PROTECT

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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

Benefit-Risk Integration and Representation

IMI-PROTECT Symposium

Benefit-Risk Integration and Representation Workshop

18th February 2014

PROTECT Work Package 5 and 6

Workshop objectives

The objectives of this workshop are to introduce:

1. the main concepts of benefit-risk assessment
2. a range of methodologies used in connection with benefit-risk assessment
3. key methods via worked examples
4. a range of visual representations to accompany benefit-risk assessment
5. a selection of visual displays via worked examples
6. the role of patient and public involvement in benefit-risk assessment

Outline

Title	Presenters
Introduction to benefit-risk assessment of medicinal products	Deborah Ashby (Chair)
Structured benefit-risk assessment	Richard Nixon
Taxonomy of benefit-risk assessment methodologies; and BR metrics	Shahrul Mt-Isa
Benefit-risk assessment: Concepts and methods	Larry Phillips
Open source software for benefit-risk modelling and clinical data analysis: ADDIS and Effects Table	Douwe Postmus
Visualising benefits and risks: concepts and ideas	Christine Hallgreen
PROTECT resources for further learning	Gerry Downey
TEA/COFFEE BREAK	
Patients and public involvement in benefit-risk assessment and decision-making: methods and applications	Ed Waddingham
Eliciting Patient Preferences: Applying decision theory to health research	Andrea Beyer
Closing remarks and take-home messages	Deborah Ashby

Deborah Ashby, PhD OBE FMedSci

INTRODUCTION TO BENEFIT-RISK ASSESSMENT OF MEDICINAL PRODUCTS

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.

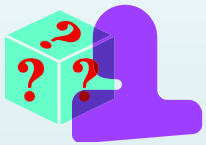
This report neither replaces nor is intended to replace or comment on any regulatory decisions made by national regulatory agencies, nor the European Medicines Agency."

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

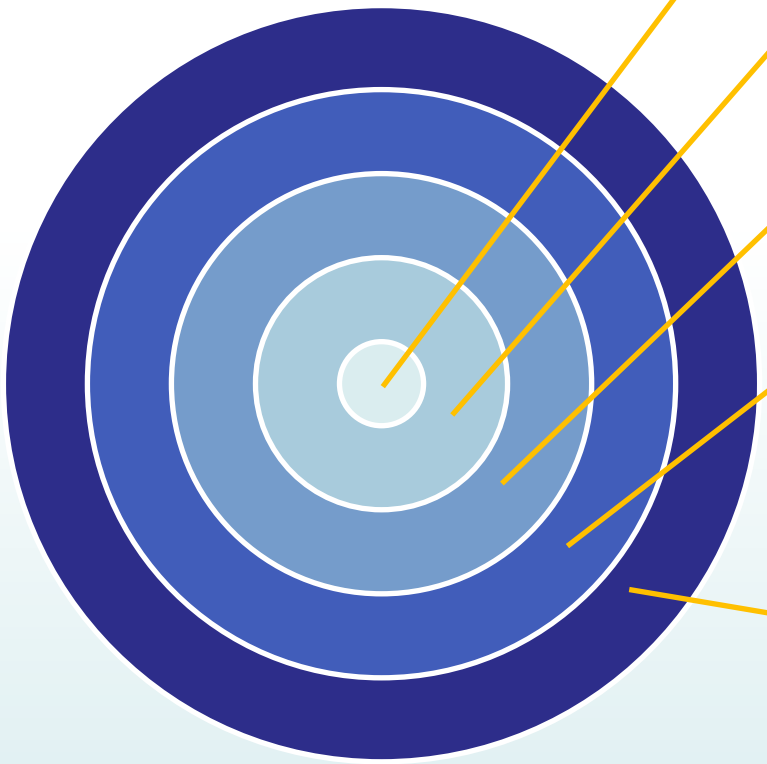
Evidence Based Medicine

"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

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?

A simple example of EBM decision-making

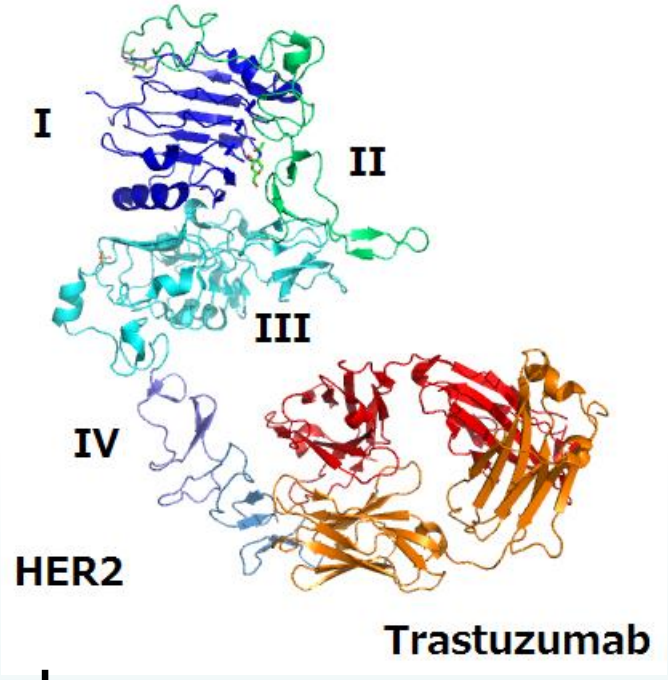
- Decision-maker
- Possible actions
- Uncertain consequences
- Sources of evidence
- Utility assessments

Key reference

Ashby D & Smith AFM, Stats in Medicine, 2000

Trastuzumab
Benefit-Risk captured with a single parameter

- Pivotal study:
  - randomised, open-label comparing trastuzumab and placebo in women with non-metastatic, operable primary invasive breast cancer over-expressing HER2 who had completed … therapy… for primary breast cancer.



Trastuzumab
Benefit-Risk captured with a single parameter

- Benefit: Disease-free survival (Placebo vs. Trastuzumab)

	Placebo	Trastuzumab
Proportion with either disease progression or death (due to any cause)	22.0%	13.9%
Proportion of death (due to any cause)	2.4%	1.8%

- Risk: Cardiotoxicity (Placebo vs. Trastuzumab)

	Placebo	Trastuzumab
Significant asymptomatic (NYHA class I) or mildly symptomatic (NYHA class II) cardiac dysfunction	0.53%	3.04%
Symptomatic congestive heart failure of NYHA class III or IV or cardiac death	0.06%	0.6%

Example: Trastuzumab for early breast cancer

Decision-maker	The woman
Possible decisions	• Take trastuzumab • Not take trastuzumab
Uncertain consequences	• Breast cancer recurrence • Death • Cardiotoxicity
Sources of evidence	A pivotal trial
Utility assessment	Increased disease-free survival and cardiotoxicity

European Medicines Agency (2006). Scientific discussion on Herceptin. Report reference EMEA/H/C/278/II/0026

Simple benefit-risk metrics

Number needed to treat (NNT)	Number needed to harm (NNH)
Number of people to be treated to observe a benefit (or to prevent an adverse event)	Number of people to be treated to observe an adverse event (or to prevent a benefit)
$$\mathrm{NNT} = \frac{1}{\Delta_p} = \frac{1}{\Pr(B\|T) - \Pr(B\|T')}$$ where $\Pr(B\|T)$ = probability of observing a benefit among treated individuals; and $\Pr(B\|T')$ = probability of observing a benefit among untreated individuals	$$\mathrm{NNH} = \frac{1}{\Delta_q} = \frac{1}{\Pr(H\|T) - \Pr(H\|T')}$$ where $\Pr(H\|T)$ = probability of observing an adverse event among treated individuals; and $\Pr(H\|T')$ = probability of observing an adverse event among untreated individuals

NNT and NNH approach for trastuzumab

$$\text{NNT} = \frac{1}{0.861 - 0.780} = 12.3$$

= for every 13 patients treated, one would

= nefit from progression–free survival

$$\text{NNH} = \frac{1}{0.0304 - 0.0053} = 39.8$$

= for every 40 patients treated, one would

= perience cardiotoxicity

NNT<NNH is desirable

Trastuzumab
Benefit-Risk captured with a single parameter

- MHRA Assessment Report: "If disease-free survival and primary cardiac events **were combined into a single endpoint** it would be dominated by the disease-free survival data with the hazard ratio favouring trastuzumab."
- Benefit: Risk captured with a single parameter assuming equal weight for progression, cardiac event and death from any cause.
- Does further quantification add anything in this type of scenario?
- Could estimate weighting that would need to be given to make the benefit: risk unfavourable, or incidence of cardiac events to make benefit: risk unfavourable given equal weight.

Recommendation Roadmap

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

Evidence gathering and data preparation

Planning

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

Analysis

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

Exploration

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

Conclusion and dissemination

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

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.

Richard Nixon, PhD

FROM QUALITATIVE TO QUANTITATIVE BENEFIT-RISK DECISION-MAKING:

STRUCTURED BENEFIT-RISK ASSESSMENT

Decide on a Multiple Sclerosis treatment

Three outcomes are important to you

- For two treatments given over a two-year period the proportion of patients experiencing each of three outcomes is:

	Treatment A	Treatment B
Disability progression	40%	30%
Flu-like reaction	5%	3%
PML*	0%	0.5%

- Which treatment would you choose?
  - How often does each outcome occur?
  - How important is each outcome if it occurs?
- In real life the decision is more complex
  - Which **outcomes** do you choose to make the decision?
  - Which **treatments** do you choose between?
  - How do you assess how **important** each outcome is to you?

* PML: Progressive multifocal leukoencephalopathy

Natalizumab – A short history

- Natalizumab was approved in 2004 by the FDA for the treatment of relapsing remitting multiple sclerosis (RRMS).
- In 2005 the drug was suspended because of an associated incidence of progressive multifocal leukoencephalopathy (PML), a rare neurological disorder.
- In 2006 it was re-introduced due to patient demand, but with strict risk minimization measures.
- In 2009, due to occurrence of further PML in monotherapy post marketing, CHMP reassessed the PML risk of Tysabri and confirmed the current approval.

The BRAT* Framework for benefit-risk

Built on methods to support decision making

- **A framework, not a recipe**
  - A tool to support decision makers, not an algorithm to replace them.
  - Helps to develop a common understanding of that is of central importance.
  - Process to structure and analyze information.
  - Visualization tools to communicate benefit-risk.
- **Built on well-established Decision Analysis principles**
  - Promotes traceability, transparency and consistency.
- **Communication tool for decision making**
  - Consolidated view of key benefit and risk outcome measures.

*Benefit Risk Action Team

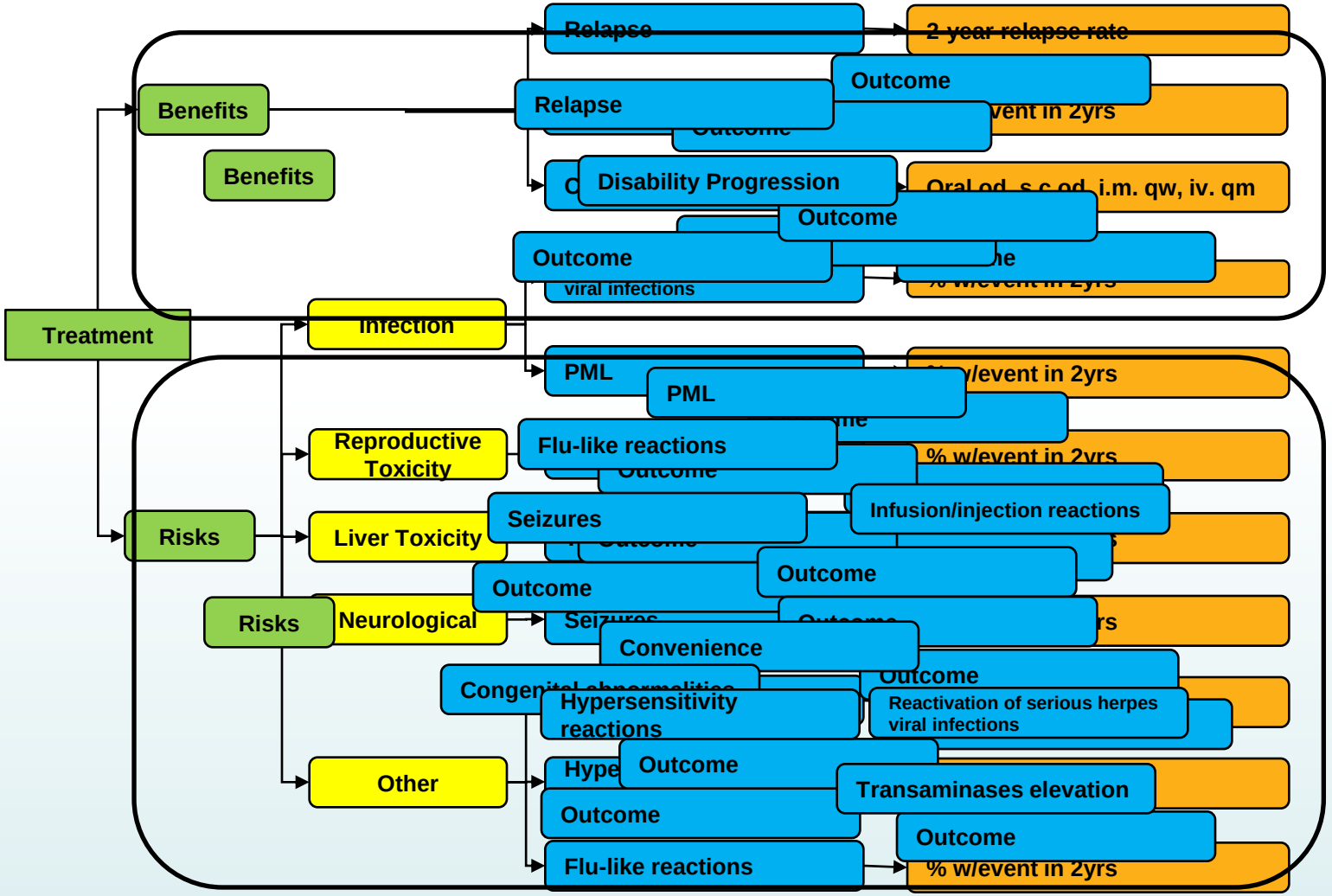
1) Define a decision context

Sets the frame of the structured benefit-risk assessment

Objective	**Should natalizumab be kept on the market given that episodes of PML are observed?**
Indication	**Relapsing remitting multiple sclerosis**
Population	**Adults with relapsing remitting multiple sclerosis**
Drug	**Natalizumab, 300mcg, iv, qm.**
Comparative Treatment Alternative(s)	**Placebo, Interferon beta-1a, 30mcg, im, qw Glatiramer acetate, 20mg, sc, qd**
Assessment time point	**Two years. For PML fives year as it takes longer to manifest.**
Stakeholder perspective	**EMA**

2) Identify key benefits and risks

Organize the key outcomes driving the benefit-risk in a value tree



3) Consolidate source data

Pool clinical data from internal and external studies

Identify

Search strategy

Search query

PubMed.gov
US National Library of Medicine
National Institutes of Health

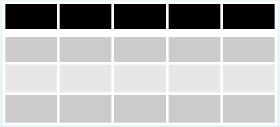
Drugs@FDA
FDA Approved Drug Products

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Select

Study eligibility criteria

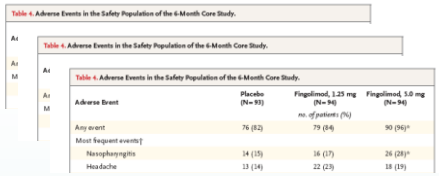
Study worksheet



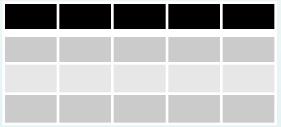
one row per study

Extract

Extraction guidelines



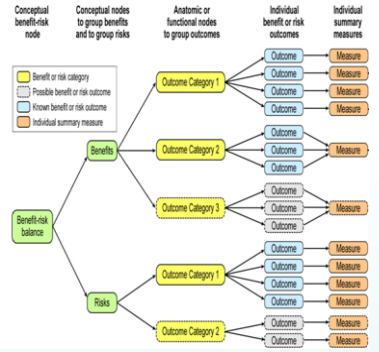
Data source table



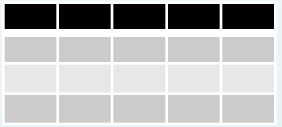
one row per study/treatment/outcome

Aggregate

e.g. meta-analysis, placebo-calibration



Data summary table



one row per outcome

4) Customize and communicate

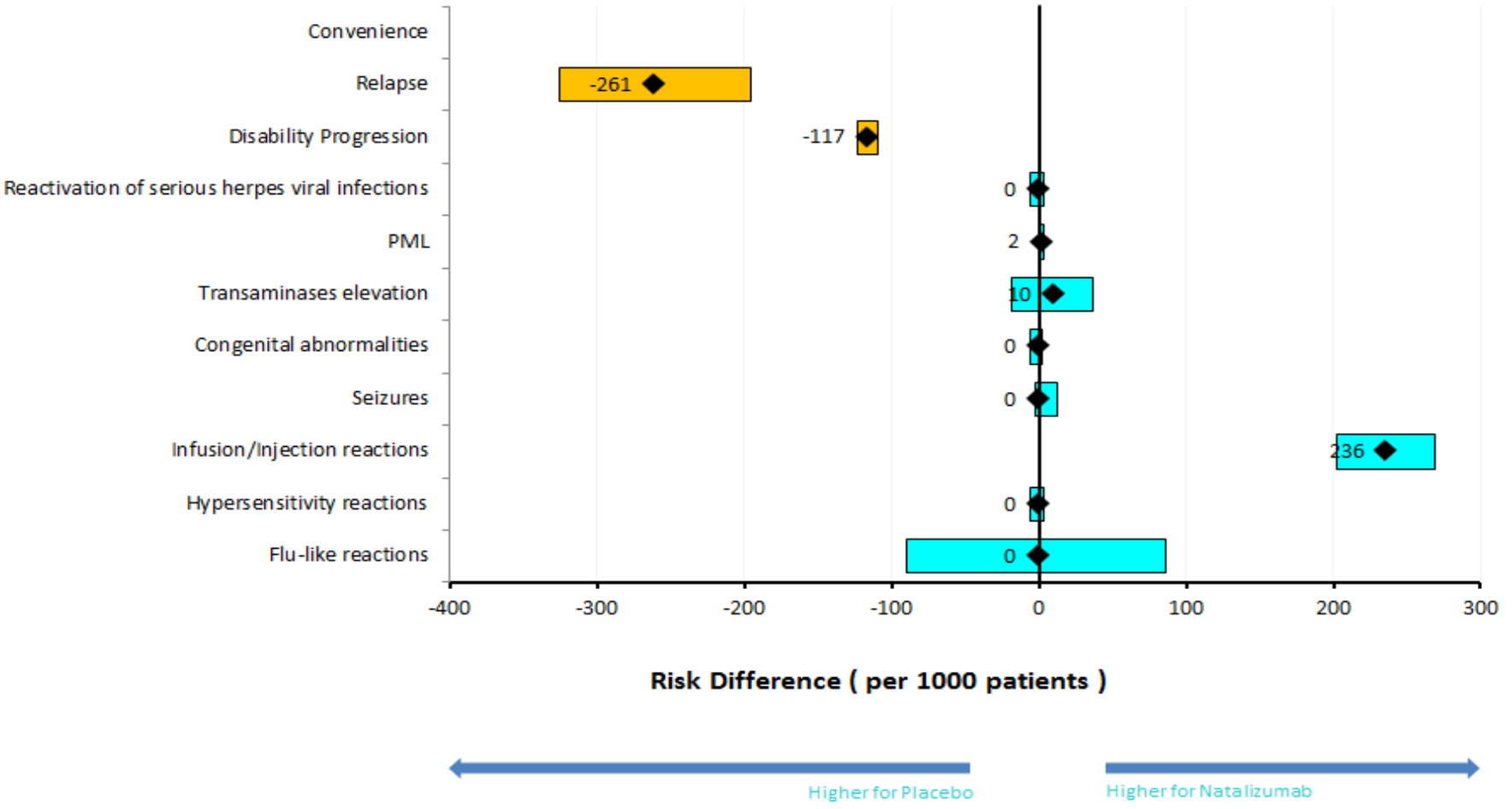
Effects table of key benefits and risks

		Outcome	Natalizumab prob / 1000pts	Placebo prob / 1000pts	Prob difference (95%CI) / 1000pts	
Benefits	Convenience Benefits	Convenience	-	-	-	(-,-)
	Medical Benefits	Relapse (# patients)	276	537	-261	(-326,-195)
		Disability Progression	113	230	-117	(-124,-110)
Risks	Infection	Reactivation of serious herpes viral infections	0	0	0	(-6,3)
		PML	1.51	0	1.51	(0,3)
	Liver Toxicity	Transaminases elevation	50	40	10	(-19,36)
	Reproductive Toxicity	Congenital abnormalities	0	0	0	(-6,3)
	Neurological Disorders	Seizures	5	5	0	(-2,12)
	Other	Infusion/Injection reactions	236	0	236	(202,269)
		Hypersensitivity reactions	0	0	0	(-6,3)
		Flu-like reactions	399	399	0	(-90,86)

Summarize in one place all the benefits and risks data that are driving the decision

4) Customize and communicate

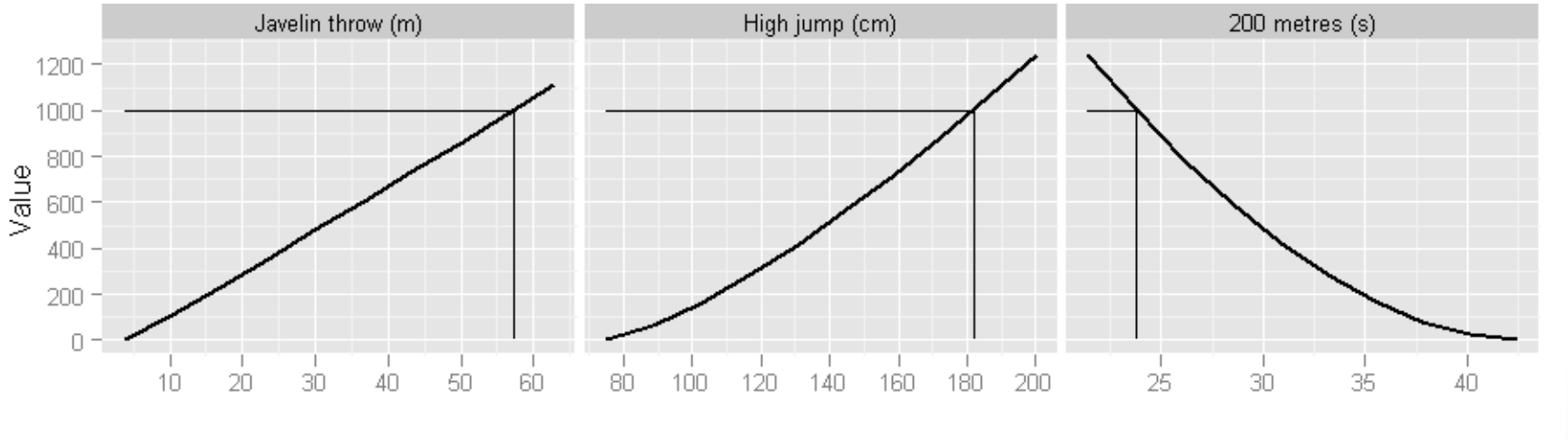
Forest plot



Relapse = Number of patient with at least one relapse

5) Assess outcome importance

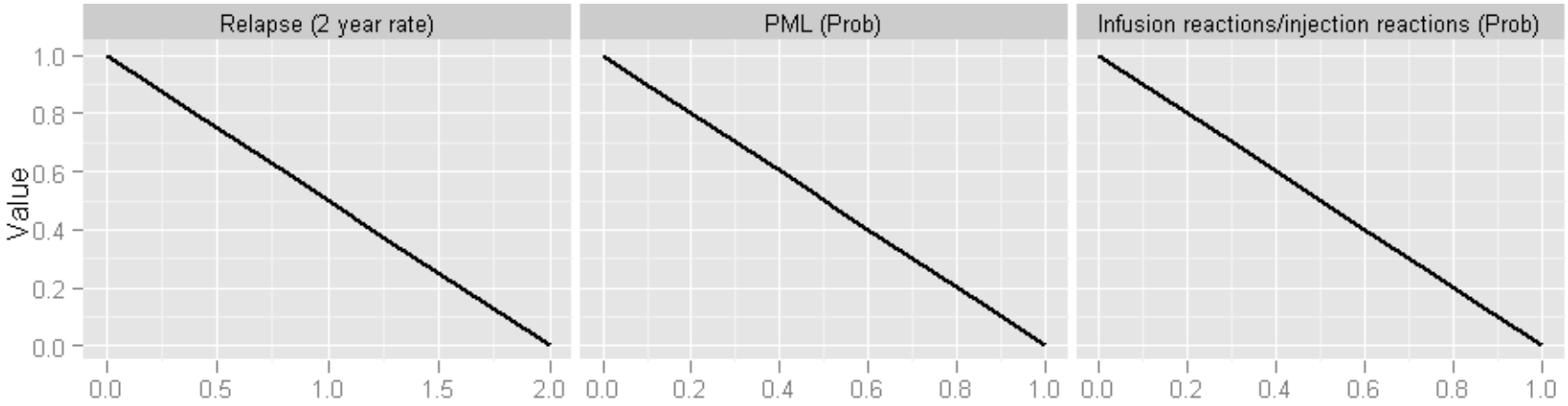
MCDA and the Women's heptathlon



Event	Jessica Ennis	Value	Lilli Schwarzkopf	Value	Tatyana Chernova	Value
Javelin throw (m)	47.49	812	51.73	894	46.29	789
High Jump (cm)	186	1055	183	1016	180	979
200 metres (s)	22.83	1096	24.77	909	23.67	1013
Total		**2963**		**2819**		**2781**

5) Assess outcome importance

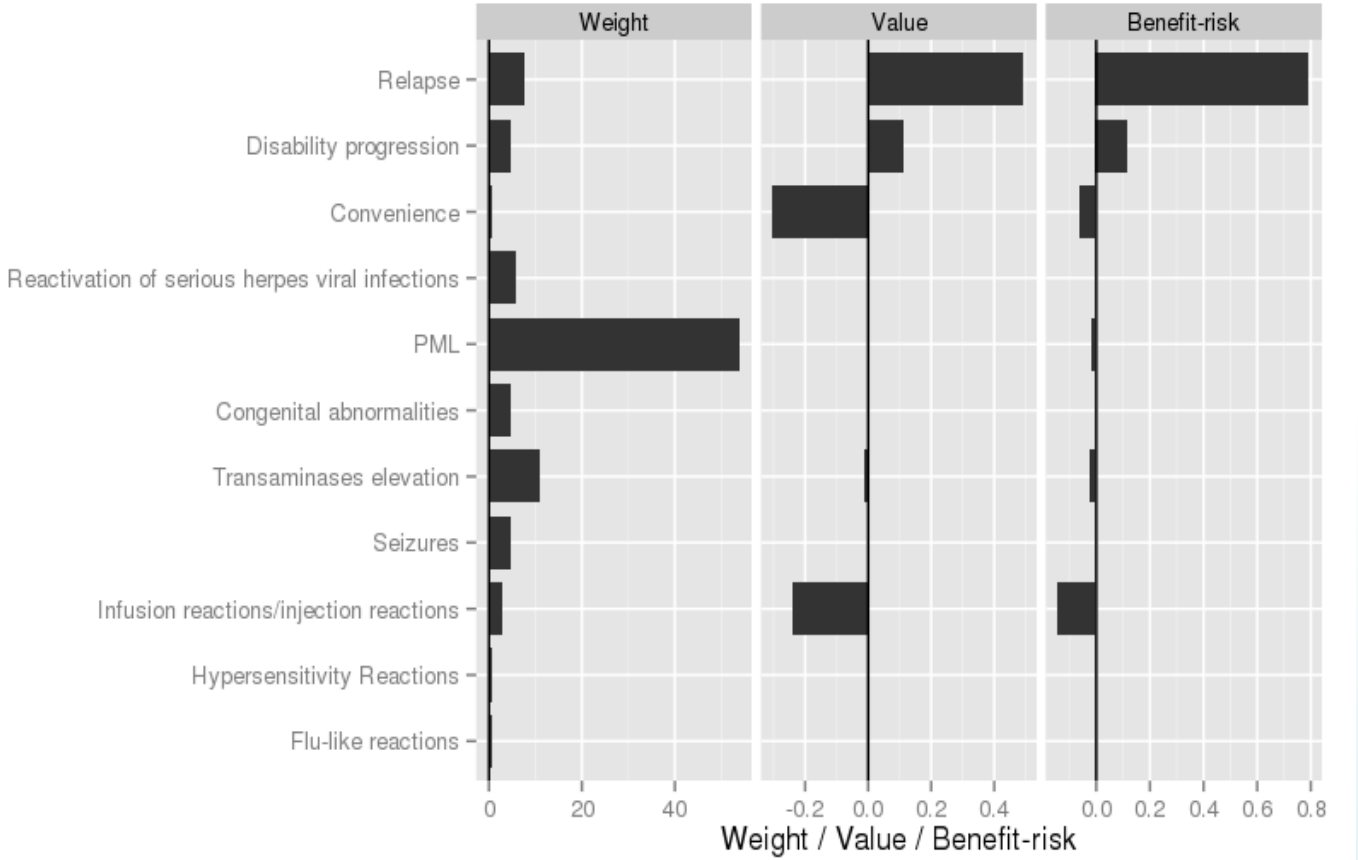
MCDA and multiple sclerosis drugs



		Placebo			Natalizumab		
Outcome	**Weight**	**Measure**	**Value**	**Benefit-risk**	**Measure**	**Value**	**Benefit-risk**
Relapse	8%	1.46	0.27	0.022	0.47	0.766	0.061
PML	54%	0	1	0.54	0.0015	0.998	0.54
Infusion reactions injection reactions	3%	0	1	0.03	0.24	0.764	0.02
Total				**0.59**			**0.62**

Drill down to the values and the weights

Incremental benefit-risk of natalizumab – placebo

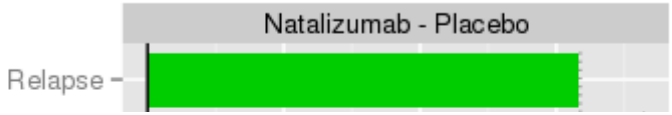


This shows which outcomes are contributing most to the total benefit-risk.

Even though the weight given to PML is large, the incidence is small, leading to a small contribution to the benefit-risk.

Waterfall plot

Incremental benefit-risk of natalizumab – placebo

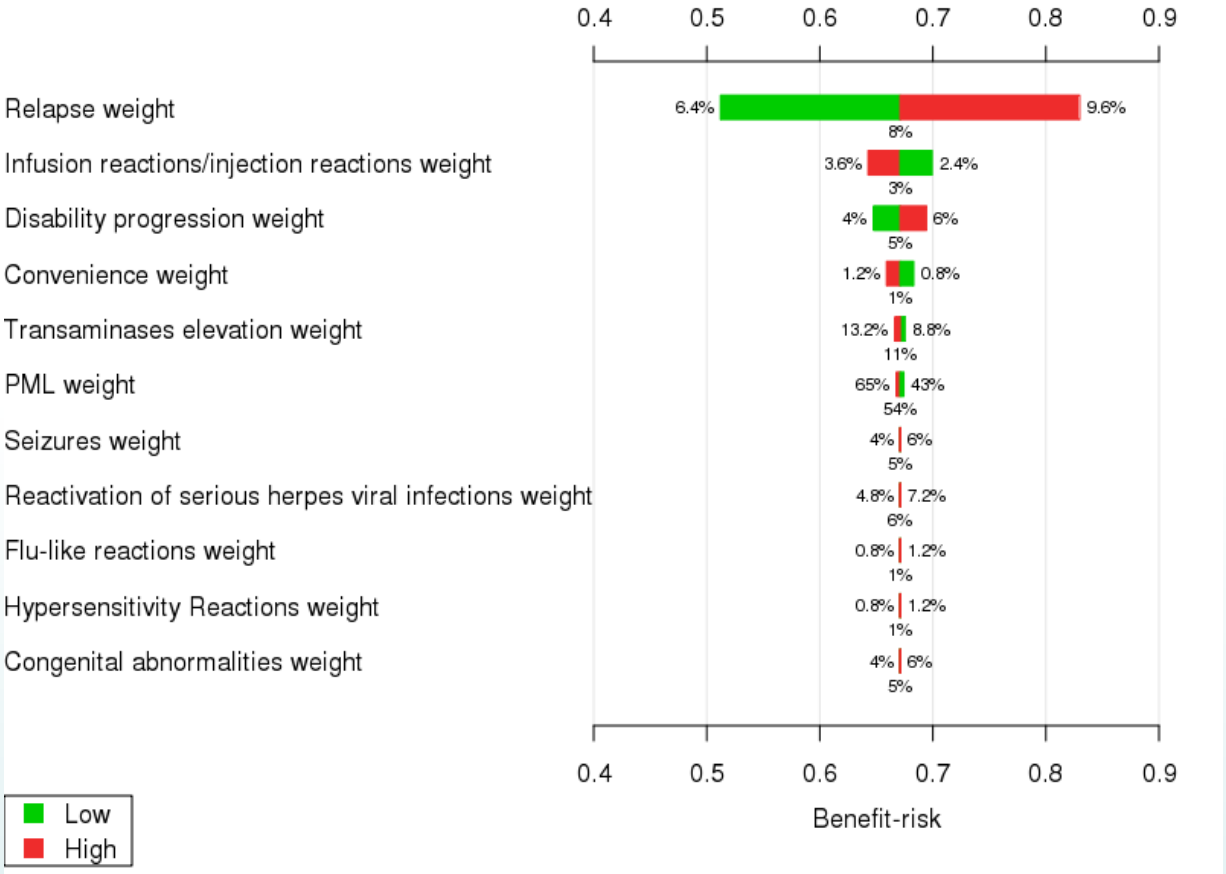


Outcome

- The length of each bar gives the contribution to the overall BR.
- End of the last bar gives the overall benefit-risk.
  - Denominated in the BR of one EDSS progression
- Green = positive BR.
- Red = negative BR.
- The contribution to the overall BR of PML is very small.

Sensitivity analysis on the weights

Incremental benefit-risk of natalizumab – placebo



- The weights are shown under each bar.
  - The base case weight is shown in the middle, with a +/- 20% range given at the ends.
- The weights are changed one at a time.
- The most important weight is the one given to relapses.

Current vs. future benefit-risk communication

From a narrative to a structured framework

"Traditional" benefit-risk communication

- Narrative describing benefits and risks.
- Lacking explicit identification of **key** benefit and **key** risk outcomes.
- Limited systematic comparison of active drug vs. comparators for all key benefits and key risks.
- No structured, quantitative summary of all key benefit and key risk outcomes.

Structured benefit-risk leads to communication that is transparent and defensible

- Which key benefits and key risks were considered and why.
- Which comparators were chosen.
- The magnitude of benefit and risk effects.
- Presentation in a graphical/tabular summary together with concise text.
- Written in such a way as to meet the Health Authority reviewer needs and expectations.

