Benefit-Risk modelling of pharma-ceuticals: Where are we now?

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and

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EFSPI-FMS-DSBS Benefit-Risk Assessment Methodology Workshop

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Regulators need to refine their methods of assessing benefit-risk balances and switch from “implicit” to “explicit” decision making—that is, to an approach involving explicit descriptions not only of all decision criteria and interpretations of data but also valuations, such as the weighting factors for potential treatment outcomes

Ideally, regulators should also shift from the use of qualitative statements to quantitative descriptions of the size of the net health benefits.

Source: Eichler, H.-G., Abadie, E., Raine, J. M., & Salmonson, T. (2009). Safe drugs and the cost of good intentions. *New England Journal of Medicine, 360(14), 1378-1380.*

EMA Benefit-Risk Project (2009-11)

Purpose

To develop and test tools and processes for balancing multiple benefits and risks as an aid to informed regulatory decisions about medicinal products

transparency, communicability, consistency
= clarity of decisions

Work Packages

1. Description of current practice ✓
2. Applicability of current tools and methods ✓
3. Field tests of tools and methods
    1. LSE MSc students modelled four drugs ✓
    2. 5 drugs for European Agencies ✓
4. Development of tools and methods for B/R ✓
5. Training module for assessors ongoing

WP1: How do regulators decide? By…

Discussing

Voting

But no quantitative modelling is used by any regulator anywhere in the world to deal with the massive amounts of data—10GB more or less!

WP1: Interviews—6 European Agencies

What is a benefit?

1. Everything good
2. Improvement in health state
3. Real-world effectiveness
4. Clinical relevance
5. Improvement in illness
6. Suffering reduced
7. Positive action of drug
8. Meets unmet medical need
9. Positive improvement in health state as perceived by patient
10. Safety improvement
11. Value compared to placebo
12. Change in managing patient

:

37. Statistically significant effect

What is a risk?

1. All that is negative
2. Adverse events
3. Reduction in quality
4. Kinetic interactions
5. Side effects
6. Serious adverse effects
7. Bad effects
8. Danger for the patient
9. Tolerance of a drug compared to serious side effects
10. Harm
11. Severity of side effects
12. Frequency of side effects

:

51. Potential or theoretical risks

Defining ‘benefit’ and ‘risk’

Favourable Effects	Uncertainty of Favourable Effects
Unfavourable Effects	Uncertainty of Unfavourable Effects

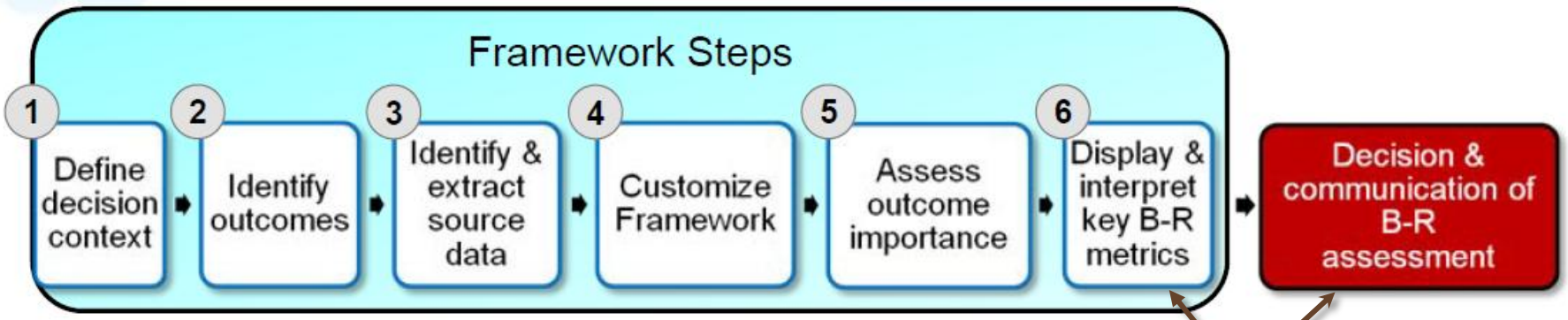
These four cells are now included and elaborated in the Guidance Document for preparing the 80-day Assessment Report.

WP2 Report: Review of methods and approaches for benefit/risk assessment

- 3 qualitative and 18 quantitative approaches
- 3 approaches quantify effects *and* uncertainties
  - Bayesian statistics (for revising beliefs in light of new data)
  - Decision trees/influence diagrams (for modelling uncertainty)
  - Multi-criteria decision analysis (for modelling B/R trade-offs)
- 5 other approaches for supplementary role
  - Probabilistic simulation (for modelling effect uncertainty)
  - Markov processes and Kaplan-Meier estimators (for health-state changes over time)
  - QALYs (for modelling health outcomes)
  - Conjoint analysis (for assessing trade-offs among effects)

See report at ema.europa.eu, “Special topics” tab, “Benefit risk methodology”.

Pharma-BRAT (Benefit-Risk Action Team)



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

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

Originally sponsored by PhRMA, now being further developed as UMBRA (Universal Method for Benefit-Risk Assessment) by CIRS (Centre for Innovation in Regulatory Science.

