Imperial College London

President's Invited Lecture, ISCB-33:
A Benefit-Risk Analysis of using Formal Benefit-Risk Approaches for Decision-Making in Drug Regulation

Deborah Ashby

Bergen, 22nd August 2012

Outline

- Evidence-based medical decision-making
- Benefit-risk initiatives and IMI-PROTECT
- Motivation and PROTECT Benefit-Risk Project methodology review
- Tysabri case study: Applications of MCDA
- Acomplia case study: Applications of SMAA
- Benefits and risks of taking this approach

Evidence Based Medicine

"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."

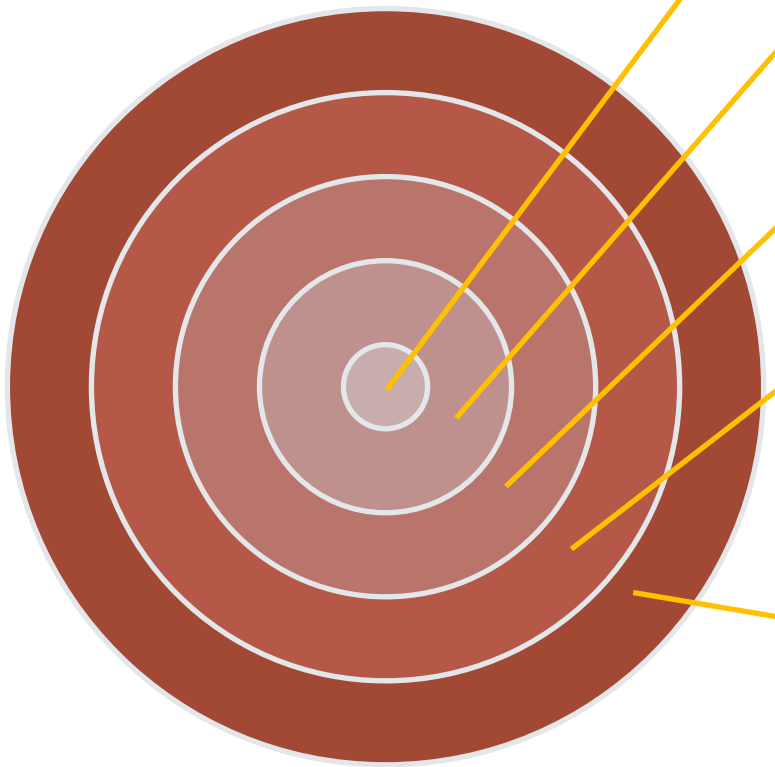
Sackett et al, 1996

Some background in decision making

- In high school maths curricula in UK
- Maths BSc module in many universities
- Not routinely part of MSc Medical Statistics training in UK
- Decision-making under uncertainty closely allied with Bayesian statistics for decades, especially in health applications e.g. Raiffa, Schlaiffer, Cornfield, Lindley, Smith AFM, Smith J, Spiegelhalter, Berry, Parmigiani- see Ashby, SiM, 2006 for key references

Imperial College London

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

Challenges in medical decision-making

- 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?

The licensing challenge

- The task of regulators (EMA, FDA, DKMA, AEMPS, NoMA 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?

Outline

- Evidence-based medical decision-making
- Benefit-risk initiatives and IMI-PROTECT
- Motivation and PROTECT Benefit-Risk Project methodology review
- Tysabri case study: Applications of MCDA
- Acomplia case study: Applications of SMAA
- Benefits and risks of taking this approach

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 (EFSPI) Benefit-Risk SIG
- IMI-PROTECT Benefit-Risk Integration and Representation Project

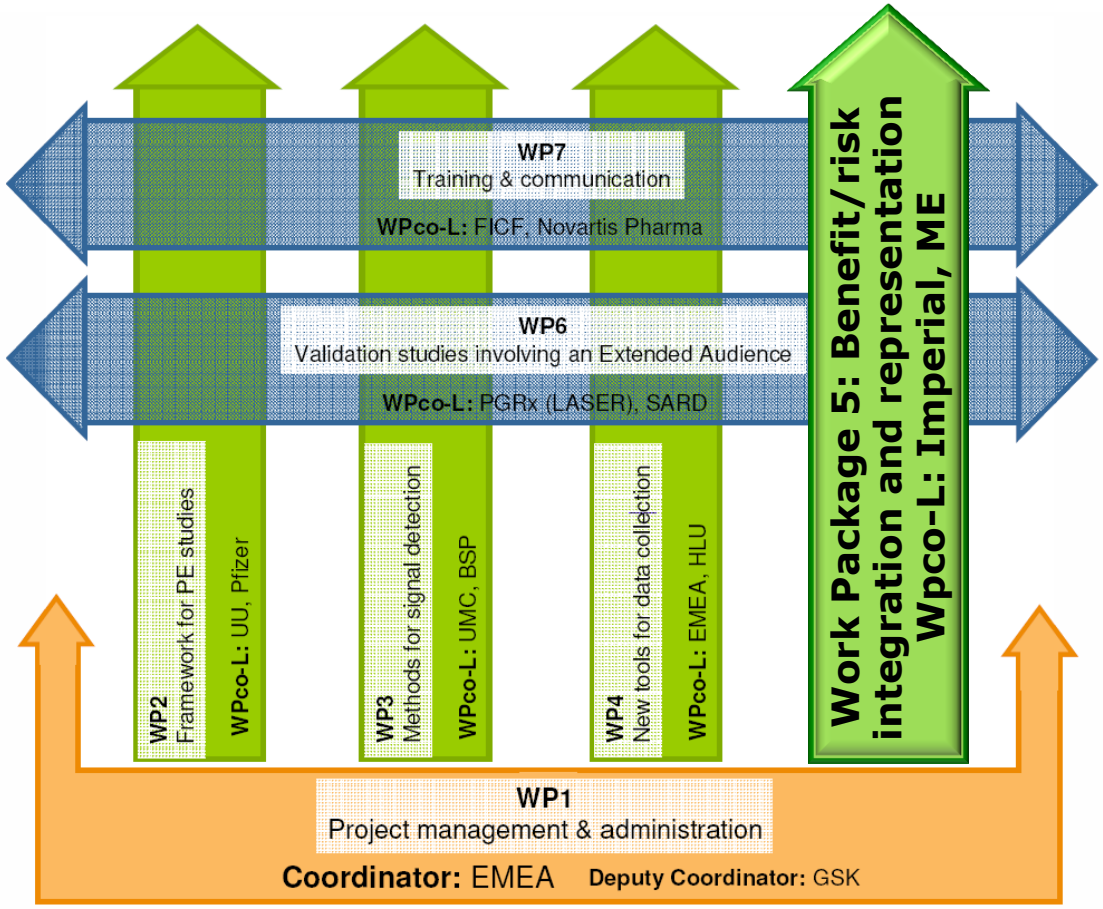
The IMI-PROTECT

- 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)

Work Packages



- One WP concerned with all aspects of the organisation and management of PROTECT
- Four "vertical" WPs targeting the specific objectives and methodological developments
- Two "horizontal" WPs concerned with the communication, validation and integration of the scientific work into an integrated and cohesive European activity

PROTECT BRIR (membership)

