Communication of Benefits and Risks of Treatments for Decision-Making

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Outline

- Evidence-based medical decision-making
- Benefits and risks in decision-making: RITUXILUP example
- IMI-PROTECT and WP5
- Natalizumab case study
- Benefits and risks of quantitative benefit-risk modelling
“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.”

Sackett et al, 1996
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
Should we formalise decision-making at all?
Which quantitative approach(es) to use?
Whose value preferences take priority – regulators, pharma, physicians or patients?
How do we find these preferences – 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?
How do we communicate benefits and risks?
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Benefits and risks in decision-making

• Treatment decisions are rarely about one endpoint, but balancing benefits and risks

• eg RITUXILUP study: RCT of Rituximab vs standard treatment (steroids) for lupus nephritis (funded by Arthritis Research UK)

• Steroids are associated with many dangerous and unpleasant side effects

• Expect similar efficacy from rituximab, but a significant safety benefit
Safety results might be (say):

- 20 out of 100 patients will experience SAEs on either treatment
- 20 out of 100 patients will be prevented from experiencing SAEs by taking the study drug
- 60 out of 100 patients will not experience SAEs

- Therefore in terms of efficacy, the trial only has to show non-inferiority to standard treatment in order to achieve better B-R balance
- What about more complex problems – more endpoints, difficult trade-offs, etc?
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The IMI-PROTECT

- PROTECT\(^1\) (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium)

- “Improving and strengthening the monitoring of the benefit/risk of medicines marketed in the EU” including graphical representation of risk-benefit led by EMA with 31 public and private partners, 2009-2014 (www.imi-protect.eu)

\(^1\) PROTECT is receiving funding from the European Community’s Seventh Framework Programme (F7/2007-2013) for the Innovative Medicine Initiative (www.imi.europa.eu)
Objectives:

- To assess and test methodologies for the benefit-risk assessment of medicines
- To develop tools for the visualisation of benefits and risks of medicinal products

- Individual and population-based decision making
- Perspectives of patients, healthcare prescribers, regulatory agencies and drug manufacturers
- From post-approval through lifecycle of products
Methodologies available (and tested)

All B-R assessment approaches

Benefit-risk assessment framework

Descriptive framework

Quantitative framework

Threshold indices

Health indices

Trade-off indices

Approaches excluded and not appraised

Metric indices for B-R assessment

Estimation techniques

Utility survey techniques

Legend:

Main categories

Sub-categories

PrOACT-URL Framework

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

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

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

Decision & communication of B-R assessment
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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.”
Quantitative B-R: MCDA

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

<table>
<thead>
<tr>
<th>Drug of interest</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>
</tbody>
</table>
| 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 |
| Data source      | EPARs |
| Comparators      | Placebo, interferon $\beta$-1a, glatiramer acetate |
Natalizumab: value tree

Benefits

- Relapse
  - 2-year relapse rate
- Disability Progression
  - % progressing in 2yrs
- Convenience
  - Frequency and route of administration
Natalizumab: value tree

- **Risks**
  - Infection
    - Herpes
    - PML
  - Reproductive
    - Congenital abnormalities
  - Liver Toxicity
    - Transaminases elevation
  - Neurological
    - Seizures
    - Infusion/injection reactions
    - Hypersensitivity reactions
  - Other
    - Flu-like reactions

% with event in 2 years
Natalizumab: Visualizing MTC evidence network

- Natalizumab
  - Direct (Polman 2006, EPAR)
  - Indirect

- Placebo
  - Direct (Johnson 1998)
  - Direct (Jacobs 1996)
  - HR=0.77
  - HR=1.34

- Glatiramer acetate
  - Direct
  - HR=0.77

- Interferon beta-1a
  - Direct
  - HR=1.34
Natalizumab: MCDA weighted utilities analysis
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 site reactions are the worst risk.
Natalizumab: Criteria contribution
Stacked bar chart for natalizumab vs. all other treatments

- Same information shown as a stacked bar chart.
- Positive incremental benefit-risk components above the x-axis and negative ones below.
- Total benefit-risk shown as the dark blue bar.
Natalizumab: Criteria contribution
Waterfall plot for Natalizumab - placebo

- 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.
- Green = positive BR
- Red = negative BR

http://public.tableausoftware.com/views/T_Waterfall/WaterfallRisk
Natalizumab: Bayesian sensitivity analysis
Distribution of overall benefit-risk score

\[ P(\text{natalizumab ranked 1}\text{st}) = 1 \]
Results http://www.imi-protect.eu/results.shtml

Review of methodologies
Mt-Isa et al, Review of methodologies for benefit and risk assessment of medication, May 2013

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 A et al, Supplement 1 to Wave 1 case study report Efalizumab, Feb 2013
Phillips et al, Supplement 2 to Wave 1 case study report Efalizumab, Feb 2013
Natalizumab
Nixon et al, Benefit Risk Wave 1 Case study report Natalizumab, May 2013

Visualisation methods for representation of benefit risk assessment of medicine
Review of methods
Part one
Mt-Isa et al, Review of visualisation methods for the representation of benefit risk assessment of medication, Feb 2013
Part two
Mt-Isa et al, Review of visualisation methods for the representation of benefit risk assessment of medication, April 2013

Wave 2 Case Studies
Rimonabant
Juhaeri et al, Benefit Risk Wave 2 Case study report Rimonabant, Jan 2012
Rosiglitazone
Philips 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
Remarks

- Formally structured benefit-risk assessment can aid with transparency and communication of benefits and risks.
- These methodologies do not make decisions themselves. They support decision-making and are not intended to replace medical expertise.
- Stakeholders such as patients and public involvement may add value and would lead to more clinically relevant decisions.
Outline

• Evidence-based medical decision-making
• IMI-PROTECT
• Motivation and PROTECT Benefit-Risk Project methodology review
• Natalizumab case study: Applications of MCDA
• Benefits and risks of taking this approach
### Benefits and risks of quantitative B-R modelling

#### Benefits
- Puts benefits and risks on same page
- Gives a framework to include patients’ views
- Transparency facilitates discussion
- It’s fun!

#### Risks
- Trade-off between being too simplistic or just incomprehensible
- Can be seen as a ‘black box’
- Pharma want to know what regulators want
Acknowledgments

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Key achievements of PROTECT

Framework for pharmacoepidemiology studies
- Presentations (24)
- Publications (5)
- Reports and Databases (1)

Methods for Signal Detection
- Presentations (14)
- Publications (4)
- Reports and Databases (1)

New Methods for data collection from consumers
- Presentations (3)
- Publications
- Reports and Databases

Benefit- Risk integration and representation
- Presentations (14)
- Publications
- Reports and Databases (14)

Replication studies
- Presentations (1)
- Publications
- Reports and Databases

Training and Communication
- Presentations
- Publications
- Reports and Databases (1)

http://www.imi-protect.eu/results.shtml#