

Future directions of benefit-risk assessment in Europe

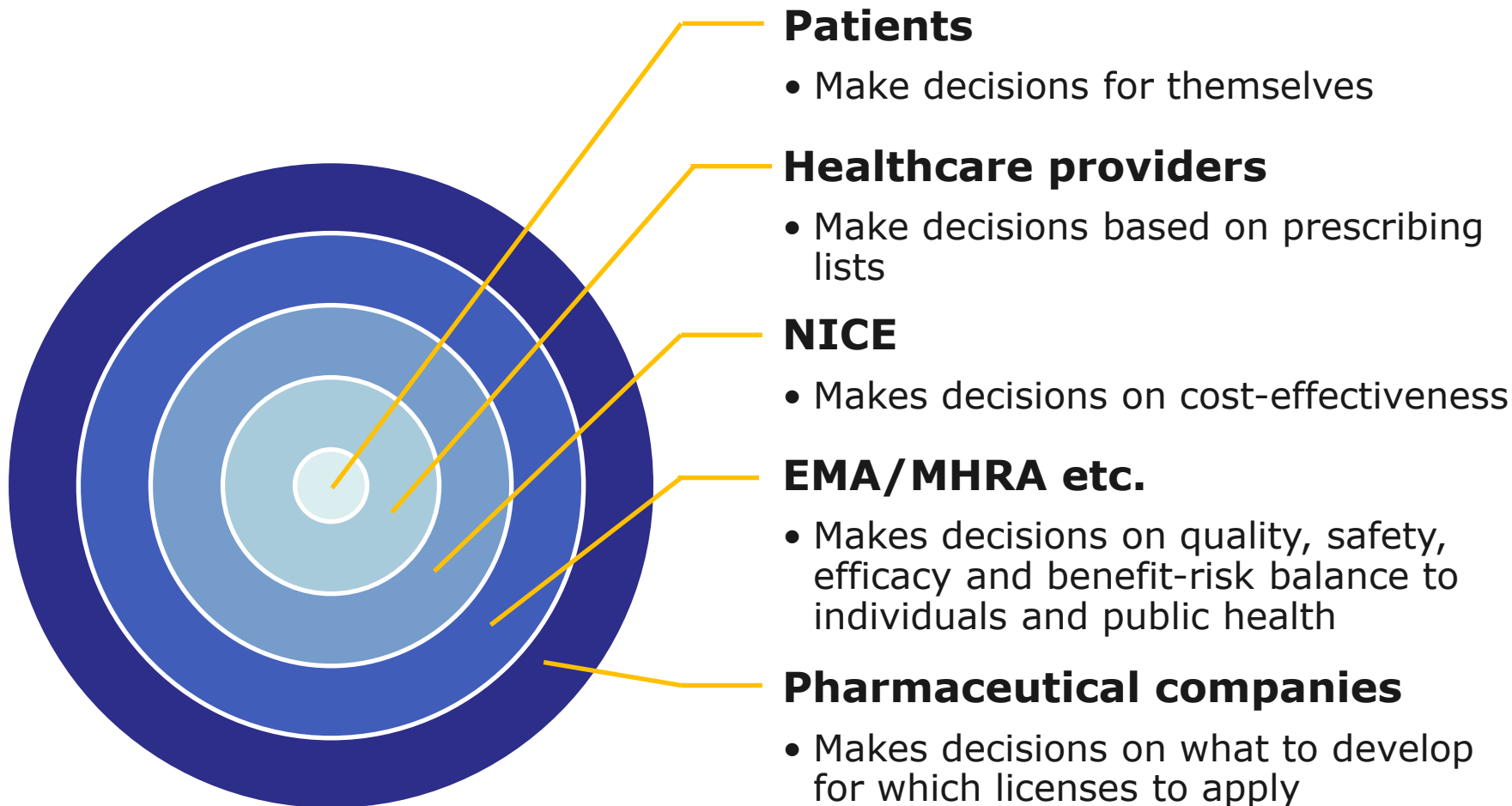
ISPE Mid-year meeting, Munich, Germany
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Imperial College London

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
- Patient involvement and final remarks

Decision makers – who are they? (UK)



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?