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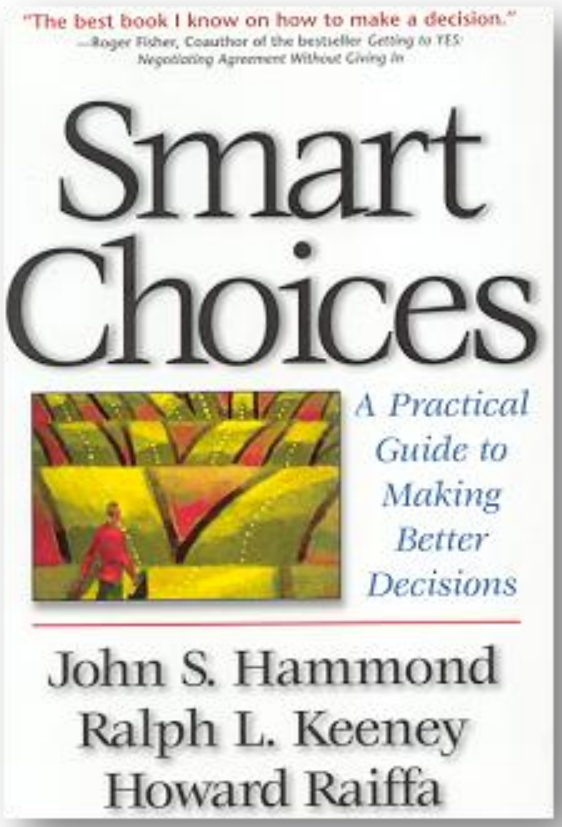
PrOACT-URL adapted as B-R framework



- Problem
- Objectives
- Alternatives
- Consequences
- Trade-offs
- Uncertainty
- Risk attitude
- Linked decisions

PrOACT is currently in use to guide modelling in the EMA's PROTECT project.

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Benefit-Risk Assessment Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Summary of evidence:	Conclusions (implications for decision):
Unmet Medical Need	Summary of evidence:	Conclusions (implications for decision):
Benefit	Summary of evidence:	Conclusions (implications for decision):
Risk	Summary of evidence:	Conclusions (implications for decision):
Risk Management	Summary of evidence:	Conclusions (implications for decision):
Benefit-Risk Summary and Assessment		

Is there a Gold Standard?

A comprehensive method should:

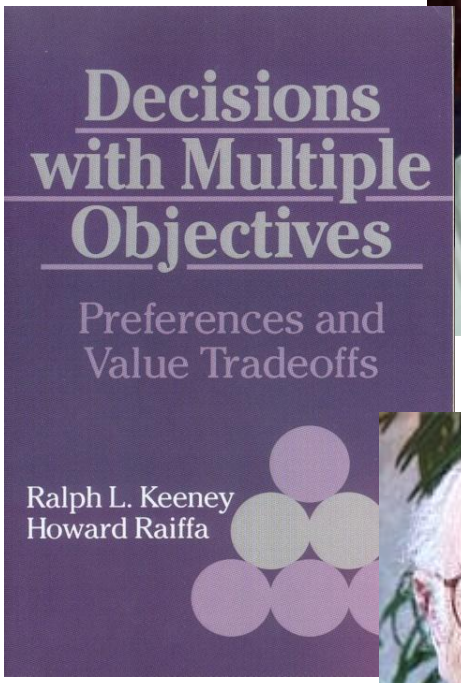
1. Express all effects, favourable and unfavourable, in comparable units
2. Accept any performance measures: measurable quantities, scoring systems, relative frequencies, health outcomes, etc.
3. Distinguish between performance measures (data) and their clinical relevance (judgements)
4. Capture trade-offs among the effects
5. Be based on sound theory, not ad-hockery

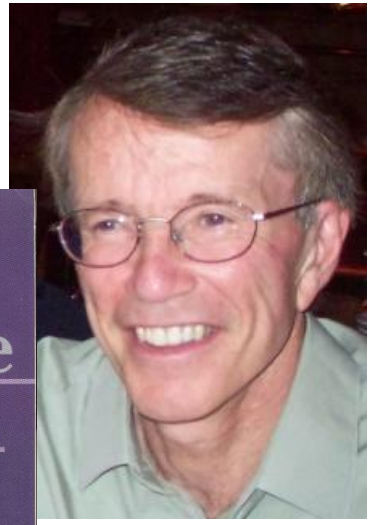
14 drugs modelled, 2009-2011

	Product	Indication	Quantitative Method
Lilly	Drug X	Idiopathic short stature	MCDA
LSE MSc students	Acomplia	Obesity	MCDA
	Cimzia	Rheumatoid Arthritis	MCDA + simulation
	Sutent	Gastrointestinal cancer	Decision Tree + Markov
	Tyverb	Breast cancer	MCDA + simulation
EMA B-R Project (new drugs)	Tafamidis	Transthyretin amloid polyneuropathy	MCDA
	Ozespa	Chronic plaque psoriasis	MCDA
	Caprelsa	Inoperable thyroid cancer	MCDA
	RoActemra	Systemic juvenile idiopathic arthritis	MCDA
	Benlysta	Systemic lupus erythematosus	MCDA
IMI PROTECT project	Tysabri	Multiple schlerosis	MCDA, Forest plot
	Acomplia	Obesity	MCDA, simulation
	Ketek	Respiratory tract infections	MCDA, simulation
	Raptiva	Psoriasis	MCDA

MCDA (Multi-Criteria Decision Analysis)

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





Reference: Keeney, R. L., & Raiffa, H. (1976). *Decisions With Multiple Objectives: Preferences and Value Tradeoffs. New York: John Wiley.*

A system *not* based on MCDA

MCDA converts all input evaluations of decision outcomes into the common currency of *value added*.