Go to backup slides

Acknowledgements and further details: Special issue of the Biometrical Journal

Biometrical Journal **00** (2015) 0, 1–20 DOI: 10.1002/bimj.201300248 1

A case study using the PrOACT-URL and BRAT frameworks for structured benefit risk assessment

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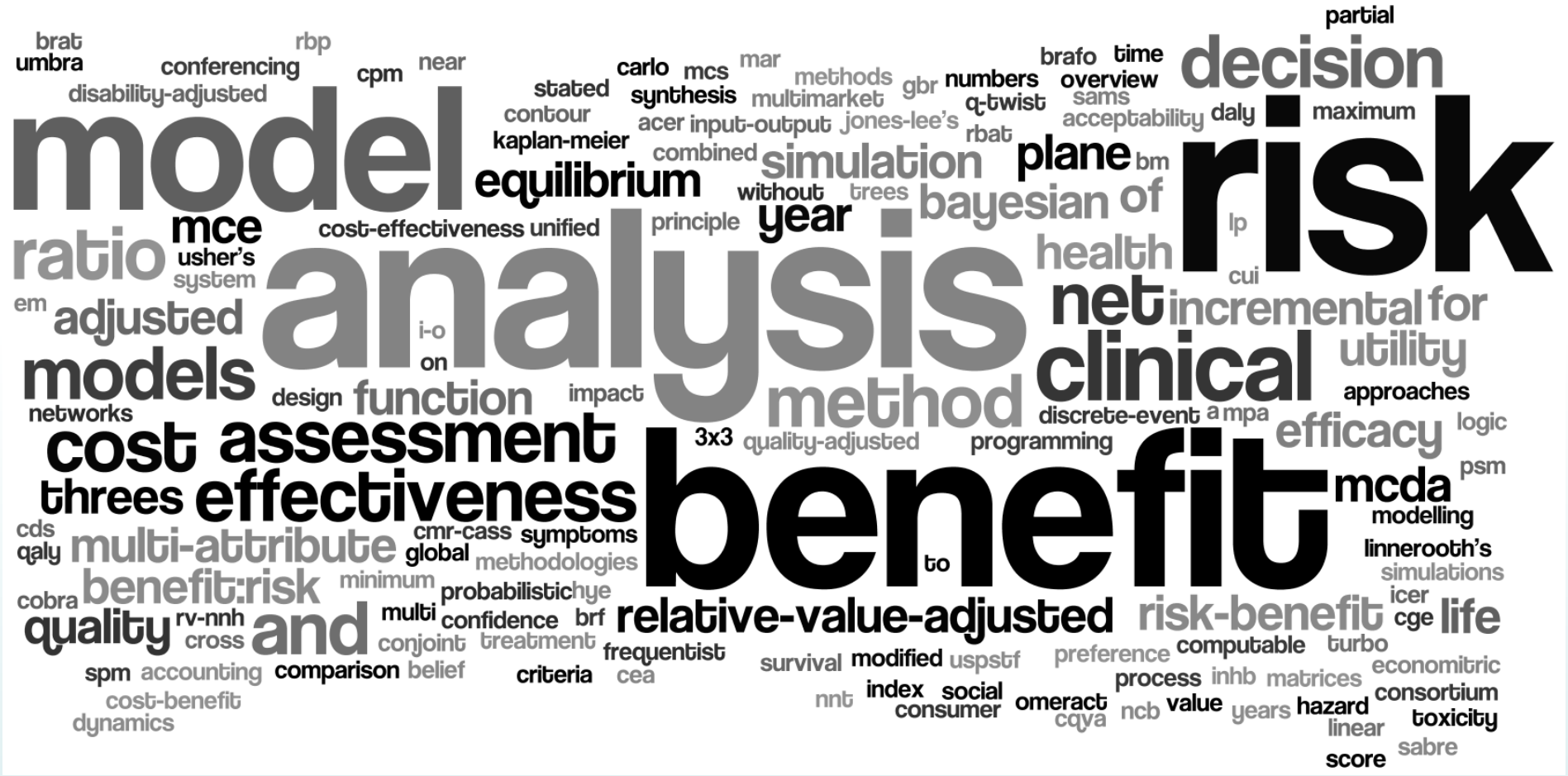
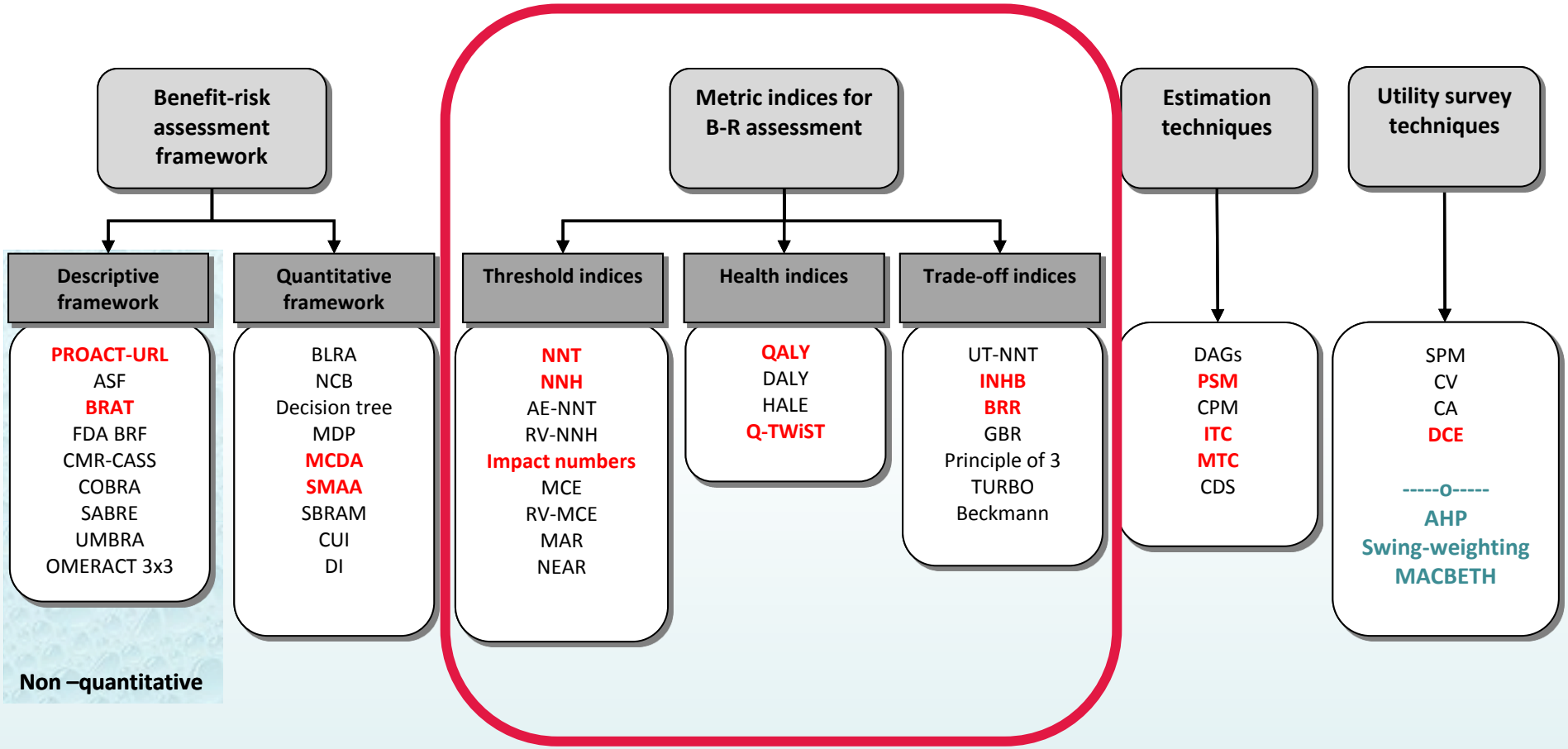
Shahrul Mt-Isa, PhD

TAXONOMY OF BENEFIT-RISK ASSESSMENT METHODOLOGIES, AND BENEFIT-RISK METRICS

Which benefit-risk methodology?



Methodologies available



Mt-Isa *et al*. Balancing benefit and risk of medicines: a systematic review and classification of available methodologies. Pharmacoepidemiology and Drug Safety 2014. DOI: 10.1002/pds.3636.

Metric indices

- To quantitatively describe and communicate benefit-risk assessment results:
  1. ~~Number Needed to Treat / Harm (NNT/H)~~
  2. Benefit-Risk Ratios (BRR)
  3. Incremental Net Health Benefit (INHB)
  4. Impact numbers
  5. ~~QALY~~
  6. ~~Q-TWiST~~

Benefit-risk ratio (BRR)

- Benefit divided by risk
- Benefit is expressed as multiples of risk
- BRR is a simple idea but can be powerful
- In practice, equilibrium in most cases is not 1
  - Region of equivalence must be established *a priori*
  - Trastuzumab example

$$\frac{\text{Benefit}}{\text{Risk}} = \frac{\text{NNT}}{\text{NNH}} = \frac{12.3}{39.8} = 0.3\ (< 1)$$

Incremental net health benefit (INHB)

- Specifically difference between QALY gained (benefit) and QALY lost (risk)
  - QALY is the quality adjusted life years based on time spent in certain health state e.g. using EQ5D index
  - Q-TWiST proposed health states for cancer therapy
- More generally, not using health index

$$\begin{aligned}\text{INB} &= (\text{incremental benefit}) - (\text{incremental risk}) \\ &= (B_1 - B_0) - (R_1 - R_0)\end{aligned}$$

Incremental net health benefit (INHB)

- In the trastuzumab example:

$$\begin{aligned}\text{INB} &= (\text{incremental benefit}) - (\text{incremental risk}) \\ &= (B_1 - B_0) - (R_1 - R_0) \\ &= (0.861 - 0.780) - (0.0304 - 0.0053) \\ &= 0.0559\end{aligned}$$

- So in this case, the incremental net benefit is 0.0559 in favour of trastuzumab

Impact numbers

- Extend NNT concept to public health perspective
  - Uses background data from the intended population
- "Population Impact Measures (PIM)"
  - Population attributable risk (PAR)
  - Exposure impact number (EIN) ≡ NNT
  - Population impact number of eliminating a risk factor over time *t* (PIN-ER-*t*)
  - Number of events prevented in the population (NEPP)
- Descriptive measure

Verma *et al.* Population Impact Analysis: a framework for assessing the population impact of a risk or intervention. J Public Health (Oxf). 2012 Mar; 34(1):83-9. doi: 10.1093/pubmed/fdr026.

Impact numbers: trastuzumab example

- Say we want to know, how many event free survivals (EFS) over one year in 1000 women with breast cancer. 50% of whom already receiving trastuzumab, and we would like to increase the uptake to 75% in the population.
  - attributed to receiving trastuzumab
  - will be prevented by receiving trastuzumab under the new regime
  - Assume baseline EFS rate is 0.780 (rate in control group in e.g.)

Impact numbers: trastuzumab example

PIM	Calculation	Interpretation
PAR	$= \frac{0.5 \times 0.104}{1 + (0.5 \times 0.104)}$ $= 0.049$	5% EFS are due to trastuzumab in the general population
PIN-ER-t	$= n \times r_u \times \text{PAR}$ $= 1000 \times 0.780 \times 0.049$ $= 38.6$	39 women of the 1000
EIN	$= \frac{1}{0.861 - 0.780}$ $= 12.3$	13 women had to take trastuzumab to see one EFS
NEPP	$= n \times P_e \times r_u \times (\text{RR} - 1)$ $= 1000 \times (0.75 - 0.5) \times 0.780 \times 0.104$ $= 20.3$	20 extra EFS when increase intake from 50% to 75%

Remarks

- Recommendations for further testing are toolkit to aid methodology selection
  - Complexity and purpose
- Benefit-risk assessment methodologies are NOT tools that can make choices
- Using metric indices alone does not guarantee structured, transparent and/or robust assessment
- Sufficient for simple decision problems, or as quick initial descriptions
- There is a trade-off between being too simplistic and just being too incomprehensible

Lawrence Phillips, PhD

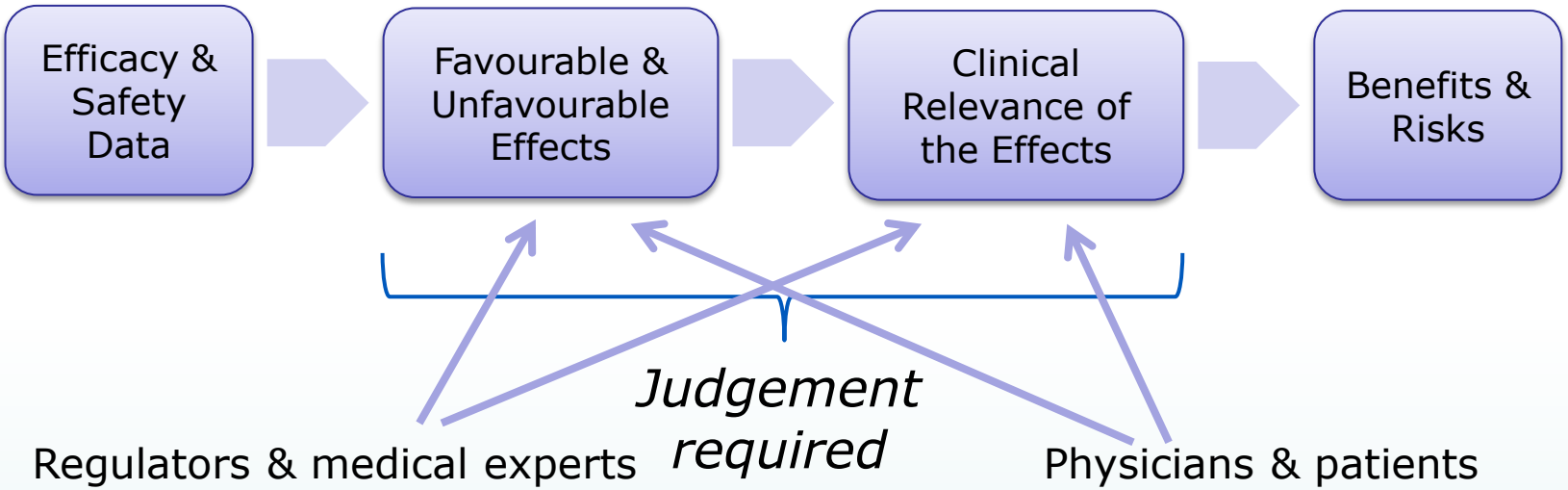
FROM QUALITATIVE TO QUANTITATIVE BENEFIT-RISK DECISION-MAKING:

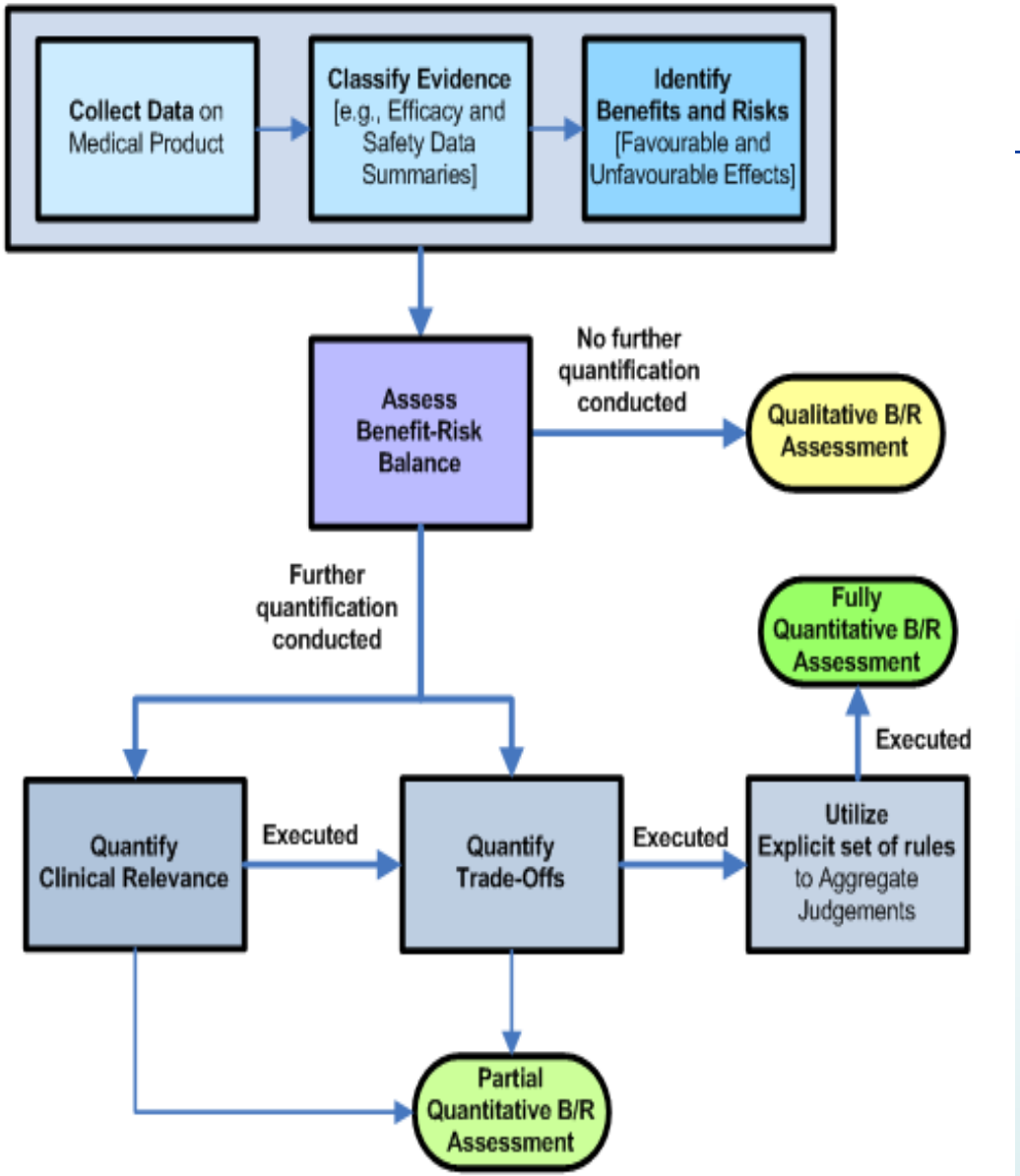
CONCEPTS AND METHODS

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

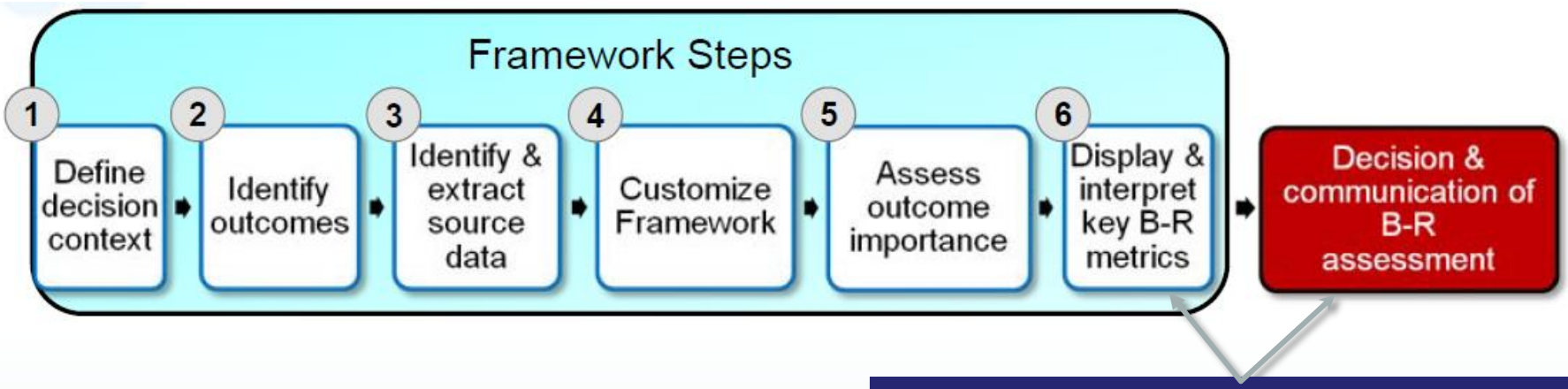
Qualitative B-R assessment

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

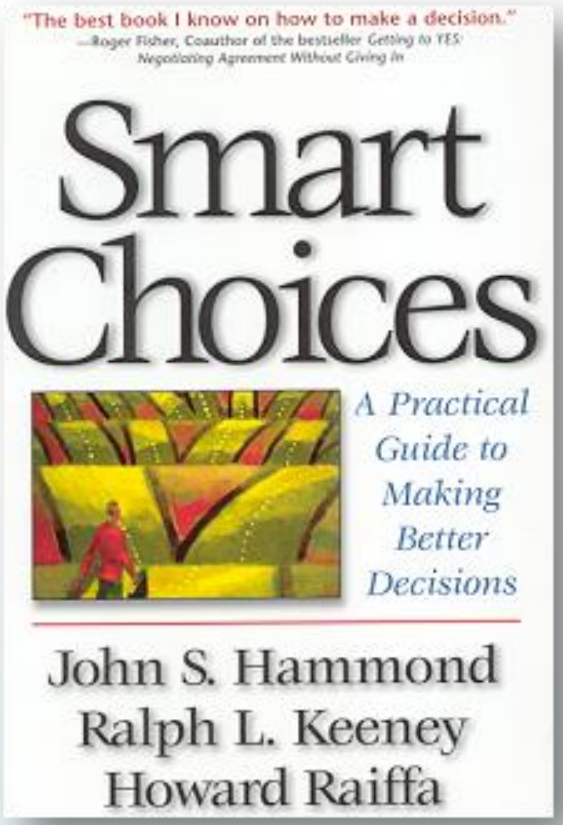


Can be applied at any stage of drug development, approval and post-approval.

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

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

PrOACT-URL framework

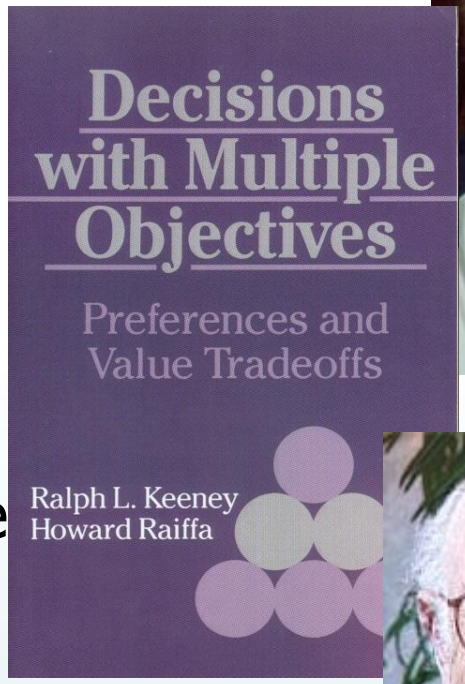


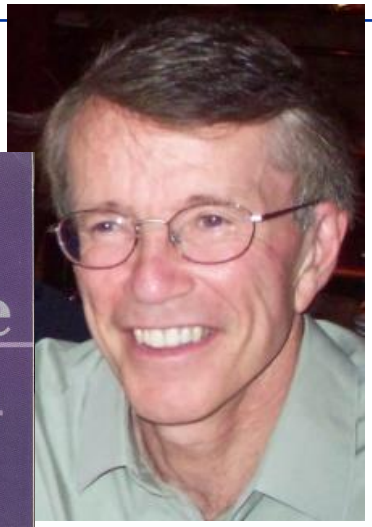
- **Pr**oblem
- **O**bjectives
- **A**lternatives
- **C**onsequences
- **T**rade-offs
- **U**ncertainty
- **R**isk attitude
- **L**inked decisions

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

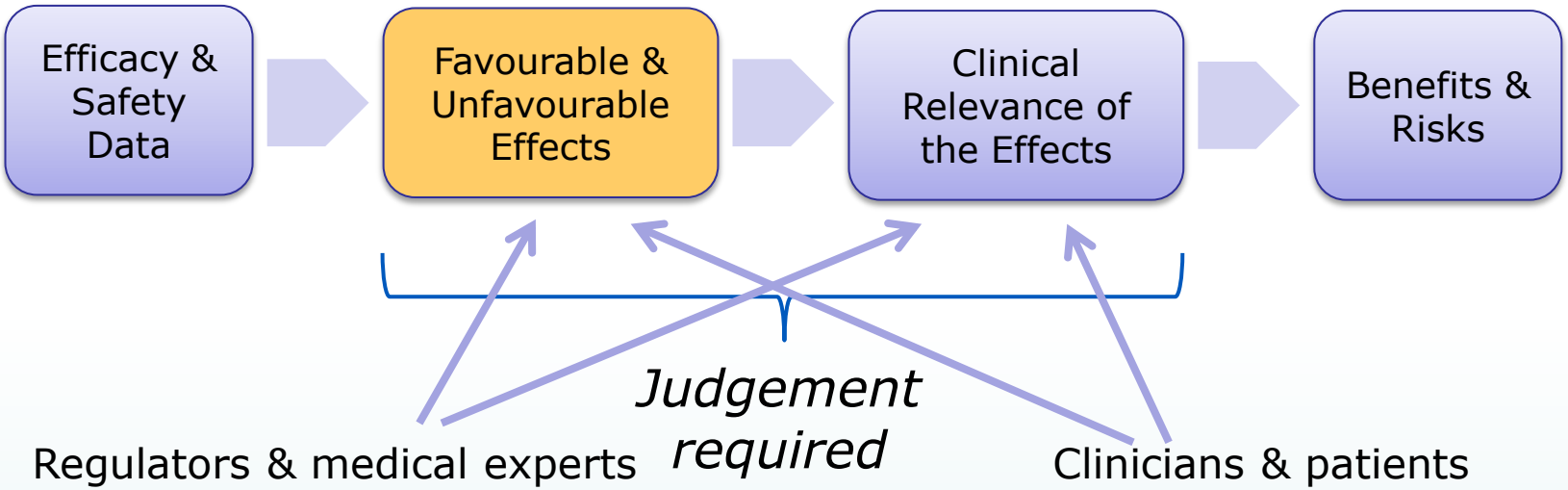
Source: Phillips, L. D. (2007). Decision Conferencing. In W. Edwards, R. F. Miles & D. von Winterfeldt (Eds.), *Advances in Decision Analysis: From Foundations to Applications. Cambridge: Cambridge University Press.*

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

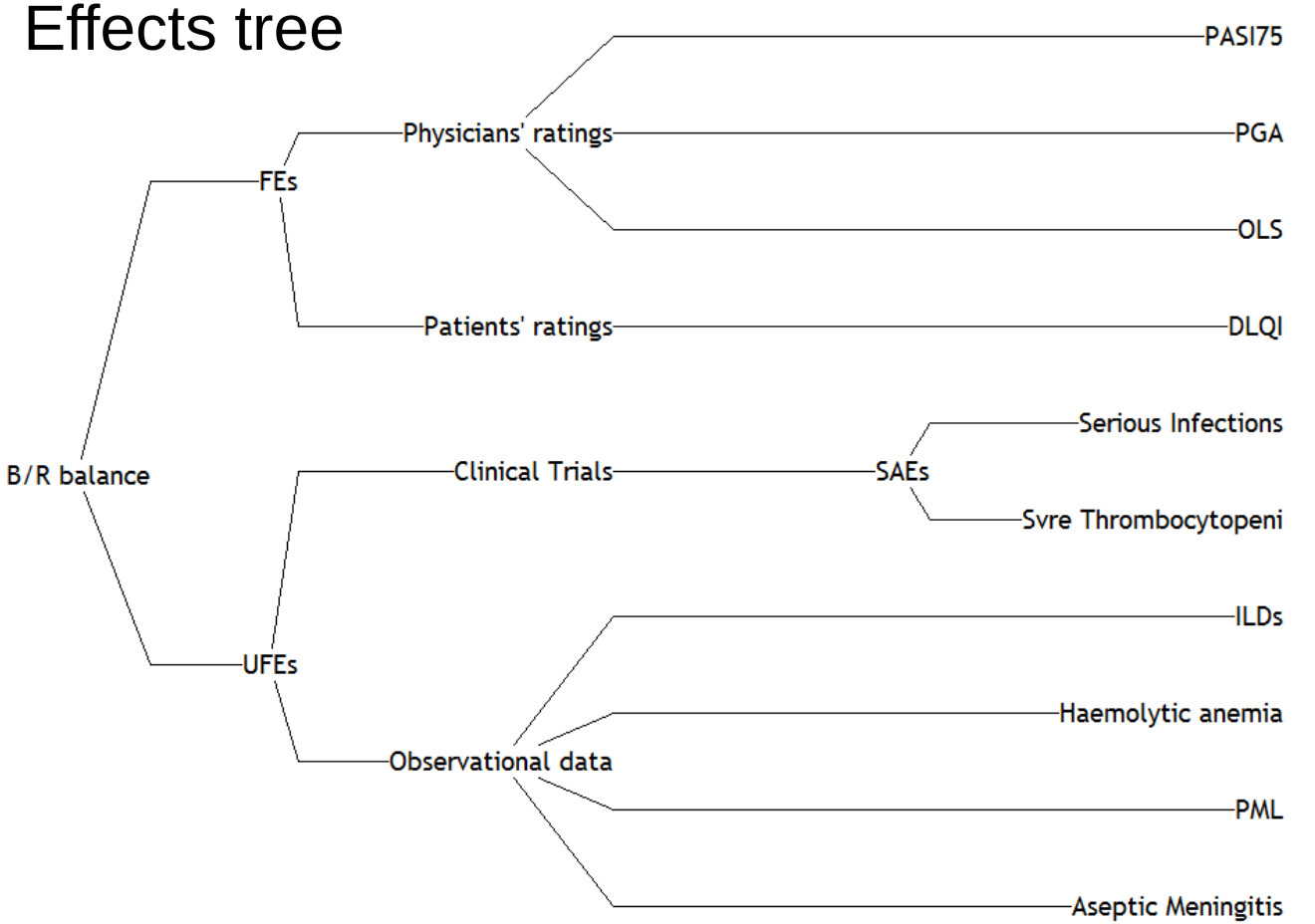
Model source for this project: Hiview3, originally developed at the London School of Economics, now available from Catalyze Ltd, www.catalyze.co.uk

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

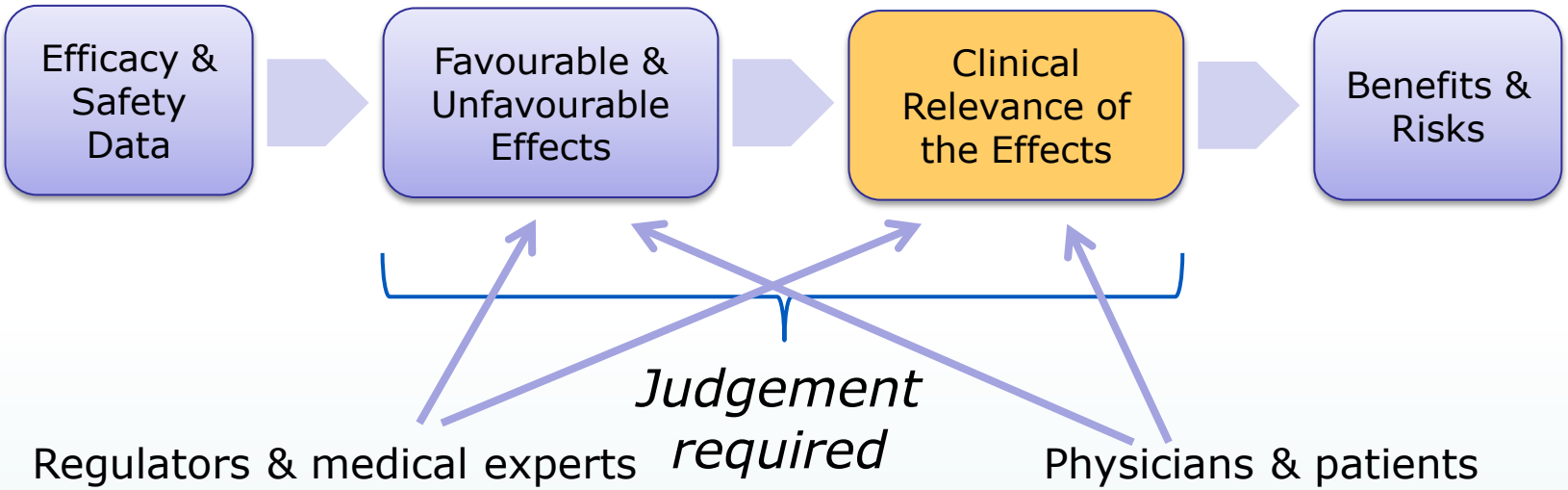
[1]PASI is a measure of the average redness, thickness and scaliness of the lesions (each graded on a 0-4 scale), weighted by the body region and the area affected. PASI range is from 0 to 72.

[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.

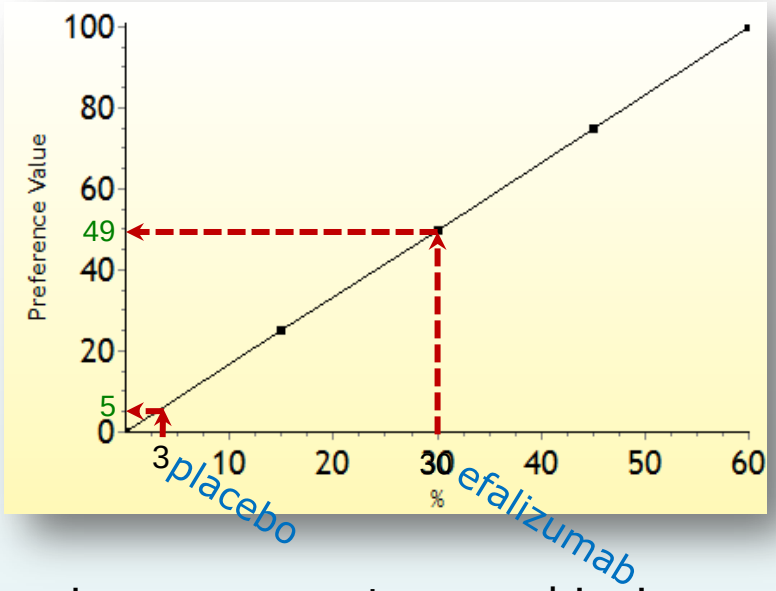
Efficacy & Safety ⇒ Benefits & Risks



Scoring clinical relevance of data

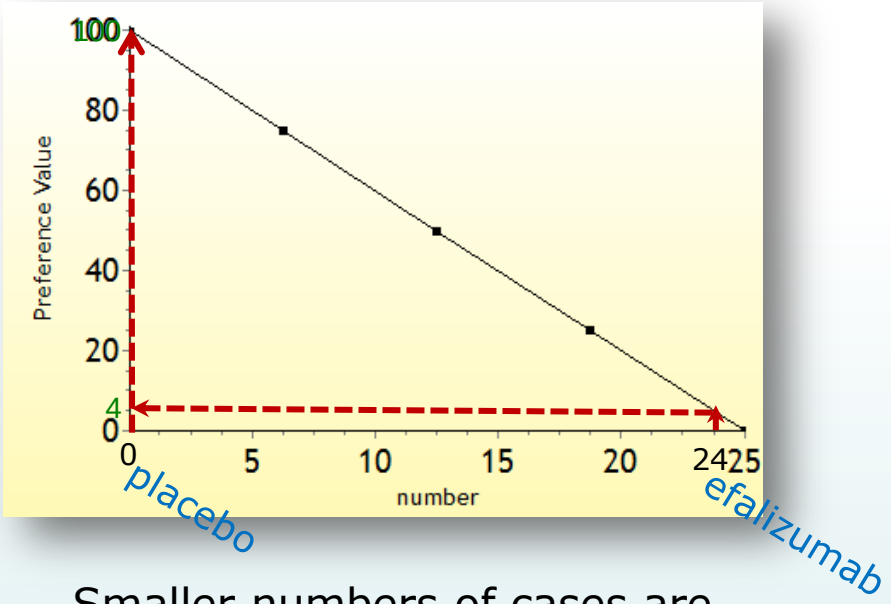
Linear conversions of data to preference values

FE: PASI 75



Larger percentages achieving PASI 75 are preferred

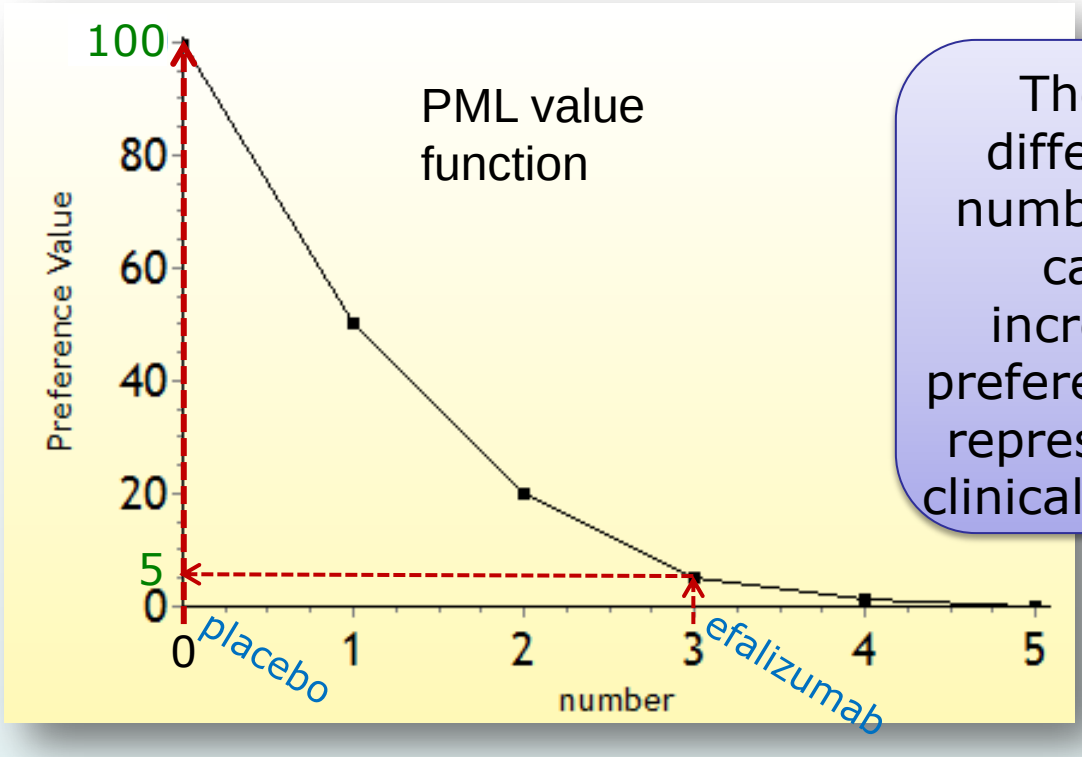
UFE: Haemolytic anaemia



Smaller numbers of cases are preferred

Scoring clinical relevance of data: PML

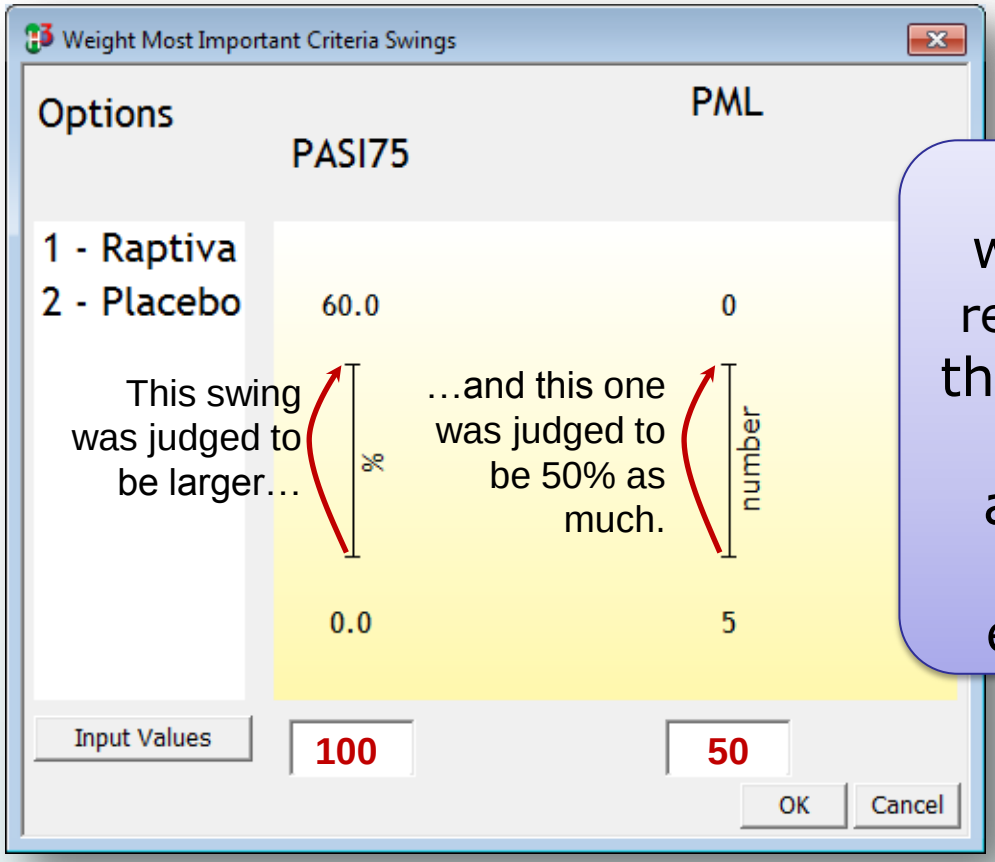
Non-linear conversion to clinical preference values