Disclaimers

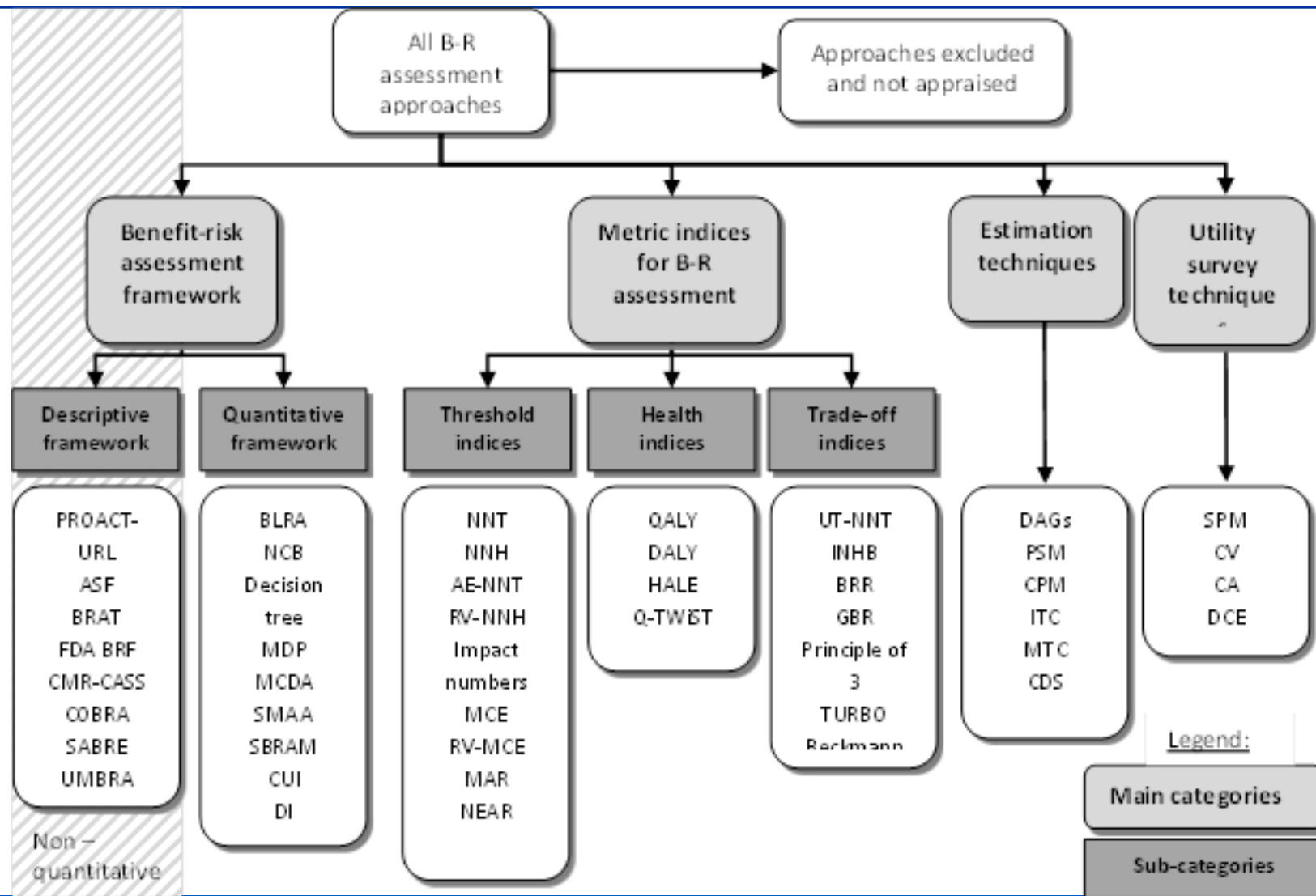
“The processes described and conclusions drawn from the work presented herein relate solely to the testing of methodologies and representations for the evaluation of benefit and risk of medicines.

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.”

