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Emerging methods in benefit-risk assessment and decision-making for medicinal products

European Statistical Forum

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Outline

- Challenges in medical decision-making
- Emerging methods in benefit-risk assessment
- Descriptive frameworks
- Case study I: Applications of MCDA
- Case study II: Applications of SMAA
- Prospects in the regulatory context

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

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

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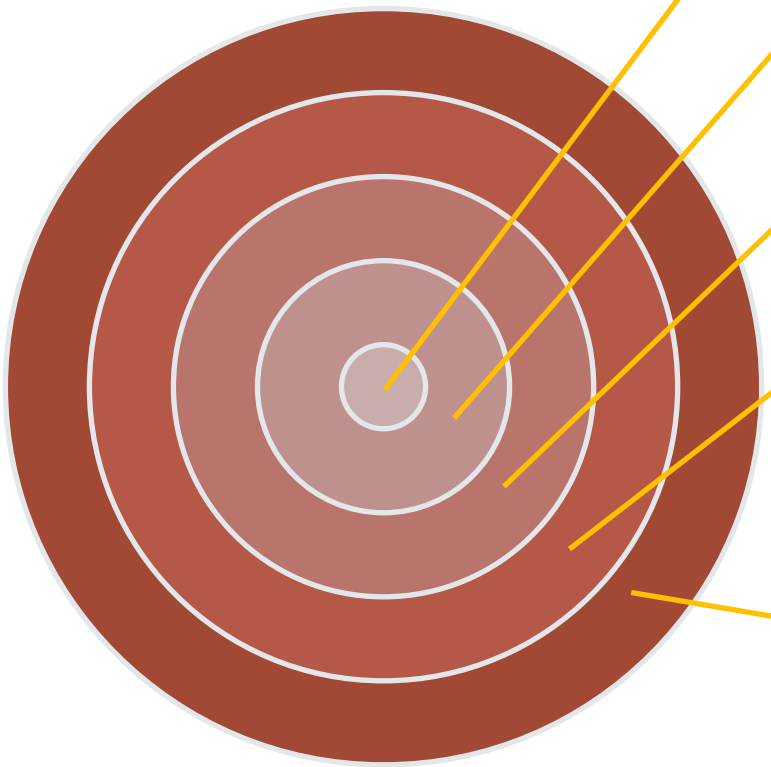
Decision makers – who are they?



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, MHRA, DHMA, AEMPS, BfArM, PEI 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
- Consortium on Benefit-Risk Assessment (COBRA)
- ISPOR Risk-Benefit Management Working Group
- European Federation of Statisticians in Pharmaceutical Industry (EFSPI) Benefit-Risk SIG
- IMI-PROTECT Benefit-Risk Integration and Representation Project

IMI-PROTECT and WP5

- 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)

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

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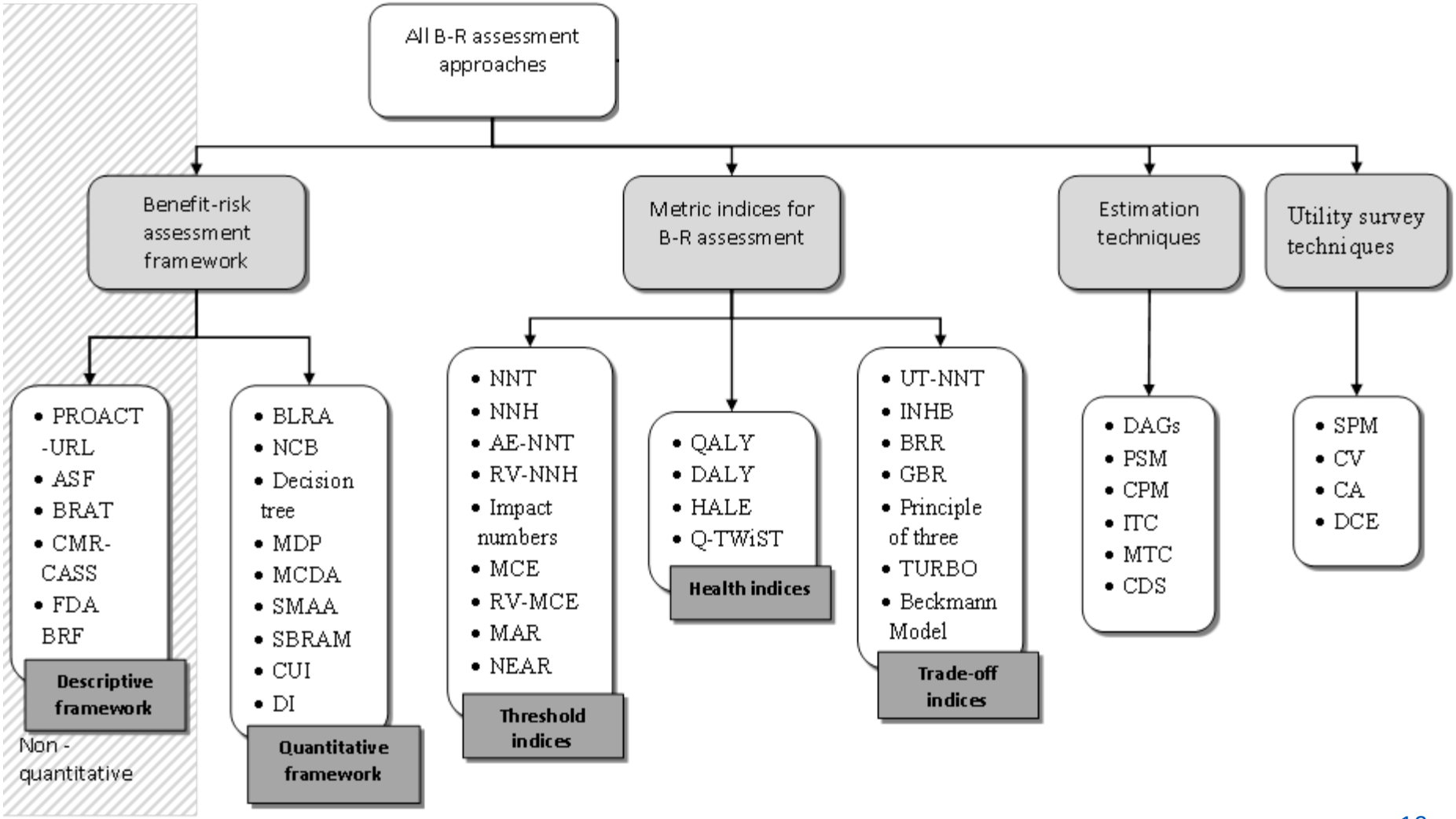
Disclaimers

"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."

