PROTECT

imi efpia

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

FROM QUALITATIVE TO QUANTITATIVE BENEFIT-RISK DECISION-MAKING:
CONCEPTS AND METHODS

IMI-PROTECT Symposium

Benefit-Risk Integration and Representation Workshop

18th February 2015

Lawrence Phillips, PhD

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.

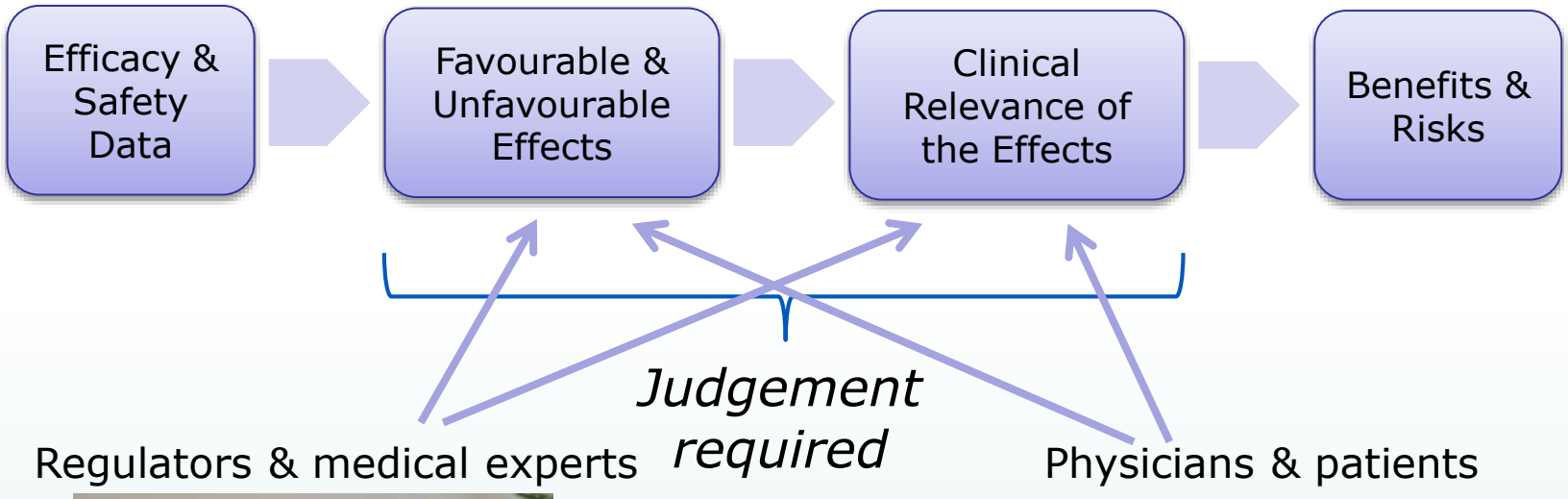
This report neither replaces nor is intended to replace or comment on any regulatory decisions made by national regulatory agencies, nor the European Medicines Agency."

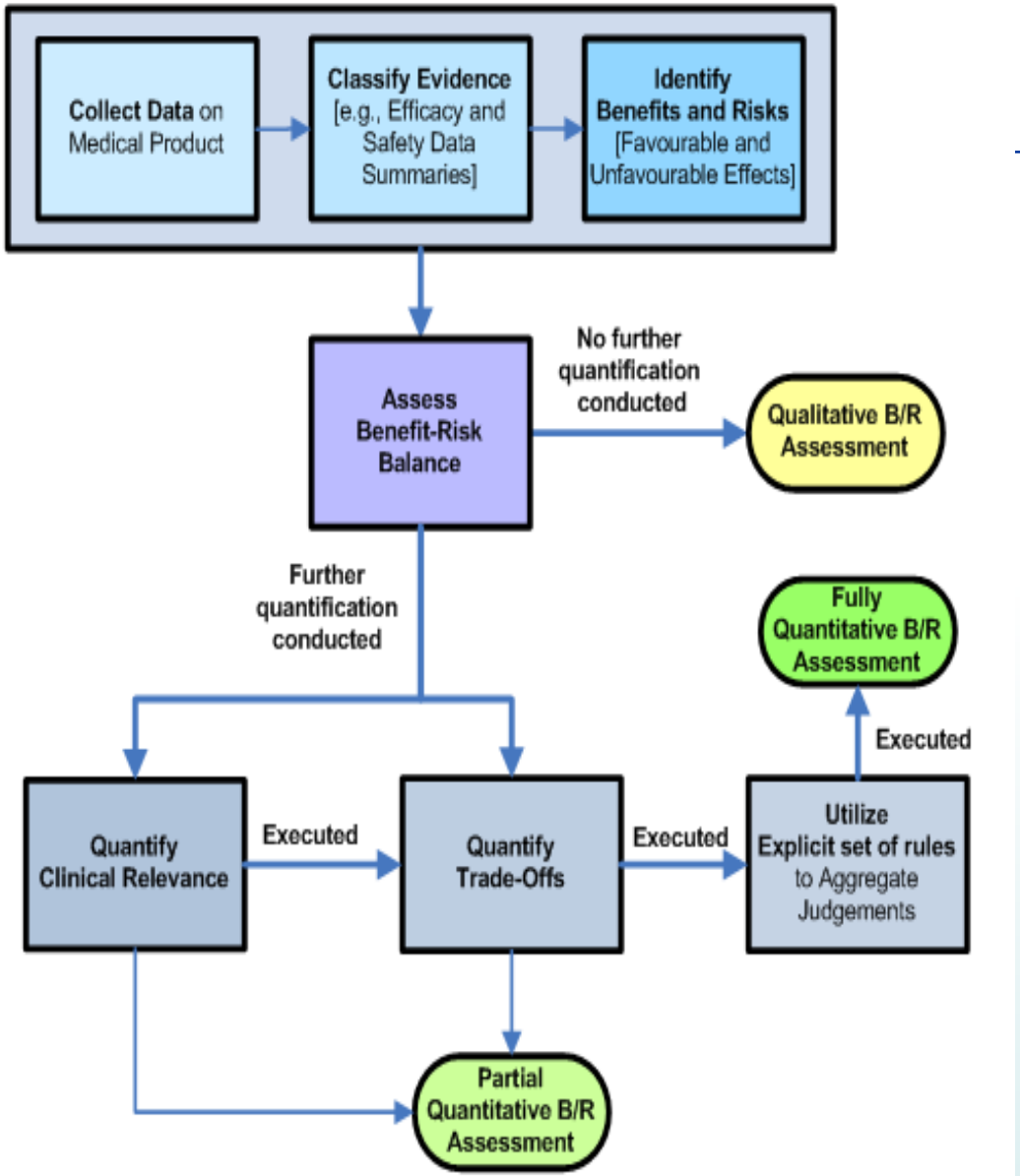
PROTECT is receiving funding from the European Community's Seventh Framework Programme (F7/2007-2013) for the Innovative Medicine Initiative (www.imi.europa.eu)

By the end of this presentation, you will…

- …see how efficacy and safety data are transformed into benefits and risks
- …know the distinctions between qualitative, semi-quantitative and fully quantitative B-R approaches
- …appreciate the role of judgement in each approach
- …understand how a fully quantitative approach can integrate data and clinical judgement
- …recognise how disagreements amongst experts can be synthesised into shared understanding with decision conferencing
- …see how frameworks and approaches can help assessors develop insight about a drug's benefit-risk

