W12: Decision-Making in Health Technology Assessment (HTA)

ISPOR, Taipei, Taiwan
4th September 2012

Neil Hawkins, PhD, CStat
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Agenda

• HTA: Opportunities, Challenges, and Some Possible Solutions
  – Neil Hawkins, VP Health Economics, Oxford Outcomes, UK
• Experience from the UK
  – Olivia Wu, Reader, University of Glasgow, UK
• Experience from Taiwan
  – Jasmine Pwu, Director, Division of HTA CDE, Taiwan
• An Example HTA
HTA: Opportunities, Challenges, and Some Possible Solutions

ISPOR Taipei, September 2012

Neil Hawkins, PhD, CStat
Vice President, Health Economics, Oxford Outcomes, UK
Honorary Professor, University of Glasgow, UK

Cost-Effectiveness Analysis

• Helps decision-makers maximise health gain given constraints
• Provides technical efficiency
• Provide clear signals to industry regarding likely return on investment
CE Analysis Requires

- An estimate of the acceptable threshold:
  - Opportunity cost, not willingness to pay
  - The cost of obtaining a unit of health gain from the least effective technology currently funded
- Difficult to estimate, but essential
- Estimates of incremental costs and effects

HTA Evaluation

- Synthesis of available evidence: RCT, Obs., Opinion
- Extrapolation from surrogate to final endpoints
- Extrapolation over time
- Indirect comparisons
- Correction of suspected biases
- Requires assumptions and judgement
- Extrapolation = uncertainty
Constraints

• Societal Preferences
  – Burden of disease
  – Innovation
  – End of life
  – Orphan indications
• Politico legal considerations
• Equity

Requirements of Procedural Justice

• Voice
• Neutrality
• Consistency
• Accuracy
• Reversibility
• Transparency

Challenges

• Incorporation of constraints and societal values
• Evaluating the methods used extrapolation
• Timeliness
  – Validation, re-analysis, and consultation
  – Further evidence may be needed

Some Solutions

• Templating
• Effective review processes
• Interactive models
• Contingent decisions
• Methods for incorporation of societal values
Templating

- NICE: reference case and technical support documents
- EMA CHMP: Disease specific guidance
- Review and development of Models by 3rd Parties
  - Diabetes: Mount Hood Challenge
  - NICE: MTA process

Effective review process

- Wide review and consultation
  - Part of procedural justice
  - May save time later
- Internal appeals process (may help avoid later legal challenges)
Interactive Models


Contingent Decisions

Methods for Incorporation of Societal Values

• Ultimately requires quantitative trade-offs against efficiency
• Deliberation
  – Time consuming
  – May lead to inconsistency
• MCDA
• Elicitation of public preferences
  – NICE: Citizen’s council
  – Conjoint analyses to quantify public preferences
The NICE Process

Selection  Assessment  Appraisal
• Scope sets up questions to be addressed
• Key elements of the assessment:
  – Systematic review of clinical and economic evidence
  – Cost-effectiveness analysis
  – Critical review of manufacturer submissions
Committee A – 28 members

Decisions:

- Unconditional positive guidance
- Conditional positive guidance (on particular patient characteristics)
- Negative guidance
- Recommended only in research
- Opportunity for appeal
- Decisions reviewed in the future
• “The appropriate threshold to be used is that of the opportunity cost of programmes displaced by new, more costly technologies”

• If most plausible estimate is below £20,000 per QALY gained: cost-effective use of NHS resources

• Above £20,000: are there benefits not captured by the QALY? Has quality of life aspect been adequately measured?

• Above £30,000: “... need to identify an increasingly stronger case for supporting the technology as an effective use of NHS resources”


NHS end-of-life drugs rule change

Drugs which give terminally ill patients a few extra months to live have a better chance of being approved on the NHS under new rules.

The National Institute for Health and Clinical Excellence (NICE) is to extend the threshold at which the drugs are deemed cost-effective.

But this will only be in certain cases.

The NHS has a finite pot of money for treatments.
End of life criteria:

- The treatment is indicated for patients with a short life expectancy, normally < 24 months
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment
- The treatment is licensed or otherwise indicated for small patient populations

Other Threshold Exceptions

- **Severity of the underlying illness**
  When ICERs are equivalent, society would give priority to the expensive relief of a serious condition compared with relatively inexpensive relief of a mild discomfort
- **Stakeholder persuasion**
  When symptoms are poorly reflected in clinical trials or inadequately reflected in the measure of health-related quality of life used
- **Significant innovation**
  When the technology produces a substantial, demonstrable and distinct benefit, that may not have been adequately captured in the measure of health-related quality of life used
- **Disadvantaged populations**
  E.g. poorer people and ethnic minorities
- **Children**
  Society would generally favour ‘the benefit of the doubt’ being afforded to sick children
NICE approval of ICERS >£30,000