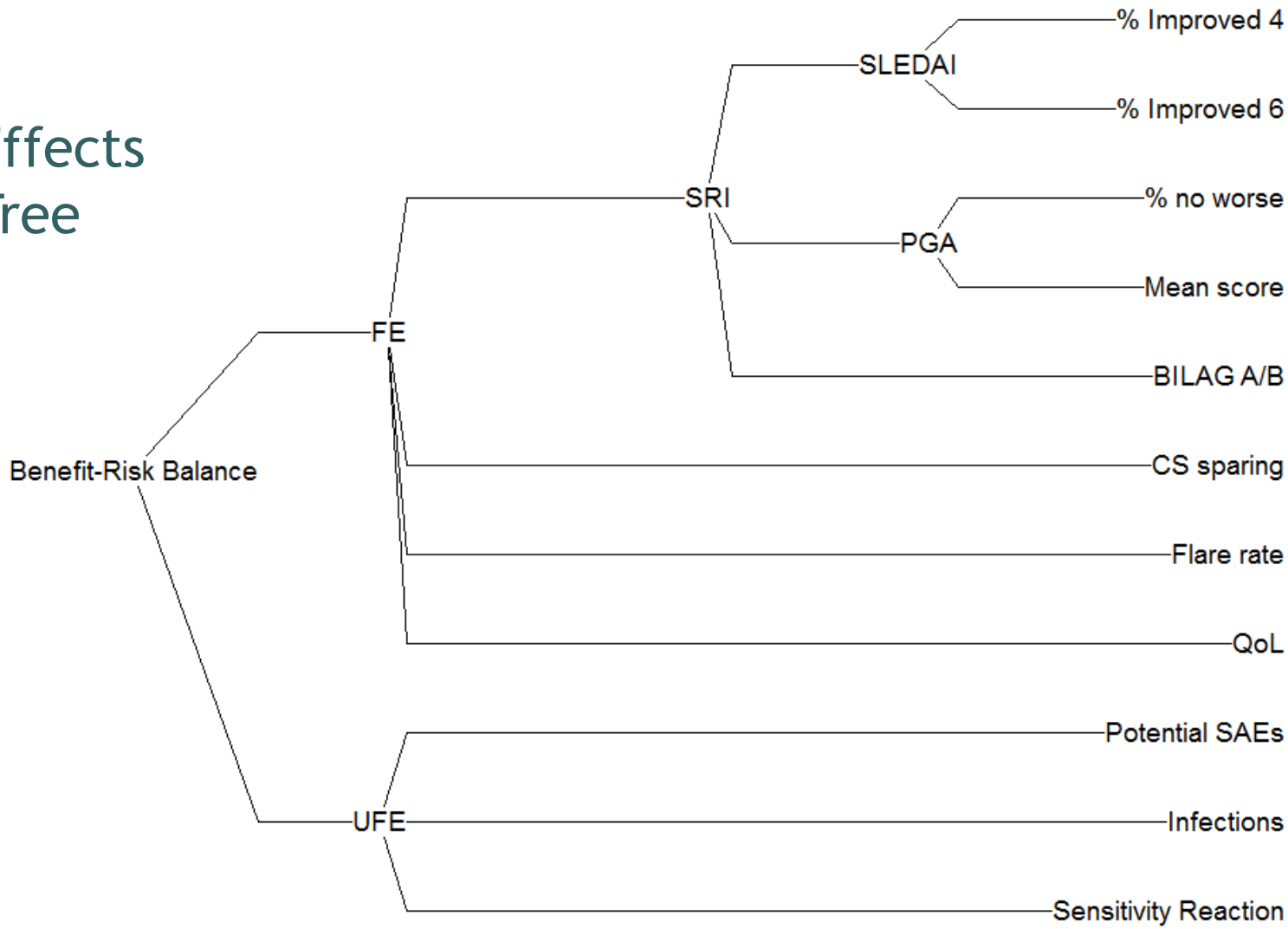
A Drug Case Study: Benlysta (belimumab)

Establish decision context

- **Indication:** Treatment of active, autoantibody-positive systemic lupus erythematosus (SLE).
- **Use:** Add-on to standard therapy (hydroxychoroquine and corticosteroids) for adult patients with a high degree of disease activity.
- **Efficacy:** Two randomised, placebo-controlled, clinical studies.
- **Safety:** Three open-label continuation trials.
- **Medical Need:** Newer, more-effective and better-tolerated therapies.

Identify objectives & their criteria

Effects Tree



Identify alternatives (options)

1. Benlysta 1mg
2. Benlysta 10mg
3. Placebo

Summarise data as an Effects Table

Effects		Name	Description	Best[1]	Worst	Units	Placebo	10 mg	1 mg
Favourable Effects	SLE Responder Index (SRI)	SLEDAI % Improved ≥ 4	Percentage of patients with at least 4 points reduction in SLEDAI[2]	100	0	%	41	53	48
		SLEDAI % Improved > 6	Percentage of patients with more than 6 points reduction in SLEDAI	100	0	%	23	37	33
		PGA % no worse	Percentage of patients with no worsening in Physician's Global Assessment[3] (worsening = an increase of less than 0.3 points)	100	0	%	66	75	76
		PGA Mean score	Overall mean change of PGA score from baseline for the study population	1.0	0	Differ-ence	0.44	0.48	0.45
		BILAG A/B	Percentage of patients with no new BILAG[2] A/2B	100	0	%	69.0	75.2	70.1
	Secondary Endpoints	CS Sparing	Percentage of patients that reduced the dose of corticosteroids by more than 25% and to less than 7.5 mg/day	100	0	%	12.3	17.5	20.0
		Flare rate	Number of new BILAG A cases per patient year	0	5	Number	3.51	2.88	2.90
		QoL	Mean change in the total score of SF 36 (Short Form)	0	100	Differ-ence	3.5	3.4	3.7
Unfavourable Effects		Potential SAEs	Potential for developing tumour, adverse interactions with vaccines and AE on pregnancies	100	0	Judge-ment	100	0	90
		Infections	Proportion of patients with serious infections that are life-threatening	0	10.0	%	5.2	5.2	6.8
		Sensitivity Reaction	Proportion of patients with hypersensitivity reactions at any time in the study	0	2.0	%	0.10	0.40	1.30

How do you put it all together?

