PRESENTING UNCERTAINTY AROUND COST-EFFECTIVENESS ESTIMATES TO DECISION MAKERS: HOW SURE ARE WE?

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Overview of workshop

- Present a brief review of the different methods used to incorporate uncertainty into economic analysis
- Examine issues with current approaches
- Explore alternate approaches to present uncertainty to decision makers
Economic Analysis in Health Care

- Cost-effectiveness analysis often used by decision makers to understand whether an intervention provides good value for money
- Incremental Cost-effectiveness Ratio (ICER) is the metric commonly used to make decisions regarding cost-effectiveness
- Net Health Benefit (NHB) and Net benefit (NB) are alternate metrics that have been proposed
Definitions

- **ICER**
  \[
  \text{ICER} = \frac{\Delta C}{\Delta Q}
  \]
  - C – Cost
  - Q – QALYS

- **NHB**
  \[
  \text{NHB} = \Delta Q - \frac{\Delta C}{V}
  \]
  - V – Societal WTP per QALY

- **NB**
  \[
  \text{NB} = V \times (\Delta Q - \Delta C)
  \]
CEA Decision Criterion

- We will pay at most $V (often $50,000) for each additional QALY
- So we will choose A compared to B (A being more costly and more effective) if
  - $\text{ICER}_{AB} < V$
  - $\text{NHB}_{AB} > 0$
  - $\text{NB}_{AB} > 0$
Estimating ICER

- Effectiveness (efficacy) estimates obtained from clinical trials
  - These data commonly used as input to models that provide QALY estimates
  - May require extrapolation beyond trial period
- Costs obtained from either clinical trials or secondary data sources
  - Long-term costs and cost offsets are modeled
- Uncertainty around the cost and effectiveness estimates result in uncertainty around the ICER
Sources of Uncertainty

- Uncertainty around model inputs (Parameter Uncertainty)
  - Utility associated with health states
  - Cost associated with health states
  - Transition probabilities

- Uncertainty around model structure (Model Uncertainty)
  - Not commonly accounted for
Options for Incorporating Uncertainty

- (Deterministic) Sensitivity Analysis
  - Vary 1 or 2 inputs at a time
  - Scenario analysis
- Confidence Intervals
- Cost-effectiveness Acceptability Curves
- Stochastic league tables
Sensitivity Analysis - Tornado Diagram

Base Case

Efficacy (± 10%)
Drug Cost (± 10%)
Utility (± 10%)
Discount rate (0% - 10%)

ICER
Issues with One/Two-Way Sensitivity Analysis

- No standards to determine which parameter should be varied and how much
- Sensitivity analysis involving more than two parameters difficult to present
- Still, these analyses are easy for Decision Makers to comprehend and can be valuable in some cases
Scenario Analysis

- Best or Worst case scenarios
- Alternate realistic scenarios
  - Accounts for correlations between input parameter values
  - May be easier for decision makers to understand
Confidence Interval

- A 95% confidence interval for a parameter, based on sample data, has the property that 95% of the intervals will contain the true data
  - The interval has 95% probability of containing the true value of the parameter
- A number of different approaches have been described to estimate the confidence interval around the ICER
  - Many methods only described for the two product case
Confidence Interval

ΔC

ΔQ

Expected Value
Estimating the confidence interval around ICER

- Utilizes the distribution of $\Delta C$ and $\Delta Q$
- Methods
  - The box method
  - Taylor’s series
  - Fieller’s method
  - Non-parametric bootstrap
  - Parametric bootstrap
  - Jackknife
- A Comparison of the first four methods found Feiller’s method and non-parametric bootstrap to perform the best [Polsky D. et al. Health Econ. 6:243]
Choice of method to estimate CI

- Are the required assumptions satisfied?
- Is the required data available?
Cost-Effectiveness Acceptability Curves (CEAC)

- Estimate probability that a given intervention will meet the CEA decision criterion, and hence will be the optimal intervention
- CEACs commonly derived using probabilistic sensitivity analysis (PSA)
  - Specify probability distributions for all uncertain input parameters
  - Propagate uncertainty through the model using simulation
  - Derive probability that each intervention is optimal
CEAC

Prob
(ICER >
WTP)

Drug A

WTP per QALY
CEAC – Example for two products
CEAC – Example for multiple products

![Graph showing WTP per QALY for different drugs]
CEAC – Recognized Issues

- Does not contain a decision rule
- The product with the highest probability of being optimal may not be the one with the largest expected net benefit
  - Modification proposed to examine the probability that the product with the largest expected net benefit is the optimal product

Claxton et al. Health Economics 14:339
Fenwick et al. Health Economics 10:779
Stochastic League Tables

