PROTECT

imi efpia

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

Benefit-Risk Integration and Representation

IMI-PROTECT Symposium

20th February 2014

Work Package 5 and 6

Outline

Title	Presenters
Recommendations of the PROTECT Benefit-Risk Group: A roadmap in pursuit of robustness, transparency and harmonisation.	Deborah Ashby
Benefit-risk assessment: a real-life experience	Billy Amzal
In sickness and in health, and for the greater good: Involving patients and the public in benefit-risk decision-making	Susan Talbot
WP6-WS2 VISUALizE: Visualizing Uncertainty Among Laypersons and Experts	Andrea Beyer
The past, the present and the future: Impact assessment of a multi-stakeholders collaboration in Europe (and beyond) [Summary and Panel discussion]	Deborah Ashby, Hans-Georg Eichler, Hans Hillege

Deborah Ashby

A ROADMAP IN PURSUIT OF ROBUSTNESS, TRANSPARENCY AND HARMONISATION

RECOMMENDATIONS OF THE PROTECT BENEFIT-RISK GROUP

Acknowledgement

- 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.

- The PROTECT project has received support from the Innovative Medicine Initiative Joint Undertaking (www.imi.europa.eu) under Grant Agreement n° 115004, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

Disclaimer

"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.

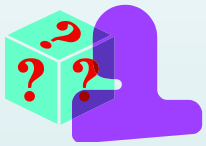
This report neither replaces nor is intended to replace or comment on any regulatory decisions made by national regulatory agencies, nor the European Medicines Agency."

PROTECT is receiving funding from the European Community's Seventh Framework Programme (F7/2007-2013) for the Innovative Medicine Initiative (www.imi.europa.eu)

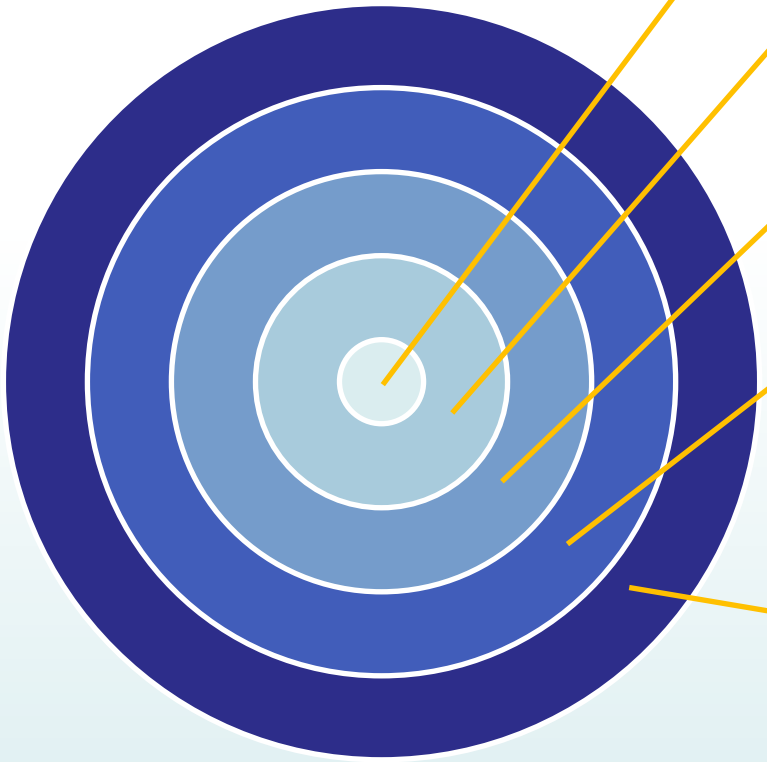
Evidence Based Medicine

"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



Decision makers – hierarchical?