Public	Private
Imperial College (co-leader)	Merck KGaA (co-leader)
EMA	AMGEN
DKMA	AstraZeneca
AEMPS	Bayer
MHRA	GSK
Mario Negri Institute	Lilly
GPRD	Novartis
LA-SER	Novo Nordisk
IAPO	Pfizer
	Roche
	Sanofi-Aventis
	Takeda

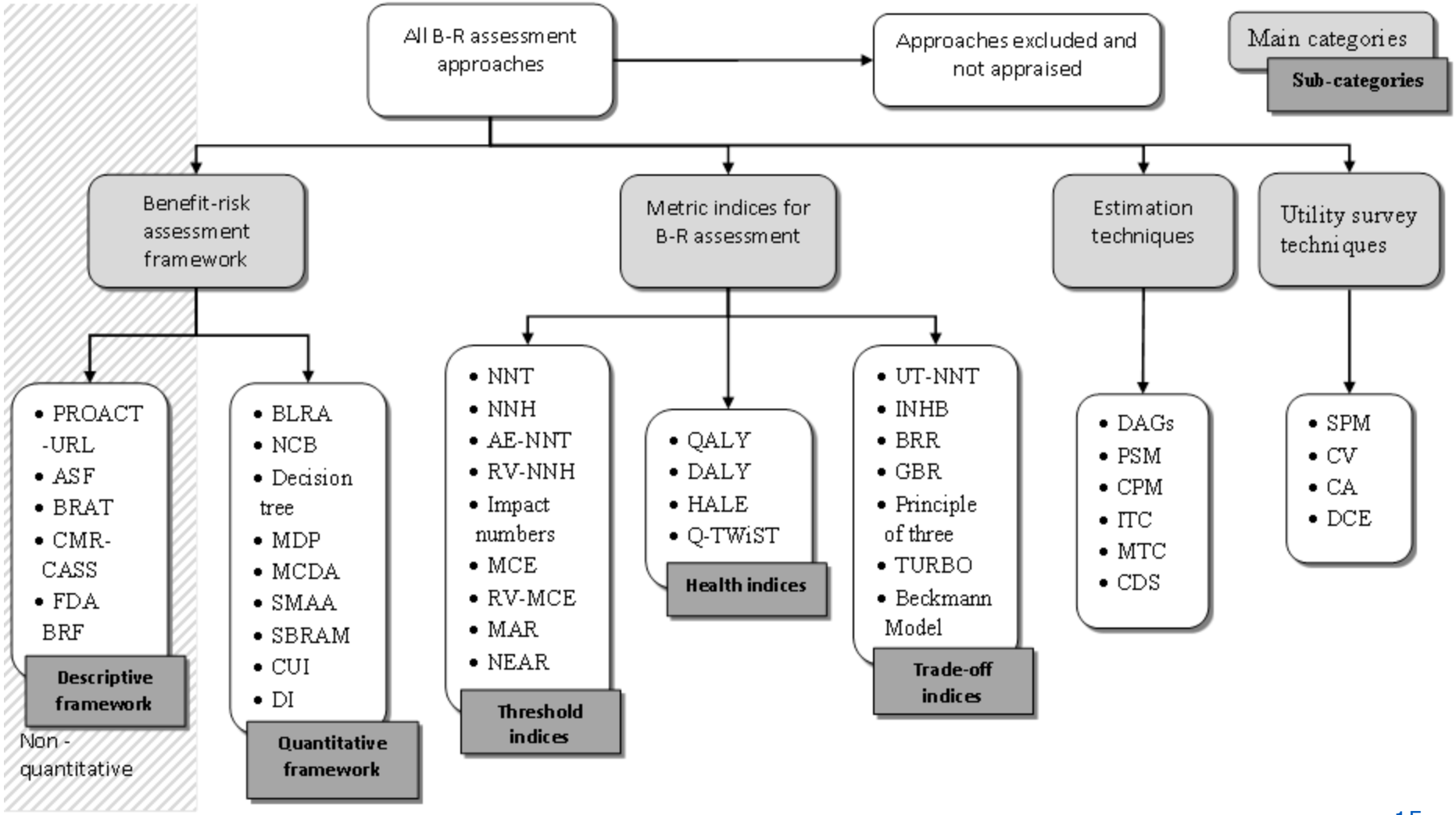
Outline

- Evidence-based medical decision-making
- Benefit-risk initiatives and IMI-PROTECT
- Motivation and PROTECT Benefit-Risk Project methodology review
- Tysabri case study: Applications of MCDA
- Acomplia case study: Applications of SMAA
- Benefits and risks of taking this approach

Case study motivation

- Complex licensing issues
- Delicate benefit-risk balance
- Multiple criteria
- Rare events
- Non-normal benefit-risk data
- Variation in stakeholders' preferences

Classifications of approaches



Wave 1 Case studies: Applications

	Acomplia	Ketek	Raptiva	Tysabri
PrOACT-URL	✓	✓	✓	✓
BRAT	✓	✓	✓	✓
MCDA	✓	✓	✓	✓
SMAA	✓	✓		
NNT & NNH	✓			✓
Impact Number	✓			
QALY				
Q-TWiST				
INHB	✓			
BRR	✓	✓	✓	✓
PSM	✓	✓		✓
MTC				✓
DCE				
Other:	Direct utility elicitation	SBRAM, Swing-weighting	Decision conferencing	Decision conferencing