- Presents the probability that a specific intervention would be included in the optimal mix of interventions for various levels of resource availability\(^1\)
- Analysis presented for multiple sets of mutually exclusive alternatives

\(^1\)Hutubessy et al. Health Economics 10:473
Application of Uncertainty Analysis in Real World Decision Making
Model

Drug Efficacy

Drug Cost

Other Model Parameters

ICER
Communicating Results to Decision Makers

- A lack of understanding of the calculations of the ICER can lead to
  - Angry rejection
  - Unquestioned acceptance

- It is critical to communicate the model structure, key inputs and assumptions first

- Parameter uncertainty and model uncertainty can then be addressed
Influence Diagram
Corresponding to Model

- Response to Drug
- Disease progression rate from moderate to Severe
- Time spent in Moderate and Severe disease states
- Total QALYs
- Total Cost
Need to communicate

- What are the key inputs that drive the model results?
- What are the data sources for these key inputs?
  - What is the uncertainty around these input parameters?
- How do these key inputs drive the final results?
  - E.g. How does the time spent in each health state change with efficacy assumptions
Tornado Diagram

- Efficacy (± 10%)
- Drug Cost (± 10%)
- Utility (± 10%)
- Discount rate (0% - 10%)

Base Case

ICER
Present Best vs Worst vs most-likely case scenarios

- Based on the range of values for the key input parameters present, Best, Worst, and Most likely scenario analysis
  - Could be included in the tornado diagram
- Need to provide justification for the choice of the parameter values for these scenarios
Questions that the Decision Maker may ask

- Which treatment should I choose
  - Could use the model results for the most likely scenario analysis
- If I choose a particular treatment
  - What is the probability that I chose a treatment that is not optimal
    - Provided by the CEAC
  - What is the magnitude of the loss in welfare in scenarios where my choice is not the optimal one (Downside risk)
Issues with the CEAC

- CEAC as currently used provides only the probability that a given product is the optimal choice for a given value of $V$
- CEAC does not provide information for cases where it is not the optimal product what the loss of net benefit is compared to the optimal product
  - This information may be important to the decision maker
Example

<table>
<thead>
<tr>
<th></th>
<th>Drug A</th>
<th>Drug B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ΔCost(^1)</strong></td>
<td>$12,000</td>
<td>$15,000</td>
</tr>
<tr>
<td><strong>ΔQALY(^1)</strong></td>
<td>1.2</td>
<td>1</td>
</tr>
</tbody>
</table>

- There is a 80% probability that drug A is optimal
- Which Drug should the decision maker choose

\(^1\)Compared to current standard of care
### Example - Continued

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Drug A</th>
<th>Drug B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ΔCost</strong></td>
<td><strong>ΔQALY</strong></td>
<td><strong>ΔCost</strong></td>
</tr>
<tr>
<td>Scenario 1 (20%)</td>
<td>$20,000</td>
<td>-2</td>
</tr>
<tr>
<td>Scenario 2 (80%)</td>
<td>$10,000</td>
<td>2</td>
</tr>
<tr>
<td>Expected</td>
<td>$12,000</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Should the decision maker be provided this information

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1 Compared to current standard of care
Proposed modification to CEAC

- Plot the cumulative distribution of the difference in NB between a given intervention X and the next best intervention
  - In cases where X is not the optimal intervention, this will be the difference in NB between X and the optimal intervention, and will be negative
  - In cases where X is the optimal intervention, this difference will be positive
    - So, the point where the curve intersects the Y-axis provides the probability that X is the optimal intervention (the point on the CEAC)
Modified CEAC

Drug A

$\Delta NB$ vs next best option

$p_1$

$p_2$

$p$

$-1,000$

$0$

$1,000$
Modified CEAC

\[ \Delta NB \] vs next best option
How should the information be used to make a formulary decision

- Should the model results be used to always identify a single optimal intervention?
  - If so, should this be based solely on expected value
- Alternatively, should it be used to identify a set of interventions in cases where interventions cannot be clearly differentiated from a cost-effectiveness perspective
  - Do these models capture all relevant information?
  - How good is the benefit measure?
Use of CI-s in decision making: CE panel report

- Test hypothesis regarding the sign and magnitude of the ICER
- Allow the decision maker to determine how much confidence they should place in the ICER
- Guide decision about future research
An alternative to CEAC?

Choose A
Need Better Information

Choose B

A

B

V

NHB
Conclusions

- It is widely accepted that uncertainty around cost-effectiveness estimates should be presented to decision makers.
- However, whether decision makers can understand and incorporate this information into decision making is not well understood.
- Further examination on how we can most effectively present this information is needed.