Benefit – Risk integration and representation: EU PROTECT

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on behalf of PROTECT Work Package 5

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Agenda

- Changing environment
- IMI - PROTECT
- PROTECT WP5: B-R integration and representation
- Examples
- Remarks

BR analysis: new environment

- More systematic approaches to BR assessment are emerging within the regulatory environment
- This shift impacts not only regulators and industry
- Expected to drive research agendas across academia
- Several initiatives in Europe and the US

FDA structured approach

- CDER identified the need for more structured BR analysis
- Starting in 2009, efforts to develop a more systematic approach
- Review of quantitative methods, 2 concerns:
  - Cannot capture the nuanced assessments
  - Obscuring subjective expert judgment
- Decision – structured qualitative approach
  - Use quantitative analysis to aid rather than replace judgment
  - Flexible to accommodate supporting quantitative analysis
- 5 year plan
  - 2012: road-testing in “live” reviews
  - 2013: further improvement
  - 2014-2017: Implementation

http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm

EMA Perspective

- Need consistency and transparency of the benefit–risk assessment for medicinal products
  - three-year project started in early 2009
- 2 level approach
  - Qualitative approach
  - Quantitative approach:
    - Multi-Criteria Decision Analysis (MCDA) method to derive a numerical value for the benefit–risk balance
    - recommended for more complex situations
- Implementation of MCDA in the assessment
  - practical challenges
  - to be addressed in the last work package of the project

*Zafiropoulos N, Phillips L, Pignatti F, Luria X. Evaluating benefit-risk: an agency perspective. Reulatory Rapporteur 2012 (9): 5-8

PhRMA BRAT

- Benefit-Risk Action Team (BRAT)
- PhRMA project
- Formed in 2006 with a key objective to formulate a framework for the benefit-risk assessment:
  - to provide a greater structure, transparency, predictability, and consistency
  - to facilitate the sponsor-regulator discussion
  - to facilitate the regulatory decision making throughout the product life cycle
- A semi-quantitative framework was developed by the team members in 2008
- Next Step Working Group (NSWG):
  - PhRMA, FDA, EMEA, Health Canada, & academic members to enhance B/R methods and foster collaboration between B/R stakeholders

Other Initiatives

- The Unified Methodologies for Benefit-Risk Assessment (UMBRA)
    - established by the Centre for Innovation in Regulatory Science (CIRS) in 2012
- Consortium on Benefit-Risk Assessment (COBRA)
- ISPOR Risk-Benefit Management Working Group
- European Federation of Statisticians in Pharmaceutical Industry (EFSPI) Benefit-Risk SIG
- South Asian Benefit Risk Evaluation group

The Innovative Medicines Initiative (IMI)

- The largest public-private partnership in Europe to improve the drug development process by supporting a more efficient discovery and development of better and safer medicines for patients
- A joint project between the European Union and the pharmaceutical industry association EFPIA

IMI Projects

- Call for proposals, 1st Call in 2008 on Safety
- Currently a total of 40 projects, including:
  - Eu2P: European programme in Pharmacovigilance and Pharmacoepidemiology
  - MARCAR: Biomarkers and molecular tumour classification for non-genotoxic carcinogenesis
  - eTOX
  - EUPATI
  - **PROTECT**

What is PROTECT?

- Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium
- Goals
  - to enhance early detection and assessment of adverse drug reactions from different data sources (clinical trials, spontaneous reporting and observational studies)
  - to enable the integration and presentation of data on benefits and risks

Partners

Public

Regulators:
EMA (Co-ordinator)
DKMA (DK)
AEMPS (ES)
MHRA (UK)

Academic Institutions:
University of Munich
FICF (Barcelona)
INSERM (Paris)
Mario Negri Institute (Milan)
Poznan University of Medical Sciences
University of Groningen
University of Utrecht
Imperial College London
University of Newcastle