<table>
<thead>
<tr>
<th>Topic</th>
<th>ICER (£1000s)</th>
<th>Severity</th>
<th>End of BIf</th>
<th>Stakeholder persuasion</th>
<th>Significant innovation</th>
<th>Disadvantaged population</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab (lymphoma)</td>
<td>50-60</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Trastuzumab (advanced breast cancer)</td>
<td>37.5</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Insulin (chronic kidney disease)</td>
<td>36-45</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Insulin (postnatal insulinoma)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Farnesoid (maligant mesothelium)</td>
<td>34.5</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ranitidine (GERD, esophageal ulcer)</td>
<td>50</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Omeprazole for reflux symptoms</td>
<td>&gt;50</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Statin (advanced renar cancer)</td>
<td>50</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Lenalidomide (multiple myeloma)</td>
<td>42</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Somatostatin (growth hormone deficiency)</td>
<td>n/a</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Chronic subcutaneous insulin infusion</td>
<td>n/a</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*End of BfI considerations have only been explicitly taken into account since January 2009 on the basis of supplementary advice from the Institute to the Appraisal Committee, EER, incremental cost-effectiveness ratio at per cost-adjusted life year.


Value based pricing:

- There is currently no link between clinical guidelines, HTA and medicines pricing
- UK Government committed to changing Pharmaceutical Price Regulation Scheme (PPRS) to ensure better use of NHS resources
- Basic idea is that the price of a medicine should be related to cost effectiveness based on clinical evidence
- All branded medicines would be evaluated against alternatives including generics
Industry sets price initially

Evidence gathered on clinical effectiveness

Comparison made with therapeutic value of alternatives

Cost effectiveness established

Reimbursement to NHS/industry dependent on clinical value

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**Decision Making in Health Technology Assessment: Taiwan Experience**

Jasmine R. F. Pwu, PhD
Division of HTA, CDE
Taiwan
Disclaimer

The views presented in this presentation do not necessarily reflect those of the CDE

“health technology assessment”...

- What is it, really?  
  - A fancy term  
  - Another barrier  
  - Economic evaluation, CEA...  
  - A report? An organization? Or a process?  
  - “The magic bullet”
HTA in Taiwan ... Started small

- Not easy to build a whole new institute
  - Research, pilot program
  - Gradually to 14 headcounts
- Aimed on NHI decision aid

A new division was granted since 2008
CDE – HTA Division

Role is to provide evidence for public health policy decisions

Major tasks

• New drug application
  – Every case, except new combination drugs
  – HTA reports in 42 days
• New Medical device application
  – Only some “tough” applications (i.e., large impact)
• Referred research topics
  – Cost-effectiveness analysis of certain (or multiple) products
  – BIA under reimbursement criteria change
Major tasks (cont’d)

• HTA research
  – Worldwide HTA systems
  – Latest methodology
• Promotion/education
• International collaboration

HTA and listing decision
### Consideration factors for listing

<table>
<thead>
<tr>
<th>Regulatory body</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Safety</td>
</tr>
<tr>
<td>• Efficacy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BNHI</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Comparative effectiveness</td>
</tr>
<tr>
<td>• Budget impact</td>
</tr>
<tr>
<td>• Cost-effectiveness</td>
</tr>
<tr>
<td>• Ethical/Law/Social/Political Impact</td>
</tr>
</tbody>
</table>

### Decisions made during DBC meetings

- Listing or not
- Reimbursement price
- Reimbursement criteria/restrictions
## Categories for New Drugs

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>Shown <em>substantial</em> improvement in effectiveness, comparing to the best currently-used drug (therapy)</td>
</tr>
<tr>
<td>Category 2A</td>
<td>Shown <em>moderate</em> improvement</td>
</tr>
<tr>
<td>Category 2B</td>
<td>Shown <em>similar</em> clinical values</td>
</tr>
</tbody>
</table>

## Price decision

![Price decision diagram](diagram.png)
**Listing Review Process with HTA**

1. Application received
2. Evidence
3. Nominate 2+ DBC members as principal reviewers
4. Principal reviewers made written recommendations
5. DBC meeting

Assessment Report in 42 days

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**Listing Review Process**

- Application Received
- Effectiveness Assessment + Economic Assessment = Evidence Report
- Drug Beneficiary Committee

42 Days
CDE process

1. Effectiveness

- Understand the product
  - Licensing
  - Place in therapy

- Find the comparators
  - Same WHO/ATC class
  - Head-to-head RCTs
  - Experience from other HTA reports

- Effectiveness/Safety
  - Trial results
  - Reviews done by others

CDE process

2. Economic

- Burden of illness
  - Prevalence, incidence, etc.
  - Resource use

- Cost-effectiveness
  - Experience from other HTA reports
  - Industry-submitted
  - Database search

- Budget impact
  - Industry-submitted
  - Estimates of our own
Submission Forms (since 2010)

- Helped on revising the submission forms
- Promoting the HTA concept through the new form
  - Systematic reviews, PICOS,...
  - Local PE studies
  - Budget impact analysis

Reports online since 2011

“Local PE report checklist”

- Waiting for approval as of August 2012
- CDE will use this template to review the CEA attached in company dossiers
  - To encourage provision of a CEA that fits local decision needs

At this time point, our opinions regarding ...

