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Formal benefit-risk assessment approaches in regulatory decision-making of medicinal products

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Presented by:
Shahrul Mt-Isa
Imperial College London

Outline

- Challenges in medical decision-making
- Formal benefit-risk approaches and transparency
- Case study I: Applications of MCDA
- Case study II: Applications of SMAA

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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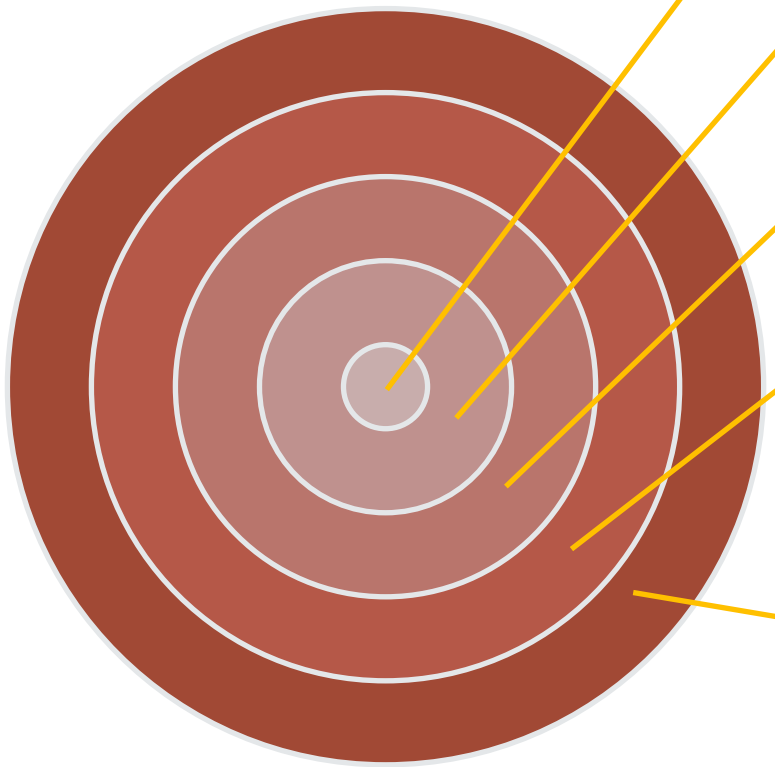
Decision makers – who are they?



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, DKMA, AEMPS, NoMA, Swissmedic 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
- 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