Patients

- Make decisions for themselves

Healthcare providers

- Make decisions based on prescribing lists

Health technology assessors

- Makes decisions on cost-effectiveness

Regulators

- Makes decisions on quality, safety, efficacy and benefit-risk balance to individuals and public health

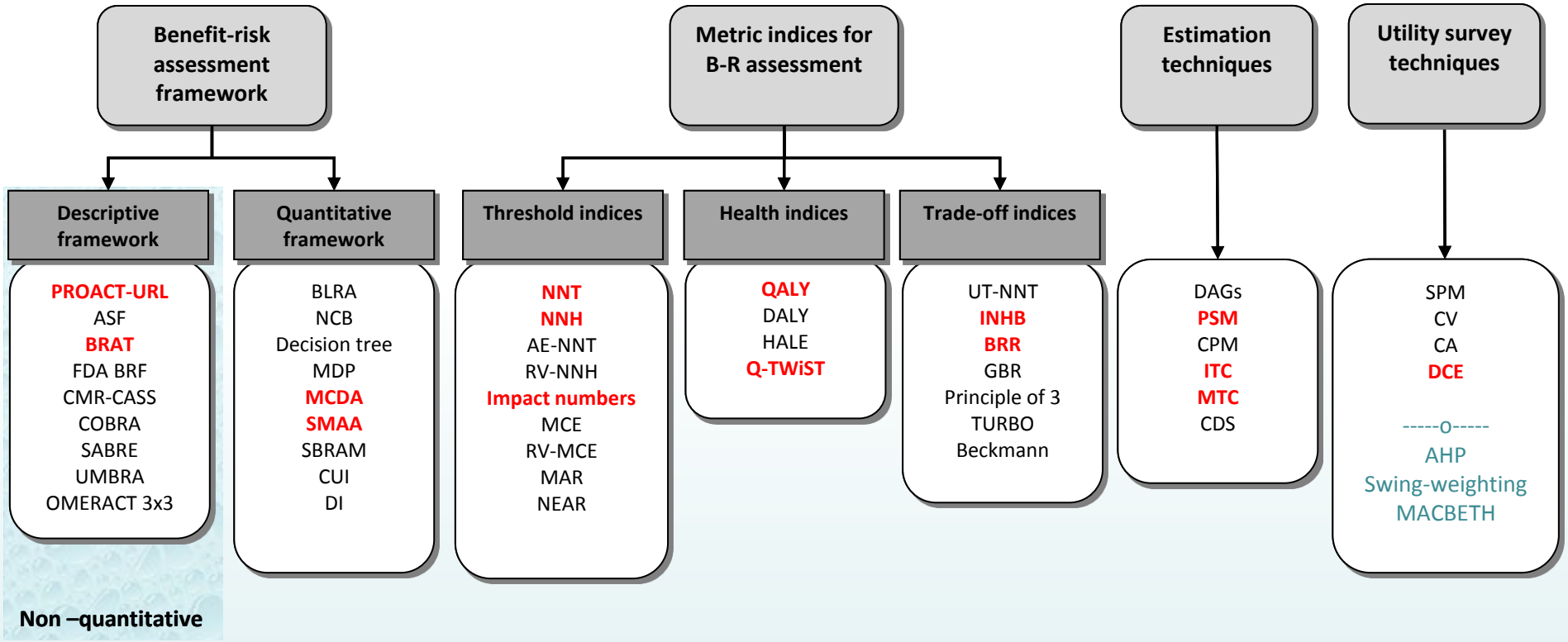
Pharmaceutical companies

- Makes decisions on what to develop for which licenses to apply

IMI-PROTECT Benefit-Risk Group

- IMI-PROTECT Benefit-Risk Group conducted a:
  - Benefit-Risk Methodology Review,
  - Executed a Visualisation Review in two stages.
  - Applied selected Methodologies and Visualizations to six discrete case studies, conducted in two waves
    - Rimonabant, Telithromycin, Efalizumab, Natalizumab
    - Rosiglitazone, Warfarin (W2 Rimonabant, W2 Natalizumab)
  - Created a Patient and Public Involvement (PPI) Workstream to develop a toolbox for incorporating PPI into medical benefit-risk decision making.

Methodologies available



Case studies: Methodologies

	Rimonabant	Telithromycin	Efalizumab	Natalizumab	Rosiglitazone	Warfarin
PrOACT-URL	✓	✓	✓	✓	✓	
BRAT	✓	✓	✓	✓		✓
MCDA	✓	✓	✓	✓	✓	
SMAA	✓	✓				✓
NNT & NNH	✓			✓		
Impact Number	✓					
QALY						
Q-TWiST						
INHB	✓					
BRR	✓	✓	✓	✓		
PSM	✓	✓		✓		
MTC	✓			✓		
DCE	✓					
Other:	Direct utility elicitation, Dashboard, MCDA simulations	SBRAM, Swing-weighting	Decision conferencing	Decision conferencing MACBETH, AHP	Decision conferencing Probabilistic MCDA model	Individual benefit risk assessment (NCB)