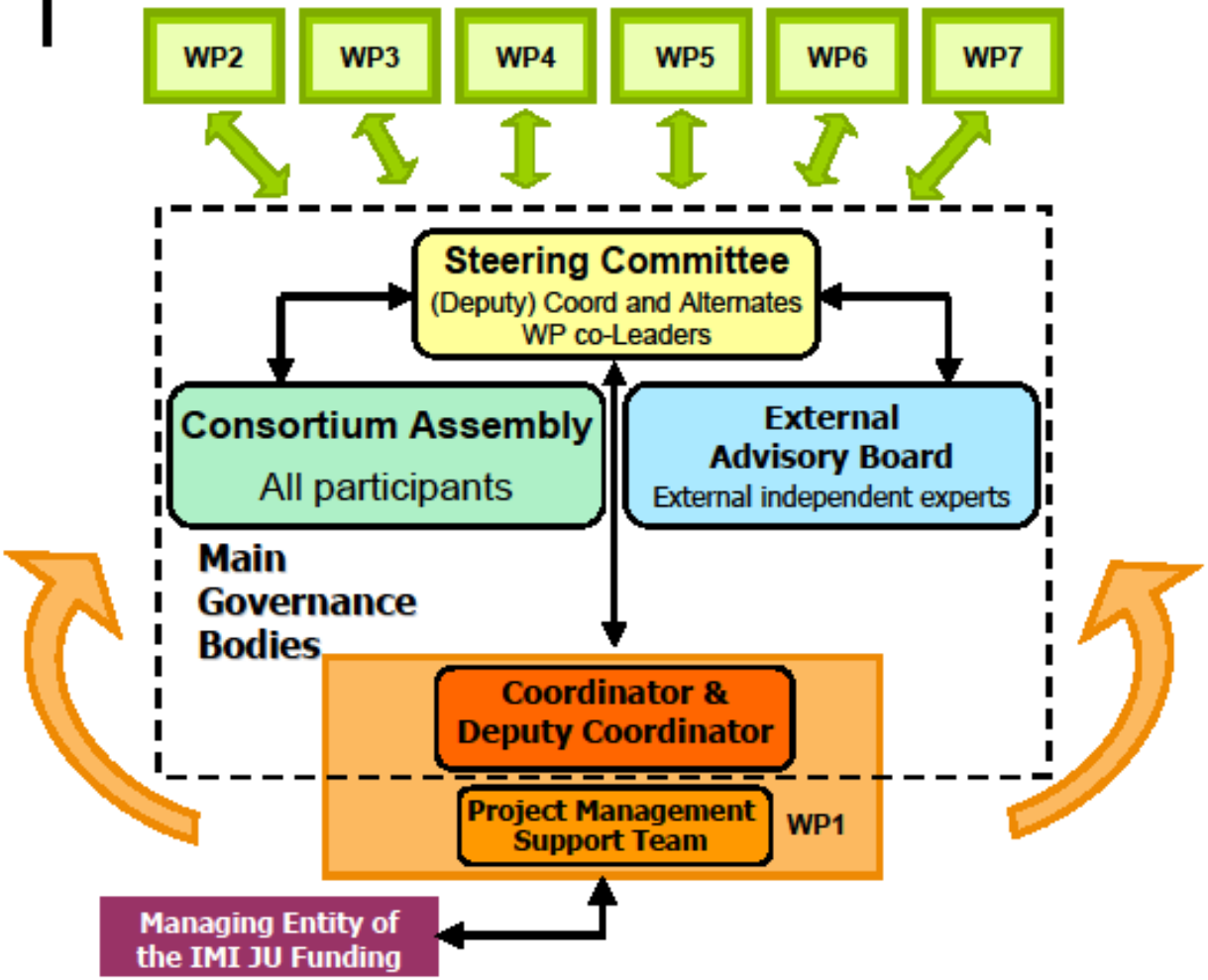
SMEs:
Outcome Europe
PGRx (LA-SER)

Others:
WHO UMC
GPRD
IAPO
CEIFE

Private

EFPIA companies:
GSK (Deputy Co-ordinator)
Sanofi
Roche
Novartis
Pfizer
Amgen
Genzyme
Merck Serono
Bayer
Astra Zeneca
Lundbeck
NovoNordisk
Takeda
Eli Lilly

Management structure



Working Packages

- WP1: project management and administration
- WP2: framework for pharmacoepidemiological studies
- WP3: Signal detection
- WP4: Data collection from consumers
- **WP5: Benefit-Risk Integration and Representation - to assess and test quantitative methodologies for the benefit-risk assessment of medicines**
- WP6 – Validation studies involving an Extended Audience
- WP7: Training and communication

