Imperial College London

What role should formal risk-benefit decision-making play in the regulation of medicines?

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Outline

- Evidence-based medical decision-making
- About IMI-PROTECT
- PROTECT Work Package 5 methodology review
- Benefit-risk methodologies examples from case studies

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

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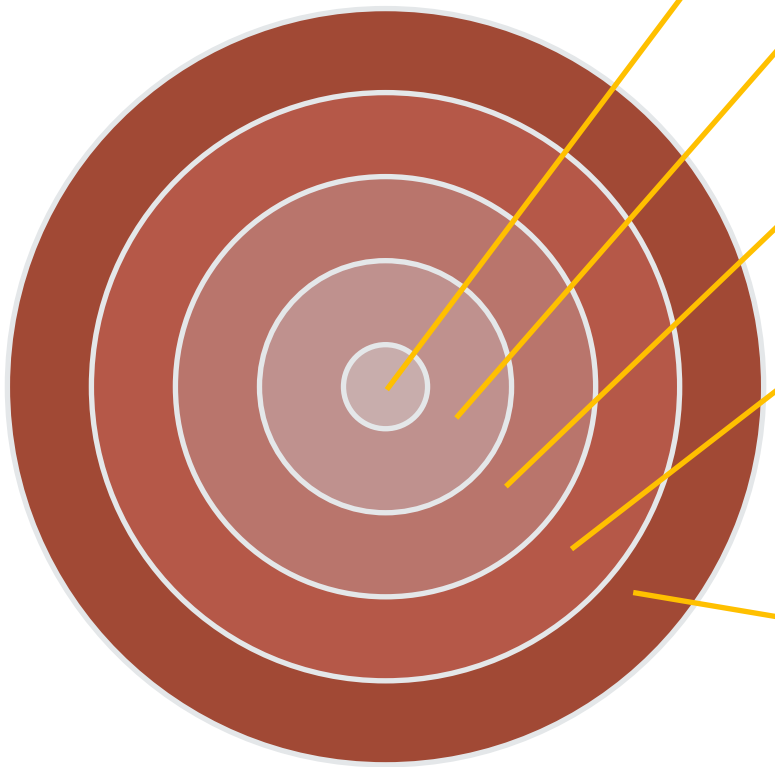
Decision makers – who are they?



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

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 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?

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The IMI-PROTECT

- PROTECT[1] (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium)

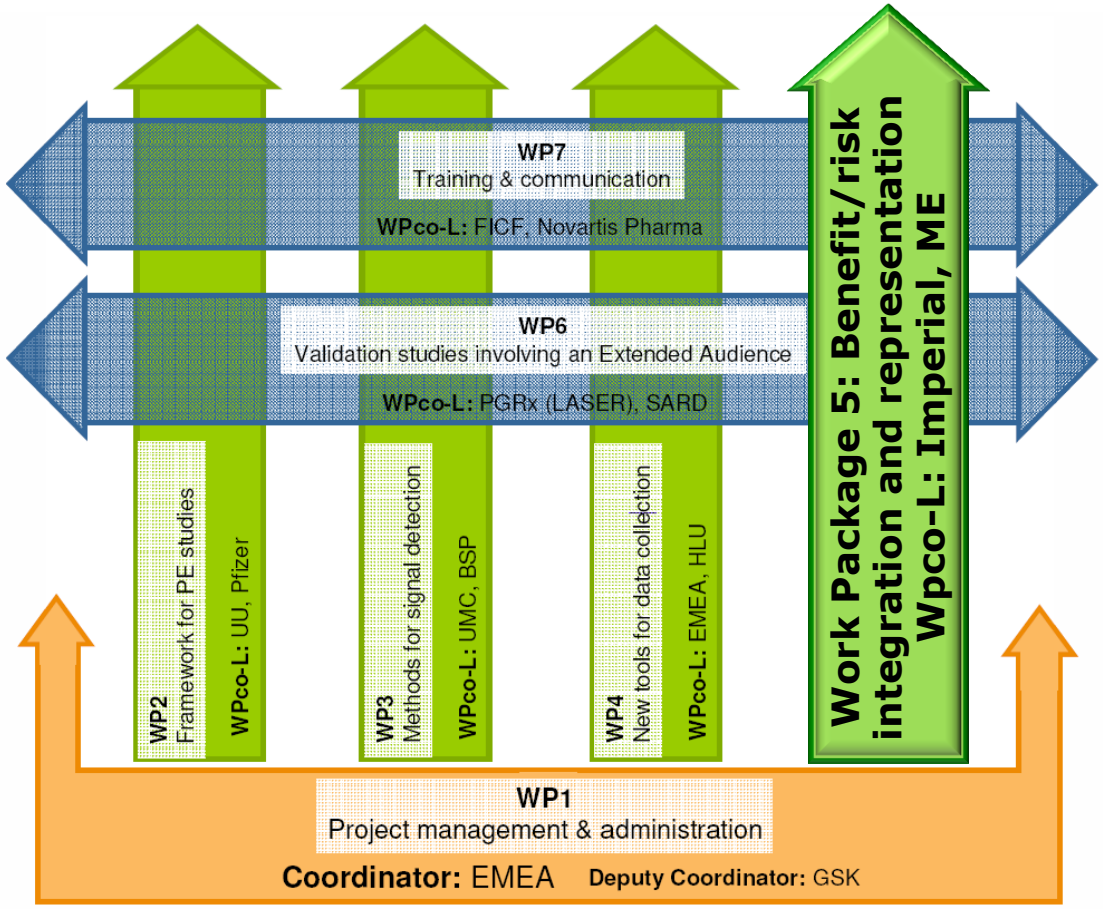
- "Improving and strengthening the monitoring of the benefit/risk of medicines marketed in the EU" including graphical representation of risk-benefit led by EMA with 31 public and private partners, 2009-2014 (www.imi-protect.eu)

[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)

The Innovative Medicines Initiative (IMI)

- Mission
  - The Innovative Medicines Initiative (IMI) is Europe's largest public-private partnership aiming to improve the drug development process by supporting a more efficient discovery and development of better and safer medicines for patients.
  - IMI supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe.

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

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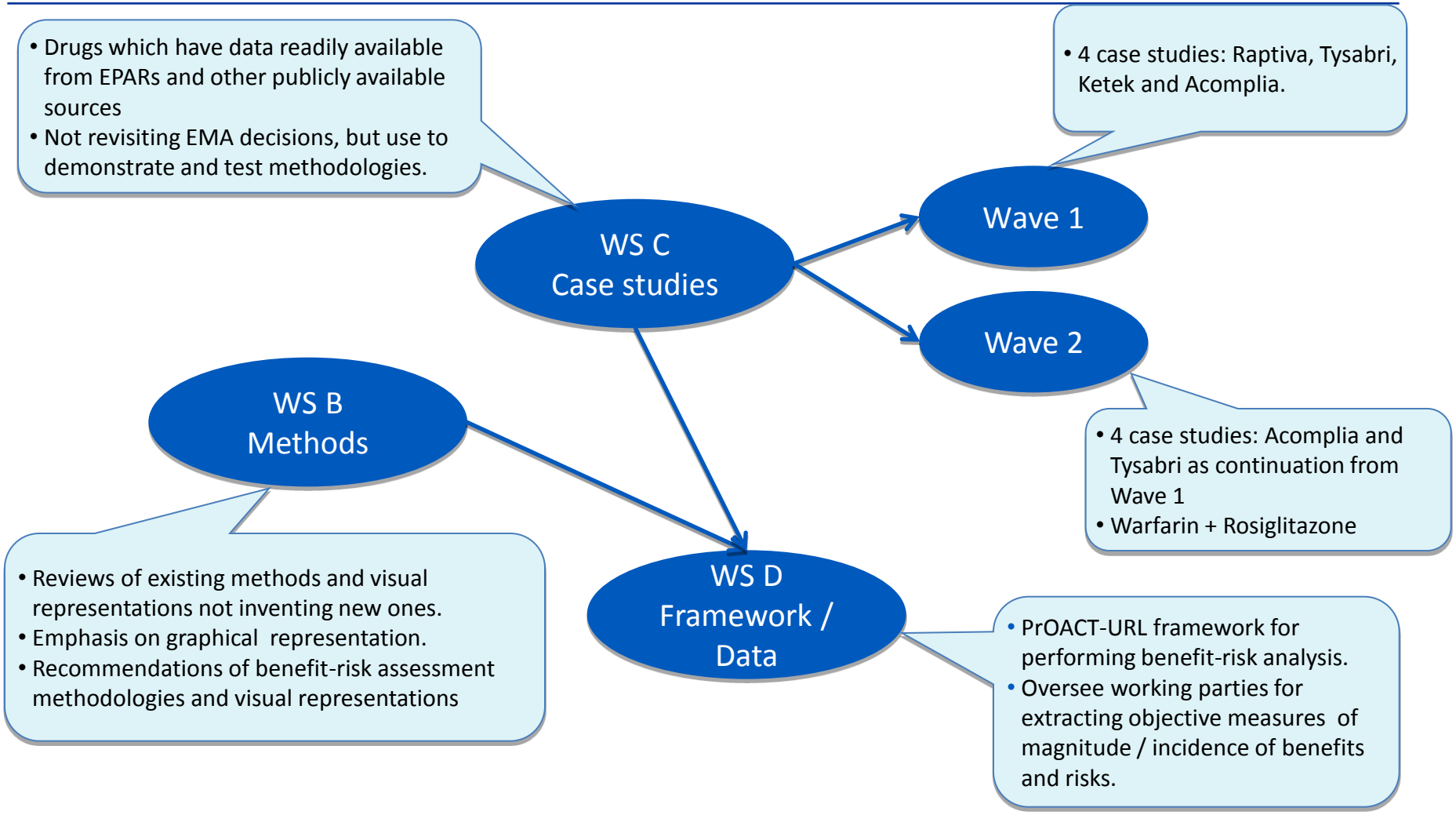
Work Package 5 of PROTECT (membership)