Efficacy & Safety ⇒ Benefits & Risks





B-R Assessment

- Qualitative
- Partially Quantitative
- Fully Quantitative

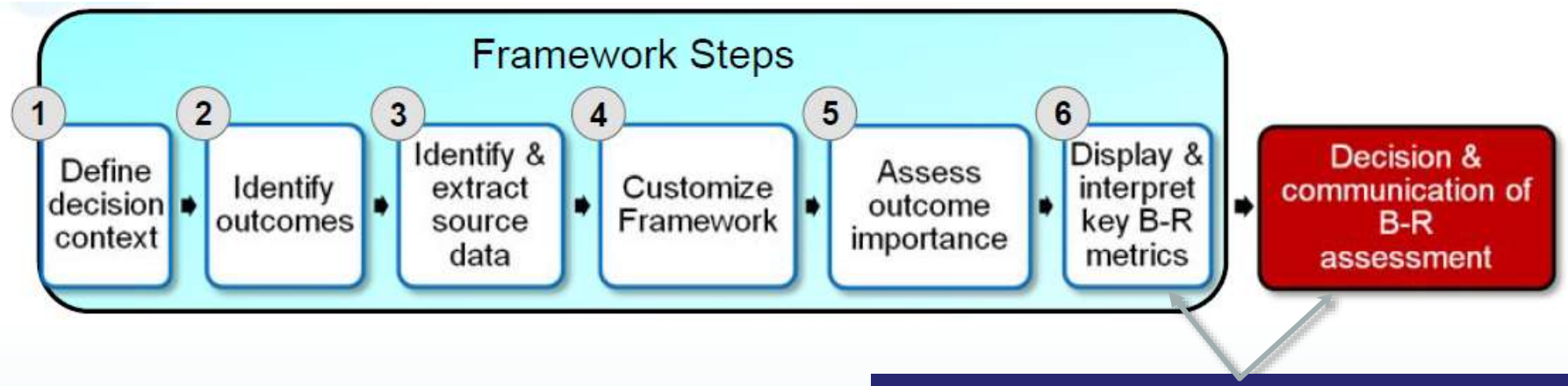
Qualitative B-R assessment

Discussing

Voting

No quantitative modelling is used by any regulator anywhere to deal with the massive amount of data—10GB more or less!

Pharma-BRAT framework

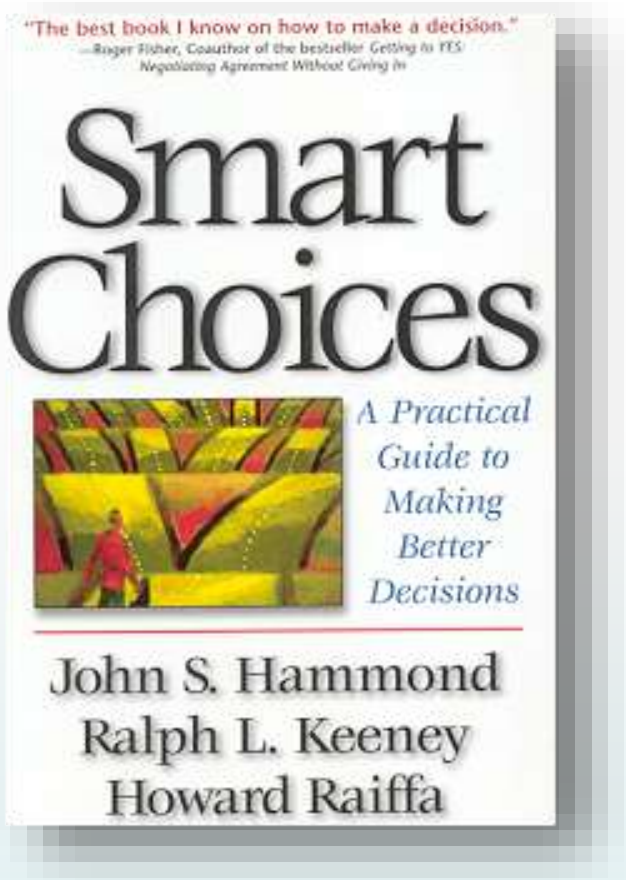


Can be applied at any stage of drug development, approval and post-approval.

Missing: Clinical relevance of the metrics and uncertainty of the effects

See http://www.cirs-brat.org/download-link/

PrOACT-URL framework

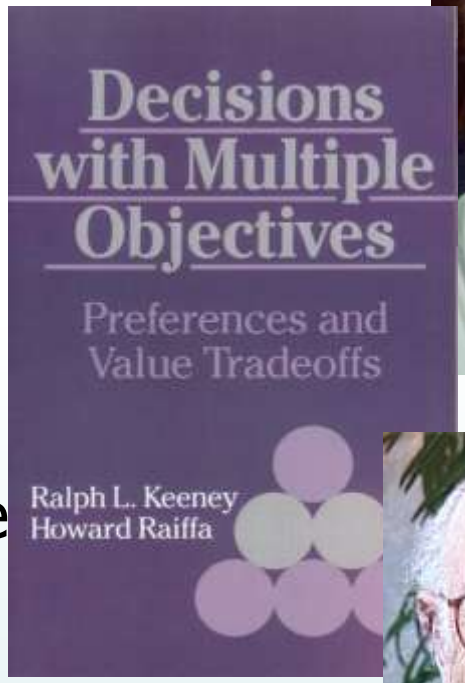


- **Pr**oblem
- **O**bjectives
- **A**lternatives
- **C**onsequences
- **T**rade-offs
- **U**ncertainty
- **R**isk attitude
- **L**inked decisions

See the Appendix of EMA B-R Project Work Package 4 report at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/03/WC500123819.pdf.

MCDA (Multi-Criteria Decision Analysis)

- An extension of decision theory that covers any decision with multiple objectives.
- A methodology for appraising options on individual, often conflicting criteria, and combining them into one overall appraisal.



A quick overview: Chapter 6 of Dodgson, J., Spackman, M., Pearman, A., & Phillips, L. (2000) *Multi-Criteria Analysis: A Manual*. Available online at http://eprints.lse.ac.uk/12761

Decision Conferencing

- One or more workshops to solve a 'hot' problem
- Attended by key players representing diversity of perspectives on the issues
- Facilitated by an impartial specialist in group processes & decision analysis
- Using a requisite (just-good-enough) MCDA model created on-the-spot to provide structure to thinking

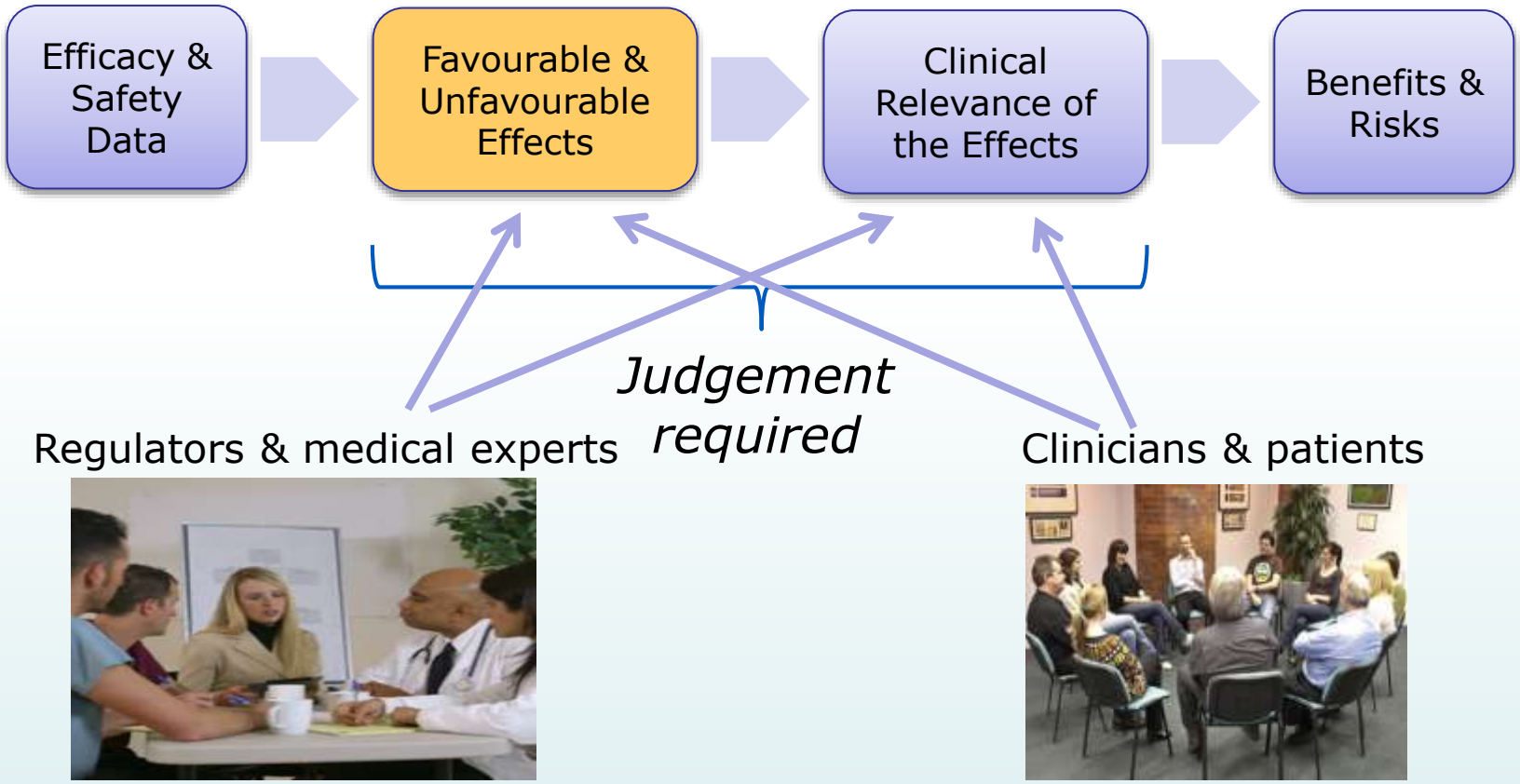
Source: Phillips, L. D. (2007). Decision Conferencing. In W. Edwards, R. F. Miles & D. von Winterfeldt (Eds.), *Advances in Decision Analysis: From Foundations to Applications. Cambridge: Cambridge University Press.*

Efalizumab (Raptiva) case study

- Drug approved in 2004 for chronic plaque psoriasis
- Emerging safety issues signalled CHMP to give opinion in Jan 2009 on benefit-risk
- Maintain, vary, suspend or withdraw Marketing Autorisation? It was suspended
- PROTECT Task Force developed quantative model from regulator's 2009 perspective

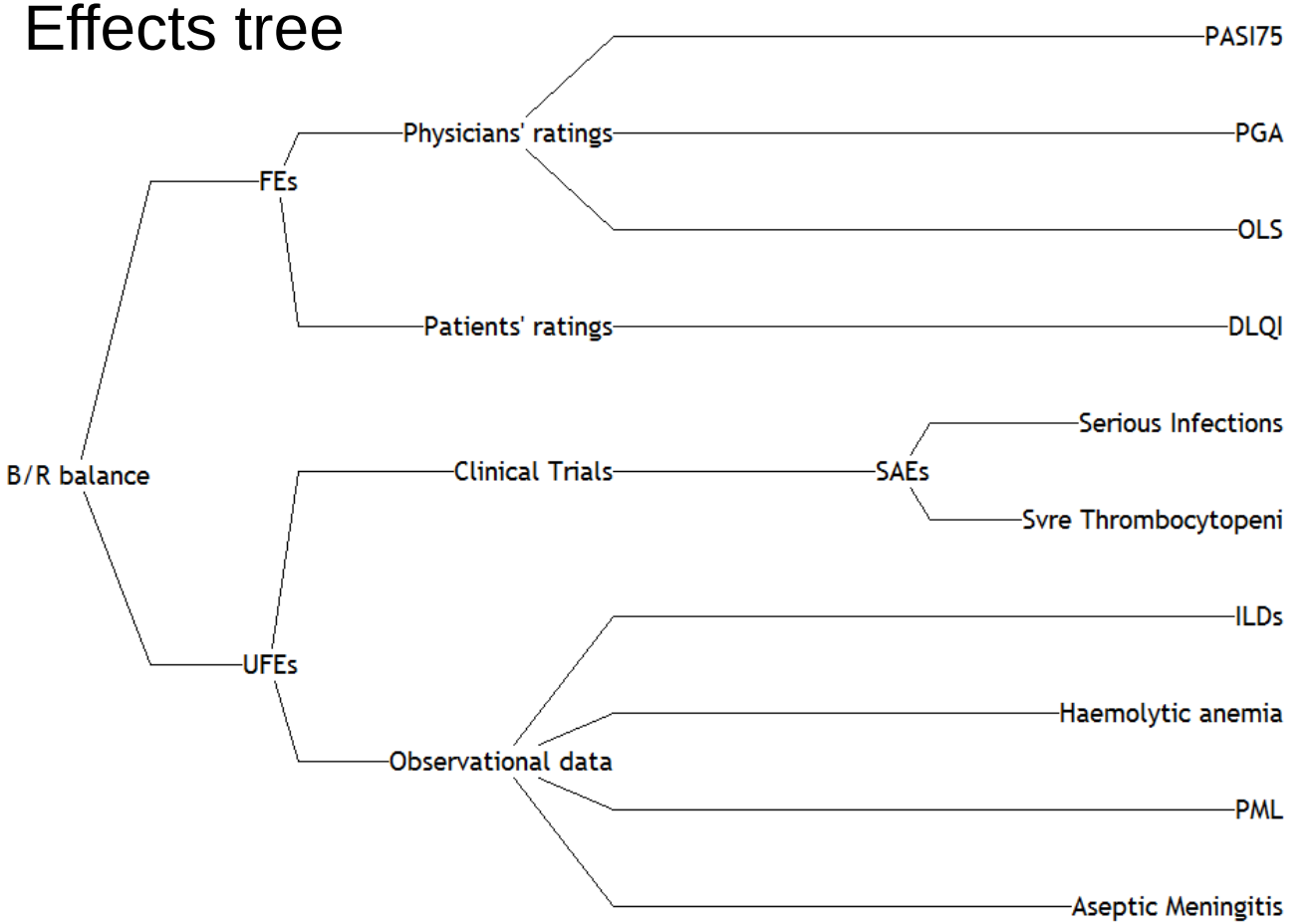
Model source for this project: Hiview3, originally developed at the London School of Economics, now available from Catalyze Ltd, www.catalyze.co.uk

Efficacy & Safety ⇒ Benefits & Risks



Choose favourable & unfavourable effects

Effects tree



- Select only effects that are relevant to the B-R balance.
- Include patients' views.
- Agree definitions of all effects with key players.

