Cost-effectiveness analyses that use randomized trials: instrumental variable approaches for handling non-compliance

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Acknowledgements

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In many RCTs, non-compliance, for example treatment switching
Intention-To-Treat (ITT), can be insufficient for decision-making
Level of non-compliance may differ in RCT vs routine practice
RCT design does not meet policy-makers needs
Alternative estimand, complier average causal effect (CACE) or Local Average Treatment Effect (LATE)
Melanoma drug £49,000 per QALY (CACE) vs £95,000 (ITT)
Context

• Instrumental variable (IV) methods for univariate outcomes (e.g. Latimer 2013)
• Multivariate outcomes problem, must recognise correlations
• Uncertainty around cost-effectiveness measures
• Resort to Per Protocol analyses: biased
• AIM: compare alternative IV estimation methods for multivariate outcomes, for example cost-effectiveness
• Interest in homogenous linear additive treatment effect on continuous outcomes for compliers, CACE
Motivating example: REFLUX for GORD

<table>
<thead>
<tr>
<th></th>
<th>Medical</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>88</td>
<td>84</td>
</tr>
<tr>
<td><strong>N (%) switched</strong></td>
<td>1(1.14)</td>
<td>18(21.4)</td>
</tr>
<tr>
<td><strong>Mean (SD) cost [£]</strong></td>
<td>1,316(1,728)</td>
<td>2,982(1,813)</td>
</tr>
<tr>
<td><strong>Mean (SD) QALY</strong></td>
<td>3.52(0.99)</td>
<td>3.74(0.90)</td>
</tr>
<tr>
<td><strong>Correlation: costs &amp; QALYs</strong></td>
<td>-0.18</td>
<td></td>
</tr>
</tbody>
</table>

Routine practice setting, only 5% of patients switched from surgery to medical
Endogeneity

U:
- patients health (including QoL)
- expected gain from surgery versus medicine
- belief about surgery versus medicine
- centre context; physician characteristics
- level of risk aversion
Complier average causal effect (CACE)

Criteria for instrument
1. Predict D
2. Independent of U
3. Only effect on Y via D

\[ \text{CACE} = \frac{\text{ITT}}{\alpha} \]

Estimation of CACE
2 stage least squares (2SLS)
1. Regress D on Z
2. Regress Y on predicted D

BUT estimating CACE by 2sls ignores correlation costs and outcomes
Estimating the CACE: 3SLS
Greene 2012

• Extends 2SLS & Seemingly unrelated regression (SUR)

Stage 1: \[ D_i = \alpha_0 + \alpha_1 Z_i + u_{0i} \]

Stage 2: \[ Y_{ci} = \beta_{0c} + \beta_{1CACE,c} D_i + u_{ci} \]
\[ Y_{Qi} = \beta_{0Q} + \beta_{1CACE,Q} D_i + u_{Qi} \]

Stage 3: Estimate the covariance matrix from stage 2

Allows unbiased estimation of point estimates and covariance

• Avoids assuming error terms normally distributed
• Asymptotic properties may not be satisfied
• Has not been previously been considered for non-compliance
Bayesian ‘predictor substitution’ (B2Pred)

\[ D_i \sim N(\mu_{Di}, \sigma_D^2) \quad Y_{Ci} \sim N(\mu_{Ci}, \sigma_C^2) \quad Y_{Qi} \sim N(\mu_{Qi}, \sigma_Q^2) \]
\[ \mu_{Di} = \alpha_0 + \alpha_1 Z_i \]
\[ \mu_{Ci} = \beta_0 + \beta_1 \mu_{Di} \]
\[ \mu_{Qi} = \gamma_0 + \gamma_1 \mu_{Di} + \gamma_2 (y_{ci} - \mu_{Ci}) \]

- Motivation Bayesian bivariate models (Nixon and Thompson, 2005)
- Allows for correlation between costs and QALYs
- Costs as marginal distribution, outcomes conditional on cost.
- Randomisation instrument for treatment received
- But treatment received, modelled independently of costs and QALYs
- Choice of priors may be important (Kleibergen and Zivot 2003)
Bayesian Full Likelihood (BFL)

Burgess and Thompson (2012)