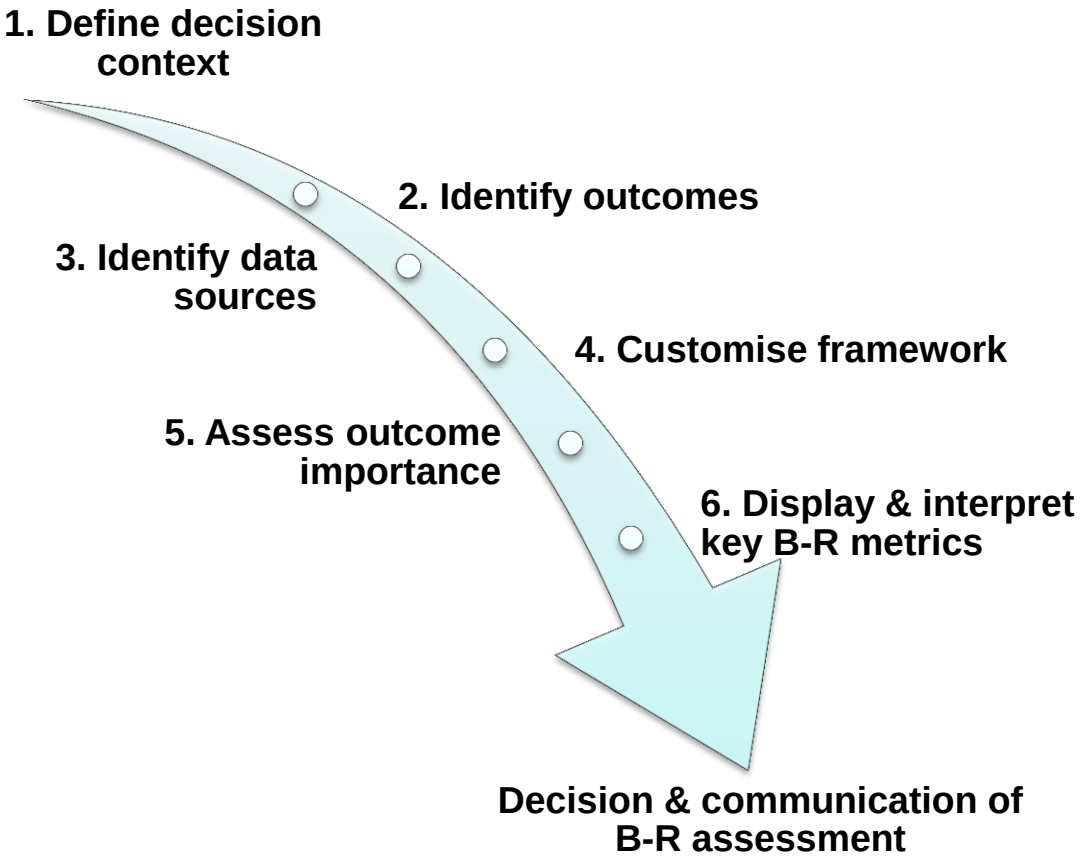
Wave 2 Case studies: Applications

	Acomplia	Tysabri	Rosiglitazone	Warfarin
PrOACT-URL	✓ (jointly)		✓	
BRAT	✓ (jointly)	✓		✓
MCDA		✓	✓	
SMAA	✓	✓		
PSM		✓	✓	
MTC/ITC	✓	✓	✓	✓
DCE	✓			
AHP		✓		
Swing-weighting		✓	✓	
MACBETH		✓		

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

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."

Outline

- Evidence-based medical decision-making
- Benefit-risk initiatives and IMI-PROTECT Work Package 5
- Motivation and PROTECT Benefit-Risk Project methodology review
- Tysabri case study: Applications of MCDA
- Acomplia case study: Applications of SMAA
- Benefits and risks of taking this approach

Quantitative B-R: MCDA

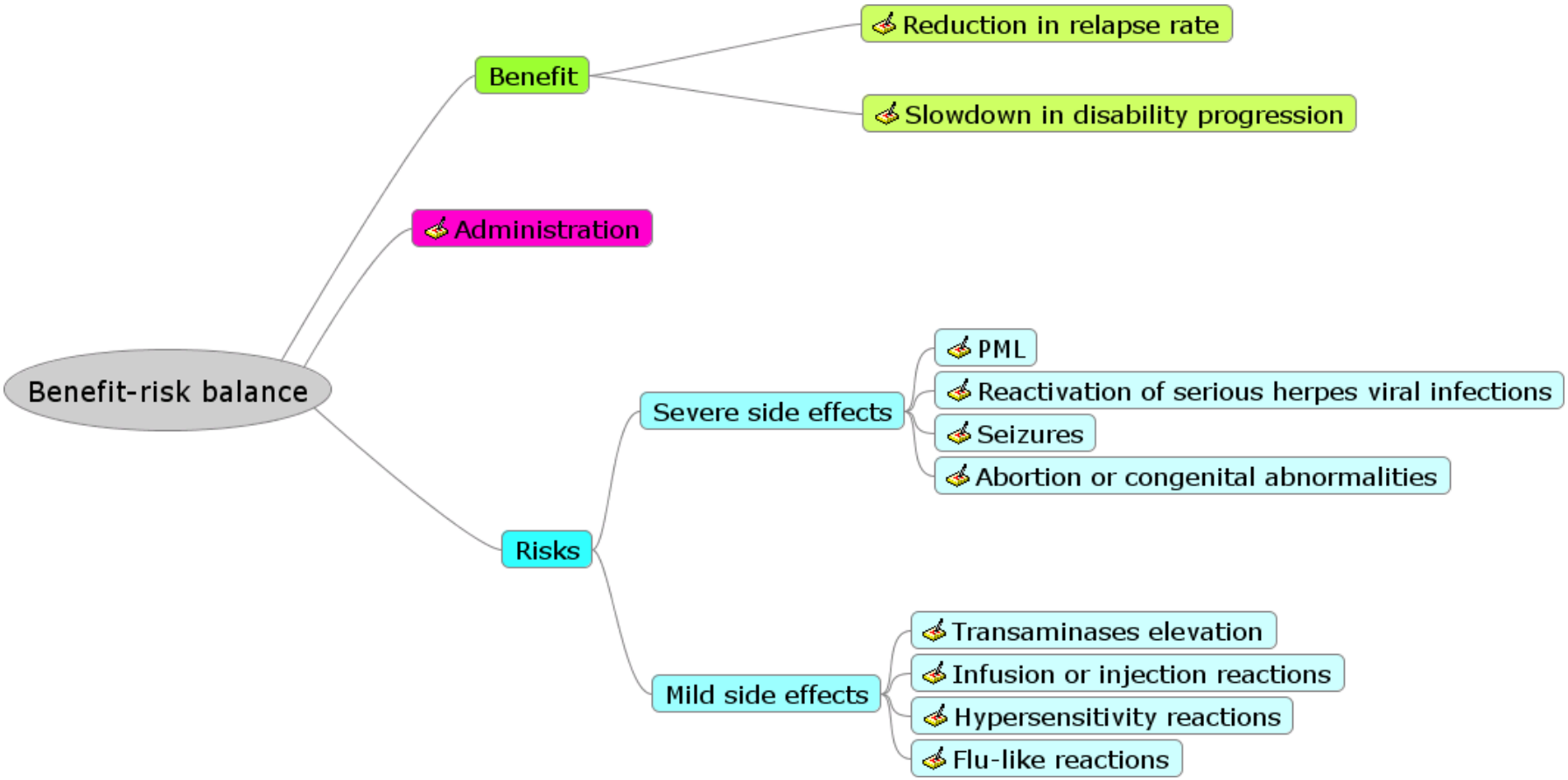
- Deals with multiple conflicting criteria
- MAUT with requisite criteria
- Requires utilities, probabilities, weights
- Governed by PrOACT-URL for structure and transparency
- Deterministic analysis