SLEDAI % Improved ≥ 4

SLEDAI % Improved > 6

PGA % no worse

PGA Mean score

BILAG A/B

CS Sparing

Flare rate

QoL

Potential SAEs

Infections

Sensitivity Reaction

Biased decisions

MCDA modelling + Social process = Smart Decisions

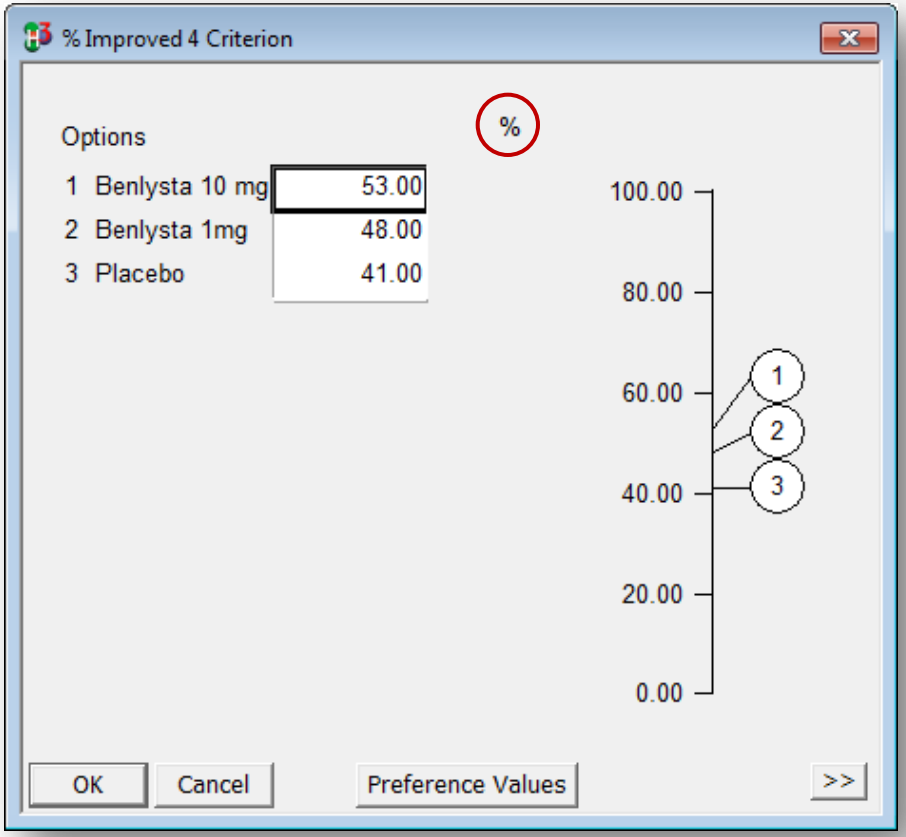
Phillips' Law: Never rely on a single expert!

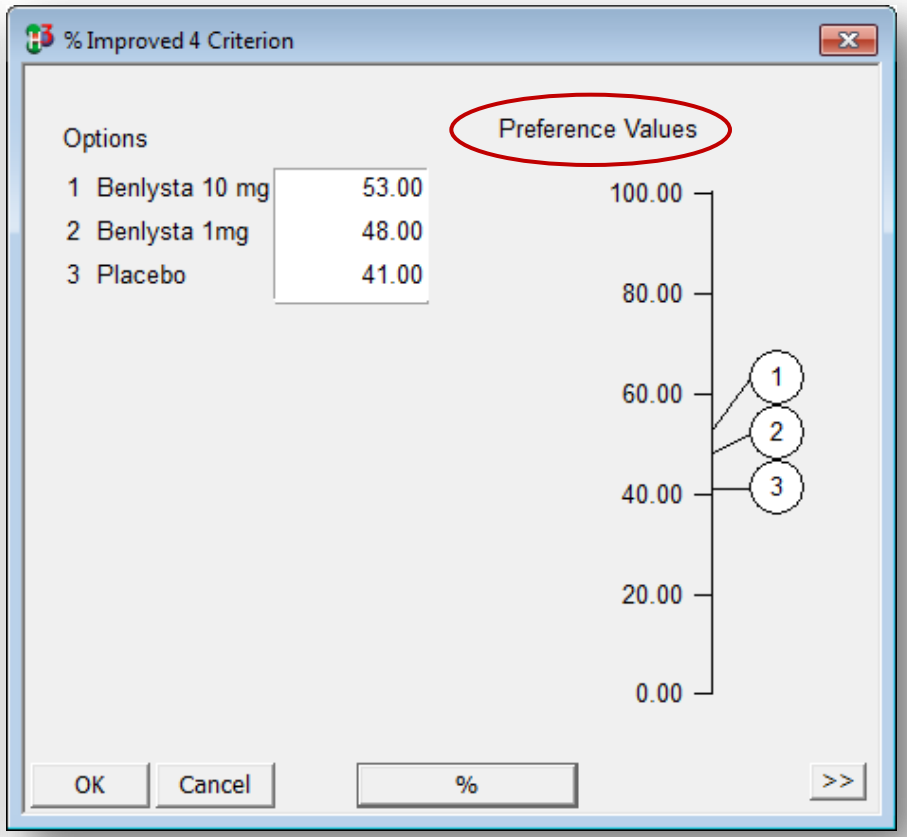
Decision Conferencing

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

Describe the consequences

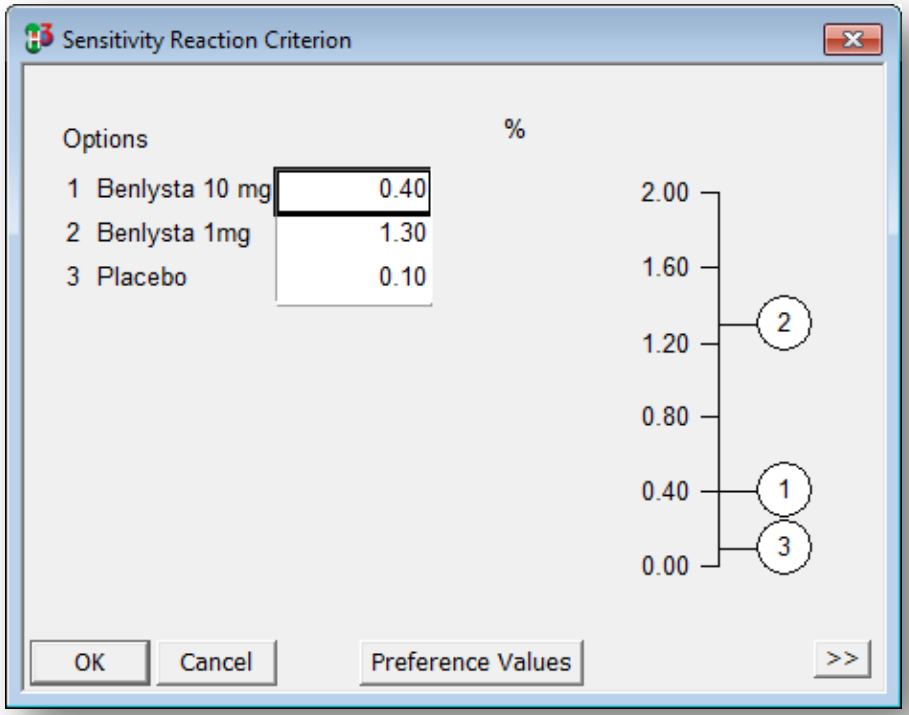
Linear direct conversion to preference values