Summarise information as an 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
	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	Severe infections	Proportion of patients experiencing infections serious enough to require hospitalisation.	3.00	0.00	%/100ptyrs	2.83	1.4
	Severe Thrombo-cytopenia	Number of cases exhibiting severe (grade 3 and above) thrombocytopenia[4].	10	0	number	9	0
	Intersticial Lung Disease	Number of cases of interstitial lung disease.	20	0	number	18	0
	Haemolytic anemia	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

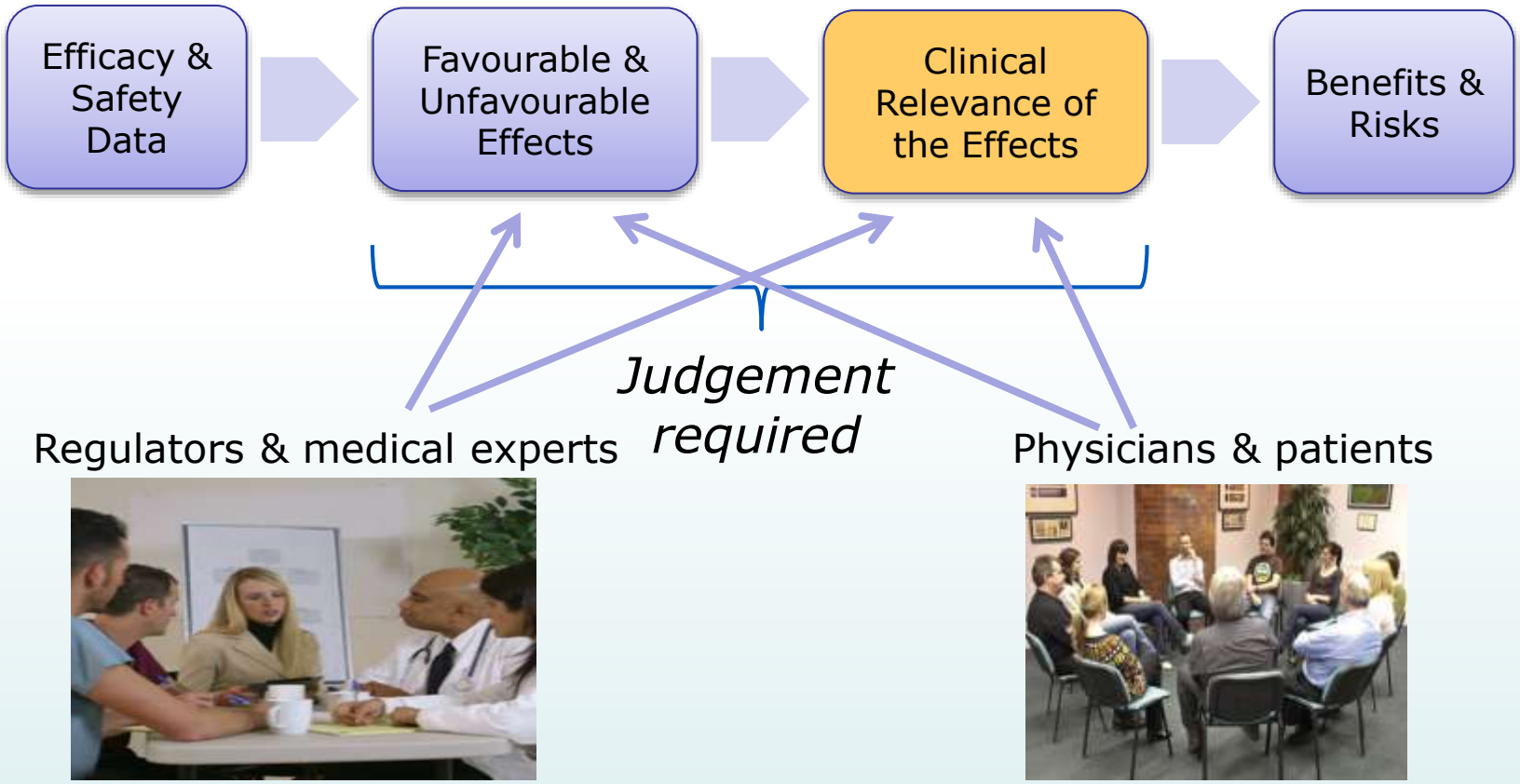
[1]PASI is a measure of the average redness, thickness and scaliness of the lesions (each graded on a 0-4 scale), weighted by the body region and the area affected. PASI range is from 0 to 72.

[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.

[4]As shown in laboratory test results that indicate a decrease in number of platelets in a blood specimen.

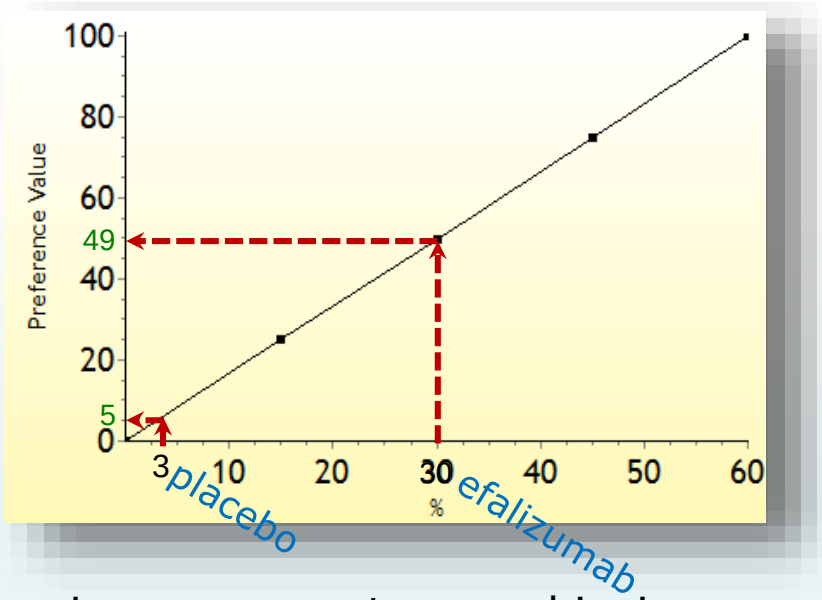
Efficacy & Safety ⇒ Benefits & Risks



Scoring clinical relevance of data

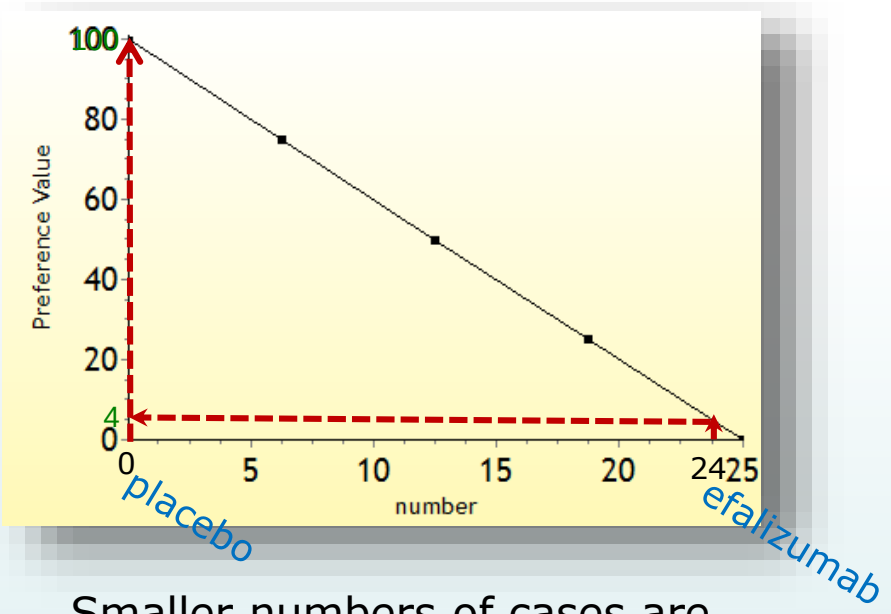
Linear conversions of data to preference values