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

Weighting clinical relevance of effects

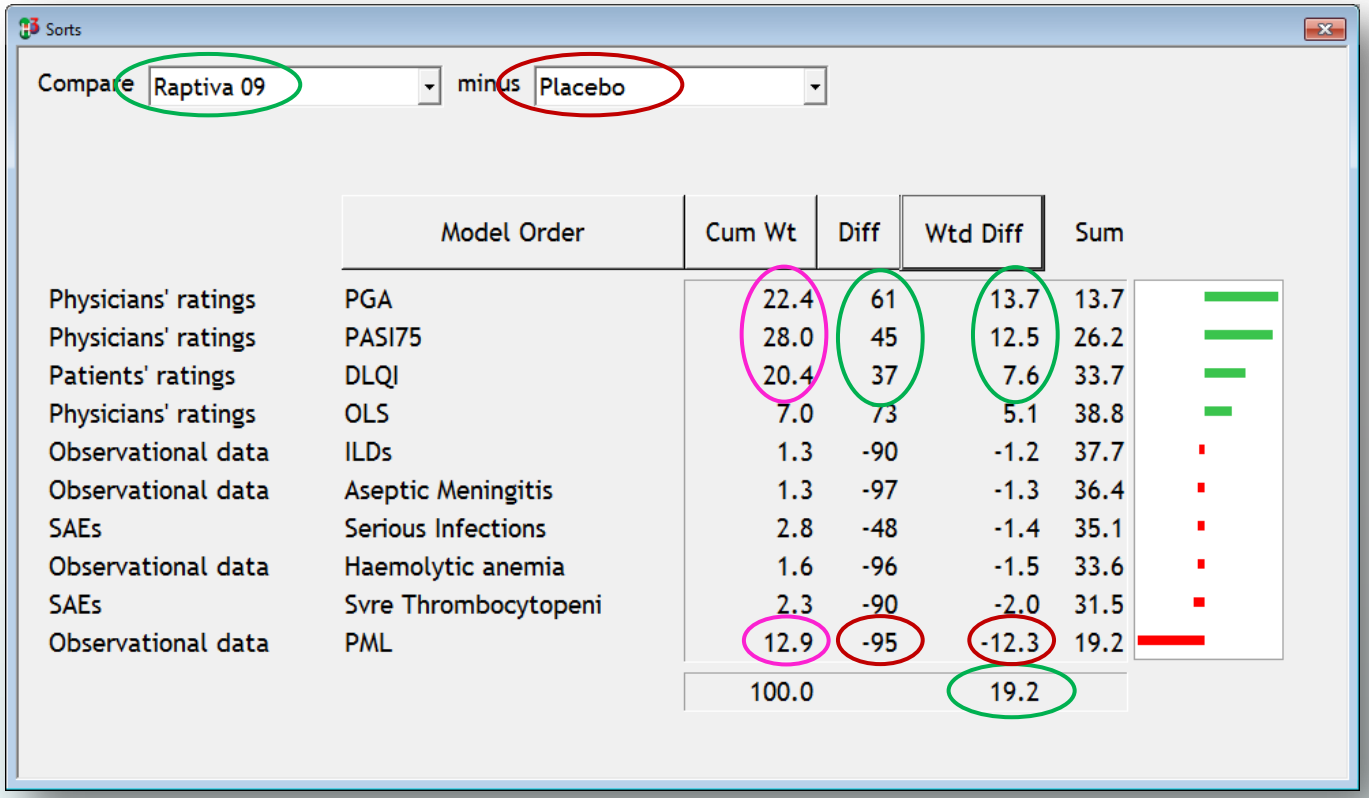
- Swing-weight favourable effects
- Swing-weight unfavourable effects
- Swing-weight most favourable against most unfavourable



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

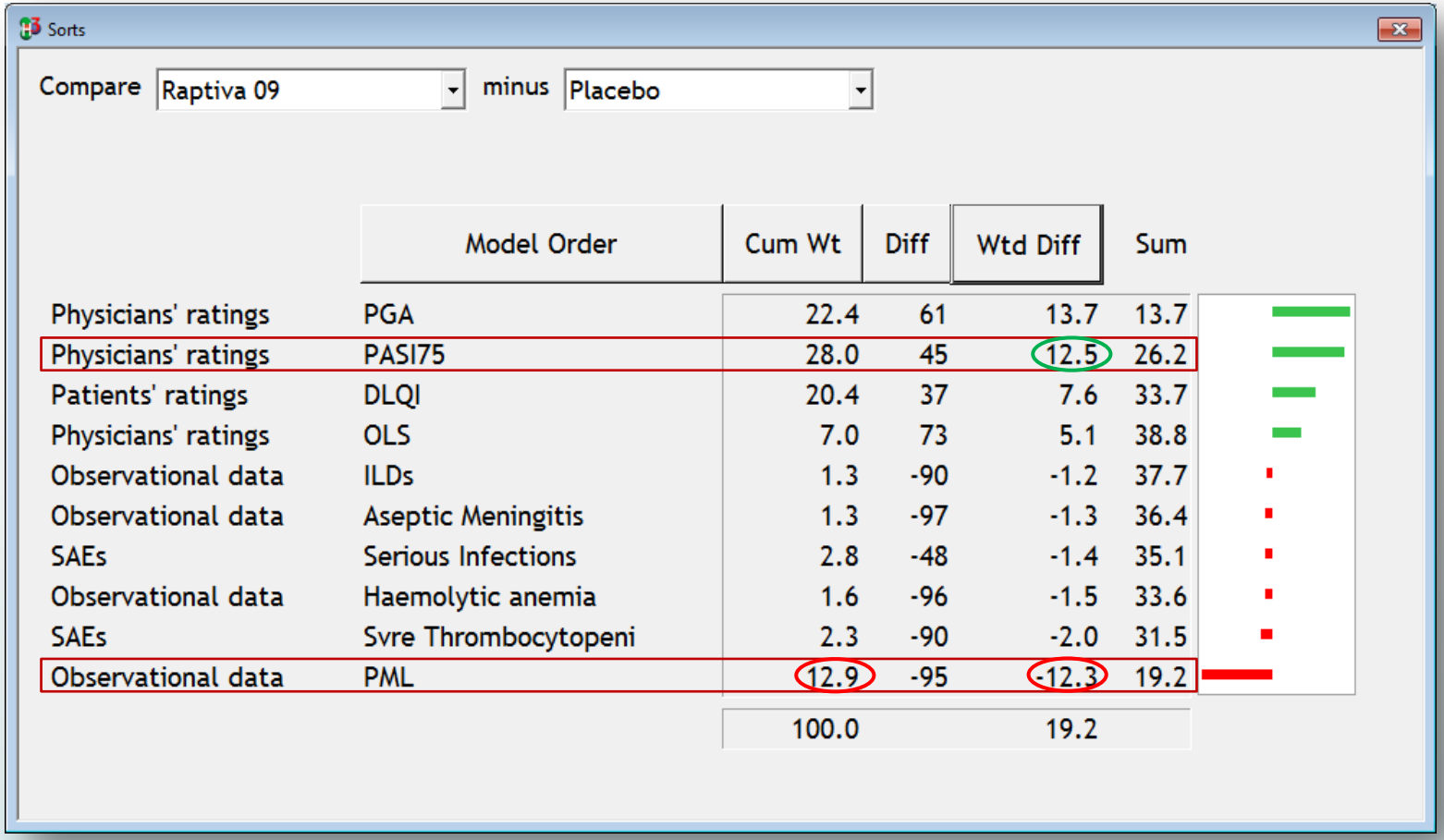


	Model Order	Cum Wt	Diff	Wtd Diff	Sum
Physicians' ratings	PGA	22.4	61	13.7	13.7
Physicians' ratings	PASI75	28.0	45	12.5	26.2
Patients' ratings	DLQI	20.4	37	7.6	33.7
Physicians' ratings	OLS	7.0	73	5.1	38.8
Observational data	ILDs	1.3	-90	-1.2	37.7
Observational data	Aseptic Meningitis	1.3	-97	-1.3	36.4
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



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Physicians' ratings	PGA	22.4	61	13.7	13.7
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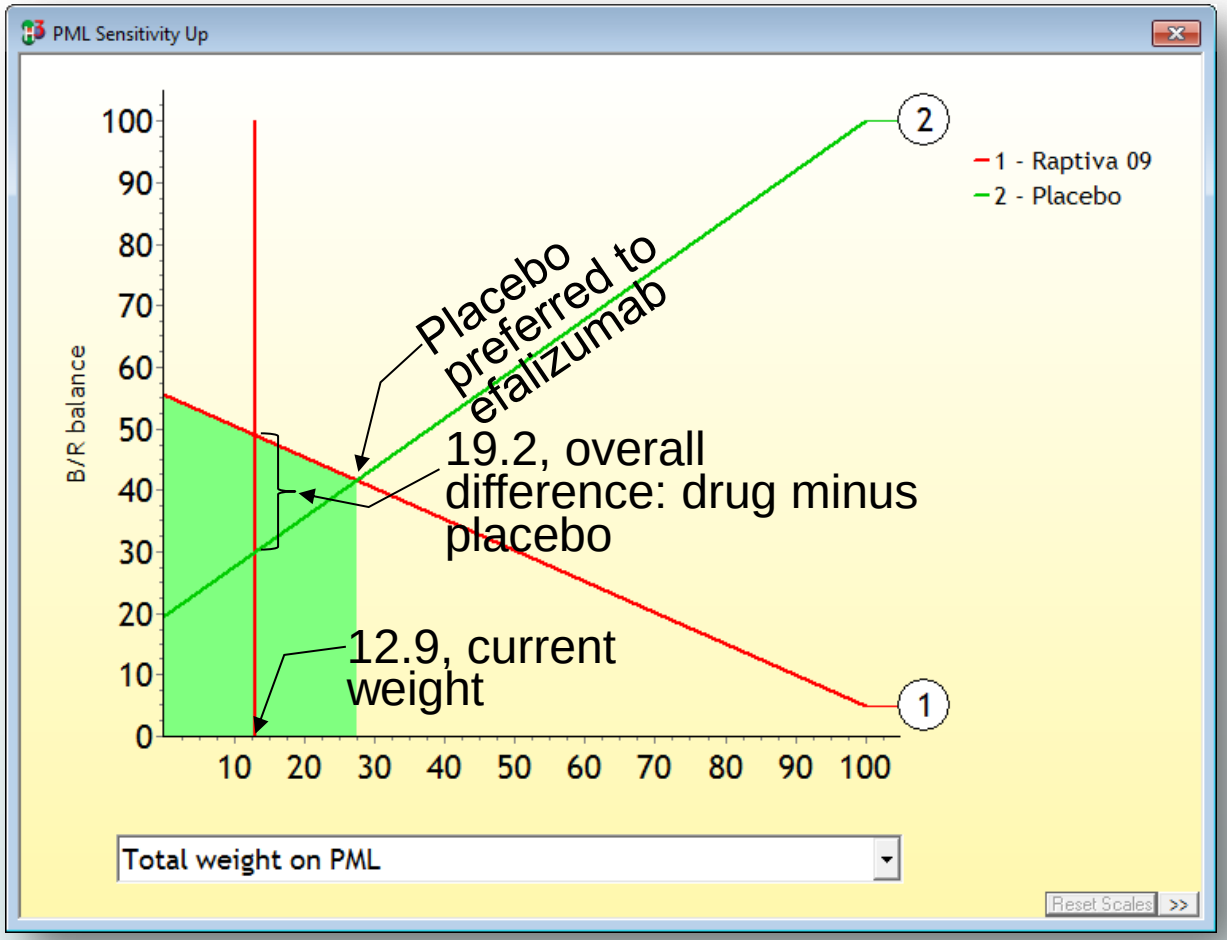
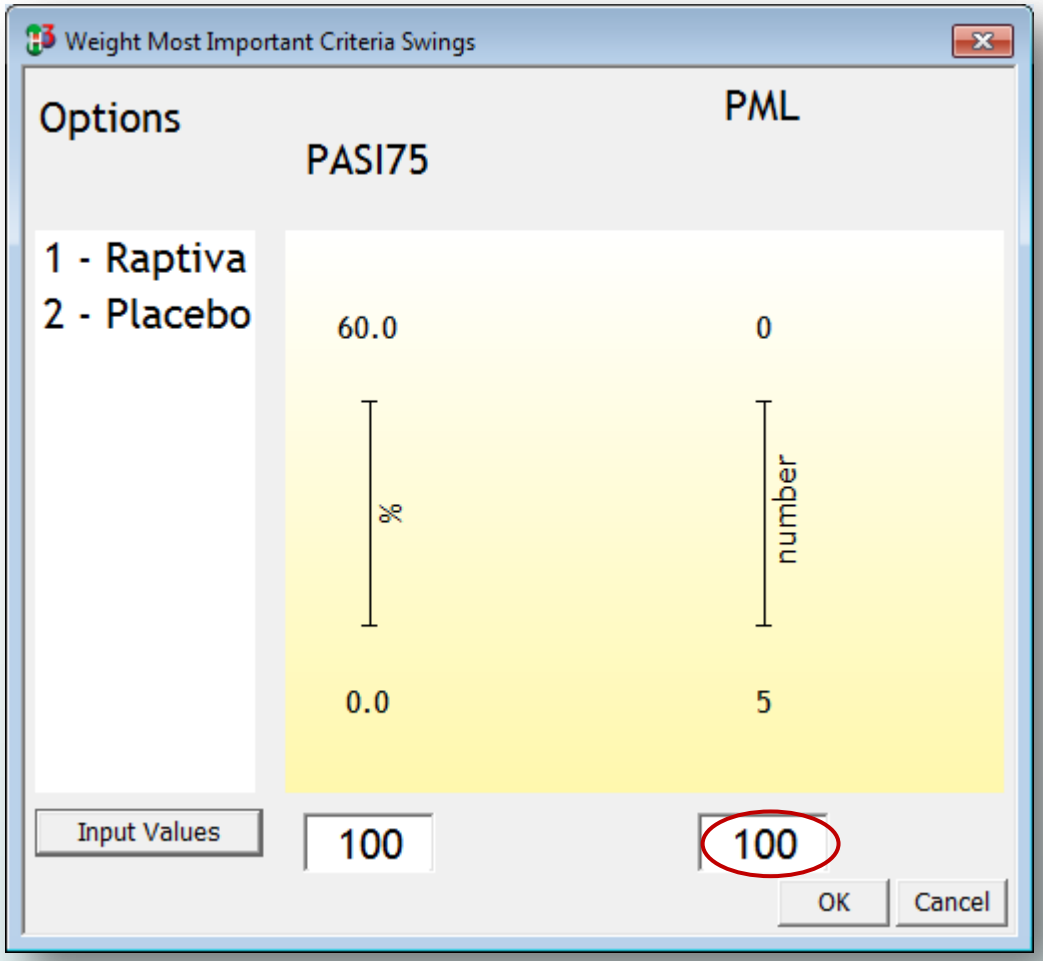
Observational data	PML	12.9	-95	-12.3	19.2
		100.0		19.2	

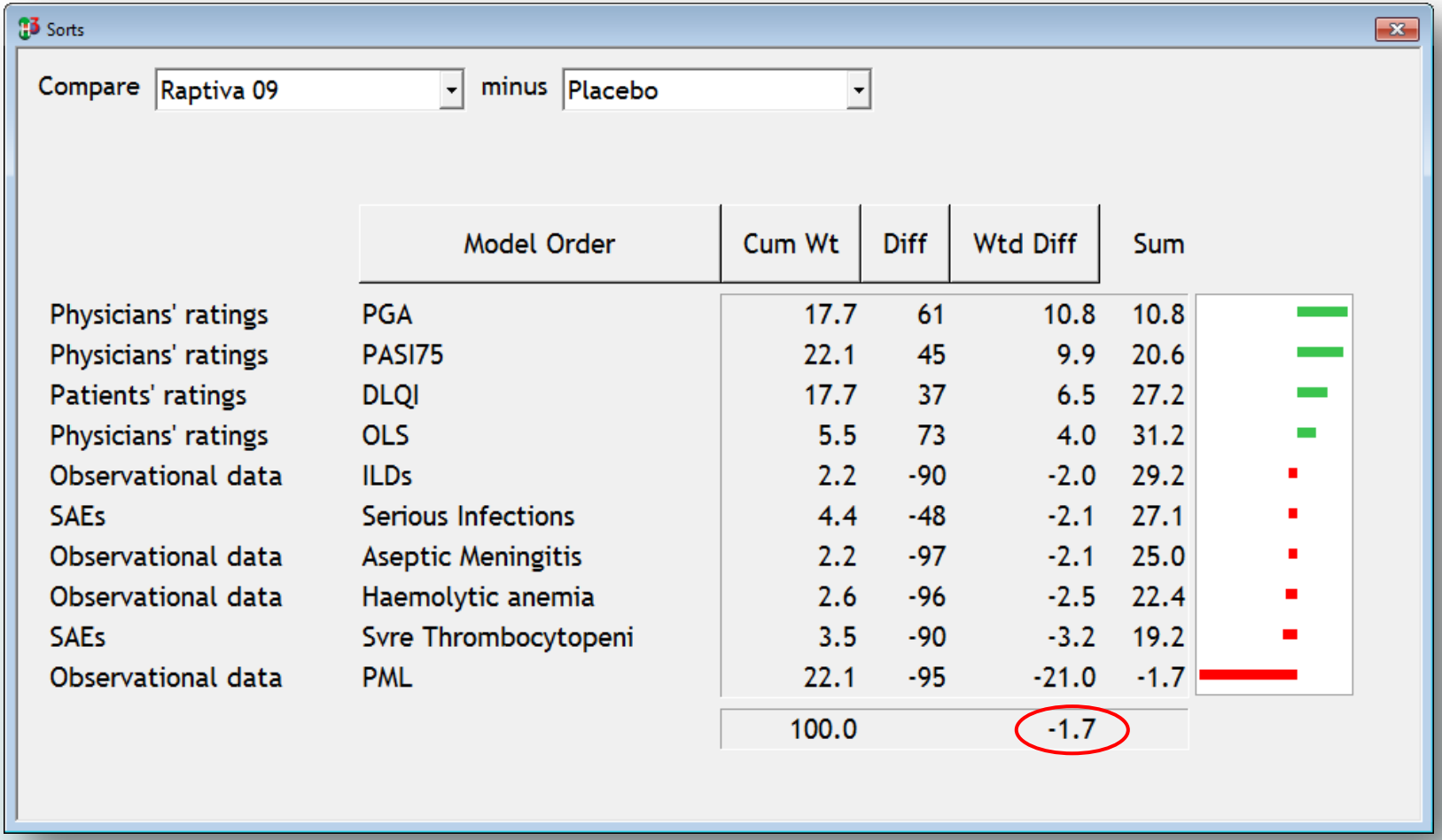
Sensitivity Analysis on PML



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.

Douwe Postmus, PhD

AGGREGATED DATA DRUG INFORMATION SYSTEM (ADDIS)

AN EVIDENCE-BASED DECISION SUPPORT SYSTEM FOR THE BENEFIT-RISK ASSESSMENT OF MEDICAL PRODUCTS

The 3 pillars of structured decision making

- Well-defined and transparent process
  - PrOACT-URL (EMA benefit-risk methodology project)
- Guidance on how to conduct the various steps in this process
  - IMI PROTECT benefit-risk group recommendations report
  - IMI PROTECT website and training materials
- Supporting software
  - ADDIS

ADDIS – a brief history

- The development of ADDIS started in 2009 as part of work package 3.2 of the Escher project
- This has resulted in the development of ADDIS 1
- ADDIS 2 is a web-based redevelopment of the previous prototype desktop application
- ADDIS 2 is currently still under heavy development but the software in now becoming useable as an analytical tool
- Both ADDIS 1 and 2 are open source and freely accessible from our website www.drugis.org

ADDIS 2: functional perspective

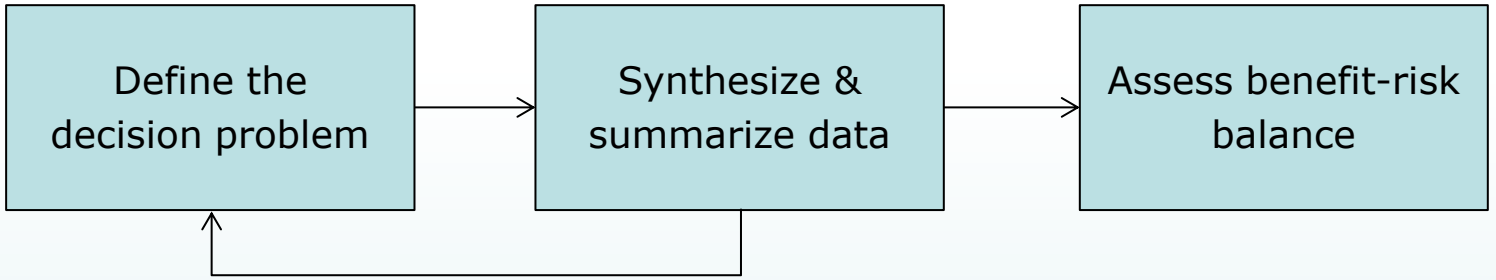
Quantitative methods

(network) meta-analysis

MCDA/SMAA

Disease progression modelling

Workflow



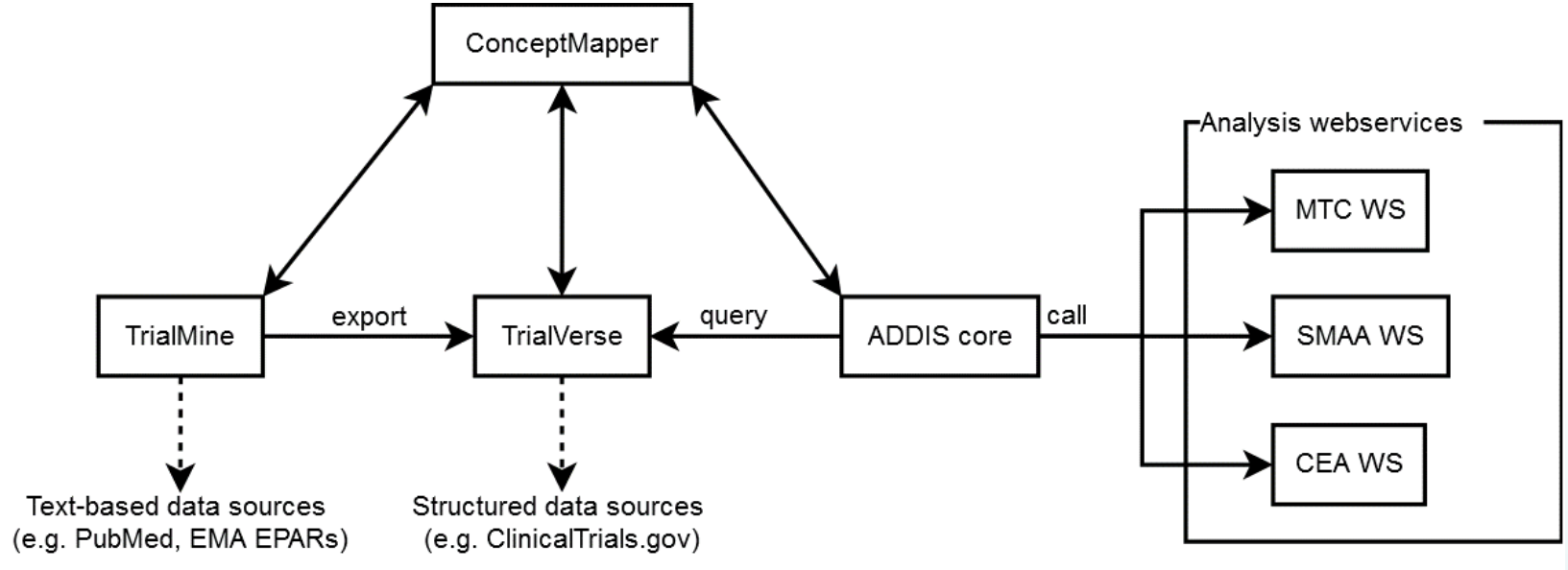
Visualisations

Value tree

Effects table

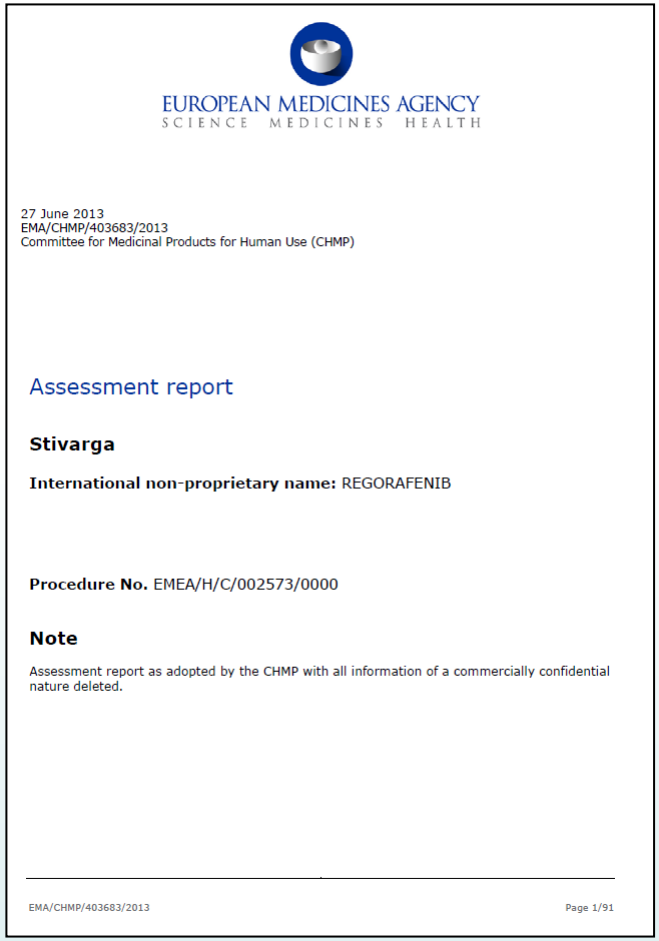
SMAA descriptive indices

ADDIS 2: technical perspective



MCDA WEB INTERFACE

Illustrative case study



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2013
EMA/CHMP/403683/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Stivarga

International non-proprietary name: REGORAFENIB

Procedure No. EMEA/H/C/002573/0000

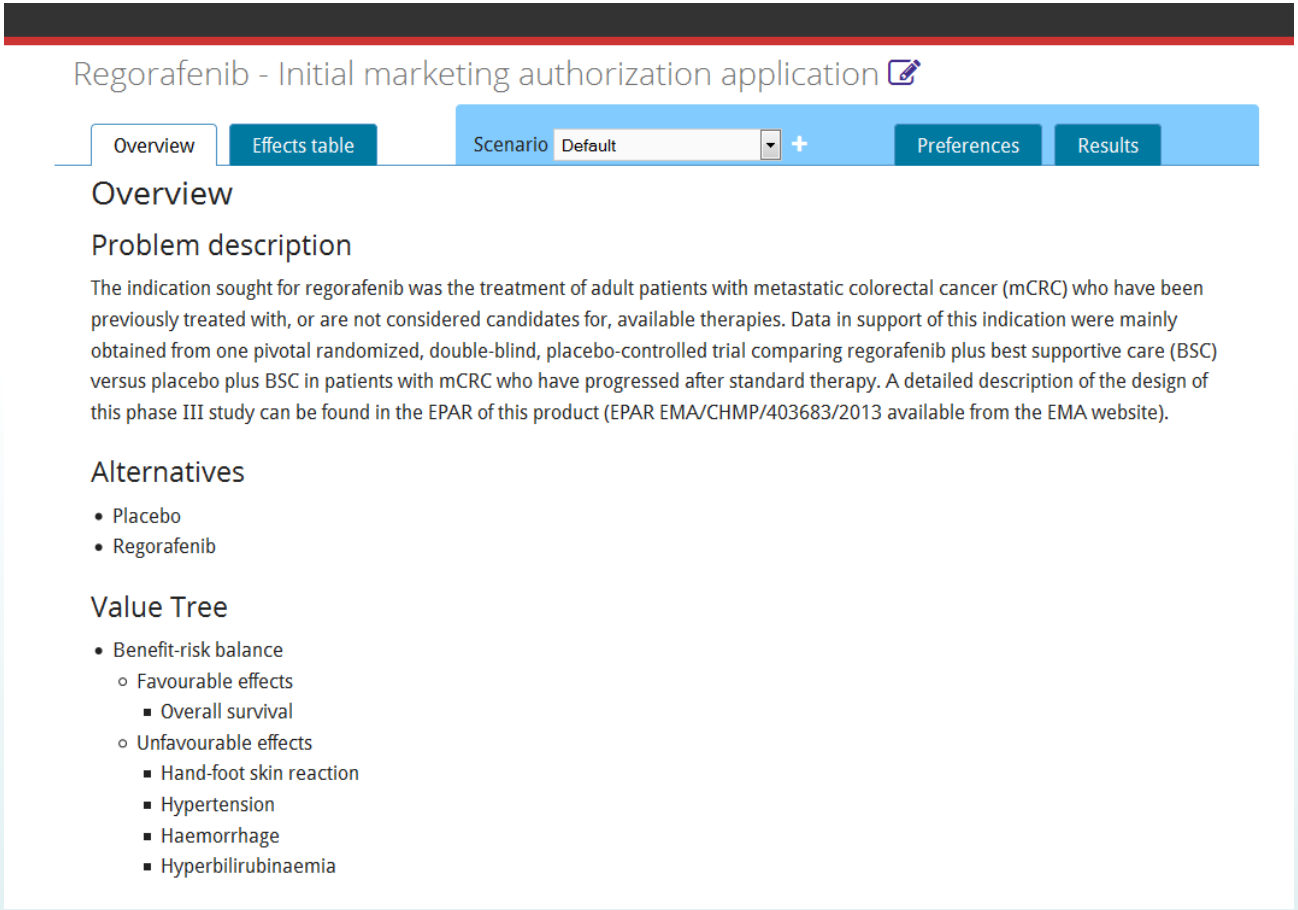
Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

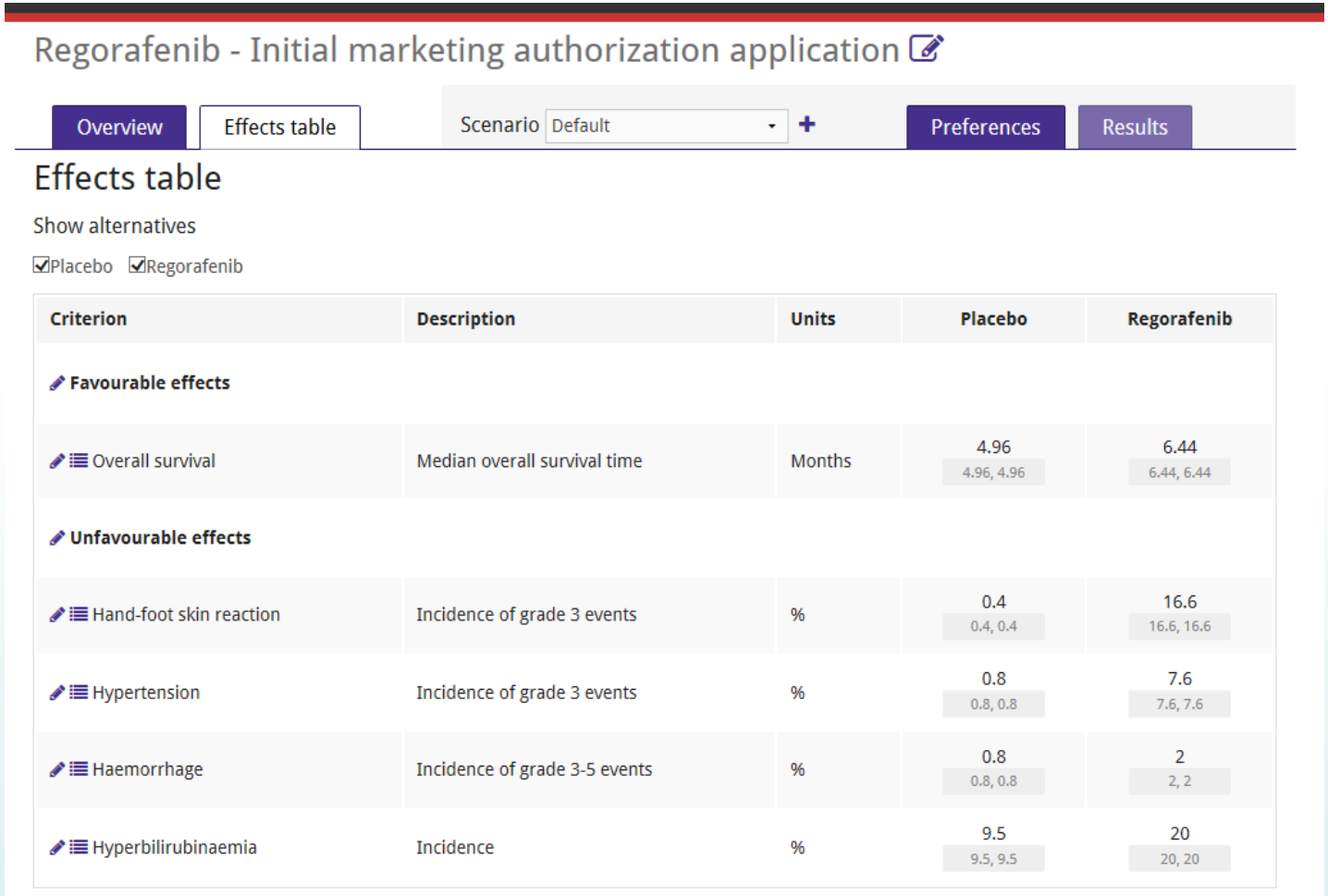
EMA/CHMP/403683/2013 Page 1/91

- We consider the problem of assessing the benefit-risk balance of regorafenib using the data available at the time of the initial marketing authorization application of this product
- All data used for this assessment were directly taken from the EPAR of this product (EPAR EMA/CHMP/403683/2013 available from the EMA website)
- The value judgments provided throughout this example are hypothetical and do not reflect the opinion of the CHMP

Overview of the decision problem



Effects table



Regorafenib - Initial marketing authorization application

Overview | Effects table | Scenario Default + | Preferences | Results

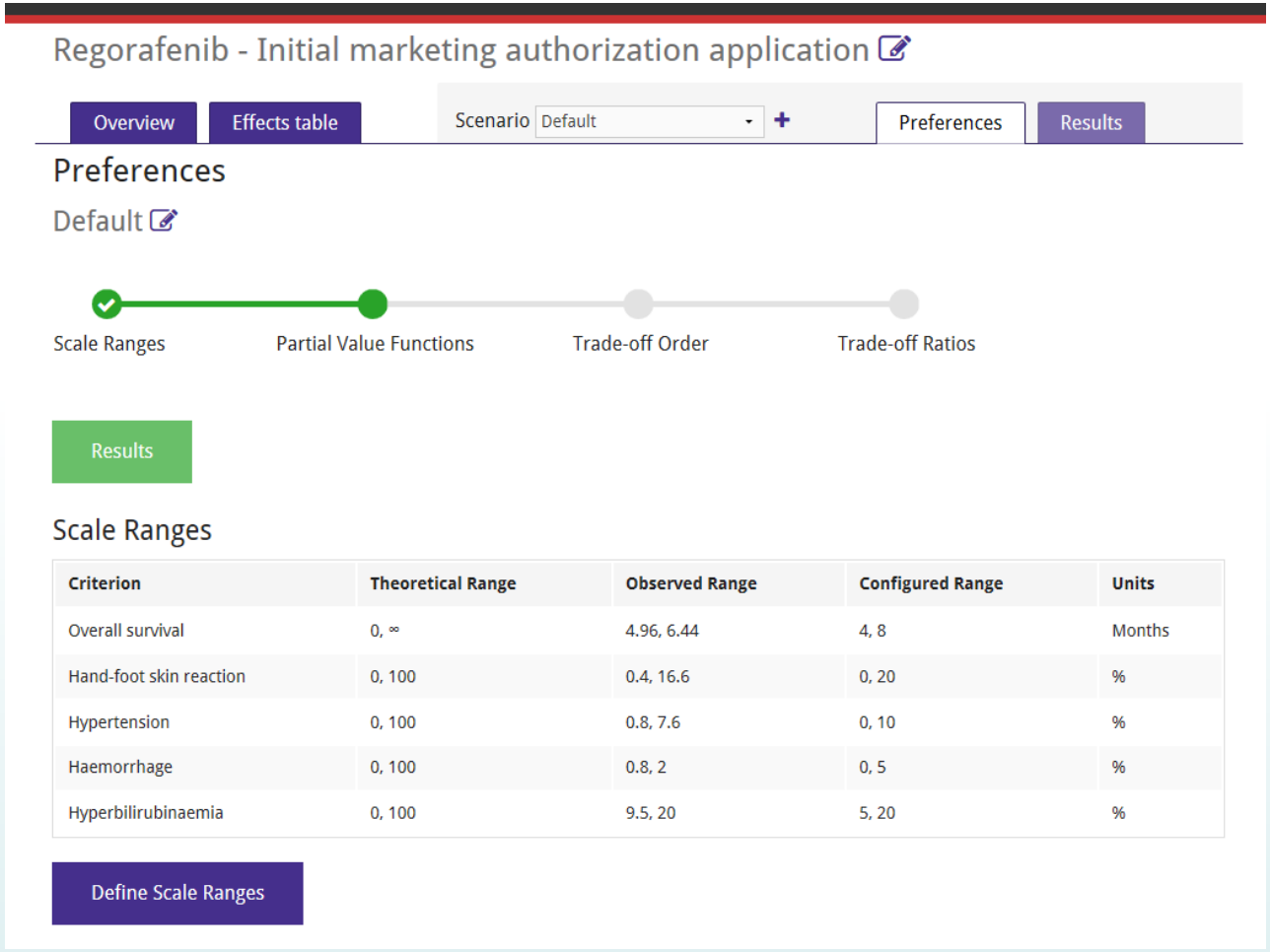
Effects table

Show alternatives

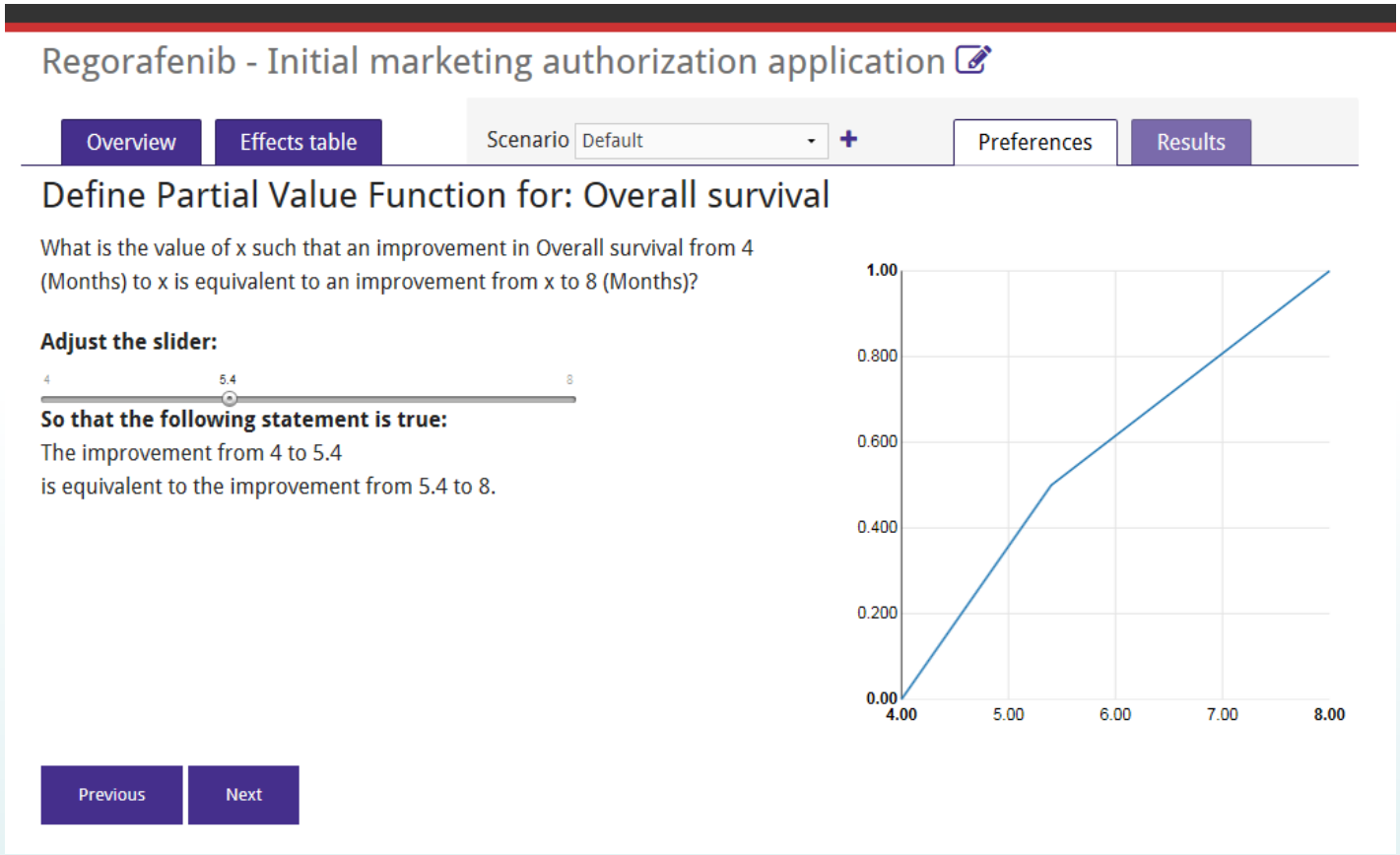
☑Placebo ☑Regorafenib

Criterion	Description	Units	Placebo	Regorafenib
Favourable effects				
Overall survival	Median overall survival time	Months	4.96 4.96, 4.96	6.44 6.44, 6.44
Unfavourable effects				
Hand-foot skin reaction	Incidence of grade 3 events	%	0.4 0.4, 0.4	16.6 16.6, 16.6
Hypertension	Incidence of grade 3 events	%	0.8 0.8, 0.8	7.6 7.6, 7.6
Haemorrhage	Incidence of grade 3-5 events	%	0.8 0.8, 0.8	2 2, 2
Hyperbilirubinaemia	Incidence	%	9.5 9.5, 9.5	20 20, 20