PROTECT

Tysabri example

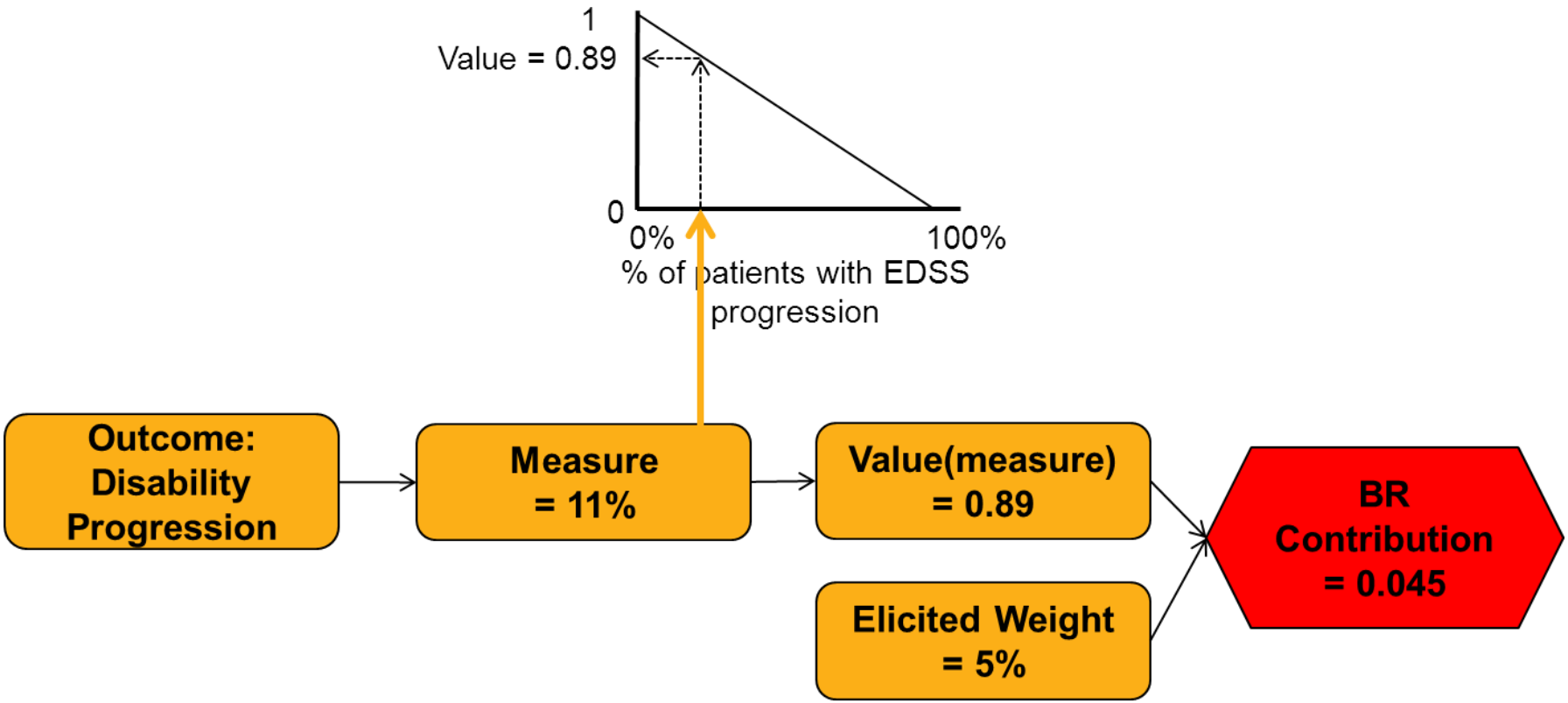
Active drug	Natalizumab
Indication	Relapsing remitting multiple sclerosis
Regulatory history	Approved 2004 License withdrawn 2005 Re introduced because of patient demand 2006 CHMP reassessed the PML risk and continue approval 2009
Severe side effects	Progressive Multifocal Leukoencephalopathy
Data source	EPAR
Comparators	Placebo, Avonex, Copaxone

Tysabri: Structure by value tree



Tysabri: MCDA calculating weighted utility

For each criterion (outcome)



PROTECT

Tysabri: MCDA Calculating expected utility

Combined all criteria (multiple outcomes)

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

w_j = preference weight for criterion j

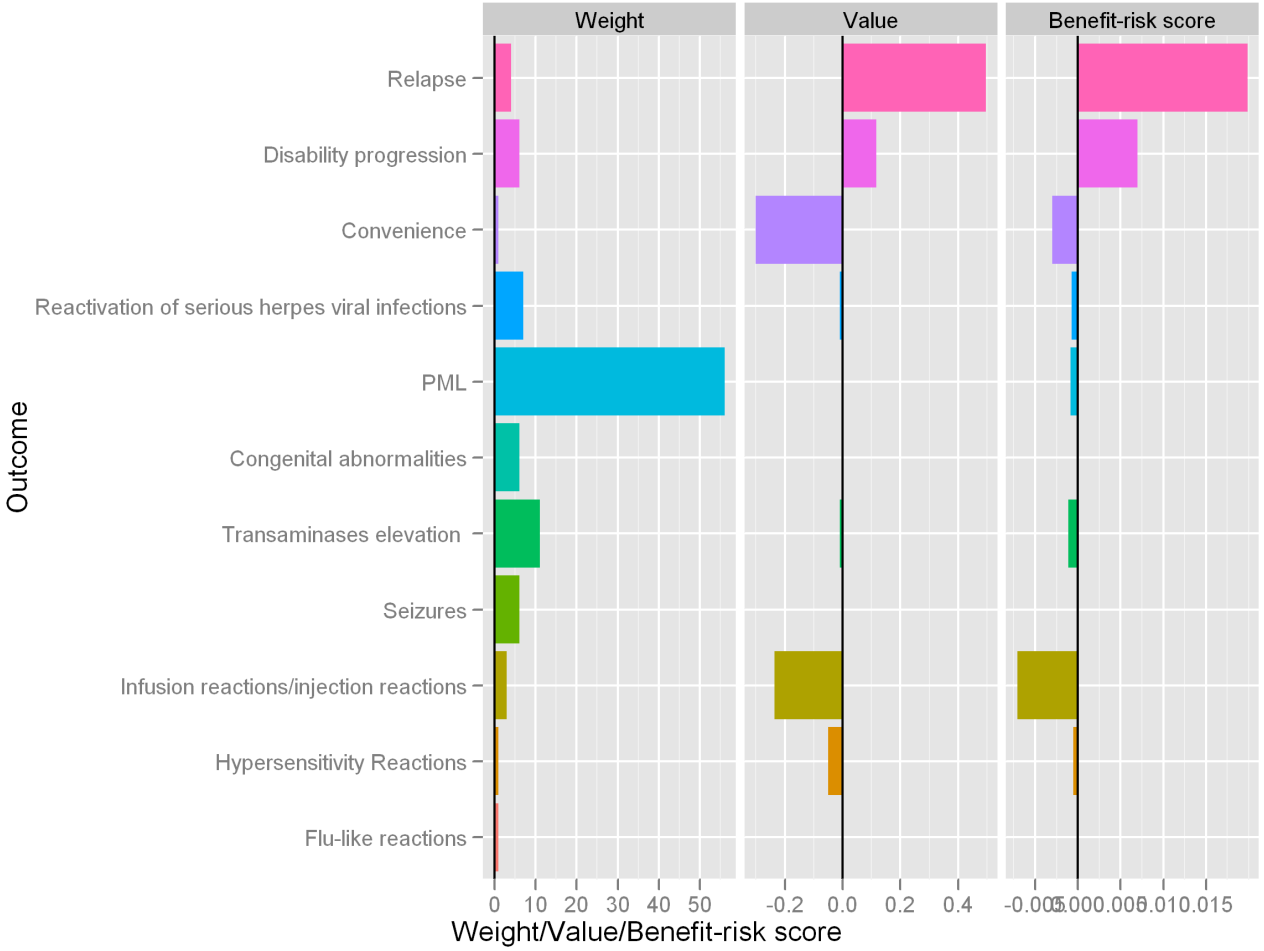
With constraint $\sum_{j=1}^{k} w_j = 1$ for k number of criteria