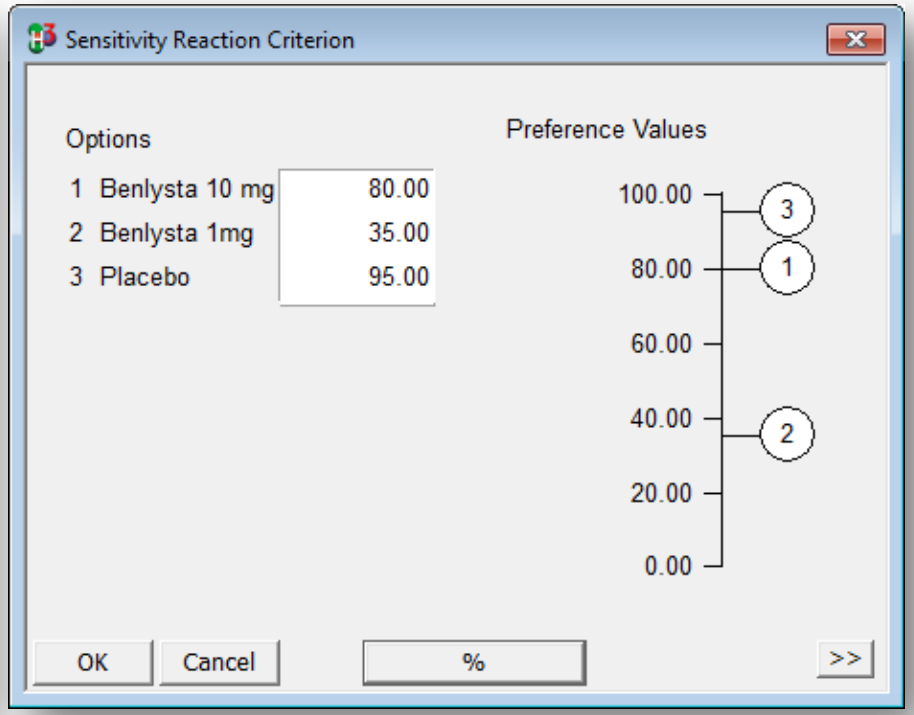




Describe the consequences

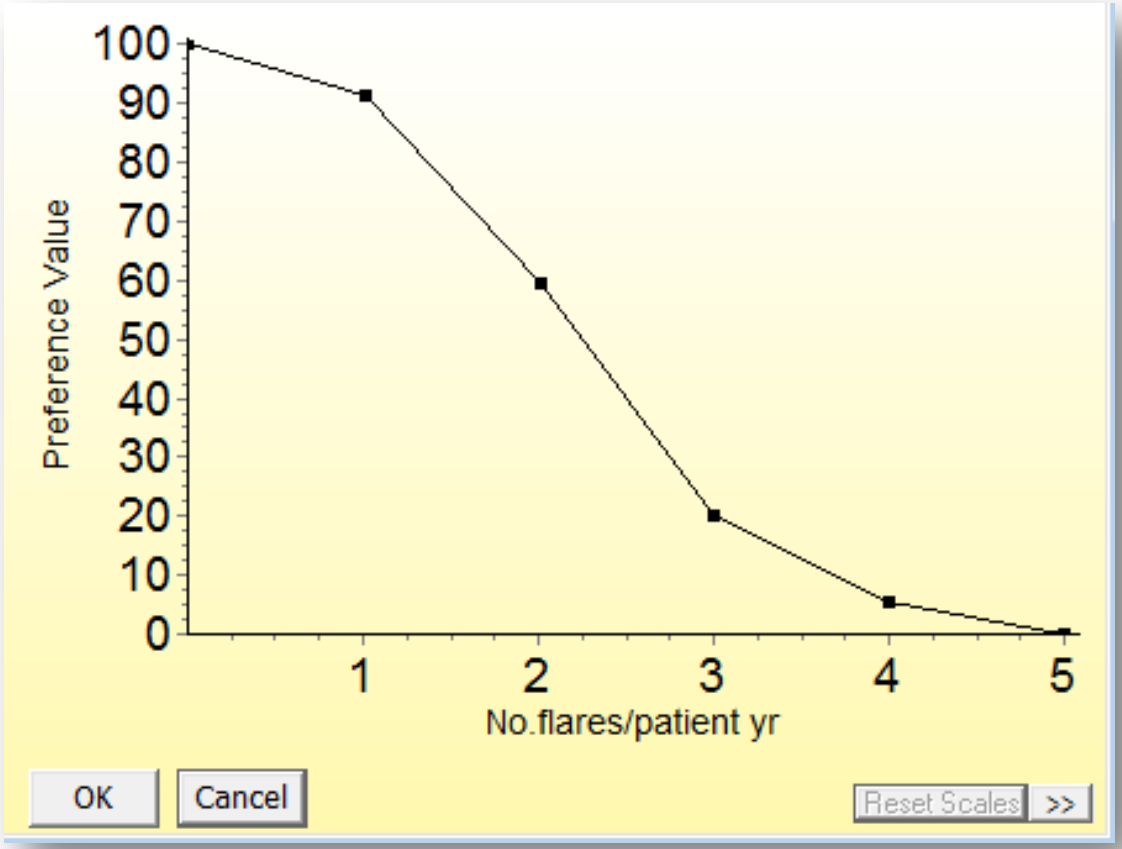
Linear inverse conversion to preference values





