FROM QUALITATIVE TO FULLY QUANTITATIVE APPROACHES TO BALANCING BENEFITS AND RISKS OF MEDICINAL PRODUCTS FOR DECISION-MAKING

EFSPi/PSI WEBINAR
16\textsuperscript{TH} AND 29\textsuperscript{TH} JUNE 2015

Shahrul Mt-Isa, PhD
• Current decision-making in benefit-risk assessment
• PROTECT Benefit-Risk and resources
• Qualitative to fully quantitative BR decision-making
  – A multi-criteria decision analysis example

• Learning outcomes
  – Why qualitative approaches are less desirable
  – Why more quantitative approaches are more desirable
  – Not
    • How to conduct BR assessment!
Qualitative benefit-risk assessment

Discussing

Voting

No quantitative modelling is used by any regulator anywhere to deal with the massive amount of data – 10GB more or less!
Evidence based medicine decision-making

- Current best evidence
- Individual patients predicaments, rights and preferences
- Clinically relevant research

Evidence based medicine, Sackett et al.

“EBM is the conscientious explicit, and judicious use of current best evidence in making decisions about the care of individual patients” … taking into account… “individual patients predicaments, rights and preferences using best evidence from clinically relevant research.”
Plethora of methodologies in the literature
Welcome to the PROTECT Benefit-Risk Website

PROTECT, the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium, contains a number of work programmes whose goal is to strengthen the monitoring of the benefit-risk balance of medicines in Europe and to enhance early detection and assessment of adverse drug reactions from different data sources.

The evaluation of the balance between benefits and risks of drugs is fundamental to numerous stakeholders including patients, healthcare providers, health technology assessors, regulators and biopharmaceutical companies. Decision-making with regards to benefit-risk assessment is often complex. It is important to ensure transparent, robust and comprehensive methodologies are used, and also that patient and public preferences on benefits and risks feed into the decision-making process.

PROTECT Benefit-Risk Integration and Representation

http://www.protectbenefitriskeu/

@PROTECT_BR
Benefit-risk assessment

- Qualitative
- Partially quantitative
- Fully quantitative
A “dominant” drug example

- **Drug 1**
  - Dominant alternative
  - Outperforms drug 2 in all benefit and risk criteria
  - Greatest benefits and smallest risks
- **Drug 2**
- A rational DM would favour drug 1 vs 2
- **Qualitative**

### Benefits

<table>
<thead>
<tr>
<th></th>
<th>Drug 1</th>
<th>Drug 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in cholesterol</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>20%</td>
<td>18%</td>
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</table>

### Risks

<table>
<thead>
<tr>
<th></th>
<th>Drug 1</th>
<th>Drug 2</th>
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</thead>
<tbody>
<tr>
<td>Transient nausea</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>5%</td>
<td>6%</td>
</tr>
</tbody>
</table>
A not so “dominant” drug example

- No dominant alternative
- Drug 1
  - Less transient nausea
- Drug 3
  - Greater cholesterol reduction
- Implicit weighting of relative importance
- Qualitative

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Drug 1</th>
<th>Drug 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in cholesterol</td>
<td>50%</td>
<td>60%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>20%</td>
<td>20%</td>
</tr>
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</table>

<table>
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<tr>
<th>Risks</th>
<th>Drug 1</th>
<th>Drug 2</th>
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</thead>
<tbody>
<tr>
<td>Transient nausea</td>
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<tr>
<td>Gastric ulcer</td>
<td>5%</td>
<td>5%</td>
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</tbody>
</table>
Narrative to structured BR assessment

“Traditional” benefit-risk communication

- Narrative describing benefits and risks.
- Lacking explicit identification of key benefit and key risk outcomes.
- Limited systematic comparison of active drug vs. comparators for all key benefits and key risks.
- No structured, quantitative summary of all key benefit and key risk outcomes.

Structured benefit-risk leads to communication that is transparent and defensible

- Which key benefits and key risks were considered and why.
- Which comparators were chosen.
- The magnitude of benefit and risk effects.
- Presentation in a graphical/tabular summary together with concise text.
- Written in such a way as to meet the Health Authority reviewer needs and expectations.
Disclaimer

“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 presentation neither replaces nor is intended to replace or comment on any regulatory decisions made by national regulatory agencies, nor the European Medicines Agency.”
Efalizumab (Raptiva®) case study

- Drug approved in 2004 for chronic plaque psoriasis
- Emerging safety issues signalled CHMP to give opinion in Jan 2009 on benefit-risk
- Maintain, vary, suspend or withdraw Marketing Authorisation? It was suspended
- PROTECT Task Force developed quantitative model from regulator’s 2009 perspective

Model source for this project: Hiview3, originally developed at the London School of Economics, now available from Catalyze Ltd, www.catalyze.co.uk

Benefit-risk assessment

- Qualitative
- Partially quantitative
- Fully quantitative
Choose favourable & unfavourable effects

- Select only effects that are relevant to the B-R balance.
- Include patients’ views.
- Agree definitions of all effects with key players.
Benefit-risk assessment

