Current practices and gaps in benefit-risk assessment: Opportunities for combining MCDA with model-based approaches

Kevin Marsh, PhD
Presenter

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- Director of patient preference and multi-criteria decision analysis (MCDA) teams
- Co-chair of International Society for Pharmacoeconomics and Outcomes Research (ISPOR) MCDA Good Practices Task Force
Objectives

- Illustrate how quantitative BRA is undertaken by industry to demonstrate the value of technologies.
- Illustrate how quantitative BRA can be incorporated into model-based approaches to trial design.
- Identify the challenges, and potential solutions to using quantitative BRA to inform trial design.
Clarification on terminology

- Quantitative BRA = MCDA with preferences elicited by any method (that correspond with the axioms of utility theory)
  - Direct methods e.g. swing weighting
  - Indirect methods (‘stated preference’) e.g. discrete choice experiment

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Option A</th>
<th>Option B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Benefit</td>
<td>5 out of 100 patients achieve a clinical improvement</td>
<td>20 out of 100 patients achieve a clinical improvement</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>2 out of 100 patients have an adverse reaction</td>
<td>10 out of 100 patients have an adverse reaction</td>
</tr>
<tr>
<td>Convenience</td>
<td>No impact on daily life</td>
<td>Significant impact on daily life</td>
</tr>
</tbody>
</table>

Which treatment would you choose? [ ] Option A [X] Option B
When is quantitative BRA useful?

**BRA Throughout the Drug Lifecycle**

**Exploratory clinical development**

1. Which product profiles to invest in
2. Which evidence to gather

**Clinical development**

1. Trial design: sample size, endpoint selection, population

**Launch**

1. Authorisation
2. Reimbursement

**Early-to-mid lifecycle**

1. Keep your product on the market (e.g. PBRARs)
2. Communicate value to decision makers
3. Support prescription decisions

**Loss of Exclusivity**
When is quantitative BRA useful?

**BRA Throughout the Drug Lifecycle**

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- **Loss of Exclusivity**
Approved a weight-loss device with an increased mortality risk.

- Given evidence that a subgroup of patients were willing to accept the increased risk for the benefits.

- Voluntary submission of patient preference data.

- Recommendations for how to collect patient preference data.

- Recommendations for including patient preference information in labeling.

Similar signals from CDER teams:

e.g. Miller and Woodcock, Value in Health, In Press:

“In the near future, CDER [Centre for Drug Evaluation and Research] plans to issue a series of guidances to enable patient groups, and others, to collect and provide structured input on patient preferences in determining benefit-risk trade-offs, the burden of disease, and patient assessment of present treatments….”
Quantitative BRA

Current Regulatory Opinion – FDA (CDRH)


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Does a treatment have a positive BR balance?

Benefit-risk MCDA of Tysabri versus Comparators
What is the probability that a treatment has a positive BR balance?

**Stochastic Multi-criteria Acceptability Analysis**

$$v(x) = \sum_{k=1}^{n} w_k \cdot v_k(x_k)$$

- Draw weight and performance samples, and in each iteration:
  1. Calculate $v(x)$ for each treatment
  2. Rank treatments in descending order according to $v(x)$

- Then, estimate rank probabilities as shares of iterations in which the treatment obtained the rank
What is the probability that a treatment has a positive BR balance?

**Stochastic Multi-criteria Acceptability Analysis**
If a measure of overall benefit for the comparison of interventions is to be determined [...] procedures for multi-criteria decision-making or determining preferences can be applied……the analytic hierarchy process (AHP) and the conjoint analysis (CA)
qBRA in HTA

*Is a treatment on the efficiency frontier?*

Combined with performance data to estimate aggregate benefit

<table>
<thead>
<tr>
<th>Patient-relevant outcome measure</th>
<th>Group priority Professionals (position in rank order)</th>
<th>Group priority Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>0.061 (5)</td>
<td>0.324</td>
</tr>
<tr>
<td>Improvement of cognitive function</td>
<td>0.062 (4)</td>
<td>0.125</td>
</tr>
<tr>
<td>Reduction of anxiety</td>
<td>0.054 (6)</td>
<td>0.118</td>
</tr>
<tr>
<td>Improvement of social function</td>
<td>0.090 (3)</td>
<td>0.107</td>
</tr>
<tr>
<td>Avoidance of relapse</td>
<td>0.144 (2)</td>
<td>0.091</td>
</tr>
<tr>
<td>Remission</td>
<td>0.475 (1)</td>
<td>0.085</td>
</tr>
<tr>
<td>Reduction of pain</td>
<td>0.033 (7)</td>
<td>0.054</td>
</tr>
<tr>
<td>No other serious adverse events</td>
<td>0.029 (8)</td>
<td>0.039</td>
</tr>
<tr>
<td>No (attempted) suicide</td>
<td>0.022 (9)</td>
<td>0.026</td>
</tr>
<tr>
<td>No other adverse events</td>
<td>0.020 (10)</td>
<td>0.023</td>
</tr>
<tr>
<td>No sexual dysfunction</td>
<td>0.007 (11)</td>
<td>0.007</td>
</tr>
</tbody>
</table>
qBRA in HTA