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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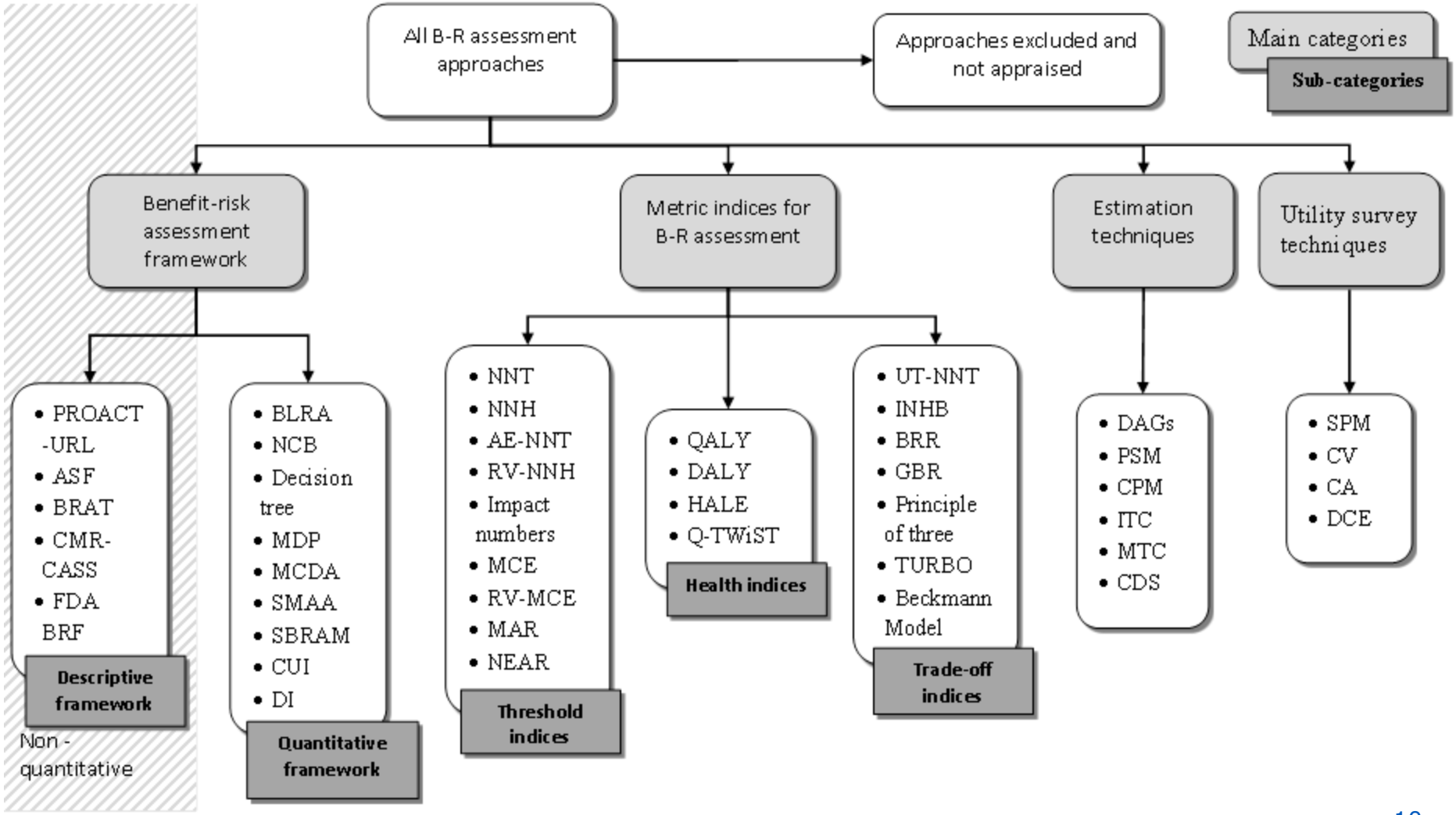
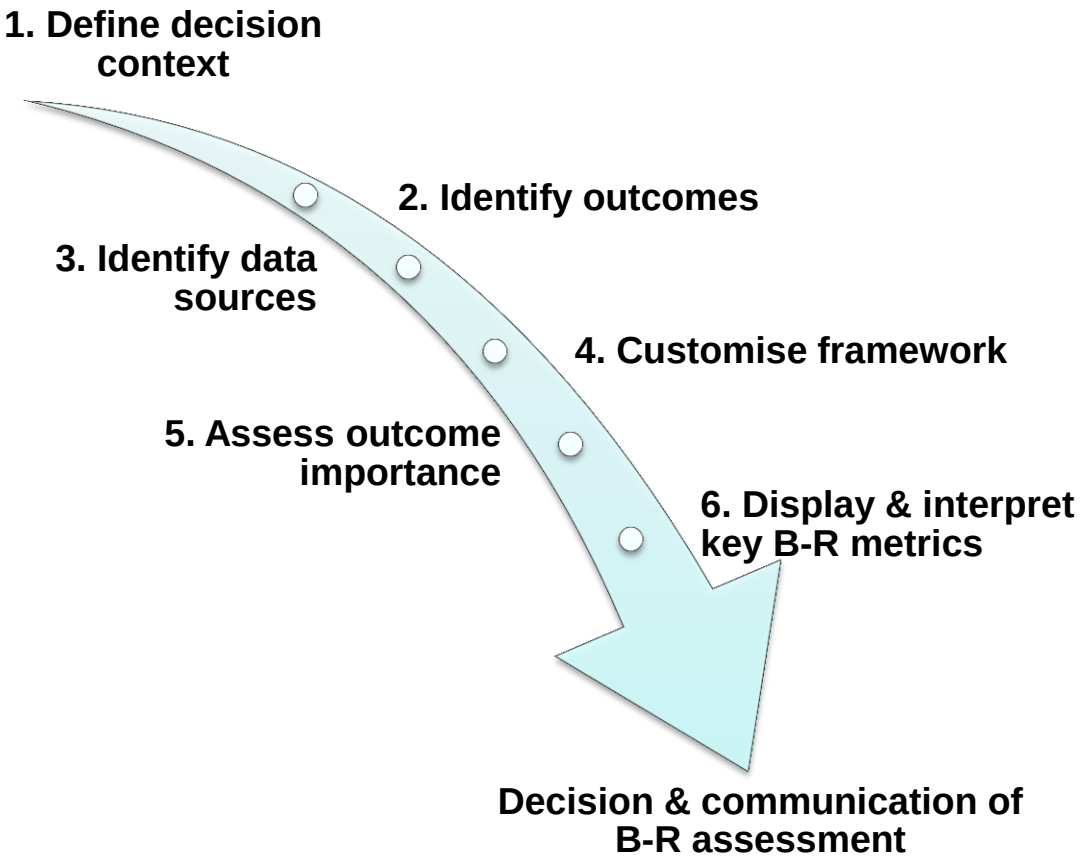
Classifications of approaches



PrOACT-URL Framework

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

BRAT Framework



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

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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."