Efalizumab case study

Drug of interest	Efalizumab
Indication	Psoriasis
Severe side effect	Progressive Multifocal Leukoencephalopathy (PML)
Regulatory history	2004 Approved in September 2009 Marketing authorisation was suspended in February Marketing authorisation withdrawn in June
Data source	EPAR, SPC, PSUR10

Efalizumab case study

Comparators	Placebo
Questions addressed	Given the emergence in the post-marketing setting of PML (Progressive Multifocal Leucoencephalopathy) in addition to other serious risks (cardiotoxicity, neurotoxicity, serious infections including tuberculosis), are there in January 2009 any risk minimisation measures which could be rapidly implemented, thus maintaining the benefit balance of the drug as positive? If not, should the Market Authorisation be suspended/revoked?
Perspectives	Regulator
Reasons for selection	Initial Market authorisation was controversial; later withdrawn due to serious safety concerns.
Methods used	BRAT, PrOACT-URL, MCDA, BRR

Recommendation Roadmap

- robustness
- sensitivity
- assumptions and uncertainties
- other consequences
- impact or added value to the RMPs

- relevant evidence
- data collection
- data aggregation
- missing/incomplete data

Evidence gathering and data preparation

Exploration

Analysis

- Evaluate data
- Quantify benefits and risks
- Weigh or integrate

Conclusion and dissemination

- communicate results/consensus
- any influence on future actions
- transparent audit trail
- ensures "big picture" is not lost

Planning

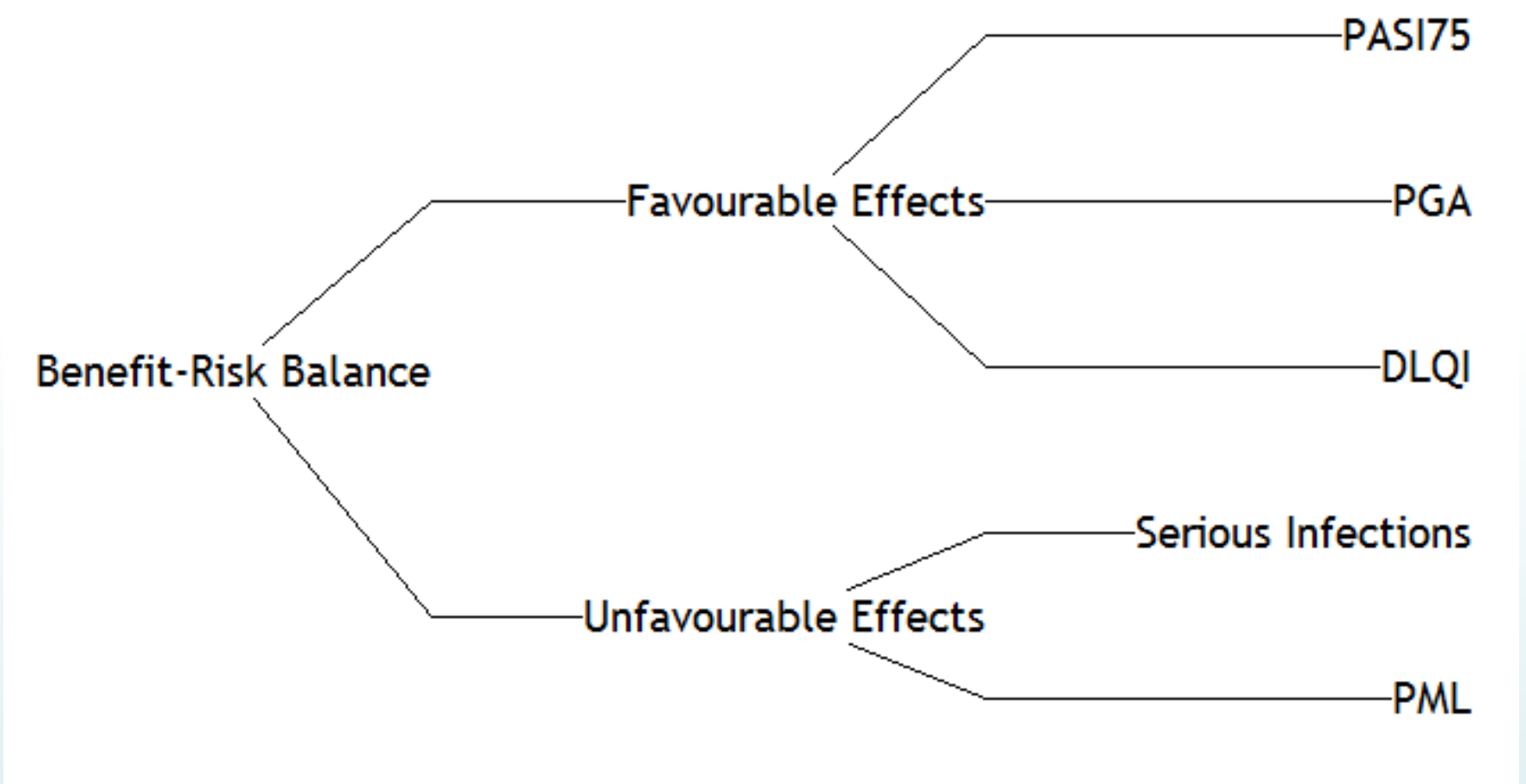
- critical issues
- think & discuss purpose and context
- documentation
- foundations for future analyses and updates