Classifications of approaches



Recommendations for further testing

Framework	Metric indices	Estimation techniques	Utility survey techniques
Descriptive • PrOACT-URL • BRAT *Quantitative* • MCDA • SMAA	*Threshold indices* • NNT and NNH • Impact number *Health indices* • QALY • Q-Twist • INHB *Trade-off indices* • BRR	• PSM • MTC or ITC	• DCE

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Descriptive: PrOACT-URL

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

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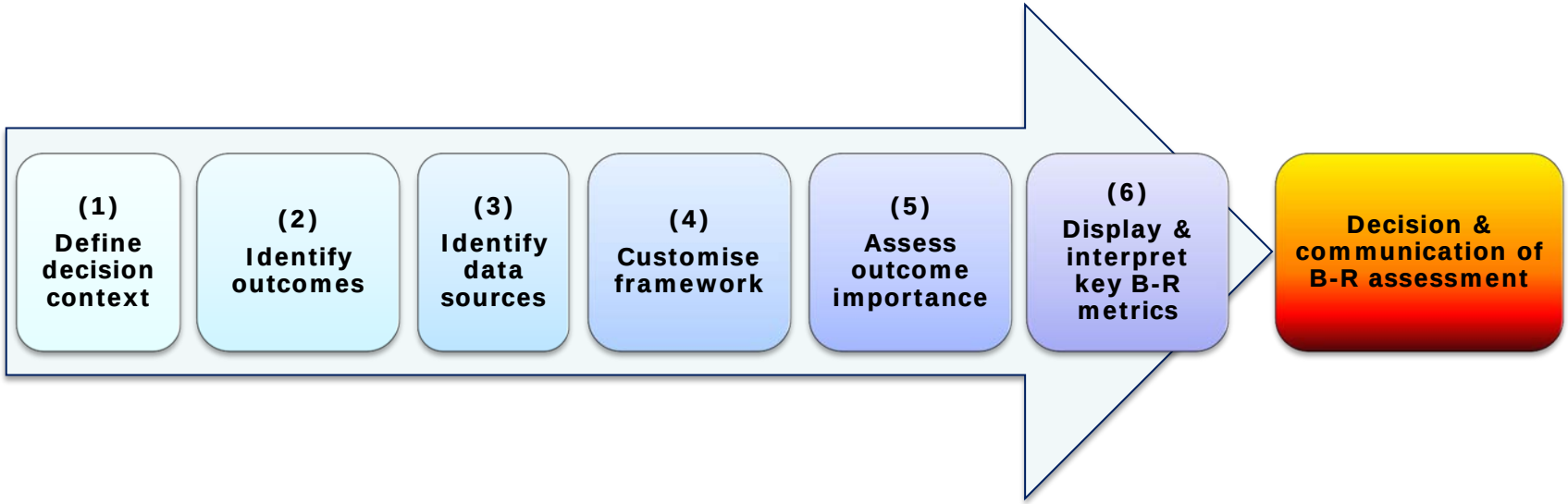
PrOACT-URL 'effects table'

	Name	Description	Fixed Upper	Fixed Lower	Units	Weight	Drug A	Placebo
Favourable Effects	PASI75	Percentage of patients achieving 75% reduction in baseline PASI[1] at week 12.	60.0	0.0	%	1.0	29.5	2.7
	PGA	Percentage of patients achieving Physician's Global Assessment[2] clear/almost clear at week12.	40.0	0.0	%	0.8	295	5.1
	OLS	Percentage of patients with Overall Lesion Severity rating of minimal or clear at FT (day 84).	40.0	0.0	%	0.25	32.1	2.9
	DLQI	Dermatology Life Quality Index[3]. Mean percentage of patients showing an improvement.	10.0	0.0	Change score	0.8	5.8	2.1
Unfavourable Effects	AEs	Percentage of patients exhibiting injection site reactions, mild to moderate dose-related acute flu like symptoms.	50.0	20.0	%/100ptyrs	0.2	41.0	24.0
	Severe infections	Proportion of patients experiencing infections serious enough to require hospitalisation.	3.00	0.00	%/100ptyrs	1.0	2.83	1.4
	Severe Thrombocytopenia	Number of cases exhibiting severe (grade 3 and above) thrombocytopenia[4].	10	0	number	0.8	9	0
	Psoriasis Severe Forms	Percentage of patients developing severe forms of psoriasis (erythrodermic, pustular).	4.0	0.0	%	0.05	3.2	1.4
	Hypersensitivity Reactions	Percentage of patients exhibiting hypersensitivity reactions, arthralgia, psoriatic arthritis, flares, back pain asthenia, ALT and Ph. Alk increase.	10.0	0.0	%	0.05	5.0	0
	Interstitial Lung Disease	Number of cases of interstitial lung disease.	20	0	number	0.1	18	0
	Inflammatory Polyradiculopathy	Number of cases of inflammatory polyradiculopathy.	5	0	Data	0.02	4	0
	SAEs	Number of cases of haemolytic anemia.	25	0	number	0.12	24	0
	PML	Number of cases of progressive multifocal leukoencephalopathy.	5	0	number	1.0	3	0
	Aseptic Meningitis	Number of cases of aseptic meningitis.	30	0	number	0.1	29	0

Descriptive: BRAT



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

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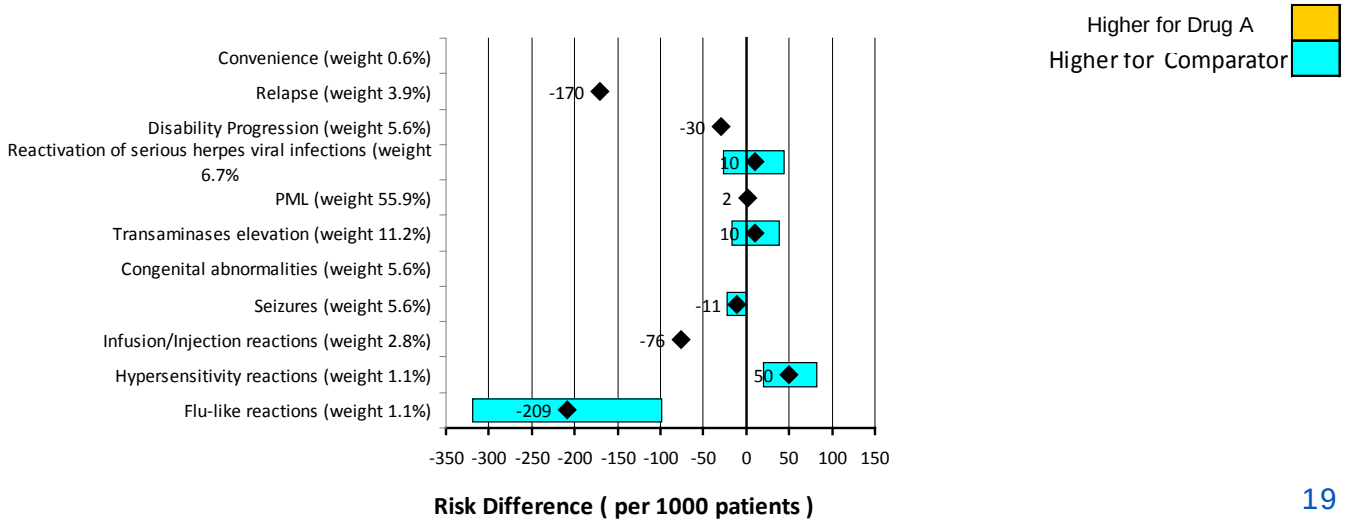
BRAT 'source data table'