Describe the consequences

Non-linear conversion to preference values

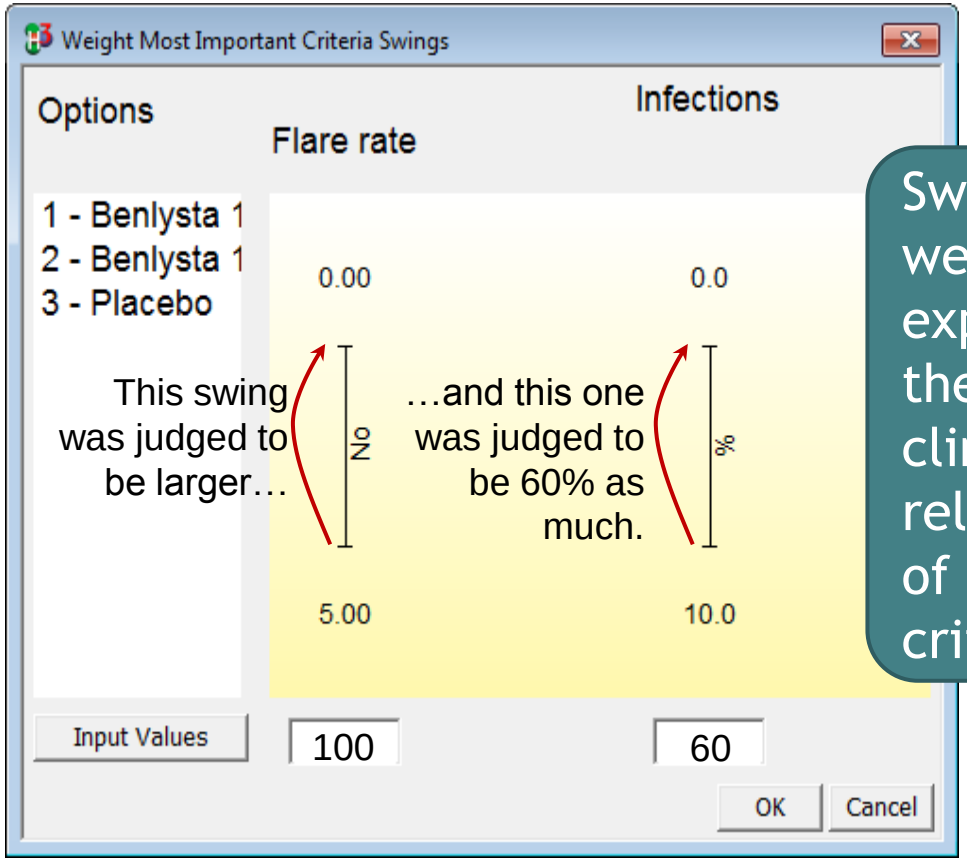


Trade-offs: assess swing-weights

1. Trade-offs among the favourable effects

2. Trade-offs among the unfavourable effects

3. Trade-off between the most important favourable effect and the most important unfavourable effect



Swing weights express the clinical relevance of the criteria

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

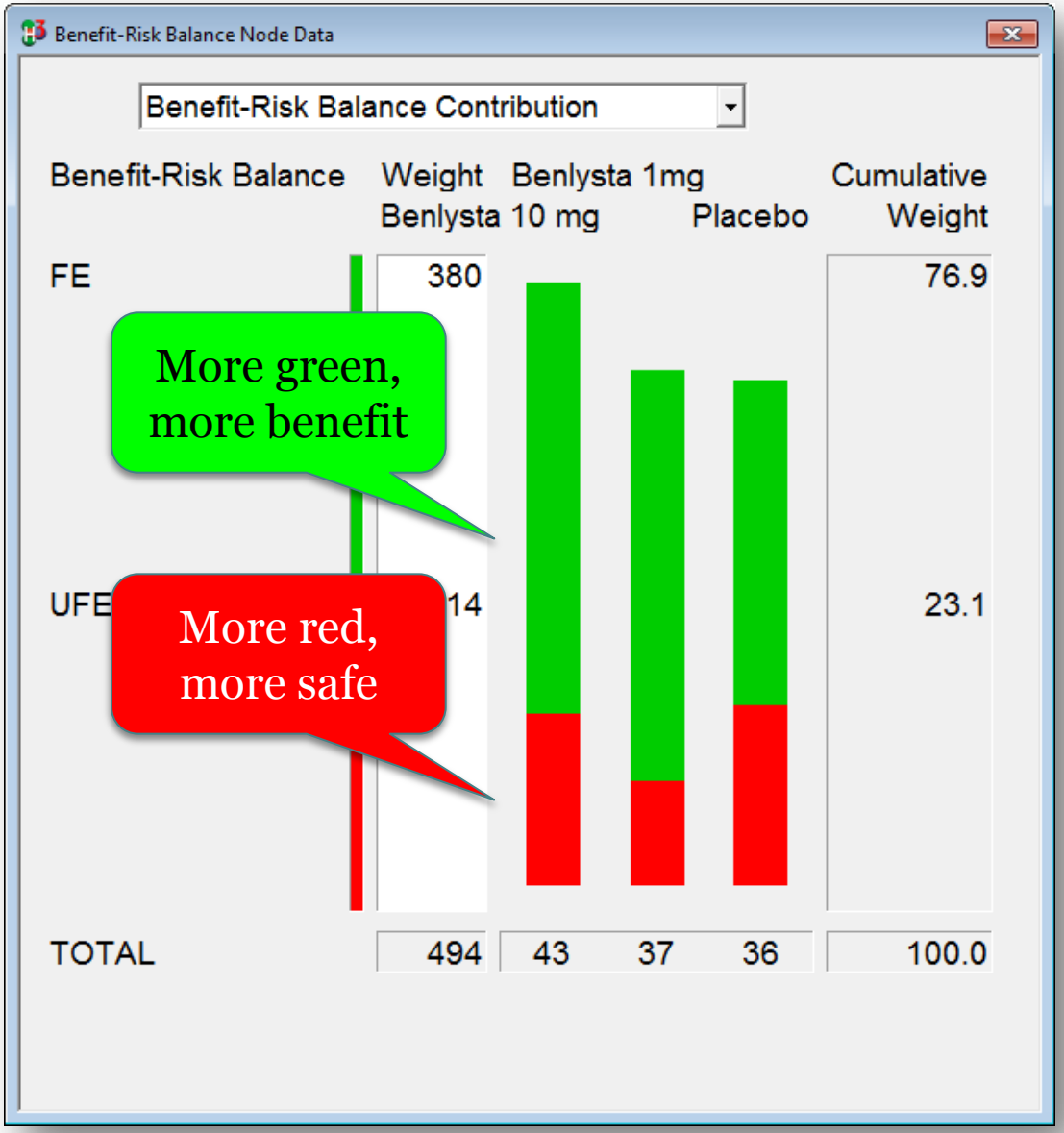