Hierarchy

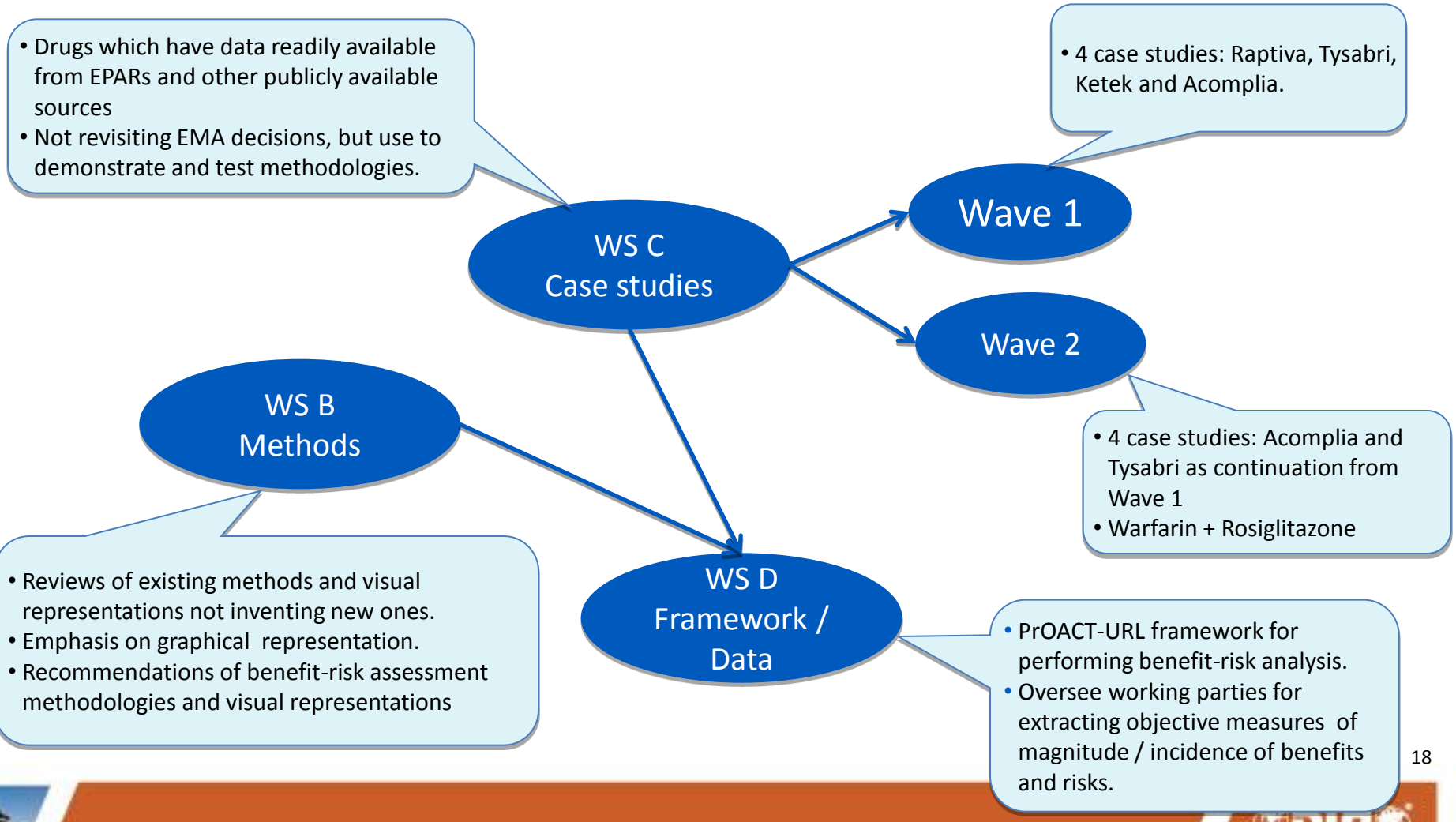
Work Package 5 of PROTECT (membership)