Study ID	Value Tree Category	Outcome	Measure	Study Drug	Study Drug Estimate	Ref Group	Ref Group Estimate	Study Estimate
Polman 2006/ EPAR	Disease Activity	Relapse	Annualized Relapse rate[95%CI]	Drug A	0.23 [0.19-0.28]	Placebo	0.73 [0.62 –0.87]	0.32 [0.26 – 0.40]
Jacobs 1996	Disease Activity	Relapse	Annualized Relapse rate[95%CI]	Drug B	0.67 [n.a.]	Placebo	0.82 [n.a.]	0.82 [0.56 – 1.20]
Johnson 1998	Disease Activity	Relapse	Annualized Relapse rate[95%CI]	Drug C	0.65 [n.a.]	Placebo	0.91 [n.a.]	0.71 [0.47 – 1.08]
…								
Polman 2006	Liver Tox	ALT>5x ULN	n/N (%)	Drug A	31/627 (5%)	Placebo	12/312 (4%)	RR = 1.25
Jacobs 1996	Liver Tox	ALT>5x ULN	n/N (%)	Drug B	Not reported	Placebo	Not Reported	RR = 1
Johnson 1998	Liver Tox	ALT>5x ULN	n/N (%)	Drug C	Not reported	Placebo	Not Reported	RR = 1
…								

BRAT results representations

		Outcome	Drug A 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%)	280	450	-170	(-, -)
		Disability Progression (weight 5.6%)	110	140	-30	(-, -)
Risks	Infection	Reactivation of serious herpes viral infections (weight 6.7%)	80	70	10	(-26, 45)
		PML (weight 55.9%)	2	0	2	(-, -)
	Liver Toxicity	Transaminases elevation (weight 11.2%)	50	40	10	(-16, 38)
	Reproductive Toxicity	Congenital abnormalities (weight 5.6%)	-	-	-	(-, -)
	Neurological Disorders	Seizures (weight 5.6%)	0	11	-11	(-23, 0)
	Other	Infusion/Injection reactions (weight 2.8%)	236	312	-76	(-, -)
		Hypersensitivity reactions (weight 1.1%)	90	40	50	(20, 82)
		Flu-like reactions (weight 1.1%)	399	608	-209	(-320, -98)



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Brief on MCDA

- Multi-Criteria Decision Analysis
- Deals with multiple conflicting criteria
- MAUT with requisite criteria
- Requires weights probabilities (data), (weight elicitation), utilities (value function elicitation)
- Governed by PrOACT-URL for structure and transparency
- Deterministic analysis

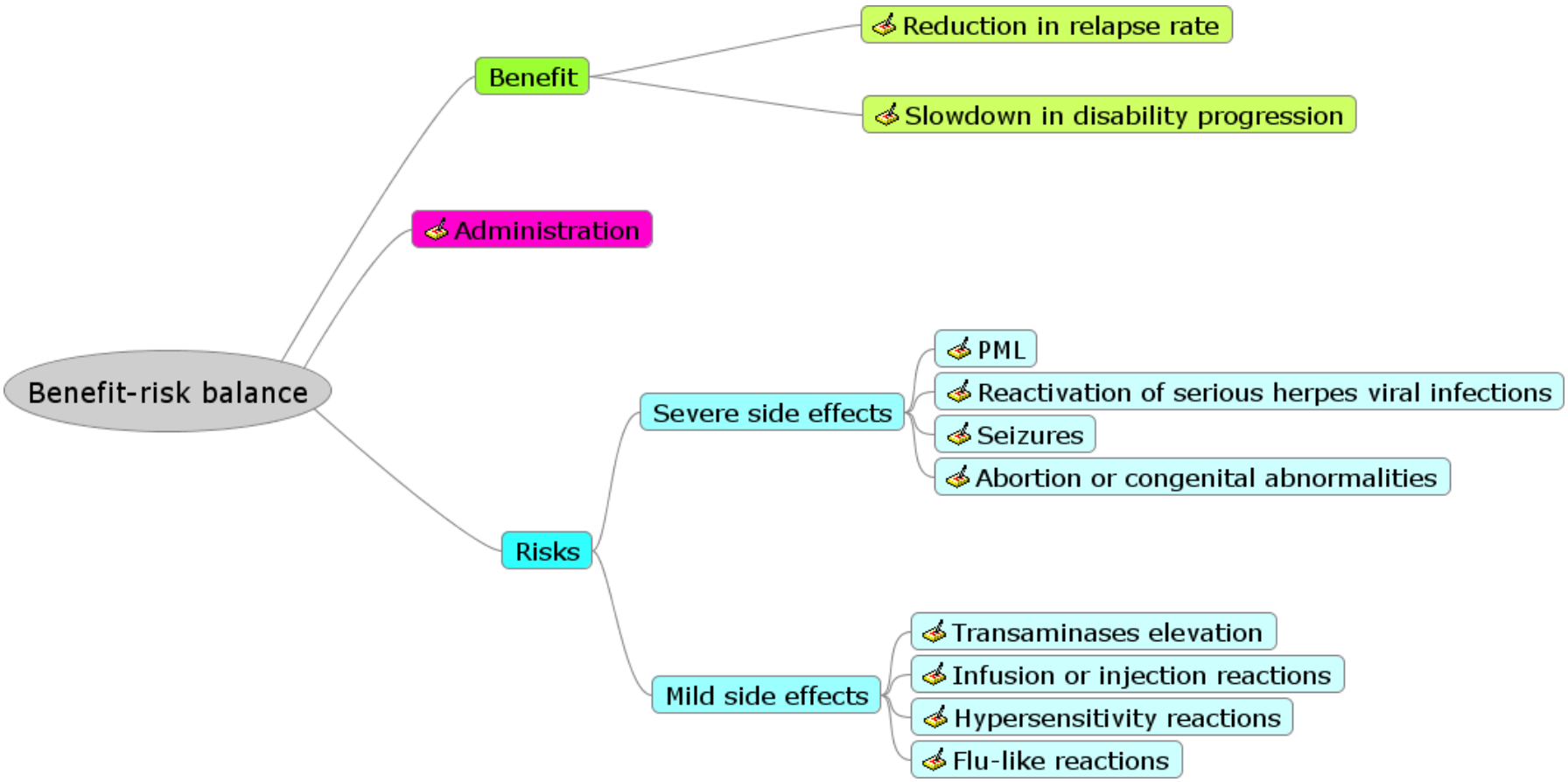
Some weight elicitation approaches

- Subjective assessment but not arbitrary
  - Reflects expert clinical experience and judgement supported by objective information
- Some formal approaches
  - Swing-weighting – based on utility theory
  - MACBETH (Measuring Attractiveness by a Categorical Based Evaluation Technique)
  - AHP (Analytic Hierarchy Process)
  - DCE (Discrete Choice Experiment)