- Qualitative
- Partially quantitative
- Fully quantitative
<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Fixed Upper</th>
<th>Fixed Lower</th>
<th>Units</th>
<th>Efalizumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favourable Effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASI75</td>
<td>Percentage of patients achieving 75% reduction in baseline PASI¹ at week 12.</td>
<td>60.0</td>
<td>0.0</td>
<td>%</td>
<td>29.5</td>
<td>2.7</td>
</tr>
<tr>
<td>PGA</td>
<td>Percentage of patients achieving Physician's Global Assessment² clear/almost clear at week 12.</td>
<td>40.0</td>
<td>0.0</td>
<td>%</td>
<td>295</td>
<td>5.1</td>
</tr>
<tr>
<td>OLS</td>
<td>Percentage of patients with Overall Lesion Severity rating of minimal or clear at FT (day 84).</td>
<td>40.0</td>
<td>0.0</td>
<td>%</td>
<td>32.1</td>
<td>2.9</td>
</tr>
<tr>
<td>DLQI</td>
<td>Dermatology Life Quality Index³. Mean percentage of patients showing an improvement.</td>
<td>10.0</td>
<td>0.0</td>
<td>Change score</td>
<td>5.8</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Unfavourable Effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe Infections</td>
<td>Proportion of patients experiencing infections serious enough to require hospitalisation.</td>
<td>3.00</td>
<td>0.00</td>
<td>%/100ptys</td>
<td>2.83</td>
<td>1.4</td>
</tr>
<tr>
<td>Severe Thrombocytopenia</td>
<td>Number of cases exhibiting severe (grade 3 and above) thrombocytopenia⁴.</td>
<td>10</td>
<td>0</td>
<td>number</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Interstitial Lung Disease</td>
<td>Number of cases of interstitial lung disease.</td>
<td>20</td>
<td>0</td>
<td>number</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Haemolytic anemia</td>
<td>Number of cases of haemolytic anemia.</td>
<td>25</td>
<td>0</td>
<td>number</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>PML</td>
<td>Number of cases of progressive multifocal leukoencephalopathy.</td>
<td>5</td>
<td>0</td>
<td>number</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Aseptic Meningitis</td>
<td>Number of cases of aseptic meningitis.</td>
<td>30</td>
<td>0</td>
<td>number</td>
<td>29</td>
<td>0</td>
</tr>
</tbody>
</table>

¹PASI is a measure of the average redness, thickness and scaliness of the lesions (each graded on a 0-4 scale), weighted by the body region and the area affected. PASI range is from 0 to 72.

²PGA is a seven point scale with 7 being clear, 6 almost clear, 5 mild, 4 mild to moderate, 3 moderate, 2 moderately severe and 1 severe psoriasis.

³DLQI is a 10-item quality of life index scored by the patient on a four point scale.

⁴As shown in laboratory test results that indicate a decrease in number of platelets in a blood specimen.
Benefit-risk assessment

- Qualitative
- Partially quantitative
- Fully quantitative
Scoring clinical relevance of data

Linear conversions of data to preference values

FE: PASI 75

UFE: Haemolytic anaemia

Larger percentages achieving PASI 75 are preferred

Smaller numbers of cases are preferred
Scoring clinical relevance of data: PML

Non-linear conversion to clinical preference values

The 0 – 3 difference in number of PML cases is increased in preference value, representing its clinical relevance.
Weighting clinical relevance of effects

- Swing-weight favourable effects
- Swing-weight unfavourable effects
- Swing-weight most favourable against most unfavourable

“How big is the difference, and how much do you care about it?”
Benefit-risk assessment

- Qualitative
- Partially quantitative
- Fully quantitative
Overall, clinical value of efalizumab is greater than the placebo. Just three favourable effects & one unfavourable effect account for this difference in clinical value.

<table>
<thead>
<tr>
<th>Model Order</th>
<th>Cum Wt</th>
<th>Diff</th>
<th>Wtd Diff</th>
<th>Sum</th>
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</thead>
<tbody>
<tr>
<td>Physicians’ ratings</td>
<td>PGA</td>
<td>22.4</td>
<td>61</td>
<td>13.7</td>
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<tr>
<td></td>
<td>PASI75</td>
<td>28.0</td>
<td>45</td>
<td>12.5</td>
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<tr>
<td>Patients’ ratings</td>
<td>DLQI</td>
<td>20.4</td>
<td>37</td>
<td>7.6</td>
</tr>
<tr>
<td>Physicians’ ratings</td>
<td>OLS</td>
<td>7.0</td>
<td>75</td>
<td>5.1</td>
</tr>
<tr>
<td>Observational data</td>
<td>ILDs</td>
<td>1.3</td>
<td>-90</td>
<td>-1.2</td>
</tr>
<tr>
<td></td>
<td>Aseptic Meningitis</td>
<td>1.3</td>
<td>-97</td>
<td>-1.3</td>
</tr>
<tr>
<td></td>
<td>Serious Infections</td>
<td>2.8</td>
<td>-48</td>
<td>-1.4</td>
</tr>
<tr>
<td></td>
<td>Haemolytic anemia</td>
<td>1.6</td>
<td>-96</td>
<td>-1.5</td>
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<tr>
<td>Observational data</td>
<td>PML</td>
<td>12.9</td>
<td>-95</td>
<td>-12.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100.0</td>
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</tr>
</tbody>
</table>
Aggregate criteria

Let $S_{ij} =$ utility score for criterion $j$ in alternative $i$

$w_j =$ preference weight for criterion $j$

With constraint $\sum_{j=1}^{k} w_j = 1$ for $k$ number of criteria

Then, the overall expected utility for alternative $i$ is

$$U_i = \sum_{j=1}^{k} w_j S_{ij} = w_1 S_{i1} + w_2 S_{i2} + \cdots + w_k S_{ik}$$
Final remarks

- Recommendations for further testing are toolkit to aid methodology selection
  - Complexity and purpose
- There are trade-offs between being too simplistic and just being too incomprehensible
  - Cognitive strain
  - Facilitates thinking
  - Transparency – path to resolving disagreements
- Benefit-risk assessment methodologies are NOT tools that make the decisions
ACKNOWLEDGEMENT
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