectives

- To model the level of resource use within the context of an international RCT
  - To obtain country-specific estimates
  - To estimate country-specific total costs

- Accounting for
  - Hierarchical structure of the data
  - Underlying distribution

- Using twin 1-year multinational multicentre RCTs
  - Enrolling approximately 2,000 patients
  - Suffering from a chronic respiratory disease
  - Recruited in 20 different countries from all continents and more than 100 centres
  - RU collected:
    - GP visits, specialist visits, emergency room visits, hospital days
    - Concomitant medication treatment days by therapeutic class
Multi-level modelling

Factors → fixed effect

Centre effect: drawn from a specific distribution

Residual country effect: drawn from a specific distribution

Final set of factors
Model development

- Develop Generalised Linear Multilevel Models
  - To account for the specific underlying distributions
  - No issue of back transformation

- Underlying distribution function
  - Potential distribution function:
    - Healthcare resource contacts: Poisson, Negative Binomial, Zero Inflated Poisson (ZIP)
    - Concomitant medication: Poisson, Negative Binomial, Zero Inflated Poisson (ZIP), ZIP overdispersed (ZIPO), 2-part log Normal
  - Selection
    - Estimate univariate models (including treatment only)
    - Select distribution minimising the deviance

- Bayesian framework
  - Robust and flexible to develop complex models
% patients using HCRU by treatment group

- Hospitalisations: T1 6.7%, T2 5.7%
- Emergency room visits: T1 3.7%, T2 3.9%
- Specialist visits: T1 9.0%, T2 10.2%
- GP visits: T1 31.4%, T2 28.7%
Observed distributions

Most appropriate distribution function: ZIP for healthcare resource contacts and ZIPO for concomitant medication treatment days
Between-country heterogeneity well captured
Conclusion

- Advantages of the approach
  - Model homogeneous endpoints
    - As opposed to cost, which may provide better model fit
  - Costs can easily be estimated for several countries in the trial
    - With sufficient number of patients
  - Cost components estimated
    - Better understanding of the treatment effect

- Possible improvement
  - Include informative priors
    - Using external source of evidence
  - Develop multivariate model
    - To account for the correlation between RU
  - Explore other potential distributions