Workshop: Eliciting Formal Patient Preferences for Assessing Benefits and Risks of Medicines

Eliciting Formal Patient Preferences for Assessing Benefits and Risks of Medicines

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Disclaimers

The processes described and conclusions drawn from the work presented herein relate solely to the testing of methodologies and representations for the evaluation of benefit and risk of medicines. This report neither replaces nor is intended to replace or comment on any regulatory decisions made by national regulatory agencies, nor the European Medicines Agency. The views expressed herein represent those of the presenter and do not necessarily represent the views or practices of the presenter’s employer or any other party.
Learning objectives

- To understand how formal elicitation processes can help contribute to benefit-risk decision-making in medicine
- To understand how changes in patients’ preference can affect benefit-risk balance
- To understand potential issues associated with using benefit-risk assessment and elicitation methodologies

Outline

- Introduction to patient-centred decision-making
- Motivating case studies
- Making decisions under uncertainty
- Elicitation methods
- Interpretation and communication
**Introduction to PATIENT-CENTRED DECISION-MAKING**

**Patients**
- Make decisions for themselves

**Healthcare providers**
- Make decisions based on prescribing lists

**NICE**
- Makes decisions on cost-effectiveness

**EMA/MHRA etc.**
- Makes decisions on quality, safety, efficacy and benefit-risk balance to individuals and public health

**Pharmaceutical companies**
- Makes decisions on what to develop for which licenses to apply
MOTIVATING CASE STUDIES

- Rimonabant for weight loss
- Natalizumab for relapsing remitting multiple sclerosis

Rimonabant case study

It is an interesting case study because: Despite some benefits in patients, risk of psychiatric disorders emerged post-marketing, resulting first in label changes and then voluntary withdrawal in the EU.

**Drug of interest**  Rimonabant

**Indication**  Weight loss in obese and overweight patients with co-morbidities in adults (>18y)

**Severe side effect**  Increased risk of psychiatric disorders

**Regulatory history**  2006 Approved in June
                      2009 Voluntary withdrawal in January by the MAH
Rimonabant: Value tree

Benefit-risk balance comparing rimonabant to placebo

- Benefit
  - Achieved 10% weight loss
  - Change in HDL Cholesterol

- Risk
  - Cardiovascular disorders
  - Psychiatric disorders
  - Gastrointestinal disorders

- Number of people who achieved at least 10% weight loss at 1 year
- Physician's view on the HDL cholesterol levels
- Number of people who died from cardiovascular events
- Number of people who experienced depression
- Number of people who experienced diarrhoea or constipation

Natalizumab case study

It is an interesting case study because: It is an effective treatment for a serious disease, with a rare but very serious side effect. License suspended in the US but then reintroduced due partly to patient pressure.

- Drug of interest: Natalizumab
- Indication: Relapsing remitting multiple sclerosis
- Severe side effect: Progressive Multifocal Leukoencephalopathy (PML)
- Regulatory history:
  - 2004 Approved in the US
  - 2005 License suspended in the US
  - 2006 Re-introduced because of patient demand in the US and approved in the EU
  - 2009 CHMP reassessed the PML risk and continued approval
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**Natalizumab: Value tree**

- **Benefits**
  - Reduction in relapse rate
  - Slowdown in disability progression

- **Risks**
  - PML
  - Reactivation of serious herpes viral infections
  - Seizures
  - Abortion or congenital abnormalities
  - Transaminase elevation
  - Infusion or injection site reactions
  - Hypersensitivity reactions
  - Flu-like reactions

- **Benefit-risk balance**
  - Administration
  - Serious side effects
  - Mild side effects

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**Shahrul Mt-Isa**

- The sources and role of uncertainty in decision-making
- A multi-criteria analysis approach to handle uncertainties

**MAKING DECISIONS UNDER UNCERTAINTY**
The flaw of averages

"Plans based on average assumptions are wrong on average!"

And What to Do About It

http://flawofaverages.com/

Methodology requirements

- Most multiple criteria methods for benefit-risk assessment require:
  - Favourable (benefit) and unfavourable (risk) effects data
    - From clinical trials, post-marketing surveillance, epidemiological studies
  - Preference data
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Scoring and weighting

- **Outcome:** Achieved 10% weight loss
- **Measure:** 40% (range 24% - 59%)
- **Value (measure):** 50% (range 29% - 74%)
- **Weight space:** 57% (range 21% - 100%)

**BR Contribution:** 29% (range 9% - 68%)

Central (typical, average) weights

- Preference-free model
- Understand what kind of weights favour certain alternatives
- No clinical significance

Typical weight assigned on each criteria when respective drug achieved first rank

*Note: Simplified CW vectors with all risk criteria collapsed at higher level*
Distributions of utilities

