Visualizing Benefit-Risk for Drug Regulations

Basel PhUSE SDE
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Basel, CH

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Decision makers – who are they?

**Patients**
- Make decisions for themselves

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

**Health technology assessors**
- Makes decisions on cost-effectiveness

**Regulators**
- 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 (e.g. EMA, FDA) 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?
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.”

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

<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 effect</td>
<td>Progressive Multifocal Leukoencephalopathy (PML)</td>
</tr>
<tr>
<td>Regulatory history</td>
<td>2004 Approved in the US</td>
</tr>
<tr>
<td></td>
<td>2005 License suspended in the US</td>
</tr>
<tr>
<td></td>
<td>2006 Re-introduced because of patient demand in the US and approved in the EU</td>
</tr>
<tr>
<td></td>
<td>2009 CHMP reassessed the PML risk and continued approval</td>
</tr>
</tbody>
</table>
Recommendation Roadmap

**Planning**
- critical issues
- think & discuss purpose and context
- documentation
- foundations for future analyses and updates

**Evidence gathering and data preparation**
- relevant evidence
- data collection
- data aggregation
- missing/incomplete data

**Exploration**
- relevant evidence
- data collection
- data aggregation
- missing/incomplete data

**Analysis**
- Evaluate data
- Quantify benefits and risks
- Weigh or integrate

**Conclusion and dissemination**
- communicate results/consensus
- any influence on future actions
- transparent audit trail
- ensures "big picture" is not lost

• robustness
• sensitivity
• assumptions and uncertainties
• other consequences
• impact or added value to the RMPs
Recommendation Roadmap

1. Planning
2. Evidence gathering and data preparation
3. Exploration
4. Analysis
5. Conclusion and dissemination
Planning Toolbox

- Useful methodologies include:
  - non-quantitative / descriptive frameworks to organize data e.g. PrOACT-URL and BRAT frameworks

- Preferred visualisation techniques include:
  - tree diagrams and structured tables providing useful means of visualisation
## Planning the Natalizumab case study

<table>
<thead>
<tr>
<th>PrOACT-URL</th>
<th>BRAT</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problem</td>
<td>Define decision context</td>
<td>What is the benefit-risk balance of natalizumab following the occurrence of PML cases?</td>
</tr>
<tr>
<td>Objective</td>
<td>Identify benefit and risk outcomes</td>
<td>Benefits: Reduction in relapse rate, slowdown in disability progression. Risks: PML, reactivation of serious herpes viral infections, seizures, abortion or congenital abnormalities, transaminases elevation, infusion or injection site reactions, hypersensitivity reactions, flu-like reactions</td>
</tr>
<tr>
<td>Alternative</td>
<td>Define the decision context</td>
<td>Interferon beta-1a, glatiramer acetate, placebo. Which option to choose?</td>
</tr>
<tr>
<td>Consequence</td>
<td>Extract source data</td>
<td>Build a data source data table (BRAT) or an effects table (PrOACT-URL)</td>
</tr>
<tr>
<td></td>
<td>Customise framework</td>
<td>If required, repeat step 2 following in regards to available data</td>
</tr>
<tr>
<td>Trade-off</td>
<td>Assess outcome importance</td>
<td></td>
</tr>
<tr>
<td>Uncertainty</td>
<td>Display &amp; interpret key BR metrics</td>
<td>Dealt with in stages 3 (Analysis) and 4 (Exploration)</td>
</tr>
<tr>
<td>Risk tolerance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linked decisions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Value tree: Natalizumab case study

- **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

- **Serious side effects**

- **Mild side effects**

- **Benefit-risk balance**

- **Administration**
Recommendation Roadmap

- **Planning**
- **Evidence gathering and data preparation**
- **Analysis**
- **Exploration**
- **Conclusion and dissemination**
Evidence Gathering and Data Preparation Toolbox

- Useful methodologies include:
  - Indirect/Mixed Treatment Comparison (ITC/MTC)
  - Probabilistic Simulation Method (PSM)

- Preferred visualisation techniques include:
  - Visualisation techniques such as structured and colour-coded tables, and network graphs to enhance the communication of data.
An example of MTC network in the natalizumab case study

- Natalizumab
  - Direct (Polman 2006, EPAR)

- Placebo
  - Direct (Johnson 1998)
  - Direct (Jacobs 1996)

- Glatiramer acetate
  - Indirect

- Interferon beta-1a
  - Indirect
An example of colour-coded tables of data summary

