Trial based economic evaluation: just another piece of evidence

Claxton K
Department of Economics and Centre for Health Economics,
University of York, UK

Is the purpose of evaluation to inform decisions?
• What are the decisions?
• What is required?
• Which evidence is relevant?
• Does uncertainty matter?
• What is the role of trials?
• Are there any dangers?

What decisions?
• Given existing evidence:
  – Which interventions/strategies should be implemented?
  – For which patient/population groups?
  – For what type of indications/settings?
• Is further evidence required to support decisions?
  – What type of evidence
  – What type of studies
  – For which patient groups
  – How much evidence
• Delay implementation until the evidence is available?

So what’s required?
  – Joint distribution of cost and outcomes
  – For all alternative interventions/strategies
  – Explore the full range of clinical policies
  – For range of patient groups
  – In the relevant decision context
  – Over an appropriate time horizon

Should we consider all the evidence?
• Should social decision making consider all the evidence of relative effect?
  – Central tenant of EBM
  – Expected cost and outcomes
  – Characterisation of the uncertainty
• Should we compare all alternative interventions or only the selection included in a particular study?
• Should we also consider all the evidence for other parameters?
• Should we consider both direct and indirect evidence for all parameters?

Direct and indirect evidence?
• Synthesis 1 and 2
• But compare all interventions?
  – Pair wise comparisons?
  – Use all the information
  – Estimate joint posterior LOR with correlations

<table>
<thead>
<tr>
<th>Alternative interventions</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>4</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>5</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Direct and indirect evidence?

- Estimates of parameter values
- Uncertainty surrounding estimates
- Correlations between parameters

Does decision uncertainty matter?

- Is an assessment of the consequences of decision uncertainty necessary for rational (expected value) decision making?
- Is a characterisation of decision uncertainty a prerequisite for an assessment (formal or informal) of its consequences?
- Does this require a synthesis of all evidence from a variety of sources?

Some examples from NICE

<table>
<thead>
<tr>
<th>Case Study</th>
<th>Estimate (Relative Risk)</th>
<th>Population EVPI</th>
<th>Patient Group</th>
<th>Case Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative risk of progression for copaxone, Betaferon and rebif (22mg) (£14m, £13.6m and £7m respectively)</td>
<td>£86.2m Relapsing remitting and primary progressive multiple sclerosis (scenario 2)</td>
<td>Disease modifying therapies for multiple sclerosis Specificity (£3.6m)</td>
<td>£20m Women aged 18 to 64 years (scenario 3)</td>
<td>Liquid Based Cytology</td>
</tr>
<tr>
<td>Also the cost of care, costs of relapse and quality of life (£10m, £7m and £6m respectively)</td>
<td>£250m £710m £240m Stroke</td>
<td>£865m</td>
<td>Quality of life with and without PDT (£3,370,000 for 20/40)</td>
<td>£6.2m Visual acuity 20/40 £15.3m Visual acuity 20/80</td>
</tr>
<tr>
<td></td>
<td>£865m £250m £710m £240m Stroke</td>
<td>£865m £250m £710m £240m Stroke</td>
<td>£865m</td>
<td></td>
</tr>
<tr>
<td>Relative risk of death for non-acute PCI for GPA as medical management and for Clopidogrel (£85,041,000, and £68,137,000 respectively)</td>
<td>£171m Acute treatment following non-ST-elevation acute coronary syndrome (scenario 2)</td>
<td>Glycoprotein IIb/IIIa</td>
<td>£171m</td>
<td></td>
</tr>
<tr>
<td>Quality of life with and without PDT (£3,370,000 for 20/40)</td>
<td>£6.2m Visual acuity 20/40 £15.3m Visual acuity 20/80</td>
<td>£66.7m Otherwise healthy adults not at elevated risk of complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Can any single study provide a basis for decision making?

- Should we adopt a technology?
- Is further evidence required?
- When would a trial be sufficient basis
  - Trial follow-up and time horizon identical
  - All relevant comparators included as arms
  - Patients and practice relevant to decision-making context
  - All parameters estimated
- Only source of evidence for all parameters

So what is the role of trials?

- As measurement
  - Particularly parameters subject to selection bias
  - Input to the synthesis of all evidence
- Implications for design
  - Useful for synthesis
  - Pragmatic trials (what is exchangeable)?
- Implications for reporting of evaluations
  - ICERs and certainly CEACs make little sense
  - Value of information without synthesis makes no sense

Do we need economic trials?

- Peto vs Drummond: its an empirical question

Value of a trial updating all parameters
Do we need economic trials?
- Peto vs Drummond: it's an empirical question

Value of a portfolio of studies

Why trial based evaluation?
- Historical dominance of frequentist analysis
  - Probability is the relative frequency of repeated events
  - Traditional Inferential rules
- Fully Bayesian decision theoretic analysis
  - Priors based on synthesis of accumulated evidence
  - Specification of the loss function (decision framework)

Leon Trotsky, Preface to The History of the Russian Revolution
- Entirely exceptional conditions, independent of the will of persons or parties, are necessary in order to tear off the fetters of conservatism and bring the masses to insurrection
- The masses go into revolution not with a preprepared plan of social reconstruction, but with a sharp feeling that they cannot endure the old regime

Leon Trotsky, Preface to The History of the Russian Revolution