THE VALUE OF HETEROGENEITY (VoH) FOR COST-EFFECTIVENESS SUBGROUP ANALYSIS

Methods and application

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The Value of Heterogeneity: Dimensions of value in a continuum

- Decisions on Average (EVPI, EVPPi)
- Decisions based on subgroups (Value of stratification)
- Decisions at Individual Level (EVIC)

What else should be taken into account?

- Two dimensions of value: static and dynamic value of heterogeneity
- Transaction costs might hinder the implementation of decisions at individual level


I. Cost-Effectiveness Subgroup Analysis under Current Information

- Definition of specifications
  - Biological plausibility, ethical and equity concerns, need to be operationalized in practice
- Sources of Heterogeneity
  - Baseline risk, treatment effect, quality of life, preferences and costs
- Estimation of NB across subgroups

\[ TNB_s = \sum_{s=1}^{S} w_s (\max_j NB_j) \]

- Static Value of Heterogeneity

\[ \Delta_s TNB = \sum_{s=1}^{S} w_s (\max_j NB_j) - \max_j NB \]

<table>
<thead>
<tr>
<th></th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>NB1</th>
<th>NB2</th>
<th>NB3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>21</td>
<td>18</td>
<td>22</td>
<td>20,000</td>
<td>10,000</td>
<td>25,000</td>
<td>20</td>
<td>17.5</td>
<td>20.75</td>
</tr>
<tr>
<td>A (25%)</td>
<td>23</td>
<td>16</td>
<td>21</td>
<td>20,000</td>
<td>7,000</td>
<td>24,000</td>
<td>22</td>
<td>15.65</td>
<td>19.8</td>
</tr>
<tr>
<td>B (25%)</td>
<td>19</td>
<td>21</td>
<td>22</td>
<td>20,000</td>
<td>8,000</td>
<td>30,000</td>
<td>18</td>
<td>20.6</td>
<td>20.5</td>
</tr>
<tr>
<td>C (25%)</td>
<td>18</td>
<td>17</td>
<td>24</td>
<td>20,000</td>
<td>10,000</td>
<td>25,000</td>
<td>17</td>
<td>16.5</td>
<td>22.75</td>
</tr>
<tr>
<td>D (25%)</td>
<td>24</td>
<td>18</td>
<td>21</td>
<td>20,000</td>
<td>15,000</td>
<td>21,000</td>
<td>23</td>
<td>17.25</td>
<td>19.95</td>
</tr>
</tbody>
</table>

TNB = [(22 x 0.25) + (20.6 x 0.25) + (22.75 x 0.25) + (23 x 0.25)]

TNB = 22.08

TNB = 20.75

\[ \Delta TNB = TNB_s - TNB = 22.0875 - 20.75 = 1.33 \] units of net benefits

*Assuming a threshold of £20,000/unit of benefit
II. Decision Uncertainty in Cost-Effectiveness Subgroup Analysis

- Expected net benefit with perfect information for the subgroup $s$
  \[ E_{\theta_s} \max_j NB_{j_\theta}(j, \theta_j) \]

- Expected value of perfect information for a single subgroup ($EVPI_s$)
  \[ EVPI_s = E_{\theta_s} \max_j NB_{j_\theta}(j, \theta_j) - \max_j E_{\theta_s} NB_{j_\theta}(j, \theta_j) \]

- Expected Value of Perfect Information for subgroups ($EVPI_{S_s}$)
  \[ EVPI_{S_s} = \sum_{s=1}^{S} EVPI_s w_s \]

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**Static and Dynamic VoH**

![Diagram showing Static and Dynamic Value of Heterogeneity](image)

- **a) Static Value of Heterogeneity**
- **b) Dynamic Value of Heterogeneity**

Dynamic Value of Heterogeneity: Difference between the expected maximum NHB of the stratified decision compared to a non- or less stratified decision.
UNCERTAINTY AND HETEROGENEITY: How many subgroups?