What is the probability that a treatment is on the efficiency frontier?
When is quantitative BRA useful?

**BRA Throughout the Drug Lifecycle**

- **Exploratory clinical development**
  - 1. Which product profiles to invest in
  - 2. Which evidence to gather

- **Clinical development**
  - 1. Trial design: sample size, endpoint selection, population

- **Launch**
  - 1. Authorisation
  - 2. Reimbursement

- **Early-to-mid lifecycle**
  - 1. Keep your product on the market (e.g. PBRARs)
  - 2. Communicate value to decision makers
  - 3. Support prescription decisions

**Loss of Exclusivity**
qBRA to support trial design

An input into trial simulation

- Objective:
  - Understand the likely impact of trial design scenarios
  - Lower development costs, improve the chance of ‘success’

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Dose</th>
<th>Population</th>
<th>Etc....</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strategy A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strategy B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strategy C</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
qBRA to support trial design
An input into trial simulation
qBRA to support trial design

An input into trial simulation

1. BR balance
2. Probability endpoint profile preferred by patients

Strategy A
Strategy B
Strategy C

Trial simulation
Endpoint A
Endpoint B
Endpoint C

Utility model

PoS A
€ A
PoS B
€ B
PoS C
€ C

Evaluation criteria
Trial outputs
Strategy
**qBRA to support trial design**

*Illustrative outputs*

<table>
<thead>
<tr>
<th>Strategy</th>
<th>€m</th>
<th>Benefit-risk (BR)</th>
<th>Value for money (£/BR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>110</td>
<td>0.6</td>
<td>183</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>150</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>130</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>150</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Graph 1:**
- Y-axis: Benefit-risk
- X-axis: Strategy
- Points for each strategy representing Benefit-risk values.

**Graph 2:**
- Vertical bars for each strategy
- Different colors for each rank
- Y-axis: Percentage
- X-axis: Strategy
- Ranks 1 to 6 distinguished by color.
qBRA to support trial design

An input into trial simulation

- Strategy
- Trial outputs
- Evaluation criteria

Different perspectives
- Internal
- Reimbursement

MCDA

Strategy A ➔ Endpoint A ➔ PoS A ➔ € A
Strategy B ➔ Endpoint B ➔ PoS B ➔ € B
Strategy C ➔ Endpoint C ➔ PoS C ➔ € C
Miller and Woodcock (CDER staff), Value in Health, In Press:

“In the near future, CDER plans to issue a series of guidances to enable patient groups, and others, to collect and provide structured input on patient preferences in determining benefit-risk trade-offs, the burden of disease, and patient assessment of present treatments. This input will be used to inform subsequent CDER guidances on ensuring that the structure and assessment of clinical trials are meaningful to patients…”
qBRA to support trial design

An input into trial simulation – FDA’s view

FDA with (i) Medical Devices Innovation Consortium, and (ii) Michael J Fox Foundation

“Collaboration to Move Clinical Trials from Generic p-value of 0.05 to Therapy-Specific Patient Values”

Demonstrate “methods to use Patient Preference Research as an explicit means to set significance levels in clinical trial design can transform the way FDA approves medical devices”.
## Challenges implementing qBRA earlier

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncertainty in performance ranges</td>
<td>Use experts to specify likely ranges</td>
</tr>
<tr>
<td>Longer list of attributes</td>
<td>Elicitation method (e.g. swing weighting)</td>
</tr>
<tr>
<td>Preference method</td>
<td>Good practice is still a work in progress E.g. IMI PREFER</td>
</tr>
<tr>
<td>Recruitment</td>
<td>Depends on the disease area/ perspective</td>
</tr>
</tbody>
</table>
Thank you

Questions?

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