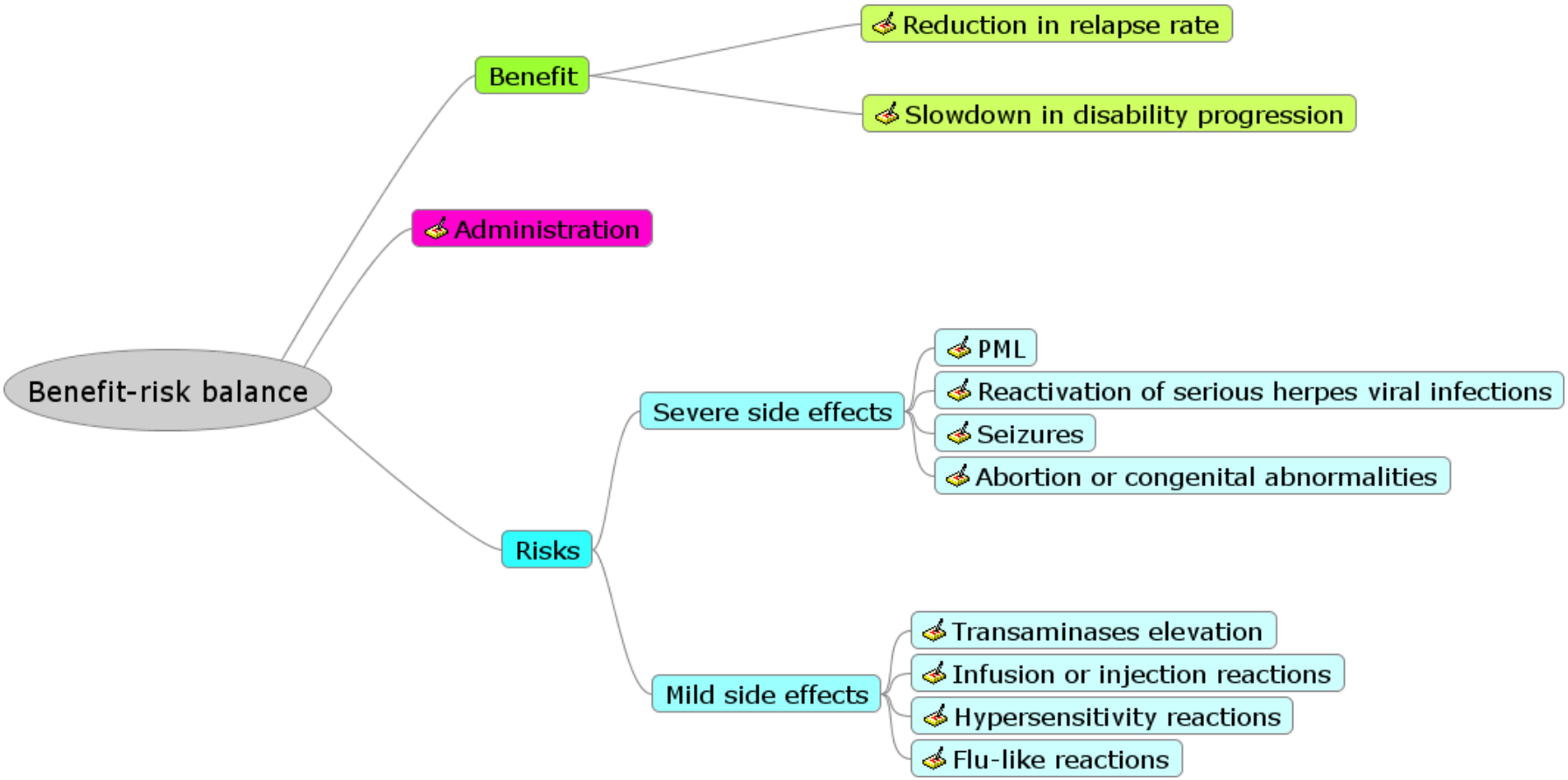
Brief on MCDA

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

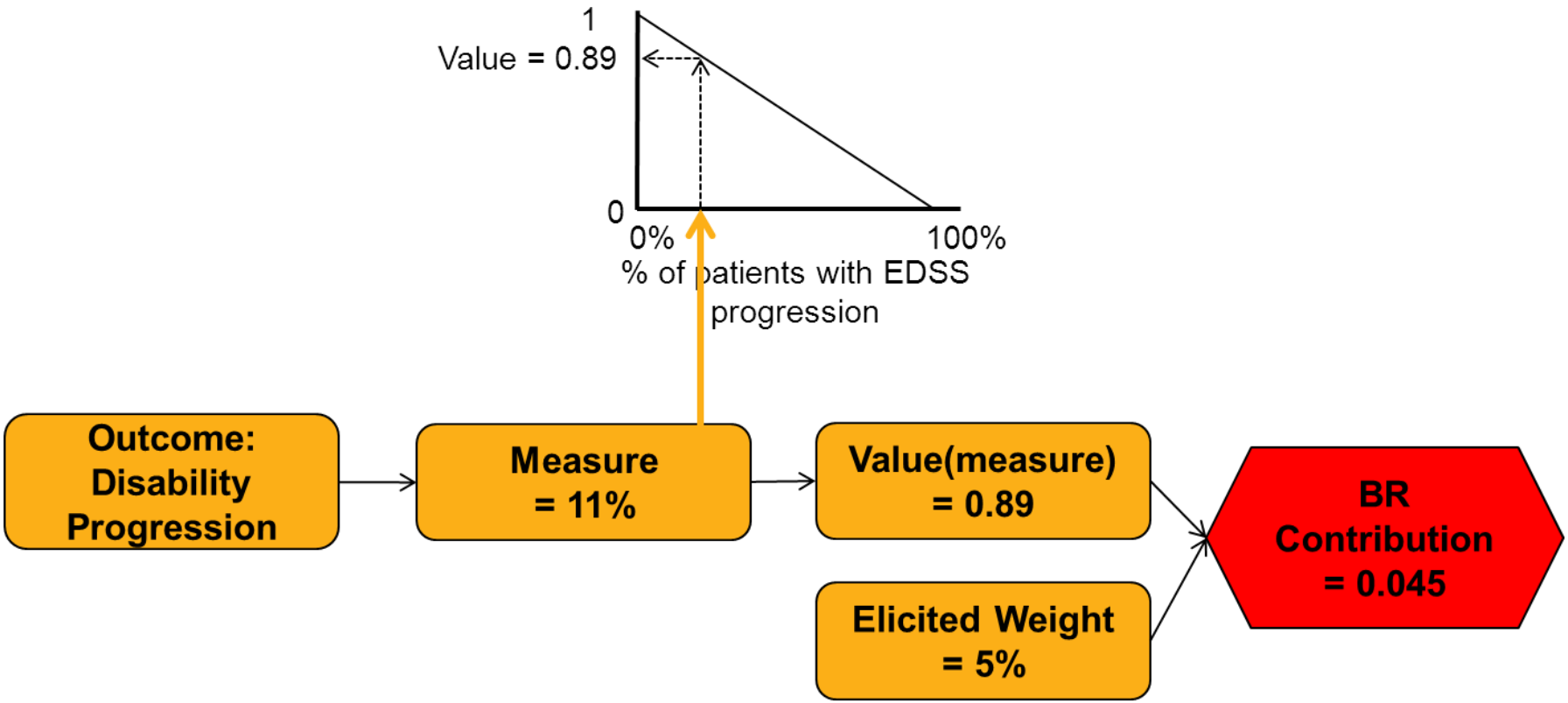
Natalizumab case study

Active drug	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