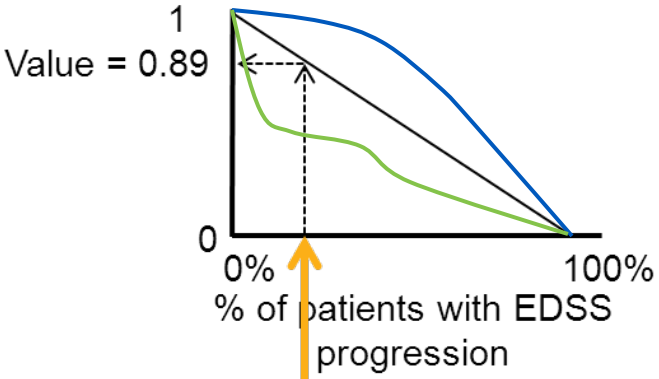
Natalizumab case study

Drug of interest	Natalizumab
Indication	Relapsing remitting multiple sclerosis
Severe side effects	Progressive Multifocal Leukoencephalopathy (PML)
Regulatory history	2004 Approved 2005 License withdrawn 2006 Re-introduced because of patient demand 2009 CHMP reassessed the PML risk and continue approval
Data source	EPARs
Comparators	Placebo, interferon β-1a, glatiramer acetate

Natalizumab: Value tree for MCDA



Natalizumab: Weighted utility



Outcome: Disability Progression → **Measure = 11%** → **Value(measure) = 0.89**

Elicited Weight = 5%

BR Contribution = 0.045

Expected utility for each alternative

Let

$$w_j = \text{preference weight for criterion } j$$

$$S_{ij} = \text{utility score for criterion } j \text{ in alternative } i$$

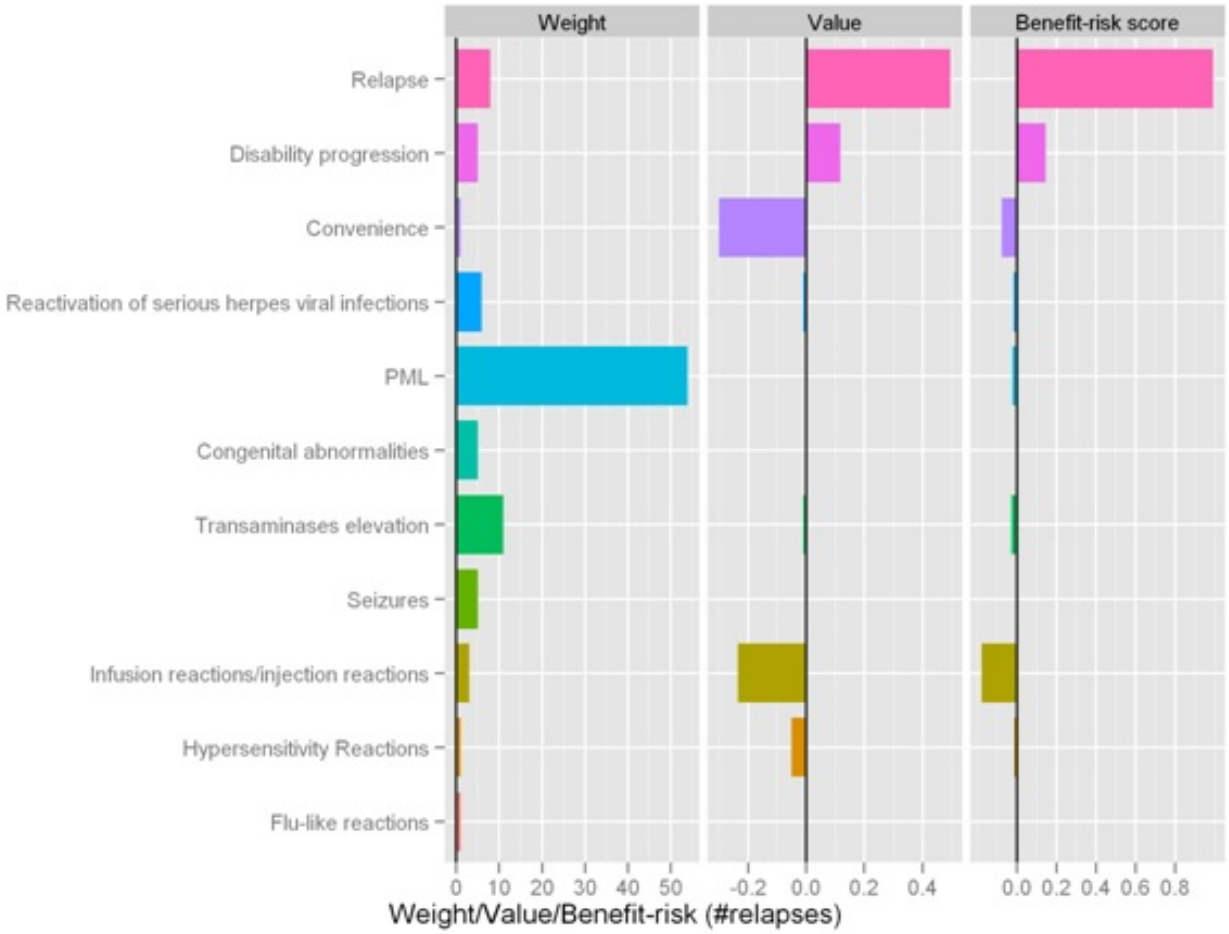
With constraint $\sum_{j=1}^{k} w_j = 1$ for k number of criteria

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

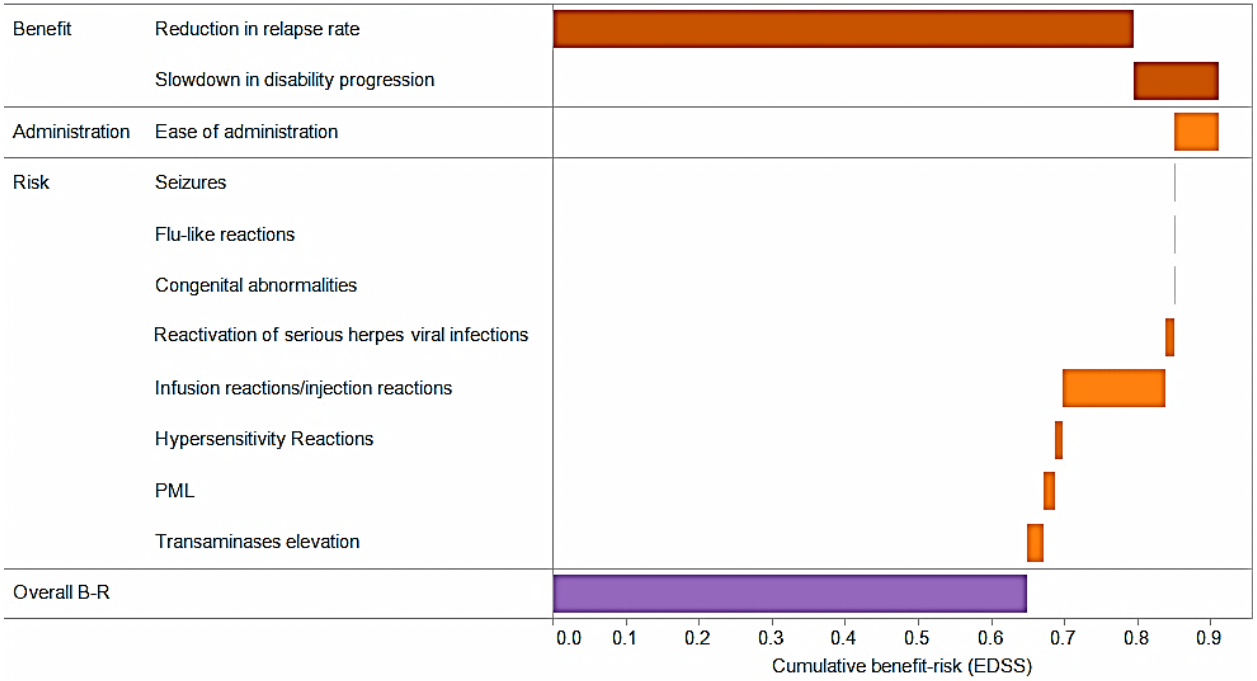
Contribution of each outcome for Natalizumab vs. placebo