- Non-missing weights model elicited from study team
- Drugs
  - Placebo
  - Orlistat
  - Sibutramine
  - Rimonabant

Performance ranking

- Non-missing weights model
- Drugs
  - Placebo
  - Orlistat
  - Sibutramine
  - Rimonabant
- Interactive version allows own weights

Direct preference elicitation

- Simple
- Unstructured
- May result in inconsistency
- Lack transparency

Kimberley Hockley

- Swing-weighting
- MACBETH
- Analytical Hierarchy Process (AHP)
- Discrete Choice Experiment (DCE)

ELICITATION METHODS
Perception on benefit-risk of medicines

Swing-weighting

For each outcome category

1. Rank outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>PML</td>
<td>1</td>
</tr>
<tr>
<td>Reactivation of serious herpes viral infections</td>
<td>2</td>
</tr>
<tr>
<td>Seizures</td>
<td>3</td>
</tr>
<tr>
<td>Abortion or congenital abnormalities</td>
<td>4</td>
</tr>
</tbody>
</table>

2. Relative importance

How much more important it is to avoid the top-ranked event compared to the others?

- PML
- Reactivation of serious herpes viral infections
- Seizures
- Abortion or congenital abnormalities
Swing-weighting
The top ranked outcome in each category is carried up the tree

- Move bottom-up through the tree and compare the top-ranked outcomes from each category
- Finally, the top-ranked benefit is compared to the top-ranked risk
- The individual weights for each outcome can then be calculated

MACBETH

- **Step 1**: Qualitatively assess how much more attractive it is to move from worst to best for outcome $i$ vs. moving from worst to best for outcome $j$ and keeping everything else at the worst measure (Do this for each pair of criteria)
- **Step 2**: Check consistency of answers
- **Step 3**: Compute initial guess at weights with optimisation
- **Step 4**: Refine weights while maintaining consistency
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**MACBETH**

- Weights are elicited by making pairwise comparisons between criteria
- "How much more important is outcome $i$ vs. outcome $j$?"
- Must provide number from 1 to 9 on relative scale
- Weight is calculated by finding the dominant eigenvector of the corresponding matrix
- Value functions are computed in a similar manner (do not necessarily come from linear function)
- No consistency check, but rather a score <0.1

**Analytic Hierarchy Process (AHP)**

- Weights are elicited by making pairwise comparisons between criteria
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### AHP

<table>
<thead>
<tr>
<th></th>
<th>PML (A)</th>
<th>Reactivation of serious herpes viral infections (B)</th>
<th>Seizures (C)</th>
<th>Abortion or Congenital abnormalities (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PML (A)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reactivation of serious herpes viral infections (B)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures (C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abortion or Congenital abnormalities (D)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Comparative overview of elicitation methods

<table>
<thead>
<tr>
<th></th>
<th>Swing-weighting</th>
<th>MACBETH</th>
<th>AHP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responses</td>
<td>Quantitative</td>
<td>Qualitative</td>
<td>Quantitative</td>
</tr>
<tr>
<td>Questioning format</td>
<td>How much more attractive is a swing in criterion x compared to a swing in criterion y?</td>
<td>How much more attractive is criterion x compared to criterion y?</td>
<td>What is the relative importance of criterion x over criterion y?</td>
</tr>
<tr>
<td>Consistency</td>
<td>N/A</td>
<td>Inconsistencies must be resolved</td>
<td>Computes a consistency score</td>
</tr>
<tr>
<td>Weight calculation</td>
<td>Direct</td>
<td>Linear optimisation (plus tuning)</td>
<td>Principal eigenvector</td>
</tr>
</tbody>
</table>
DCE example: Rimonabant case study

- **Aim:**
  - To evaluate the attractiveness of obesity treatments by observing how people choose between treatments while comparing and trading off specified levels of benefits and risks
  - To apply the results to the benefit-risk profile of rimonabant

- **Method: Discrete choice experiment (DCE)**
  - Respondents are shown a series of hypothetical scenarios that compare two treatments for weight loss, each with a unique benefit and risk profile
  - They select the option that they consider to be most preferable

Example of a DCE choice set

Two treatments for obesity are described in the table below. Please imagine that you have an option of receiving one of the treatments, and consider which one you would prefer to receive.