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Outcome</th>
<th>Natalizumab Risk / 1000 pts</th>
<th>Comparator Risk / 1000 pts</th>
<th>Risk Difference (95% CI)/1000 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convenience Benefits</td>
<td>Convenience (weight 0.6%)</td>
<td>-</td>
<td>-</td>
<td>- (-, -)</td>
</tr>
<tr>
<td></td>
<td>Relapse (weight 3.9%)</td>
<td>280</td>
<td>450</td>
<td>-170 (-, -)</td>
</tr>
<tr>
<td></td>
<td>Disability Progression (weight 5.6%)</td>
<td>110</td>
<td>140</td>
<td>-30 (-, -)</td>
</tr>
<tr>
<td>Medical Benefits</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reactivation of serious herpes viral infections (weight 6.7%)</td>
<td>80</td>
<td>70</td>
<td>10 (-26, 45)</td>
</tr>
<tr>
<td></td>
<td>PML (weight 55.9%)</td>
<td>2</td>
<td>0</td>
<td>2 (-, -)</td>
</tr>
<tr>
<td></td>
<td>Transaminases elevation (weight 11.2%)</td>
<td>50</td>
<td>40</td>
<td>10 (-16, 38)</td>
</tr>
<tr>
<td></td>
<td>Congenital abnormalities (weight 5.6%)</td>
<td>-</td>
<td>-</td>
<td>- (-, -)</td>
</tr>
<tr>
<td></td>
<td>Seizures (weight 5.6%)</td>
<td>0</td>
<td>11</td>
<td>-11 (-23, 0)</td>
</tr>
<tr>
<td></td>
<td>Infusion/Injection reactions (weight 2.8%)</td>
<td>236</td>
<td>312</td>
<td>-76 (-, -)</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity reactions (weight 1.1%)</td>
<td>90</td>
<td>40</td>
<td>50 (20, 82)</td>
</tr>
<tr>
<td></td>
<td>Flu-like reactions (weight 1.1%)</td>
<td>399</td>
<td>608</td>
<td>-209 (-320, -98)</td>
</tr>
</tbody>
</table>

Higher for Drug A
Higher for Comparator
Recommendation Roadmap

- Evidence gathering and data preparation
- Planning
- Exploration
- Analysis
- Conclusion and dissemination
Analysis toolbox - methodologies

• Useful methodologies include
  – metric indices which provide numerical representations of benefits and risks e.g. Number Needed to Treat / Number Needed to Harm (NNT/NNH), Impact numbers
  – quantitative frameworks which model benefit-risk trade-off and balance benefits and risks e.g. Multi-Criteria Decision Analysis (MCDA), Stochastic Multi-criteria Acceptability Analysis (SMAA)
  – utility survey techniques which elicit stakeholders’ preference information e.g. Discrete Choice Experiment (DCE)
Analysis toolbox – visualisations

- Preferred visualisation techniques include:
  - visualisation techniques specific for eliciting value preferences e.g. tree diagram, method-specific visualisations such as MACBETH grid, Analytic Hierarchy Process (AHP) table, swing-weighting ‘thermometer’ scale, drop-down list
  - visualisations for presenting analysis results e.g. tables, forest/interval plots for descriptive analyses; ‘Difference display’ (MCDA) and stacked or grouped bar charts for quantitative analyses
MACBETH grid and scale

Consistent judgements

Fine tuning...
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 the 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 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></td>
<td>Congenital abnormalities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reactivation of serious herpes viral infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infusion reactions/injection reactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypersensitivity Reactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PML</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transaminases elevation</td>
</tr>
<tr>
<td>Overall B-R</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

- a horizontal bar chart, except that 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
Recommendation Roadmap

- Evidence gathering and data preparation
- Planning
- Analysis
- Exploration
- Conclusion and dissemination
Exploration toolbox

• Useful methodologies include:
  – ITC/MTC, PSM, SMAA
  – Utility survey techniques e.g. DCE, AHP, Swing-weighting, MACBETH

• Preferred visualisation techniques include:
  – the box, distribution, scatter, and forest/interval plots; tornado diagram; and techniques that are interactive with the user.
Natalizumab: Uncertainty
Tornado plot for Natalizumab vs. placebo