Natalizumab: Expected utility

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

w_j = preference weight for criterion j

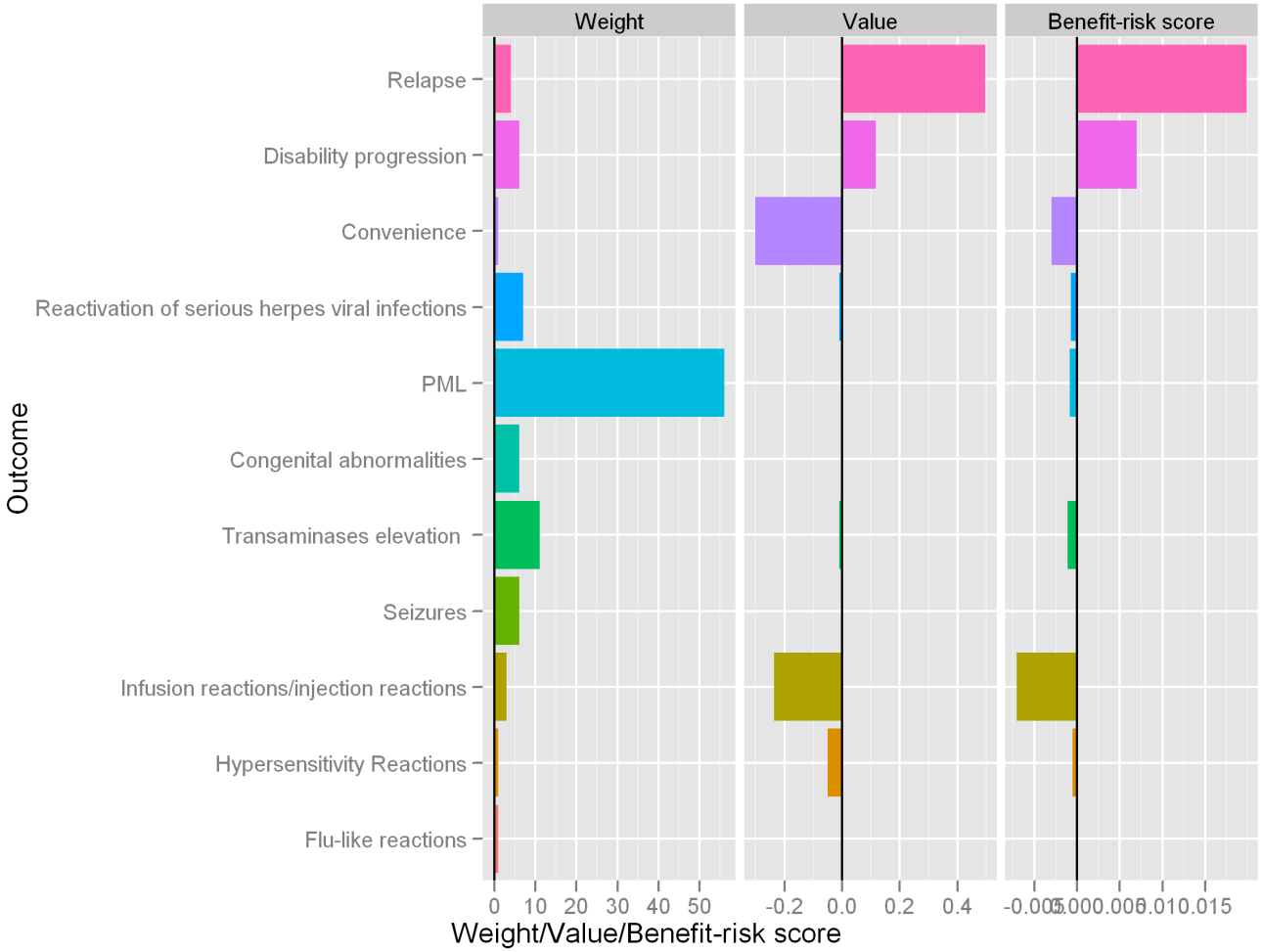
With constraint $\sum_{j=1}^{k} w_j = 1$ for k number of criteria