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

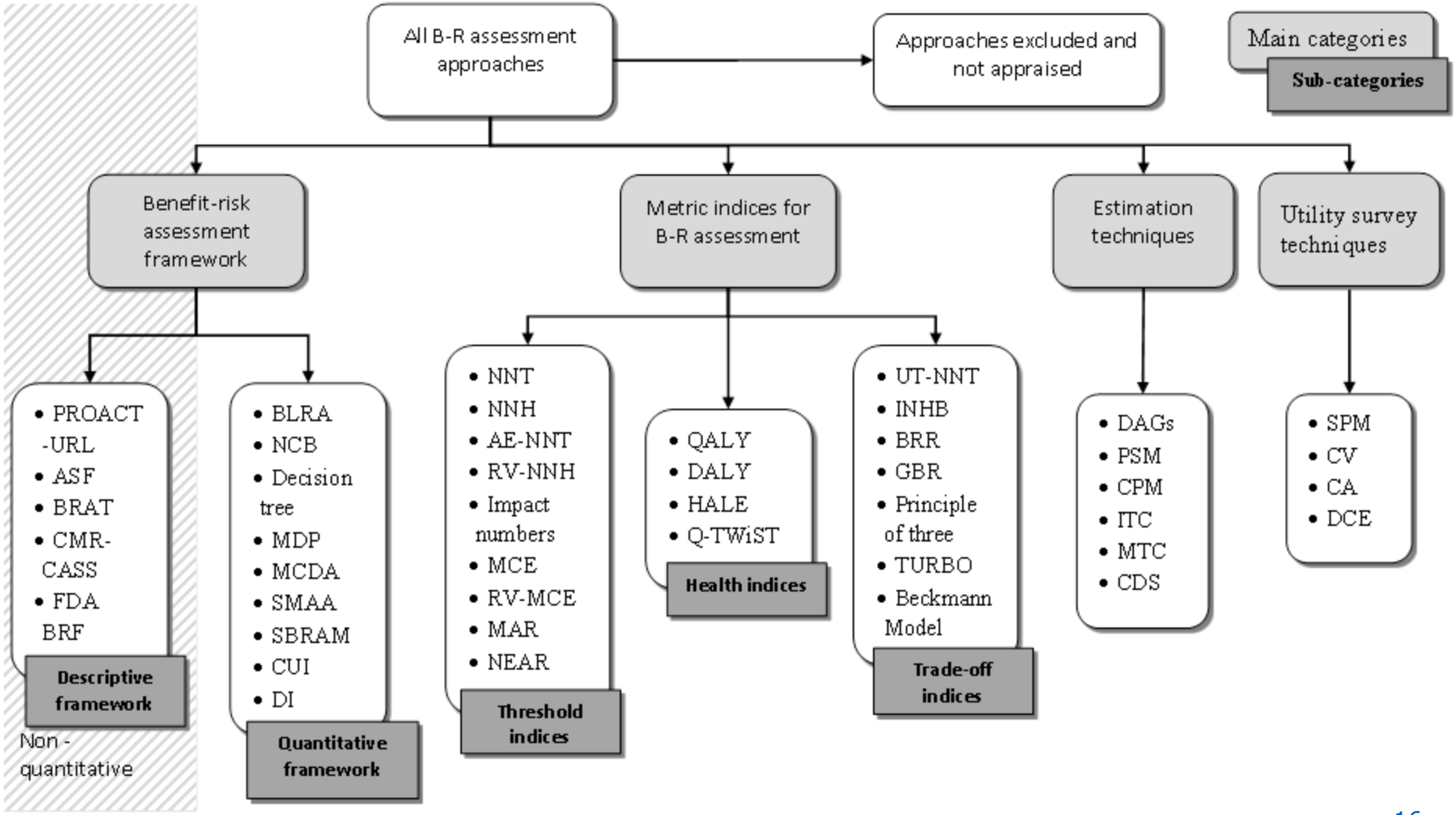
Work Package 5 of PROTECT

- Charter
  - 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
  - Communication (publications)

Work Package 5: Overview



Classifications of approaches



Recommendations for further testing

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

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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."

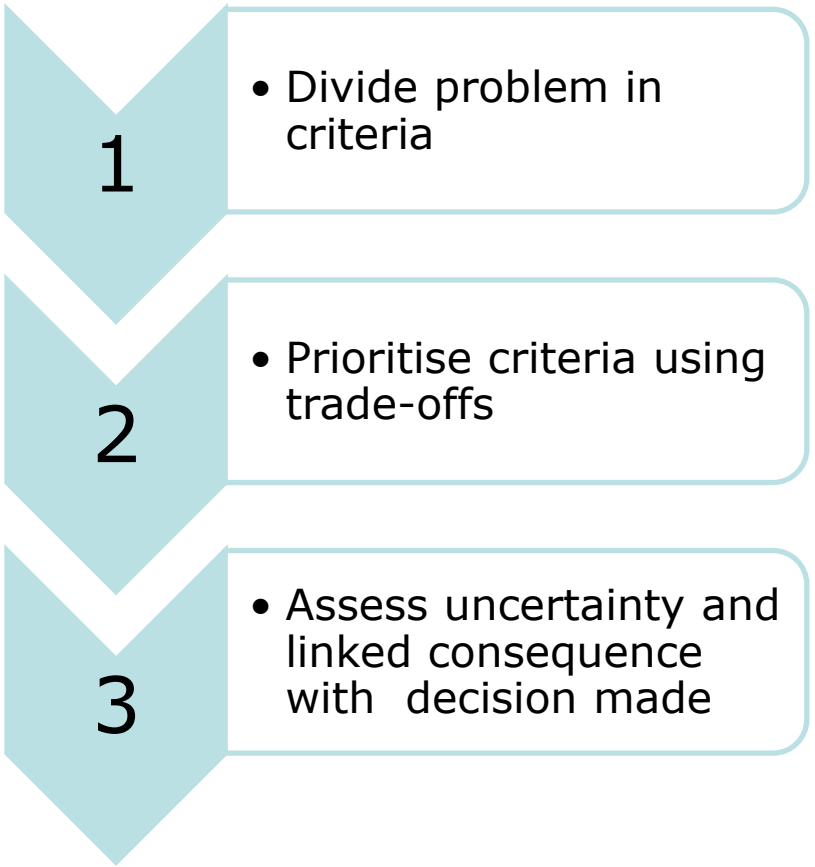
Wave 1 Case studies: Methodologies

	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

PrOACT-URL Framework

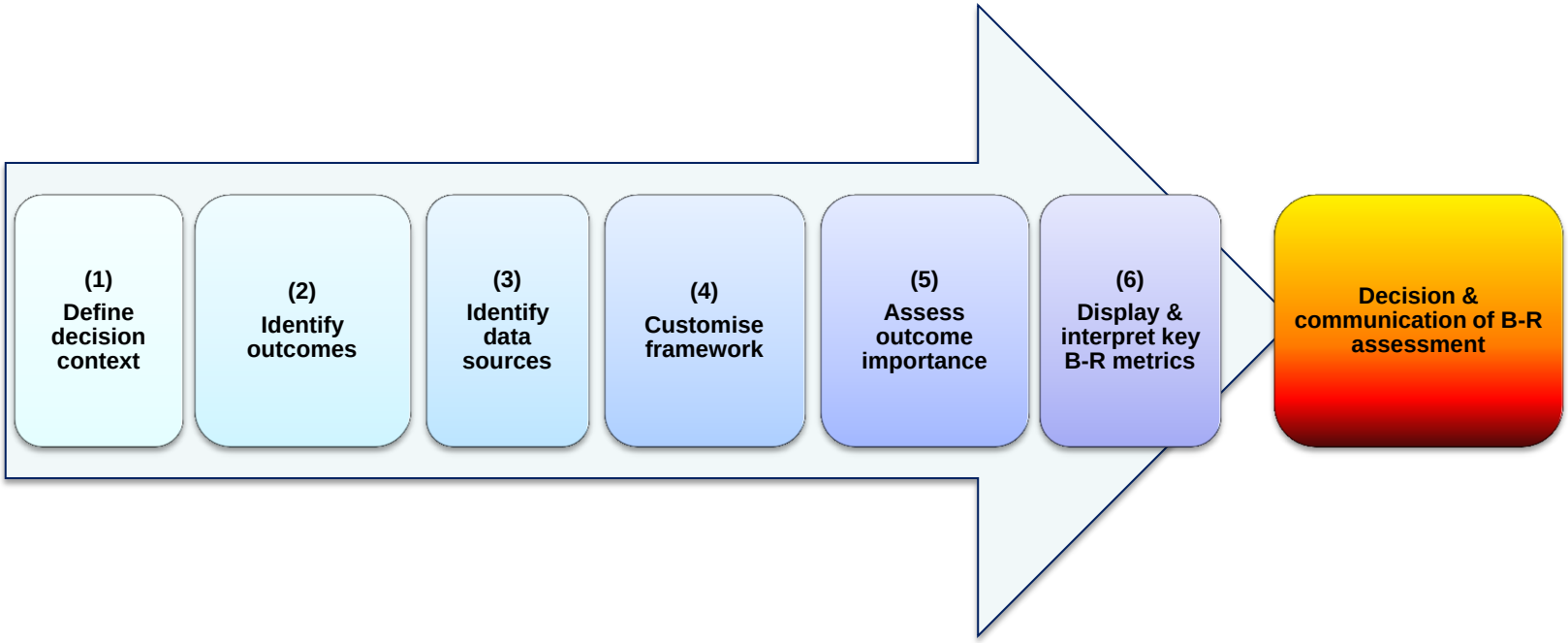
- A generic framework to structure the decision problem

Problem
Objective
Alternatives
Consequences
Trade-off
Uncertainty
Risk tolerance
Linked decisions



BRAT Framework

- Divide decision making process in the following 6 steps



Raptiva example

Active drug	Efalizumab
Indication	Psoriasis
Severe side effects	Progressive Multifocal Leukoencephalopathy
Regulatory history	Approved 2004 License withdrawn 2009
Data source	EPAR SPC PSUR10
Methodologies tested	PrOACT-URL, BRAT, MCDA, BRR + Decision conferencing to elicit value preference using swing-weighting