Then, the overall expected utility for alternative i is

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

Tysabri: Weighted Scores

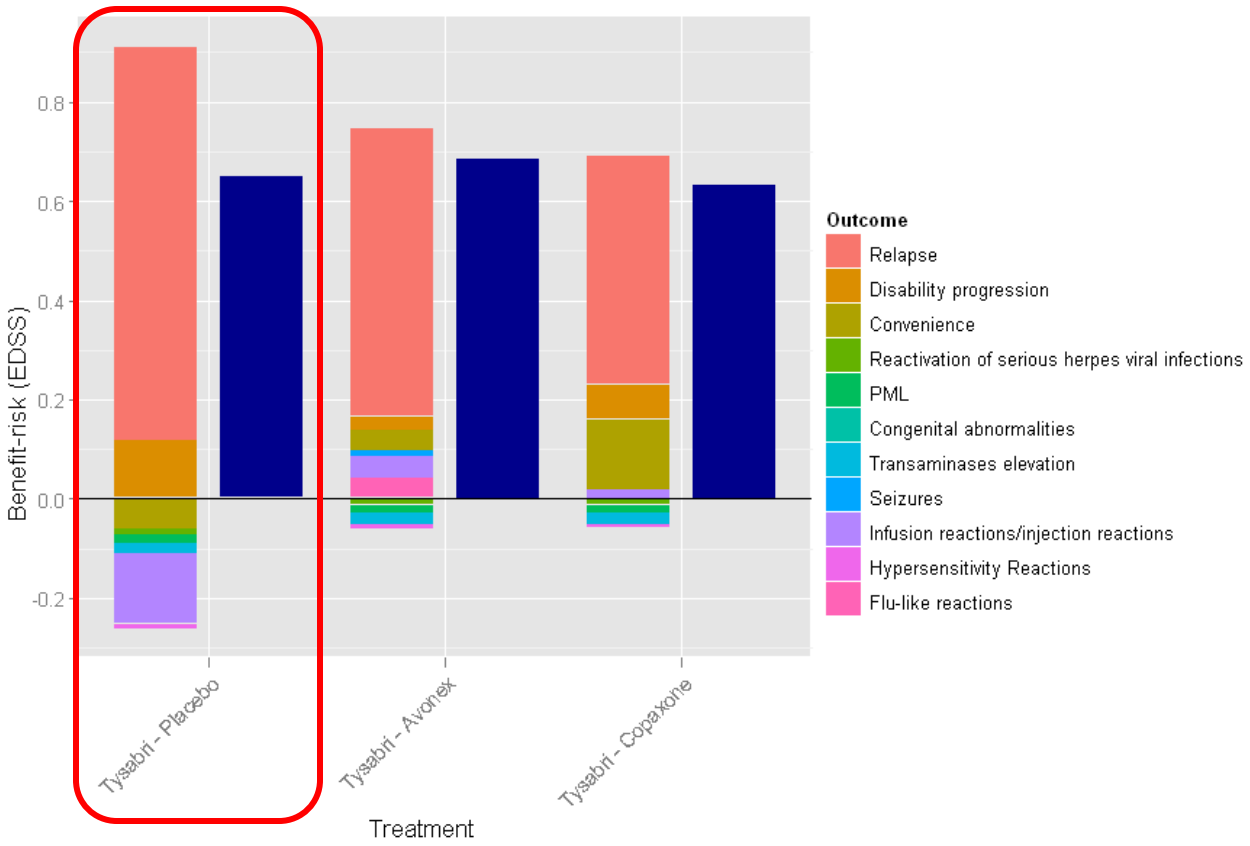
Contribution of each outcome for Tysabri - placebo



- 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

Tysabri: Criteria contribution

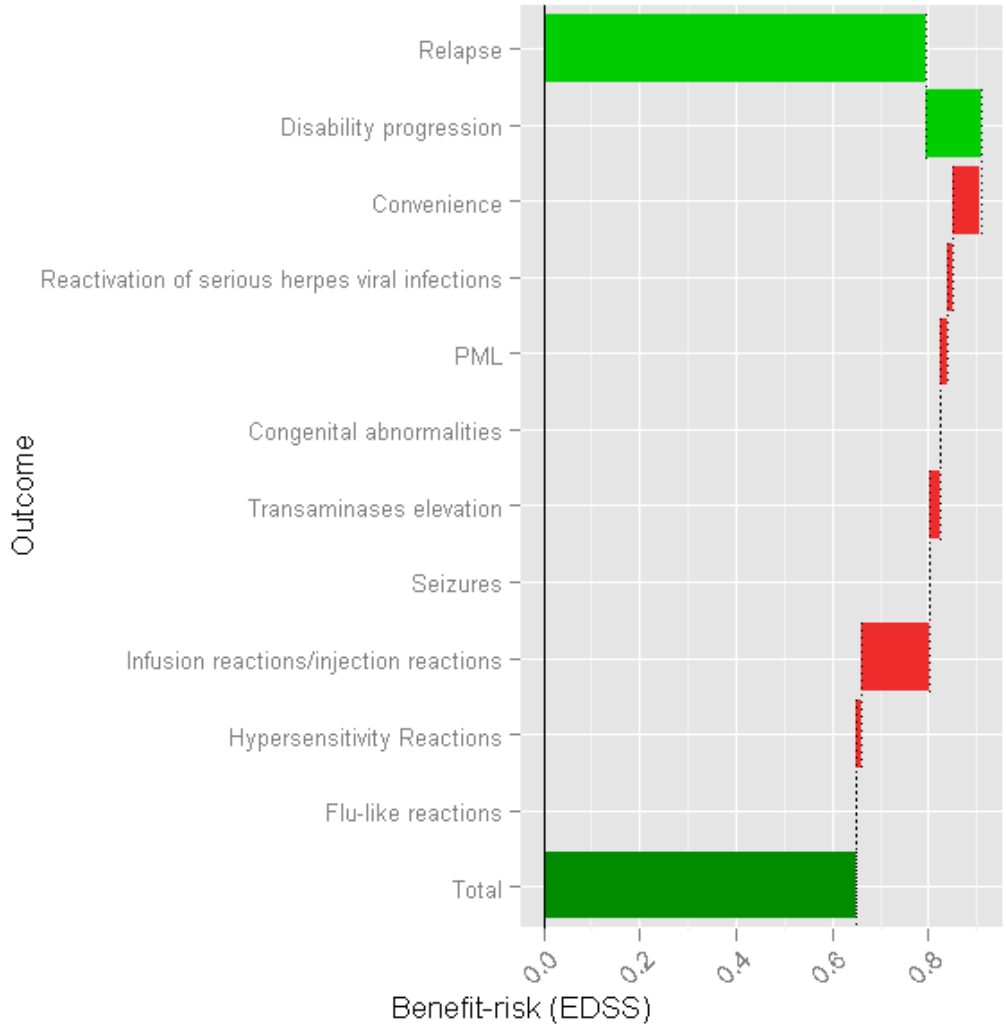
Stacked bar chart for Tysabri vs. all the other treatments.



- 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.