Then, the overall expected utility for alternative i is

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

Natalizumab: Weighted Scores

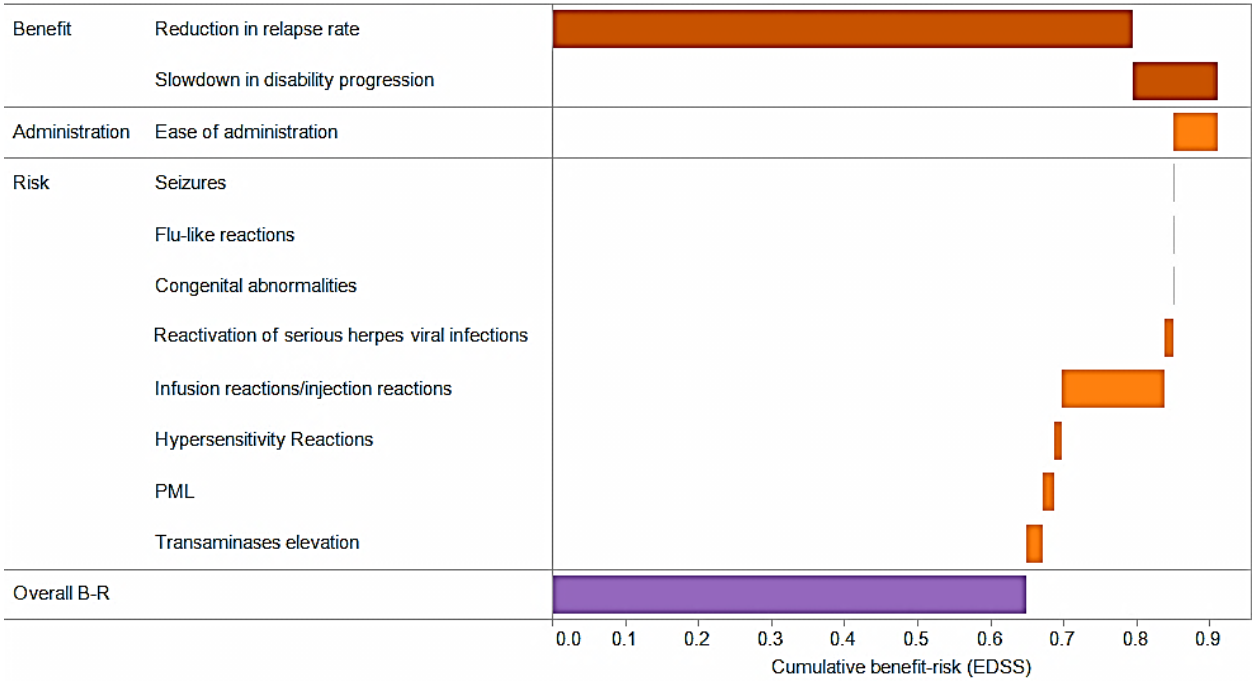
Contribution of each outcome for Natalizumab vs. placebo