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Treatment A</th>
<th>Treatment B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician's view on HDL</td>
<td>Mild Improvement</td>
<td>No change</td>
</tr>
<tr>
<td>Cholesterol levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of people who experience a 10% weight loss</td>
<td>10 out of 1000</td>
<td>450 out of 1000</td>
</tr>
<tr>
<td>Risks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of people who experience psychiatric conditions</td>
<td>100 out of 1000</td>
<td>1 out of 1000</td>
</tr>
<tr>
<td>Number of people who experience cardiovascular conditions</td>
<td>1 out of 1000</td>
<td>100 out of 1000</td>
</tr>
<tr>
<td>Number of people who experience gastrointestinal conditions</td>
<td>1 out of 1000</td>
<td>None</td>
</tr>
</tbody>
</table>

*6. After considering them, please answer the following question: Which treatment would you prefer to receive?*
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An application of DCE

- **Identify attributes and assign levels**
  - Attribute: characteristics used to describe treatments
  - Level: measurement units used to describe attributes

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician's view on HDL cholesterol levels</td>
<td>Got worse, No change, Mild improvement, Moderate improvement</td>
</tr>
<tr>
<td>Number of people who experience a 10% weight loss (out of 1000)</td>
<td>10, 150, 300, 450</td>
</tr>
<tr>
<td>Number of people who experience psychiatric conditions (out of 1000)</td>
<td>None, 1, 10, 100</td>
</tr>
<tr>
<td>Number of people who experience cardiovascular conditions (out of 1000)</td>
<td>None, 1, 10, 100</td>
</tr>
<tr>
<td>Number of people who experience gastrointestinal conditions (out of 1000)</td>
<td>None, 1, 10, 100</td>
</tr>
</tbody>
</table>

**Experimental design**: fractional factorial design

Characteristics of respondents

- **Sample**: members of Weight Concern (obesity charity)
- **Questionnaires**:
  - Total: 191
    - 24 incomplete
    - 1 failed consistency
    - 166 included in analysis
- **Gender**:
  - 150 female, 15 male, 1 chose not to disclose
- **Age**:
  - 79% aged 40 and above
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Susan Shepherd

- Communicating complex methods to patients and public
- Misperception and misleading information
- Putting things into perspective and resolving conflicts

INTERPRETATION AND COMMUNICATION

Communicating complex methodologies
**DCE results: preferences (probit model)**

Table shows impact on choice for one unit increment

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Coefficient</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% Weight loss (%)</td>
<td>0.034**</td>
<td>0.030 to 0.039</td>
</tr>
<tr>
<td>Psychiatric disorders (%)</td>
<td>-0.134**</td>
<td>-0.158 to -0.110</td>
</tr>
<tr>
<td>Cardiovascular disorders (%)</td>
<td>-0.097**</td>
<td>-0.114 to -0.080</td>
</tr>
<tr>
<td>Gastrointestinal disorders (%)</td>
<td>-0.035**</td>
<td>-0.053 to -0.018</td>
</tr>
<tr>
<td>Physician’s view on HDL cholesterol level (per level)</td>
<td>0.306**</td>
<td>0.224 to 0.387</td>
</tr>
</tbody>
</table>

* p ≤ 0.05, ** p ≤ 0.001; Log-likelihood = -577.88

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**DCE results: overall interpretation**

We can combine data on how the respondents value the benefits and risks from this analysis with publically available efficacy and safety data for rimonabant using mathematical formulae.

When we do this, rimonabant is preferred over placebo 67.3% of the time.
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DCE results: individual interpretation

Interactive version (Tableau Public)
http://public.tableau.com/views/DCE1/DCE1?:embed=y&:display_count=no

Putting things into perspective
DISCUSSION AND CONCLUSION

Discussions

- How easy or difficult was it to complete the two questions?
  - What did you find easy?
  - What did you find difficult?
- Are the tasks described well and easy to understand?
- How can we improve the exercises?
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Acknowledgements

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Review of methodologies

**Wave 1 Case Studies**

Rimonabant:
- Juhaeri et al., Benefit Risk Wave 1 Case study report Rimonabant, Oct 2011
- Mt-Isa et al., Supplement to Wave 1 Case study report Rimonabant, Oct 2011

Telithromycin:
- Quartey et al., Benefit Risk Wave 1 Case study report Telithromycin, Feb 2012

Efalizumab:
- Micaleff et al., Benefit Risk Wave Case study report Efalizumab, Feb 2013
- Micaleff et al., Supplement 1 to Wave 1 case study report Efalizumab, Feb 2013

Efalizumab:
- Phillips et al., Supplement 2 to Wave 1 case study report Efalizumab, Feb 2013

Natalizumab:
- Nixen et al., Benefit Risk Wave 1 Case study report Natalizumab, May 2013

Review of visualisation methods for representation of benefit risk assessment of medicine

**Wave 1 Case Studies**

Rimonabant:
- Juhaeri et al., Review of visualisation methods for the representation of benefit risk assessment of medication, Feb 2013

Rosiglitazone:
- Phillips et al., Benefit Risk Wave 2 Case study report Rosiglitazone, Feb 2013

Natalizumab:
- Nixon et al., Benefit Risk Wave 2 Case study report Natalizumab, March 2013

Warfarin:
- Hallgreen et al., Benefit Risk Wave 2 Case study report Warfarin, March 2013

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