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

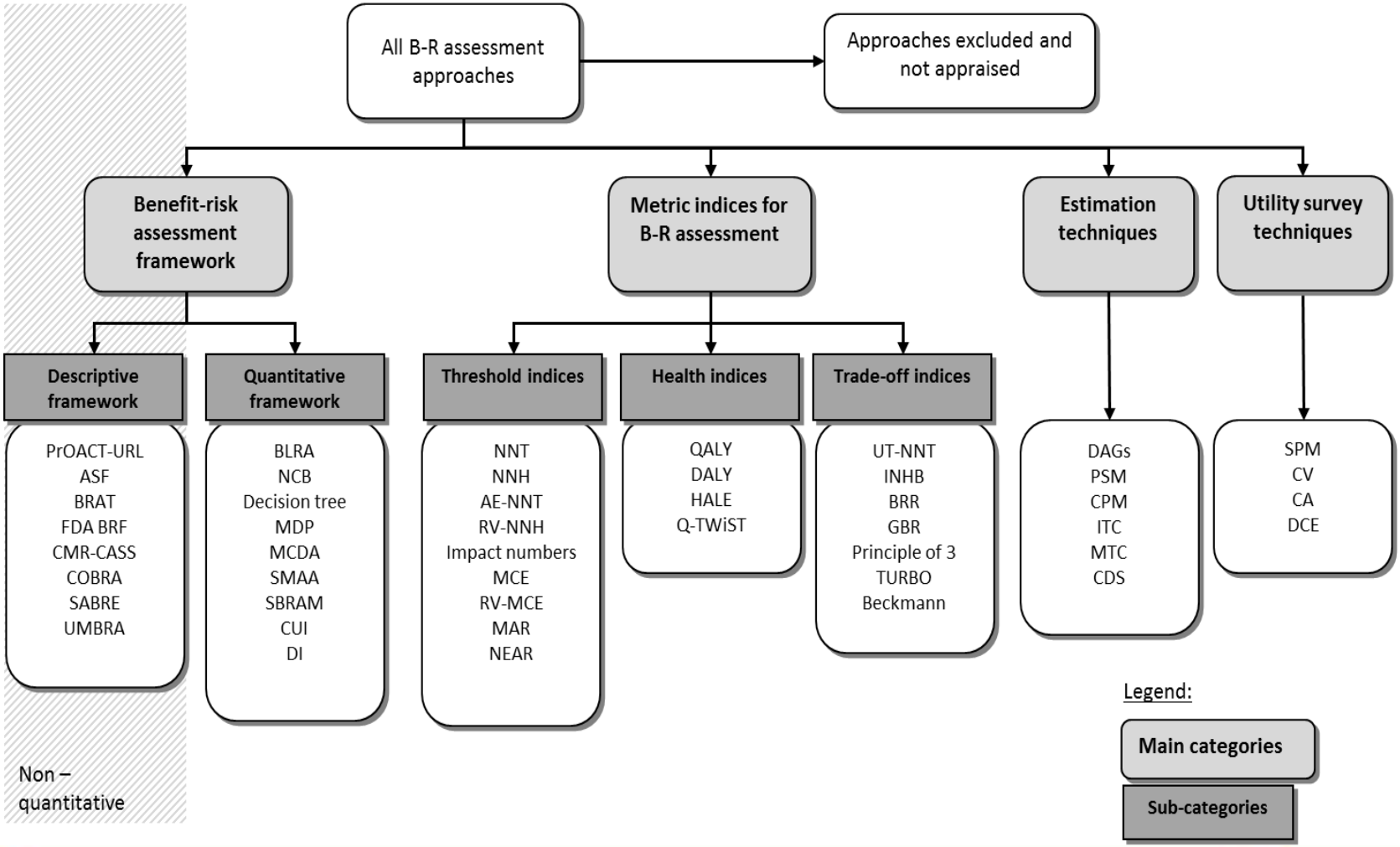
Work Package 5 of PROTECT: Charter

- 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



Wave 1 Case studies: Methodologies

	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

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

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.

