The Use of a Probabilistic Sensitivity Analysis for Decision Making: The example of Drug-Eluting Stents

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Seminar at Harvard Clinical Research Institute, 17th August 2004
Outline

- Rationale for probabilistic sensitivity analysis
- Overview of methods of PSA
- Case study – drug eluting stents
Policy background

- Cost-effectiveness analysis increasingly used for health service decision making
- Important role for decision modelling
  - Compare all relevant interventions
  - Synthesise available evidence
  - Extrapolation
  - Generalisation
- Decision models can identify:
  - Best option given available evidence
  - Probability of making the wrong decision
  - Value of additional research
- Part of the new NICE Reference Case
Uncertainty and variability

- Overall variability between patients
  - 1\textsuperscript{st} order uncertainty
  - Reflected in standard deviations associated with a mean value
- Parameter uncertainty
  - 2\textsuperscript{nd} order uncertainty
  - Uncertainty in mean parameter values
  - Reflected in standard error of the mean
- Sub-group heterogeneity
  - ‘Base-line’ characteristics ‘explain’ a proportion of overall variability between patients (e.g. age, sex)
  - Generate mean parameter values per sub-group
  - Variability within sub-group will remain
- Structural uncertainty
  - Uncertainty regarding modelling assumptions
Parameter uncertainty

Why probabilistic sensitivity analysis?

- Numerous parameters in decision models
- Each estimated with uncertainty
- Standard sensitivity analysis unwieldy
- Need to propagate joint parameter uncertainty in terms of decision uncertainty
- Quantification of decision uncertainty provides starting point for assessing the value of additional research
- In non-linear models, probabilistic models provide the only unbiased estimate of mean cost-effectiveness
Probabilistic sensitivity analysis

Steps in the process

• Identify sources of parameter uncertainty
• Characterise uncertain parameters as probability distributions
• Define correlations as appropriate:
  – Patient-level data
  – Use of regression methods
• Propagate uncertainty through model using Monte Carlo simulation
Monte Carlo simulation
Second order simulation (1)
Monte Carlo simulation
Second order simulation (2)

Live

C(L)

p1

ADE

No ADE

p2

C(ADE)

Die

1-p1

C(D)

Costs: 300
Effects: 40

Costs: 220
Effects: 35

Costs: 420
Effects: 42

Costs: 380
Effects: 38

Costs: 250
Effects: 49

Costs: 290
Effects: 46

Costs: 350
Effects: 42
Selecting distributions

- Universe of possible distributions available
- Often criticised as arbitrary
- But choice for a given distribution is relatively small
- Parametric choices are frequently made in statistics
## Selecting distributions

### Commonly used distributions

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Distribution</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probabilities</td>
<td>Beta</td>
<td>Between 0 and 1</td>
</tr>
<tr>
<td>Costs</td>
<td>Log-normal</td>
<td>Ranging from 0 to $\infty$</td>
</tr>
<tr>
<td></td>
<td>Gamma</td>
<td></td>
</tr>
<tr>
<td>Utilities</td>
<td>Beta</td>
<td>Minus $\infty$ to 1</td>
</tr>
<tr>
<td></td>
<td>Gamma $(1 - U)$</td>
<td></td>
</tr>
<tr>
<td>Relative risks</td>
<td>Log-normal</td>
<td>Ratios</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Additive on log scale</td>
</tr>
</tbody>
</table>
Case-study - background

- 2,100 deaths per million from coronary artery disease in UK – one of the highest in the world
- 1.4 million suffer from angina in the UK
- Percutaneous coronary interventions (PCI) provide a major therapeutic option in patients resistant to medical therapy
- About 85% of PCIs now undertaken using coronary stents in the UK
- Restenosis is a common problem with PCI
- Drug eluting stents have been shown to reduce restenosis
- Can their acquisition cost be justified?
Case-study - objectives

- To assess the cost-effectiveness of sirolimus-eluting stent (CYPHER™) compared to bare metal stents
- Based on treatment effects taken from three randomised trials
- Express health benefits in terms of quality-adjusted life-years
- Assess variation in cost-effectiveness by patient characteristics
- Use probabilistic sensitivity analysis to assess decision uncertainty
Key methods

- Base-case assumption of no differential effect on mortality
- QALY decrement through restenosis: symptomatic time waiting for further revascularisation
- Time horizon of 12 months based on trial follow-up
- Health service (payer) perspective
### Source of data on treatment effects

<table>
<thead>
<tr>
<th>Trial characteristic</th>
<th>Ravel</th>
<th>E-SIRIUS</th>
<th>SIRIUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>238</td>
<td>352</td>
<td>1058</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>19</td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td>Multi-vessel disease (%)</td>
<td>30</td>
<td>36</td>
<td>42</td>
</tr>
<tr>
<td>Reference vessel diameter (mm, mean ± SD)</td>
<td>2.62 ± 0.53</td>
<td>2.55 ± 0.37</td>
<td>2.80 ± 0.47</td>
</tr>
<tr>
<td>Length of lesion (mm, mean ± SD)</td>
<td>9.58 ± 3.25</td>
<td>15.0 ± 6.0</td>
<td>14.4 ± 5.8</td>
</tr>
</tbody>
</table>
## Key data inputs – treatment effects