- Clinical parameters uncertain
- So benefit-risk balance is uncertain
- Perform sensitivity analysis
Natalizumab: Bayesian sensitivity analysis
Distribution of overall benefit-risk score

\[
P(\text{natalizumab ranked 1}^{\text{st}}) = 1
\]
Recommendation Roadmap

1. Planning
2. Evidence gathering and data preparation
3. Analysis
4. Exploration
5. Conclusion and dissemination
Stage 5: Conclusion and dissemination

• The point at which a conclusion is reached
• The results and consensus from the BR assessment are communicated to a wider audience
• Explicitly states findings and conclusions that could influence future actions
• Emphasises a transparent audit trail of the whole assessment process i.e. brings everything together and sets the course of action
• Ensures the "big picture" overview is not lost
Other data visualisation initiatives

- https://www.ctspedia.org
- http://www.thedrugsbox.co.uk
- http://www.cirsci.org
- http://www.gapminder.org
- http://understandinguncertainty.org
- http://www.improving-visualisation.org
- http://www.informationisbeautiful.net
- http://flowingdata.com
- http://www.perceptualedge.com
- http://www.guardian.co.uk/news/datablog
Fishing for ideas

http://robslink.com/SAS/Home.htm
http://www.ats.ucla.edu/stat/stata/library/GraphExamples/default.htm
http://www.tableausoftware.com/public/gallery
http://prefuse.org/gallery/
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.
Benefits and risks of quantitative B-R modelling and visual representation

**Benefits**

- Puts benefits and risks on same page
- Gives a framework to include patients’ views
- Transparency facilitates discussion
- Visual representations assist cognition & influence perception
- 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
- Visual representations influence perception
RESOURCES
Acknowledgements

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• 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.
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
# Work Package 5 of PROTECT (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>DHMA</td>
<td>AstraZeneca</td>
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<tr>
<td>MHRA</td>
<td>Bayer</td>
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<tr>
<td>Mario Negri Institute</td>
<td>GSK</td>
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<tr>
<td>GPRD</td>
<td>Lilly</td>
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<tr>
<td>La-SER</td>
<td>Novartis</td>
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<td>IAPO</td>
<td>Novo Nordisk</td>
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<td>Pfizer</td>
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<td></td>
<td>Roche</td>
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<td></td>
<td>Sanofi-Aventis</td>
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<td>Takeda</td>
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</tbody>
</table>
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#
Balancing benefit and risk of medicines: a systematic review and classification of available methodologies†

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5GlaxoSmithKline Research and Development Ltd, Middlesex, UK
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7Genentech, South San Francisco, CA, USA
8Bayer Schering Pharma AG, Berlin, Germany
9Merck KGaA, Geneva, Switzerland


ABSTRACT

Background The need for formal and structured approaches for benefit-risk assessment of medicines is increasing, as is the complexity of the scientific questions addressed before making decisions on the benefit-risk balance of medicines. We systematically collected, appraised and classified available benefit-risk methodologies to facilitate and inform their future use.

Methods A systematic review of publications identified benefit-risk assessment methodologies. Methodologies were appraised on their fundamental principles, features, graphical representations, assessability and accessibility. We created a taxonomy of methodologies to facilitate understanding and choice.

Results We identified 49 methodologies, critically appraised and classified them into four categories: frameworks, metrics, estimation techniques and utility survey techniques. Eight frameworks describe qualitative steps in benefit-risk assessment and eight quantify benefit-risk balance. Nine metric indices include threshold indices to measure either benefit or risk; health indices measure quality-of-life over time; and trade-off indices integrate benefits and risks. Six estimation techniques support benefit-risk modelling and evidence synthesis. Four utility survey techniques elicit robust value preferences from relevant stakeholders to the benefit-risk decisions.

Conclusions Methodologies to help benefit-risk assessments of medicines are diverse and each is associated with different limitations and strengths. There is not a ‘one-size-fits-all’ method, and a combination of methods may be needed for each benefit-risk assessment. The taxonomy introduced herein may guide choice of adequate methodologies. Finally, we recommend 13 of 49 methodologies for further appraisal for use in the real-life benefit-risk assessment of medicines. Copyright © 2014 John Wiley & Sons, Ltd.

KEY WORDS—review; benefit–risk; decision-making; medicines; quantitative; qualitative; framework; pharmacoepidemiology

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  - Kosslyn SM. Graph design for the eye and mind. Oxford University Press; 2006.
References

• Visual design guides:

• Colour choices:
  - The Color Brewer website (http://colorbrewer2.org)
  - J*FLY website (http://jfly.iam.u-tokyo.ac.jp/color)
References

• Reviews: