PROTECT

imi efpia

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

# A Case Study Using the BRAT Framework and Quantitative Methods for Benefit-Risk Assessment

***Christoph Dierig***
*Global Integrated Analysis and Life Cycle Management Statistics, Bayer Pharma*

# 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."

# Acknowledgments


- 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.

# Outline

- Introduction
  - IMI PROTECT
  - Natalizumab Case Study
- In a nutshell: Application of the BRAT Framework
- Quantitative Methods for Benefit-Risk Assessment
  - Generalization of the NNT/NNH concept
  - Multi-Criteria Decision Analysis (MCDA)
- Visualization of Benefit-Risk Assessment
- Conclusions

# IMI (Innovative Medicines Initiative) PROTECT

- PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium)
  - Collaborative European project coordinated by the EMA
  - Multi-national consortium of 32 partners including academics, regulators, and pharmaceutical companies

- Work program 5 (WP5) is focusing on **Benefit-Risk integration and representation**
  - In wave 1, four case studies were performed to evaluate various **frameworks** and **quantitative methods** for benefit-risk assessment

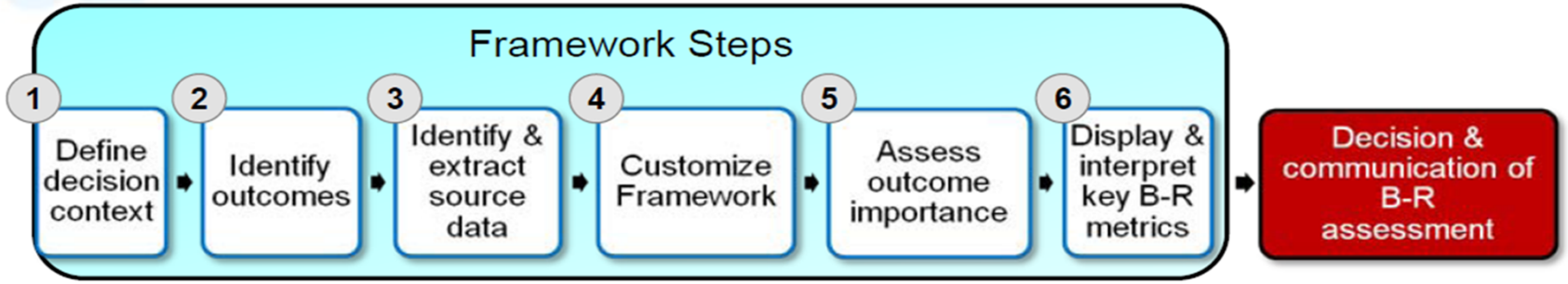
# Natalizumab Case Study - Background

- Natalizumab was approved in 2004 by the FDA for the treatment of relapsing remitting multiple sclerosis (RRMS).
- In 2005 the drug was suspended because of an associated incidence of progressive multifocal leukoencephalopathy (PML), a rare neurological disorder.
- In 2006 it was re-introduced due to patient demand, but with strict risk minimization measures.
- In 2009, due to occurrence of further PML in monotherapy post marketing, the Committee for Medicinal Products for Human Use (CHMP) reassessed the PML risk of Natalizumab and confirmed the current approval.

# In a nutshell: Application of the BRAT Framework

**Benefit Risk Action Team (BRAT) framework**

- Developed by PhRMA (**Ph**armaceutical **R**esearch & **M**anufacturers of **A**merica)
- Structured **6-step approach** for defining the decision context and selecting, organizing, evaluating, and displaying relevant benefit-risk information

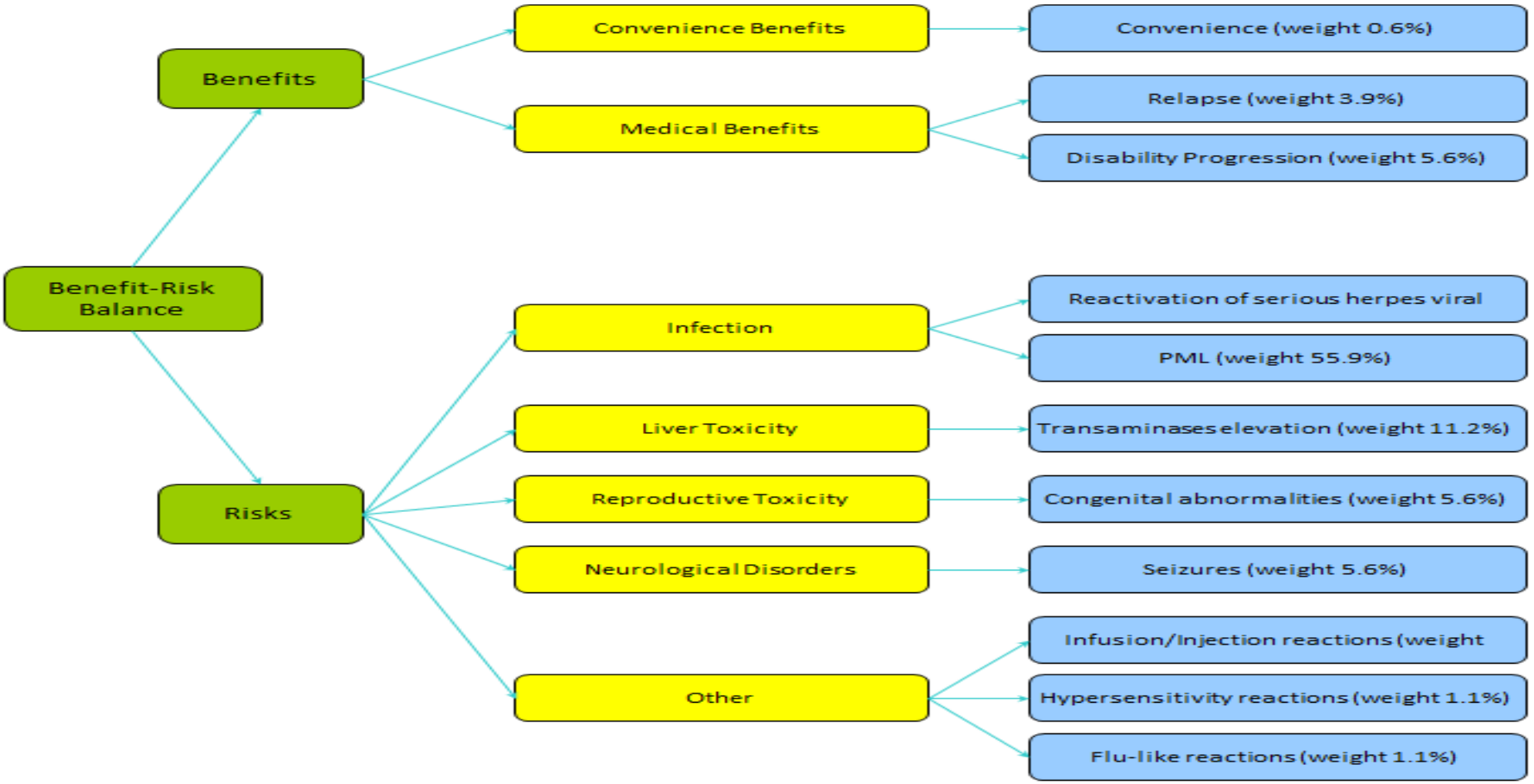



- Process is supported by an EXCEL based tool

# Decision Context of Natalizumab Case Study

- Decision question:
  - Should Natalizumab be given marketing approval at the time of first registration?
  - Should Natalizumab be kept on the market given that increased episodes of PML were observed?
- Indication: Relapsing remitting multiple sclerosis
- Drugs to compare: Natalizumab vs. Placebo (and vs. two active comparators)
- Decision perspective: European Medicines Agency (EMA)
- Time frame: 2 years of treatment

# Identification of Benefit and Risk Outcomes – Value Tree Creation



# Key Benefit-Risk Summary for Natalizumab vs. Placebo

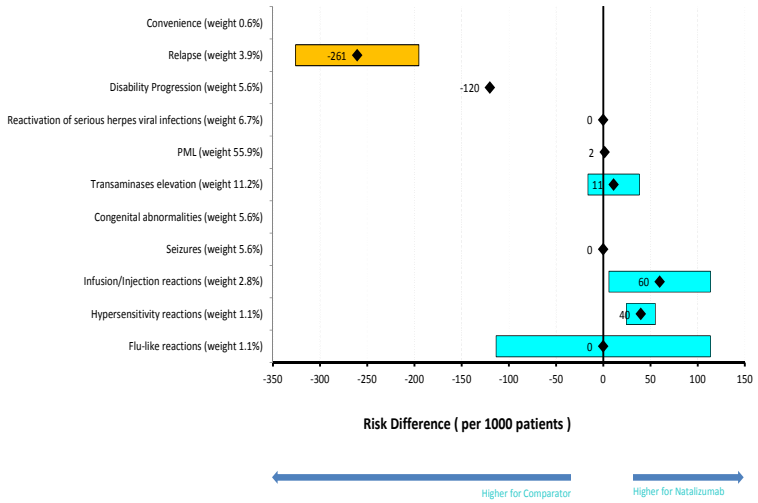
## Key Benefit-Risk Summary Table

| | | Outcome | Natalizumab Risk / 1000 pts | Comparator Risk / 1000 pts | Risk Difference (95% CI)/ 1000 pts | |
|---|---|---|---|---|---|---|
| Benefits | Convenience Benefits | Convenience (weight 0.6%) | - | - | - | (-, -) |
| | Medical Benefits | Relapse (weight 3.9%) | 276 | 537 | -261 | (-326, -195) |
| | | Disability Progression (weight 5.6%) | 110 | 230 | -120 | (-, -) |
| Risks | Infection | Reactivation of serious herpes viral infections (weight 6.7%) | 0 | 0 | 0 | (-, -) |
| | | PML (weight 55.9%) | 2 | 0 | 2 | (-, -) |
| | Liver Toxicity | Transaminases elevation (weight 11.2%) | 49 | 38 | 11 | (-16, 38) |
| | Reproductive Toxicity | Congenital abnormalities (weight 5.6%) | - | - | - | (-, -) |
| | Neurological Disorders | Seizures (weight 5.6%) | 0 | 0 | 0 | (-, -) |
| | Other | Infusion/Injection reactions (weight 2.8%) | 236 | 176 | 60 | (6, 114) |
| | | Hypersensitivity reactions (weight 1.1%) | 40 | 0 | 40 | (25, 55) |
| | | Flu-like reactions (weight 1.1%) | 399 | 399 | 0 | (-114, 114) |

Higher for Natalizumab

Higher for Comparator

## Forest Plot



# Quantitative Methods for B/R Assessment

- How to properly reduce a **complex multi-dimensional problem** to a "simple" **binary decision?**
  - Regulator: to approve the drug (no/yes)
  - Insurance: to pay for the drug (no/yes)
  - Patient: to take the drug (no/yes)

- In the Natalizumab case study two quantitative methods were investigated:
  1. Number Needed to Treat (NNT) – Number Needed to Harm (NNH) approach
  2. Multi-Criteria Decision Analysis (MCDA)

# Definition of NNT and NNH

- **Number Needed to Treat** (NNT) is defined as

$$NNT := \frac{1}{(p_C - p_T)}$$

where $p_C$ and $p_T$ denote the proportion of the disease of interest in the control group and the treatment group, respectively

**"The (average) number of patients to be treated in order to avoid one case of the disease"**

- Similarly, **Number Needed to Harm** (NNH) is defined as

$$NNH := \frac{1}{(q_T - q_C)}$$

# Benefit-Risk Assessment based on NNT / NNH

- Benefit outweighs the risk if

$$\frac{NNT}{NNH} < 1 \quad \left( or\ alternatively : NNT < NNH \right)$$

- **Limitation:** NNT/NNH approach only works in case of
  - one benefit
  - one risk
  - benefit and risk are of comparable severity

# Extension of NNT/NNH concept

- Generalization of NNT/NNH expanding the ideas of Holden (2003) in order to enable
  1. Weighting
     *Note: Holden used utility weights defined as w(.)=(1-utility(.))*
  2. Multiple risks
  3. Multiple benefits

Simple case:

$$\frac{NNT}{NNH} = \frac{\frac{1}{(p_C - p_T)}}{\frac{1}{(q_T - q_C)}}$$

# Extension of NNT/NNH concept

- Generalization of NNT/NNH expanding the ideas of Holden (2003) in order to enable
  1. Weighting
     *Note: Holden used utility weights defined as w(.)=(1-utility(.))*
  2. Multiple risks
  3. Multiple benefits

$$\frac{NNT_w}{NNH_w} := \frac{\frac{1}{\sum_{i=1}^{m}\left(p_{C,i}-p_{T,i}\right)*w\left(AE_i^B\right)}}{\frac{1}{\sum_{i=1}^{k}\left(q_{T,i}-q_{C,i}\right)*w\left(AE_i^R\right)}}$$

# Extension of NNT / NNH concept

- Benefit-Risk Assessment: Compare weighted NNT with weighted NNH where benefit outweighs risk if

$$\frac{NNT_w}{NNH_w} < 1 \qquad (1)$$

Notes:

- Weighted NNH ($NNH_w$) as well as weighted NNT ($NNT_w$) can no longer be interpreted as a “number of patients to be treated in order ….”.
- Formula from previous slide doesn’t look very handy

***Can it be simplified?***

# Extension of NNT / NNH concept

- Rewriting the formula given in (1) results in

$$\sum_{i=1}^{m+k} \left( \left( p_{C,i} - p_{T,i} \right) * w\left( AE(i) \right) \right) > 0$$

  - assuming that the treatment has beneficial events with respect to events AE(i) (i=1,…,m), and detrimental effects with respect to events AE(i) (i=m+1,…,k).
  - $p_{C,1}$,…, $p_{C,m+k}$ and $p_{T,1}$,…, $p_{T,m+k}$ denote the proportions of the events AE(i) (i=1,…, m+k) in the control and the treatment group, respectively

# Extension of NNT / NNH concept - Weighted Net Clinical Benefit

- Rewriting the formula given in (1) results in

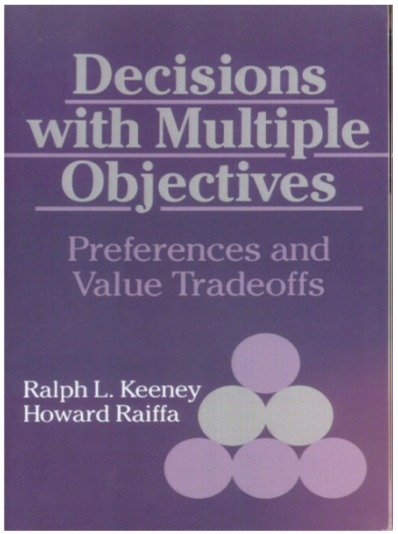
$$\sum_{i=1}^{m+k} \left( \left( p_{C,i} - p_{T,i} \right) * w\left( AE(i) \right) \right) > 0$$

- The formula above is the **weighted** version of the '**Net Clinical Benefit (NCB)**' concept described by Sutton et al. (2005)
- **Natalizumab Case Study**: weighted NCB indicates **positive** benefit-risk balance at initial approval as well as at CHMP reassessment
- **Limitation** of NCB: Benefit and risk criteria need to be measured as proportions (or rates)

***=> Need for methods allowing consideration of categorical and continuous data, too.***

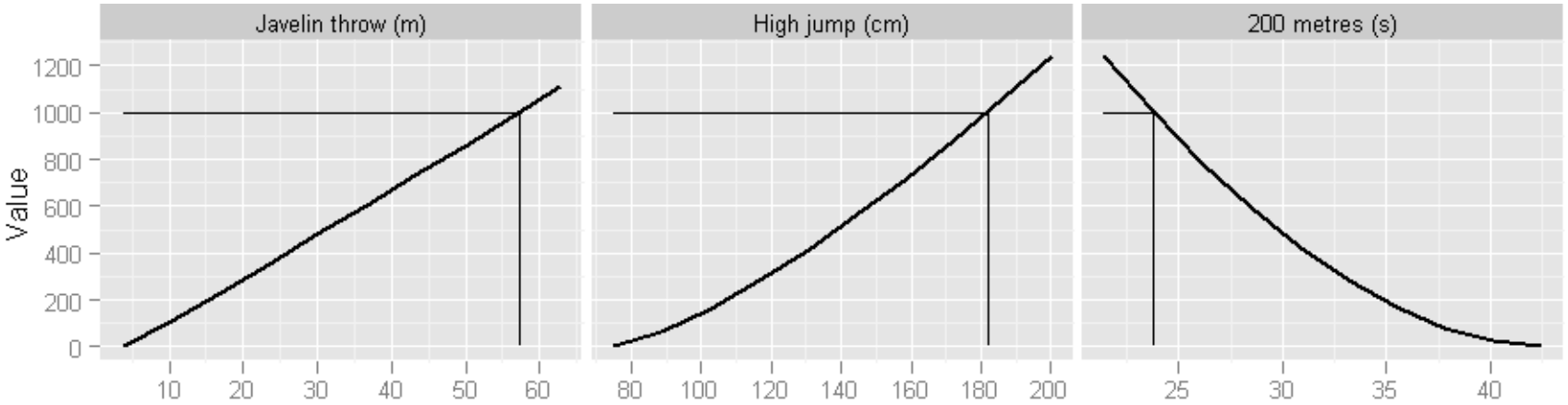
# Multi-Criteria Decision Analysis (MCDA)

- What is MCDA?
  - An extension of decision theory that covers decisions with multiple objectives.
  - A methodology for appraising options on individual, often conflicting criteria, and combining them into one overall appraisal.



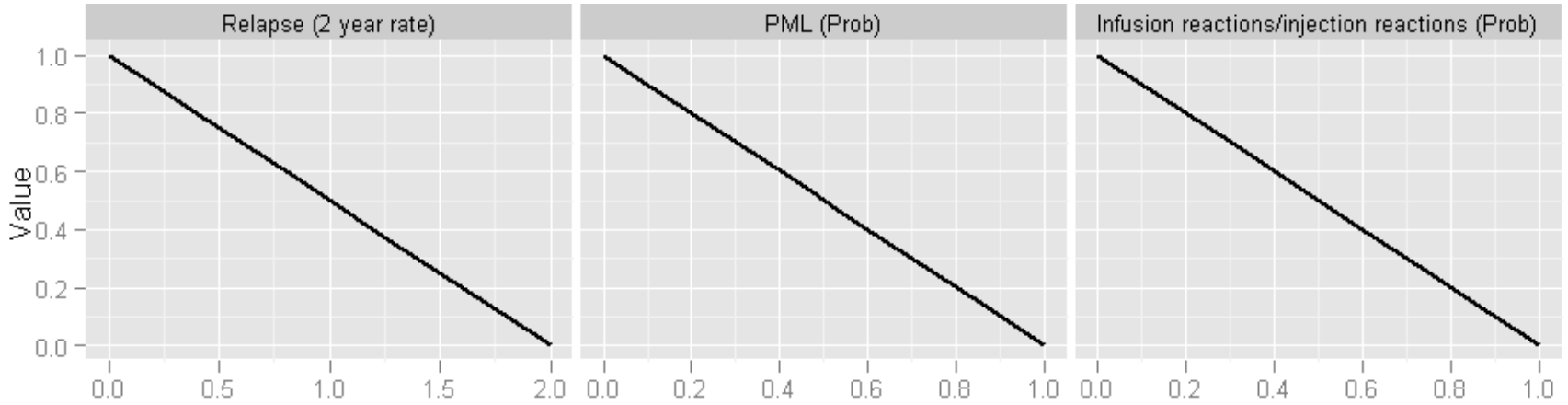

- MCDA has not been specifically developed for benefit-risk assessment, but as a general framework for decision making
- MCDA can be shown to be a generalization of the weighted Net Clinical Benefit, but has been developed much earlier

# MCDA and the Women's heptathlon




| Event | Jessica Ennis | Value | Lilli Schwarzkopf | Value | Tatyana Chernova | Value |
|---|---|---|---|---|---|---|
| Javelin throw (m) | 47.49 | 812 | 51.73 | 894 | 46.29 | 789 |
| High Jump (cm) | 186 | 1055 | 183 | 1016 | 180 | 979 |
| 200 metres (s) | 22.83 | 1096 | 24.77 | 909 | 23.67 | 1013 |
| Total | | **2963** | | **2819** | | **2781** |

# MCDA and multiple sclerosis drugs

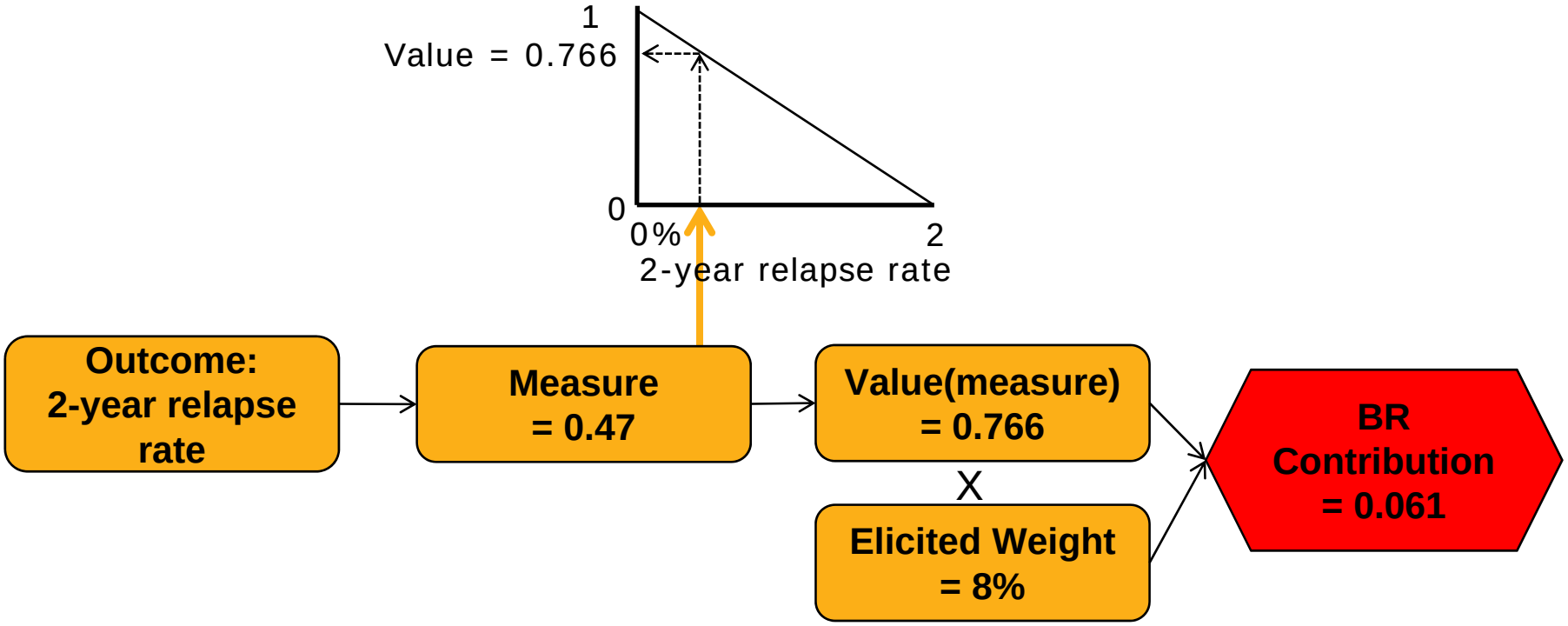



| | | Placebo | | | Natalizumab | | |
|---|---|---|---|---|---|---|---|
| **Outcome** | **Weight** | **Measure** | **Value** | **Benefit-risk** | **Measure** | **Value** | **Benefit-risk** |
| Relapse | 8% | 1.46 | 0.27 | 0.022 | 0.47 | 0.766 | 0.061 |
| PML | 54% | 0 | 1 | 0.54 | 0.0015 | 0.998 | 0.54 |
| Infusion reactions injection reactions | 3% | 0 | 1 | 0.03 | 0.24 | 0.764 | 0.02 |
| Total | | | | **0.59** | | | **0.62** |

# Assess outcome importance

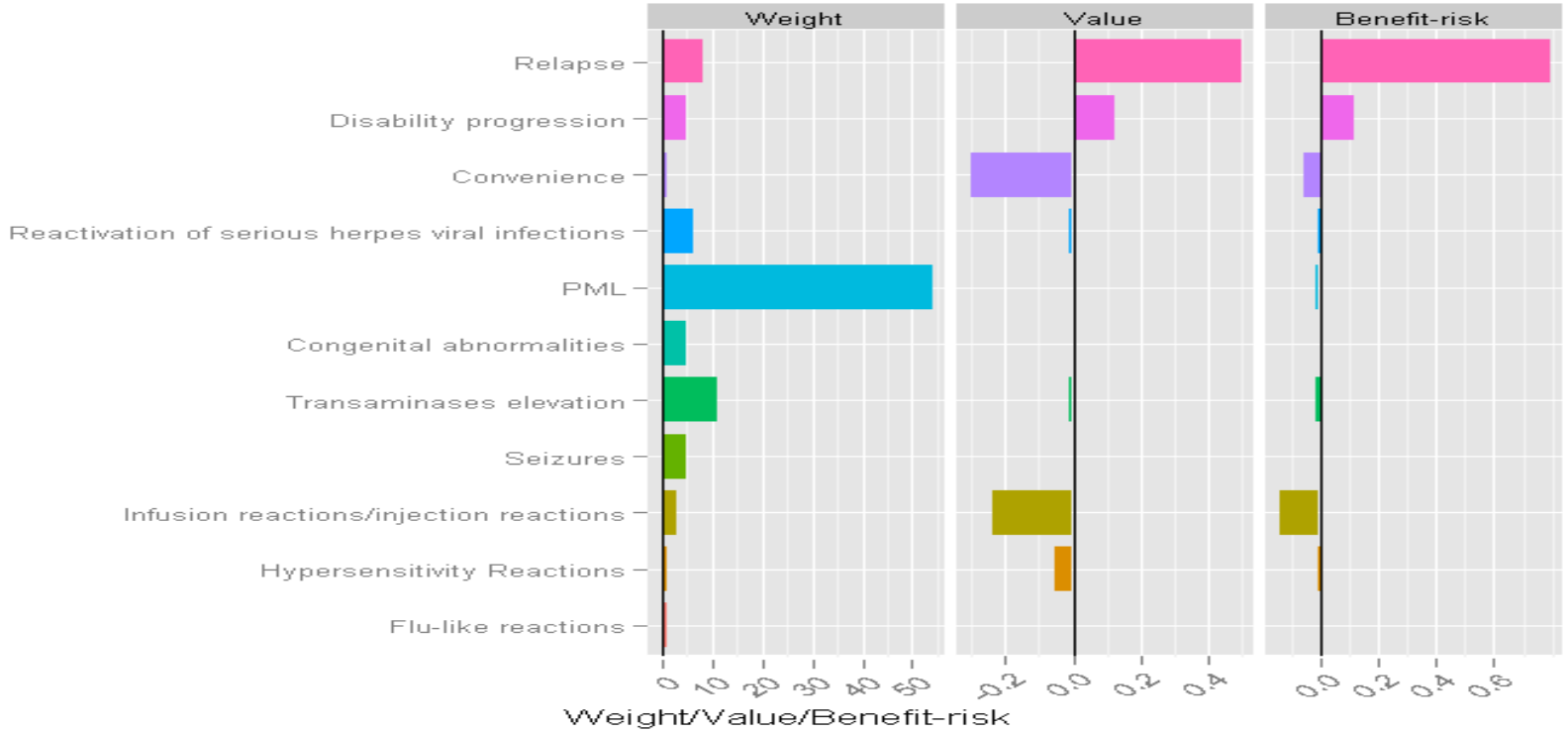
## *Linear Additive models*

- Linear Additive Models with Swing Weights
  - Value functions: Within outcome importance
  - Weights: Between outcome importance