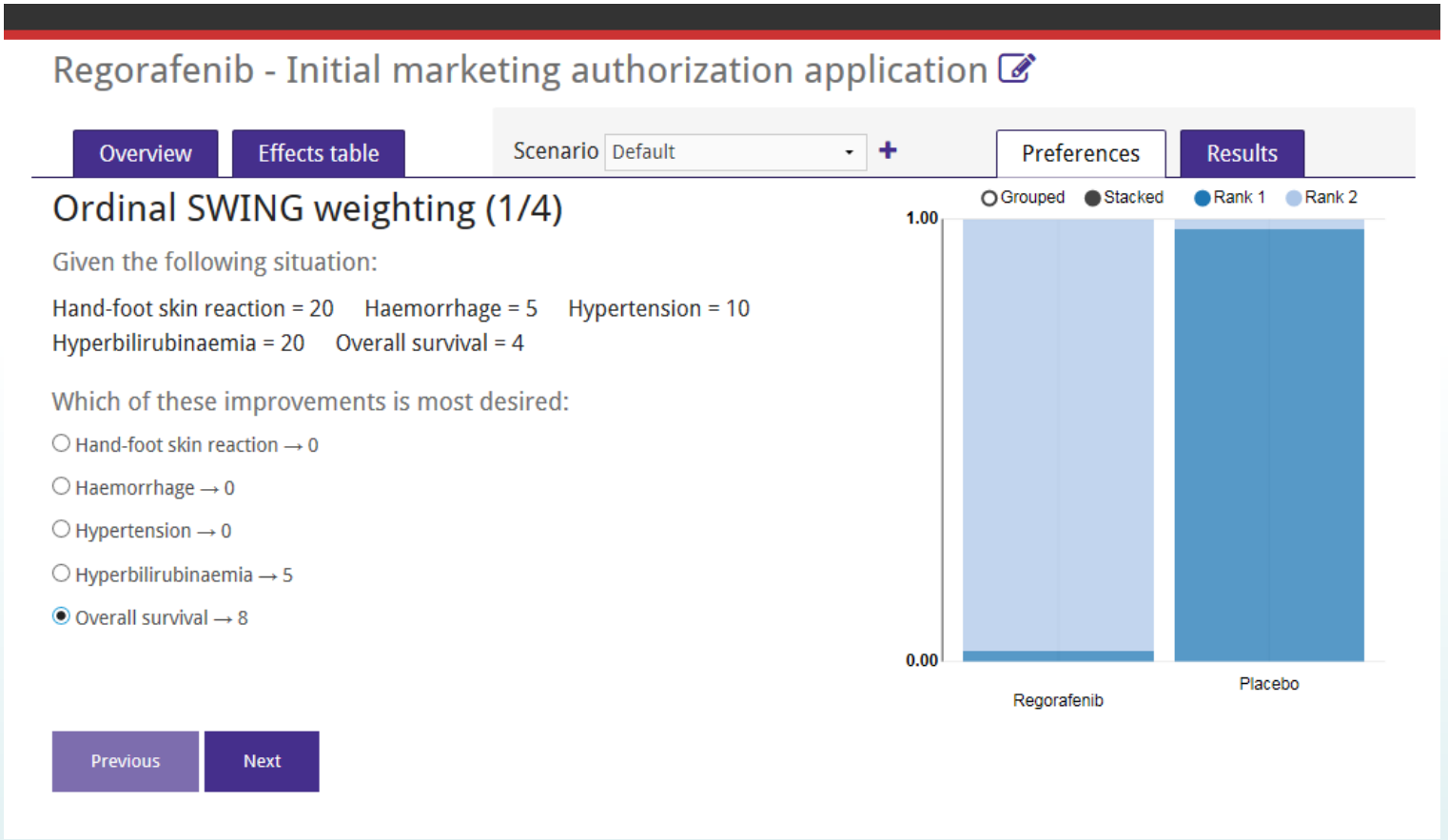
Preference elicitation: scale ranges



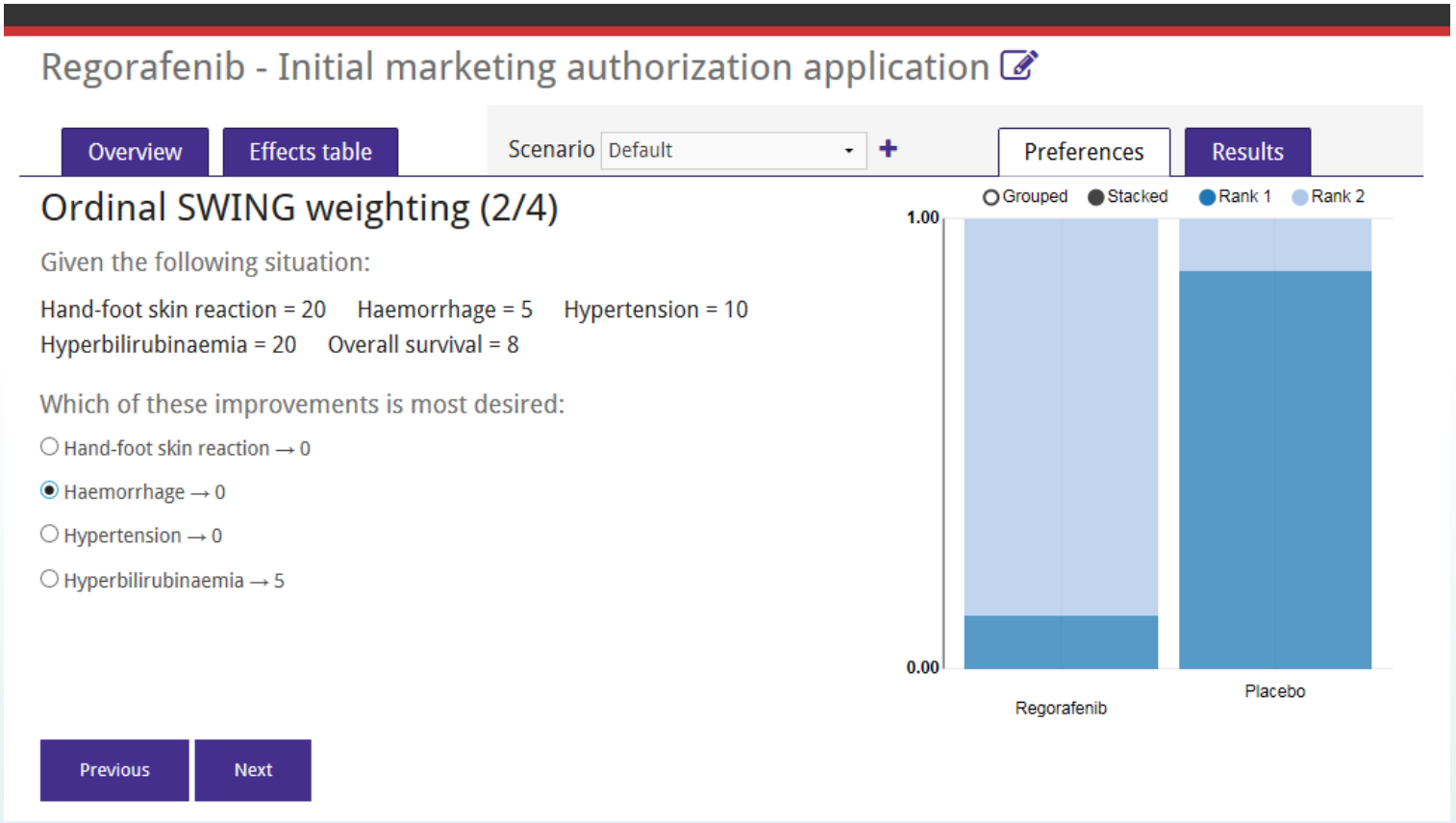
Preference elicitation: partial value functions



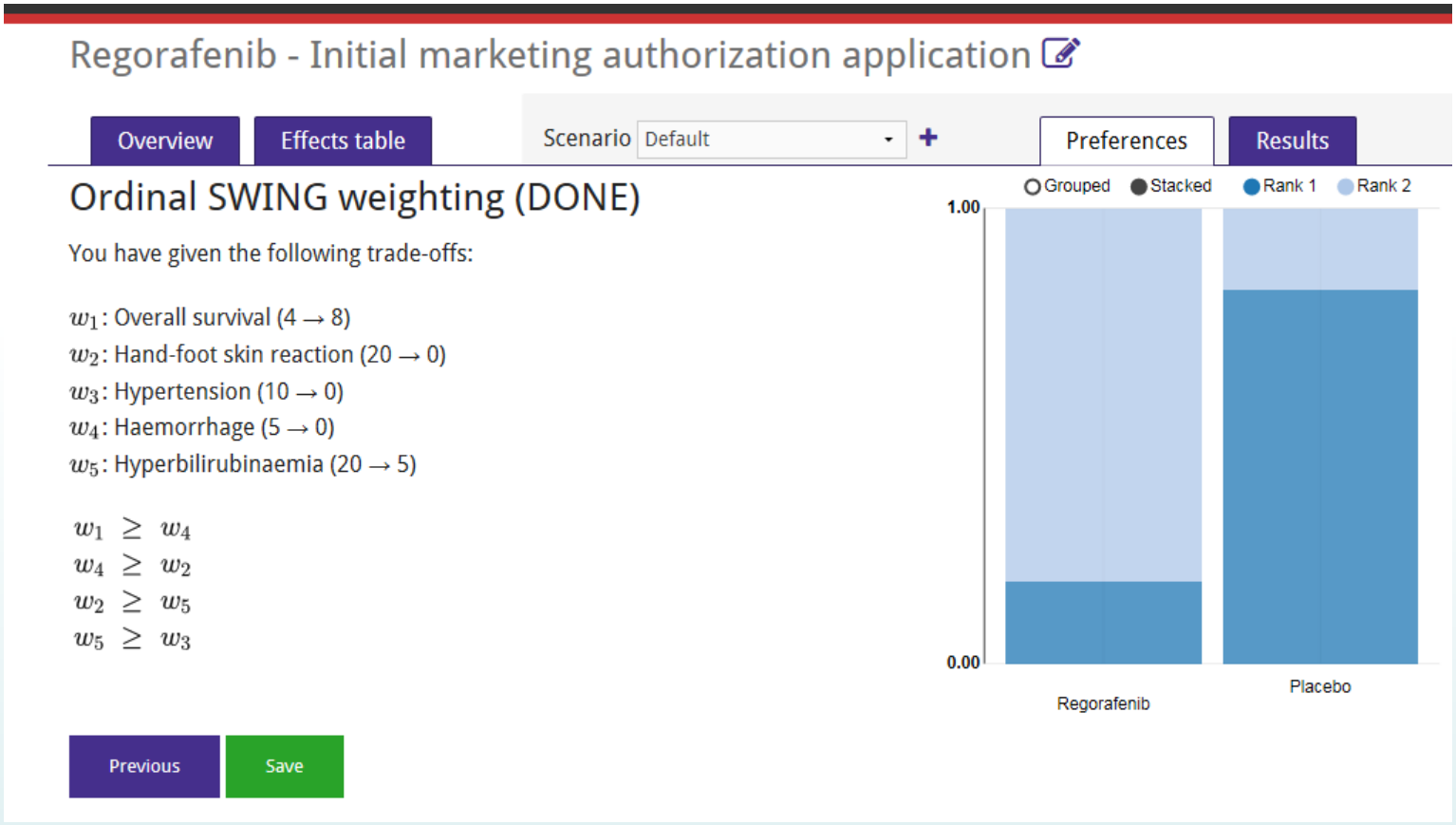
Preference elicitation: ordinal trade-offs



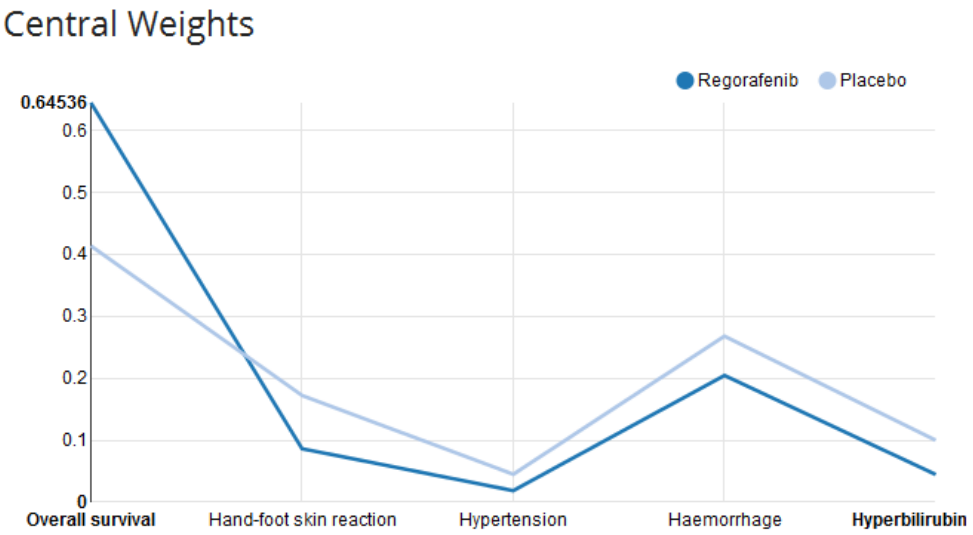
Preference elicitation: ordinal trade-offs



Preference elicitation: ordinal trade-offs

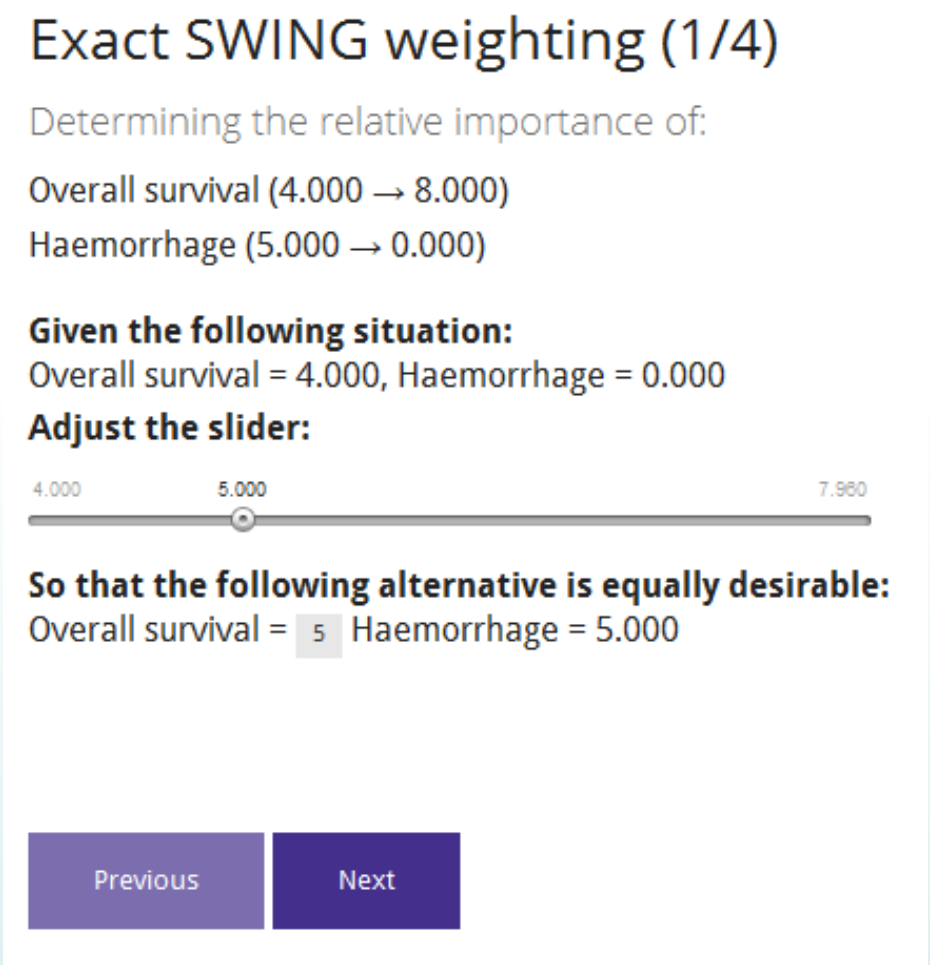


Results based on ordinal trade-offs

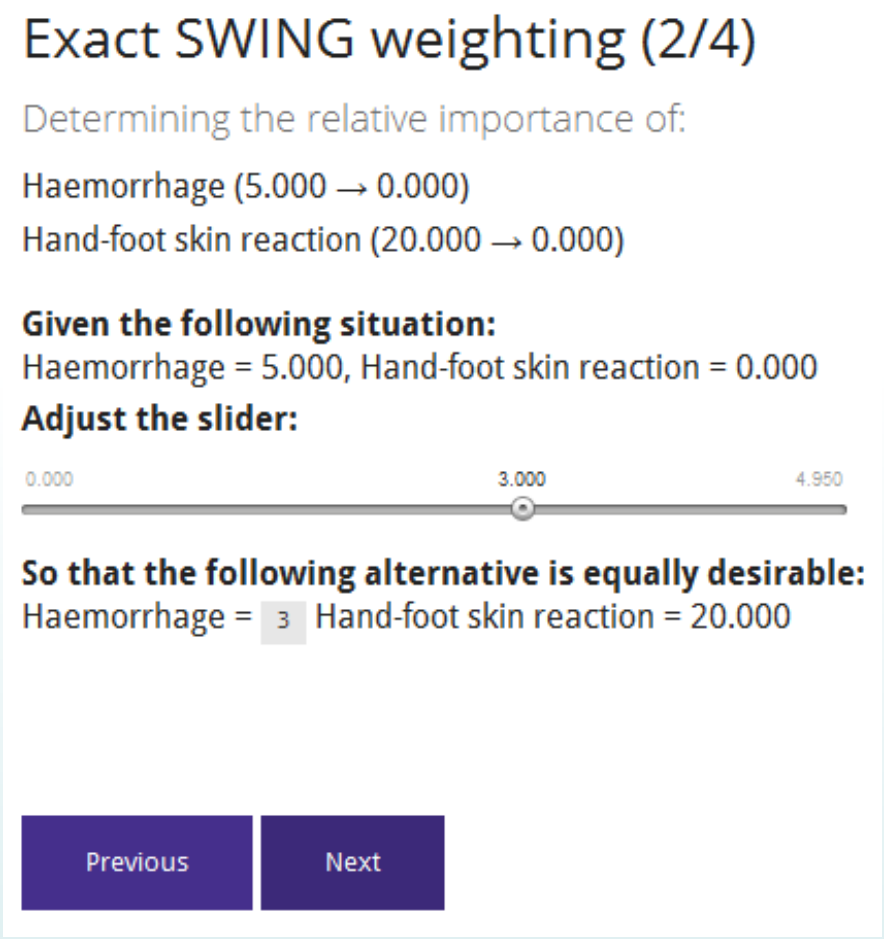


Alternative	Confidence	Hand-foot skin reaction	Haemorrhage	Hypertension	Hyperbilirubinaemia	Overall survival
Placebo	1	0.17248	0.26829	0.045044	0.10019	0.414
Regorafenib	1	0.086353	0.20483	0.018686	0.04477	0.64536

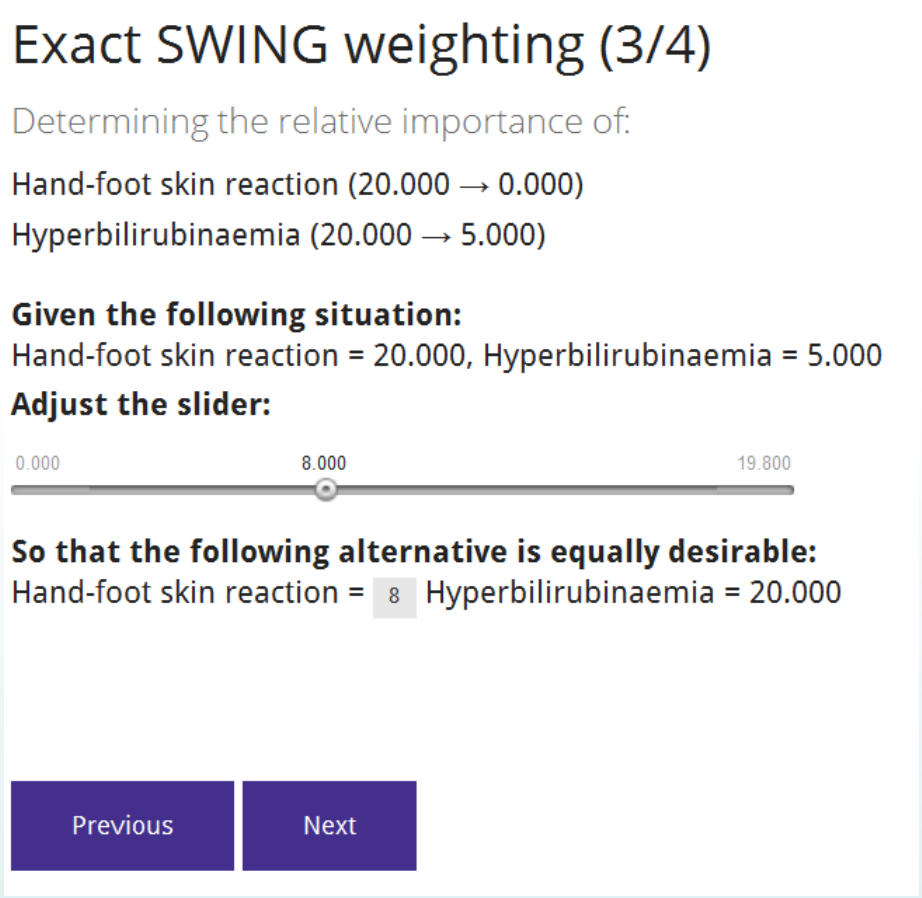
Preference elicitation: exact trade-offs



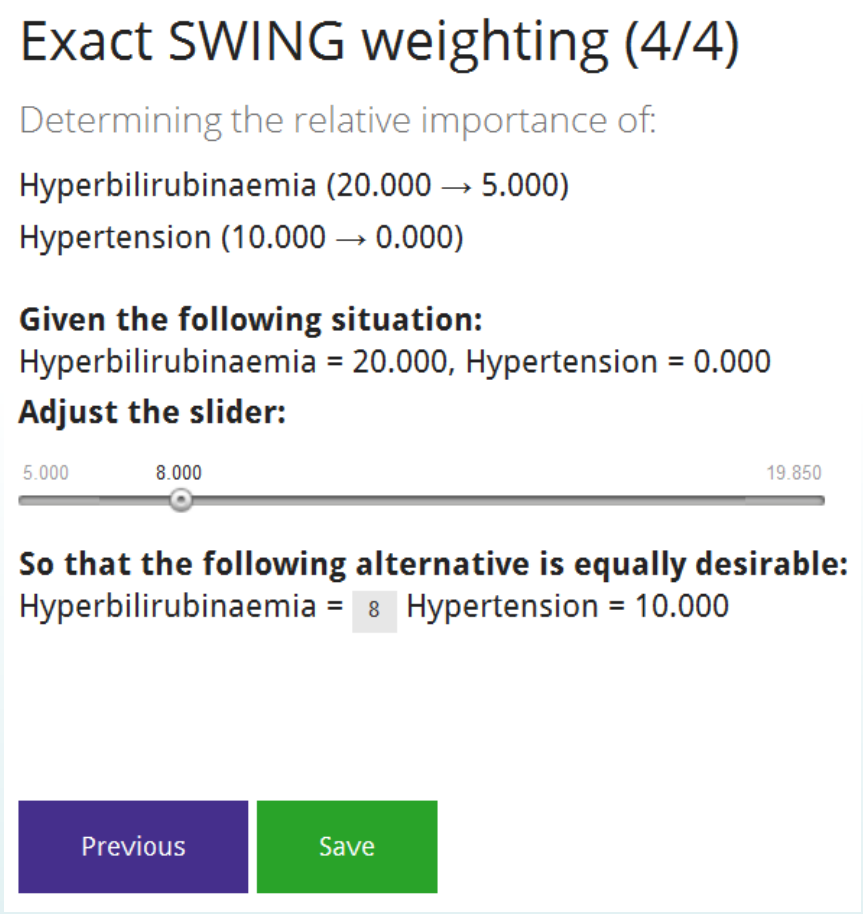
Preference elicitation: exact trade-offs



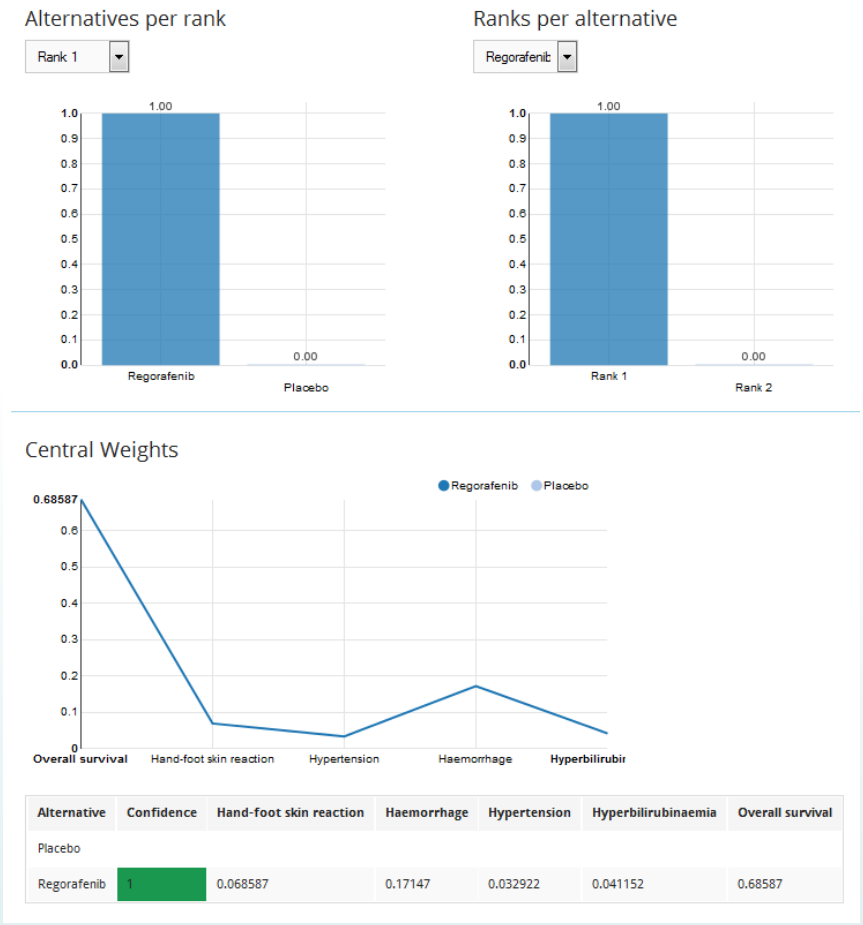
Preference elicitation: exact trade-offs



Preference elicitation: exact trade-offs



Results based on exact trade-offs



Alternative	Confidence	Hand-foot skin reaction	Haemorrhage	Hypertension	Hyperbilirubinaemia	Overall survival
Placebo						
Regorafenib	1	0.068587	0.17147	0.032922	0.041152	0.68587

Concluding remarks

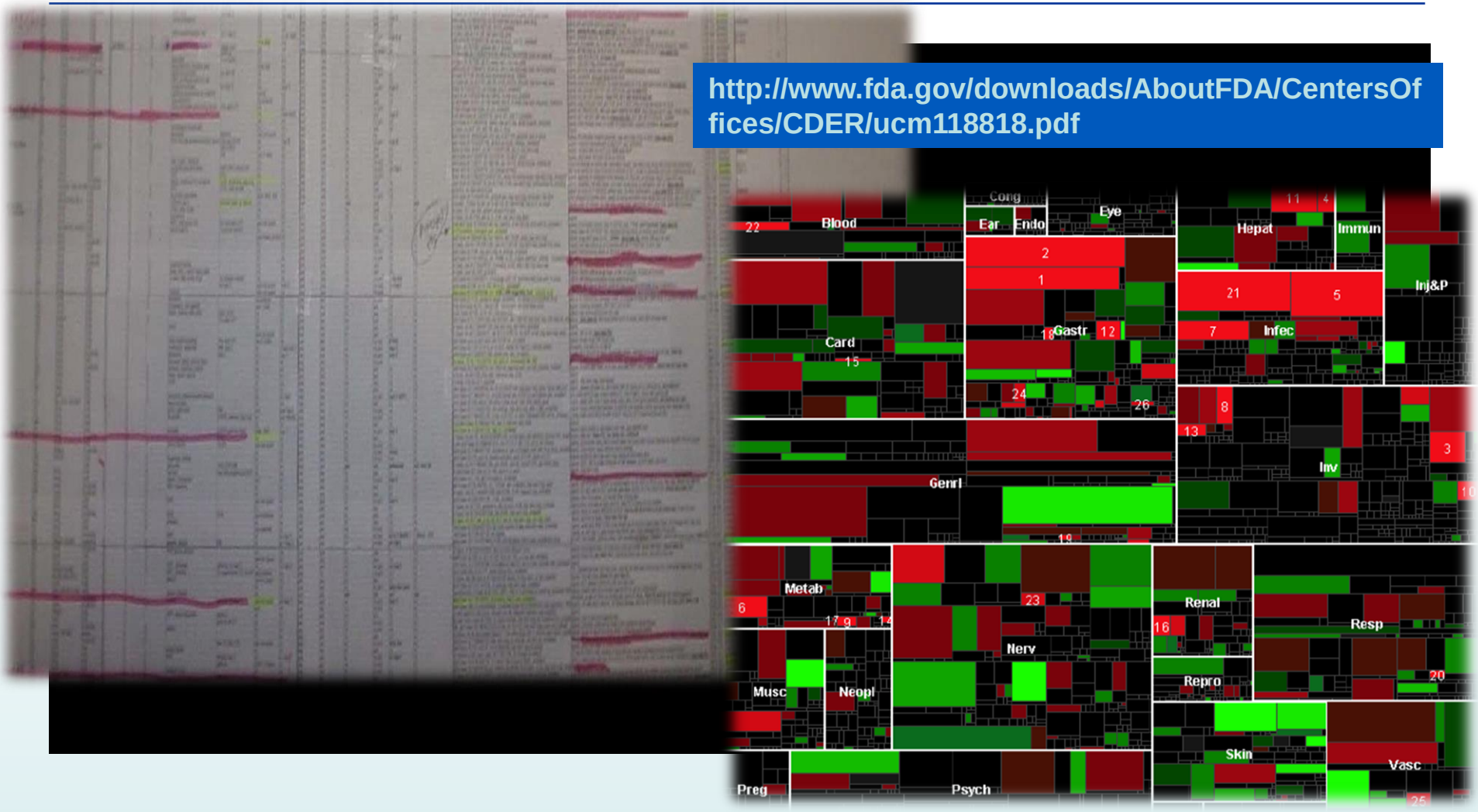
- Developing quantitative methods that are both theoretically sound and easy to use by decision makers has proven to be far from straightforward
- Our ultimate aim will be to arrive at methodologies that allow decision makers to simultaneously explore
  - Imprecision in the preference statements (i.e. shape of the partial value functions, criteria weights)
  - Uncertainty in the effect size estimates
  - Uncertainty in the long-term clinical consequences
- We have started to develop a flexible set of tools to address all these aspects (www.drugis.org)

Christine Hallgreen, PhD

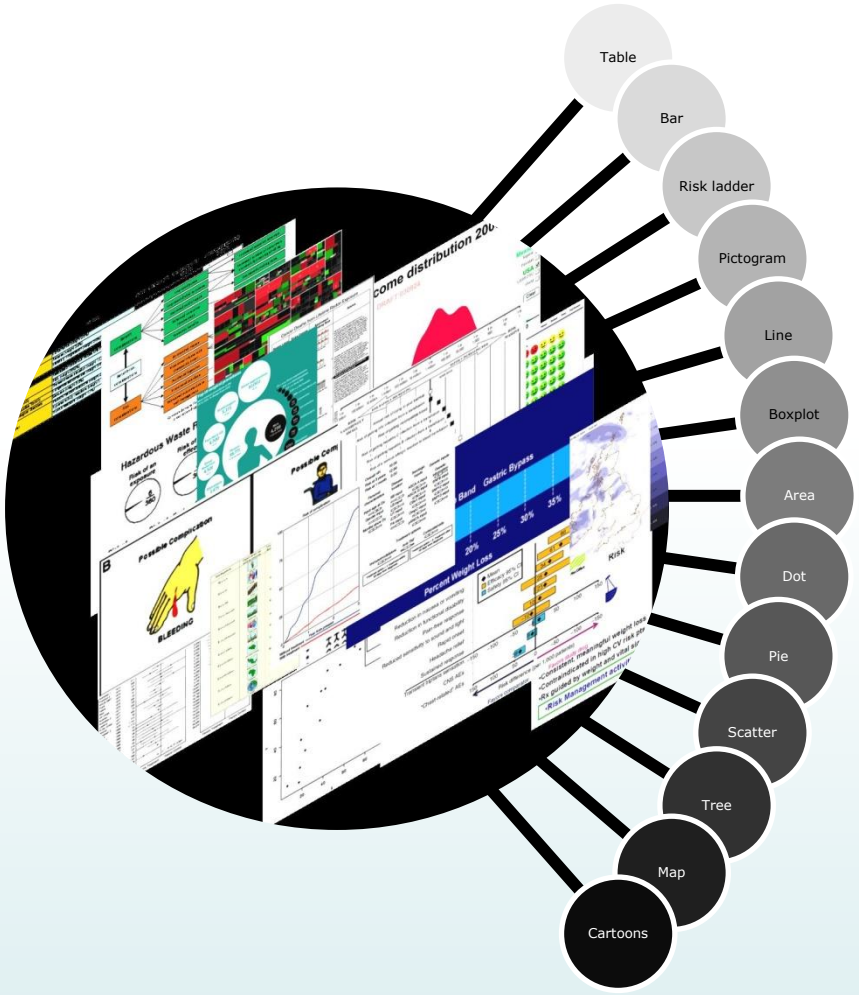
VISUALISING BENEFITS AND RISKS: CONCEPTS AND IDEAS