FE: PASI 75



Larger percentages achieving PASI 75 are preferred

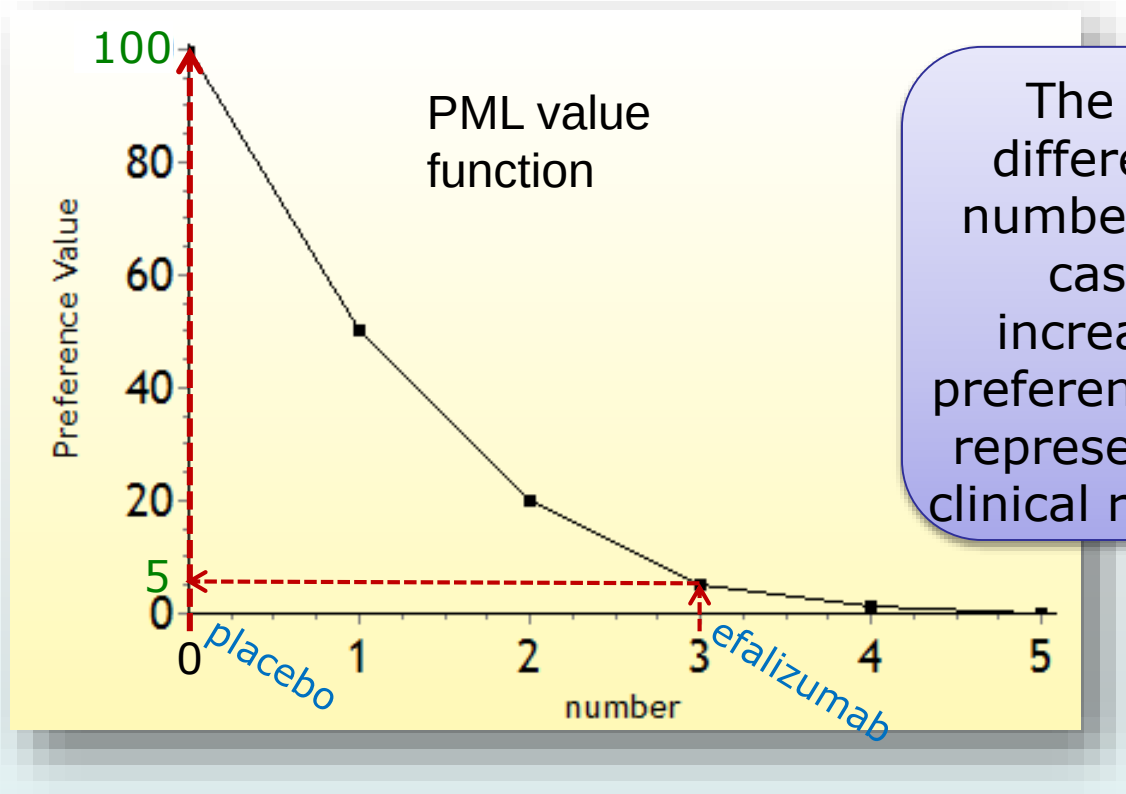
UFE: Haemolytic anaemia



Smaller numbers of cases are preferred

Scoring clinical relevance of data: PML

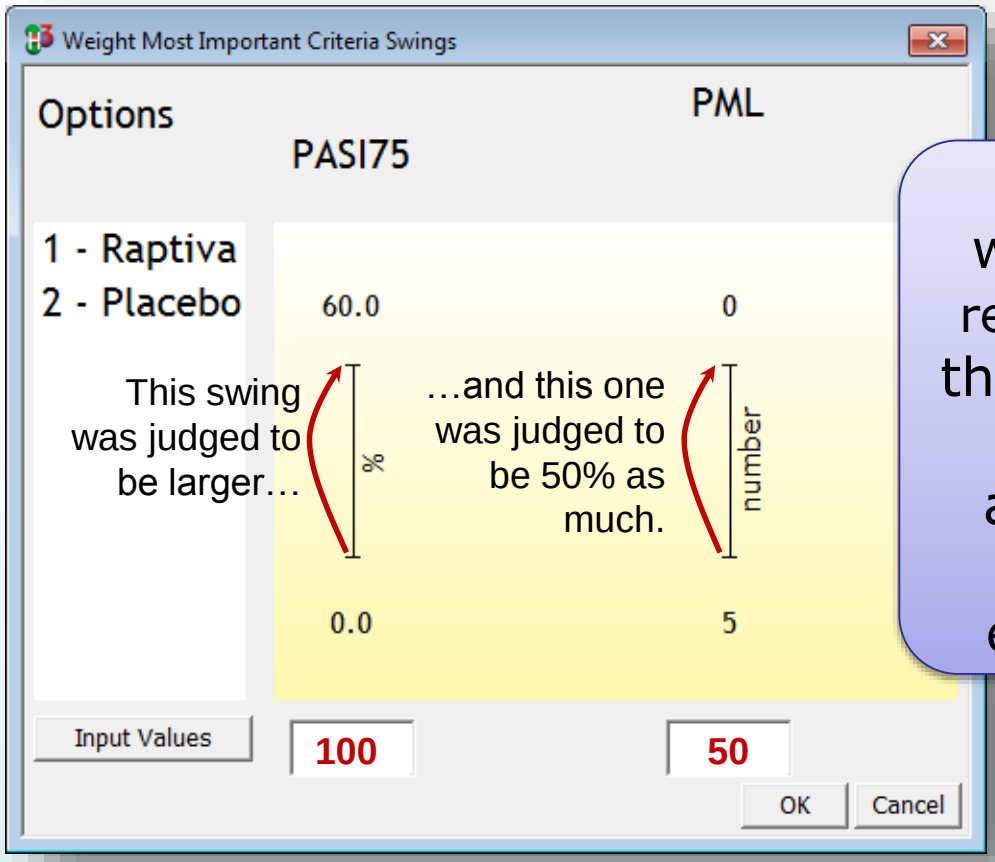
Non-linear conversion to clinical preference values



The 0 – 3 difference in number of PML cases is increased in preference value, representing its clinical relevance.