Raptiva: PrOACT-URL

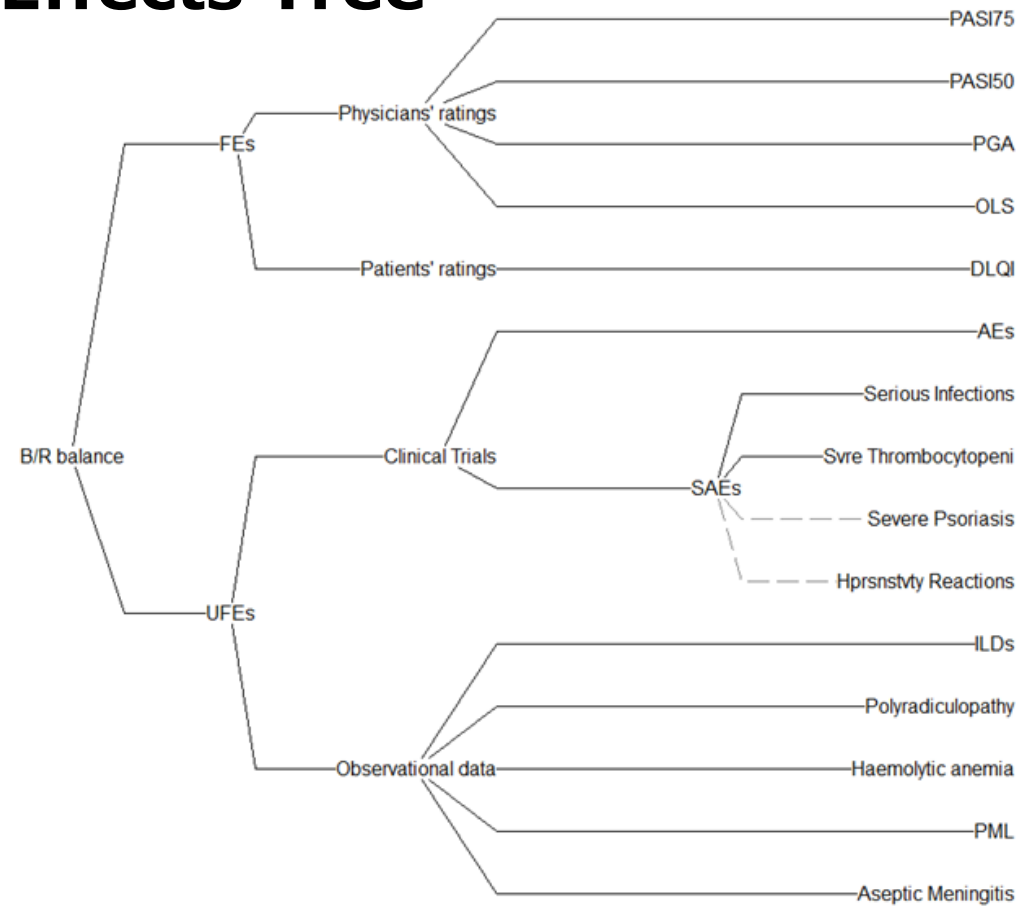
Options

- Raptiva
- Placebo

No data for vary, suspend or withdraw.

Add post-approval data; examine resulting benefit-risk balance.

Effects Tree



PROTECT

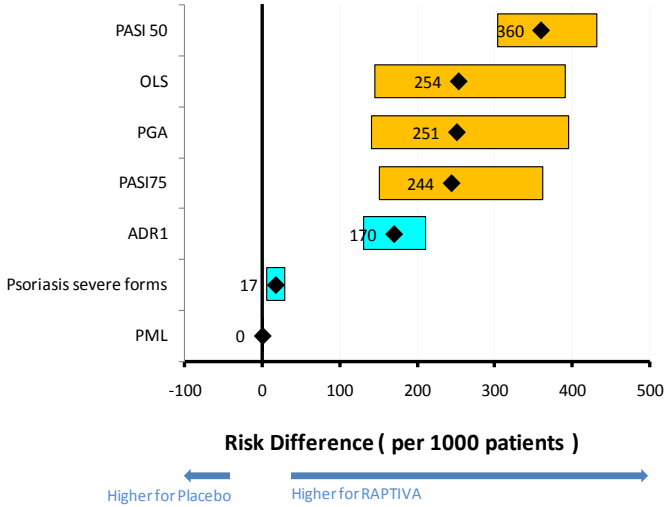
Raptiva: PrOACT-URL effects Table

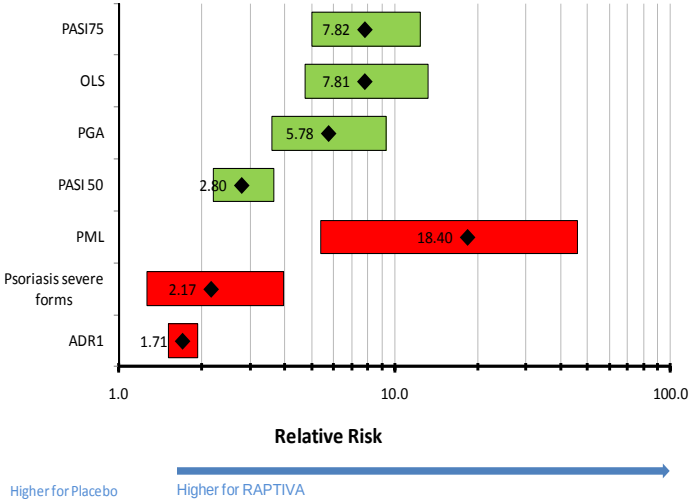
	Name	Description	Fixed Upper	Fixed Lower	Units	Raptiva	Placebo
Favourable Effects	PASI75	Percentage of patients achieving 75% reduction in baseline PASI[1] at week 12.	60.0	0.0	%	29.5	2.7
	PASI50	Percentage of patients achieving 50% reduction in baseline PASI[1] at week 12.	60.0	0.0	%	54.9	16.7
	PGA	Percentage of patients achieving Physician's Global Assessment[2] clear/almost clear at week12.	40.0	0.0	%	295	5.1
	OLS	Percentage of patients with Overall Lesion Severity rating of minimal or clear at FT (day 84).	40.0	0.0	%	32.1	2.9
	DLQI	Dermatology Life Quality Index[3]. Mean percentage of patients showing an improvement.	10.0	0.0	Change score	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	41.0	24.0
	Severe infections	Proportion of patients experiencing infections serious enough to require hospitalisation.	3.00	0.00	%/100ptyrs	2.83	1.4
	Severe Thrombocytopenia	Number of cases exhibiting severe (grade 3 and above) thrombocytopenia[4].	10	0	number	9	0
	Psoriasis Severe Forms	Percentage of patients developing severe forms of psoriasis (erythrodermic, pustular).	4.0	0.0	%	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	%	5.0	0
	Interstitial Lung Disease	Number of cases of interstitial lung disease.	20	0	number	18	0
	Inflammatory Polyradiculopathy	Number of cases of inflammatory polyradiculopathy.	5	0	Data	4	0
	SAEs	Number of cases of haemolytic anemia.	25	0	number	24	0
	PML	Number of cases of progressive multifocal leukoencephalopathy.	5	0	number	3	0
	Aseptic Meningitis	Number of cases of aseptic meningitis.	30	0	number	29	0

Raptiva: BRAT representation

- **Step 6: Display and interpret key benefit-risk metrics**

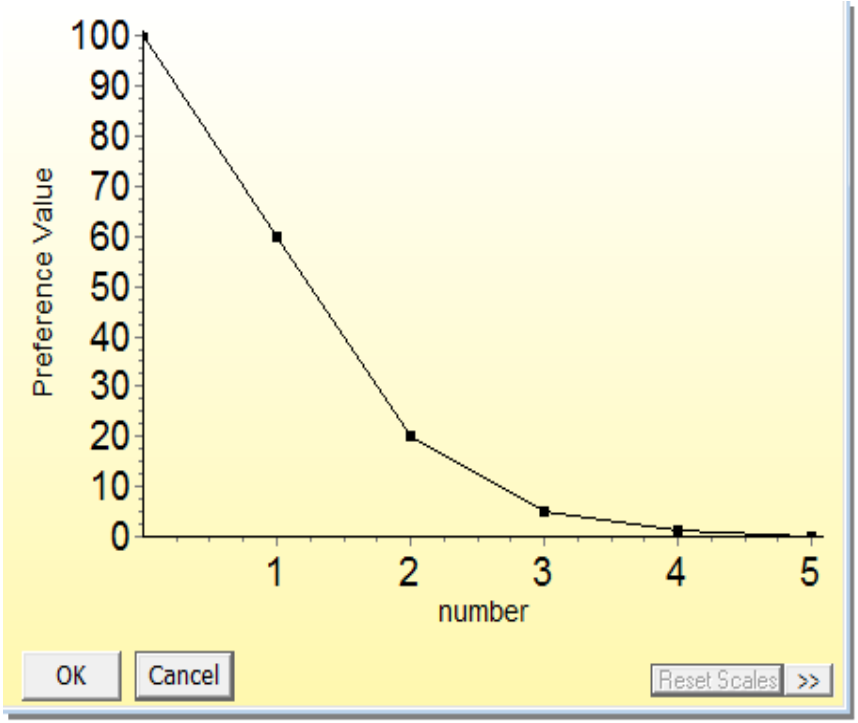
		Outcome	RAPTIVA Risk / 1000 pts	Placebo Risk / 1000 pts	Risk Difference (95% CI)/ 1000 pts		Relative Risk (95% CI)	
Benefits	Efficacy	PASI75	280	36	244	(151, 362)	7.819	(4.999, 12.380)
		PASI 50	567	200	360	(303, 431)	2.800	(2.210, 3.650)
		PGA	305	52	251	(141, 396)	5.778	(3.602, 9.337)
		OLS	292	37	254	(145, 392)	7.813	(4.731, 13.270)
Risks	Safety	PML	0	0	0	(0, 0)	18.400	(5.400, 45.960)
		ADR1	410	240	170	(130, 210)	1.710	(1.510, 1.940)
		Psoriasis severe forms	33	15	17	(6, 29)	2.170	(1.270, 3.970)