Benefit-risk initiatives

- EMA Benefit-Risk methodology project
- PhRMA BRAT Framework
- 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

Classifications of approaches



Wave 1 Case studies: Applications

	Natalizumab	Rimonabant	Telithromycin	Efalizumab
PrOACT-URL	✓	✓	✓	✓
BRAT	✓	✓	✓	✓
MCDA	✓	✓	✓	✓
SMAA		✓	✓	
NNT & NNH	✓	✓		
Impact Number		✓		
QALY				
Q-TWiST				
INHB		✓		
BRR	✓	✓	✓	✓
PSM	✓	✓	✓	
MTC	✓			
DCE				
Other:	Decision conferencing	Direct utility elicitation	SBRAM, Swing-weighting	Decision conferencing

Wave 2 Case studies: Applications

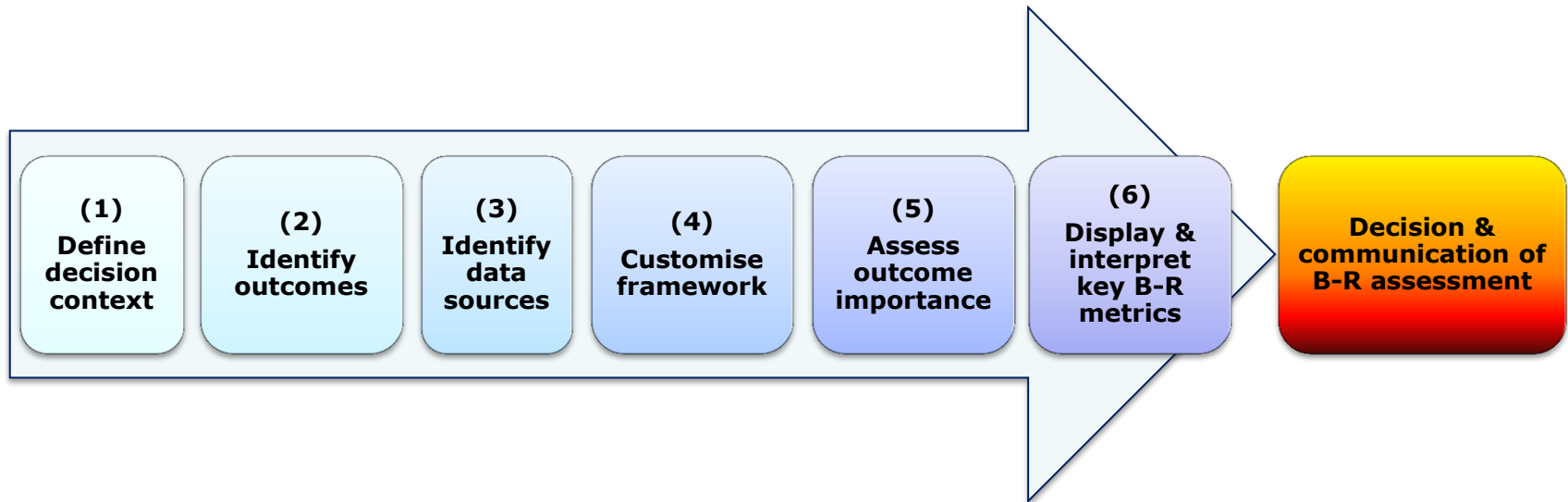
	Natalizumab	Rimonabant	Rosiglitazone	Warfarin
PrOACT-URL		✓ (jointly)	✓	
BRAT	✓	✓ (jointly)		✓
MCDA	✓		✓	
SMAA	✓	✓		
PSM	✓		✓	
MTC/ITC	✓	✓	✓	✓
DCE		✓		
<i>AHP</i>	✓			
<i>Swing-weighting</i>	✓		✓	
<i>MACBETH</i>	✓			

PrOACT-URL



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

BRAT

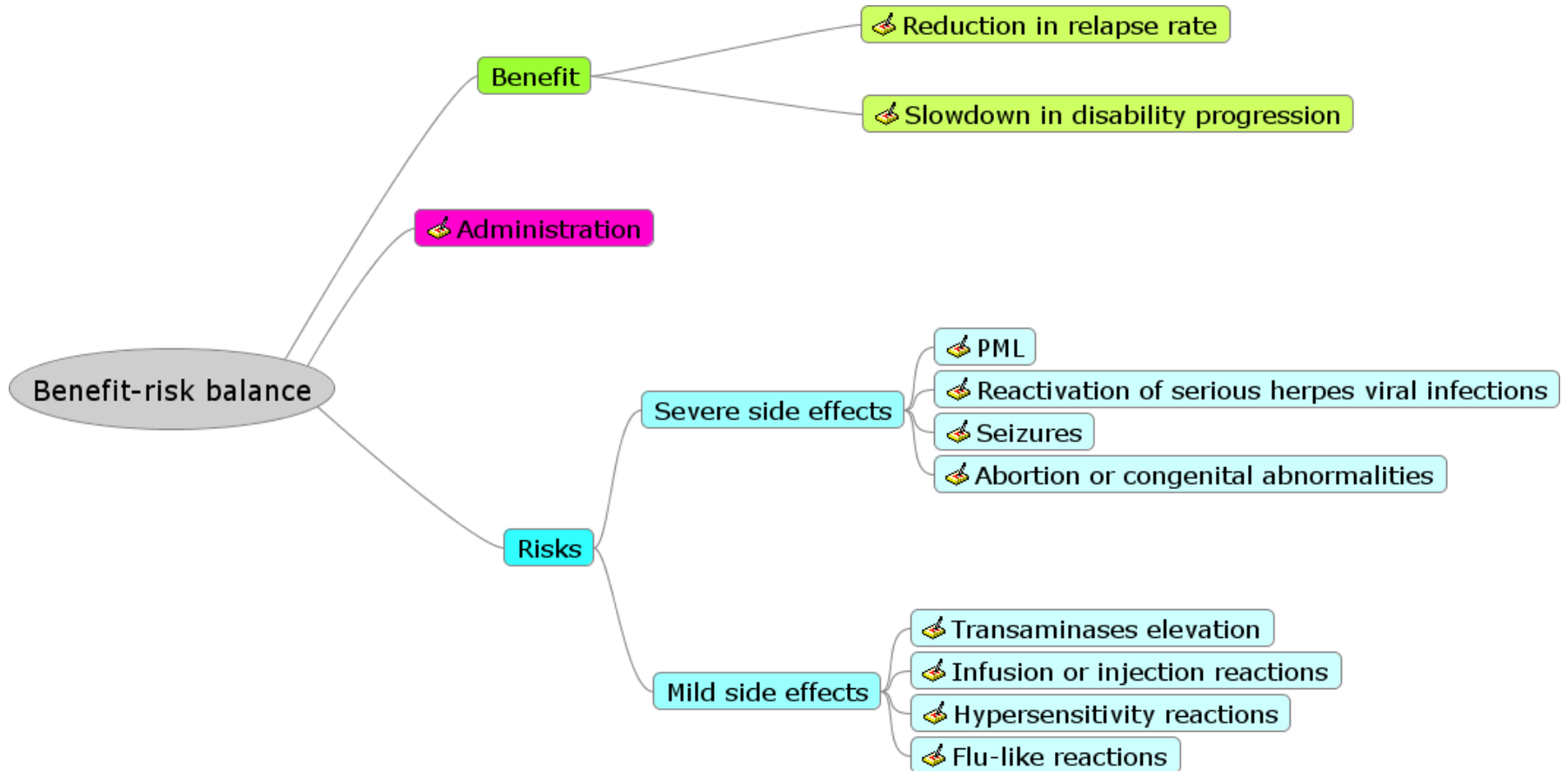


- A framework to assist benefit-risk assessment and communication
- Divide into 6 steps
- Source data table
- Emphasis on uncertainty via confidence intervals when presenting results