Weighting clinical relevance of effects

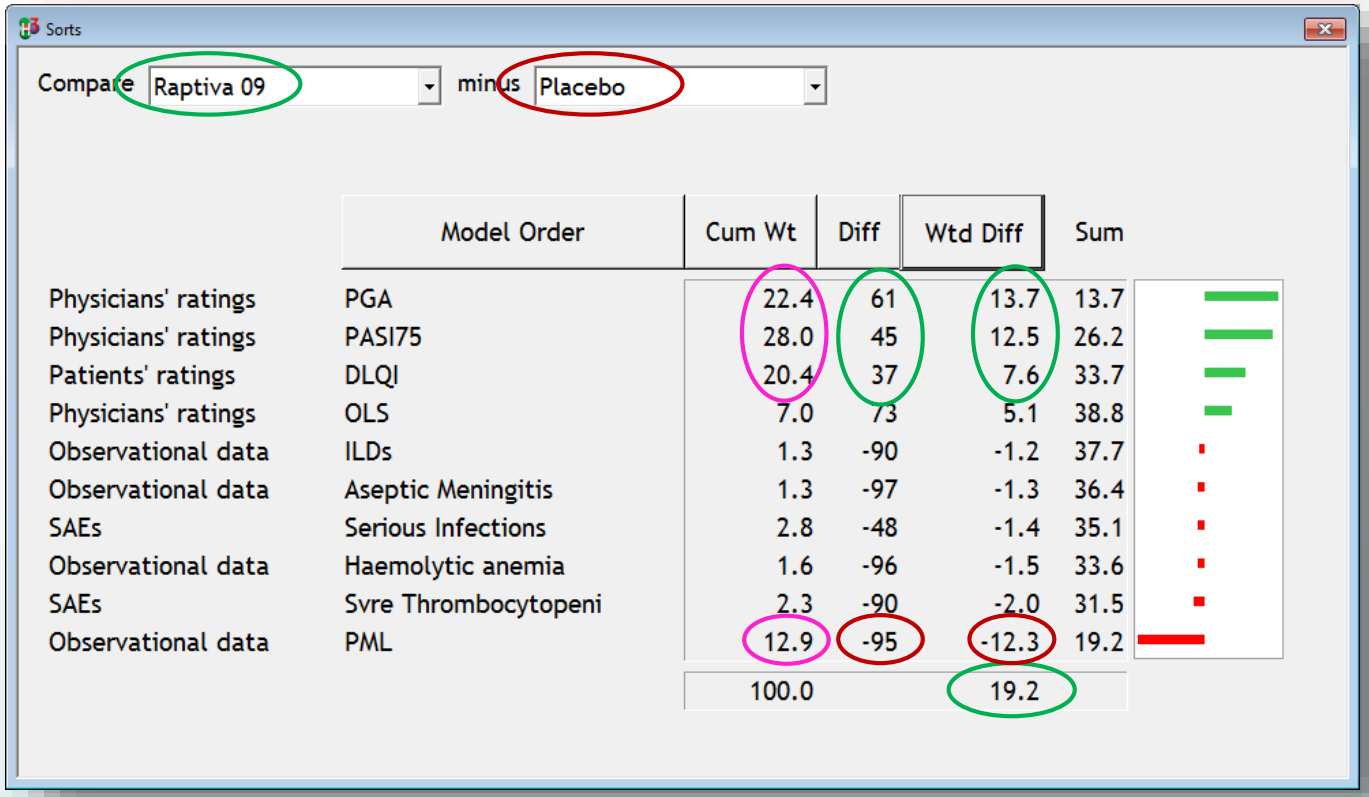
- Swing-weight favourable effects
- Swing-weight unfavourable effects
- Swing-weight most favourable against most unfavourable



Swing weights represent the trade-offs among the effects

"How big is the difference, and how much do you care about it?"

Explore results: benefit-risk differences

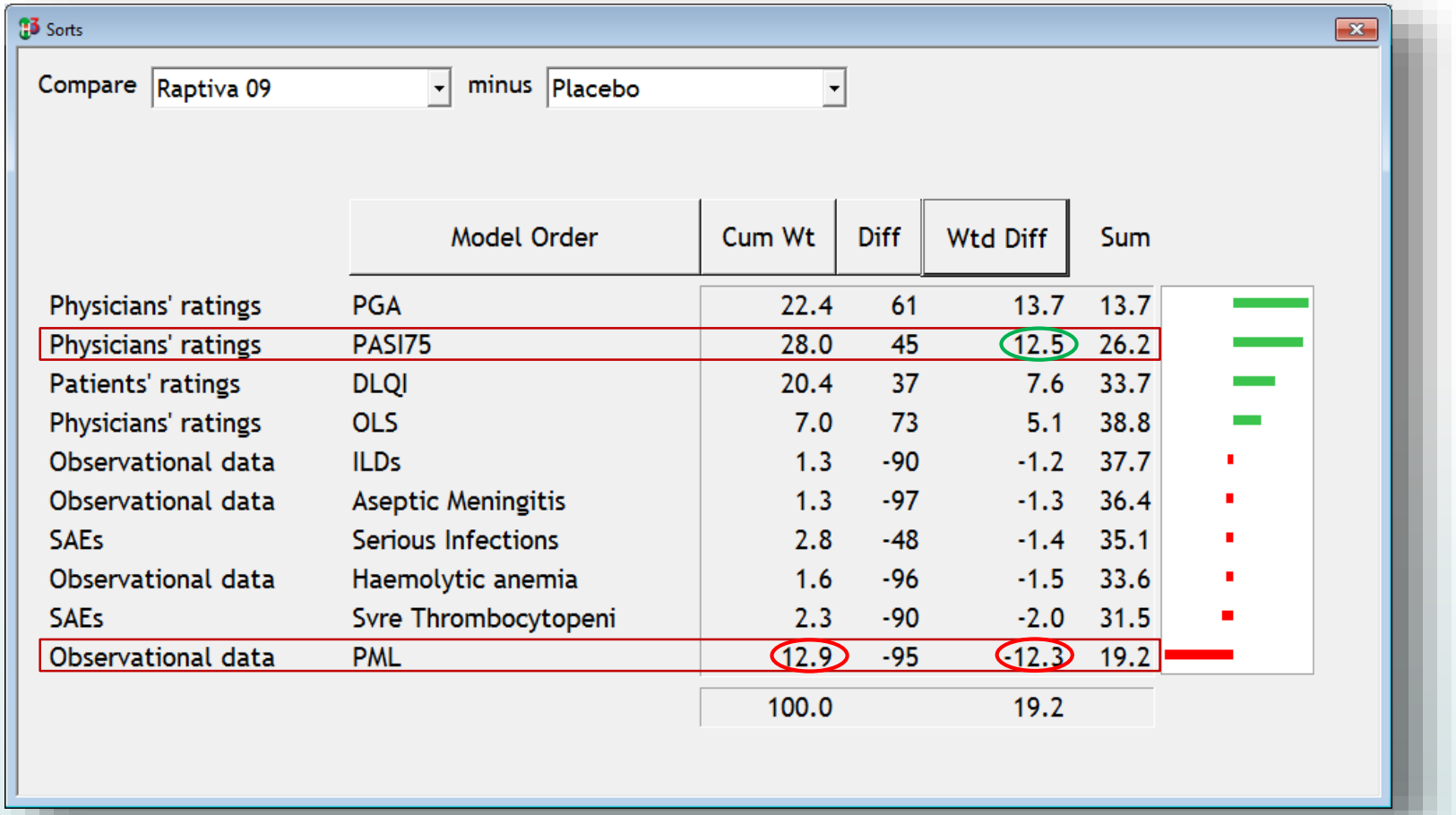


	Model Order	Cum Wt	Diff	Wtd Diff	Sum
Physicians' ratings	PGA	22.4	61	13.7	13.7
Physicians' ratings	PASI75	28.0	45	12.5	26.2
Patients' ratings	DLQI	20.4	37	7.6	33.7
Physicians' ratings	OLS	7.0	73	5.1	38.8
Observational data	ILDs	1.3	-90	-1.2	37.7
Observational data	Aseptic Meningitis	1.3	-97	-1.3	36.4
SAEs	Serious Infections	2.8	-48	-1.4	35.1
Observational data	Haemolytic anemia	1.6	-96	-1.5	33.6
SAEs	Svre Thrombocytopeni	2.3	-90	-2.0	31.5
Observational data	PML	12.9	-95	-12.3	19.2
		100.0		19.2	

Overall, clinical value of Raptiva is greater than the placebo.