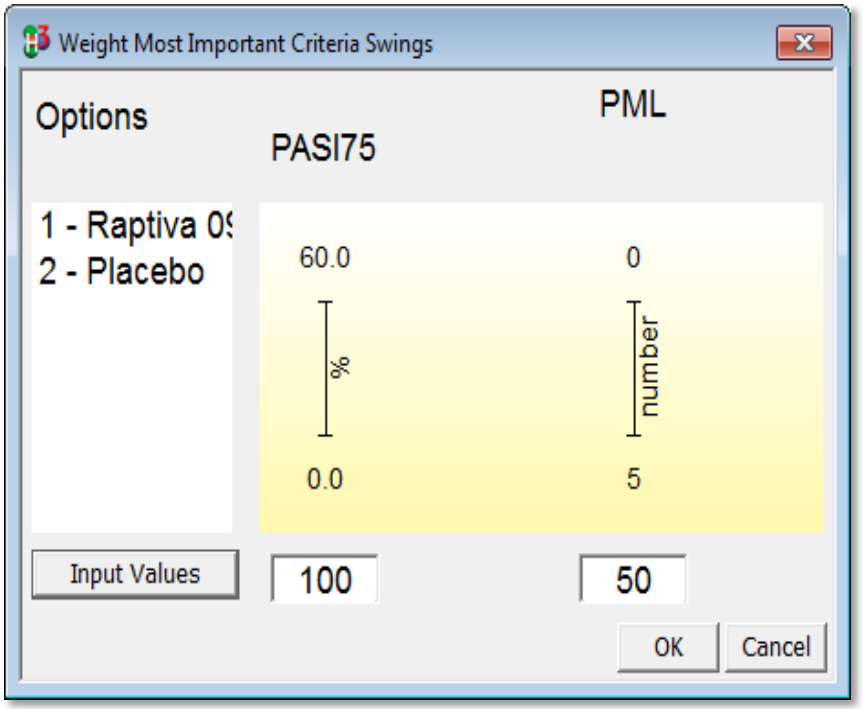


Raptiva: MCDA value function and swing-weighting

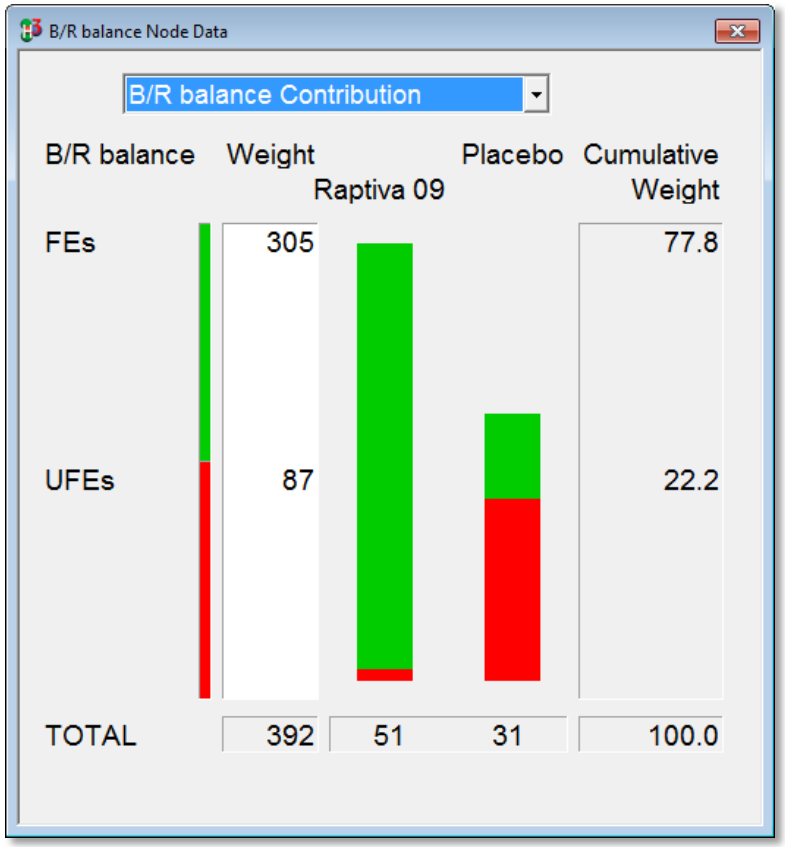
PML value function

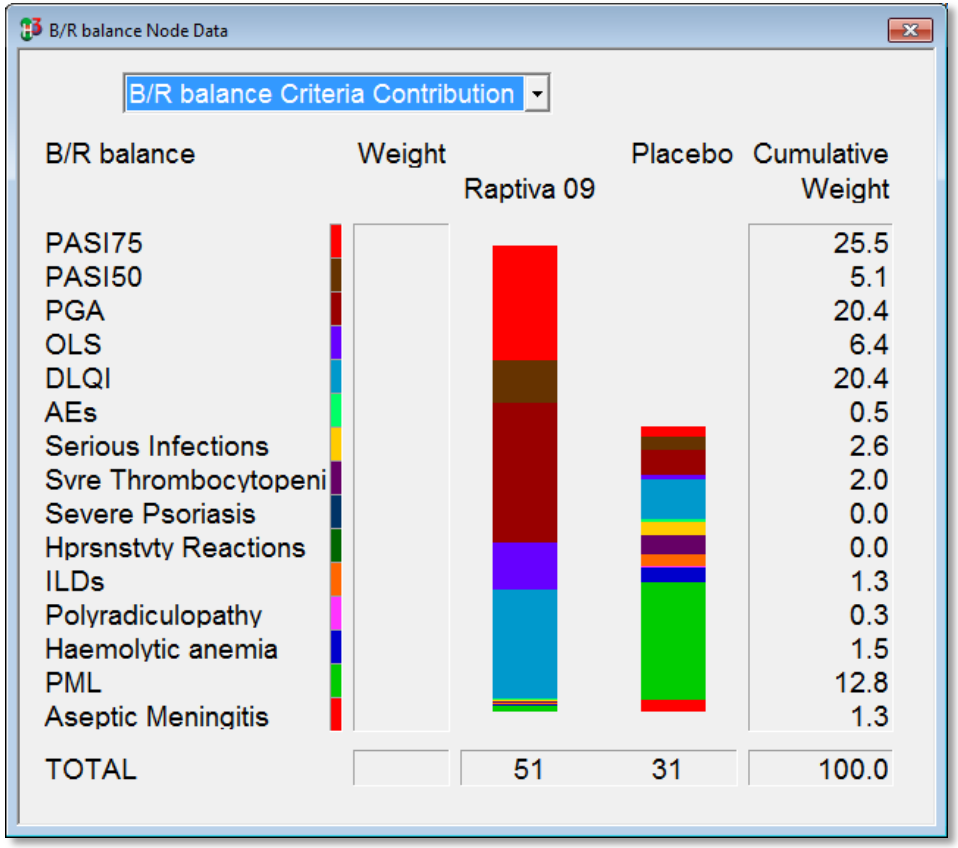


PASI 75 vs. PML

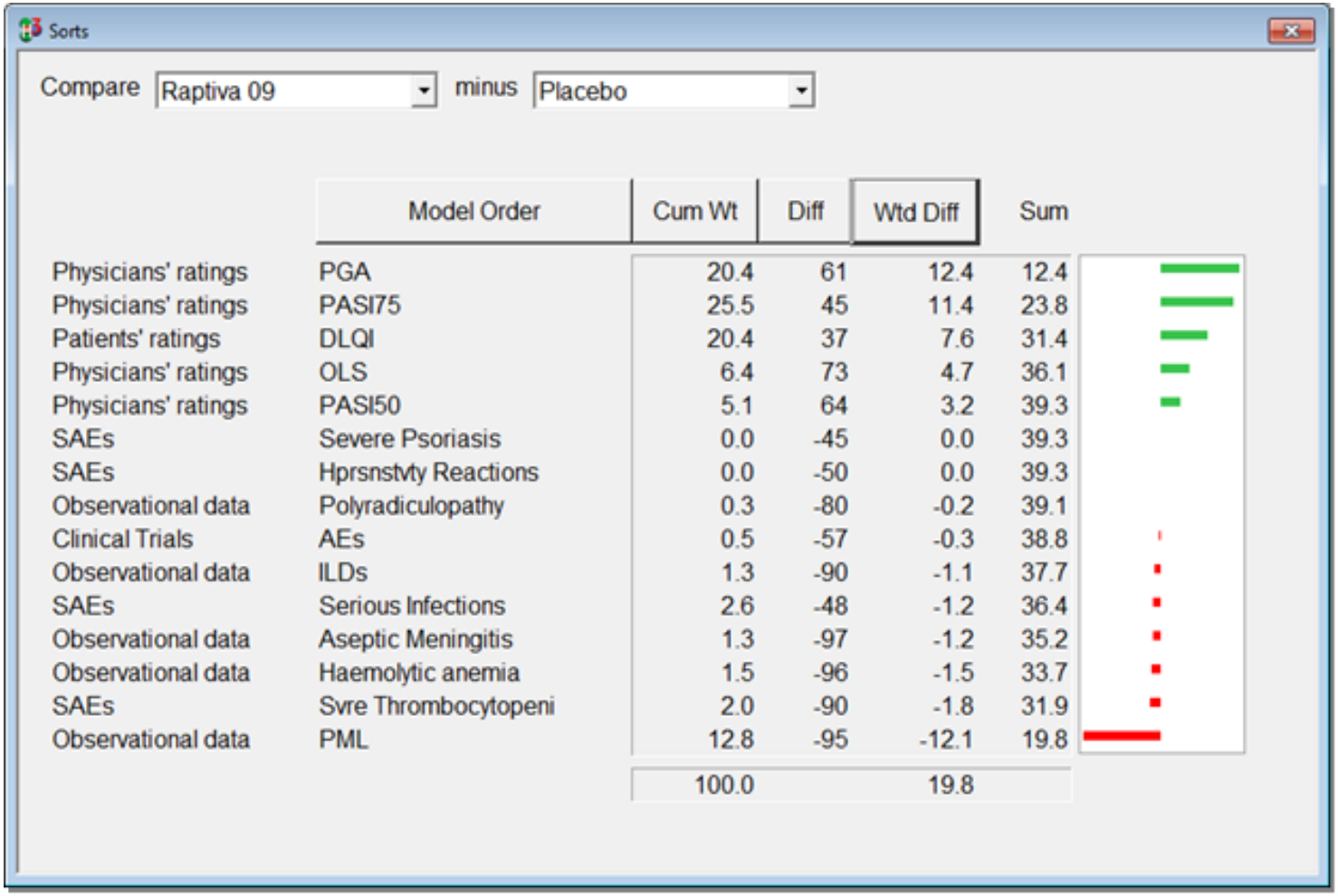


Raptiva: MCDA criteria contribution





Raptiva: MCDA difference display



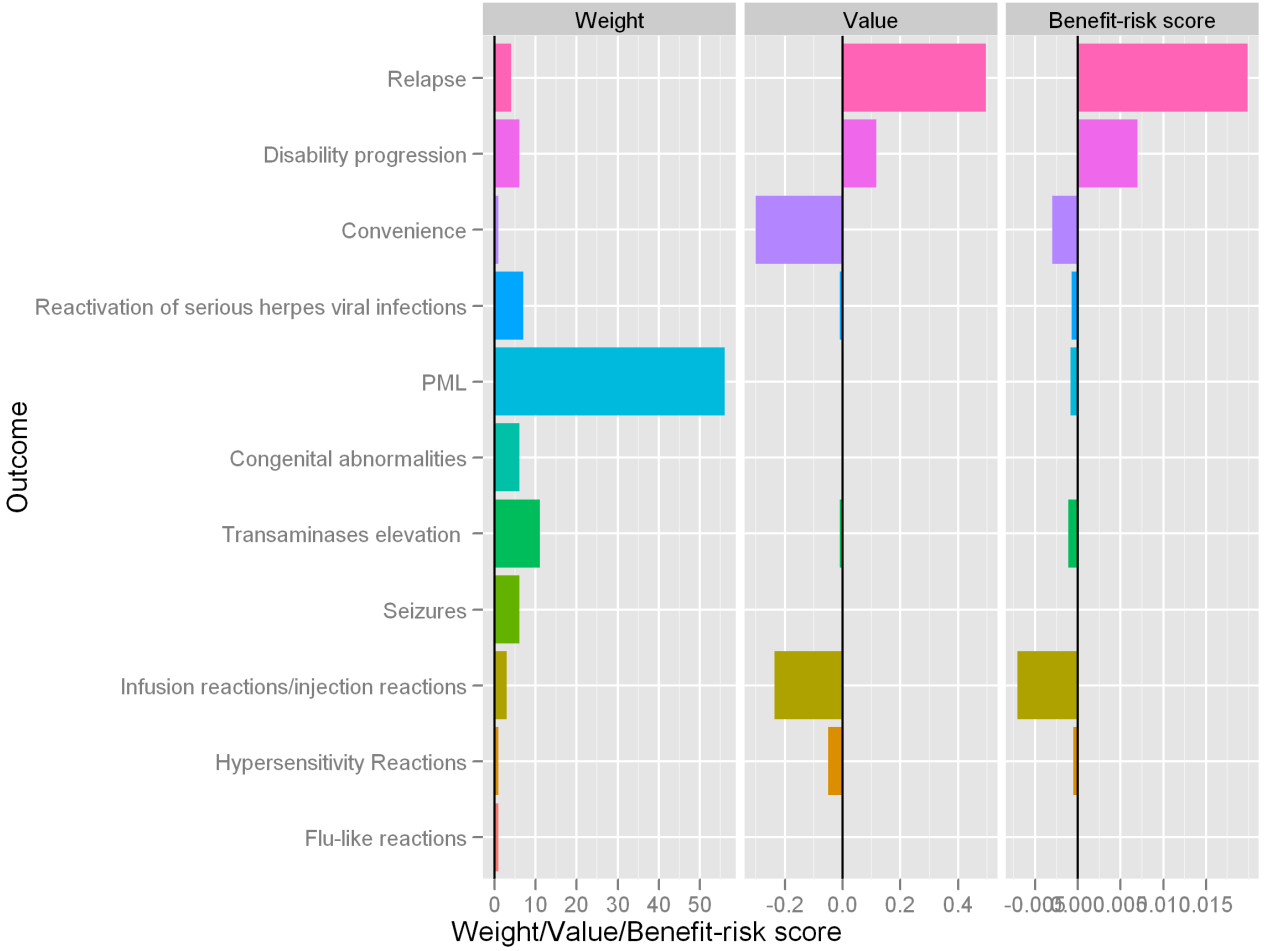
	Model Order	Cum Wt	Diff	Wtd Diff	Sum
Physicians' ratings	PGA	20.4	61	12.4	12.4
Physicians' ratings	PASI75	25.5	45	11.4	23.8
Patients' ratings	DLQI	20.4	37	7.6	31.4
Physicians' ratings	OLS	6.4	73	4.7	36.1
Physicians' ratings	PASI50	5.1	64	3.2	39.3
SAEs	Severe Psoriasis	0.0	-45	0.0	39.3
SAEs	Hprsnstvty Reactions	0.0	-50	0.0	39.3
Observational data	Polyradiculopathy	0.3	-80	-0.2	39.1
Clinical Trials	AEs	0.5	-57	-0.3	38.8
Observational data	ILDs	1.3	-90	-1.1	37.7
SAEs	Serious Infections	2.6	-48	-1.2	36.4
Observational data	Aseptic Meningitis	1.3	-97	-1.2	35.2
Observational data	Haemolytic anemia	1.5	-96	-1.5	33.7
SAEs	Svre Thrombocytopeni	2.0	-90	-1.8	31.9
Observational data	PML	12.8	-95	-12.1	19.8
		100.0		19.8	

Tysabri example

Active drug	Natalizumab
Indication	Relapsing remitting multiple sclerosis
Severe side effects	Progressive Multifocal Leukoencephalopathy
Regulatory history	Approved 2004 License withdrawn 2005 Re introduced because of patient demand 2006 CHMP reassessed the PML risk and continue approval 2009
Data source	EPAR
Methodologies tested	PrOACT-URL, BRAT, MCDA, NNT & NNH, BRR, PSM, MTC + Decision conferencing to elicit value preference directly

Tysabri: MCDA weighted Scores

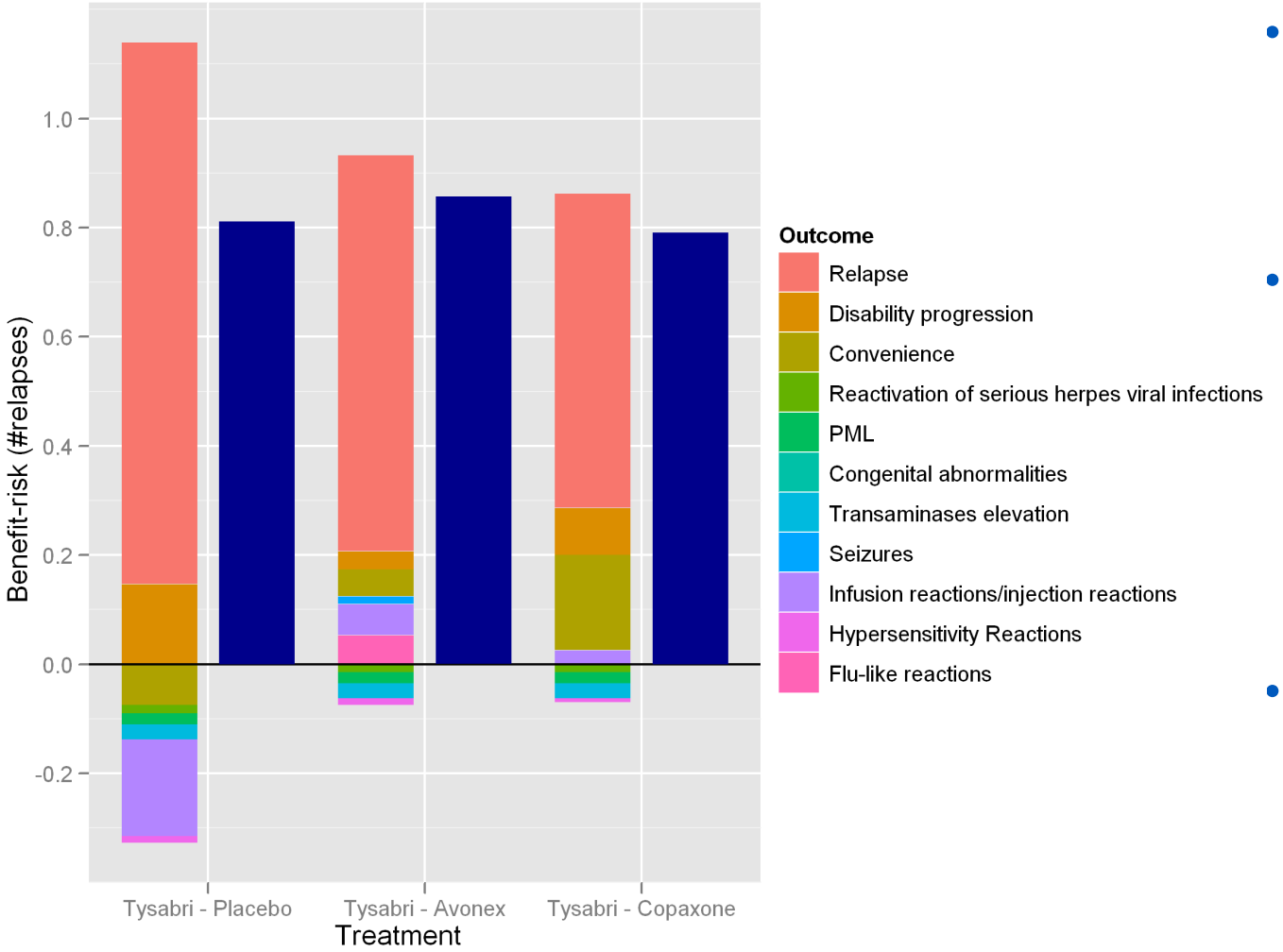
Find the BR contribution of each outcome for Tysabri - placebo