Tysabri: Criteria contribution

Waterfall plot for Tysabri - placebo

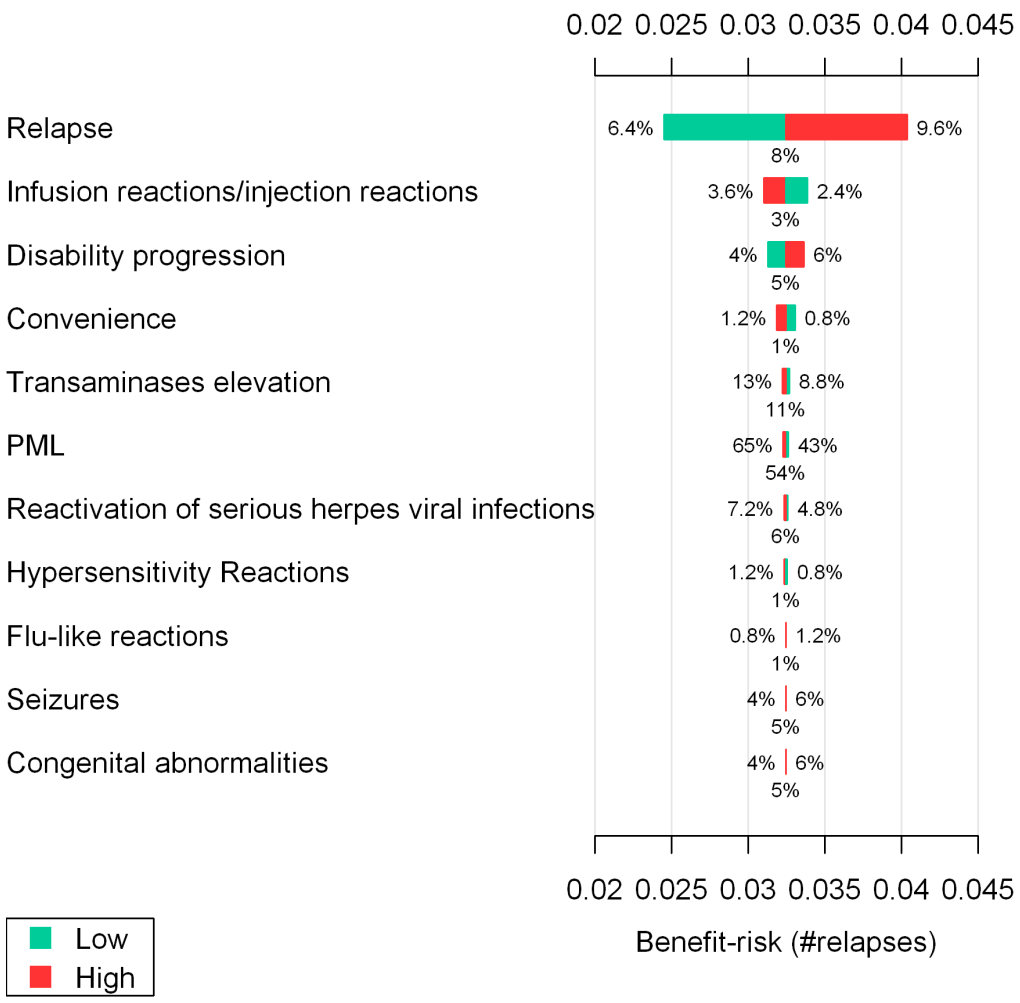


- Like a horizontal bar chart, except that the end of the previous bar determines the start of the next bar
- End of the last bar gives the overall benefit-risk.
- Green = positive BR
- Red = negative BR

http://public.tableausoftware.com/views/T_Waterfall/WaterfallRisk

Tysabri: One-way sensitivity analysis

Tornado diagram for sensitivity to weights. Tysabri - placebo



- The base case value of the weight for each outcome is shown under each bar.
- The **low values** and **high values** of ±20% change in weight are shown at the ends of the bars.
- The incremental benefit-risk at the base case is the x-axis value at the middle.
- How this changes with each weight is shown by the position of the bar ends.
- From this plot we see that changes in the weight of relapse has the most influence on the benefit-risk score.

Tysabri: MCDA comments

- In its current form, only point values are taken into account
- For Gaussian shaped data, may reflect average
- Skewed data may be misrepresented
- What about uncertainty in data?
- What about uncertainty in value preferences?
- What about missing value preferences?

Outline

- Evidence-based medical decision-making
- Benefit-risk initiatives and IMI-PROTECT
- Motivation and PROTECT Benefit-Risk Project methodology review
- Tysabri case study: Applications of MCDA
- Acomplia case study: Applications of SMAA
- Benefits and risks of taking this approach

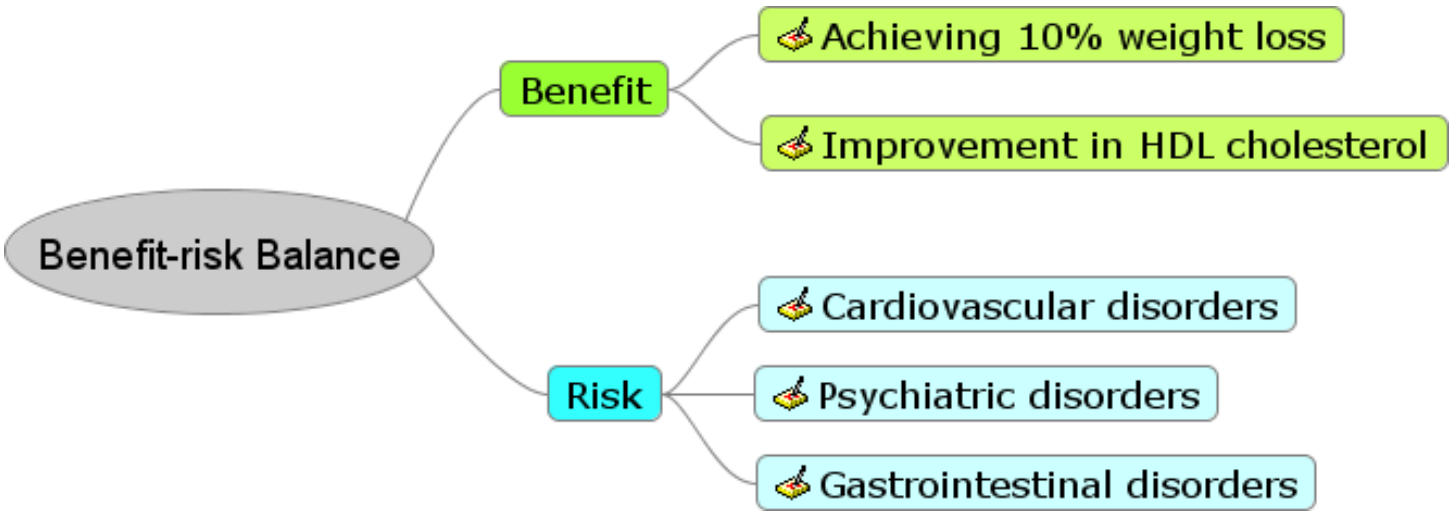
Quantitative B-R: SMAA-2

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

Acomplia

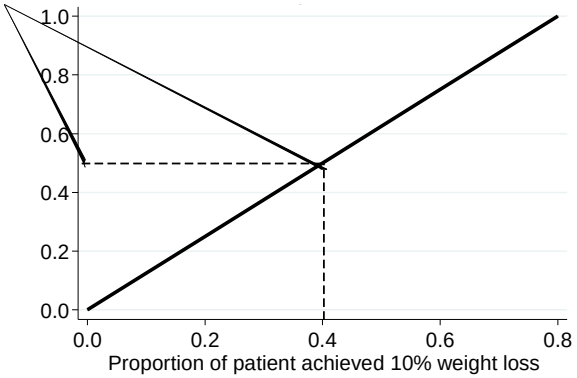
Active drug	Rimonabant
Indication	Weight loss in obese and overweight patients with co-morbidities in adults (>18y)
Regulatory history	Approved June 2006, Voluntary withdrawal in January 2009
Severe side effect	Increased risk with depression
Data source	EPAR Published clinical trials
Comparator	Placebo, Orlistat (Wave 2), Meridia (Wave 2)