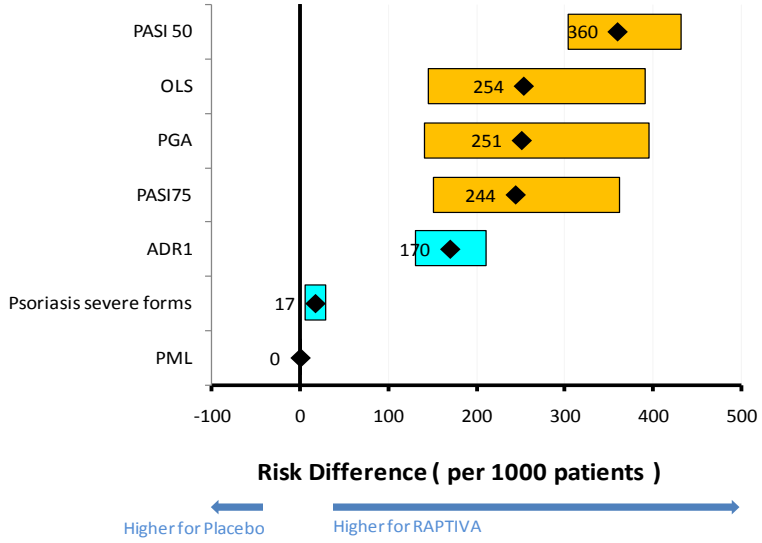
This report neither replaces nor is intended to replace or comment on any regulatory decisions made by national regulatory agencies, nor the European Medicines Agency."