- 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: MCDA criteria contribution

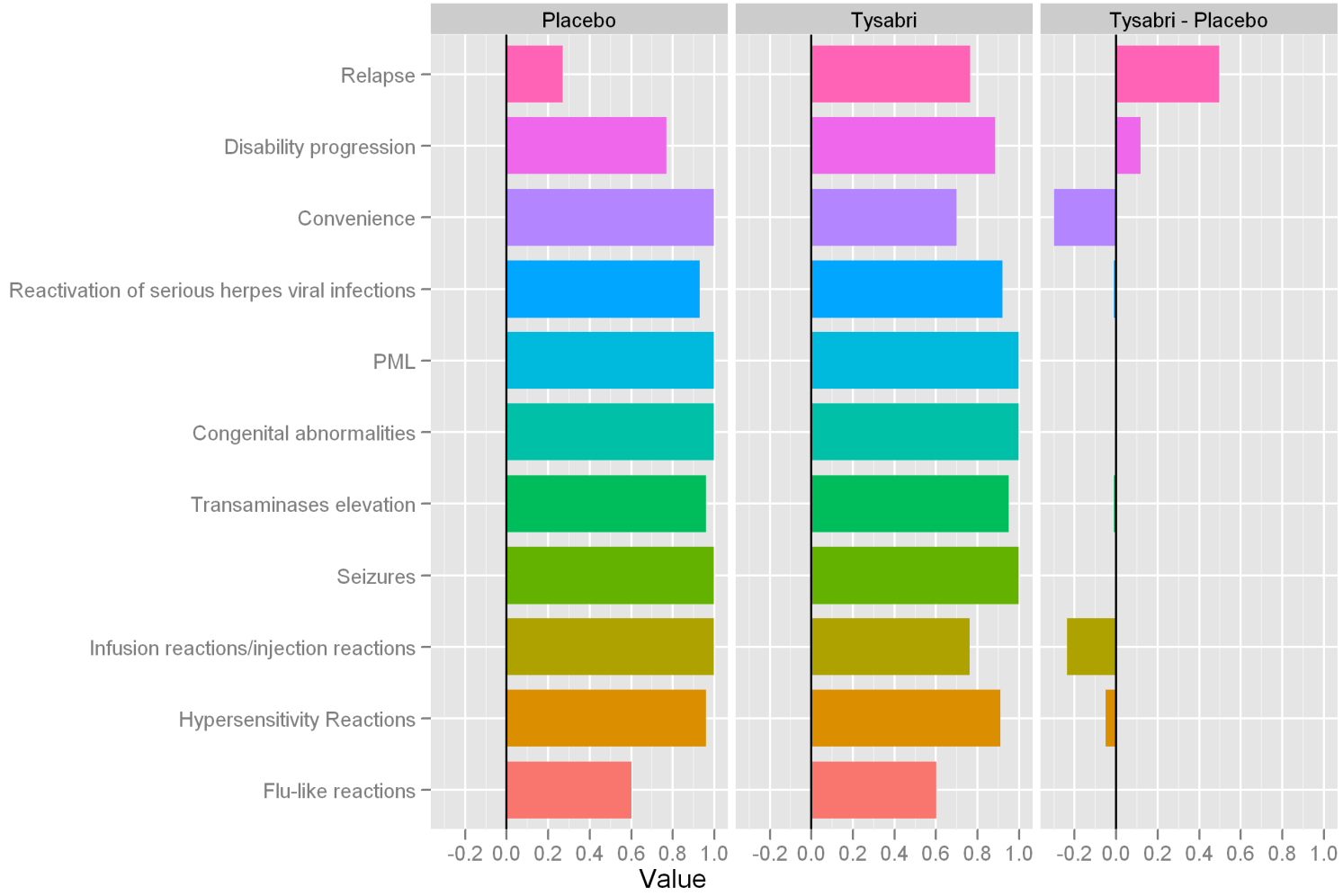
Stacked bar chart for Tysabri vs. all the other treatments.



- 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.

