Techniques to Analyse Variability Across Countries in Multi-National Economic Evaluations
Implications for the Design of Future Studies

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Starting points

- Cost-effectiveness results can vary by location:
  - Within countries
  - Between jurisdictions
  - Between centres
- This raises a number of methods issues:
  - How should trials undertaken elsewhere be extrapolated to another market?
  - How should trials undertaken in several settings be analyzed?
  - What can we learn about the design of trials for economic evaluation?

Part 1. Adapting trials between locations

- Trial undertaken in one country (e.g. USA)
- Cost-effectiveness estimates needed for another country (e.g. UK)

Adapting trials between locations

What parameters need to be country-specific?

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Location dependent</th>
<th>Independent of location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resource use</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Unit costs</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Baseline events</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Treatment effect</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Utilities</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Using decision models to extrapolate between locations

- Structure models around generalisable features of disease
  - Pathways
  - States
- Incidence of clinical events determines probabilities in model
- Costs and utilities associated with each state/pathway

Levels of extrapolation between locations

Greater use of trial data

1. Use trial data for all parameters except unit costs
2. Use trial data for all parameters except resource use and unit costs
3. Use trial data for all clinical events (treatment and control), but location-specific data for resource use, unit costs and utilities
4. Use trial data for relative treatment effects, but location-specific data on baseline event rates, costs and utilities
5. As for 4, but adjust treatment effect for baseline event rates

Great use of non-trial data
Example – the WOSCOPS Trial

Background

- WOSCOPS – cost-effectiveness of primary prevention with pravastatin in hypercholesterolaemic middle-aged men
- Higher risk of CVD in Scottish population
- Were the results generalisable to other countries?
- Case-study with Belgium
- Combined trial and non-trial data within a decision model


Example – the WOSCOPS Trial

Simplified model structure

Healthy person with hypercholesterolaemia

- Non-CVD death
- CVD event

Assign life expectancy

Parameter | WOSCOPS | Belgium
---|---|---
Resource use | Trial | Belgium
Unit costs | Scotland | Belgium
Baseline risk | Trial | Belgium*
Risk reduction | Trial | Trial
Life expectancy | Scotland | Belgium

* Based on risk equations and risk factors distribution for Belgium

Example – the WOSCOPS Trial

Combining trial and non-trial data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WOSCOPS</th>
<th>Belgium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resource use</td>
<td>Trial</td>
<td>Belgium</td>
</tr>
<tr>
<td>Unit costs</td>
<td>Scotland</td>
<td>Belgium</td>
</tr>
<tr>
<td>Baseline risk</td>
<td>Trial</td>
<td>Belgium*</td>
</tr>
<tr>
<td>Risk reduction</td>
<td>Trial</td>
<td>Trial</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>Scotland</td>
<td>Belgium</td>
</tr>
</tbody>
</table>

Recent suggested methods for multi-national trials

Tests for homogeneity

- Country-by-treatment interactions in terms of cost-effectiveness
- Distinguish qualitative (crossover) and quantitative (non-crossover) interactions
- Formal tests available in terms of incremental CE ratios and net benefit
- If cannot reject null hypothesis of homogeneity, pool data across countries
- Applied to 4S study – no significant interactions observed, therefore data pooled
- Does lack of statistically significant interaction mean no decision-relevant differences between countries?


Part 2. Analysing multi-location trials

- Multi-centre trial in one country
- Multi-national trial
- Countries include country of interest (e.g. UK) but other countries as well
- Assume trial gives
  - Country-specific data on outcomes
  - Country-specific data on resource use
  - May have country-specific unit costs

Example – the WOSCOPS Trial

Results

<table>
<thead>
<tr>
<th></th>
<th>Scotland</th>
<th>Belgium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefits discounted*</td>
<td>12,500 Euros</td>
<td>12,500 Euros</td>
</tr>
<tr>
<td>Benefits undiscounted</td>
<td>31,400 Euros</td>
<td>29,900 Euros</td>
</tr>
</tbody>
</table>

* At 5% per annum
Recent suggested methods for multi-national trials

Regression modelling

- May be preferable to model the variation between locations
- Estimate country-specific cost-effectiveness:
  - Some part of costs and outcomes are exchangeable
  - Some part of costs and outcomes are country-specific
  - Some countries will have more data than others
- Alternative regression frameworks
  - Ordinary least squares using fixed effects
  - Multi-level modelling

Use of fixed effects regression modelling

<table>
<thead>
<tr>
<th></th>
<th>Method 1</th>
<th>Method 2</th>
<th>Method 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country 1</td>
<td>11,450</td>
<td>5,921</td>
<td>46,818</td>
</tr>
<tr>
<td>Country 2</td>
<td>60,358</td>
<td>91,906</td>
<td>57,636</td>
</tr>
<tr>
<td>Country 3</td>
<td>244,133</td>
<td>90,487</td>
<td>53,891</td>
</tr>
<tr>
<td>Country 4</td>
<td>181,259</td>
<td>93,326</td>
<td>69,145</td>
</tr>
<tr>
<td>Country 5</td>
<td>CS</td>
<td>CS</td>
<td>65,800</td>
</tr>
<tr>
<td>Whole sample</td>
<td>45,892</td>
<td>45,892</td>
<td>45,892</td>
</tr>
</tbody>
</table>

Method 1: Country-specific costs and effects
Method 2: Country-specific costs and trial-wide effects
Method 3: Country-specific unit costs, trial-wide utilisation and effects

Multi-level regression modelling

Random coefficient specification

\[
NMB_{ij} = \beta_{1j} + \beta_{2j}Y_{ij} + u_{0j} + u_{1j}Y_{ij} + \epsilon_{ij}
\]

- Provides appropriate standard errors if data are hierarchical
- Provides location-specific estimates of cost-effectiveness based using shrinkage estimation
- Can use patient-level and higher-level covariates

Multi-level regression modelling

Shrinkage estimators

Source: Manca, Rice, Sculpher, Briggs, in submission

Multi-level regression modelling

Centre-specific cost-effectiveness acceptability curves

Source: Manca, Rice, Sculpher, Briggs, in submission
Design issues for multi-location trials

Selection of countries and centres

- Clinical emphasis: select countries and centres to maximise recruitment
- Economic emphasis: need location-specific cost-effectiveness estimates for decision making
  - Centre-specific
  - Jurisdiction-specific
  - Country-specific
- Select locations
  - To include main markets
  - To get range of characteristics (e.g. type of system funding)
  - Ideally, selection of representative trial locations

Conclusions

- Decisions are taken on ‘reimbursement’ at various levels
- Multi-location trials provide opportunity to assess variability in cost-effectiveness and whether decisions will change
- Can quantify location-specific cost-effectiveness (with uncertainty)
- Location-specific data (including unit costs) important
- Role of location-specific covariates
- Selection of trial locations given greater prominence

<table>
<thead>
<tr>
<th>Country-level</th>
<th>Centre-level</th>
<th>Patient-level</th>
</tr>
</thead>
<tbody>
<tr>
<td>% GDP spent on health</td>
<td>Bed occupancy</td>
<td>Age</td>
</tr>
<tr>
<td>Reimbursement system for hospitals</td>
<td>Teaching status</td>
<td>Gender</td>
</tr>
<tr>
<td>Payment method for physician</td>
<td>Range of clinical specialties</td>
<td>Disease severity</td>
</tr>
<tr>
<td></td>
<td>Socio-economic status</td>
<td></td>
</tr>
</tbody>
</table>

Collecting location-specific covariates