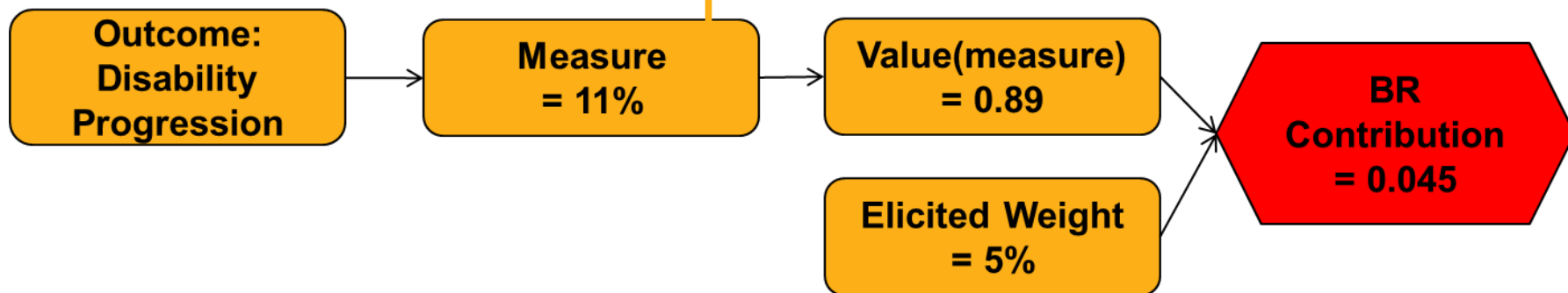
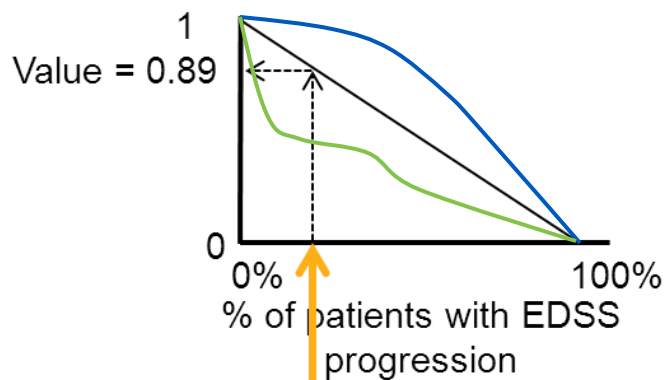
Brief on MCDA