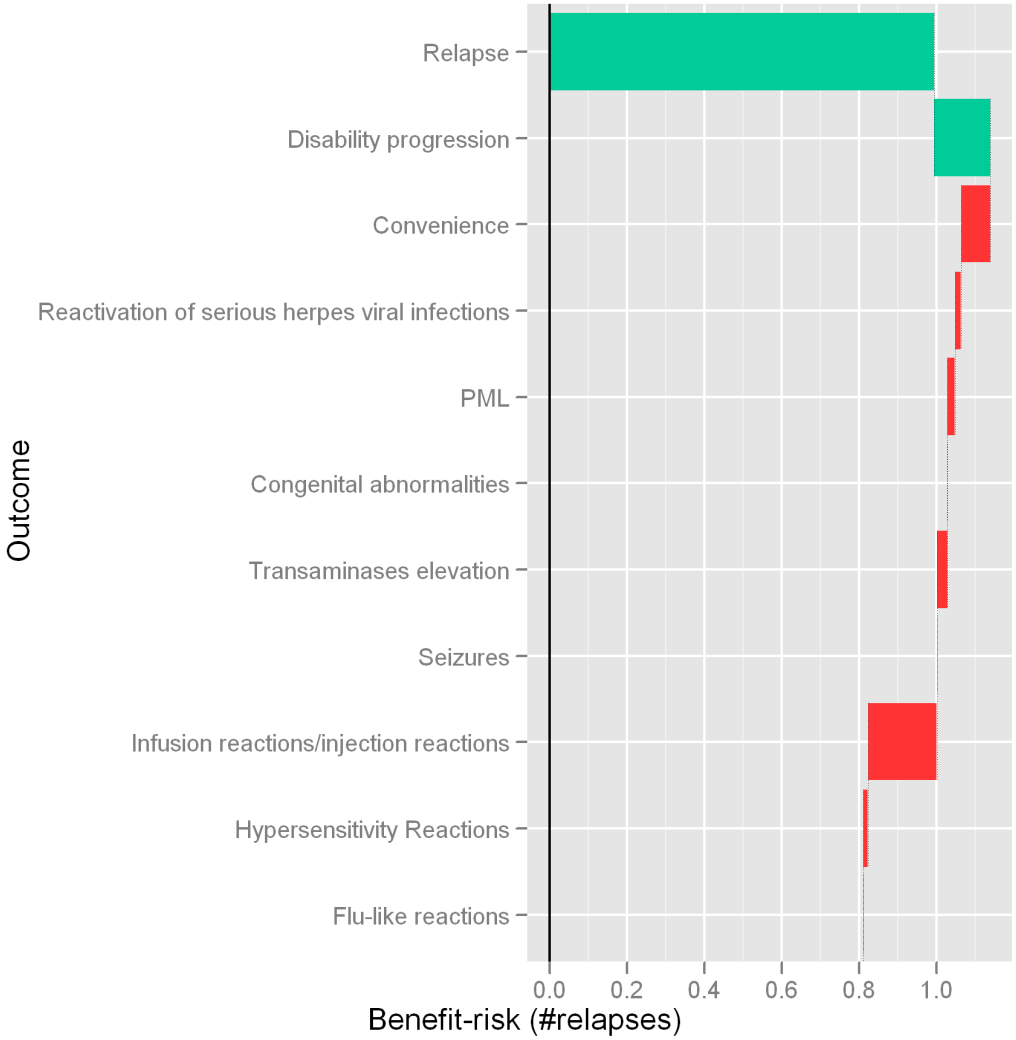
Tysabri: MCDA difference display

Incremental value scores for Tysabri compared to placebo



Tysabri: MCDA waterfall plot criteria contribution

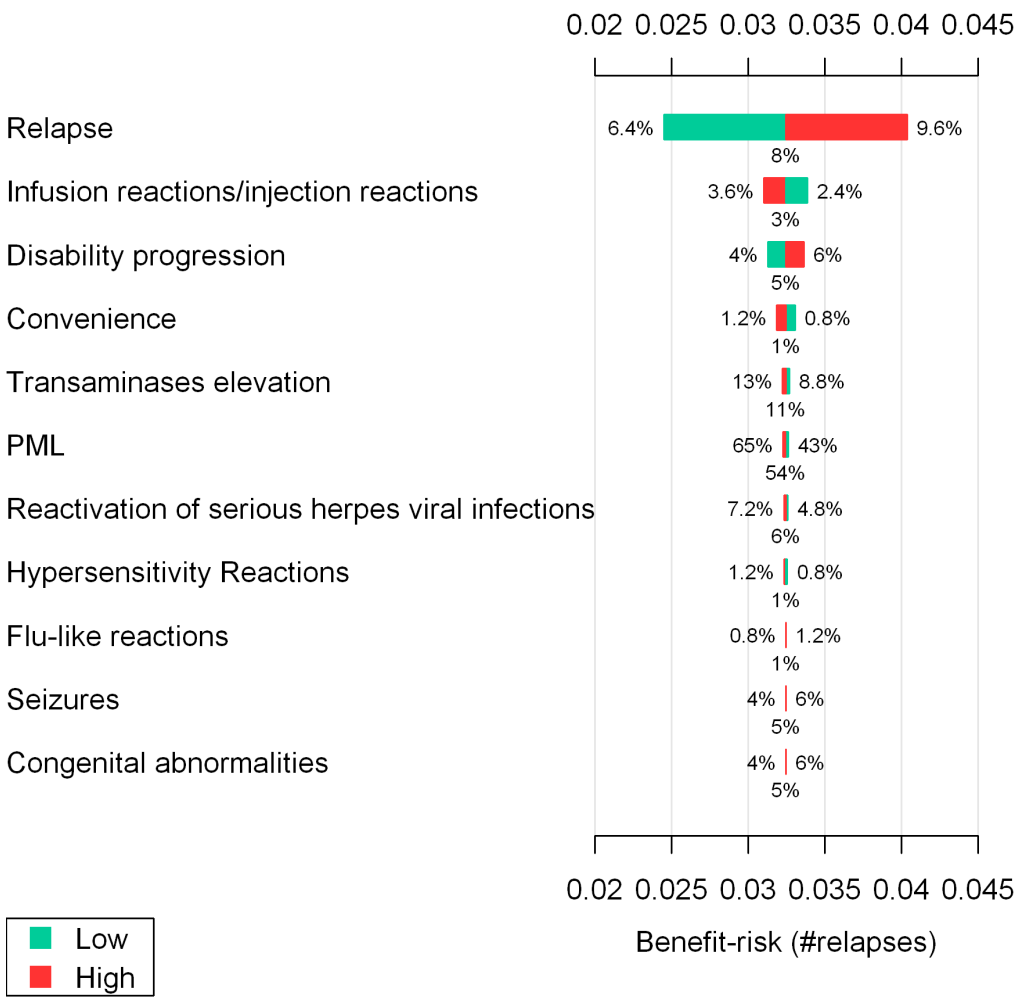
Waterfall plot for Tysabri - placebo



- 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

Tysabri: MCDA uncertainty via tornado diagram

Sensitivity to weights. Tysabri - placebo



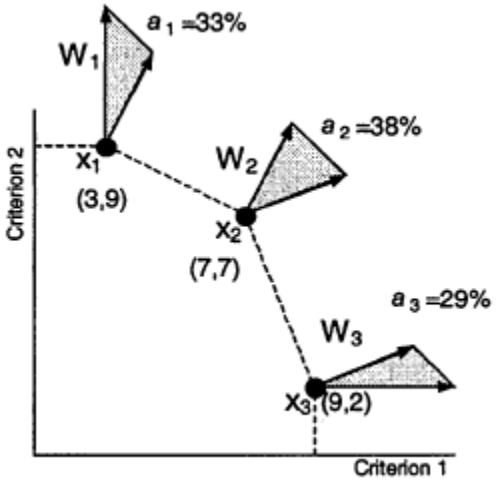
- The base case value of the weight for each outcome is shown under each bar.
- The low and high values of each weight are shown at the ends of the bars.
  Change each weight by 20% (relative change)
  Green = Low values
  Red = high values
- The incremental benefit-risk at the base case is the x-axis value at the middle.
- How this chances 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.

Ketek example

Active drug	Thelithromycin
Indication	Community acquired pneumonia Acute exacerbation chronic bronchitis Acute bacterial sinusitis Tonsilitis/Pharyngitis
Severe side effects	Cardiac syncope, Liver failure
Regulatory history	Approved July 2001, Restriction and warning revised 2007 License renewed 2011
Data source	EPAR
Methodologies tested	PrOACT-URL, BRAT, MCDA, SMAA, BRR + swing-weighting

Stochastic Multi-attribute Acceptability Analysis

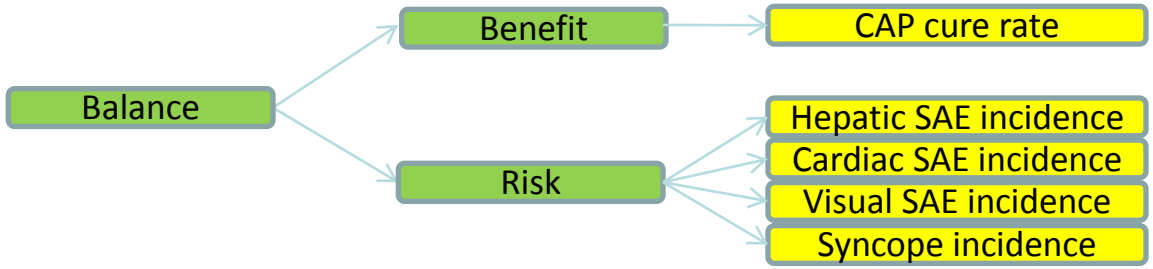
- Acceptability Index [AI]– Probability to achieve n^{th} rank in n alternatives.
- AI is computed as an integral over the criteria distribution and favourable weight space.
- In this example
  - AI for X_1 is 33%, X_2 is 38% and X_3 is 29%
  - Computed as an integral over criteria value and weight space for each option in grey



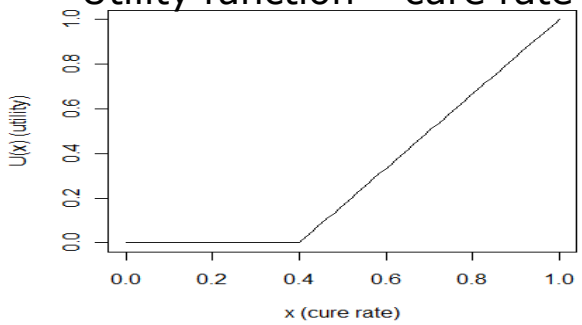
Ketek: SMAA

SMAA extends MCDA when

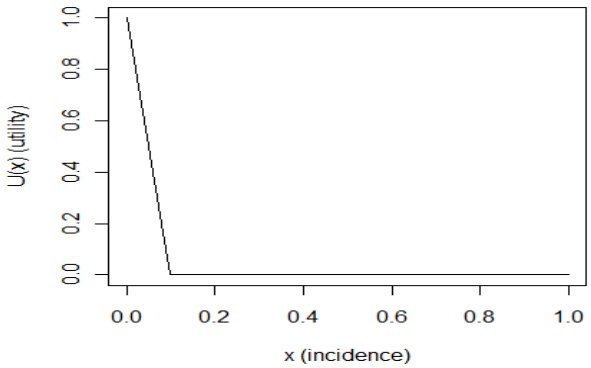
- there are uncertainties with the performances of drugs on the chosen criteria
- there are diversified opinions on the choices of weights
- Utility functions are still required, but typically defaulted to be linear



Utility function – cure rate

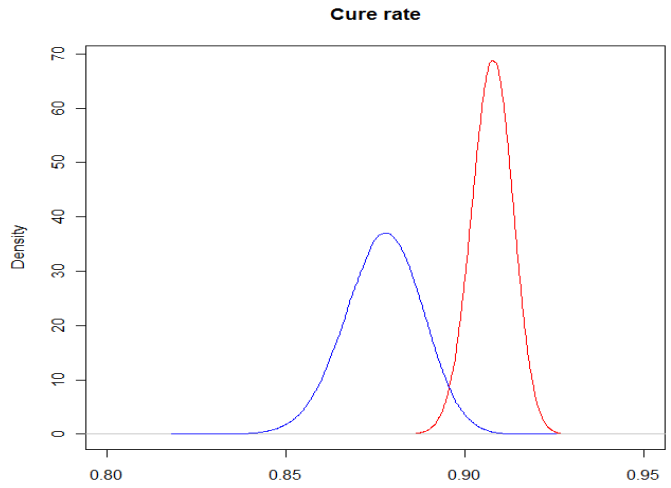


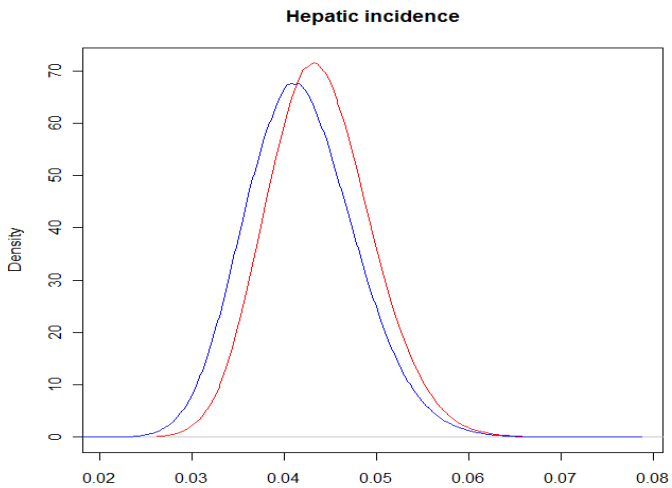
Utility function – hepatic SAE



Ketek: SMAA

- In practices, the outcome (or performance) of a drug on a criterion is hardly known exactly
- SMAA thus view the cure rate and AE incidences as distributions rather than deterministic values
- All outcome are defined as Beta distributions updated from non-informative prior Beta(1,1)





The distributions of CAP cure rate and AE incidences are estimated with Bayesian approach and presented below for Ketek (red) and its comparator (blue)

Acomplia

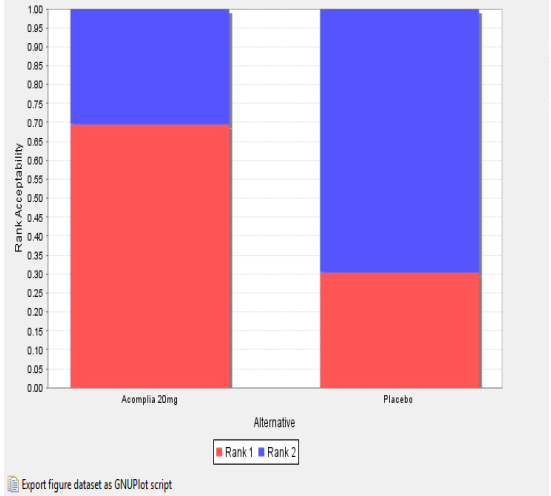
Active drug	Rimonabant
Indication	Weight loss in obese and overweight patients with co-morbidities in adults (>18y)
Regulatory history	Approved June 2006, Voluntary withdrawal in January 2009
Severe side effect	Increased risk with depression
Data source	EPAR Published clinical trials
Methodologies tested	PrOACT-URL, BRAT, MCDA, SMAA, NNT&NNH, Impact numbers, INHB, BRR, PSM + direct utility elicitation via survey

Acomplia: SMAA (preference-free)