- What is a good PE study *for listing decision*?
  - Providing *valid* economic evaluation
  - Reflecting *local scenario*
  - Regardless of the ICER value

- What is a good PE checklist *for listing decision*?
  - Discriminating ability
  - Consistency
  - Transparency
  - Grading
Four review dimensions

1. PIC
2. CEA design
3. Parameters
4. Overall quality

Summary

- Local-based analysis is needed
- A checklist is proposed, aimed to lead the communication and improvement of local CEAs
A Single Technology Appraisal (STA) For Everolimus in advanced renal cell carcinoma (aRCC)

Thank you for your attention!
Table 1 Decision problem for everolimus

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults with advanced renal cell carcinoma whose disease has progressed on or after treatment with vascular endothelial growth factor-targeted therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Everolimus 10 mg/day</td>
</tr>
<tr>
<td>Comparators</td>
<td>Best supportive care alone</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Progression-free survival</td>
</tr>
<tr>
<td></td>
<td>Overall survival</td>
</tr>
<tr>
<td></td>
<td>Tumour response rate</td>
</tr>
<tr>
<td></td>
<td>Health related quality of life and patient-reported outcomes</td>
</tr>
<tr>
<td></td>
<td>Adverse effects of treatment</td>
</tr>
<tr>
<td>Economic evaluation</td>
<td>Cost–utility of everolimus plus best supportive care versus best supportive care alone in adults with advanced renal cell carcinoma whose disease has progressed on or after treatment with vascular endothelial growth factor--targeted therapy. Analysis to be performed from the perspective of the NHS and personal social services.</td>
</tr>
</tbody>
</table>

Evidence on Clinical Effectiveness

- One multinational, double-blinded RCT – RECORD-1:
  - Everolimus + best supportive care (BSC), n = 277
  - Placebo + BSC, n = 139
- Primary endpoint: progression-free survival
- Crossover trial – placebo arm with disease progression documented radiologically were allowed to receive open-label everolimus
Figure 1: Progression free survival everolimus plus BSC versus placebo plus BSC: Final analysis

Figure 2: Overall survival outcomes by treatment at final analysis
Crossover

- 76% in placebo arm crossed over to everolimus
- Adjustment for suspected crossover bias based on inverse probability of censoring weight (IPCW)
- Overall survival - significantly longer mean of 10.1 months vs 5.1 months favouring everolimus (HR 0.55; 0.31 to 0.97)

### Table 19: Base case results presented for the Novartis Cost-Effectiveness model

<table>
<thead>
<tr>
<th>Base Case Cost-Effectiveness results per patient : WITH PAS APPLIED</th>
<th>Everolimus plus BSC*</th>
<th>BSC alone</th>
<th>Incremental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total costs £</td>
<td>25,222</td>
<td>9,517</td>
<td>15,704</td>
</tr>
<tr>
<td>QALYs</td>
<td>0.607</td>
<td>0.302</td>
<td>0.304</td>
</tr>
<tr>
<td>Incremental cost per QALY gained £</td>
<td>51,613</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Base Case Cost-Effectiveness results per patient : WITHOUT PAS APPLIED</th>
<th>Everolimus plus BSC*</th>
<th>BSC alone</th>
<th>Incremental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total costs £</td>
<td>28,178</td>
<td>9,517</td>
<td>18,661</td>
</tr>
<tr>
<td>QALYs</td>
<td>0.607</td>
<td>0.302</td>
<td>0.304</td>
</tr>
<tr>
<td>Incremental cost per QALY gained £</td>
<td>61,330</td>
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</table>

Source: Adapted from Novartis Submission. Tables 7.11 and 7.12, p.137

### Table 20: Base case output based on ITT data analysis using data from the February 2008 cut-off (without application of IPCW)

<table>
<thead>
<tr>
<th>Base Case Cost-Effectiveness results per patient : WITH PAS APPLIED</th>
<th>Everolimus plus BSC*</th>
<th>BSC alone</th>
<th>Incremental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total costs £</td>
<td>25,222</td>
<td>14,758</td>
<td>10,463</td>
</tr>
<tr>
<td>QALYs</td>
<td>0.607</td>
<td>0.492</td>
<td>0.115</td>
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<tr>
<td>Incremental cost per QALY gained £</td>
<td>91,256</td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Base Case Cost-Effectiveness results per patient : WITHOUT PAS APPLIED</th>
<th>Everolimus plus BSC*</th>
<th>BSC alone</th>
<th>Incremental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total costs £</td>
<td>27,328</td>
<td>14,758</td>
<td>12,570</td>
</tr>
<tr>
<td>QALYs</td>
<td>0.607</td>
<td>0.492</td>
<td>0.115</td>
</tr>
<tr>
<td>Incremental cost per QALY gained £</td>
<td>109,627</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1. Based on the NICE decision-making criteria, would you recommend this intervention?
2. Do you consider the NICE decision-making criteria to be sufficient in this case?

Contact Details

- Neil Hawkins
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- Jasmine Pwu
  jasmin.pwu@cde.org.tw

For details of HTA Courses hosted by the University of Glasgow see:
http://www.gla.ac.uk/researchinstitutes/healthwellbeing/research/hehta/