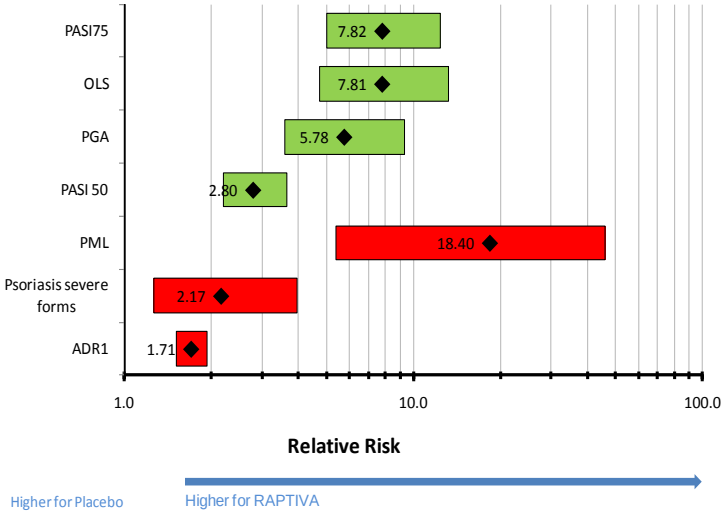
Efalizumab example

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

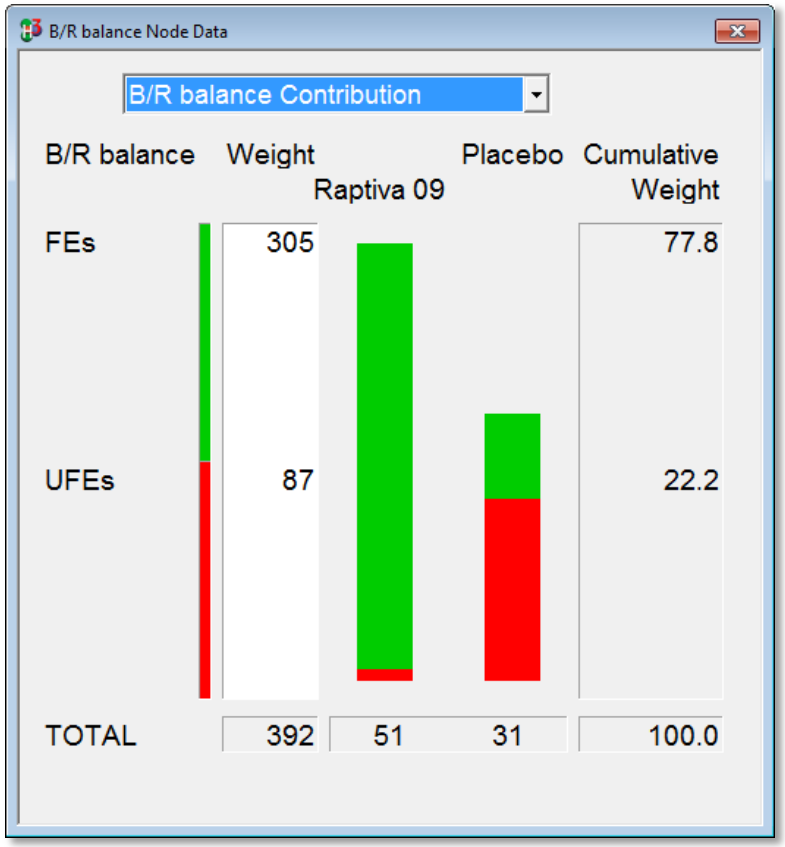
Efalizumab: BRAT representation

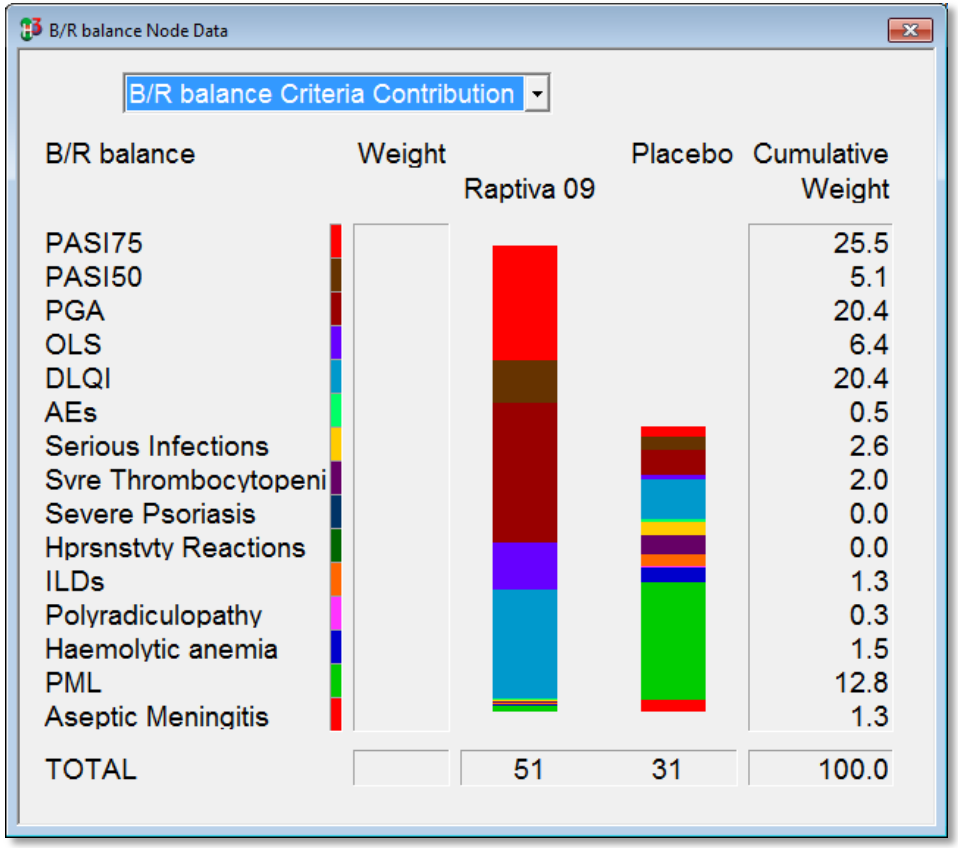
		Outcome	RAPTIVA Risk / 1000 pts	Placebo Risk / 1000 pts	Risk Difference (95% CI)/ 1000 pts		Relative Risk (95% CI)	
Benefits	Efficacy	PASI75	280	36	244	(151, 362)	7.819	(4.999, 12.380)
		PASI 50	567	200	360	(303, 431)	2.800	(2.210, 3.650)
		PGA	305	52	251	(141, 396)	5.778	(3.602, 9.337)
		OLS	292	37	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)