# Visualization of Benefit-Risk Assessment

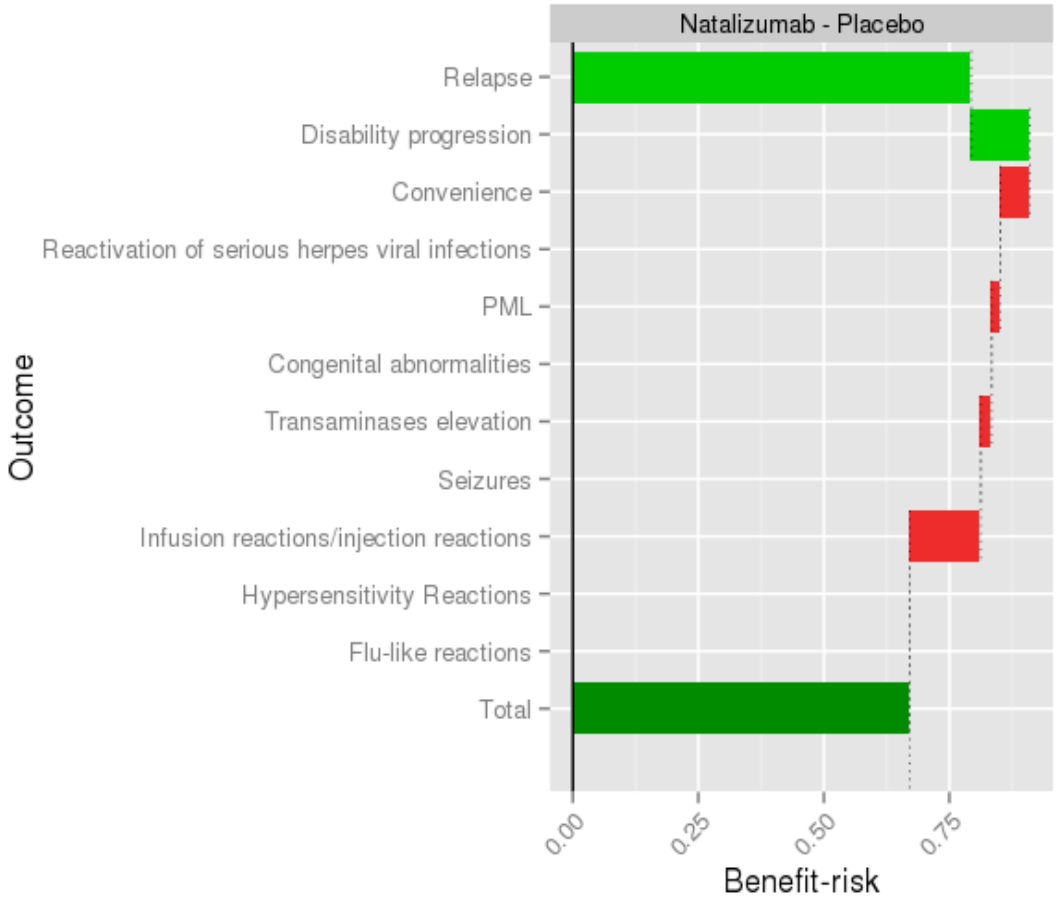
***Drill down to the values and weights***




- This shows which outcomes are contributing most to the total benefit-risk.
- Even thought the weight given to PML is large, the incidence is small, leading to a small contribution to the BR.