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

Natalizumab: Value tree for MCDA

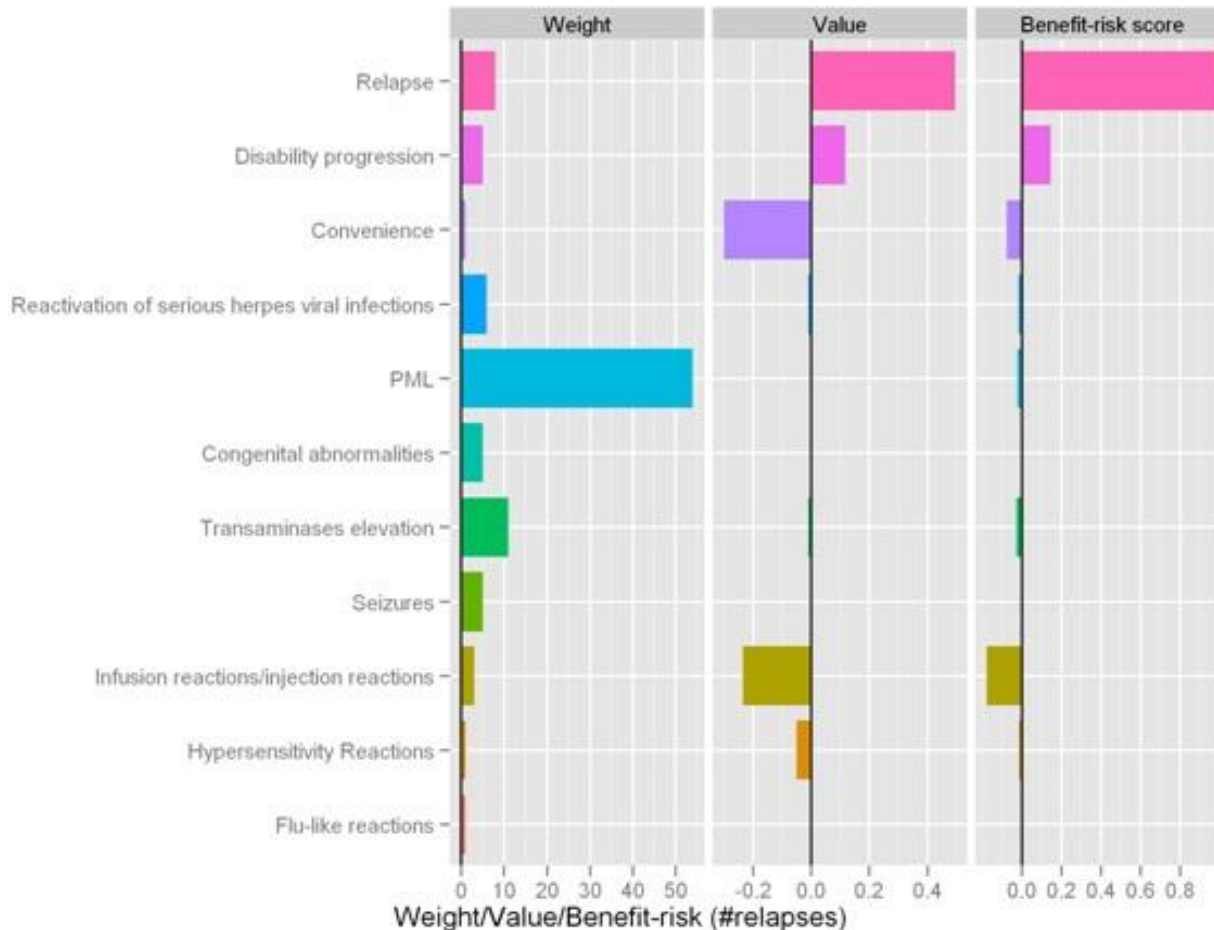


Natalizumab: Weighted utility



Natalizumab: Weighted Scores

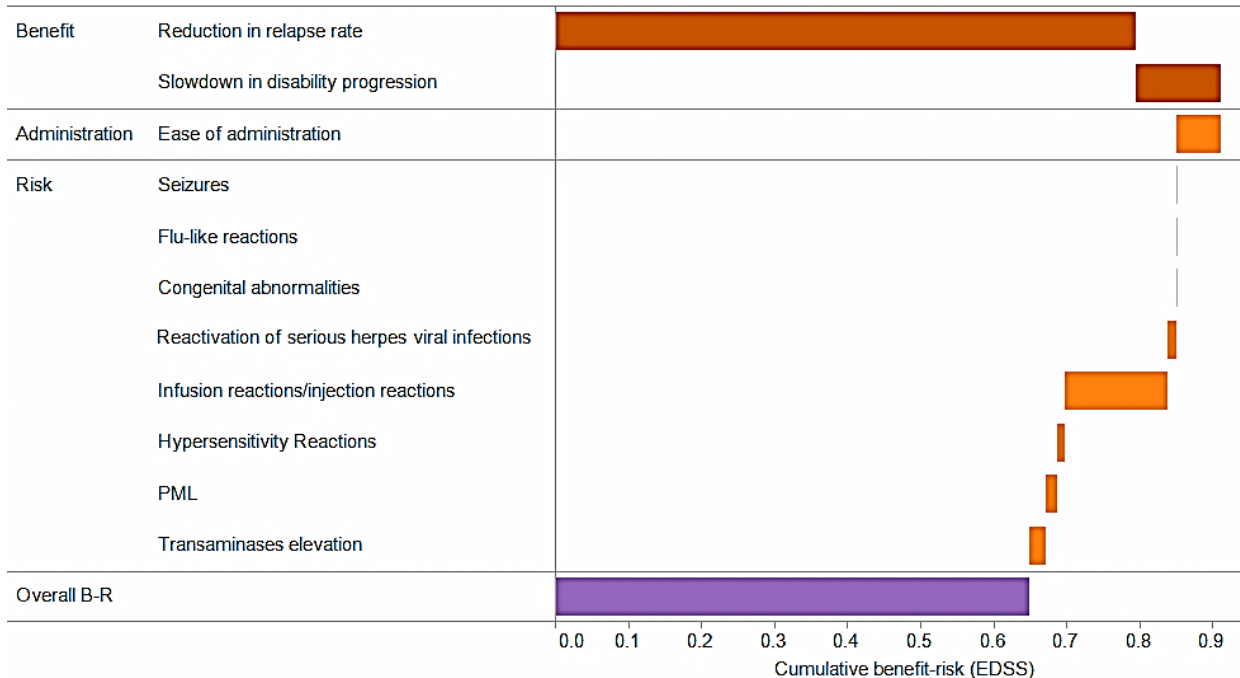
Contribution of each outcome for Natalizumab vs. placebo