- 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

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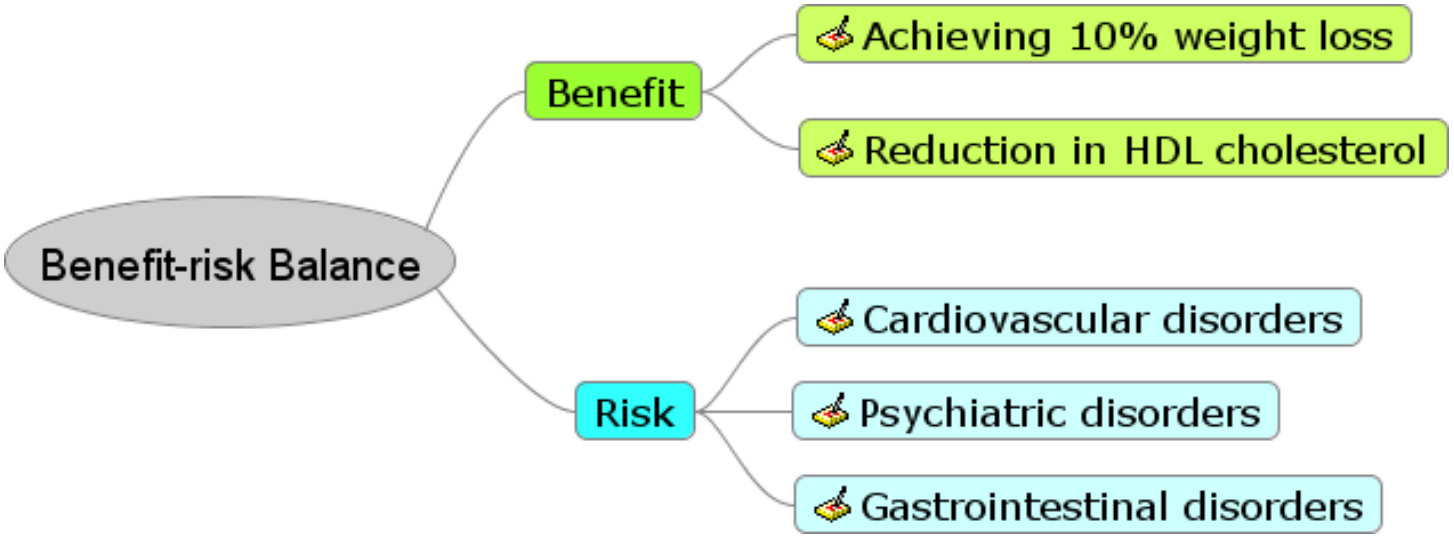
Brief on SMAA

- Similar to MCDA (MAUT)
- 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

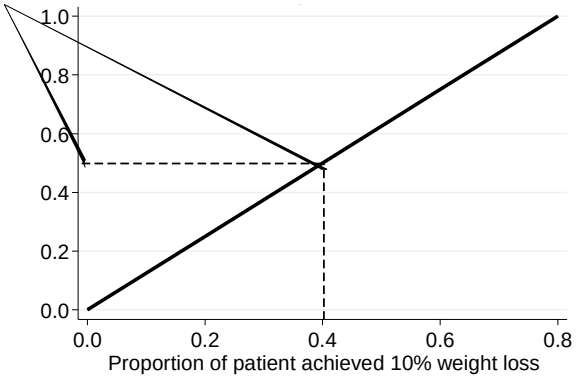
Rimonabant case study

Active drug	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
Comparator	Placebo, orlistat, sibutramine