• Simultaneous equation approach
• Allows for correlations amongst residuals
• Assume all 3 variables from multivariate Normal distribution

\[
\begin{pmatrix}
Y_{Di} \\
Y_{Ci} \\
Y_{Qi}
\end{pmatrix} \sim N \left\{ \begin{pmatrix}
\mu_{Di} \\
\mu_{Ci} \\
\mu_{Qi}
\end{pmatrix}, \Sigma \right\}
\]

\[
\Sigma = \begin{pmatrix}
\sigma_{11} & \sigma_{12} & \sigma_{13} \\
\sigma_{21} & \sigma_{22} & \sigma_{23} \\
\sigma_{31} & \sigma_{32} & \sigma_{33}
\end{pmatrix}
\]
Unrestricted ‘reduced form’ can be written as:

\[ \mu_{Di} = \alpha_0 + \alpha_1 z_i \]
\[ \mu_{Ci} = \beta_0 + \beta_1 \alpha_1 z_i \]
\[ \mu_{Qi} = \gamma_0 + \gamma_1 \alpha_1 z_i \]

Vague priors (Burgess and Thompson 2012)
- Wishart prior for precision matrix
- Flat normal priors for regression coefficients
- Gamma prior for the \( \beta_0 \) parameter

Concern how will perform with skewed costs
## Methods applied to REFLUX

### Incremental effects of Surgery vs Medicine

<table>
<thead>
<tr>
<th></th>
<th>Costs (£)</th>
<th>QALYs</th>
<th>INB (£)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>1,666</td>
<td>0.212</td>
<td>4,709 (-3,994 to 13,413)</td>
</tr>
<tr>
<td>CACE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2sls</td>
<td>2,151</td>
<td>0.274</td>
<td>6,081 (-4,999 to 17,162)</td>
</tr>
<tr>
<td>3sls</td>
<td>2,151</td>
<td>0.274</td>
<td>6,081 (-5,181 to 17,344)</td>
</tr>
<tr>
<td>B2Pred</td>
<td>2,163</td>
<td>0.277</td>
<td>6,106 (-5,357 to 17,816)</td>
</tr>
<tr>
<td>BFL</td>
<td>2,000</td>
<td>0.300</td>
<td>7,027 (-4,044 to 18,540)</td>
</tr>
</tbody>
</table>

*Incremental net monetary benefits, \( \lambda = £30,000 \) per QALY
Simulated cost-effectiveness

- Bias, confidence interval (CI) coverage and width
- 1000 datasets each scenario

<table>
<thead>
<tr>
<th>Factor</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>No patients</td>
<td>100, 1000</td>
</tr>
<tr>
<td>% non compliance</td>
<td>30, 70</td>
</tr>
<tr>
<td>Correlation, $\rho$: costs &amp; QALYs</td>
<td>-0.8, -0.4, +0.4, +0.8</td>
</tr>
<tr>
<td>Cost Distribution</td>
<td>Normal, Gamma</td>
</tr>
<tr>
<td>True INB</td>
<td>£200</td>
</tr>
</tbody>
</table>
Median (SE) Bias:
incremental cost (true=+0.4)
Non-compliance 30%,
$\rho=+0.4$ and -0.4
Median (SE) Bias:
Incremental QALY (true = +0.2)
Non-compliance 30%
$\rho = +0.4$ and $-0.4$
Median (SE) Bias:
incremental net benefit (true= +400)
Non-compliance 30%
$\rho=+0.4$ and $-0.4$
## Coverage of 95% CI for INB

<table>
<thead>
<tr>
<th>Normal Cost</th>
<th>N</th>
<th>$\rho$</th>
<th>2sls</th>
<th>3sls</th>
<th>B2Pred</th>
<th>BFL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100</td>
<td>0.4</td>
<td>0.988</td>
<td>0.953</td>
<td>0.982</td>
<td>0.966</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>-0.4</td>
<td>0.900</td>
<td>0.948</td>
<td>0.951</td>
<td>0.962</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gamma Cost</th>
<th>N</th>
<th>$\rho$</th>
<th>2sls</th>
<th>3sls</th>
<th>B2Pred</th>
<th>BFL</th>
</tr>
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<tr>
<td></td>
<td>100</td>
<td>0.4</td>
<td>0.982</td>
<td>0.948</td>
<td>0.958</td>
<td>0.956</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>-0.4</td>
<td>0.914</td>
<td>0.948</td>
<td>0.930</td>
<td>0.951</td>
</tr>
</tbody>
</table>
Discussion

- 2SLS inappropriate
- 3SLS or BFL provide unbiased and consistent estimates
- 3SLS easy to implement, BFL more flexible
- B2Pred does not fully recognise endogeneity between treatment received and outcomes
- CACE useful estimand in health economic evaluation
- For example decision nodes post randomisation
- Further research warranted in other settings, e.g. continuous levels of non-adherence.
- Will provide code and practical guidance for implementation
- http://theta.lshtm.ac.uk/