- 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

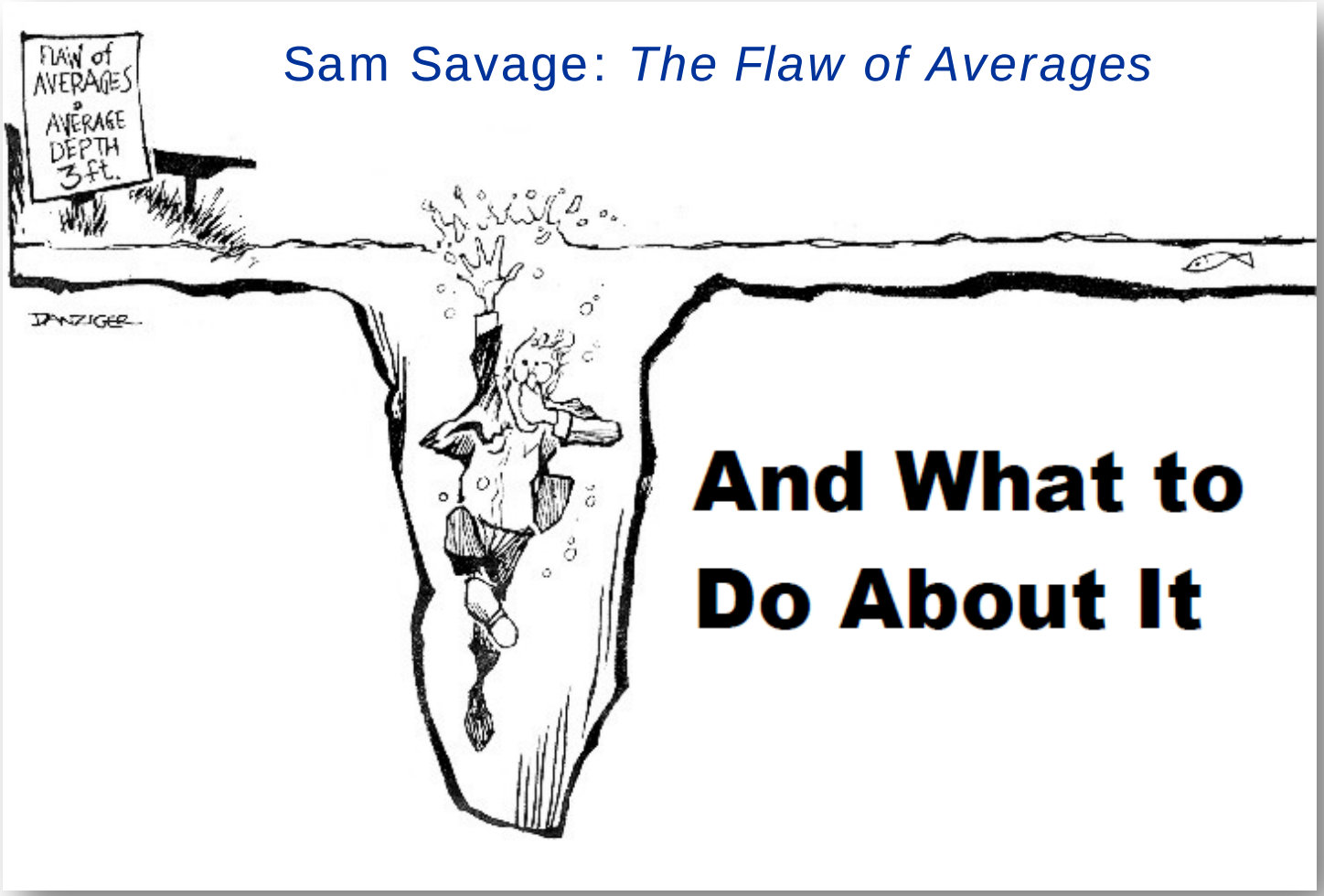
Waterfall plot for Natalizumab vs. placebo



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

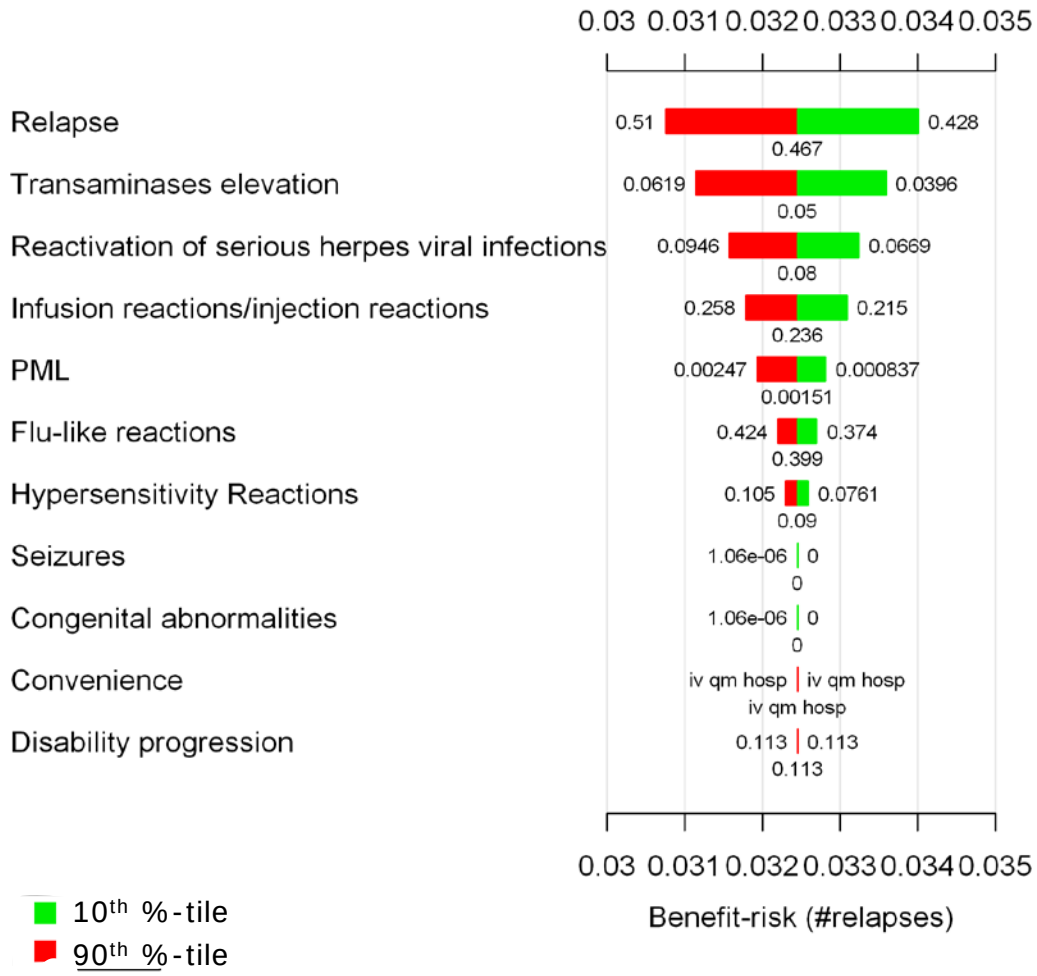
- Like a horizontal bar chart, except that the end of the previous bar determines the start of the next bar
- End of the last bar gives the overall benefit-risk.
- Brown= positive BR; Orange = negative BR; Purple = overall