Hughes D, et *al*. Recommendations for the methodology and visualisation techniques to be used in the assessment of benefit and risk of medicines. IMI-PROTECT Website 2014.

Recommendations at Stage 1

Methodologies	Visual representation
PrOACT-URL	Tree diagram
PhRMA BRAT	Structured table shells - Effects table (PrOACT-URL) - Source data table (BRAT)

Value tree (efalizumab example)



Recommendations at Stage 2

Methodologies	Visual representation
Indirect / Mixed treatment comparison (ITC/MTC)	Structured and colour-coded tables (Effects table, Source data table)
Probabilistic simulation method (PSM)	Network graphs
	Forest plots

Effects table (efalizumab example)

	Name	Description	Units	Efalizumab	Placebo
Favourable Effects	PASI75	Percentage of patients achieving 75% reduction in baseline PASI[1] at week 12.	%	29.5	2.7
	PGA	Percentage of patients achieving Physician's Global Assessment[2] clear/almost clear at week12.	%	29.5	5.1
	DLQI	Dermatology Life Quality Index[3]. Mean change from base score.	Change score	5.8	2.1
Unfavourable Effects	Severe infections	Proportion of patients experiencing infections serious enough to require hospitalisation.	%/100 ptyrs	2.83	1.4
	PML	Number of cases of progressive multifocal leukoencephalopathy.	number	3	0

[1]PASI is a measure of the average redness, thickness and scaliness of the lesions (each graded on a 0-4 scale), weighted by the body region and the area affected. PASI range is from 0 to 72.