Combine weights and scores

- Calculate overall weighted scores at each node in the value tree.
- Calculate overall weighted scores, for each option, to give the overall preference ordering of the options.

  Overall score = Σ (criterion weight × score)
- This is a role for a computer, not for you!

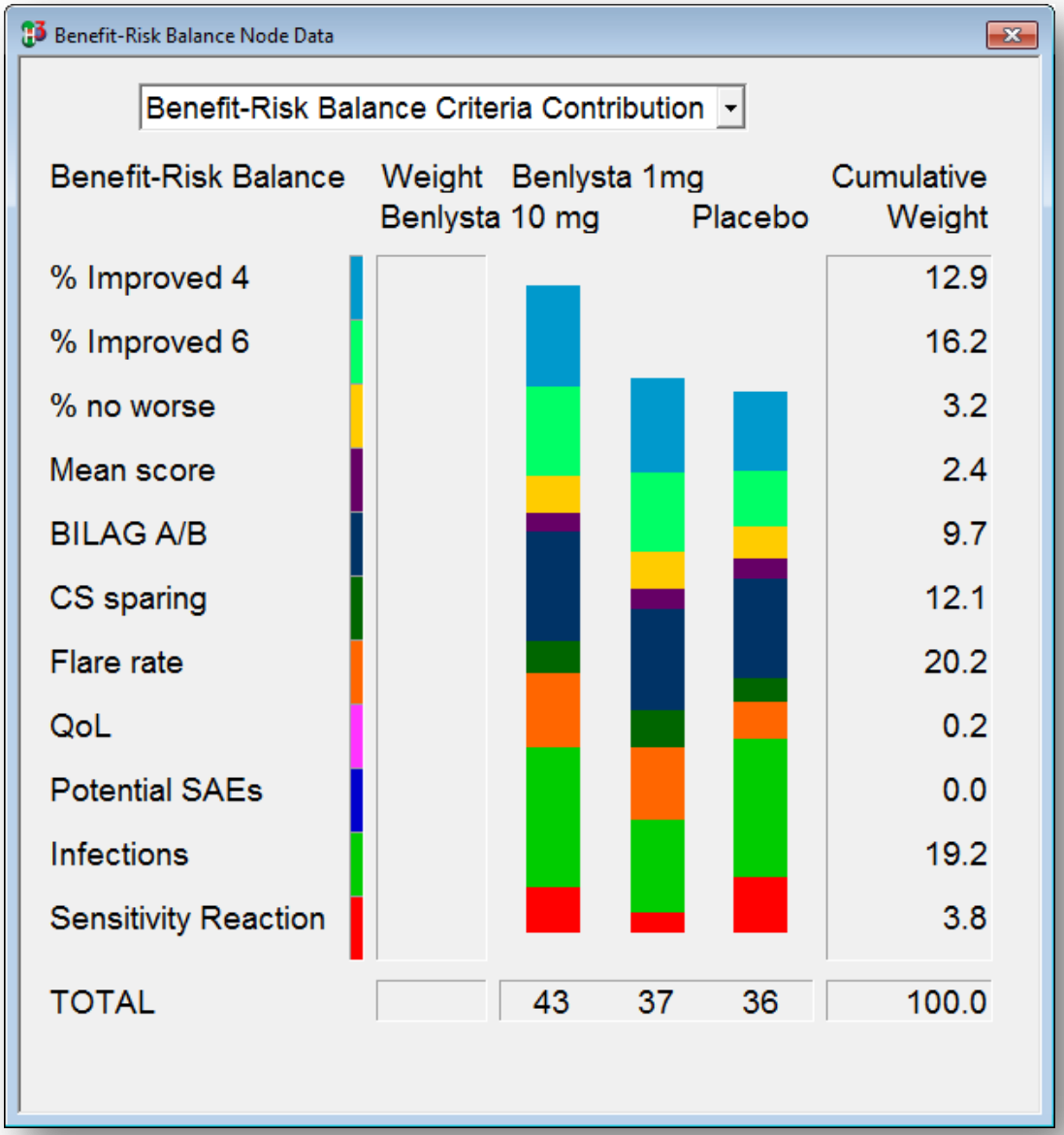
Examine results

Assuming zero weight on the criterion Potential SAEs



Examine results

Stacked bar graphs showing the added value on each criterion.