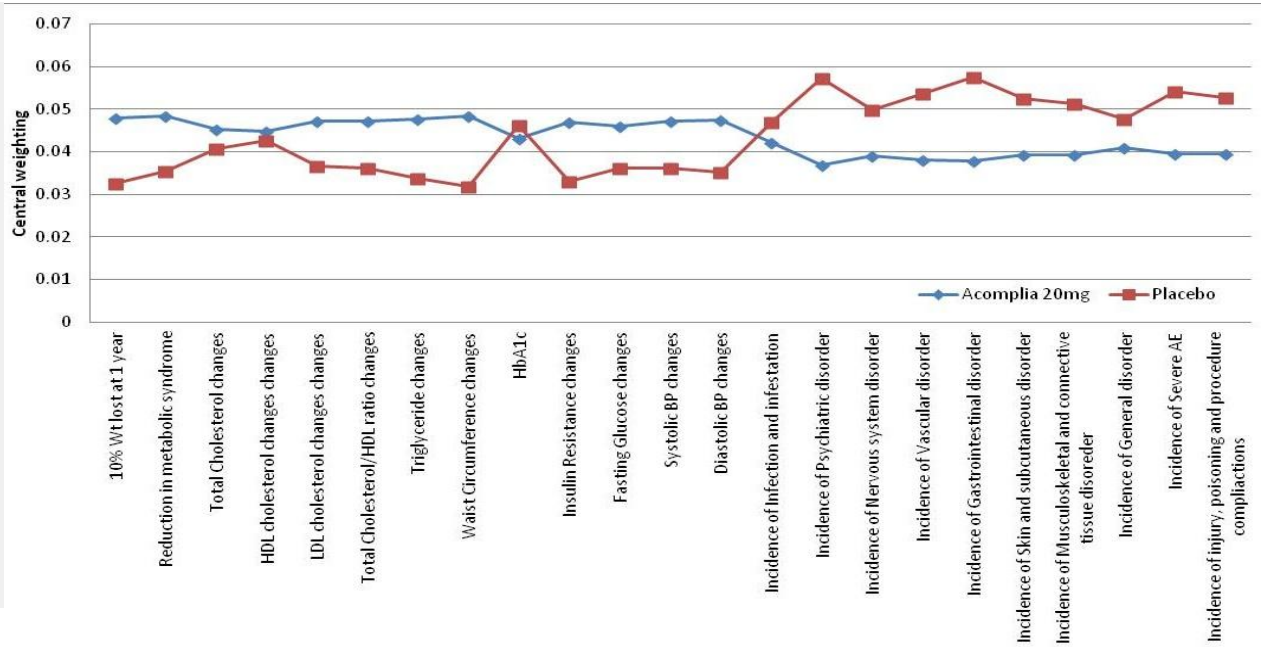
Acceptability index

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 resulting in the preference on the left



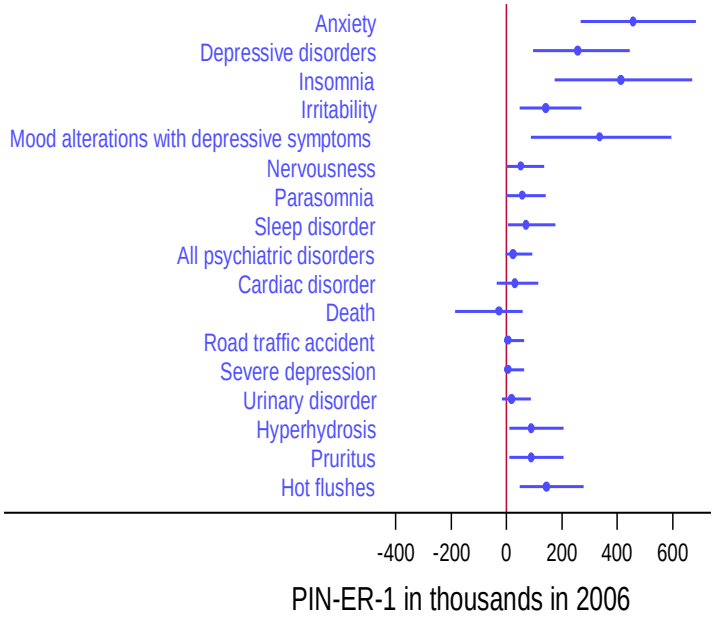
Probabilistic simulation method

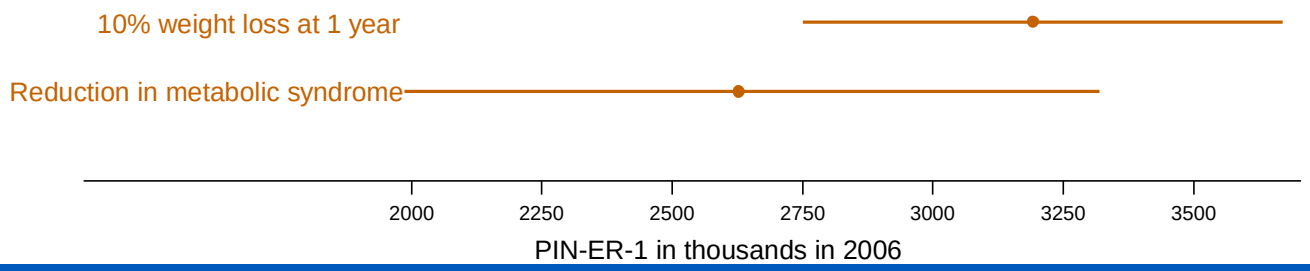
- Benefit risk assessment using Monte-Carlo and resampling methods.
- Computes the distribution of BR balance and allow to assess the possibility of chances of best and worse scenarios
- Able to deal with statistical adjustment and different kind of uncertainties
- Flexible

Acomplia: PIN-ER-1

Population impact numbers of eliminating a risk factor over one year (PIN-ER-1) in England and Wales in 2006 when Acomplia is removed from the population (sensitive to assumptions)

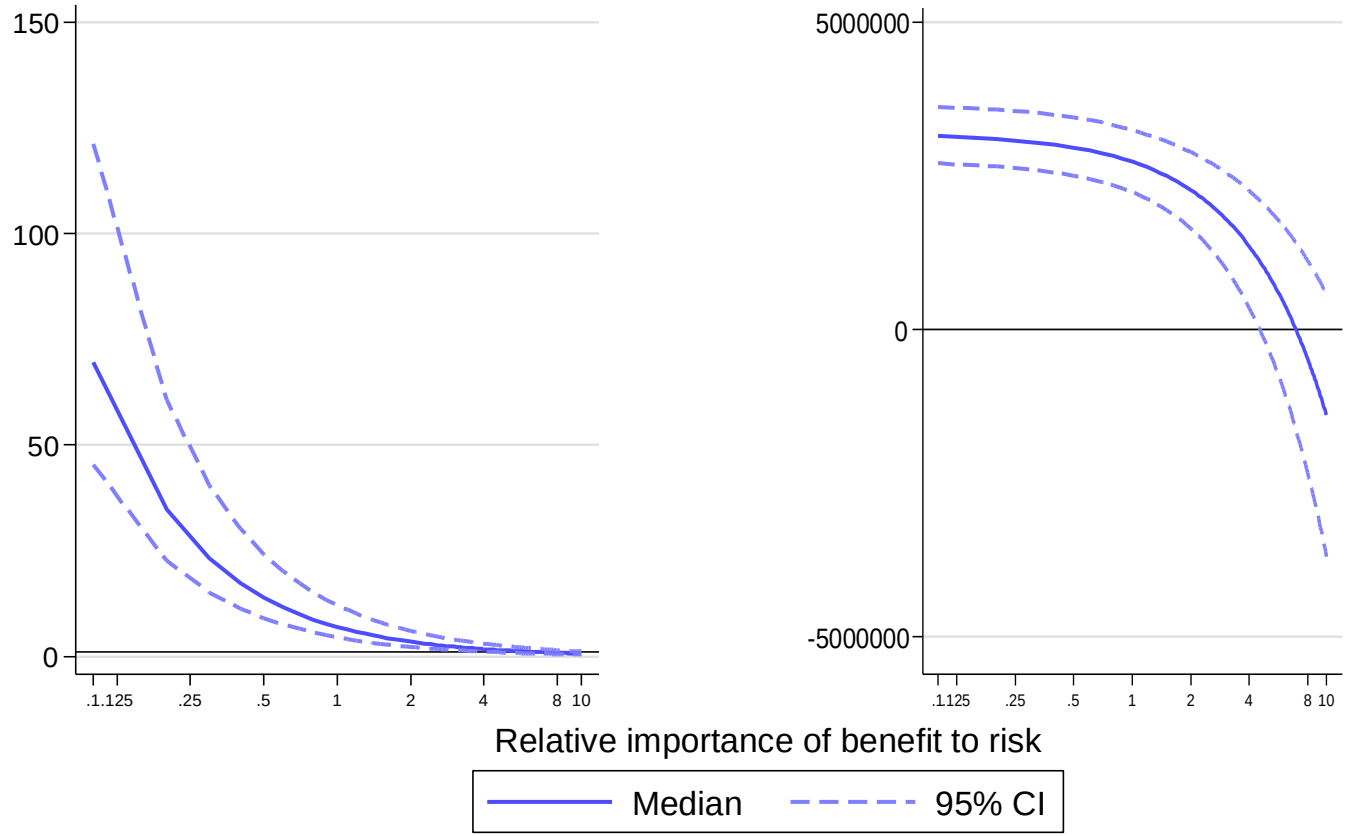
	2006		
Criterion	**Mean**	**Median**	**95% CI**
10% weight loss at 1 year	3196940	3192692	(2749747, 3670812)
Reduction in metabolic syndrome	2634463	2627721	(1986955, 3319728)
Anxiety	463429	458760	(268483, 684969)
Depressive disorders	260710	256908	(95432, 446299)
Death	-36995	-25728	(-184415, 59514)





Acomplia: Benefit-risk ratio and net clinical benefit

- Assess over a range of value preference of benefit to risk



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

- Review of and applications of modern visual representation of benefits and risk
- Wave 2 case studies
  - Two extended from wave 1 to investigate more into benefit-risk methodologies used and visual representations (Tysabri and Acomplia)
  - Two new case studies looking at more complex benefit-risk questions (Warfarin and Rosiglitazone)

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