Efalizumab: MCDA criteria contribution





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

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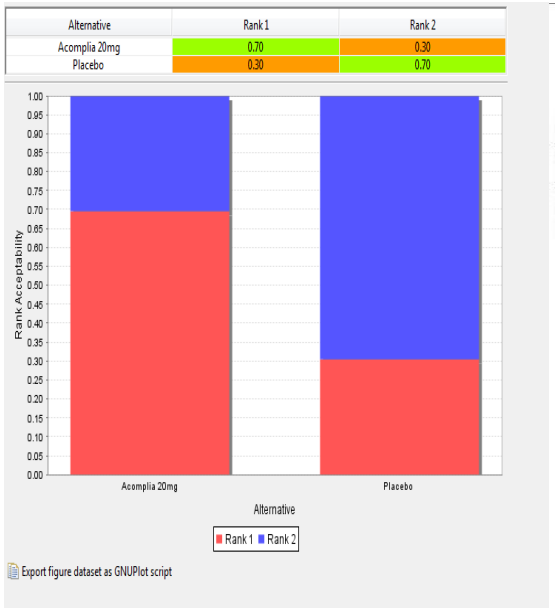
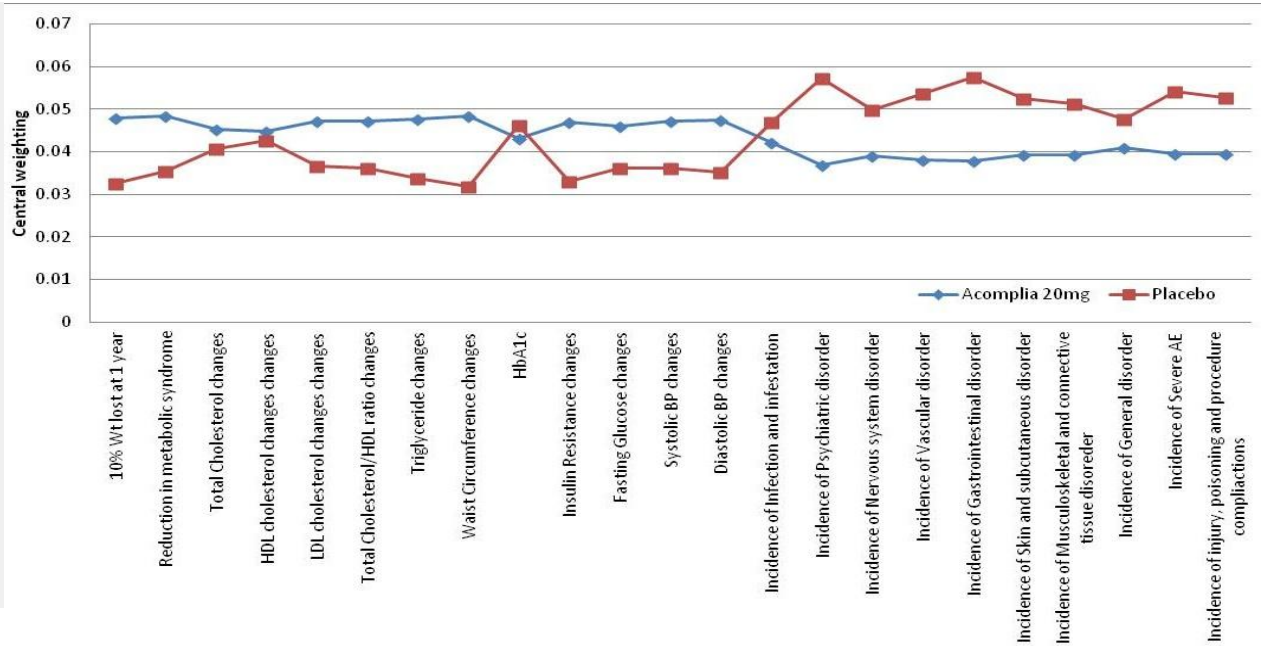
Rimonabant: SMAA (preference-free)

Acceptability index

alternative *i* is ranked *r*



Preference values for an "average" decision-maker resulting in the preference on the left



PROTECT

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Adverse Drug Reactions Database NEW
Drug Consumption Databases in Europe NEW

Key achievements of PROTECT

Framework for pharmacoepidemiology studies
- Presentations (21)
- Publications (4)
- 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)
- Publications
- Reports and Databases

Replication studies
- Presentations (1)
- Publications
- Reports and Databases

Training and Communication
- Presentations
- Publications
- Reports and Databases (1)

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

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

Acknowledgments

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