Many research on visualisations

Lack of use in formal B-R assessment



Graphics and other formats



Verbal Labels Can Triple Perceived Risk in Clinical Trials

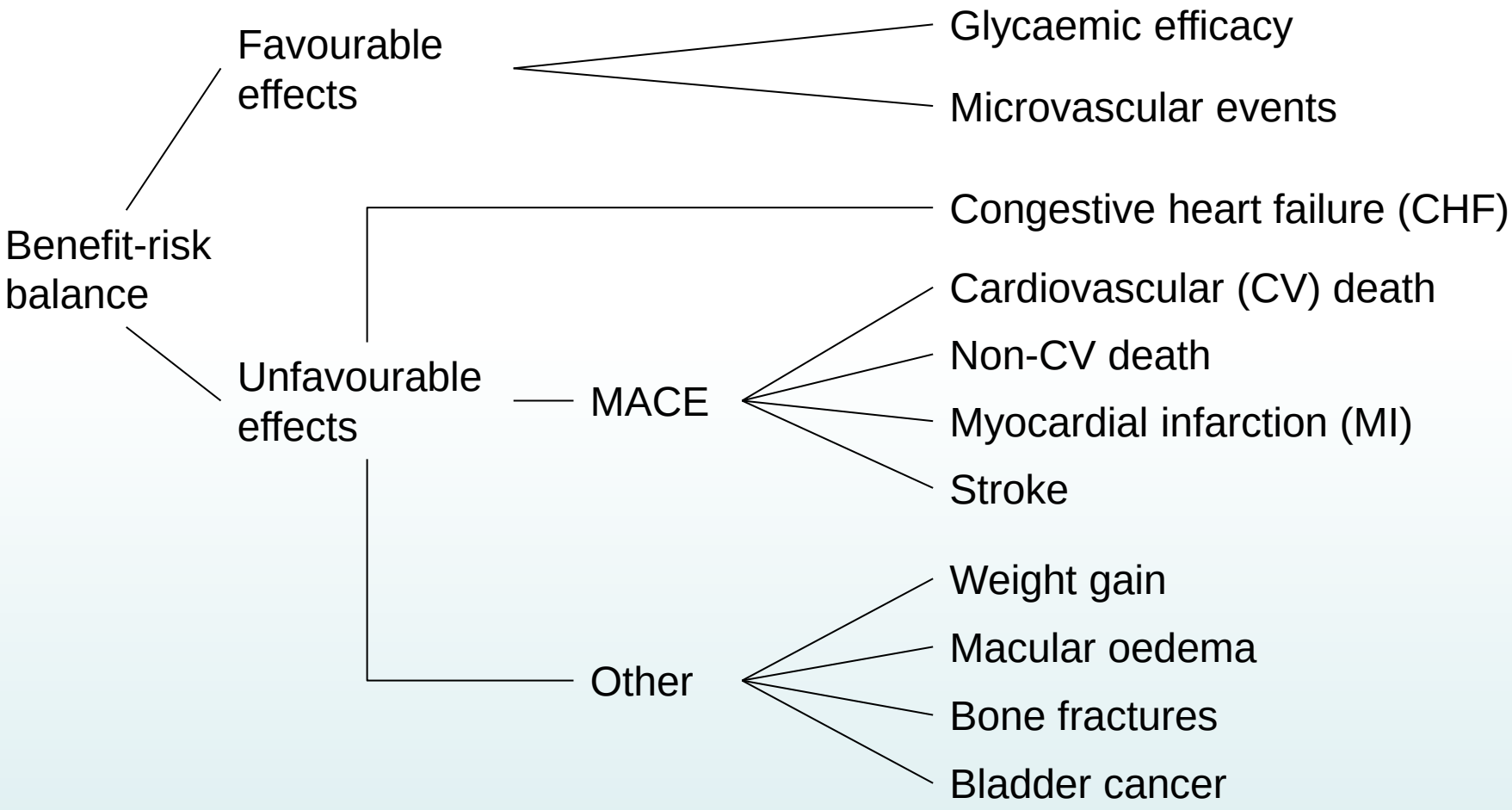
The purpose of this study was to assess whether the use of verbal descriptors, such as "common" and "rare" affects people's perceptions of the risks involved in clinical trials as well as their likelihood of entering into the trial. Participants were required to imagine that they had a serious skin condition and being asked if they would take part in a clinical trial for a new drug. They

bal labels alone or verbal labels with associated numerical values. The results showed that those given just the verbal descriptors were significantly less satisfied with the information, perceived risk to be higher (by a factor of three) and benefit to health to be lower, and indicated that they would be significantly less likely to enter the trial. We recommend that patients are informed

http://intl-dij.sagepub.com/content/40/3/249.refs

		Treatment A	Treatment B
Benefits (higher is better)	Physician's view on **HDL Cholesterol levels**	Mild improvement	No change
	Number of people who experience a **10% weight loss**	10 out of 1000	450 out of 1000
Risks (lower is better)	Number of people who experience **psychiatric conditions**	100 out of 1000	1 out of 1000
	Number of people who experience **cardiovascular conditions**	1 out of 1000	100 out of 1000
	Number of people who experience **gastrointestinal conditions**	1 out of 1000	None

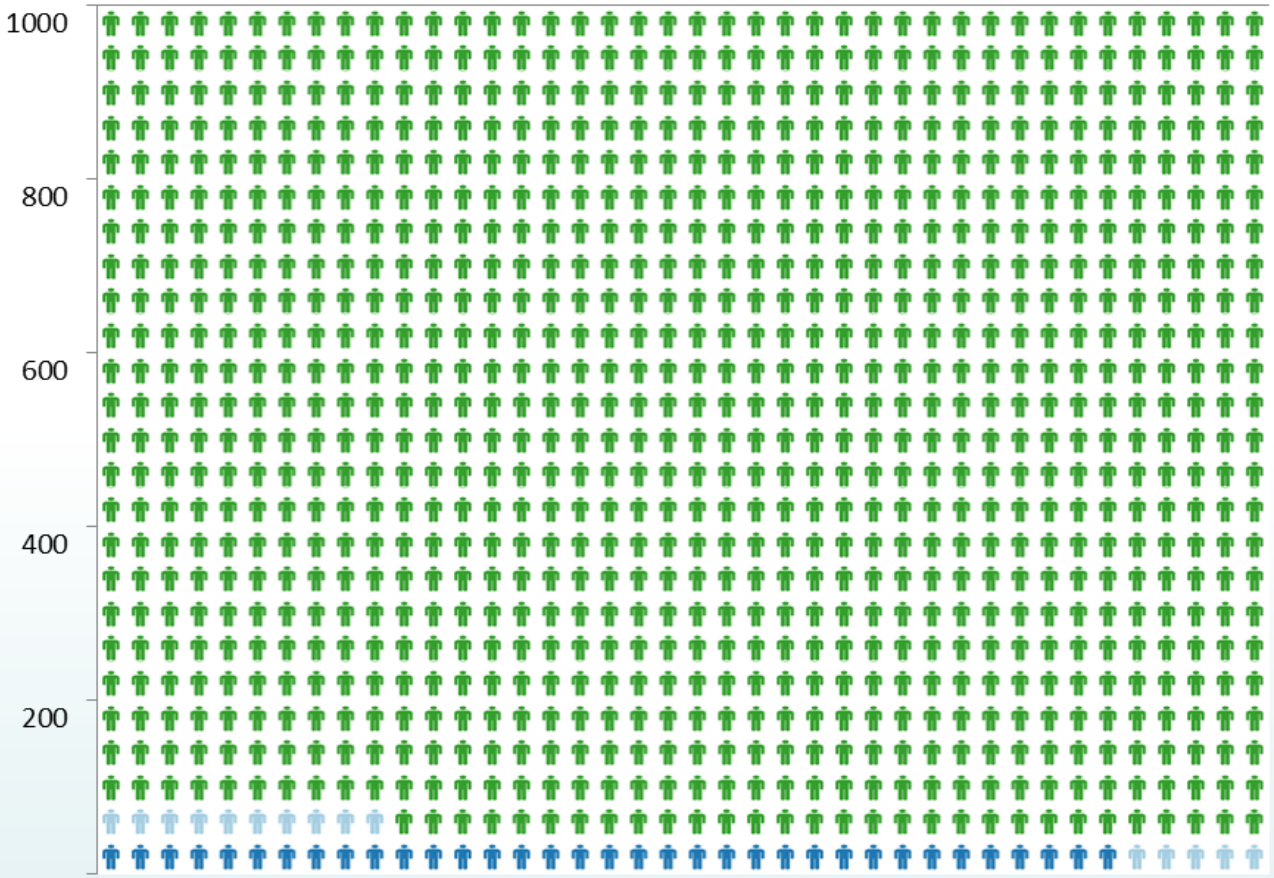
Tree diagram – a value tree



Effects table

		Name	Description	Fixed Upper	Fixed Lower	Unit	Rosi + adjunct	Adjunct only
Favourable effects		Glycaemic efficacy	(A surrogate marker of the quality of glucose regulation.) Mean change from baseline in the proportion of Hb in which A1c is greater than 48 mmol/ml.	5.00	-5.00	%	-1.18	0.06
		Micro-vascular events	Incidence of new cases of microvascular events compared to baseline (Retinopathy requiring photocoagulation, vitreous haemorrhage, & fatal or non-fatal renal failure.)	20.00	0.00	%	2.70	3.50
Unfavourable Effects		CHF	Proportion of patients experiencing congestive heart failure during the study period.	4.00	0.00	%	3.69	1.89
	MACE	CV death	The proportion of patients who died from any cardiovascular event including stroke.	4.00	0.00	%	2.70	3.19
		Non-CV death	The proportion of patients who died from any non-cardiovascular event including stroke.	4.00	0.00	%	2.97	3.86
		MI	Proportion of patients who experience a non-fatal heart attack.	5.00	0.00	%	3.33	3.01
		Stroke	Proportion of patients who experience a non-fatal ischemia stroke.	5.00	0.00	%	1.94	2.83
	Other	Weight gain	Mean change from baseline in weight gain at 1 yr.	10.00	-5.00	Kg	3.80	0
		Macular oedema	Proportion of patients who experience macular oedema.	1.00	0.00	%	1.27	0.23
		Bone fractures	Proportion of patients experiencing bone fractures.	3	0	%	8.33	5.3
		Bladder cancer	Proportion of patients contracting bladder cancer.	1.00	0.00	%	0.27	0.22

Pictogram

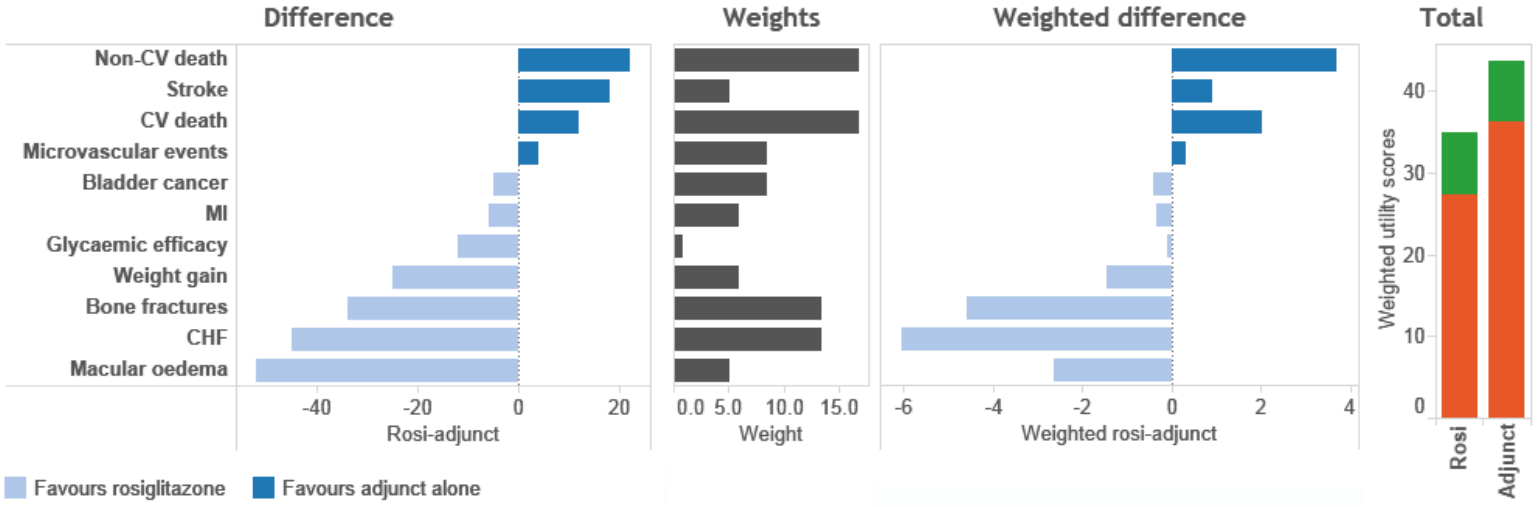

1000
800
600
400
200
Patients who will die from any-cause over a course of one year whether they take warfarin or not
Patients who will be saved from dying by any-cause over a course of 1 year by taking warfarin
Patients who will not die from any-cause over a course of one year whether they take warfarin or not

Stacked bar graph

More green, more benefit

More red, more safe

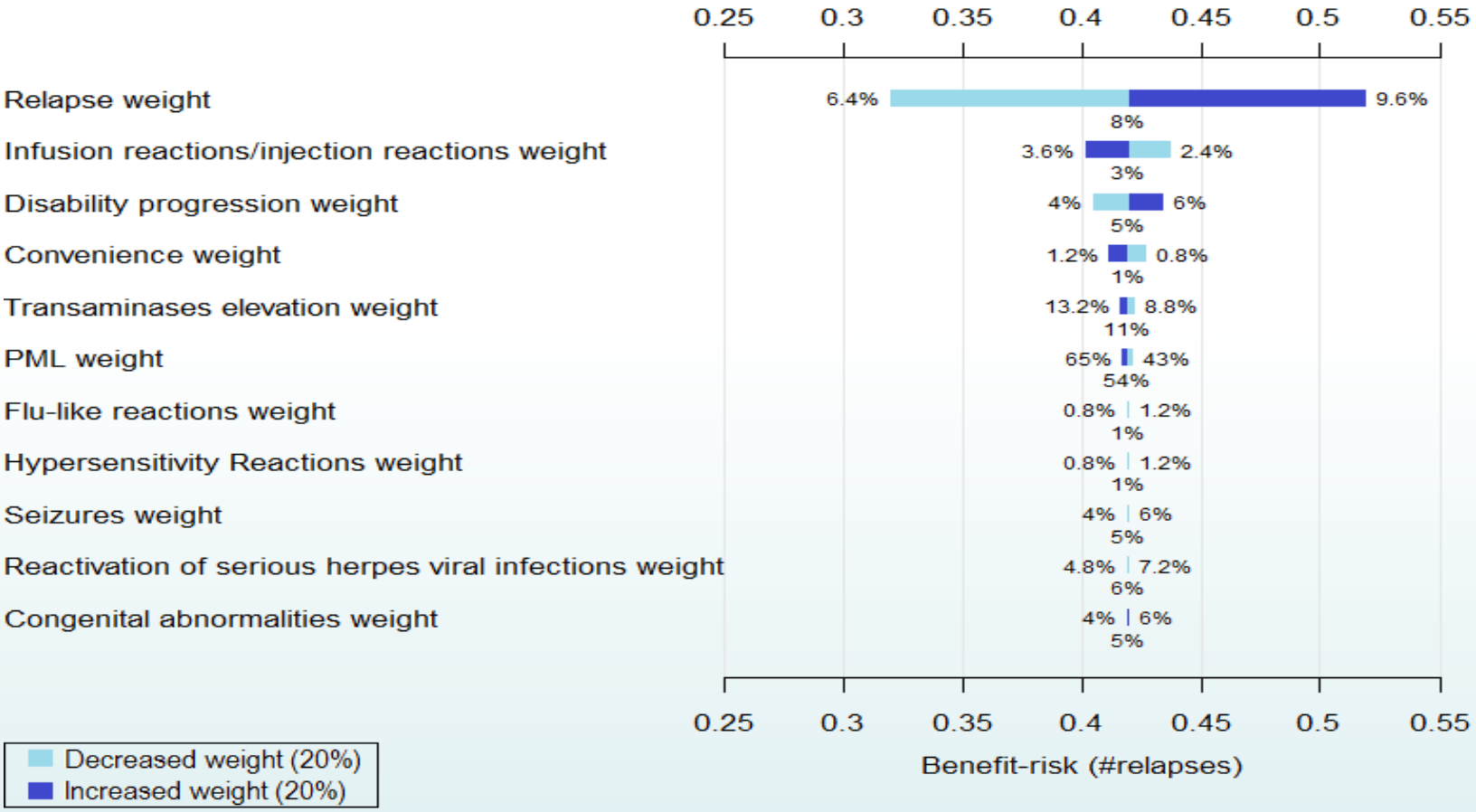
Interactive visual display



Drag sliders to assign weights on criteria

Non-CV death: 50	
CV death: 50	Bladder cancer: 25
Stroke: 15	Weight gain: 17.5
Microvascular events: 25	Macular oedema: 15
Glycaemic efficacy: 2.5	Bone fractures: 40
Myocardial infarction: 17.5	CHF: 40

Tornado-diagram



Remarks on visual representation

- No one visual type fits all
- Different visual types carry information differently
- Different user may prefer different visual representation – cannot always generalise
  - Visual type preference study shows preference towards tables and bar graphs
  - Understanding and/or preferences may still be affected by the actual information being displayed
- Visual representation formats should be tested with the intended audience before actual use

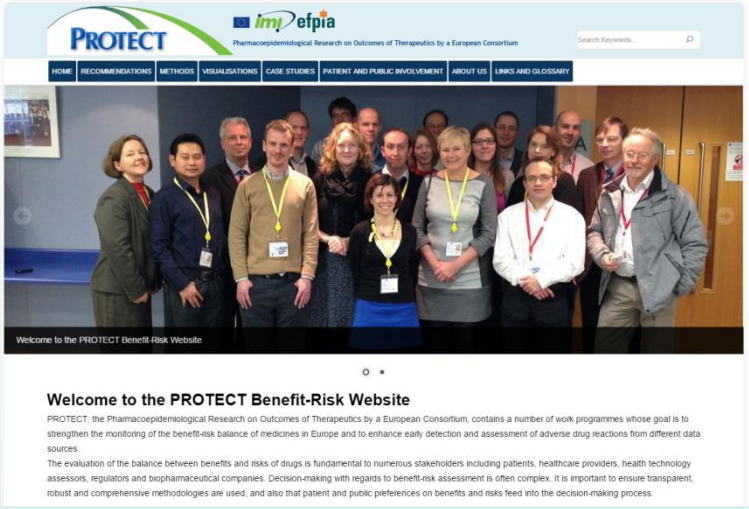
Gerry Downey, MSc CBA
Subhakanta Das, BSc

PROTECT RESOURCES FOR FURTHER LEARNING

Dissemination of results/recommendations arising from PROTECT*

- Publications & Presentations
- PROTECT Web Portal
- The ENCePP network
- Training Programmes (WP7)
- The EMEA Scientific Committees, Working Parties and regulatory activities
- Other possible means

http://protectbenefitrisk.eu/



* PROTECT Full Project Proposal / IMI Call #6 (20th January 2009)

Web design

- Responsive Web Design: “Reponses or addictiveness Quickly and Positively” to the users. It responds to users environment based on screen-size, platform and orientation.

- Offers : Smooth Navigation , Easy reading, Reduces scrolling and zooming, social media integration and excellent user experience – across a good vary of devices (from smartphones to desktops).

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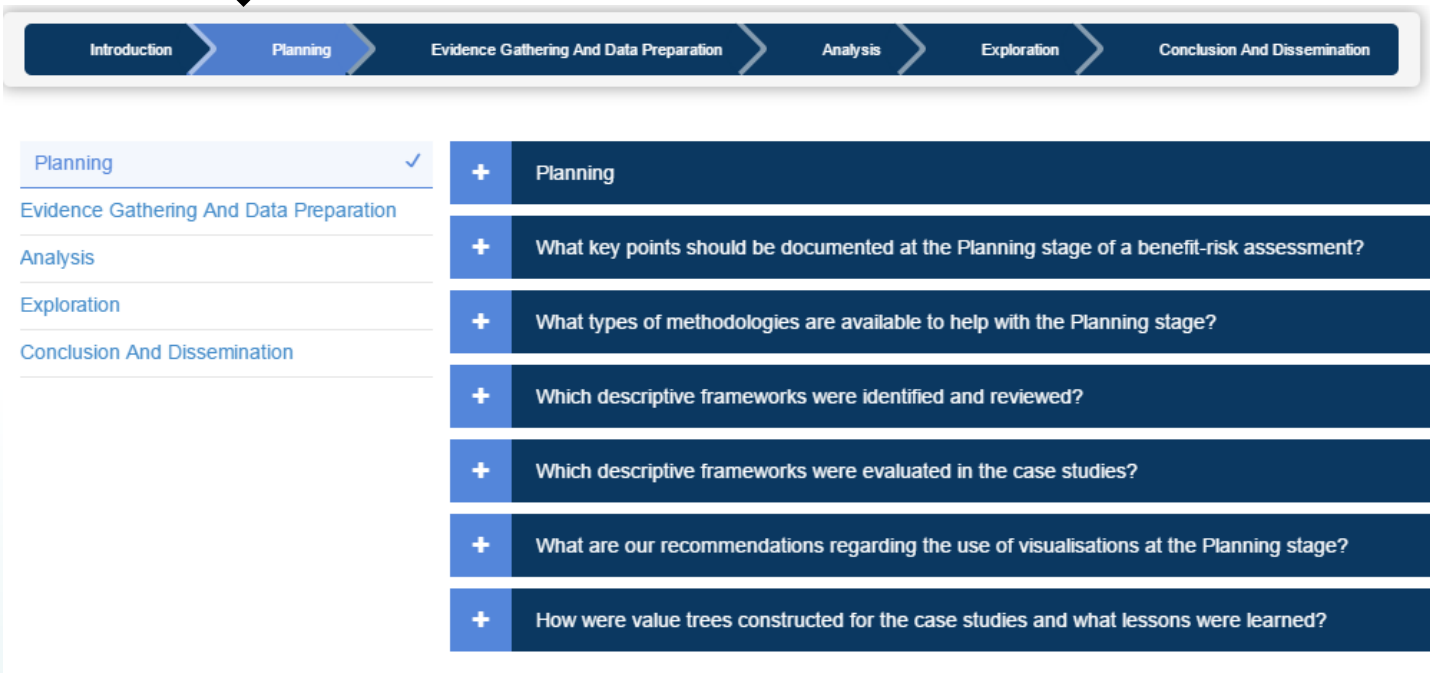
Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

HOME | RECOMMENDATIONS | METHODS | VISUALISATIONS | CASE STUDIES | PATIENT AND PUBLIC INVOLVEMENT | ABOUT US | LINKS AND GLOSSARY



- Recommendations tab is organised into five broad stages common to all benefit-risk assessments
- Interactive version of final recommendations report (Hughes et al, Nov 2013)

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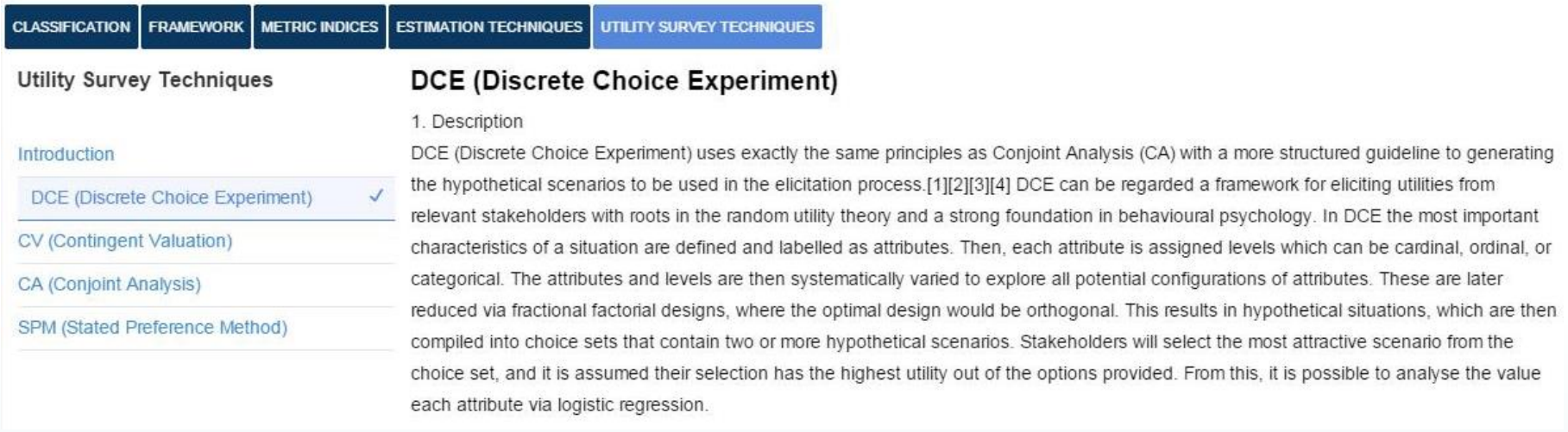
CLASSIFICATION | FRAMEWORK | METRIC INDICES | ESTIMATION TECHNIQUES | UTILITY SURVEY TECHNIQUES

Framework		Metric Indices			Estimation Techniques	Utility Survey Techniques
Descriptive	Quantitative	Threshold	Health	Trade-Off		
PrOACT-URL	MCDA	NNT	QALY	INHB	PSM	DCE
BRAT	SMAA	NNH	Q-TWiST	BRR	ITC	CV
ASF	Decision Tree	Impact Numbers	HALE	UT-NNT	MTC	CA
CMR-CASS	MDP	AE-NNT	DALY	GBR	CPM	SPM
COBRA	BLRA	RV-NNH		Principle Of threes	DAGS	
FDA BRF	NCB	MCE		TURBO	CDS	
SABRE	SBRAM	RV-MCE		BECKMAN		
UMBRA	CUI	MAR				
	DI	NEAR				

- Classification of methodologies used in benefit-risk assessment



- Taken together, they would be a sufficiently powerful toolbox for most benefit-risk assessments
- Interactive version of systematic review of methodologies (Mt-Isa et al, 2014)

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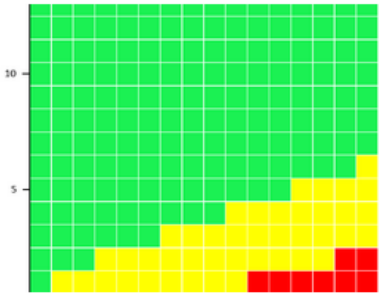
INRODUCTION | AREA GRAPH AND VOLUME CHART | BAR CHART/GRAPH | BASEBALL CARDS | BOX PLOTS | CARTOONS, ICONS AND SYMBOLS | DISTRIBUTION PLOTS | DOT CHARTS AND FOREST PLOTS

INTERACTIVE GRAPHICS | LINE GRAPHICS | PICTOGRAM | PIE CHARTS | RISK LADDERS AND RISK SCALE | SCATTER PLOT | TABLES | TREE DIAGRAM | STATISTICAL MAPS

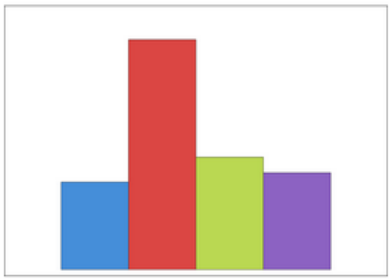
Introduction

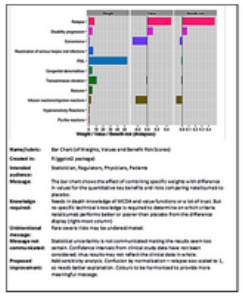
There are many ways in which benefits and risks are presented and communicated. There is an absence of a consensus on which visual representations are most suitable to display benefit-risk profiles.

The visual representation of benefits and risks review has been conducted in two stages. The first stage provided a level of evaluation as to the suitability of visuals presented in the application of benefit-risk approaches in PROTECT methodology review. However, external circumstances such as the intended audience, complexity of the benefit-risk problem, time in drug lifecycle, and other factors that are not related to the benefit-risk methodology may influence the type of visual representation to use. The second stage therefore explored and identified suitable visuals to communicate benefits and risks to different stakeholders in different situations. This included the use of visualisations in dynamic and interactive settings.



Area graph and volume chart


Bar chart/graph


Baseball cards

- Appraisal of visual representations used in benefit-risk assessment

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INTERACTIVE GRAPHICS | LINE GRAPHICS | PICTOGRAM | PIE CHARTS | RISK LADDERS AND RISK SCALE | SCATTER PLOT | TABLES | TREE DIAGRAM | STATISTICAL MAPS

- Introduction
- Flow chart of systematic review literature screening
- Flow chart to illustrate BR score
- Simple descriptive table
- BRAT master data summary table
- BRAT key benefit-risk summary table ✓
- Value function for continuous variable
- Value function for categorical variable
- Line graph of two-way sensitivity analysis
- BRAT value tree

Section 6 BRAT key benefit-risk summary table

Natalizumab versus Placebo (Comparator) at time of CHMP re-evaluation

	Outcome		Natalizumab Risk / 1000 pts	Comparator Risk / 1000 pts	Risk Difference (95% CI)/ 1000 pts	
Benefits	Convenience Benefits	Convenience (weight 0.6%)	-	-	-	(-, -)
	Medical Benefits	Relapse (weight 3.9%)	280	540	-260	(-326, -195)
		Disability Progression (weight 5.6%)	110	230	-120	(-, -)
Risks	Infection	Reactivation of serious herpes viral infections (weight 6.7%)	80	70	10	(-26, 45)
		PML (weight 55.9%)	2	0	2	(-, -)
	Liver Toxicity	Transaminases elevation (weight 11.2%)	50	40	10	(-16, 38)
	Reproductive Toxicity	Congenital abnormalities (weight 5.6%)	-	-	-	(-, -)
	Neurological Disorders	Seizures (weight 5.6%)	0	0	0	(-, -)
	Other	Infusion/Injection reactions (weight 2.8%)	236	180	56	(6, 114)
		Hypersensitivity reactions (weight 1.1%)	90	40	50	(20, 82)
		Flu-like reactions (weight 1.1%)	399	400	-1	(-114, 114)

Higher for Natalizumab
Higher for Comparator

- Seventeen recommendations for the application of visuals at key stages proposed
- Interactive version of visual review (Mt-Isa et al, Part 1 & Part 2; 2013)

- Each case study applied several methodologies and visual representations
- Interactive summary of Case Study Reports:
  - Efalizumab (Micaleff et al Wave 1 & Suppl 1; Phillips et al Suppl 2; 2013)
  - Natalizumab (Nixon et al Wave 1 and Wave 2, 2013)
  - Rimonabant (Juhaeri et al Wave 1; Mt-Isa et al Suppl 1; Juhaeri et al Wave 2, 2011/2012)
  - Rosiglitazone (Philips et al Wave 2, 2013)
  - Telithromycin (Quartey et al Wave 1, 2012)
  - Warfarin (Hallgreen et al, Wave 2, 2013)

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Patient And Public Involvement

- What is Patient and Public Involvement?
- What is the Patient and Public Involvement project? ✓
- What is benefit-risk assessment
- How benefit-risk assessment is done: our experiences
- How we found out what is important to patients: an example
- How can we display benefits and risks?
- A case study of visual preferences in obese adults

What is the Patient and Public Involvement project?

The Patient and Public Involvement project was a working group in PROTECT Benefit-Risk. We were created following a strong interest in patient and public involvement (PPI) from the PROTECT Benefit-Risk case study task forces. Our aim was to develop a toolbox for those who wish to involve patients and the public in medical benefit-risk decision making. Our technical report can be found on the IMI PROTECT website (http://www.imi-protect.eu/benefitsRep.shtml).

Our research focussed on three areas of involving patients and the public: (a) testing formal methods which can be used to value the benefits and risks of medicines, (b) testing out different visual images to see if they are understandable, trustworthy, and useful , and (c) understanding how to communicate the process and results of benefit-risk assessment.

We developed this section of the website to provide information to patients and the public and professionals who are interested and would like to learn more about the benefit-risk assessment of medicines. We would like to thank the following organisations for reviewing the content on this section of the PROTECT benefit-risk website: organisations name should be added here.

- A guide for patients and interested members of the public who are new to the benefit-risk assessment of medicines or would like to know more
  - Example case-study on "visual communication of the benefits and risks of weight loss interventions"

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HOME | RECOMMENDATIONS | METHODS | VISUALISATIONS | CASE STUDIES | PATIENT AND PUBLIC INVOLVEMENT | ABOUT US | LINKS AND GLOSSARY

About Us

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT), a collaboration amongst private and public sector partners, is a project set up under the Innovative Medicines initiative (IMI). Its goal is to strengthen the monitoring of the benefit-risk balance of medicines in Europe. This website is developed as part of the PROTECT Benefit-Risk Group who has advanced the understanding of both the integration, communication and visual representations of benefit and risk assessment methodologies.
PROTECT Benefit-Risk aims to provide practical recommendations for benefit-risk decision processes and supporting tools to various stakeholders, particularly the regulators.
We advocate for increased transparency and robust decision making by making explicit and effectively communicating the methodologies, assumptions, and outcomes utilised in the assessment of benefit-risk balance in medicine. Our experience makes what we believe is a unique contribution that complements and builds on the efforts of other benefit-risk assessment initiatives.

Our Team


Professor Deborah Ashby


Dr Alain Micaleff


Dr Steve Hobbiger


Dr Diana Hughes


Dr Ioanna Tzoulaki


Dr Shahrul Mt-Isa


Gerry Downey


Dr Ian Hirsch


Dr Richard Nixon


Dr Kimberley Hockley


Ed Waddingham


Alesia Goginsky

LINKS AND GLOSSARY

REPORTS AND DATABASES

PUBLICATIONS

PRESENTATIONS

GLOSSARY AND REFERENCES

Glossary

Term	Description
Approach	The system of methods and principles used in a particular discipline
Aseptic meningitis	A syndrome characterized by headache, neck stiffness, low grade fever, and CSF lymphocytic pleiocytosis in the absence of an acute bacterial pathogen. Viral meningitis is the most frequent cause although mycoplasma, and rickettsia infections; diagnostic or therapeutic procedures; neoplastic procedures; septic perimeningeal foci; and other conditions may result in this syndrome. (From Adams et al., Principles of Neurology, 6th ed, p745)
Aspect ratio	The ratio of the lengths of the two axes on a graph; a square graph has an aspect ratio of 1
Benefit	The positive results of a given treatment for an individual or a population (i.e., efficacy, convenience, or even quality of life)
Benefit-risk assessment	An evaluation of medical product either quantitatively or qualitatively taking both benefits and risks of the product into account
Benefit-risk model	A formal way to analyse benefit and risk consequences and their balances from a set of actions and to aid making choices amongst actions when risk aversion and preferences are specified
Bias	The systematic tendency of any factors associated with the design, conduct, analysis, and evaluation of the results of a benefit-risk assessment to make the estimate of a treatment effect deviate from its true value

- Links to all published reports from IMI PROTECT Benefit Risk.
- Complete Glossary, Abbreviations and References also provided.

Questions …

An online space has been created so that findings and recommendations can be explored interactively and will continue once PROTECT closes following this symposium.

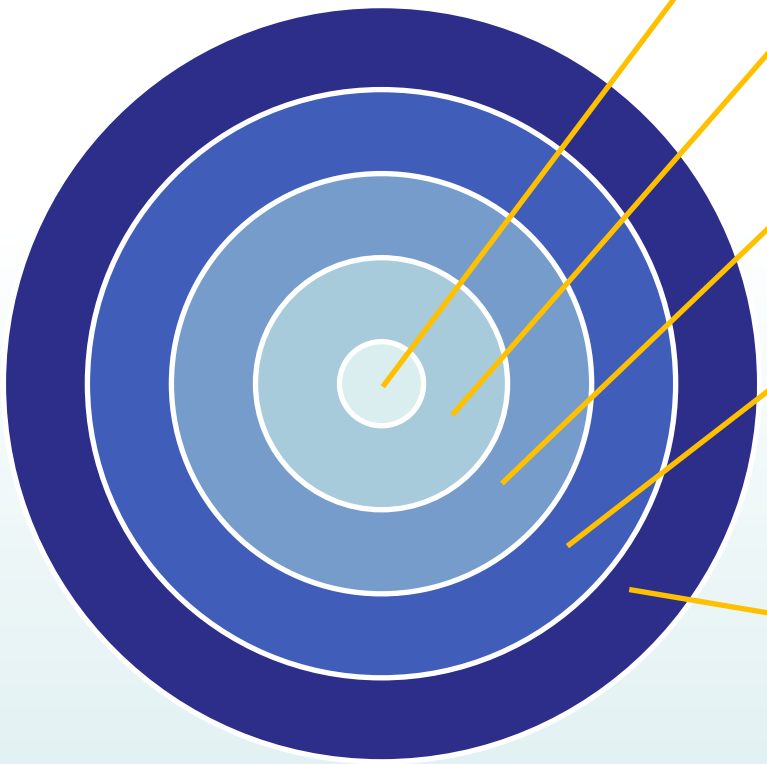
Thank you from the IMI PROTECT Benefit-Risk Team (http://protectbenefitrisk.eu/)

COFFEE/TEA BREAK
20’

Ed Waddingham

PATIENTS AND PUBLIC INVOLVEMENT IN BENEFIT-RISK ASSESSMENT AND DECISION-MAKING: METHODS AND APPLICATIONS

Decision makers



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

Patient and public involvement

Patient and public:

Clinical trial participants, patients and potential patients, disabled people, parents and guardians, people who use health and/or social care services, carers, members of the public, and the organisations who represent the interests of these consumers.

Involvement:

An active partnership between stakeholders in the research process, rather than the use of people as 'subjects' of research. Public involvement in research is often defined as doing research 'with' or 'by' the public, rather than 'to', 'about' or 'for' them.

Varying degrees of involvement

Consultation

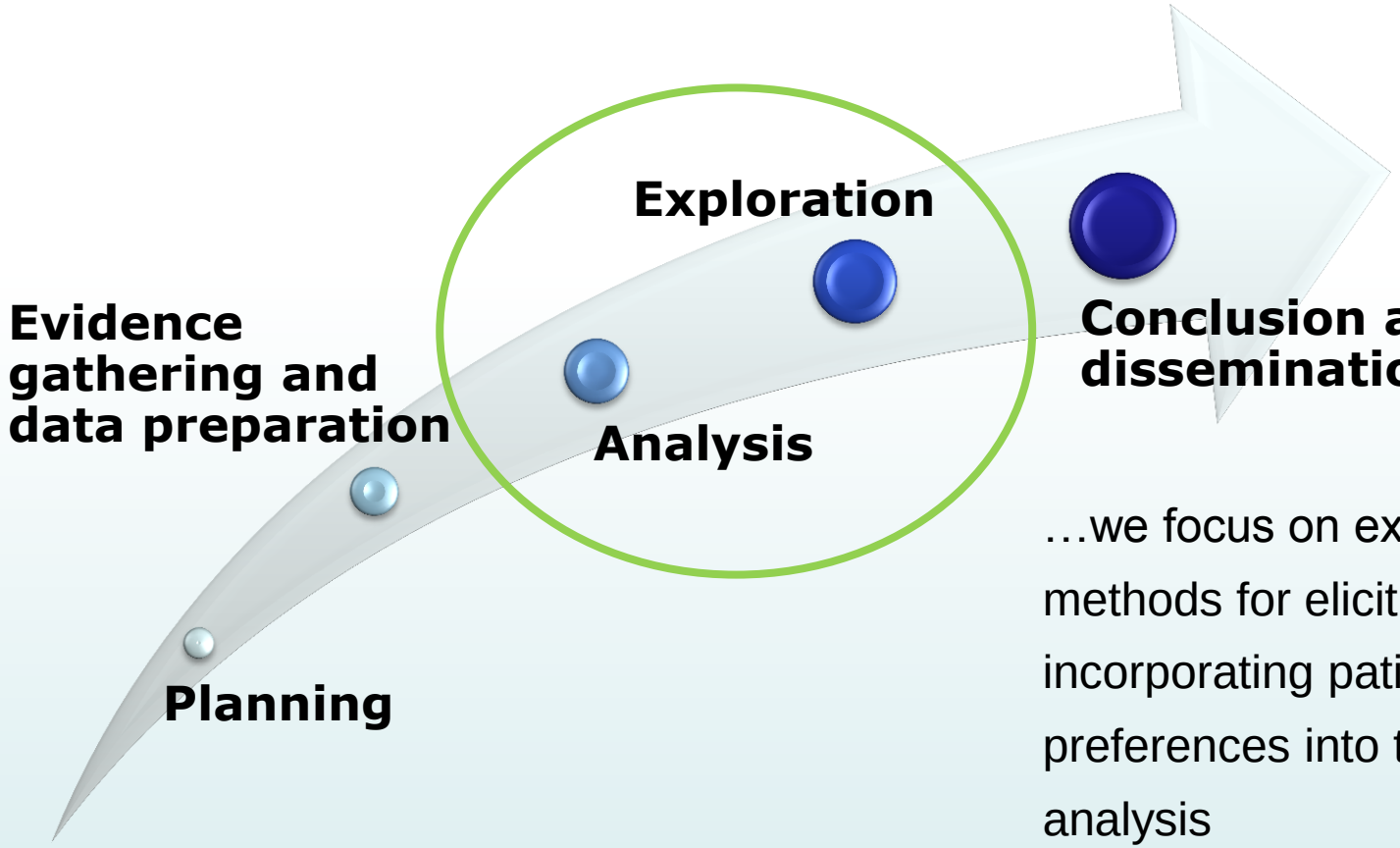
Health professionals elicit the patient and public perspective to inform the decision making process

Collaboration

Health professionals and patients and the public form an active partnership and jointly participate in decision making

At what stage can PPI occur

There is scope for patients and the public to be involved throughout the BR assessment process…



…we focus on explicit methods for eliciting & incorporating patient preferences into the analysis

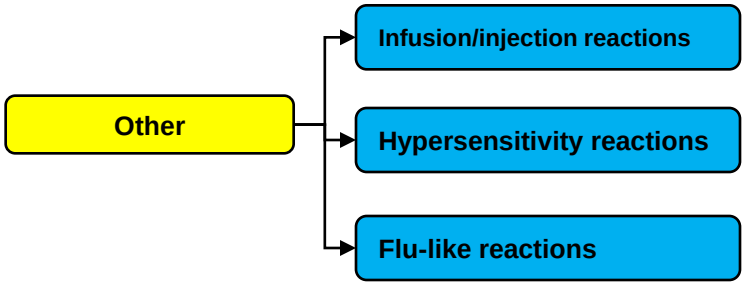
Preference elicitation

- Well-known methods for preference elicitation:
  - MCDA swing-weighting (multi-criteria decision analysis)
  - MACBETH (Measuring Attractiveness by a Categorical Based Evaluation Technique)
  - AHP (Analytic Hierarchy Process)
  - DCE (Discrete Choice Experiment)

Simple weighting

Multi Criteria Decision Analysis (MCDA)

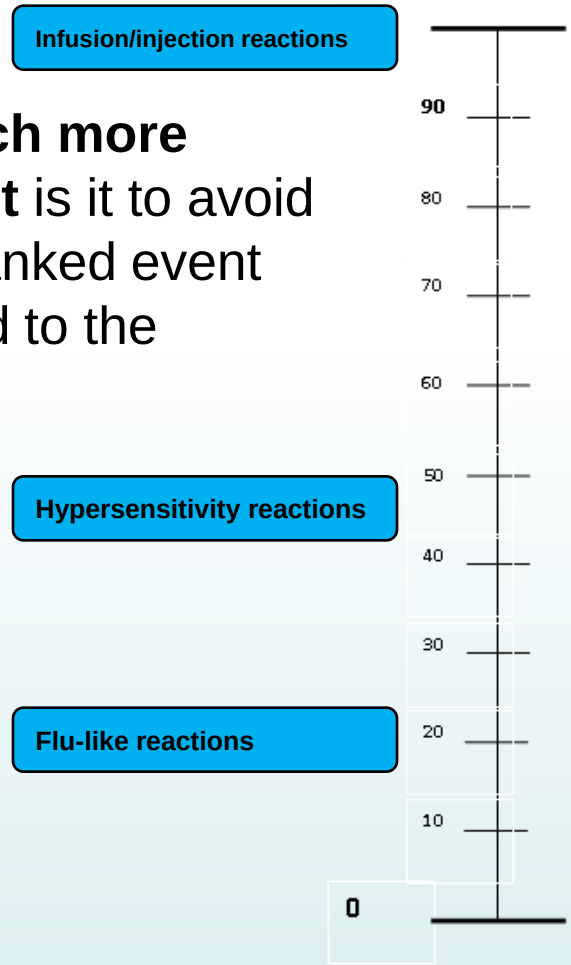
For each outcome category



1. Rank outcomes

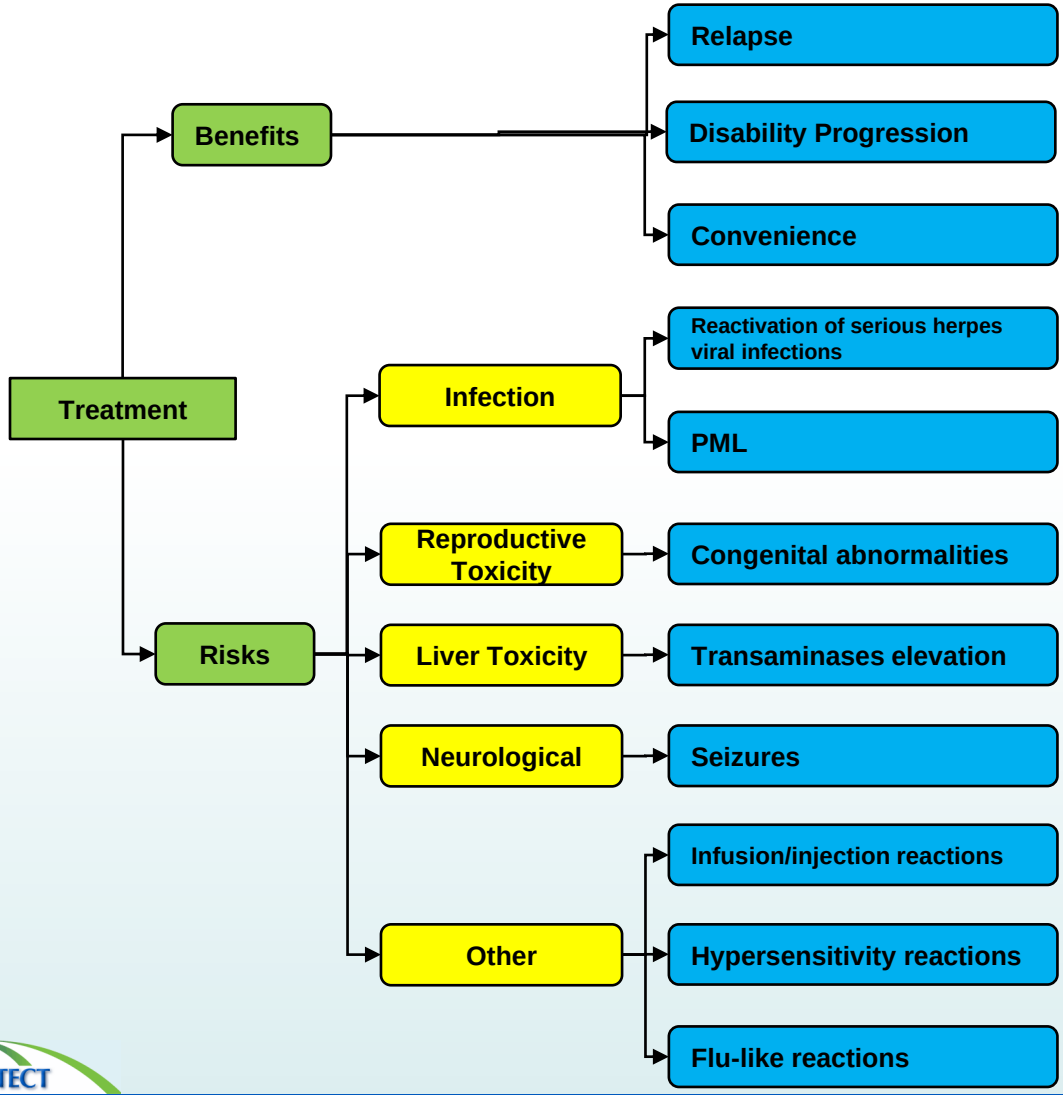
Outcome	Rank
Infusion/injection reactions	1
Hypersensitivity reactions	2
Flu-like reactions	3

2. Relative importance



Repeat this process all the way up the value tree

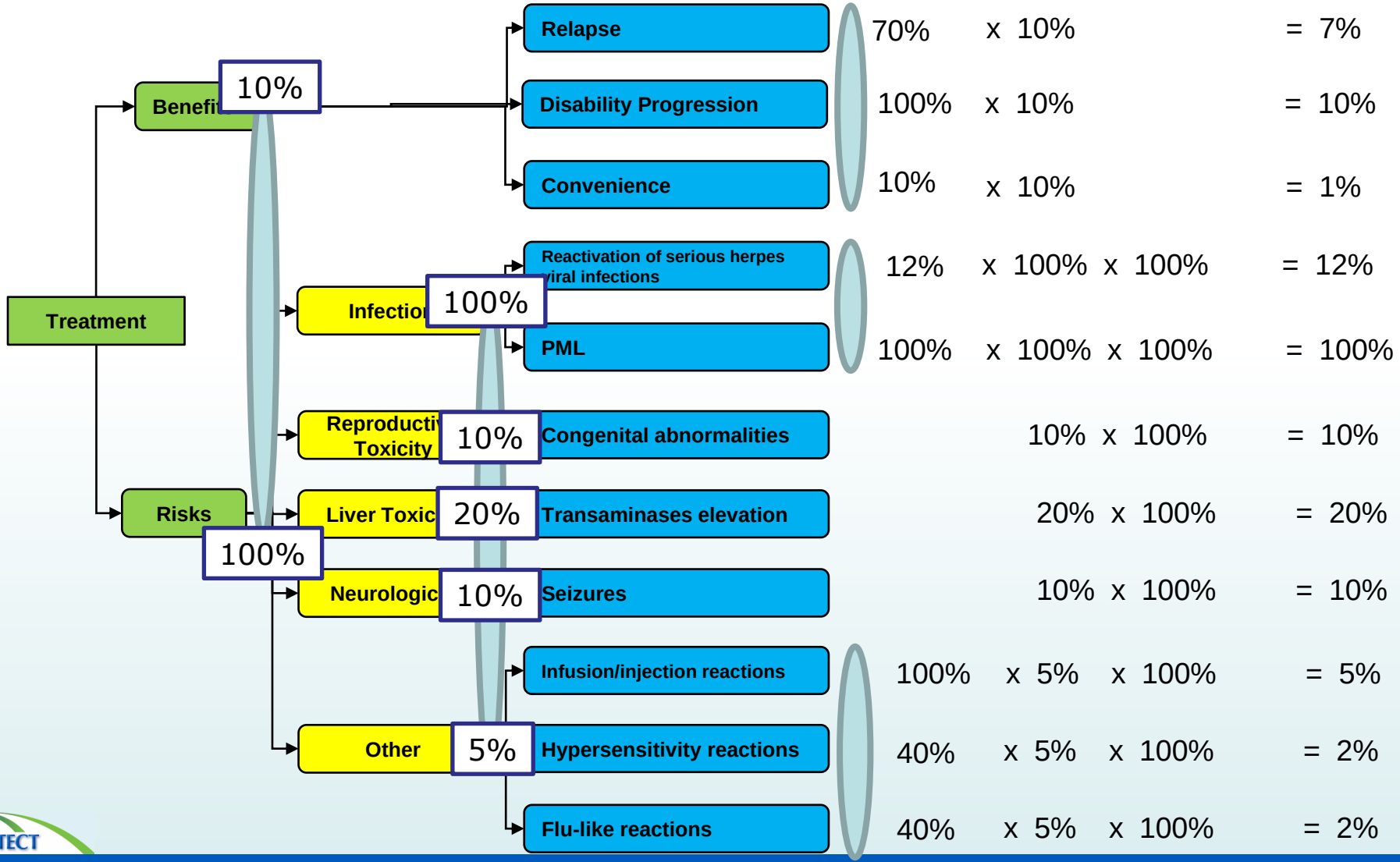
The top ranked outcome in each category is carried up the tree



- Move bottom-up through the tree and compare the **top-ranked** outcomes from each category
- Finally, the top-ranked benefit is compared to the top-ranked risk
- The individual weights for each outcome can then be calculated

Repeat this process all the way up the value tree

The top ranked outcome in each category is carried up the tree



MACBETH (Measuring Attractiveness by a Categorical Based Evaluation Technique)

Qualitative assessment

- MACBETH is similar to MCDA, except that it provides a different way to get the weights
- **Step 1**: **Qualitatively** assess relative attractiveness of outcomes on **pairwise** basis
- **Step 2**: Check consistency of answers (eg cannot have A>B>C>A)
- **Step 3**: Compute initial guess at weights with optimization
- **Step 4**: Refine weights while maintaining consistency

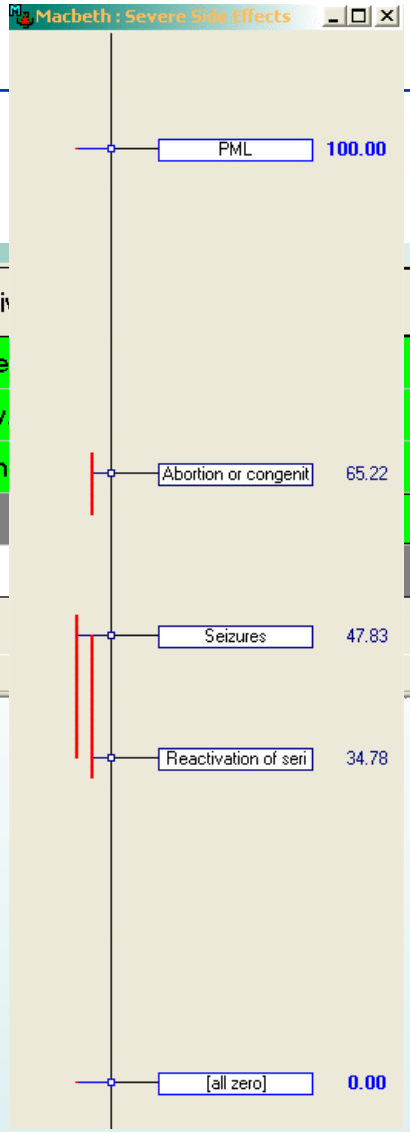
MACBETH

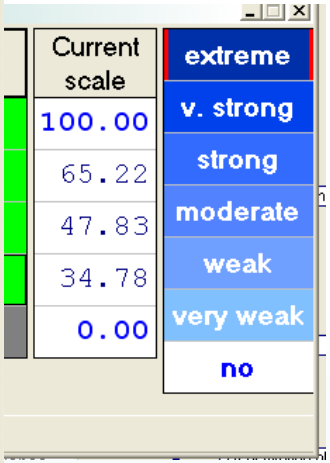
Qualitative assessment

Macbeth : Severe Side Effects

	PML	Abortion or congenit	Seizures	Reacti
PML	no	extreme	extreme	e
Abortion or congenit		no	strong	v
Seizures			no	m
Reactivation of seri				
[all zero]				

Consistent judgements



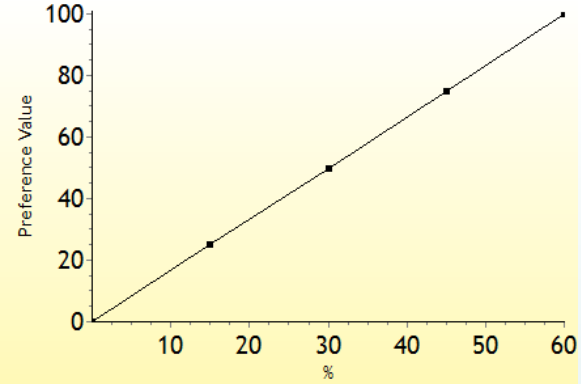


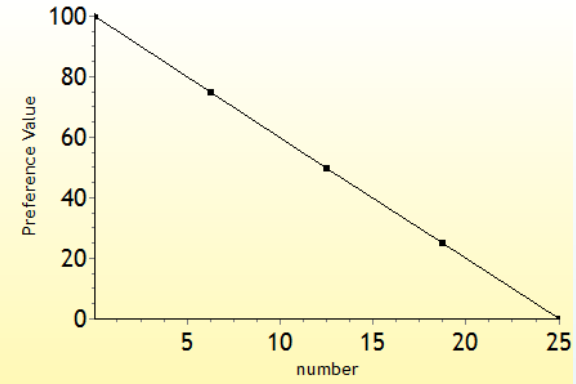
AHP (Analytic Hierarchy Process)
Qualitative assessment

- Based on qualitative pairwise comparisons (similar to MACBETH)
- No consistency check, but rather a score
- Qualitative responses are translated to a quantitative scale (integers from 1 to 9)
- Weight is calculated by finding the dominant eigenvector of the corresponding matrix, or by regression

Weighting individual events has its limits

- Examples so far involved trade-offs between individual events (eg 1 relapse vs 1 disability progression vs 1 case PML)
- This implies that events of a given type are all equal in value i.e. linear (partial) value functions

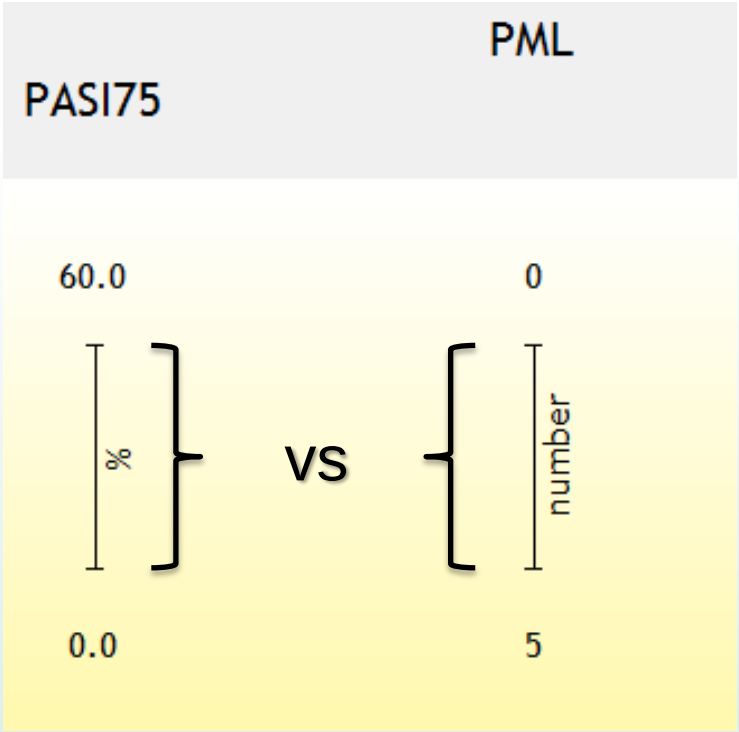




- It can be difficult to trade off events that are very different in importance (eg 1 infusion/injection reaction vs 1 case PML)

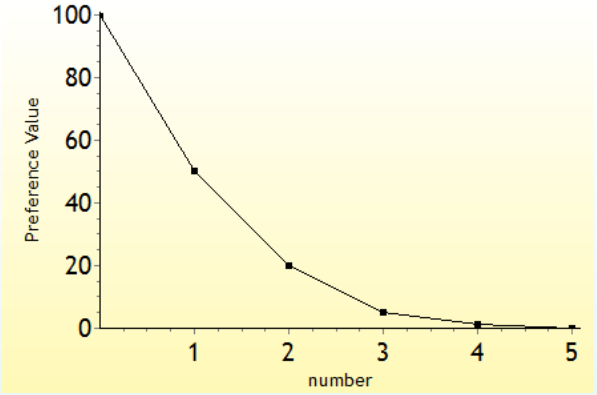
Swing weighting (1)

- Set best and worst possible figure for each outcome
- How much more attractive is it to move from worst to best for outcome A vs moving from worst to best for outcome B?



Swing weighting (2)

- Allows non-linear (partial) value functions (these can be elicited in the same way as weights)
- Helps to establish common value scale for events that are different in importance

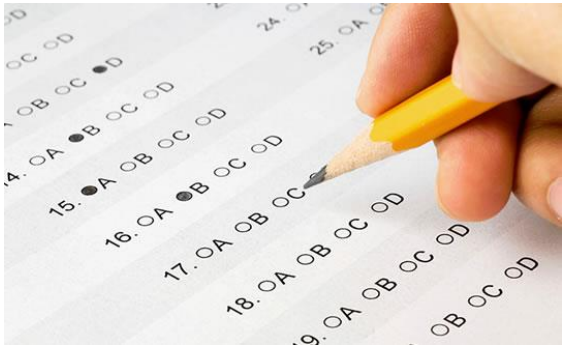


Errors to watch out for:

- **Not communicating swings clearly to participants**
- **Not accounting for swings correctly during benefit-risk assessment**

Discrete Choice Experiments (DCEs)

In A DCE, participants are asked to consider a number of choice scenarios, eg:



Attributes

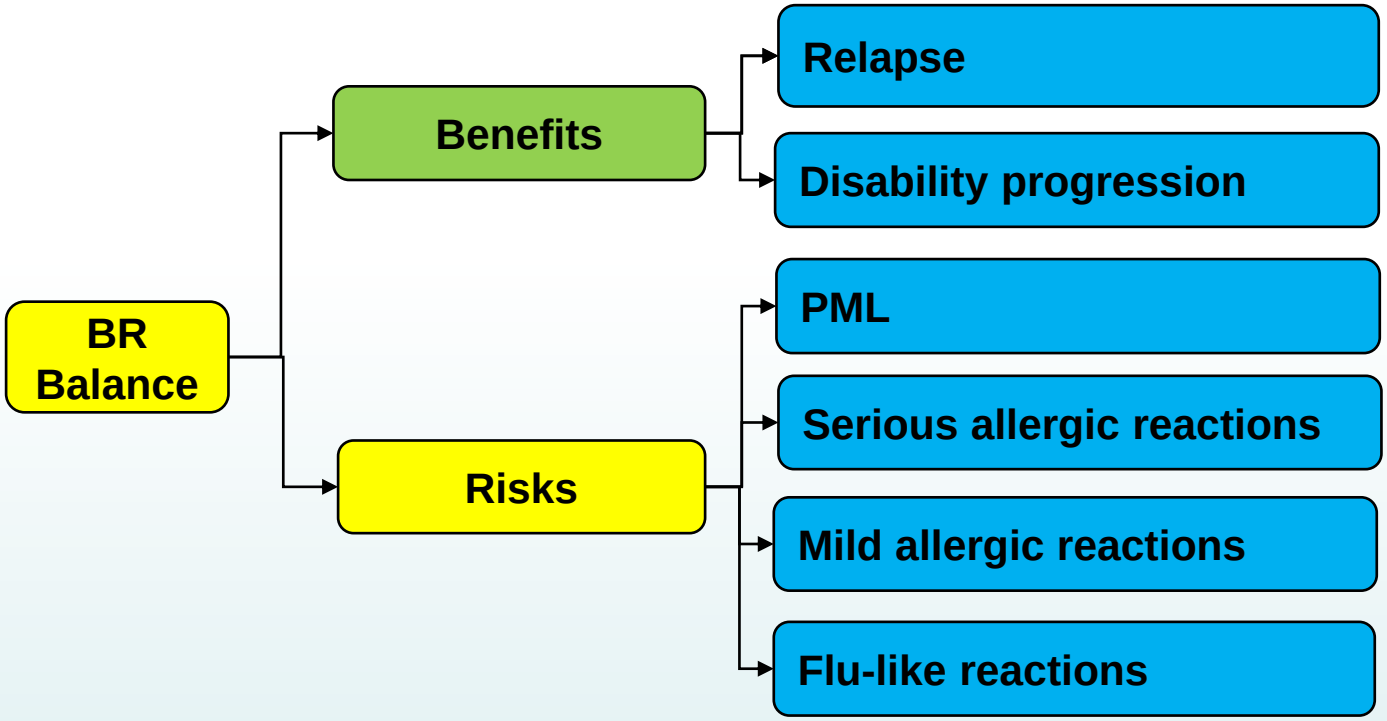
Car A	vs	Car B
• Manufacturer: Maserati		• Manufacturer: Vauxhall
• Price: £££££		• Price: £££
• Mileage: 0		• Mileage: 10,000
• Fuel efficiency: Poor		• Fuel efficiency: Good

Levels

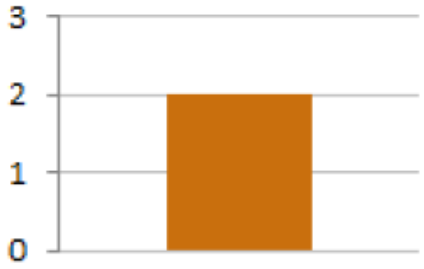
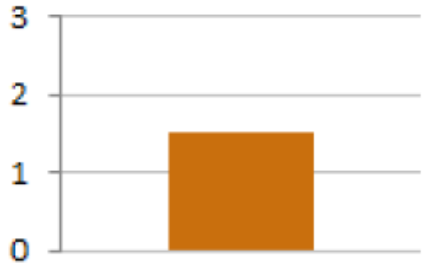
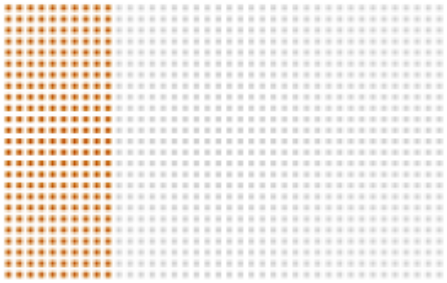
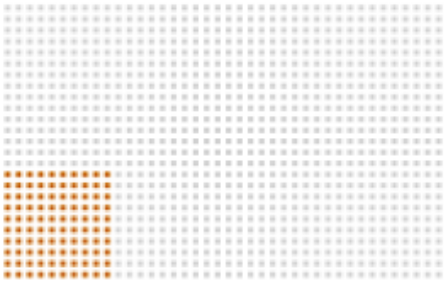
Which car would you choose?

Natalizumab DCE

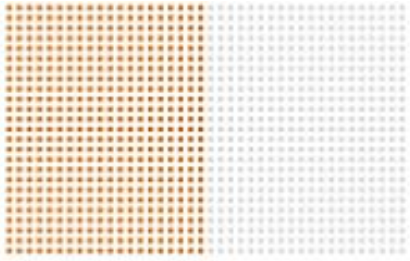
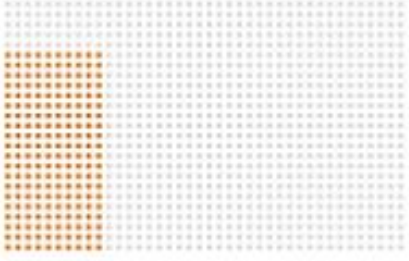
6 attributes, 2 levels each



Natalizumab DCE: questionnaire (1)

Outcome *(measured over 2 years)*	**Treatment A**	**Treatment B**
Number of relapses per patient	2 relapses 	 1 to 2 relapses
Disability progression	250 patients out of 1000 	 100 patients out of 1000
PML	3 patients out of 1000	0 patients out of 1000

Natalizumab DCE: questionnaire (2)

Mild allergic reactions	0 patients out of 1000			500 patients out of 1000
Serious allergic reactions	0 patients out of 1000			0 patients out of 1000
Depression	200 patients out of 1000			100 patients out of 1000
Which would you prefer? *(Please tick one)*	☐ **Treatment A**		☐ **Treatment B**	

DCE design – technical considerations

- Need to specify utility/value model based on multiple attributes - not restricted to linear additive models (unlike other methods such as MCDA)
- The required number of attributes and levels depends on the model that is chosen and the required level of precision
- Balance with reasonable limit on number of questions

DCE design – burden on participants

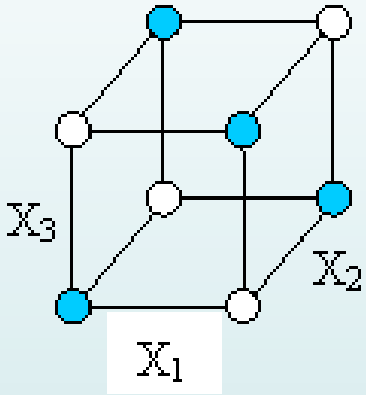
- Cognitive strain becomes an issue in all but smallest DCEs
- Need to limit number of attributes, alternatives, choice sets
- Plus usual need to ensure task & key background info is understood
- Validation questions can be included

DCE design – full / fractional factorial

- **Full factorial**: uses all (!) possible combinations of attribute levels

  # combinations = A^L if all A attributes have L levels

- **Fractional factorial**: uses a subset of the possible combinations of attribute levels
  - Not all fractional factorial designs are equally efficient
  - Efficient designs exhibit various kinds of symmetry:
    - Level balance
    - Orthogonality
    - Minimal overlap
    - Utility balance



Fractional factorial designs: like working out the dimensions of a box given the locations of some of the corners

Comparative overview of elicitation methods

	Swing-weighting	MACBETH	AHP	DCE
Responses	Quantitative	Qualitative	Qualitative or quantitative	Qualitative
How is consistency measured?	Method ensures consistency	Inconsistencies must be resolved	Computes a consistency score	Reflected in uncertainty of estimates
Weight calculation	Direct	Linear optimisation (plus tuning)	Principal eigenvector	Regression
Can be given out as a paper questionnaire?	No	No	Yes	Yes

Conclusions

- Eliciting patient preferences in regulatory assessment can add value and lead to more clinically relevant decisions
  - Political legitimacy, transparency, trust, communicability
- A number of formal methods can be used to elicit patient preferences
  - Each methodology has its own features, strengths and weaknesses
  - The PPI work from PROTECT is still ongoing…

Andrea Beyer, PhD

ELICITING PATIENT PREFERENCES: APPLYING DECISION THEORY TO HEALTH RESEARCH

Contents

- Why collect patient preferences?
- Decision Analysis
- Visualize Sub-study: eliciting patient preferences
- Study design
- Building Value Function
- Eliciting Weights
- Planned analysis
- Summary

Importance of Patients' Perception for Treatment Decisions

Regulators' view:
An increased cure rate in cancer, a potentially life-saving treatment will always outweigh a grade 1 or 2 AE (e.g. (permanent hair loss) - positive regulatory decision

Some patients' view:
This permanent hair loss is important, severe enough for me to decline the potentially curative and life-saving adjuvant therapy – negative treatment decision

"The mastectomy and loss of breast are NOTHING compared to the loss of my hair."

"Not a day goes by that I don't regret doing the NN (therapy). Oh, if we could only turn back the hands of time!"

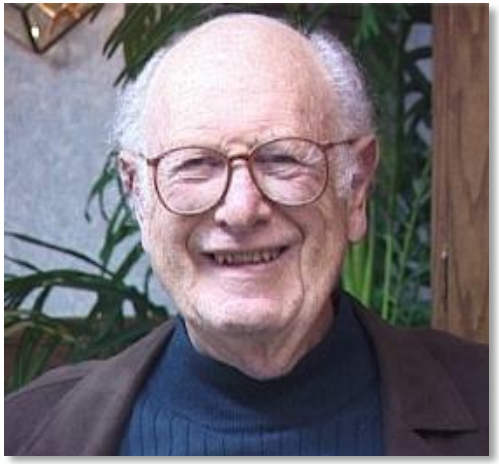
"I* never, never, never *would have agreed to take NN if I was informed of this 6.3% risk; even a 3% risk…or any risk…"

How to bring patient preferences/values into BR decisions?

- Patients with the specific disease condition know which outcomes and symptoms matter most to them
- Patients enrolled in regulatory drug trial are (ideally) the target group for treatment once a drug is licensed, yet we do not explore their values and preferences in a systematic way
- In terms of listening to the patients' voice, trial patients are an underutilized source

G. Rasi, AIFA, 2013

Can Decision Analysis Help?



"The spirit of decision analysis is divide and conquer:

decompose a complex problem into simpler problems, get one's thinking straight on these simpler problems, paste these analyses together with logical glue, and come out with a program of action for the complex problem"

(Howard Raiffa 1968, p. 271)

Visualizing Uncertainty Among Laypersons and Experts (VISUALizE)

- Objective:

  To evaluate the use of the MACBETH (**M**easuring **A**ttractiveness through a **C**ategorical **B**ased **E**valuation) software for the elicitation of patient preferences using a simple pair-wise comparison between treatment outcomes

  - determine value functions for disease attributes
  - assess weights between disease attributes (trade-offs)
- Design
  - Web-based study among patients with diabetes, atrial fibrillation
  - Supported by the NICR UK, Dutch hospitals, and Laser who recruited patients and healthcare professionals

Participant recruitment

- Target for MACBETH:1800
- Study population:
  - Patients
  - Healthcare professionals
  - Regulators supporting CHMP & PRAC
- 3 countries
  - United Kingdom
  - The Netherlands
  - France

Steps to building an elicitation procedure*

- Determine the outcomes of interest
- For each outcome determine levels, ranging from best case to worst case
- Create the value elicitation section of the questionnaire
- Create the weighting elicitation section
- Collect data from patients and convert the qualitative responses of patients to quantitative scores
- * Seek patient input/confirmation for steps 1-4

Examples of Treatment Outcomes and Levels for Atrial Fibrillation

Treatment outcome	Levels
Ischemic Stroke	No patients developing ischemic stroke
	1% of patients developing ischemic stroke
	2% of patients developing ischemic stroke
	3% of patients developing ischemic stroke
	4% of patients developing ischemic stroke
Myocardial Infarction	No patients developing myocardial infarction
	1% of patients developing myocardial infarction
	2% of patients developing myocardial infarction
	3% of patients developing myocardial infarction
	4% of patients developing myocardial infarction
Major bleeding	No patients developing a major bleed
	2% of patients developing a major bleed
	4% of patients developing a major bleed
	6% of patients developing a major bleed
	8% of patients developing a major bleed
Minor bleeding	15% of patients developing a minor bleed
	20% of patients developing a minor bleed
	25% of patients developing a minor bleed
	30% of patients developing a minor bleed
	35% of patients developing a minor bleed

Building a value scale for “Minor bleeding”

15% of patients with minor bleeding

20 % of patients with minor bleeding

25 % of patients with minor bleeding

30 % of patients with minor bleeding

35% of patients with minor bleeding

What is the difference in value between

15% of patients and **20% of patients** with a minor bleeding?