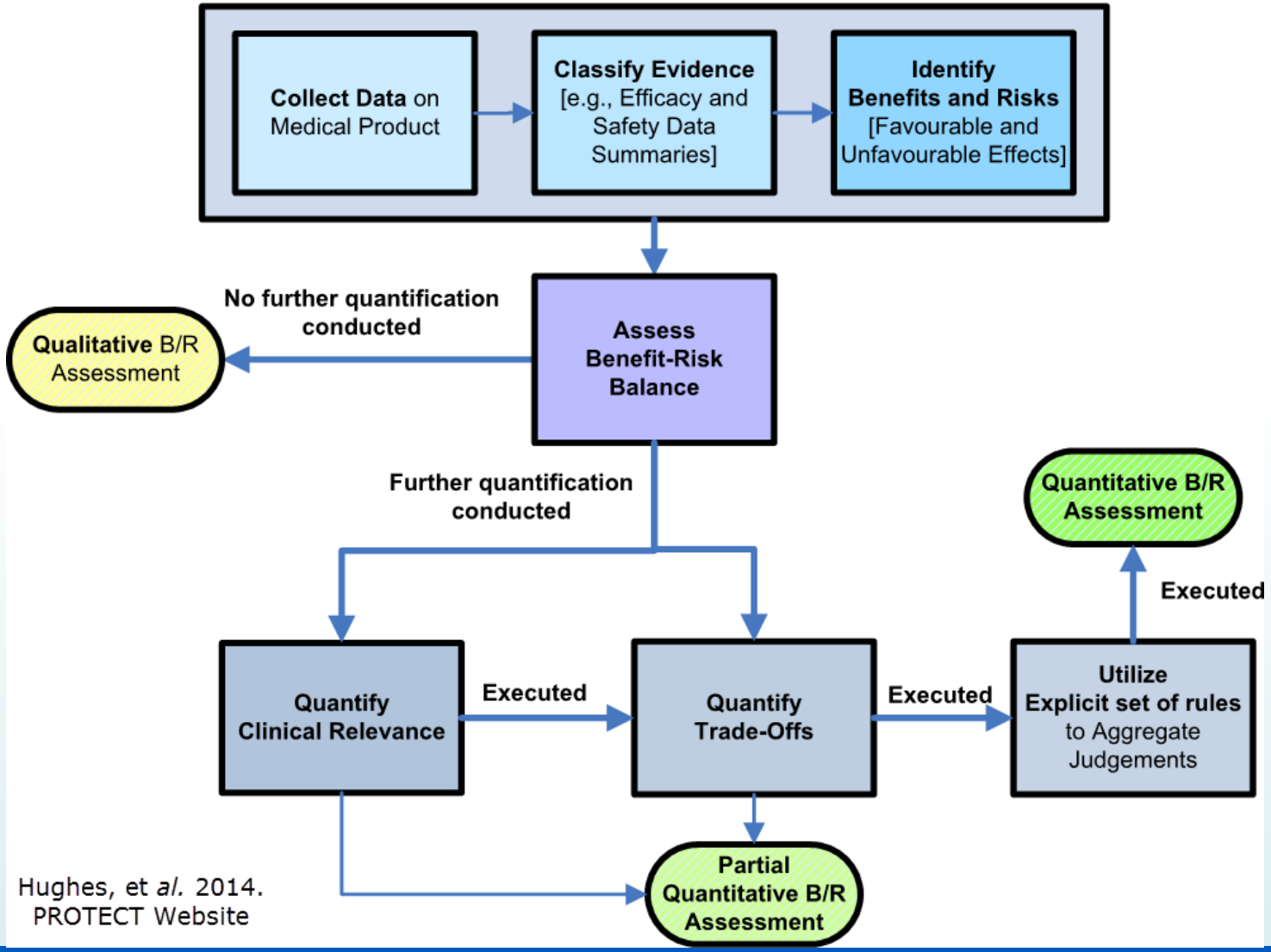
[2]PGA is a seven point scale with 7 being clear, 6 almost clear, 5 mild, 4 mild to moderate, 3 moderate, 2 moderately severe and 1 severe psoriasis.

[3]DLQI is a 10-item quality of life index scored by the patient on a four-point scale (0-3).

Recommendations at Stage 3

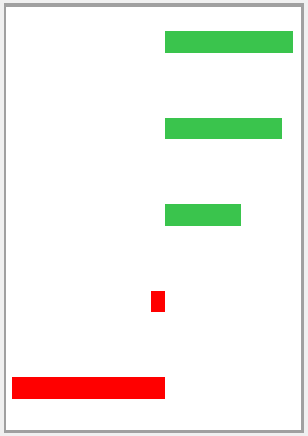
Methodologies		Visual representation
Numerical representations of benefits and risks		Elicit preference values - Tree diagram - Method-specific visual displays (e.g. MACBETH grid, AHP table, swing-weight scale, drop-down list)
- NNT/NNH - Impact numbers - QALY	- Q-TWiST - BRR - INHB	
Model benefit-risk balance - MCDA - SMAA		Present descriptive results - Tables - Forest / interval plots
Elicit stakeholders' preference - DCE		Present quantitative results - Difference display - Stacked bar charts - Grouped bar charts

Qualitative versus quantitative DM



Quantitative analysis (efalizumab example)

Favourable Effects	PGA	14.6
Favourable Effects	PASI75	13.4
Favourable Effects	DLQI	8.9
Unfavourable Effects	Serious Infections	-1.8
Unfavourable Effects	PML	-17.6
		17.5