<table>
<thead>
<tr>
<th>Input</th>
<th>RAVEL</th>
<th>E-SIRIUS</th>
<th>SIRIUS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sirolimus (Bare metal)</td>
<td>Sirolimus (Bare metal)</td>
<td>Sirolimus (Bare metal)</td>
</tr>
<tr>
<td></td>
<td>1/120 (0.008)</td>
<td>18/118 (0.153)</td>
<td>8/175 (0.046)</td>
</tr>
<tr>
<td>- PCI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- CABG</td>
<td>1/120 (0.008)</td>
<td>0/118 (0.000)</td>
<td>1/175 (0.006)</td>
</tr>
<tr>
<td>MI</td>
<td>4/120 (0.033)</td>
<td>6/118 (0.051)</td>
<td>8/175 (0.046)</td>
</tr>
</tbody>
</table>

*Further procedures (target lesions)*
<table>
<thead>
<tr>
<th>Input</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of Sirolimus-eluting stent</td>
<td>£1,762</td>
</tr>
<tr>
<td>Cost of bare metal stent</td>
<td>£1,145</td>
</tr>
<tr>
<td>Cost of PCI</td>
<td>£2,984</td>
</tr>
<tr>
<td>Cost of CABG</td>
<td>£6,450</td>
</tr>
<tr>
<td>Utility without symptoms</td>
<td>0.84 ± 0.16</td>
</tr>
<tr>
<td>Utility with symptoms</td>
<td>0.69 ± 0.20</td>
</tr>
<tr>
<td>Waiting times for revascularisation (Days)</td>
<td>196</td>
</tr>
</tbody>
</table>
Base-case results

<table>
<thead>
<tr>
<th>Input</th>
<th>RAVEL</th>
<th>E-SIRIUS</th>
<th>SIRIUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in costs</td>
<td>£166</td>
<td>£53</td>
<td>£113</td>
</tr>
<tr>
<td>Difference in QALYs</td>
<td>0.011</td>
<td>0.017</td>
<td>0.015</td>
</tr>
<tr>
<td>ICER</td>
<td>£15,198</td>
<td>£3,181</td>
<td>£7,461</td>
</tr>
</tbody>
</table>
Probabilistic sensitivity analysis
RAVEL Trial

Ravel - Equal Death

Incremental QALYs vs. Incremental cost
- Standard
- Sirolimus-Eluting

Probability Cost-Effective
- Sirolimus-Eluting
- Standard

Monetary Value of a QALY
Probabilistic sensitivity analysis

E-SIRIUS Trial

Incremental cost
Incremental QALYs

eSirius - Equal Death

- Standard
- Sirolimus-Eluting

0.00 0.01 0.02 0.03 0.04
-200 0 200 400 600

Monetary Value of a QALY
Probability Cost-Effective

- Sirolimus-Eluting
- Standard
Probabilistic sensitivity analysis
SIRIUS Trial

Sirius - Equal Death

Standard
Sirolimus-Eluting

Incremental cost vs Incremental QALYs

Probability Cost-Effective

Monetary Value of a QALY vs Probability Cost-Effective
# Further sub-group analysis

<table>
<thead>
<tr>
<th>Sub-Groups</th>
<th>ICERs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sub-group 1</strong></td>
<td></td>
</tr>
<tr>
<td>Diabetics</td>
<td>£2,848</td>
</tr>
<tr>
<td>Non-diabetics</td>
<td>£10,432</td>
</tr>
<tr>
<td><strong>Sub-group 2</strong></td>
<td></td>
</tr>
<tr>
<td>Long lesions</td>
<td>£30,864</td>
</tr>
<tr>
<td>Non-long lesions</td>
<td>DES dominates</td>
</tr>
<tr>
<td><strong>Sub-group 3</strong></td>
<td></td>
</tr>
<tr>
<td>Small vessel disease</td>
<td>£5,569</td>
</tr>
<tr>
<td>Non-small vessel disease</td>
<td>£8,746</td>
</tr>
</tbody>
</table>
Alternative assumptions about mortality

Ravel - Equal Death

Ravel - Cardiac Death

ICER = £15,198  
ICER = £1,674
Conclusions

• Based on 12-month trial data, reduction in restenosis results in cost offset to acquisition of DES
• Reduction in restenosis has an impact of quality of life
• Waiting times for procedures one way to capture these effects
• DES appears cost-effective based on standard NICE thresholds
• Decision uncertainty: 0.8 to 0.42 depending on trial and assuming equal mortality
• ICERs (and uncertainty) sensitive to assumptions about mortality