- 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



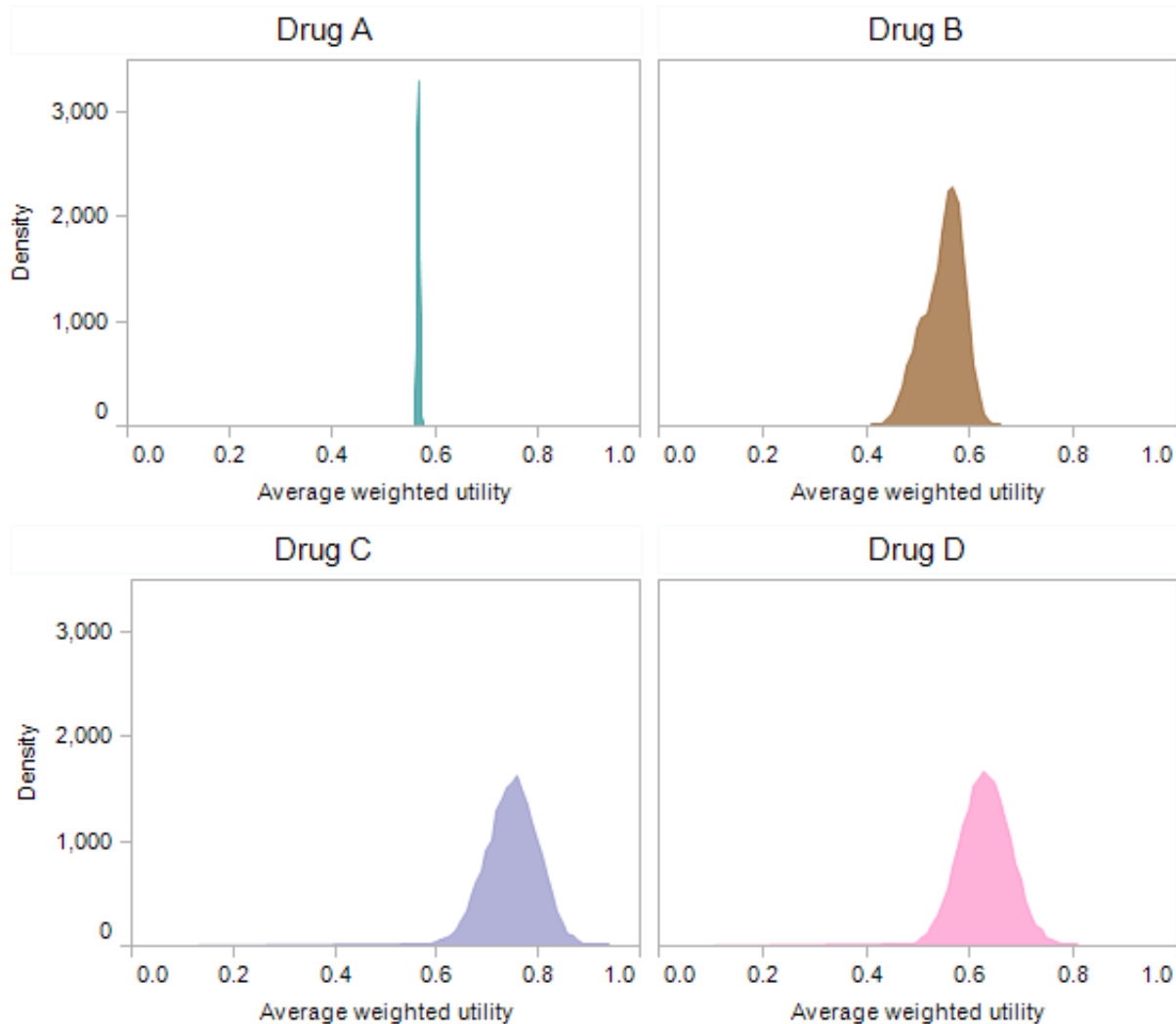
http://public.tableausoftware.com/views/T_Waterfall/WaterfallRisk