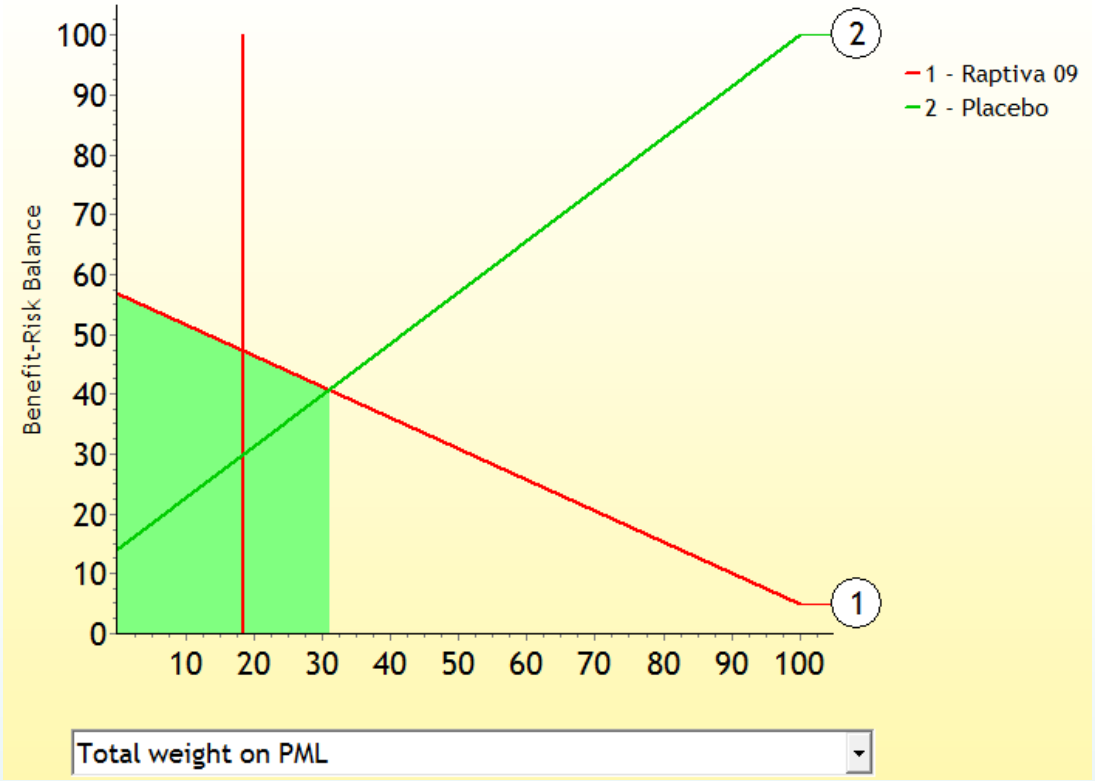


The difference display shows the contribution of the weighted difference between drug and placebo for each effect. Right-extending (green) bars favour the drug and left-extending (red) bars favour the placebo, for a 17.5 total difference (out of 100) in favour of efalizumab.

Recommendations at Stage 4

Methodologies	Visual representation
Indirect / Mixed treatment comparison (ITC/MTC)	Box plot
Utility survey techniques (DCE, AHP, swing-weighting, MACBETH)	Distribution plot
Probabilistic simulation method (PSM)	Forest / interval plot
Stochastic multi-attribute acceptability analysis (SMAA)	Tornado diagram
	Scatter plot
	Interactive visual displays

Sensitivity analysis (efalizumab example)



It shows the effect of changing the weight on the PML criterion. The vertical red line represents the current weight of 18.5 (out of a total of 100 for all five criteria). The intersections of that line with the slanting red and green lines define the 17.5 difference. If the PML weight is increased beyond 32, then the benefit-risk balance favours the placebo.

Key considerations at Stage 5

Methodological considerations

- What question(s) were the benefit-risk assessment aimed at addressing?
- What answer(s) were found?
- Is/are the answer(s) highly sensitive to the treatment effects data, the choice of analysis method, or the preference data?
- What is the supporting information on which the conclusion is based?

