Formal benefit-risk assessment approaches in regulatory decision-making of medicinal products

16th Joint Swiss Symposium on Pharmaceutical Medicine
Inselspital Berne, Switzerland
28th November 2012

Presented by:
Shahrul Mt-Isa
Imperial College London
Outline

• Challenges in medical decision-making
• Formal benefit-risk approaches and transparency
• Case study I: Applications of MCDA
• Case study II: Applications of SMAA
Challenges in formalising medical decision-making

- Plethora of quantitative methods for benefit-risk assessment, but not a general consensus
- Priority and requirement of value preferences – regulators, pharma, physicians or patients
- Various elicitation methods – simple elicitation, decision conferencing, discrete choice experiments…
- Do we need stakeholders’ preference a priori, or should we provide tools to allow individual decision-makers to explore their own preferences and the consequent decisions?
- Benefit-risk communication can be difficult to allow informative decision to be made
Decision makers – who are they?

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
The licensing challenge

- The task of regulators (EMA, FDA, DKMA, AEMPS, NoMA, Swissmedic etc.) is to make a good and defensible decisions on which medicines should receive a license for which indications, based on the available evidence of risks and benefits.
- It is increasingly important to be able to justify and explain these decisions to patients and other stakeholders.
- Can more formal approaches of decision-making, and especially more modern methods of graphical display help regulators do these better?
Benefit-risk initiatives

- EMA Benefit-Risk methodology project
- PhRMA BRAT Framework and UMBRA Initiative
- ISPOR Risk-Benefit Management Working Group
- Consortium on Benefit-Risk Assessment (COBRA)
- European Federation of Statisticians in Pharmaceutical Industry (EFSPSI) Benefit-Risk SIG
- IMI-PROTECT Benefit-Risk Integration and Representation Project
PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium) is led by the EMA with 31 public and private partners, 2009-2014 (www.imi-protect.eu)

Benefit-Risk Integration and Representation Charter (BRIR)

- **Scope**
  - Submission and post-approval, while recognising the relevance of pre-approval B-R assessment
  - individual and population-based decision making
  - the perspectives of patients, physicians, regulators and other stakeholders such as societal views needed for HTA
  - possible interdependencies with other PROTECT Work Packages as well as other relevant external initiatives.

- Review and selection of methodologies and of visualisation methods
- Choice and implementation of case studies
- Visualisation and communication (publications)
# PROTECT BRIR (membership)

<table>
<thead>
<tr>
<th>Public</th>
<th>Private</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imperial College (co-leader)</td>
<td>Merck KGaA (co-leader)</td>
</tr>
<tr>
<td>EMA</td>
<td>AMGEN</td>
</tr>
<tr>
<td>DKMA</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>AEMPS</td>
<td>Bayer</td>
</tr>
<tr>
<td>MHRA</td>
<td>GSK</td>
</tr>
<tr>
<td>Mario Negri Institute</td>
<td>Lilly</td>
</tr>
<tr>
<td>GPRD</td>
<td>Novartis</td>
</tr>
<tr>
<td>LA-SER</td>
<td>Novo Nordisk</td>
</tr>
<tr>
<td>IAPO</td>
<td>Pfizer</td>
</tr>
<tr>
<td></td>
<td>Roche</td>
</tr>
<tr>
<td></td>
<td>Sanofi-Aventis</td>
</tr>
<tr>
<td></td>
<td>Takeda</td>
</tr>
</tbody>
</table>
Outline

- Challenges in medical decision-making
- Formal benefit-risk approaches and transparency
- Case study I: Applications of MCDA
- Case study II: Applications of SMAA
Classifications of approaches

- Benefit-risk assessment framework
  - PROACT-URL
  - ASF
  - BRAT
  - CMR-CASS
  - FDA
  - BRF
  - Descriptive framework
  - Non-quantitative

- Quantitative framework
  - BLRA
  - NCB
  - Decision tree
  - MDP
  - MCDA
  - SMAA
  - SBRAM
  - CUI
  - DI

- Metric indices for B-R assessment
  - NNT
  - NNH
  - AE-NNT
  - RV-NNH
  - Impact numbers
  - MCE
  - RV-MCE
  - MAR
  - NEAR
  - Threshold indices

- Health indices
  - QALY
  - DALY
  - HALE
  - Q-TWiST

- Trade-off indices
  - UT-NNT
  - INHB
  - BRR
  - GBR
  - Principle of three
  - TURBO
  - Beckmann Model

- Estimation techniques
  - DAGs
  - PSM
  - CPM
  - ITC
  - MTC
  - CDS

- Main categories
  - Utility survey techniques
  - Non-quantitative
**PrOACT-URL Framework**

- **Problem**
- **Objective**
- **Alternatives**
- **Consequences**
- **Trade-off**
- **Uncertainty**
- **Risk tolerance**
- **Linked decisions**

- A generic framework to structure the decision problem
- Divide into 8 steps
- Effects table
- Emphasis on uncertainty via sensitivity analysis
BRAT Framework

1. Define decision context
2. Identify outcomes
3. Identify data sources
4. Customise framework
5. Assess outcome importance
6. Display & interpret key B-R metrics

- A framework to assist benefit-risk assessment and communication
- Divide into 6 steps
- Source table
- Emphasis on uncertainty in the confidence intervals when presenting results
Outline

- Challenges in medical decision-making
- Formal benefit-risk approaches and transparency
- Case study I: Applications of MCDA
- Case study II: Applications of SMAA
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.”
Brief on MCDA

- Deals with multiple conflicting criteria
- MAUT with requisite criteria
- Requires utilities, probabilities, weights
- Governed by PrOACT-URL for structure and transparency
- Deterministic analysis
# Natalizumab case study