The flaw of averages



Natalizumab: Uncertainty

Tornado plot for Natalizumab vs. placebo



- Clinical parameters uncertain
- So benefit-risk balance is uncertain
- Perform sensitivity analysis

Back to (old) school… Bayesian statistics

- 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
- Extend uncertainty analysis in a probabilistic model
- Landscape for decisions through entire distributions
- Growing applications but there is still resistance

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Brief on SMAA

- Stochastic Multi-criteria Acceptability Analysis
- Similar to MCDA (MAUT) – inverse approach
- 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

SMAA: 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

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

SMAA: Calculating central weight

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

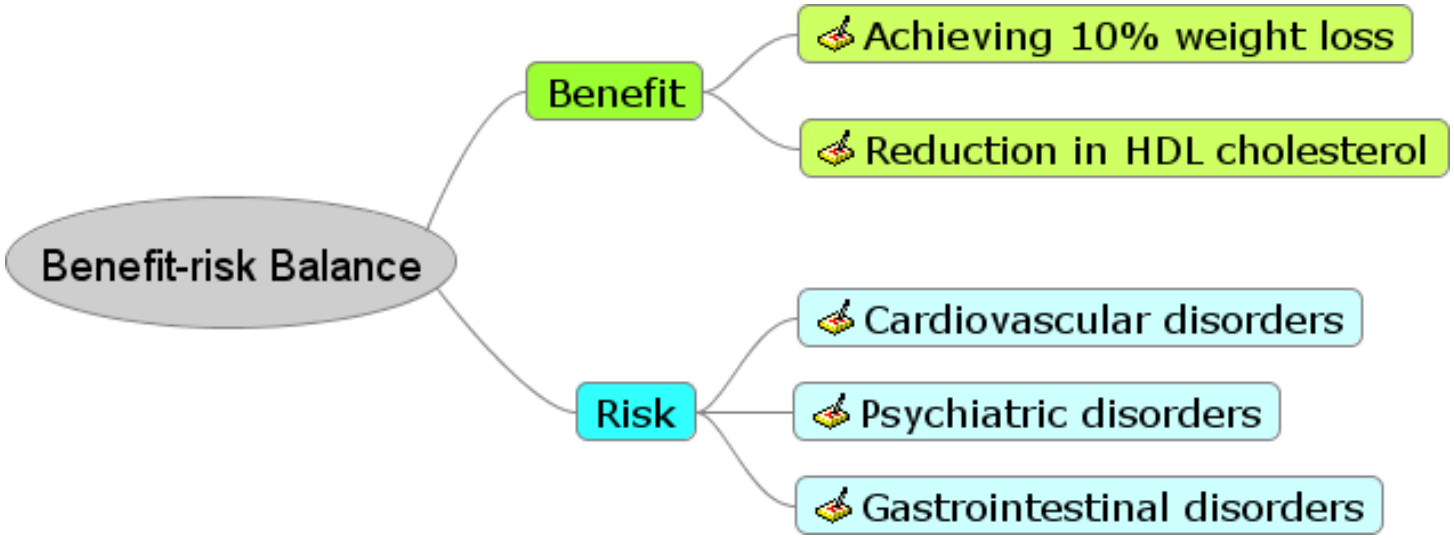
$$w_i^c = \frac{1}{b_i^1} \int_{\xi \in X} f_X(\xi) \int_{w \in W_i^1(\xi)} w f_W(w) dw d\xi$$