Visualisation considerations

- Know the intended audience – consider knowledge/interests
- Refer to established visual design principles and guidelines, e.g. Wickens, Tufte, Carswell, Kosslyn, Lipkus, Cleveland, Few

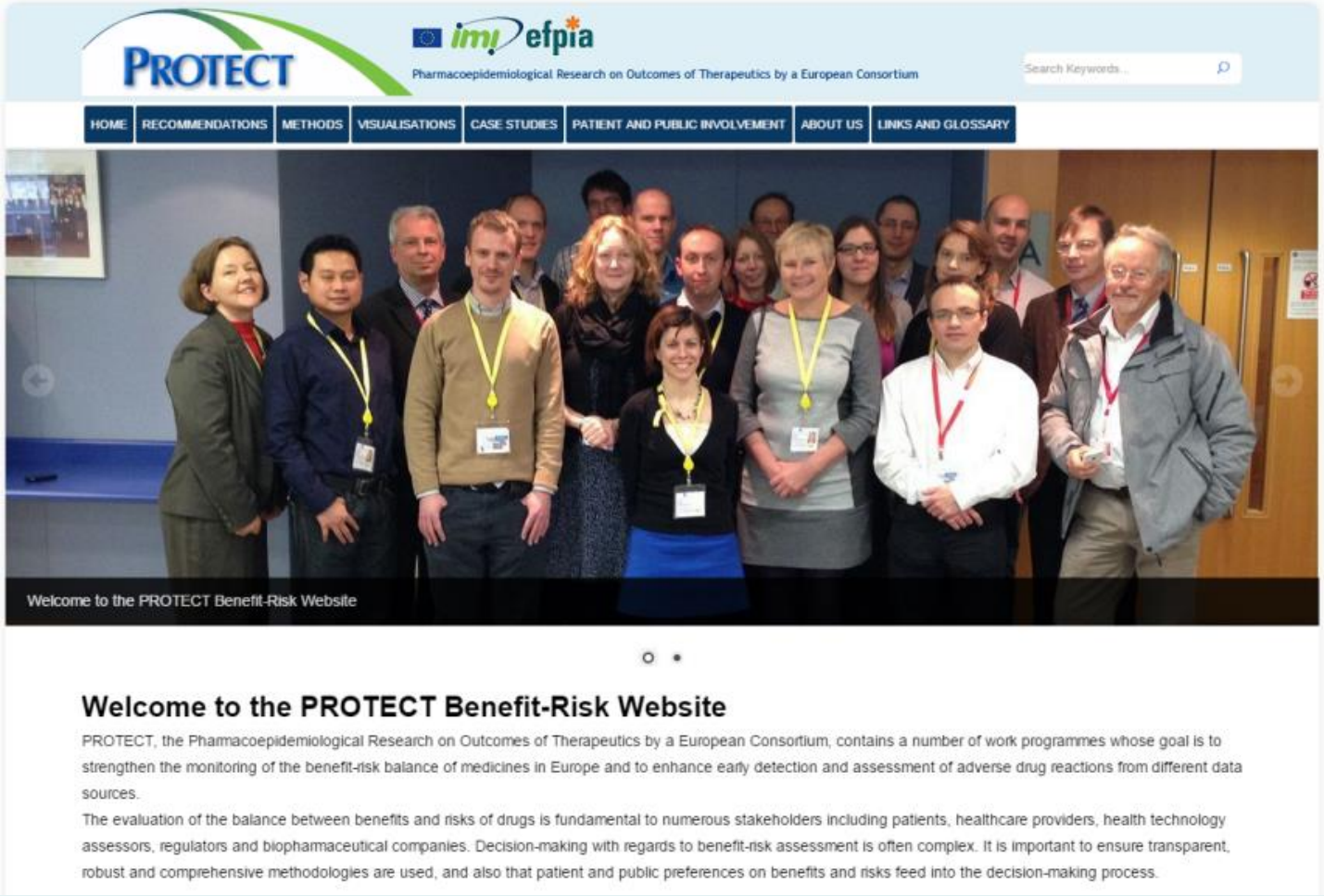
Contributions

- Taxonomy of benefit-risk assessment methodologies
- Comparative applications in real-world case studies
- Visual representation review
- Role of patient and public involvement and comparative evaluation of preference elicitation methods
- Demonstrated effective collaboration between multiple partners

Final remarks

- Benefit-risk assessment methodologies support decision-making and are not intended to replace medical expertise.
- Implementation in regulatory settings have begun but there is no harmonisation across organisations
- PROTECT BR group only provide guidance
- Future research includes:
  - Patient and public involvement
  - Vaccines
  - Different subgroups

Dissemination and recommendations arising from PROTECT



http://PROTECTBenefitRisk.eu/