<table>
<thead>
<tr>
<th>Active drug</th>
<th>Natalizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Relapsing remitting multiple sclerosis</td>
</tr>
<tr>
<td>Severe side effects</td>
<td>Progressive Multifocal Leukoencephalopathy (PML)</td>
</tr>
<tr>
<td>Regulatory history</td>
<td>2004 Approved</td>
</tr>
<tr>
<td></td>
<td>2005 License withdrawn</td>
</tr>
<tr>
<td></td>
<td>2006 Re-introduced because of patient demand</td>
</tr>
<tr>
<td></td>
<td>2009 CHMP reassessed the PML risk and continue approval</td>
</tr>
<tr>
<td>Data source</td>
<td>EPARs</td>
</tr>
<tr>
<td>Comparators</td>
<td>Placebo, interferon $\beta$-1a, glatiramer acetate</td>
</tr>
</tbody>
</table>
Natalizumab: Value tree for MCDA
Natalizumab: Weighted utility

Outcome: Disability Progression

Measure = 11%

Value(measure) = 0.89

Elicited Weight = 5%

BR Contribution = 0.045
Natalizumab: Expected utility

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

$$U_i = \sum_{j=1}^{k} w_j S_{ij} = w_1 S_{i1} + w_2 S_{i2} + \cdots + w_k S_{ik}$$
Natalizumab: Weighted Scores
Contribution of each outcome for Natalizumab vs. placebo

- The Benefit-risk is the product of the weight and the value.
- Most of the Benefit-risk contribution is coming from prevention of relapses.
- Infusion reactions are the worst risk.
**Natalizumab: Criteria contribution**

Waterfall plot for Natalizumab vs. placebo

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Reduction in relapse rate</th>
<th>Slowdown in disability progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>Ease of administration</td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td>Seizures</td>
<td>Flu-like reactions</td>
</tr>
<tr>
<td></td>
<td>Congenital abnormalities</td>
<td>Reactivation of serious herpes viral infections</td>
</tr>
<tr>
<td></td>
<td>Infusion reactions/injection reactions</td>
<td>Hypersensitivity Reactions</td>
</tr>
<tr>
<td></td>
<td>PML</td>
<td>Transaminases elevation</td>
</tr>
</tbody>
</table>

![Waterfall plot](http://public.tableausoftware.com/views/T_Waterfall/WaterfallRisk)

- Like a horizontal bar chart, except that the end of the previous bar determines the start of the next bar.
- End of the last bar gives the overall benefit-risk.
- Brown = positive BR; Orange = negative BR; Purple = overall
Outline

• Challenges in medical decision-making
• Formal benefit-risk approaches and transparency
• Case study I: Applications of MCDA
• Case study II: Applications of SMAA
Brief on SMAA

- Similar to MCDA (MAUT)
- Requires utilities, probabilities, weights
- Allows uncertainty and missing weights
- There is no formal framework but could be used with PrOACT-URL or BRAT
- Stochastic analysis
## Rimonabant case study

<table>
<thead>
<tr>
<th><strong>Active drug</strong></th>
<th>Rimonabant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Weight loss in obese and overweight patients with co-morbidities in adults (&gt;18y)</td>
</tr>
<tr>
<td><strong>Severe side effect</strong></td>
<td>Increased risk of depression</td>
</tr>
</tbody>
</table>
| **Regulatory history**     | 2006 Approved in June  
                               | 2009 Voluntary withdrawal in January |
| **Data source**            | EPAR  
                               | Published clinical trials |
| **Comparator**             | Placebo, orlistat, sibutramine |
Rimonabant: Value tree for SMAA
SMAA (rimonabant): Weighted utility

Outcome: Achieved 10% weight loss

Measure: 40% (range 24% - 59%)

Value(measure): 50% (range 29% - 74%)

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

Weight space: 57% (range 21% - 100%)
SMAA: Rank acceptability index

Let $f_X(\xi) = \text{density function on the space of all consequence } X$

$f_W(w) = \text{density function of weight space } W$

$W_i^1(\xi) = \text{alternative } i \text{ favourable weight space}$

For $X \subset R^{i \times j} \ (i \text{ alternatives and } j \text{ criteria}) \text{ and } w \in W_i^1(\xi)$

Then the probability of alternative $i$ ranked first is

$$b_i^1 = \int_{\xi \in X} f_X(\xi) \int_{w \in W_i^1(\xi)} f_W(w) \, dw \, d\xi$$
SMAA: Calculating central weight

The expected centre of gravity for $W_i^1(\xi)$ is

$$w_i^c = \frac{1}{b_i^1} \int_{\xi \in X} f_X(\xi) \int_{w \in W_i^1(\xi)} wf(w) dw d\xi$$

... which determines the best weight space for alternative $i$
Rimonabant: Distributions of utilities

- Non-missing weights model
- Drugs
  - Placebo
  - Orlistat
  - Sibutramine
  - Rimonabant
Rimonabant: Rank probabilities

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

http://public.tableausoftware.com/views/Finalwave2dashboard-fullrangeweight/Dashboardutilitydensity?:embed=y
Why do we need them?

- Frameworks ensure transparency and facilitate discussion
- Benefits and risks are placed on common scales for direct and meaningful trade-off
- Stakeholders’ value preferences can be incorporated leading to more relevant decisions
- Very few “average” patients – uncertainty should be addressed, B-R balance should be customised

Warning: Formal methodologies can only support decision-making, not make the decisions
Acknowledgements

- The research leading to these results was conducted as part of the PROTECT consortium (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, www.imi-protect.eu) which is a public-private partnership coordinated by the European Medicines Agency.

- The PROTECT project has received support from the Innovative Medicine Initiative Joint Undertaking (www.imi.europa.eu) under Grant Agreement n° 115004, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.