- 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

Brief on SMAA

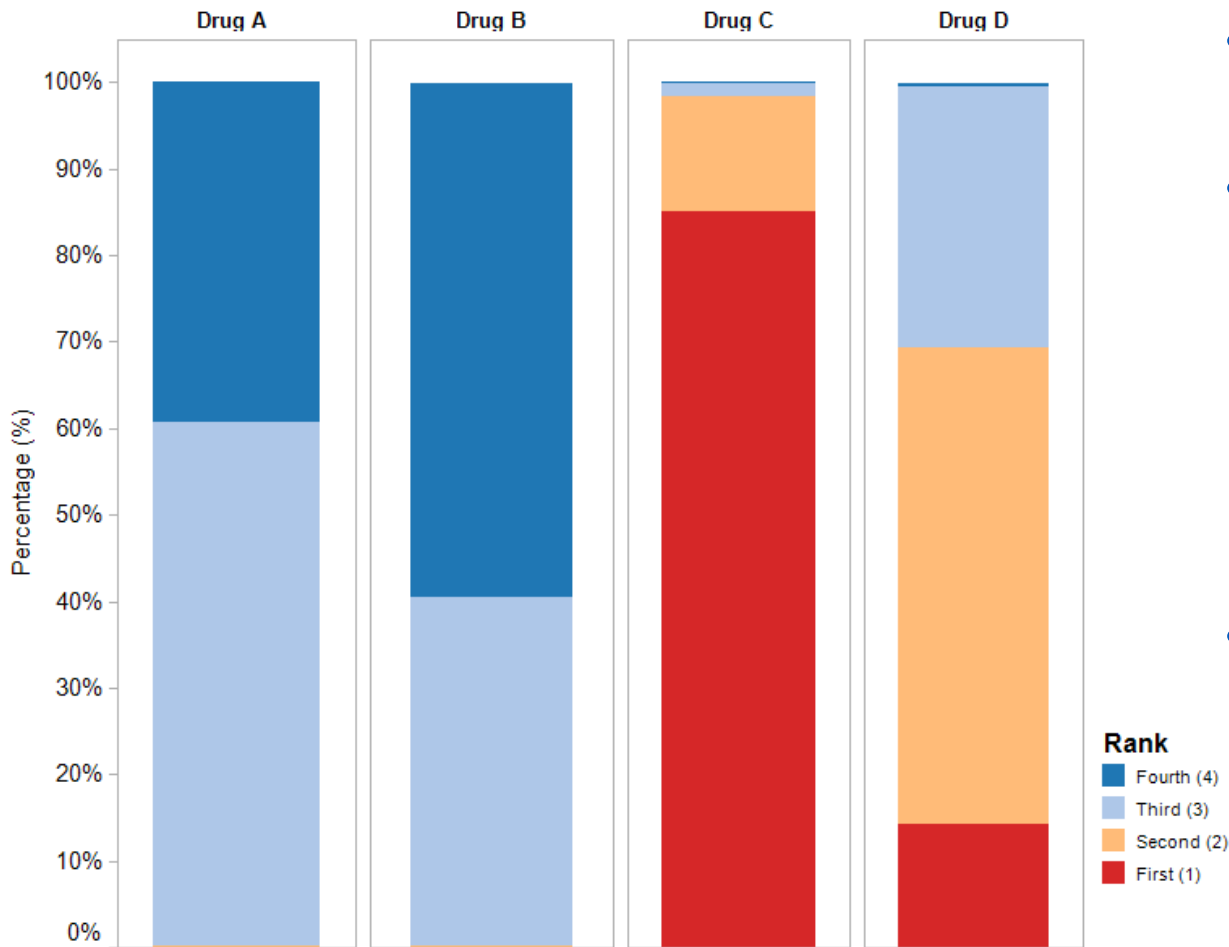
- Stochastic Multi-criteria Acceptability Analysis
- Similar to MCDA (MAUT) – inverse approach
- Requires utilities, probabilities, weights
- Allows uncertainty and missing weights
- There is no formal framework but could be used with PrOACT-URL or BRAT
- Stochastic analysis

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 involve patients and the public?

Principle	Examples
Improved governance	democratic legitimacy, accountability, trust, citizens' rights, empowerment
Social capital and social justice	tackle exclusion and increase equity, build relationships, networks and ownership
Improved quality of services, projects and programmes	more efficient and better services that meet needs and reflect broad social values
Capacity building and learning	build confidence, skills, understanding, awareness, and knowledge

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

Acknowledgements

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Framework for pharmacoepidemiology studies

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- [Reports and Databases](#) (1)

Methods for Signal Detection

- [Presentations](#) (14)
- [Publications](#) (5)
- [Reports and Databases](#) (1)

New Methods for data collection from consumers

- [Presentations](#) (3)
- [Publications](#)
- [Reports and Databases](#)

Benefit- Risk integration and representation

- [Presentations](#) (12)
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Replication studies

- [Presentations](#) (1)
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- [Publications](#)
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<http://www.imi-protect.eu/results.shtml>