… which determines the best weight space for alternative i

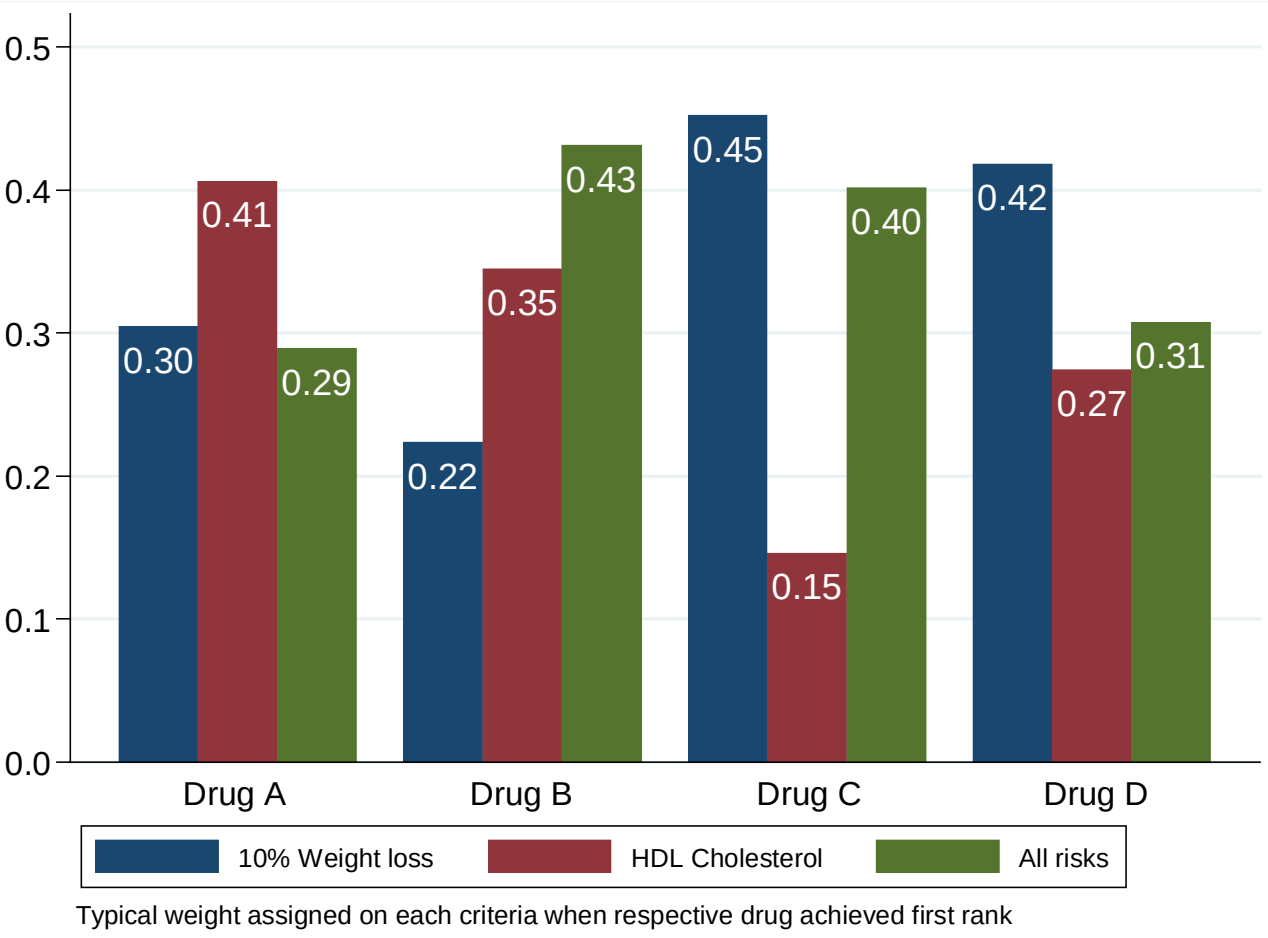
Rimonabant case study

Drug of interest	Rimonabant
Indication	Weight loss in obese and overweight patients with co-morbidities in adults (>18y)
Severe side effect	Increased risk of depression
Regulatory history	2006 Approved in June 2009 Voluntary withdrawal in January
Data source	EPAR Published clinical trials
Comparators	Placebo, orlistat, sibutramine

Rimonabant: Value tree for SMAA



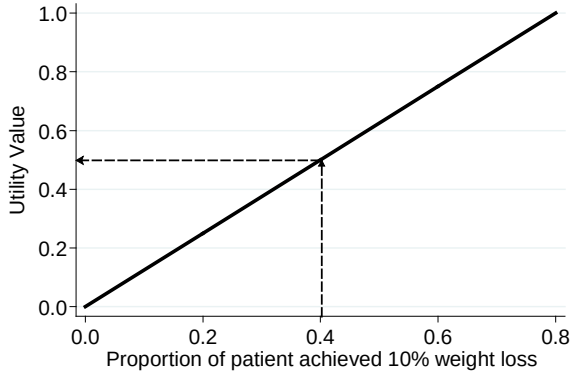
Rimonabant: Central weight vectors



Typical weight assigned on each criteria when respective drug achieved first rank

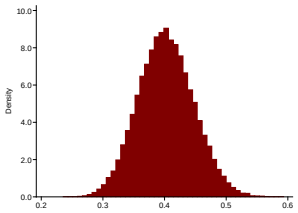
- Preference-free model
- Understand what kind of weights favour certain alternatives
- No clinical significance

SMAA (rimonabant): Weighted utility

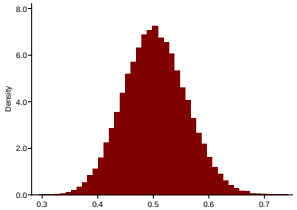


Outcome: Achieved 10% weight loss

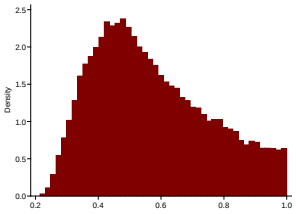
Measure: 40% (range 24% - 59%)



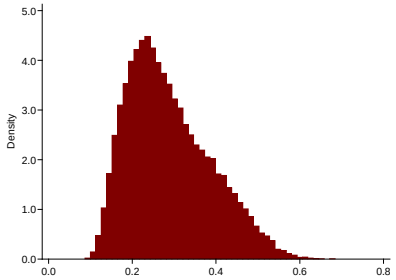
Value(measure): 50% (range 29% - 74%)



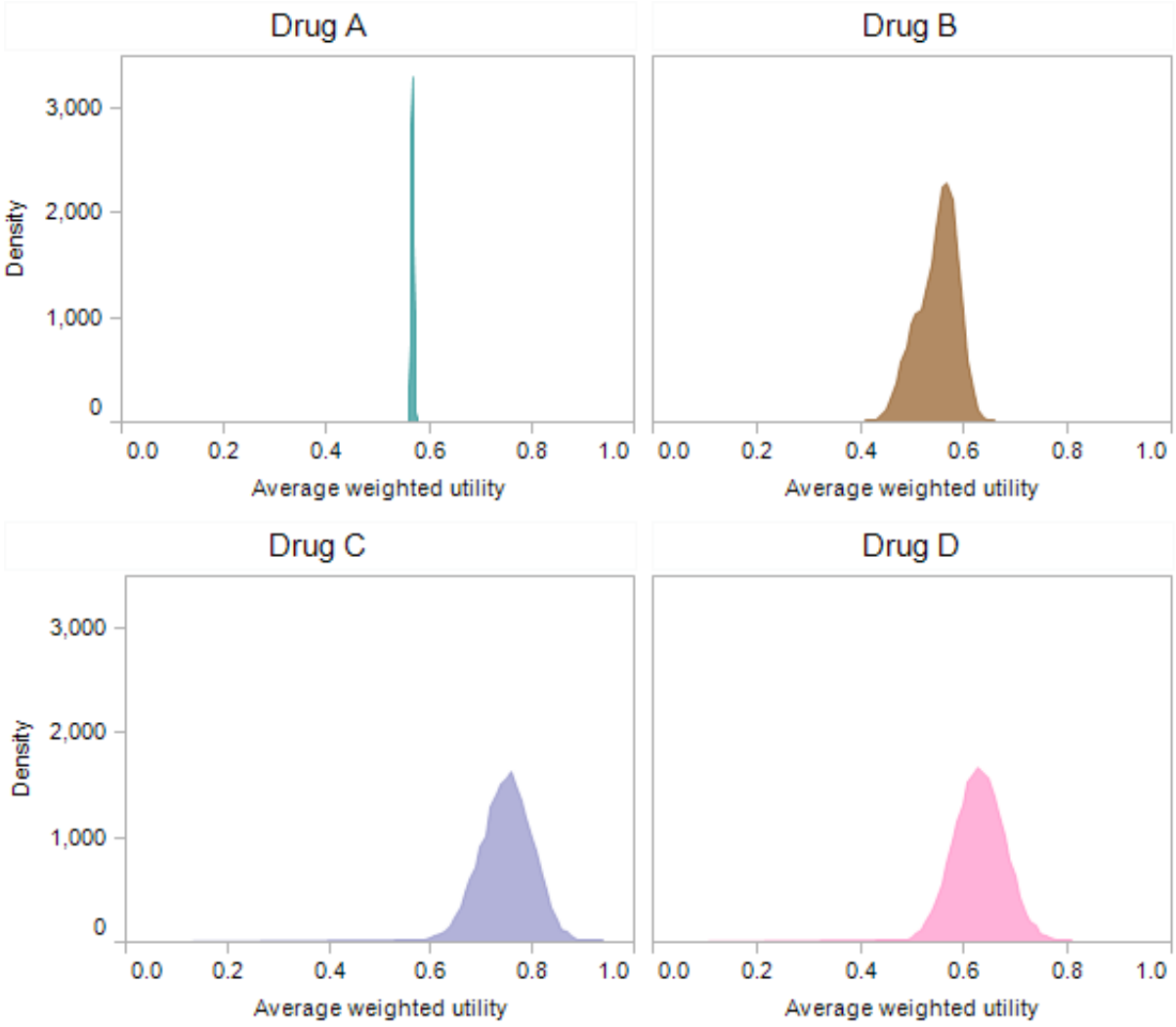
Weight space: 57% (range 21% - 100%)