Building a value scale for “Minor bleeding”

Strong

15%

20%

25%

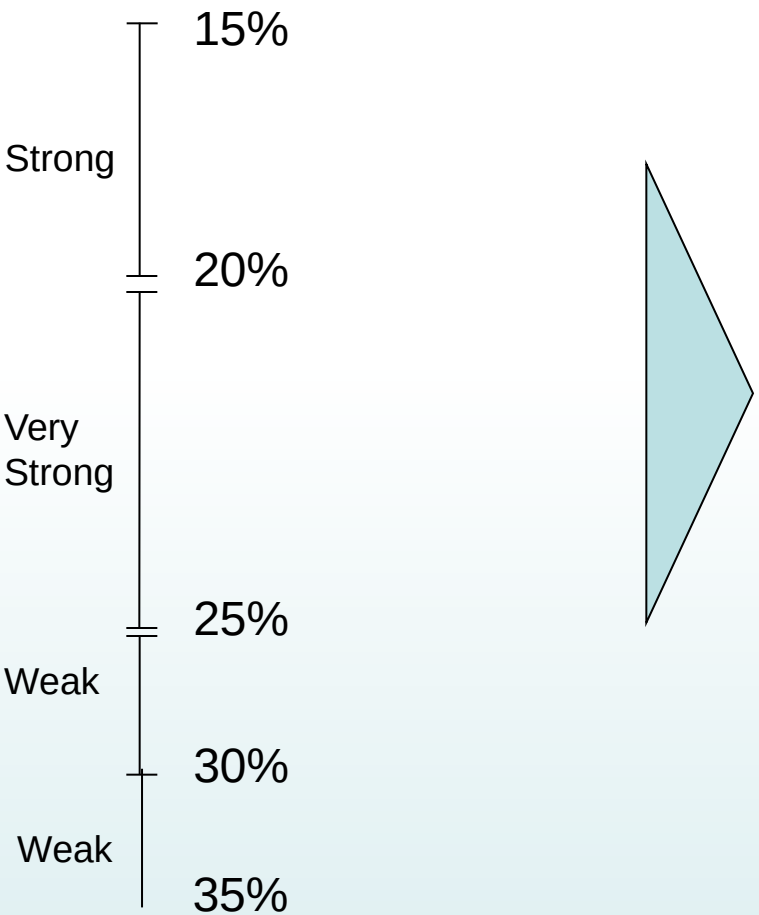
30%

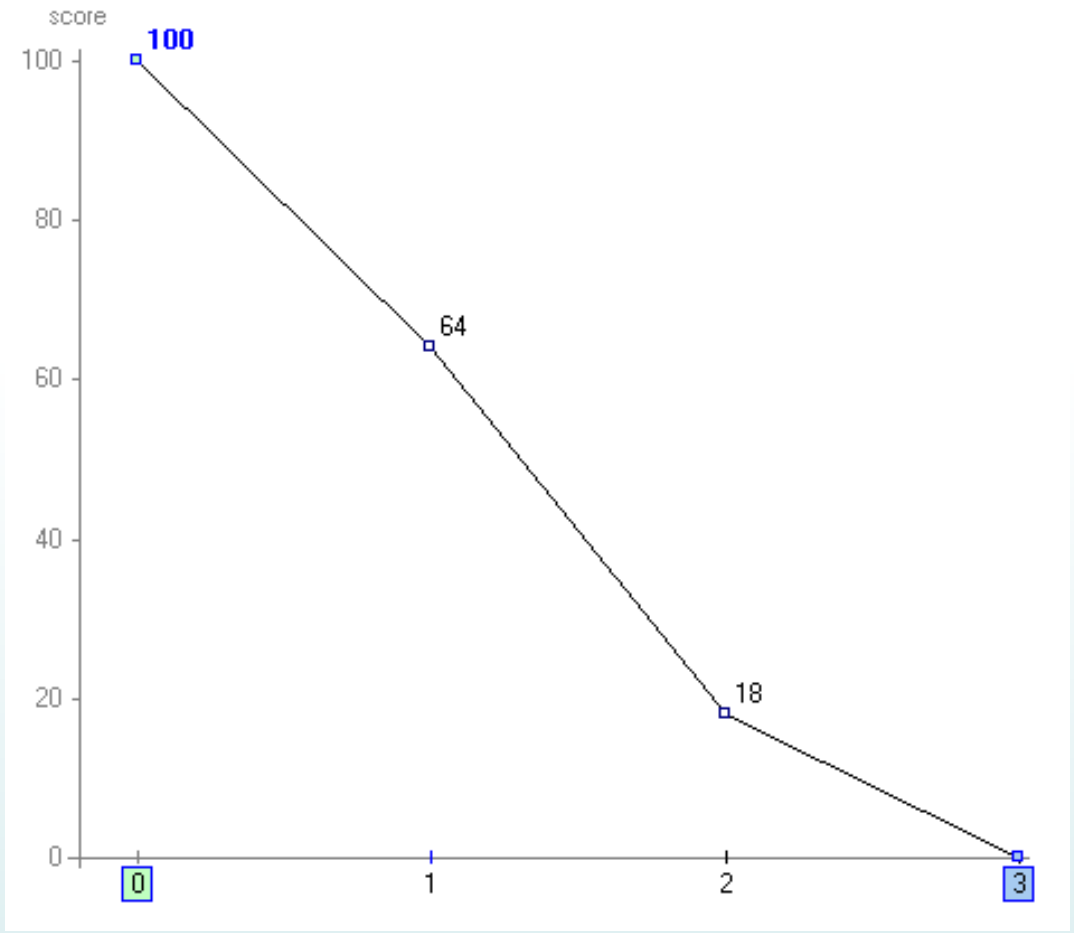
35%

What is the difference in value between

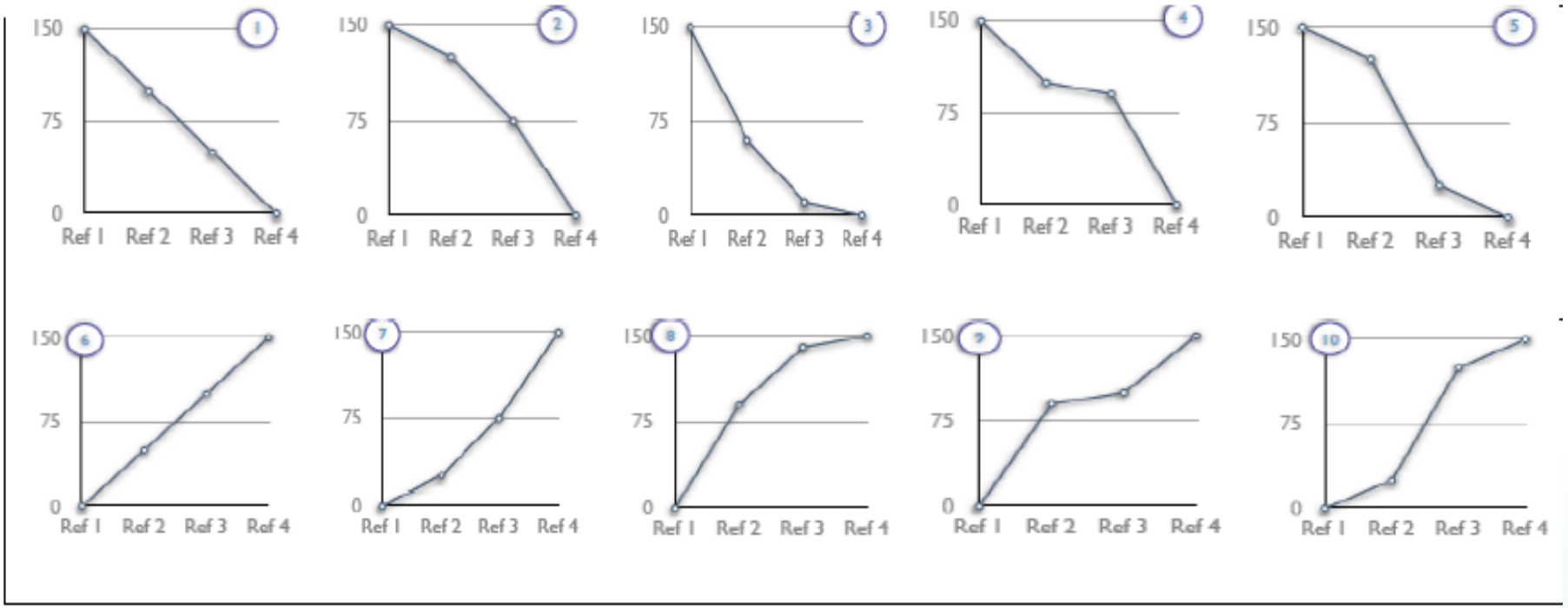
15% of patients and **20% of patients** with a minor bleeding?

Building a value scale for “Minor bleeding”



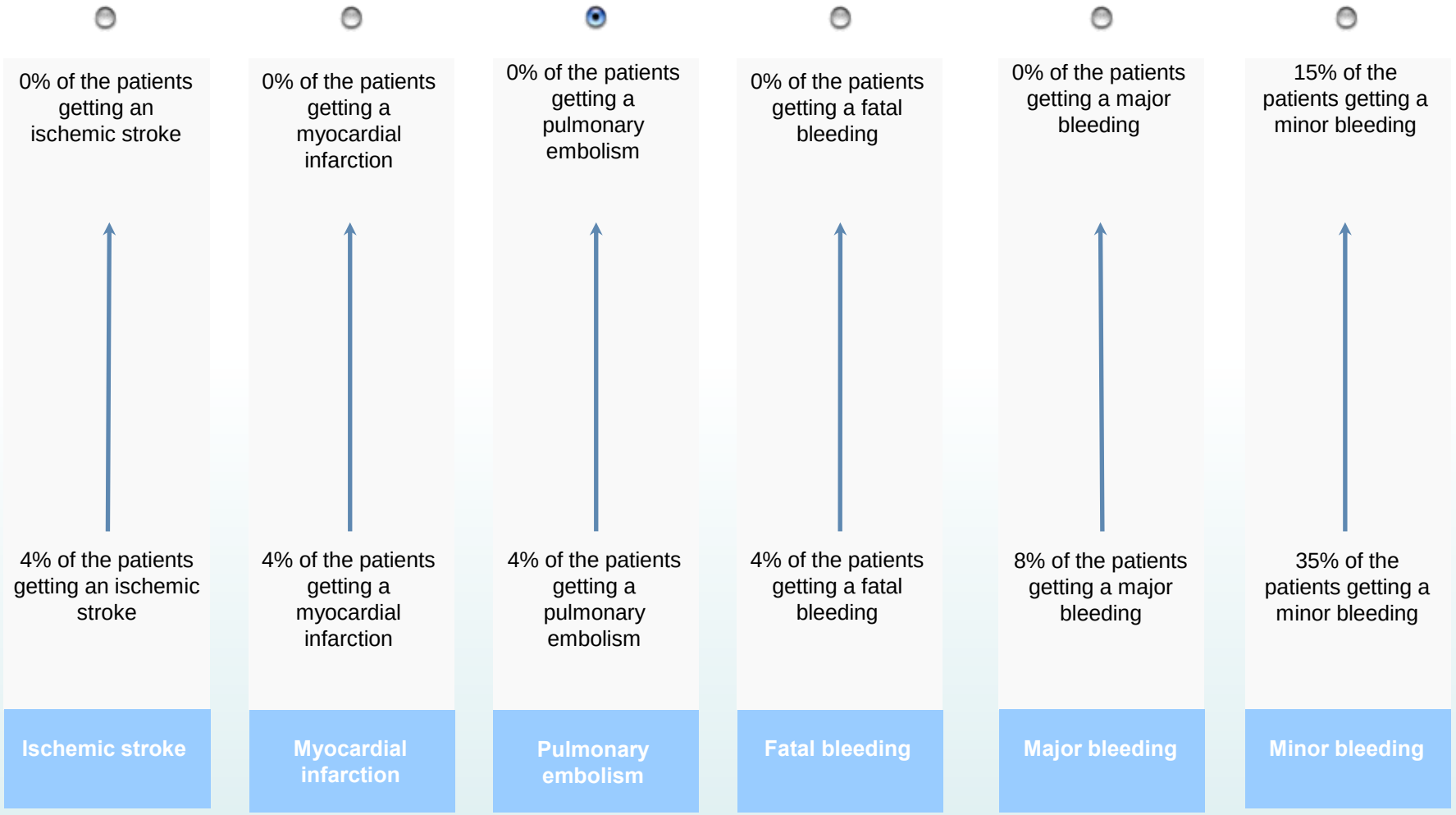


Value Function Profiles

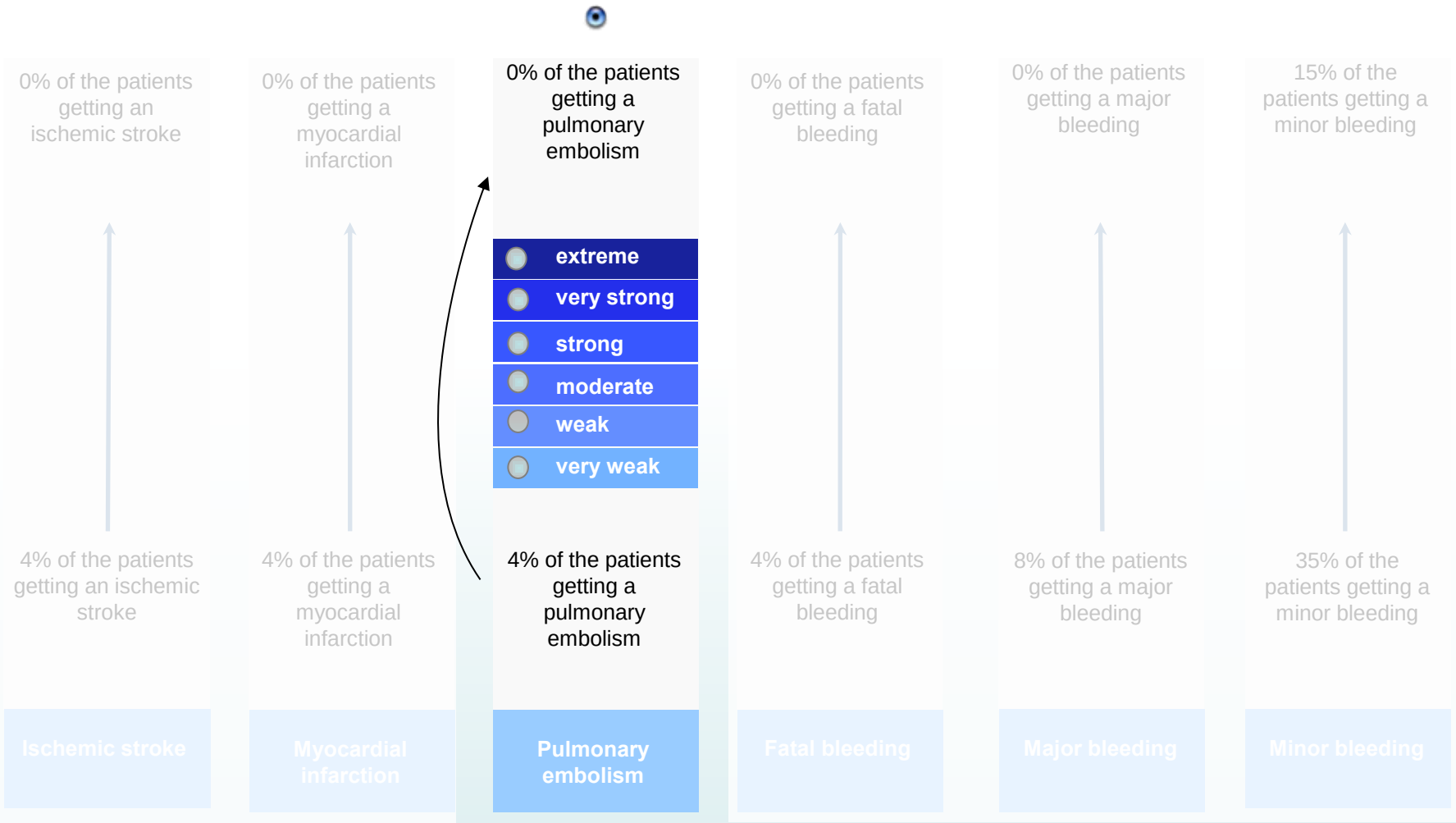


Value functions will fit one of these 10 profiles

If you could increase one treatment effect from it's worst value (on the bottom) to it's best value (on the top), which one would you increase?



How desirable is this improvement?



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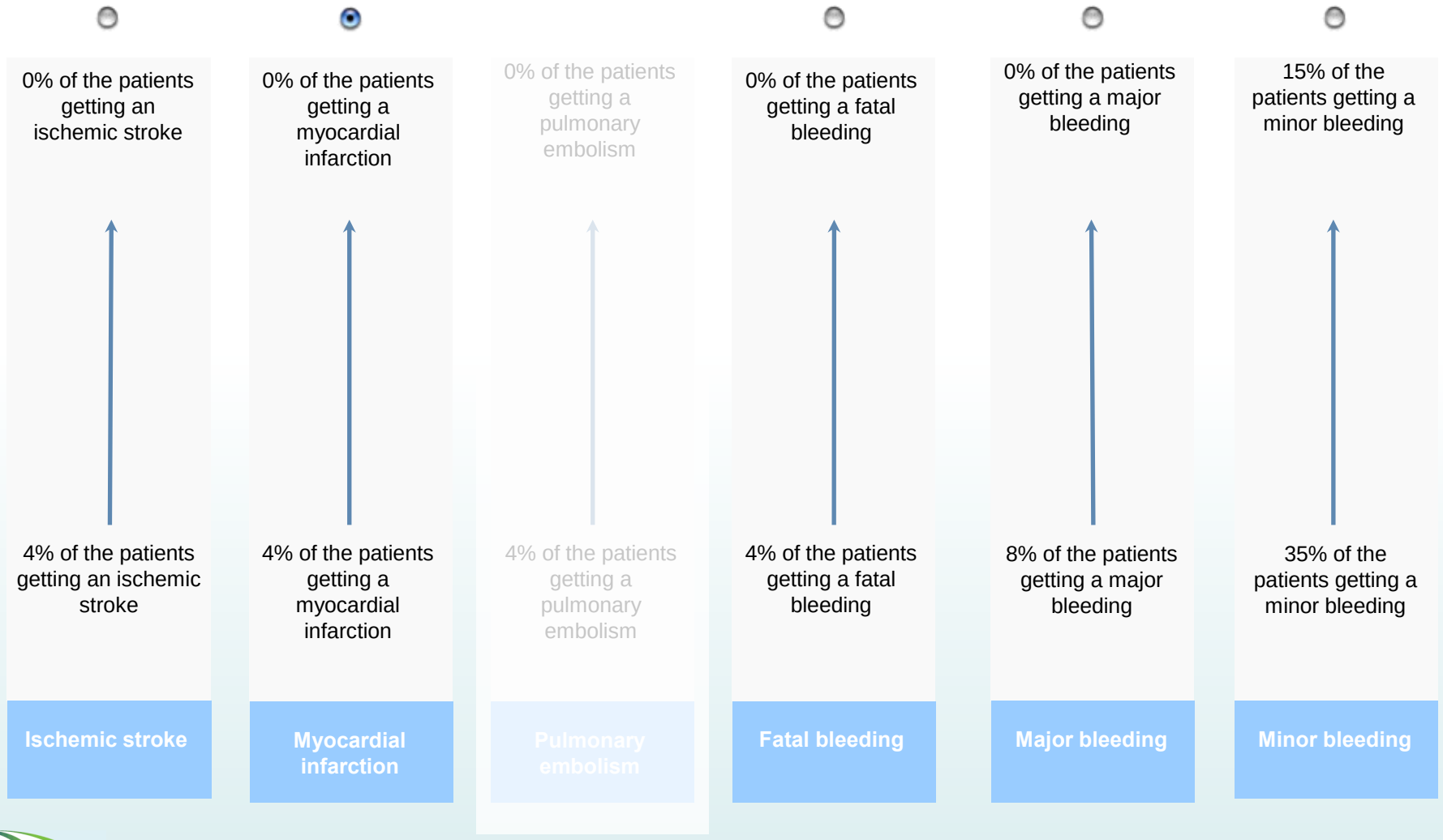
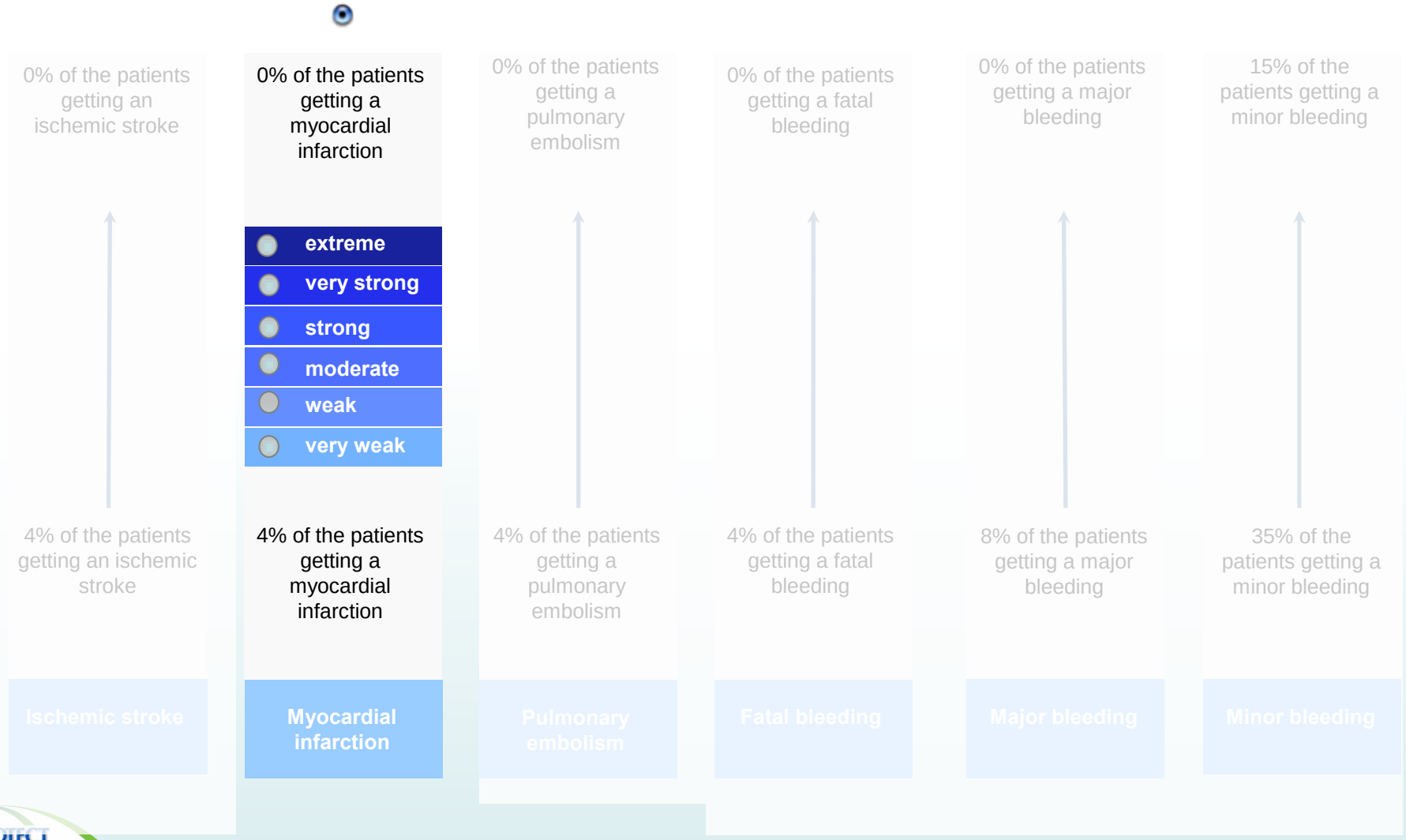
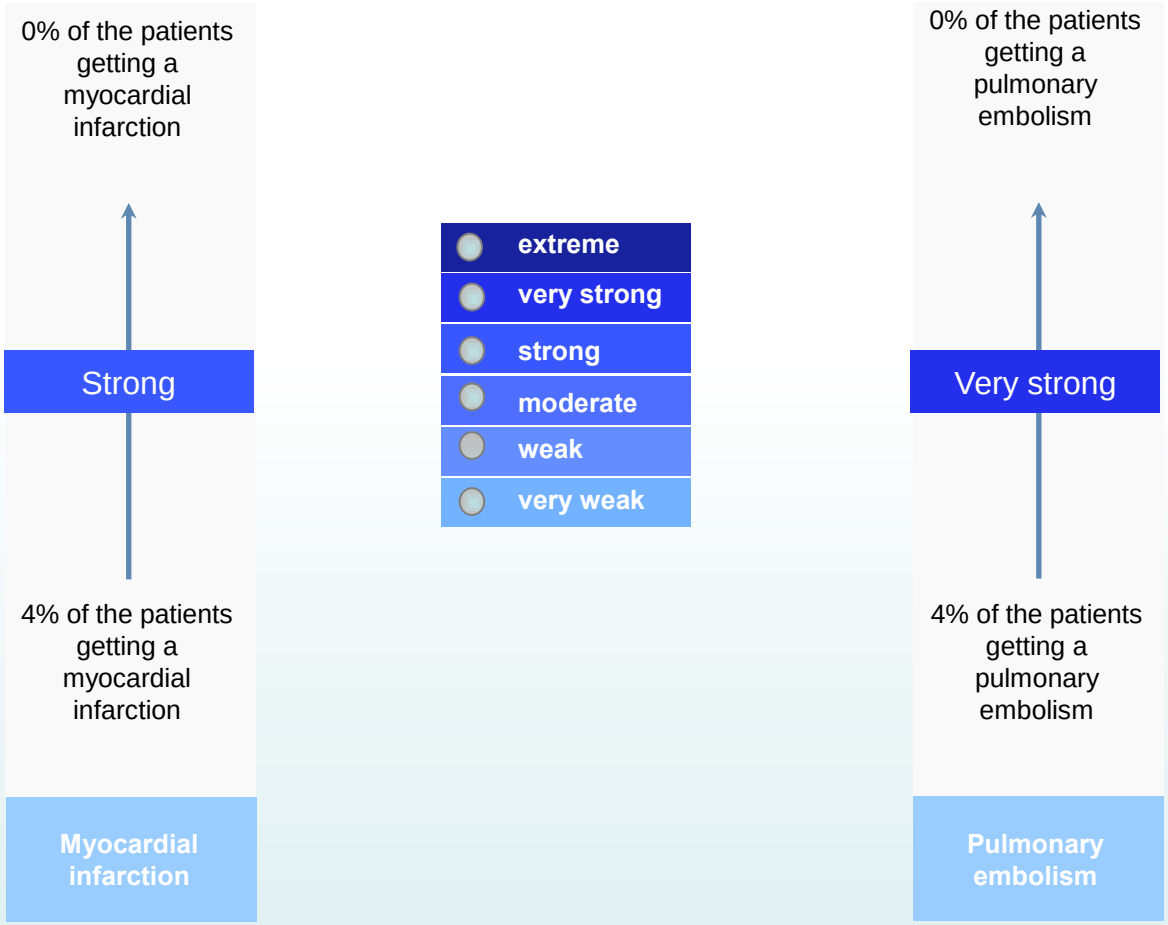


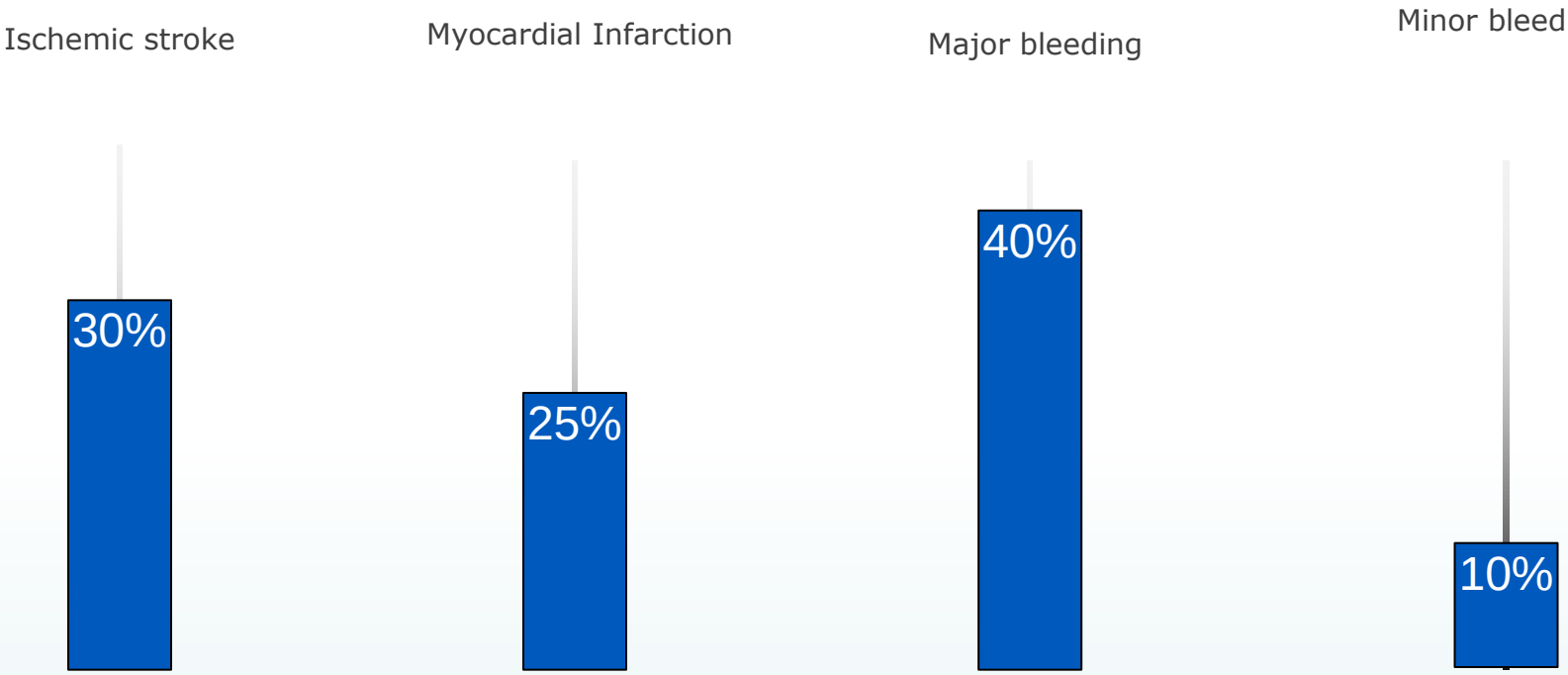
How desirable is this improvement?



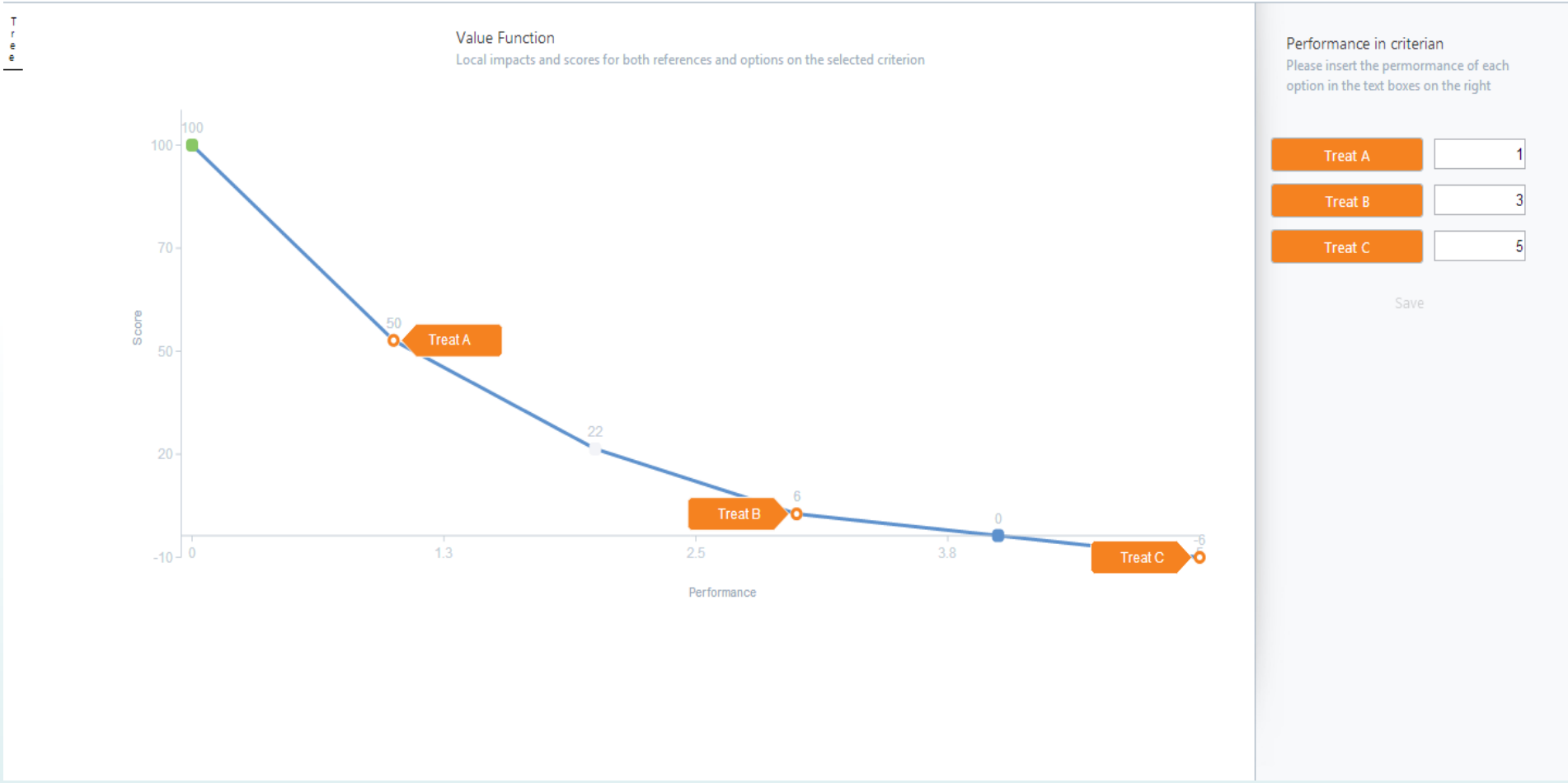
How much more desirable is the improvement on the right when compared to the one on the left?



Qualitative swing weighting



Evaluation of actual clinical data using patient values



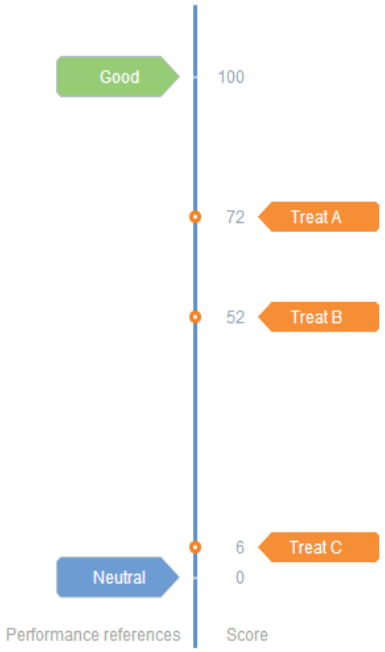
Building a decision model

Tree

Global Results

Table of global and partial scores for each option in each criteria

	Number of relapses	Time to disease prog	Disease progr...	Total
Good	100	100	100	100
Treat A	50	92	86	72
Treat B	6	89	100	52
Treat C	-6	11	29	6
Neutral	0	0	0	0
Weigths	46%	38%	15%	



Results

Global results
Tabela de pontuações globais e parciais para cada opção em cada fator de avaliação

Analysis

Profile Analysis
Pontuações das opções em todos os fatores. Selecione a opção pretendida para ver o seu perfil. A seleção de duas opções permite ver a comparação entre as duas

Sensitivity Analysis
Análise da sensibilidade dos resultados a variações nos pesos dos fatores

Summary

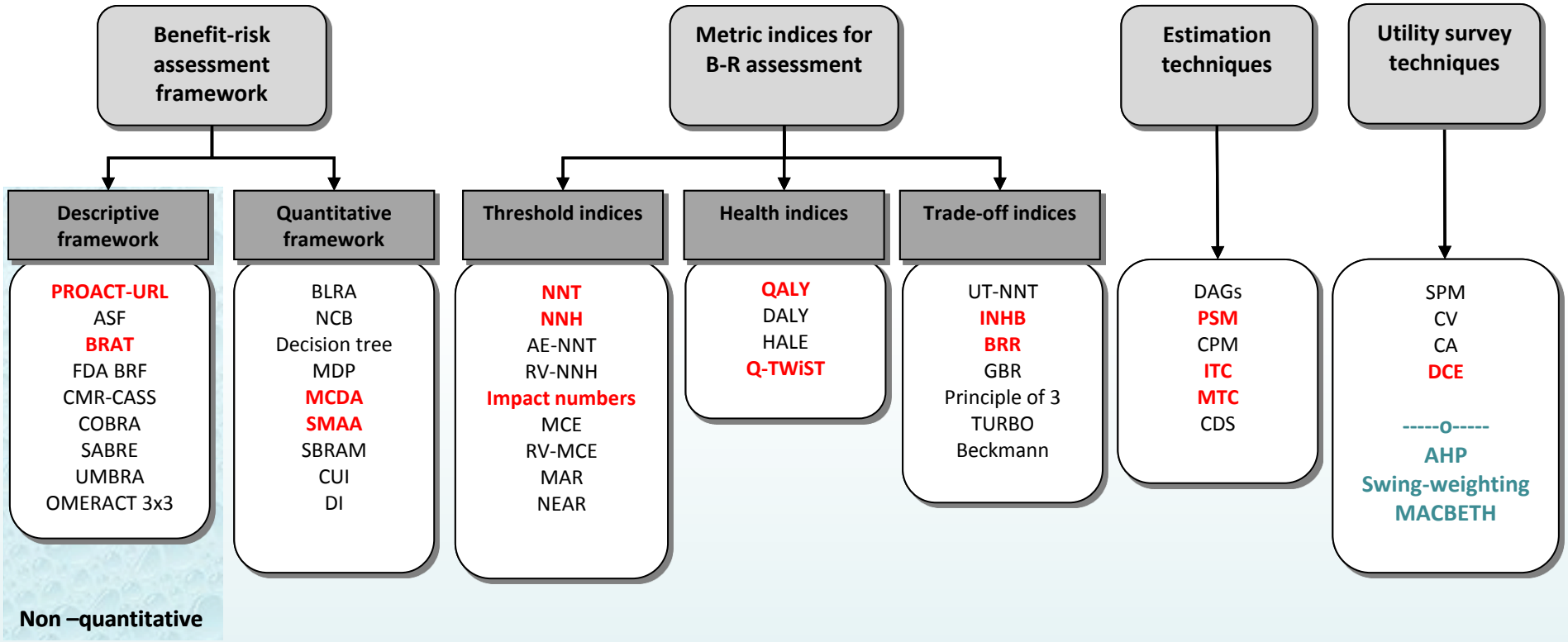
- Method can be used to collect patient preferences in a remote setting
- Can be easily extended to patients within clinical trials (advanced PRO)
- Complies with decision theoretic principles
- Further research is needed to assess aggregation of the data

Go to backup slides

Deborah Ashby, PhD

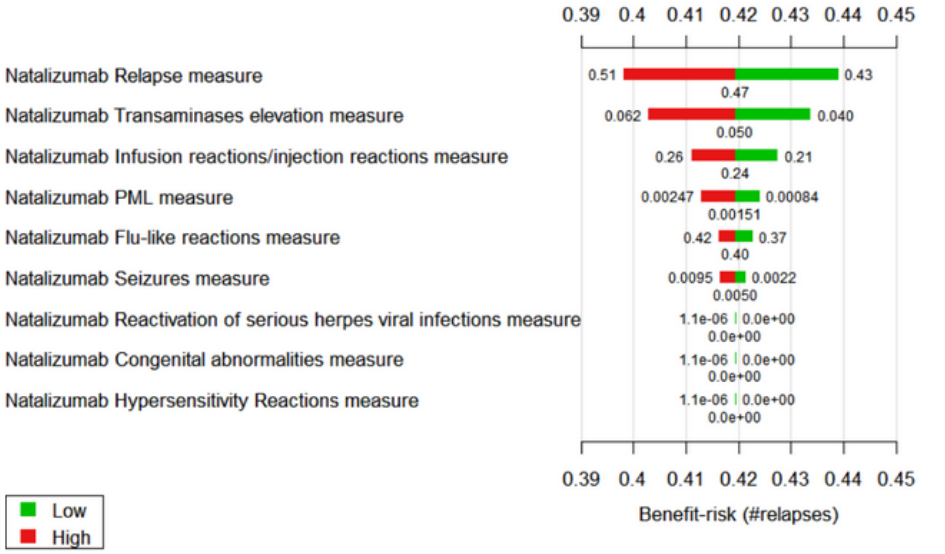
CLOSING REMARKS, TAKE-HOME MESSAGES AND ACKNOWLEDGEMENT

Benefit-risk assessment methodologies



Mt-Isa *et al*. Balancing benefit and risk of medicines: a systematic review and classification of available methodologies. Pharmacoepidemiology and Drug Safety 2014. DOI: 10.1002/pds.3636.

Visual representations of benefit and risk



Short name	Description
Name/rubric	Tornado plot
Created in	R .
Message	The tornado plot shows how the changes in the natalizumab outcome measure affect the incremental benefit-risk score. It displays the relative importance of criteria via one-way sensitivity analysis of changing a fixed amount of the measured outcomes.
Intended audience	Statisticians and regulators. Not for physicians and patients.
Knowledge required	Some knowledge on the use of sensitivity analysis and uncertainty. Some understanding of the incremental benefit-risk concept. Some knowledge on how to extract information from tornado diagrams..
Unintentional message	The legend of "high-low" is not intuitive and could be misleading..
Message not communicated	It is unclear which of the criteria are benefits and which are risks. The colour-coding is not intuitive and difficult to interpret.
Proposed improvement	Horizontal axis should be made wider to accommodate benefit-risk values. To re-label legend items to more intuitive terms. The tornado plot could also be accompanied by text annotations to aid interpretation.