Acomplia: Structure by value tree



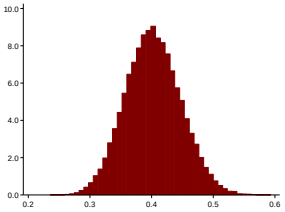
Acomplia: SMAA calculating weighted utility

For each criterion (outcome)

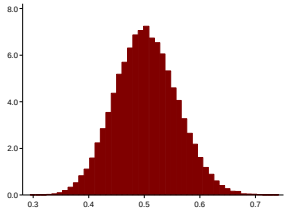


Outcome: Achieved 10% weight loss

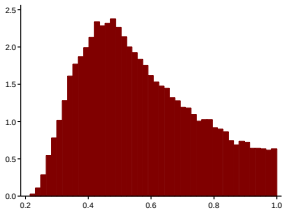
Measure: 40% (range 24% - 59%)



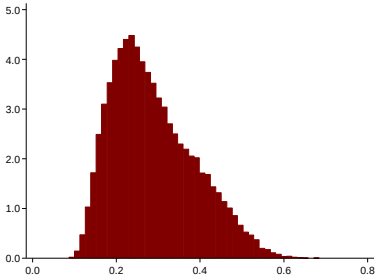
Value(measure): 50% (range 29% - 74%)



Weight space: 57% (range 21% - 100%)



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



PROTECT

Acomplia: Calculating rank acceptability index

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

$f_W(w) =$ density function of weight space W

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

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

Then the probability of alternative i ranked first is

$$b_i^1 = \int_{\xi \in X} f_X(\xi) \int_{w \in W_i^1(\xi)} f_w(w)\, dw d\xi$$

Acomplia: Calculating central weight

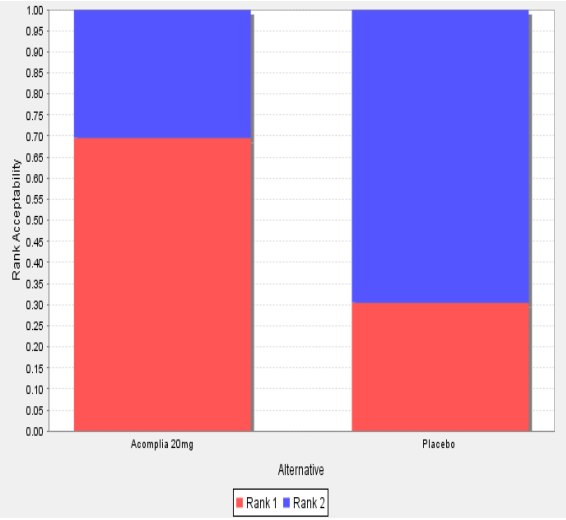
The expected centre of gravity for $W_i^1(\xi)$ is