Rimonabant: Value tree for SMAA

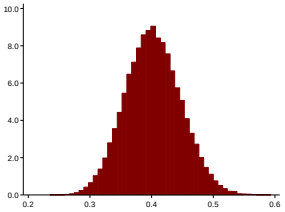


SMAA (rimonabant): Weighted utility

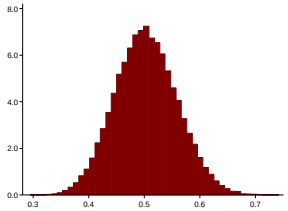


Outcome: Achieved 10% weight loss

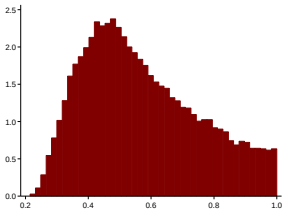
Measure: 40% (range 24% - 59%)



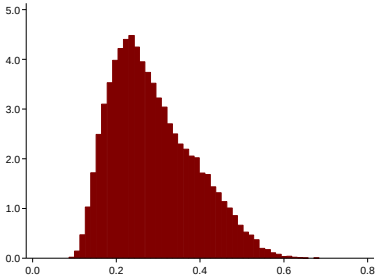
Value(measure): 50% (range 29% - 74%)



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



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



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

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

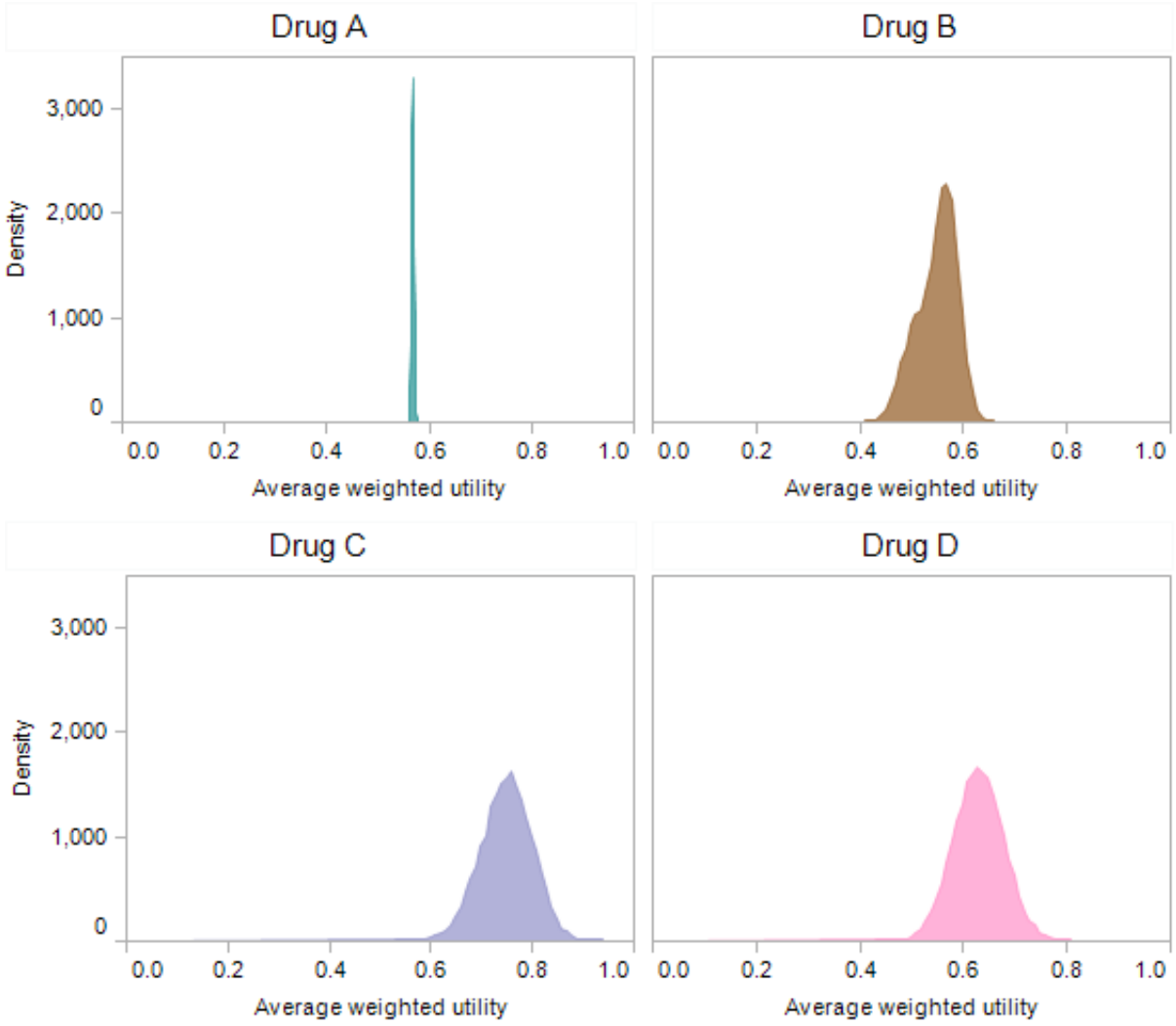
SMAA: Calculating central weight

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

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

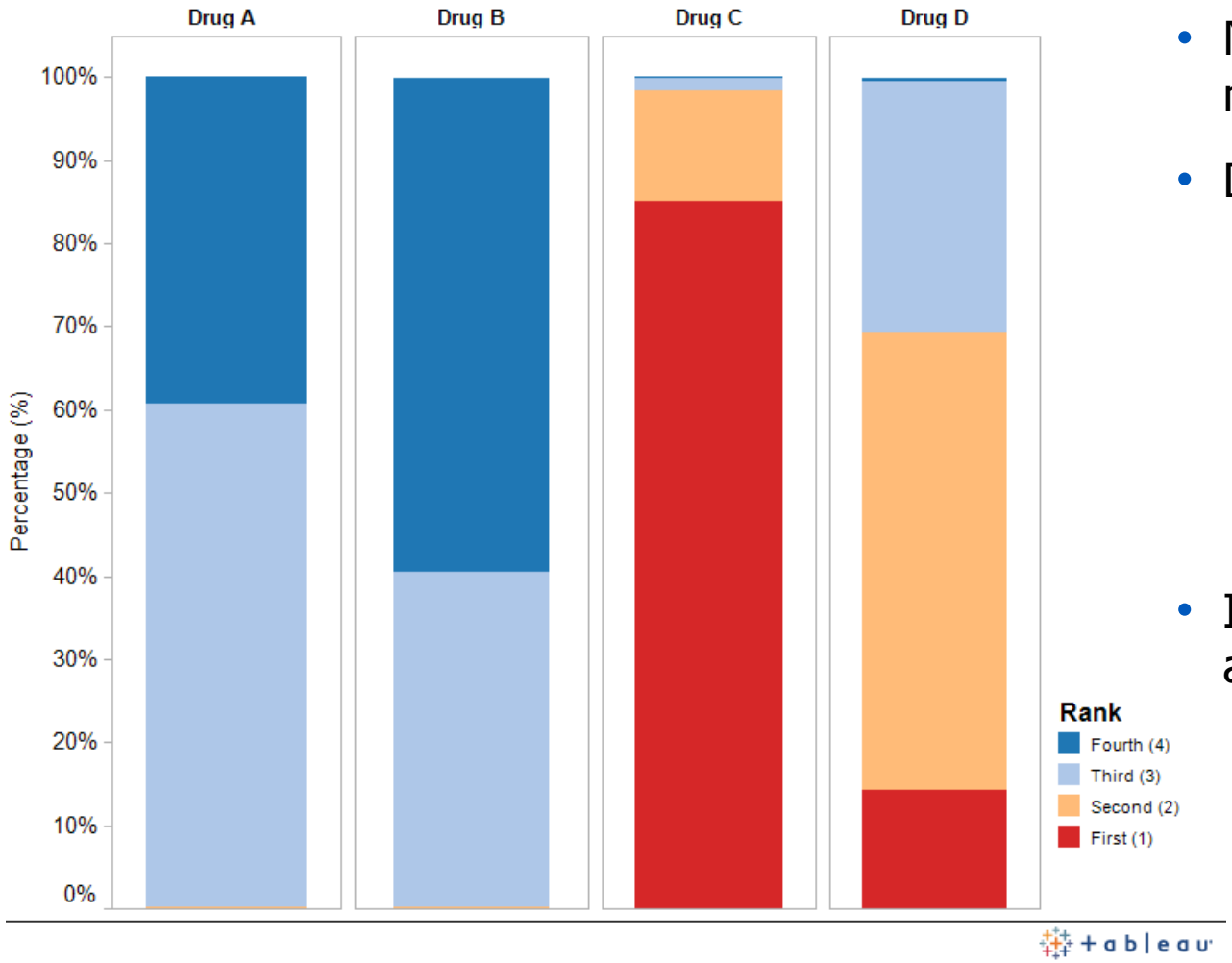
… which determines the best weight space for alternative i

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

Why do we need them?

- 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

Acknowledgements

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