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

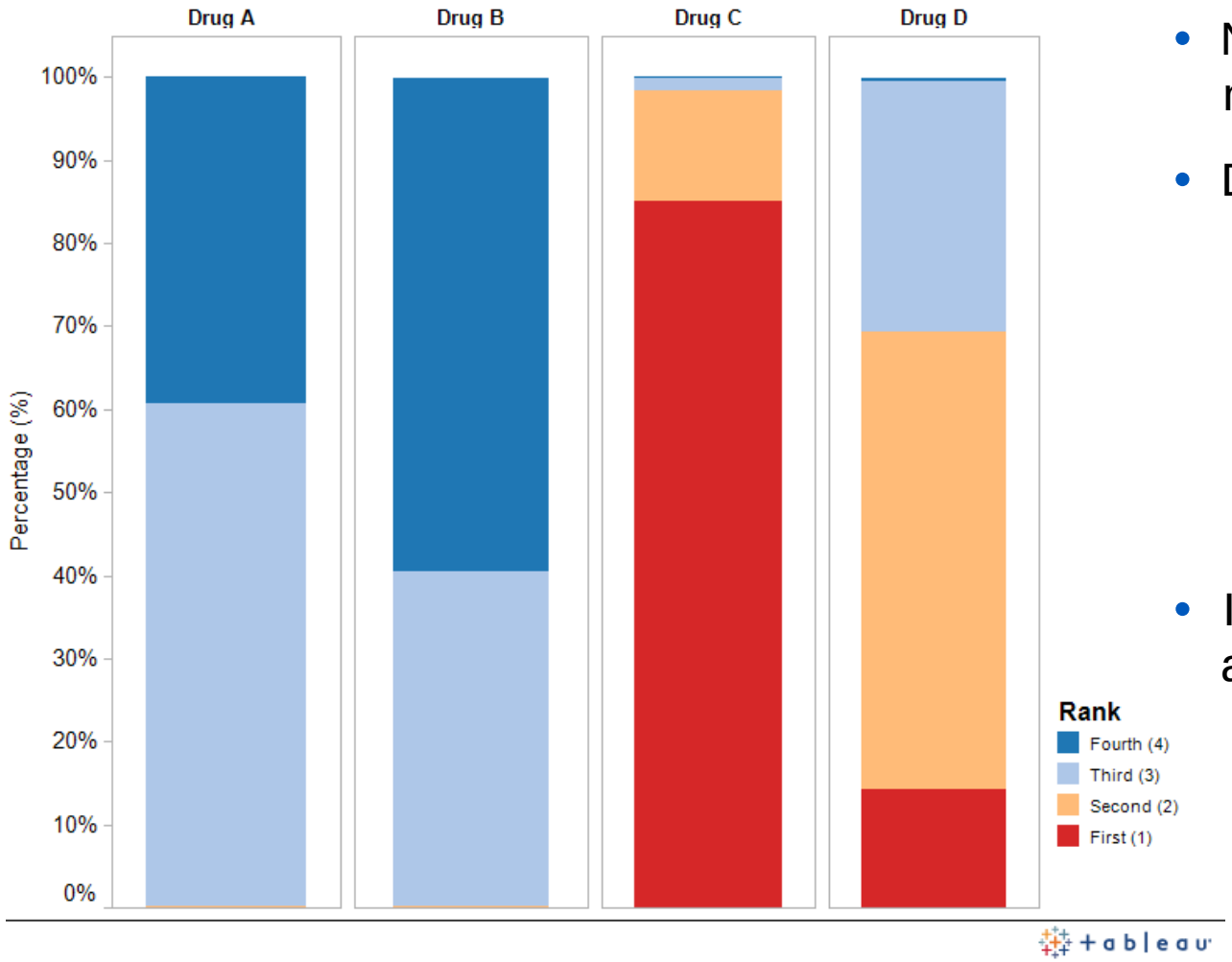


Rimonabant: Distributions of utilities



- 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

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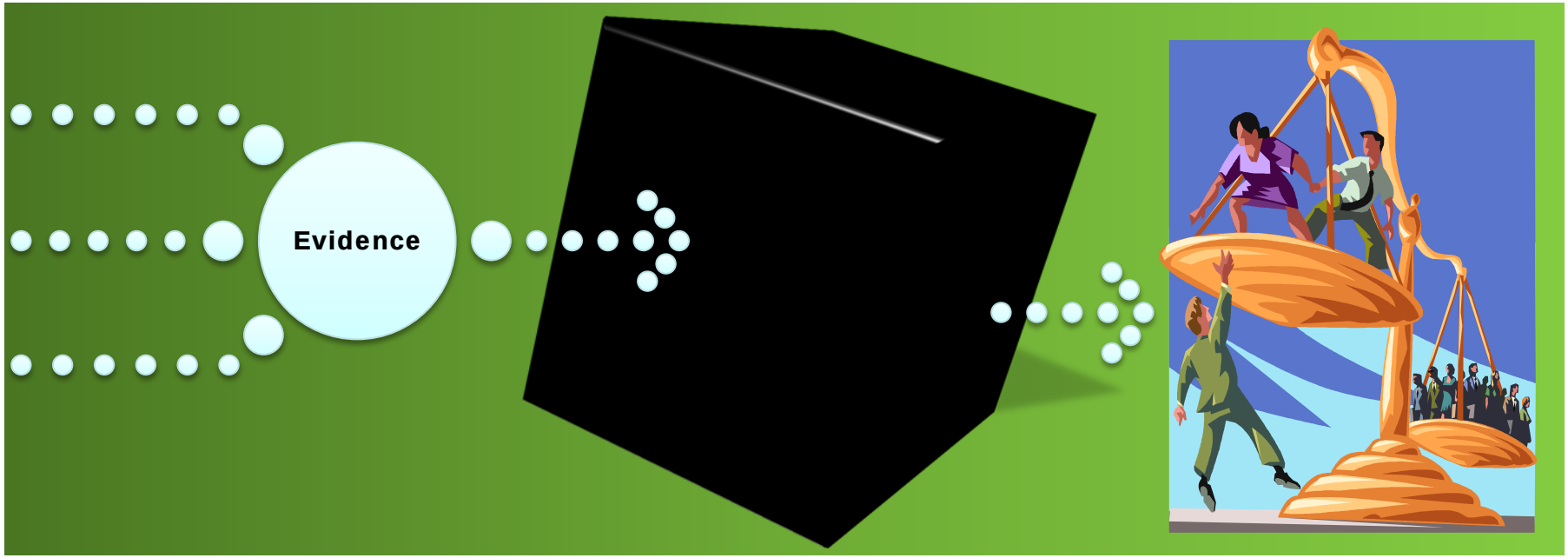
Why do we need formal approaches?

- 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

But… what is holding us back?



- the data, time and expertise required to implement this approach may not always be available.
- Trade-off for making trade-off

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