**Transaction costs:**
- Additional effort of implementing a further level of disaggregation
- Additional effort to enforce and monitor the compliance with guidelines
- Additional costs of further research to resolve uncertainty (OIR, AWR)

Motivational example: Trial RITA-3

Invasive versus conservative strategy for non-ST-elevation acute coronary syndrome (n=1810)

Invasive strategy was not cost-effective (ICER=21,960) on average

Motivational example: Trial RITA-3

- Expected costs and QALYs for each strategy for each individual
- Individuals are characterized by a set of nine covariates (age, sex, heart rate, diabetes, ST depression, left bundle branch block, previous myocardial infarction, smoking and severe angina)
- Estimation of the total Expected Value of Individualized Care (EVIC)

- Subgroup analysis conducted considering six covariates (sex, age and heart rate were excluded)
- Probabilistic Sensitivity Analysis (1,000 iterations for each individual)

<table>
<thead>
<tr>
<th>Specification</th>
<th>NHB (current information)</th>
<th>NHB (perfect information)</th>
<th>EVPI</th>
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</thead>
<tbody>
<tr>
<td>Average</td>
<td>4,397,388</td>
<td>4,408,143</td>
<td>10,755</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4,403,199</td>
<td>4,412,177</td>
<td>8,978</td>
</tr>
<tr>
<td>Diabetes and LBBB (4 subgroups)</td>
<td>4,404,566</td>
<td>4,412,841</td>
<td>8,275</td>
</tr>
<tr>
<td>Diabetes &amp; Previous MI &amp; Smoking (8 subgroups)</td>
<td>4,405,519</td>
<td>4,414,587</td>
<td>9,068</td>
</tr>
<tr>
<td>Diabetes &amp; Previous MI &amp; Smoking &amp; LBBB (16 subgroups)</td>
<td>4,406,788</td>
<td>4,415,294</td>
<td>8,505</td>
</tr>
<tr>
<td>All covariates (49 subgroups)</td>
<td>4,408,359</td>
<td>4,416,806</td>
<td>8,447</td>
</tr>
</tbody>
</table>
Concluding Remarks

• Heterogeneity analysis on the basis of subgroups is a coherent approach for a collectively funded health system
  – Because it improves efficiency in resource allocation
  – Because it considers transaction costs

• An efficiency criterion should also be considered for subgroup selection

• A systematic subgroup analysis should report two dimensions of value (static and dynamic)
The Value of Further Research: the added value of Individual-Participant level Data

PEDRO SARAMAGO
IN COLLABORATION WITH
PROF. KARL CLAXTON AND DR. MANUEL ESPINOZA

ISPOR, BERLIN 2012

Why(s)?

- Policy context
- Methodological context

Objective: Assess the added value of having access to IPD, compared to using AD only, in appropriately performing subgroup value of information analysis

Note:
AD: evidence base available in aggregate format (any reduction of IPD)
IPD: most informative format of data collected within a study (unit is the individual)
What(s)?

Conceptual framework: synthesising available evidence

- Assuming general case of a statistical synthesis model parameterized by $\theta$, and pooled statistic $\hat{\theta}$ (from $m$ studies) – posterior predictive distribution is used to populate a decision model input parameter

- Can have access to these $m$ studies at a summary level, an AD evidence base; or,

- It is possible to envisage a situation in which one has access to individual-level data from each of these $m$ studies, an IPD evidence base.

How(s)?

Value of additional research in the absence of subgroups

Conceptual framework: scenario 1.1

IPD involves an increase in parameter(s) precision, obtained distribution of relative effects will have lower or equal variance.
How(s)?

Conceptual framework: scenarios 1.2 & 1.3

IPD (relatively to AD) involves a:
(a) reduction/elimination of bias – may imply shifts in the distribution of effects; or
(b) both an increase in precision and a reduction/elimination of bias.

Value of additional research in the presence of mutually exclusive subgroups

Conceptual framework: scenario 2.1

IPD facilitates the use of formal modelling of treatment x covariate associations, which, in particular circumstances, may not be attainable when using AD – subgroup EVPI can be only estimated when IPD is available;
How(s)?
Conceptual framework: scenario 2.2 & 2.3

Real world example

- Cost Effectiveness evaluation of 7 Public Health interventions to promote the increase in provision of smoke alarms in households to prevent fire related accidents in pre-school children;

- Effectiveness evidence informing model: 11 AD and 9 IPD;

- Average cost effectiveness results: cost effective strategy is (1) Usual care
Population and subgroup level results

Further research: for which sub-population(s)?

- Same decision when considering subgroups;
- With IPD a better understanding of the contribution of each subgroup is attained.

Further research: what is the optimal number of subgroups?
Discussion points

- Different formats of the same evidence set (i.e. AD and IPD) may provide different distributional ‘scenarios’ about the same set of parameters

- IPD brings added value in:
  - identifying sources of heterogeneity and in selecting subgroup specifications to be considered in analysis;
  - exploring heterogeneity on the basis of subgroups;
  - answering: (a) for which population stratum is it valuable to conduct additional research?
  (b) What is the optimal number of subgroups?

- IPD may add extra layers of complexity to the transaction costs equation, as the task of obtaining and exploring IPD may be considered in itself a burden