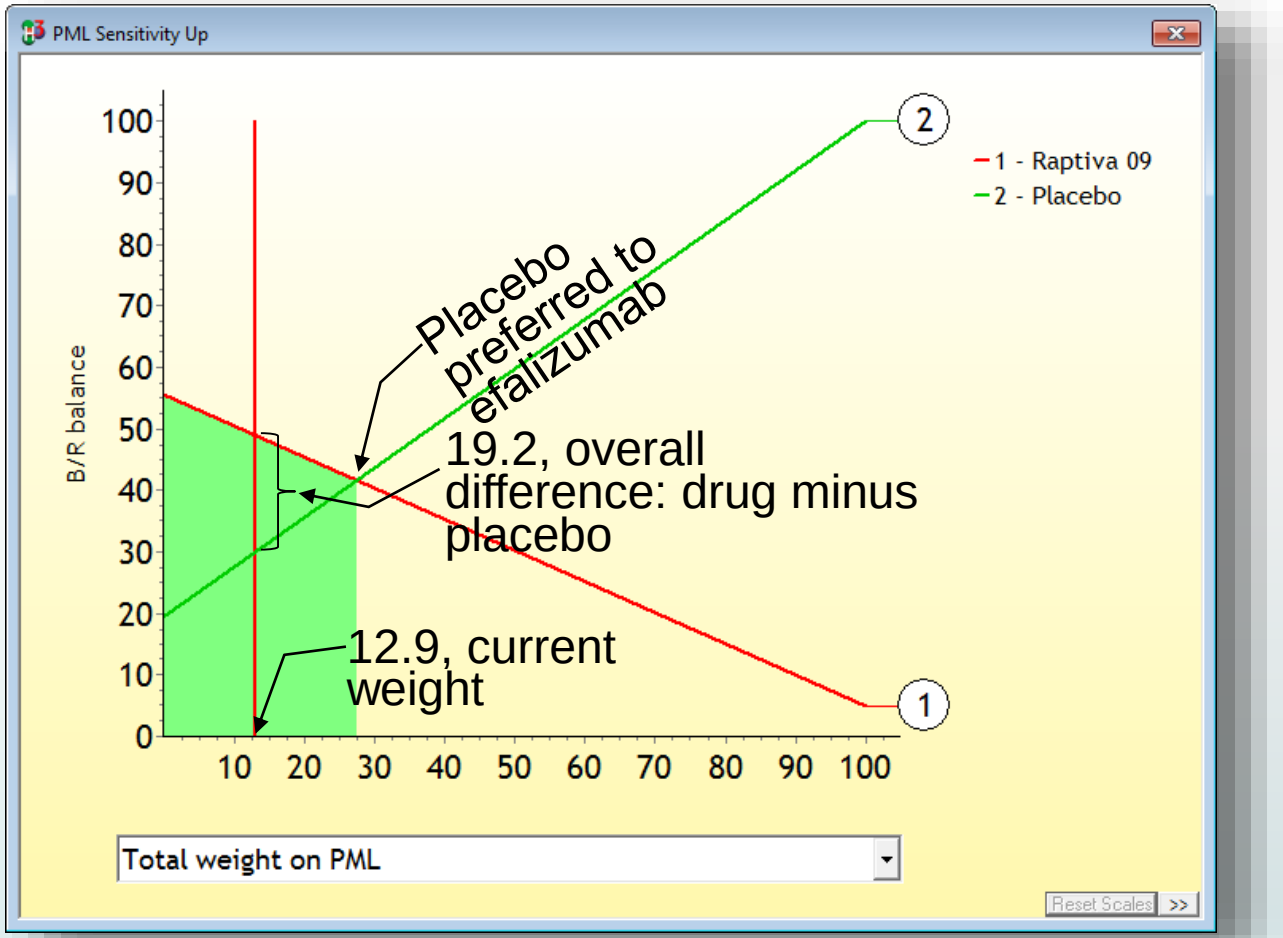
Just three favourable effects & one unfavourable effect account for this difference in clinical value.

Consider only PASI75 & PML

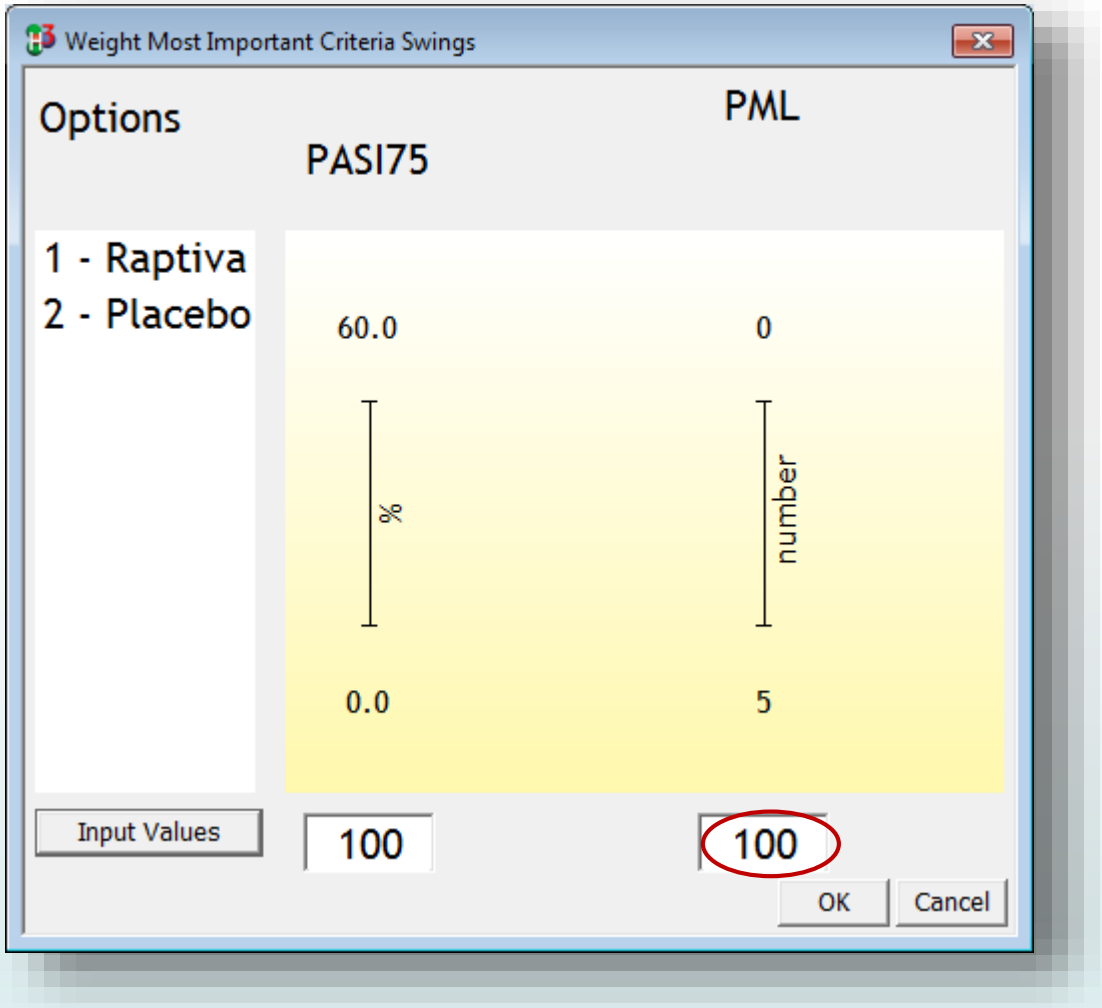


	Model Order	Cum Wt	Diff	Wtd Diff	Sum
Physicians' ratings	PGA	22.4	61	13.7	13.7
Physicians' ratings	PASI75	28.0	45	12.5	26.2
Patients' ratings	DLQI	20.4	37	7.6	33.7
Physicians' ratings	OLS	7.0	73	5.1	38.8
Observational data	ILDs	1.3	-90	-1.2	37.7
Observational data	Aseptic Meningitis	1.3	-97	-1.3	36.4
SAEs	Serious Infections	2.8	-48	-1.4	35.1
Observational data	Haemolytic anemia	1.6	-96	-1.5	33.6
SAEs	Svre Thrombocytopeni	2.3	-90	-2.0	31.5
Observational data	PML	12.9	-95	-12.3	19.2
		100.0		19.2	