Patient and public involvement

Consultation

Health professionals elicit the patient and public perspective to inform the decision making process

Collaboration

Health professionals and patients and the public form an active partnership and jointly participate in decision making

Benefits and risks of formalising benefit-risk assessment

Benefits

- Puts benefits and risks on same page
- Gives a framework to include patients' views
- Transparency facilitates discussion
- It's fun!

Risks

- Trade-off between being too simplistic or just incomprehensible
- Can be seen as a 'black box'
- Pharma want to know what regulators want

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

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Subhakanta Das, Jane Okwesa, Emily Thompson.

ADDIS

ACADEMIA:

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Erasmus University Rotterdam: Tommi Tervonen

University of Groningen: Bert de Brock

EMA BENEFIT-RISK METHODOLOGY PROJECT:

Francesco Pignatti, Andreas Kouroumalis

FUNDING SOURCES:

The MCDA web interface was initially funded by TI Pharma project Escher and integrated in ADDIS 2 with funding from IMI GetReal. Further development and the creation of training materials is supported by IMI PROTECT.

WP6 Eliciting Patient Preferences

- Hans-Georg Eichler
- Larry Phillips
- Carlos Bana e Costa
- Hans Hillege
- NICR UK
- Bana Consulting

REFERENCES AND BACKUP SLIDES

Structured assessment

Paper in press for a special issue of the Biometrical Journal:

A case study using the PrOACT-URL and BRAT frameworks for structured benefit risk assessment

Richard Nixon[*,1], **Christoph Dierig**[2], **Shahrul Mt-Isa**[3], **Isabelle Stöckert**[2], **Thaison Tong**[4], **Silvia Kuhls**[2], **Gemma Hodgson**[5], **John Pears**[6], **Ed Waddingham**[3], **Kimberley Hockley**[3], and **Andrew Thomson**[7]

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PhRMA (2011b). The PhRMA BRAT Framework for Benefit-Risk Assessment. User's Guide to the Process. http://www.cirs-brat.org/.

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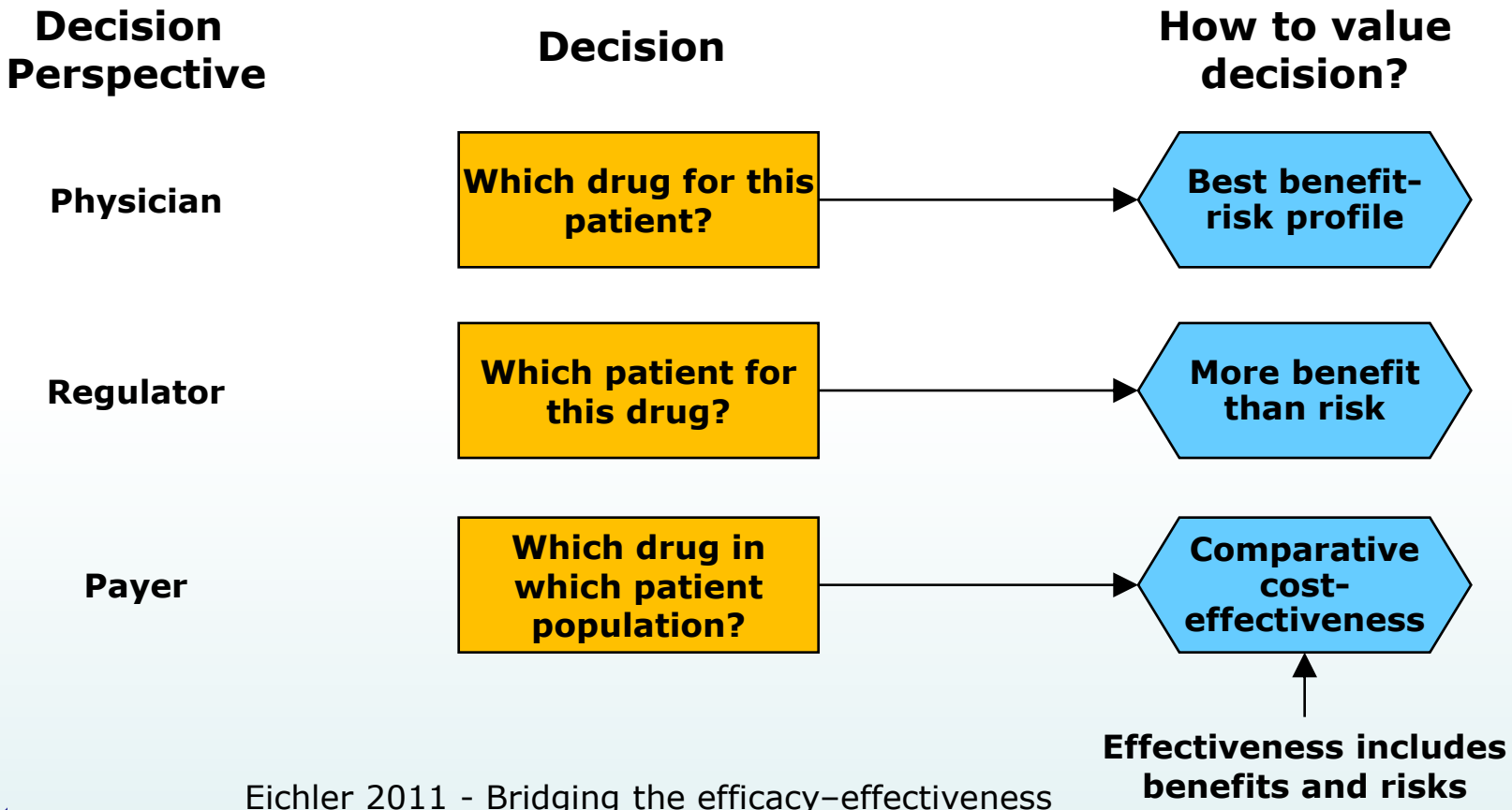
Benefit-risk is central to key decisions



Eichler 2011 - Bridging the efficacy–effectiveness gap: a regulator's perspective on addressing variability of drug response

Return

4) Customize and communicate

Re-visit key benefits and risks

- **The benefit-risk process can be iterative.**
- **The key benefits and risks may need to be "tuned".**
  - Changes outcomes in value tree if data are not available.
  - Outcome measures may be refined in response to how data are measured.
- **Guard against bias.**
  - Changing the value tree in response to observed data could bias the benefit-risk balance.

Return

6) Benefit-risk communication

Visualization of benefit-risk. Functional and perceptual tasks

- **Carswell (1992) taxonomy of functional tasks**
  - Point reading (reading one value on a graph)
  - Local comparison (reading and comparing two values on a graph)
  - Global comparison (reading and comparing more than values simultaneously on a graph)
  - Synthesis judgment (extrapolating information beyond what is explicitly shown on a graph)
- **Cleveland and McGill's (1984) perceptual tasks**
  - Position on common aligned scale (e.g. bar charts)
  - Position on common non-aligned scales (e.g. scatter plots)
  - Length (e.g. stacked bar charts)
  - Angle (e.g. pie charts)
  - Area (e.g. circles, blobs)
  - Volume (e.g. cubes)
  - Colour (e.g. coloured circles)
- **Tufte (2001) -** Ink should be reserved for data

Decreasing accuracy

Return

Required natalizumab effect on outcomes to reach a neutral benefit-risk vs. placebo

Outcome	Weight	Current Tysabri Effect	Required Tysabri effect	Required Change (Absolute)	New BR
PML	54%	0.15%	6.36%	6%	0.00
Transaminases elevation	11%	5%	36%	31%	0.00
Relapse	8%	0.47	1.31	0.84	0.00
Reactivation of serious herpes viral infections	6%	0%	56%	56%	0.00
Seizures	5%	1%	68%	67%	0.00
Congenital abnormalities	5%	0%	67%	67%	0.00
Disability progression	5%	11%	78%	67%	0.00
Infusion reactions/injection reactions	3%	24%	100%	76%	0.21
Flu-like reactions	1%	40%	100%	60%	0.55
Hypersensitivity Reactions	1%	0%	100%	100%	0.47
Convenience	1%	iv qm hosp	sc od	NA	0.53

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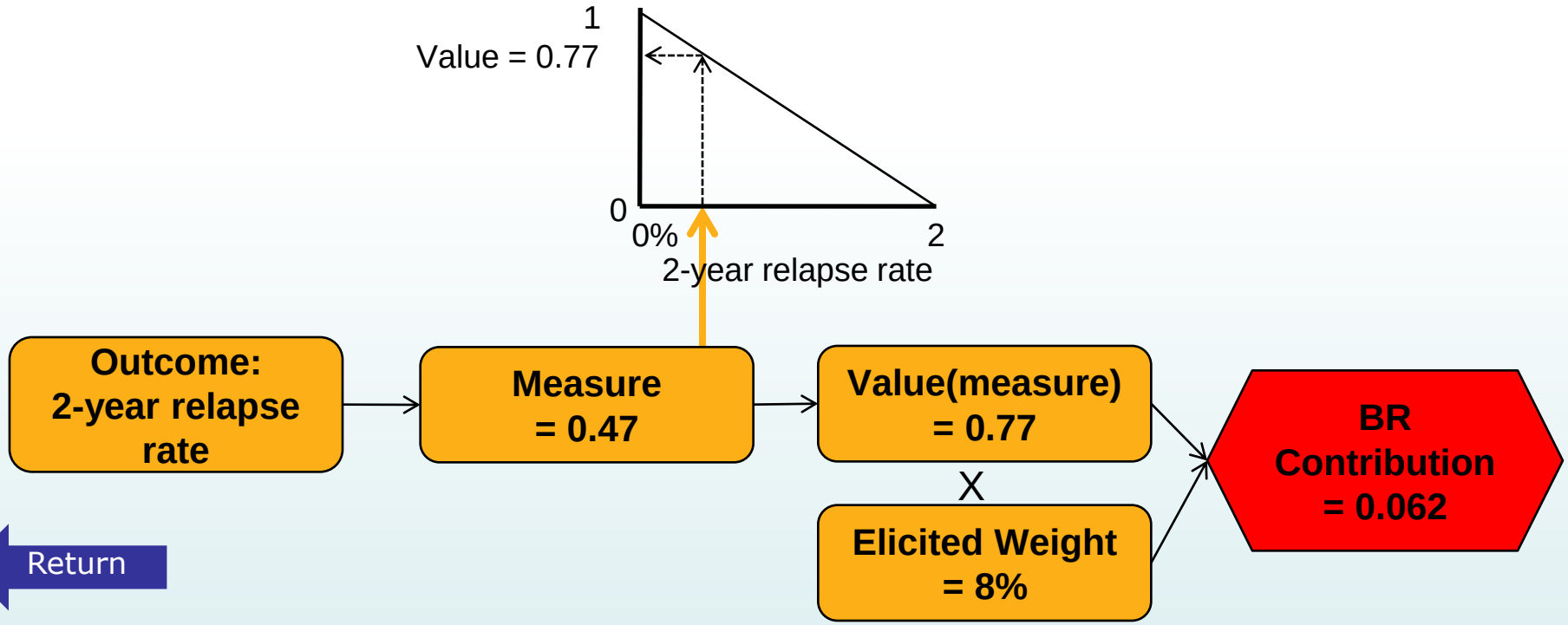
Step 5: Assess outcome importance

Linear Additive models

- Linear Additive Models with Swing Weights
  - Value functions: Within outcome importance
  - Swing weights: Between outcome importance



Step 5: Assess outcome importance

Three common methods for weight elicitation that use linear additive models

- Multi-criteria Decision Analysis (MCDA)
- MACBETH (Measuring Attractiveness by a Categorical Based Evaluation Technique)
- AHP (Analytic Hierarchy Process)

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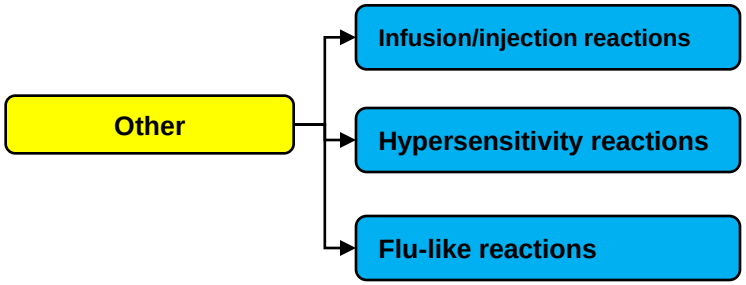
Step 5: Assess outcome importance

MCDA

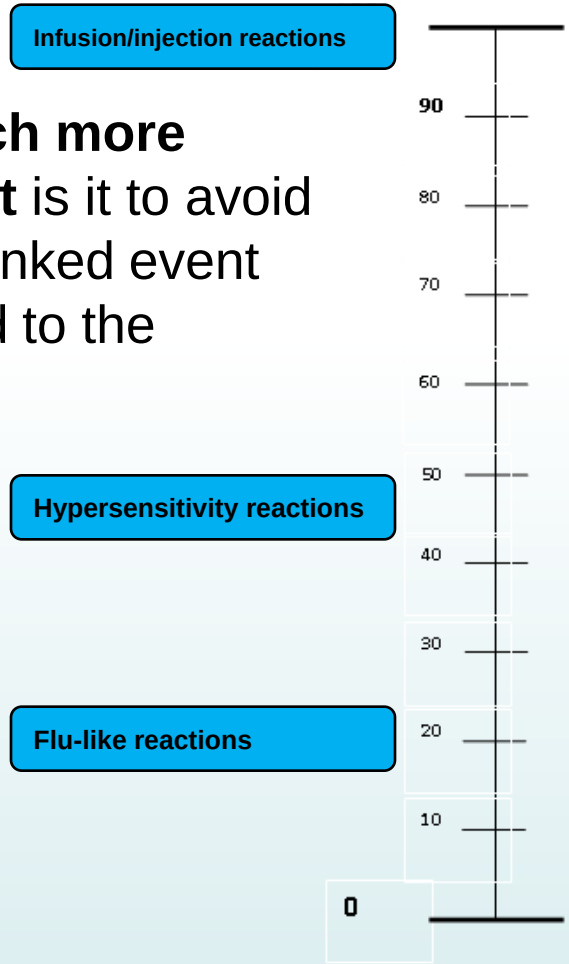
For each outcome category



1. Rank outcomes

Outcome	Rank
Infusion/injection reactions	1
Hypersensitivity reactions	2
Flu-like reactions	3

2. Relative importance



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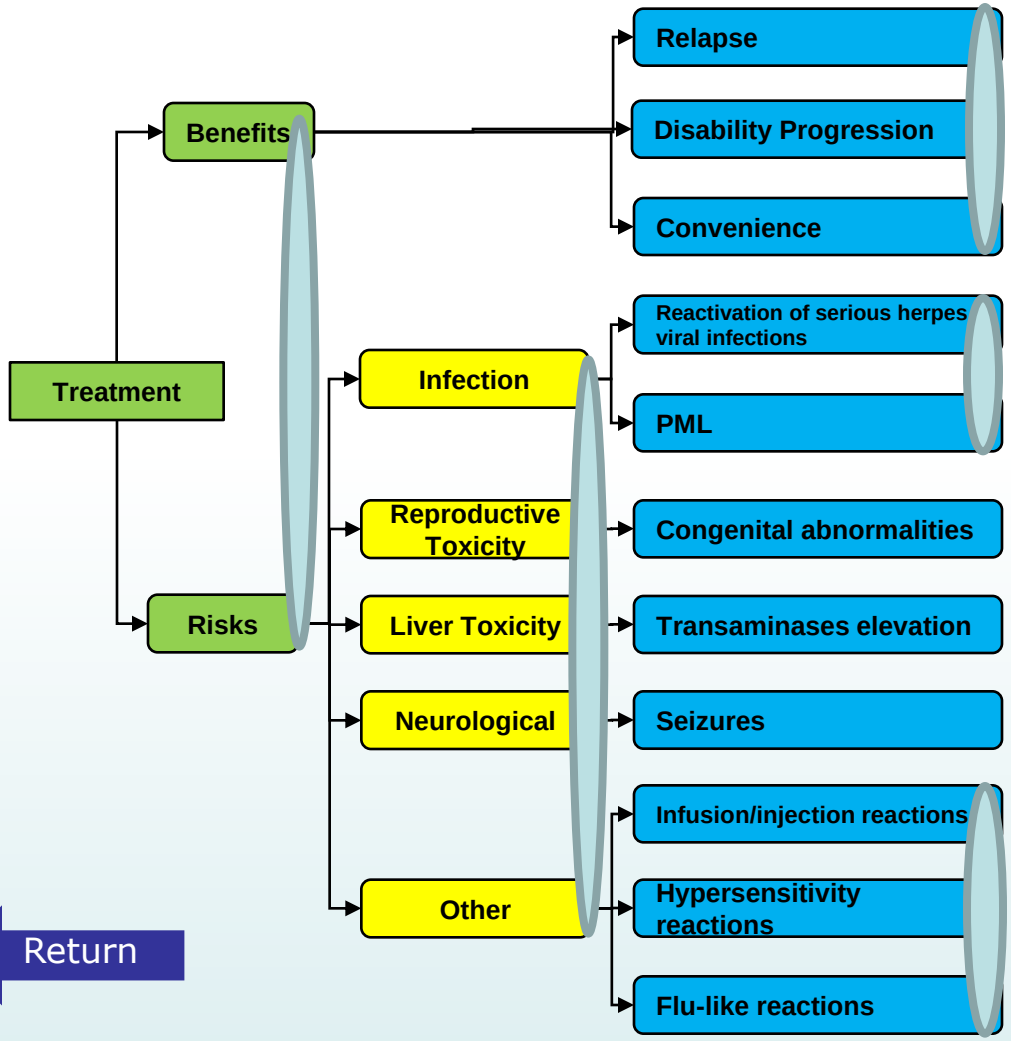
Repeat this process all the way up the value tree

The top ranked outcome in each category is carried up the tree



- Move bottom-up through the tree and compare the **top-ranked** outcomes from each category
- Finally, the top-ranked benefit is compared to the top-ranked risk
- The individual weights for each outcome can then be calculated

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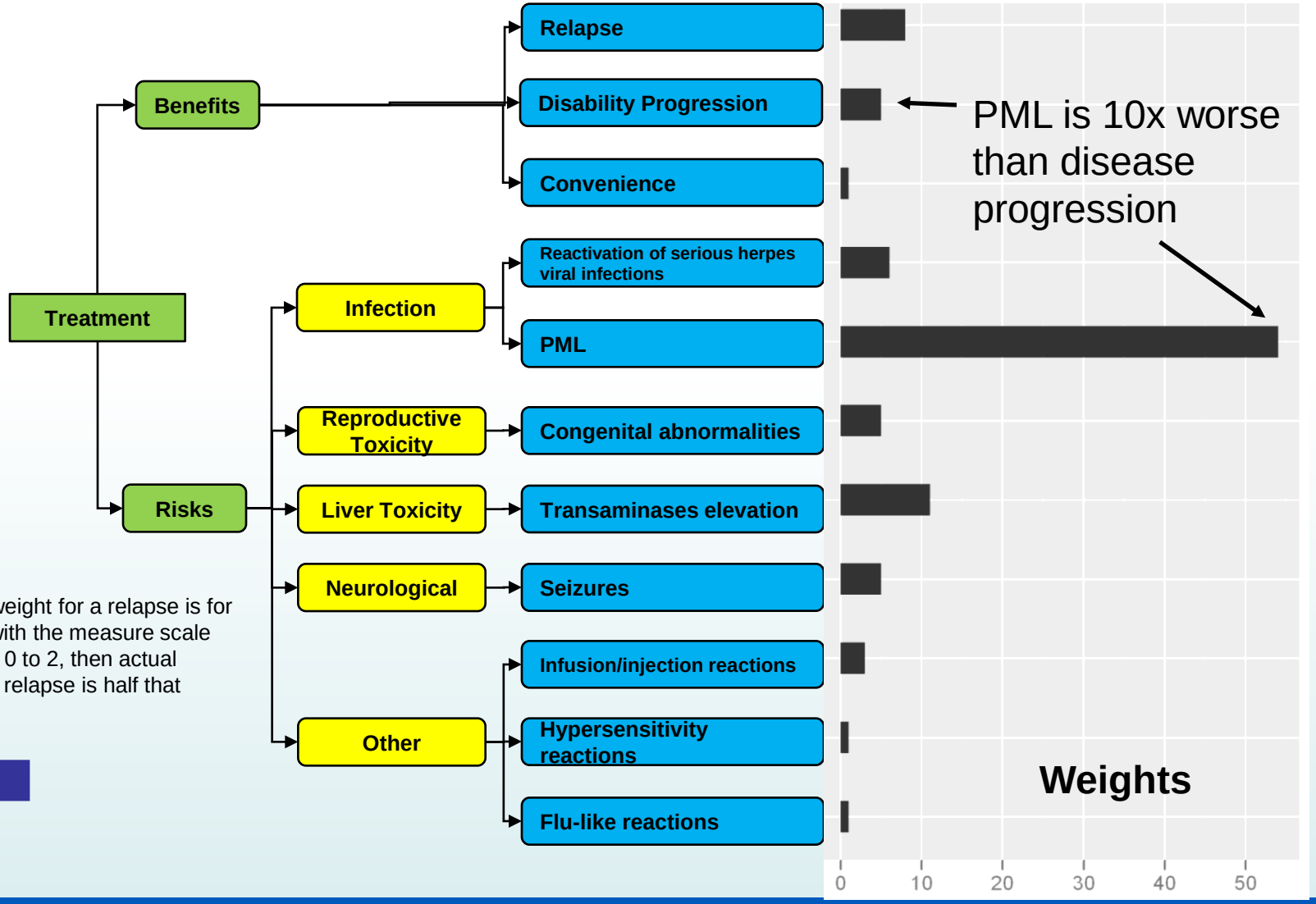
Compute the overall weights



Note that as the weight for a relapse is for a value function with the measure scale with a range from 0 to 2, then actual weight of a single relapse is half that shown here.

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Example question to assess between outcome importance

- Imagine a clinical trial of 1000 patients with 1 patient developing PML in the treatment arm.
- How many patients would need to have an EDSS progression prevented for you to be indifferent about the benefit and harm caused by the treatment?

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MACBETH (Measuring Attractiveness by a Categorical Based Evaluation Technique)

Qualitative assessment

- MACBETH is similar to MCDA, except that it provides a different way to get the weights
- **Step 1**: **Qualitatively** assess how much more attractive it is to move from worst to best for outcome i vs. moving from worst to best for outcome j and keeping everything else at the worst measure (Do this for each pair of criteria)
- **Step 2**: Check consistency of answers
- **Step 3**: Compute initial guess at weights with optimization
- **Step 4**: Refine weights while maintaining consistency

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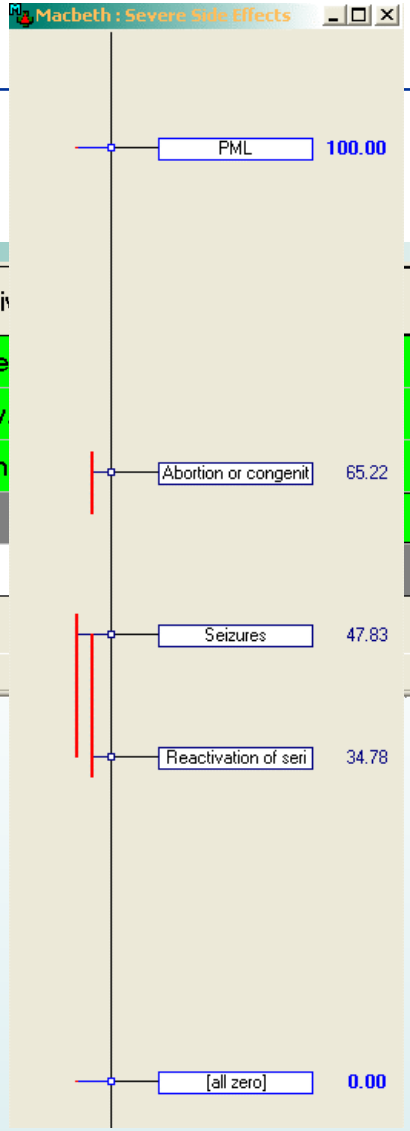
MACBETH

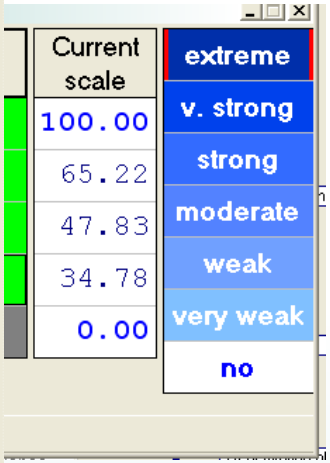
Qualitative assessment

Macbeth : Severe Side Effects

	PML	Abortion or congenit	Seizures	Reacti
PML	no	extreme	extreme	e
Abortion or congenit		no	strong	v
Seizures			no	m
Reactivation of seri				
[all zero]				

Consistent judgements





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AHP (Analytic Hierarchy Process)

Qualitative assessment

- Weights are elicited by making pairwise comparisons between criteria
- "How much more important is outcome i vs. outcome j?"
- Must provide number from 1 to 9 on relative scale
- Weight is calculated by finding the dominant eigenvector of the corresponding matrix
- Value functions are computed in a similar manner (do not necessarily come from linear function)
- No consistency check, but rather a score (<0.2 is okay)

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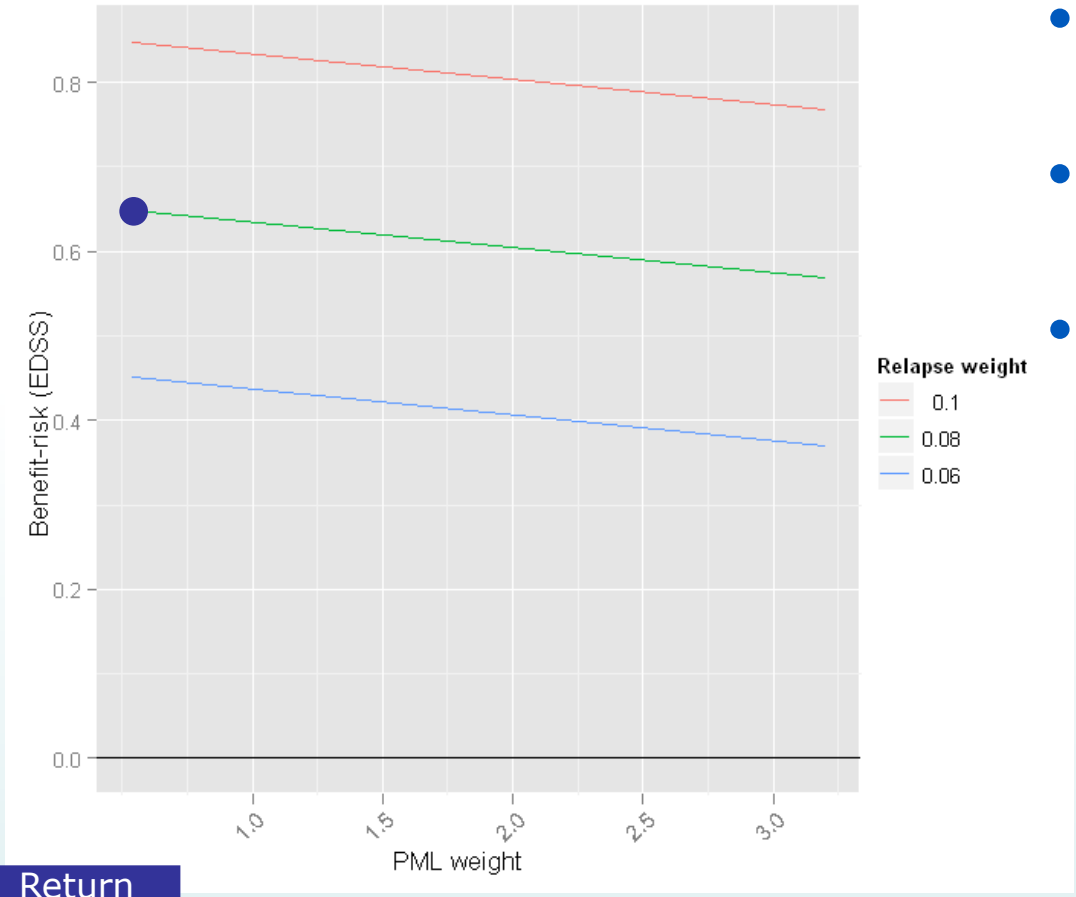
Two way sensitivity analysis on weights

Incremental Benefit-Risk of Tysabri – Placebo



- Vary the PML weight (x-axis) and the relapse weight (each line).
- Green line in the middle is the elicited weight. Change by +/- 30%.
- Again the BR is robust to these changes.

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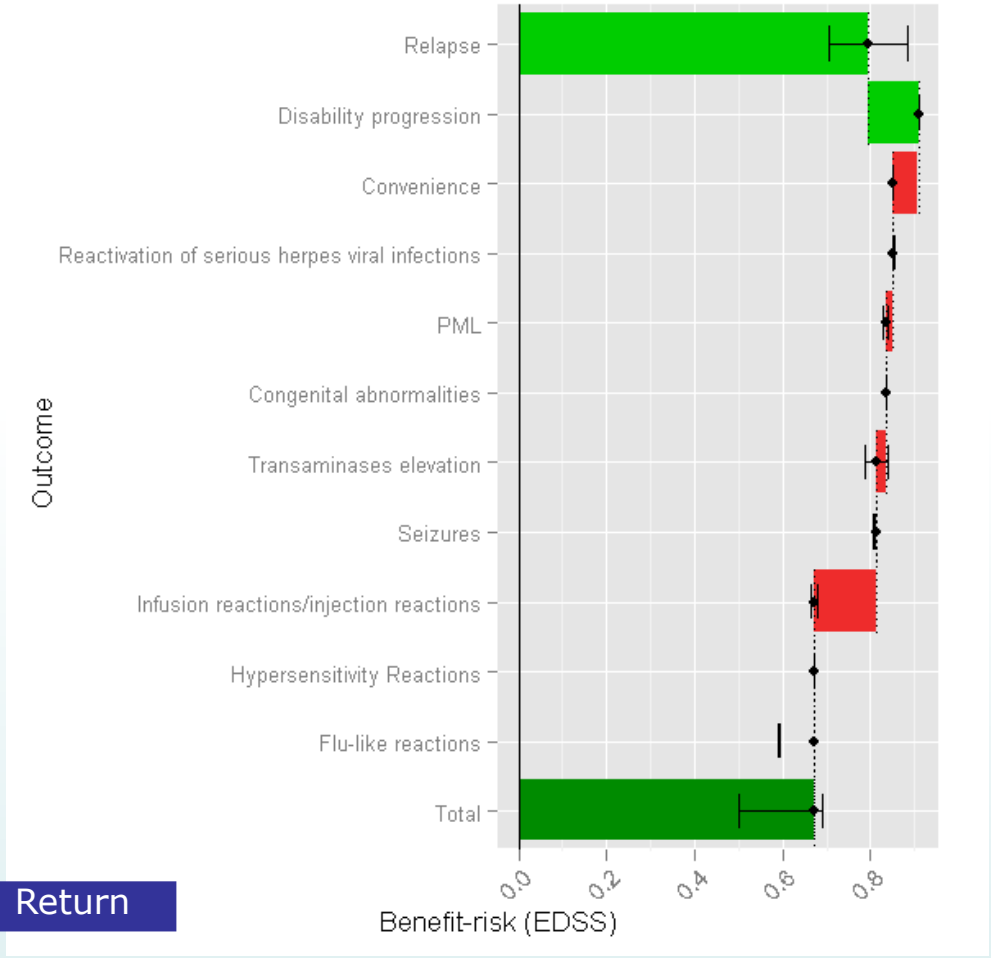
Probabilistic sensitivity analysis of the measures

Incremental Benefit-Risk of Tysabri – Placebo



- 80% CI are included in the waterfall plot.
- The uncertainty in the overall BR is robust to uncertainty in the outcome measures
- The components of the uncertainty can be seen.

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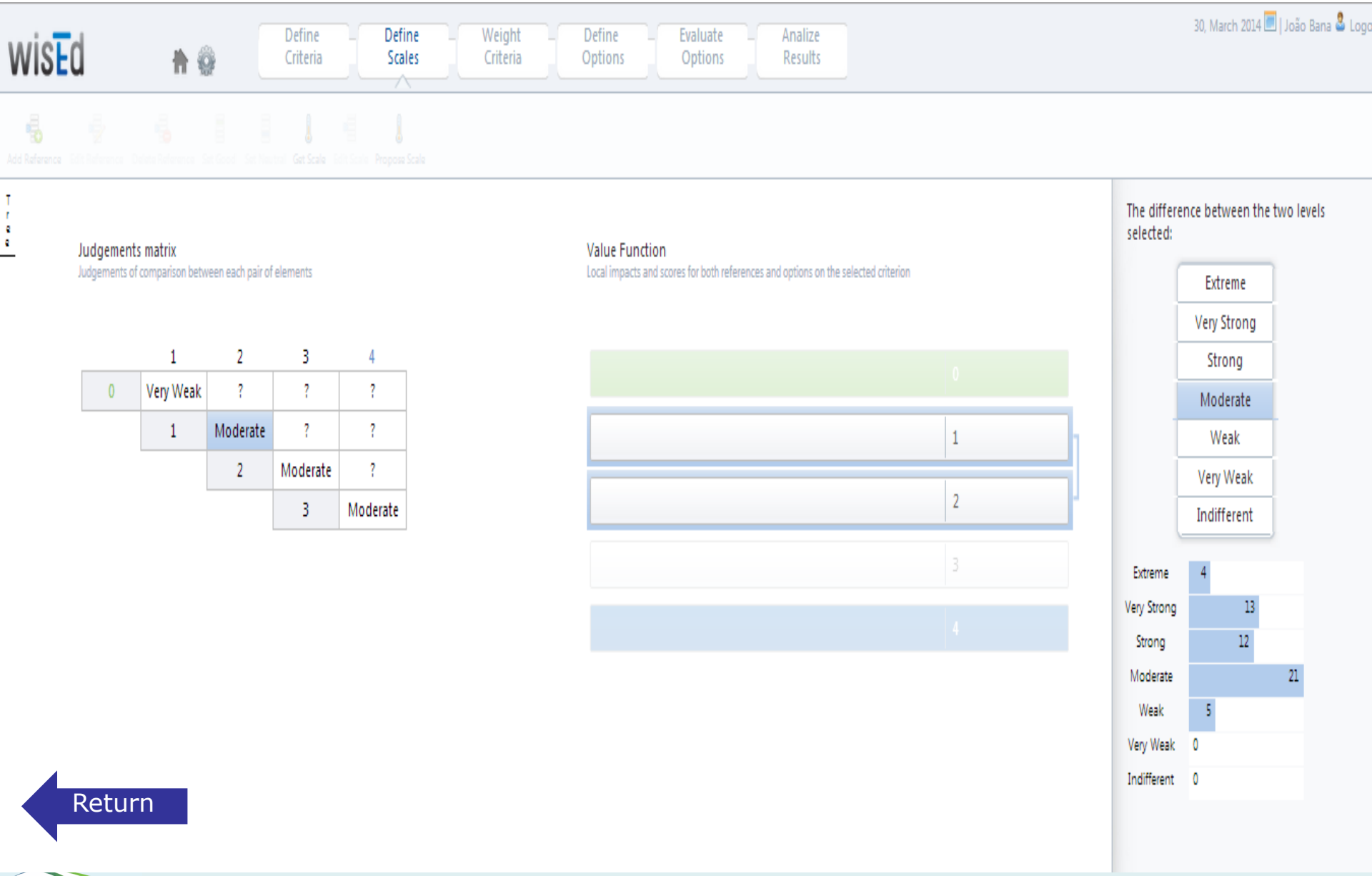
wiseEd
Define Criteria
Define Scales
Weight Criteria
Define Options
Evaluate Options
Analize Results
30, March 2014 | João Bana Logo
Judgements matrix
Judgements of comparison between each pair of elements
1 2 3 4
0 Very Weak ? ? ?
1 Moderate ? ?
2 Moderate ?
3 Moderate
Value Function
Local impacts and scores for both references and options on the selected criterion
0
1
2
3
4
The difference between the two levels selected:
Extreme
Very Strong
Strong
Moderate
Weak
Very Weak
Indifferent
Extreme 4
Very Strong 13
Strong 12
Moderate 21
Weak 5
Very Weak 0
Indifferent 0
Return

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Define Criteria | Define Scales | Weight Criteria | Define Options | Evaluate Options | Analize Results

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Add Reference | Edit Reference | Delete Reference | Set Good | Set Neutral | Get Scale | Edit Scale | Propose Scale

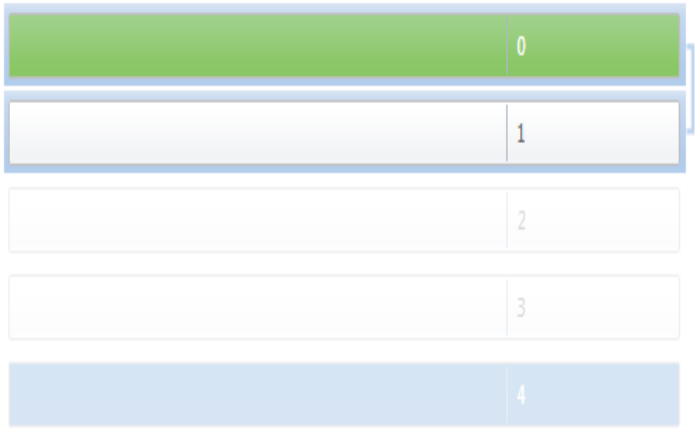
Judgements matrix

Judgements of comparison between each pair of elements

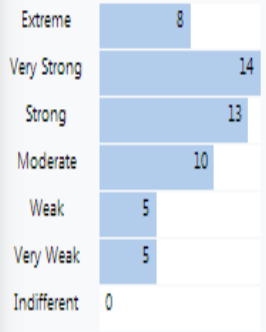
	1	2	3	4
0	Very Weak	?	?	?
	1	Moderate	?	?
		2	Moderate	?
			3	Moderate

Value Function

Local impacts and scores for both references and options on the selected criterion



The difference between the two levels selected:



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PROTECT