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

Acomplia: SMAA (Wave 1)
Preference-free model

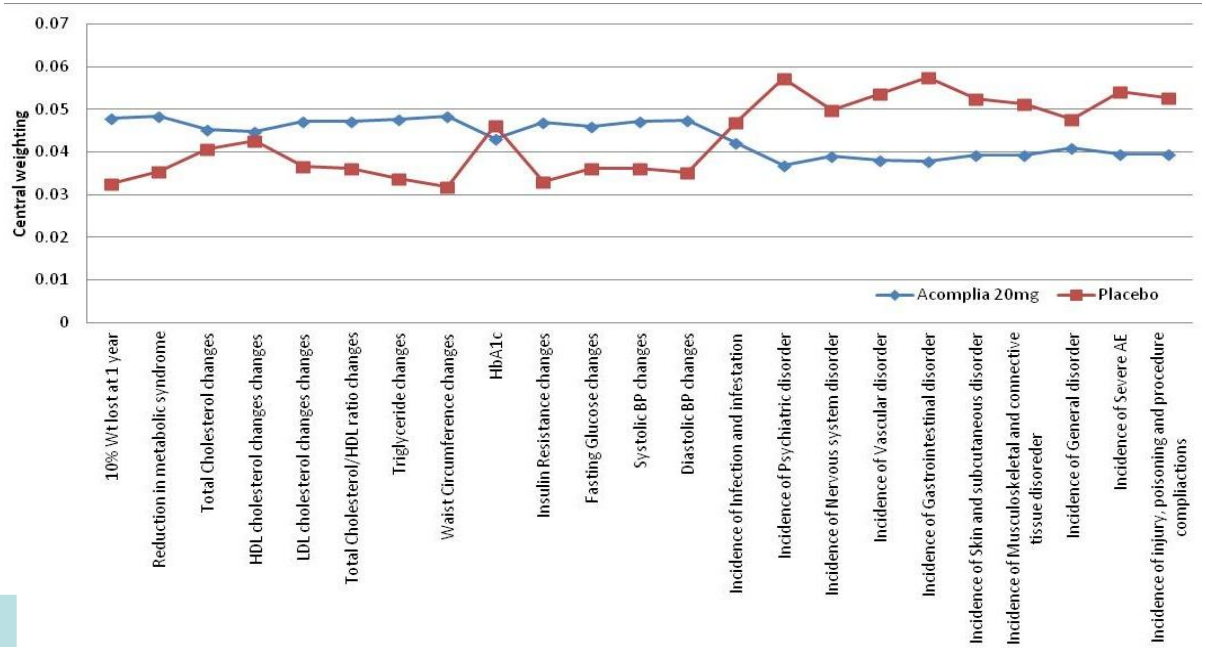
Acceptability index

alternative i is ranked r



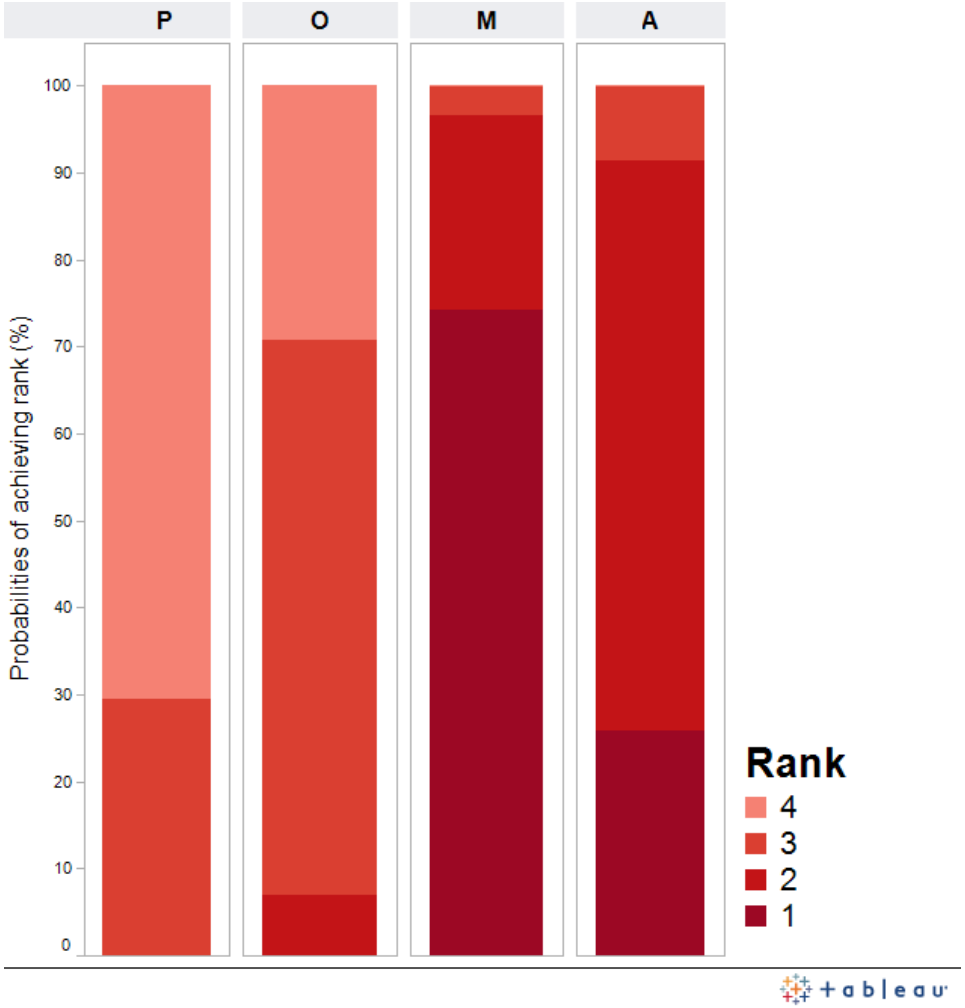
Alternative	Rank 1	Rank 2
Acomplia 20mg	0.70	0.30
Placebo	0.30	0.70

Preference values for an "average" decision-maker supporting each alternative



Acomplia: SMAA (Wave 2)

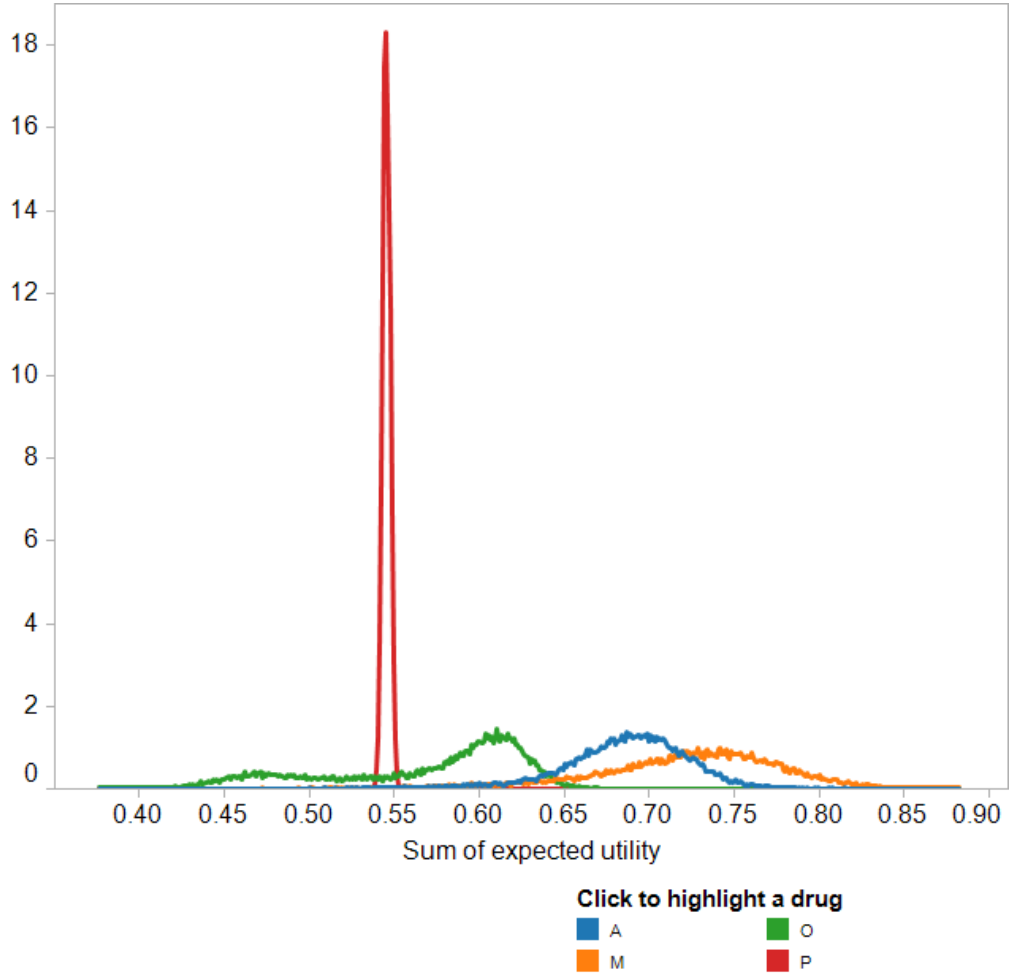
Probabilities achieving rank 1, 2, 3 or 4



- Non-missing weights model
- Drugs
  - **P**lacebo
  - **O**rlistat
  - **M**eridia
  - **A**complia

Acomplia: SMAA (Wave 2)

Utility distributions for a set of decision-maker's weights



- Drugs
  - **P**lacebo
  - **O**rlistat
  - **M**eridia
  - **A**complia
- Online interactive version allows own weights is available

http://public.tableausoftware.com/views/wave2rangeweight/Dashboard2?:embed=y

Remarks

- Frameworks are important to govern B-R assessment process and to ensure transparency
- Stakeholders' value preference may influence the benefit-risk balance
- Benefits and risks need to be on common scales to be traded off
- Uncertainties must be taken into account especially when data are skewed
- Methodologies only aid decision-making, not make the decisions

On-going work (Wave 2)

- Interactive benefit-risk visual representation and recommendations
- Individualised benefit-risk assessment (Warfarin case study)
- Bayesian modelling of MCDA
- Various methods of value preference elicitation directly from patients
  - DCE, AHP, Swing-weighting, MACBETH
  - Uncertainty in value preferences

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

- Evidence-based medical decision-making
- Benefit-risk initiatives and IMI-PROTECT
- Motivation and PROTECT Benefit-Risk Project methodology review
- Tysabri case study: Applications of MCDA
- Acomplia case study: Applications of SMAA
- Benefits and risks of taking this approach

Benefits and risks of formal benefit risk modelling

Benefits

- Puts benefits and risks on same page
- Transparency facilitates discussion
- Gives a framework to include regulators and patients' views
- Will improve design of future studies
- It's fun!

Risks

- Trade-off between being too simplistic or just incomprehensible
- Just a 'black box'?
- Pharma want to know what regulators want
- Needs modelling and observational data alongside RCTs