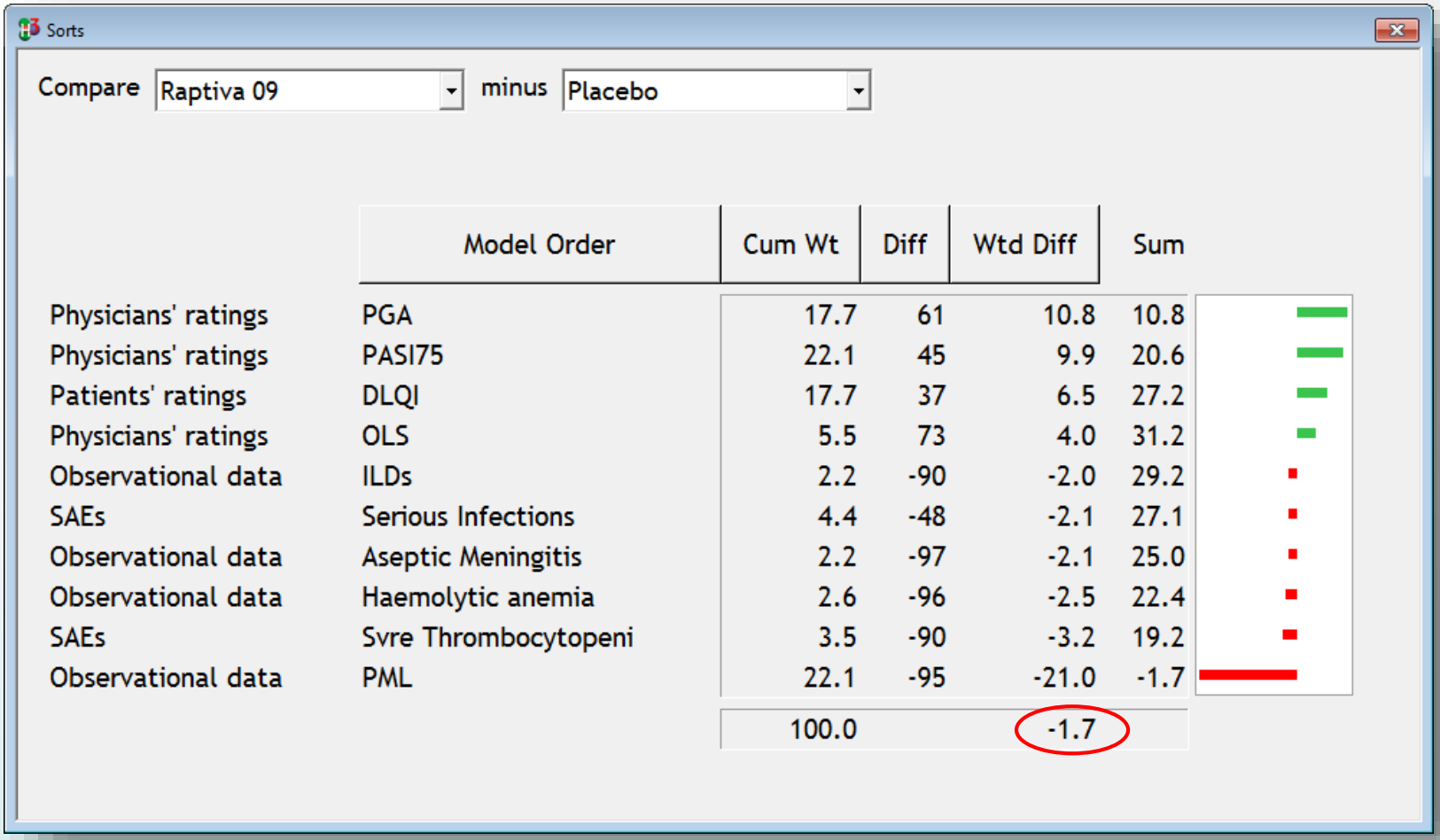
Sensitivity Analysis on PML



Double the weight on PML



Benefits and risks nearly balance



	Model Order	Cum Wt	Diff	Wtd Diff	Sum
Physicians' ratings	PGA	17.7	61	10.8	10.8
Physicians' ratings	PASI75	22.1	45	9.9	20.6
Patients' ratings	DLQI	17.7	37	6.5	27.2
Physicians' ratings	OLS	5.5	73	4.0	31.2
Observational data	ILDs	2.2	-90	-2.0	29.2
SAEs	Serious Infections	4.4	-48	-2.1	27.1
Observational data	Aseptic Meningitis	2.2	-97	-2.1	25.0
Observational data	Haemolytic anemia	2.6	-96	-2.5	22.4
SAEs	Svre Thrombocytopeni	3.5	-90	-3.2	19.2
Observational data	PML	22.1	-95	-21.0	-1.7
		100.0		-1.7	

Our conclusions

- Benefit-risk balance is favourable for efalizumab
- Conflict with 2009 CHMP decision? Not necessarily
  - Hindsight bias
  - We used only publically-available reports of effects
  - Public health interpretation of data: EPAR reports that 27% of patients achieved PASI75—a 'modest effect'
- Experts and assessors frequently disagree
- Quantitative modelling within a decision conference provides 'intellectual technology' that can enable assessors to achieve shared understanding

Summary

- Judgement is required about safety and efficacy data to assess benefit-risk.
  1) Which favourable and unfavourable effects?
  2) How clinically relevant are the data and the effects?
- Application of frameworks such as BRAT or PrOACT-URL are useful 'best-practice' approaches to B-R.
- Quantification, partial or full, can enhance under-standing, develop insight about the benefit-risk balance and facilitate communication about decisions.

ACKNOWLEDGEMENT

Support

- 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.

IMI-PROTECT Benefit-Risk Group

Deborah Ashby, Alain Micaleff, Steve Hobbiger, Ioanna Tzoulaki, Diana Hughes, Shahrul Mt-Isa.

Billy Amzal,Simon Ashworth, Alex Asiimwe, Johan Bring, Torbjorn Callreus, Edmond Kakit Chan, Christoph Dierig, Gerald Downey, David Gelb, Georgy Genov, Alesia Goginsky, Christine Hallgreen, Richard Hermann, Ian Hirsch, Kimberley Hockley, Gemma Hodgson, Juhaeri Juhaeri, Silvia Kuhls, Alfons Lieftucht, Alison Lightbourne, Davide Luciani, Marilyn Metcalf, Jeremiah Mwangi, Thai Son Tong Nguyen, Richard Nixon, Rebecca Noel, John Pears, Ruth Peters, Lawrence Phillips, George Quartey, Sinan B. Sarac, Susan Shepherd, Isabelle Stoeckert, Elizabeth J. Swain, Andrew Thomson, Laurence Titeux, Rianne van den Ham, Tjeerd van Staa, Edward Waddingham, Nan Wang, Lesley Wise.

Subhakanta Das, Jane Okwesa, Emily Thompson.