# Incremental Benefit-Risk of Natalizumab vs Placebo

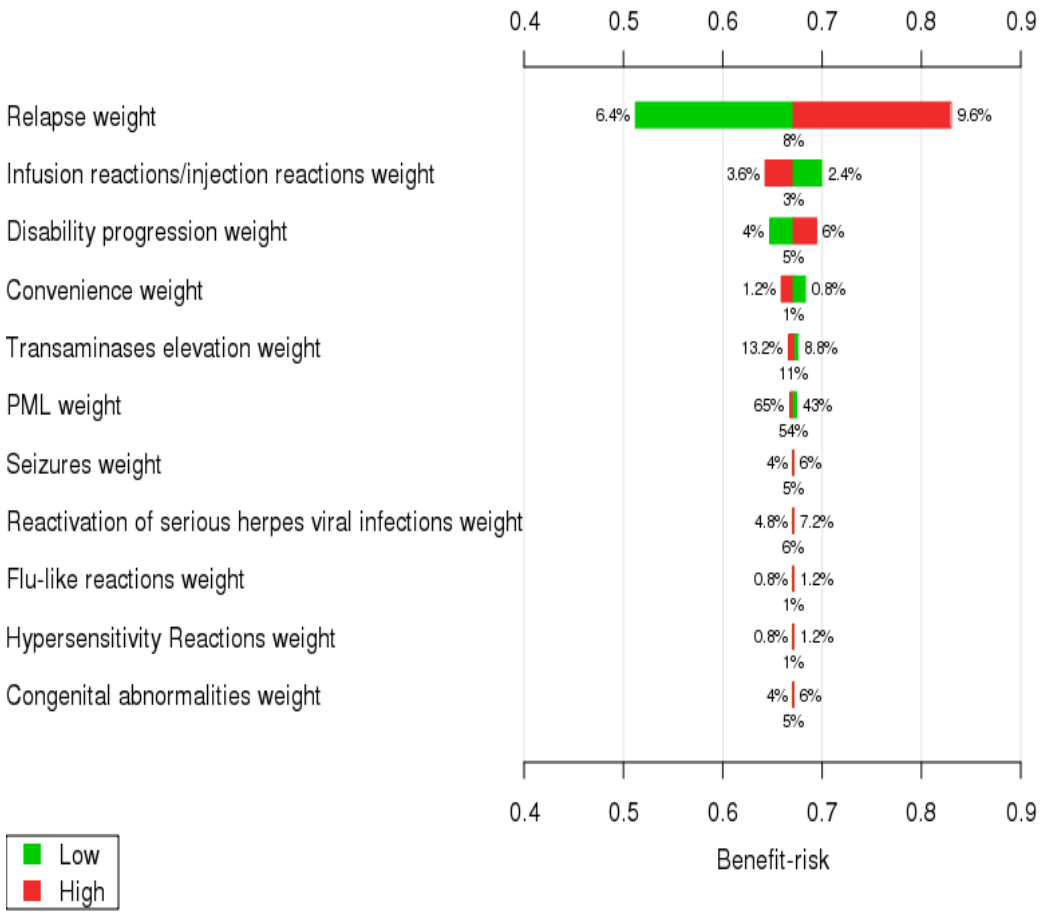
## *Waterfall Plot*




- The length of each bar gives the contribution to the overall BR
- End of the last bar gives the overall benefit-risk.
  - *Denominated in the BR of one relapse*
- Green = positive BR
- Red = negative BR

# Sensitivity analysis on the weights

## *Tornado Plot*




- The weights are shown under each bar.
  - The base case weight is shown in the middle, with a +/- 20% range given at the ends.
- The weights are changed one at a time.
- The most important weight is the one given to relapses

## Further Sensitivity Analyses

- Check robustness of benefit-risk measure by varying both, **weight** as well as **observed incidence** of, for example, PML
- Calculate for each risk individually the threshold for equipoise (i.e. benefit-risk measure equals zero)
- Repeat benefit-risk assessment using weights elicited from other stakeholders (patients, payers, etc.)
- Take into account **variability** and **correlation** of benefit-risk criteria

## Conclusions

- The BRAT is a framework well suited to benefit-risk analysis
- Benefit-risk analysis is conceptually easy but hard to operationalize – in particular:
  - To define consistent criteria across decision options, find data matching these criteria, and elicit value judgments
  - Squash the messy complexity of real life into a simple model
- A BR assessment does not necessarily give you the answer
  - It is a framework for decomposing and understanding a problem
  - Assesses the main value drivers of a decision
  - Communicates issues in a transparent, rational and consistent way
  - Allows sensitivity analysis around different perspectives (industry, regulator, patient, payer, prescriber)

## Conclusions

Quantitative methods

- Don’t replace the expert’s judgment on benefit-risk, but can be very useful if used complementary
- Support a better understand of the decision drivers and the decision’s robustness

# Acknowledgements


- Richard Nixon - Novartis
- Thai Son Tong Nguyen – ScHARR, Sheffield
- Isabelle Stoeckert - Bayer
- Silvia Kuhls - Bayer
- Gemma Hodgson - Takeda
- John Pears - Astra Zeneca
- Ioanna Tzoulaki - Imperial
- Dolores Montero - Agencia Española de Medicamentos y Productos Sanitarios

# References


- Holden W L, et al. Benefit-risk analysis: a proposal using quantitative methods, Pharmacoepidemiology and Drug Safety 2003a; 12: 611-616.
- Holden W L, et al. Benefit-risk analysis: examples using quantitative methods, Pharmacoepidemiology and Drug Safety 2003b; 12: 693-697.
- Sutton A J, et al. A Bayesian approach to evaluating net clinical benefit allowed for parameter uncertainty, Journal of Clinical Epidemiology 2005; 58: 26-40