Show results—difference display

Sorts

Compare Benlysta 10 mg minus Placebo

	Model Order	Cum Wt	Diff	Wtd Diff	Sum
FE	Flare rate	20.2	12	2.5	2.5
SLEDAI	% Improved 6	16.2	14	2.3	4.8
SLEDAI	% Improved 4	12.9	12	1.6	6.3
FE	CS sparing	12.1	5	0.6	6.9
SRI	BILAG A/B	9.7	6	0.6	7.5
PGA	% no worse	3.2	9	0.3	7.8
UFE	Potential SAEs	0.0	-100	0.0	7.8
UFE	Infections	19.2	0	0.0	7.8
FE	QoL	0.2	-0	-0.000	7.8
PGA	Mean score	2.4	-4	-0.1	7.7
UFE	Sensitivity Reaction	3.8	-15	-0.6	7.2
		100.0		7.2	

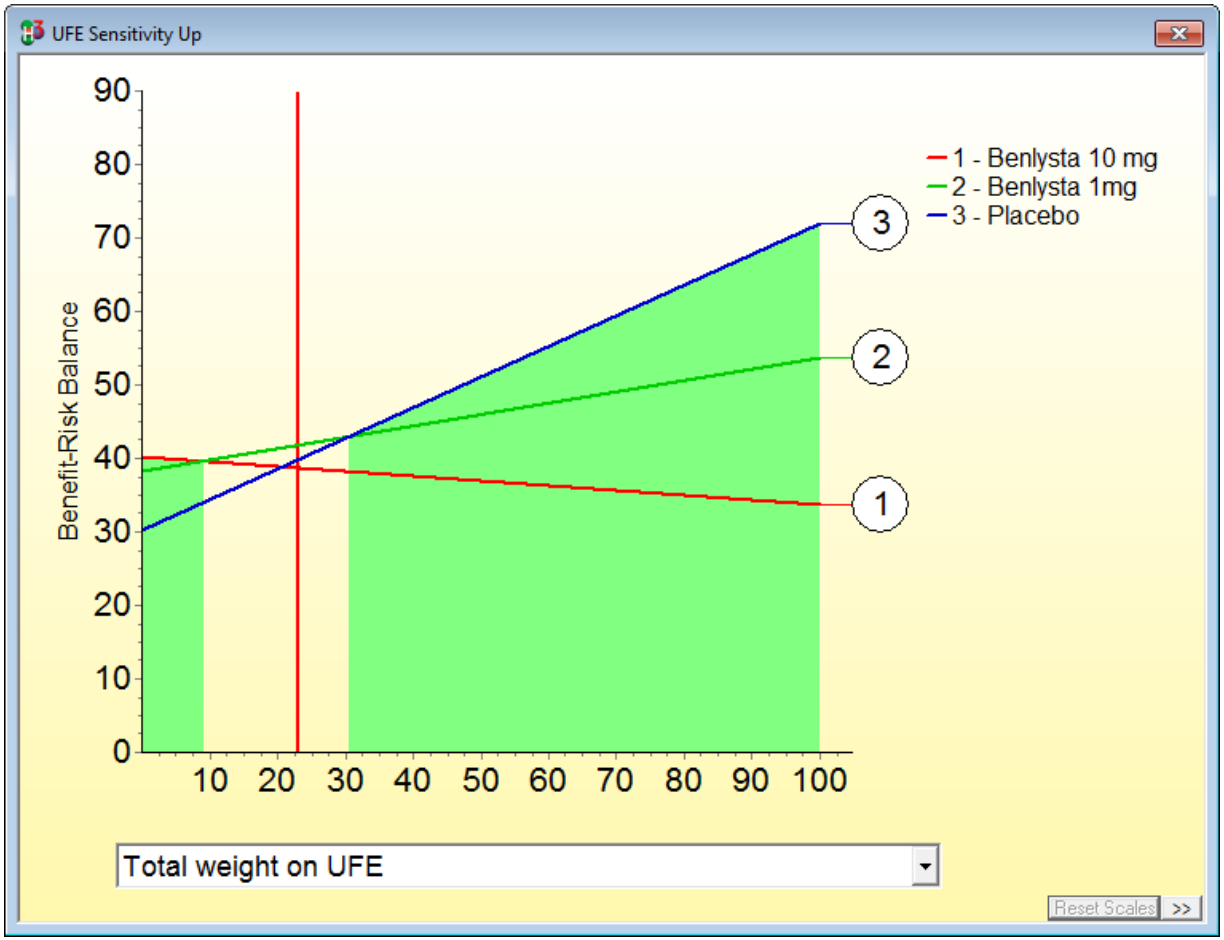
Advantages of 10mg

Advantages of Placebo

Uncertainty: Sensitivity analysis

Vary the weight on a criterion (UFE) over its entire range from 0 to 100.

Crossovers indicate a change in the most preferred option.

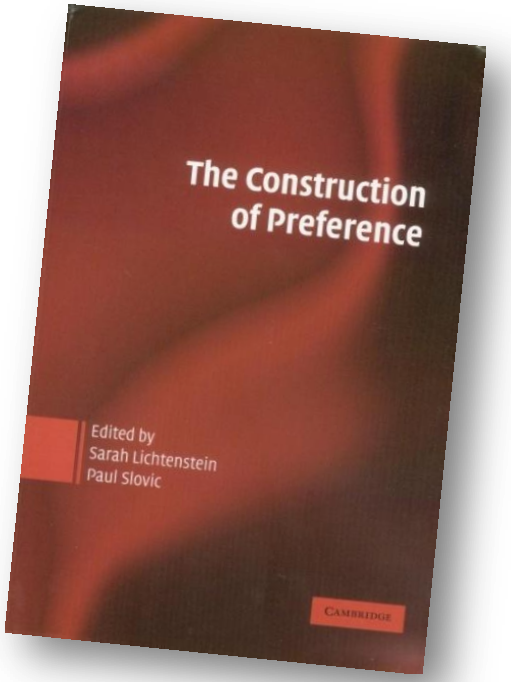


The decisions

- The US Food and Drug Administration approved the drug on 9 March 2011.
- The Committee for Human Medicinal Products of the European Medicines Agency issued a positive opinion for granting a Market Authorisation to Benlysta on 19 May 2011.
- NICE announced on 20 September 2011 that it was provisionally unable to recommend the drug.
- On 26 April 2012 the draft guidance from NICE said "belimumab could not be considered a good use of NHS resources compared with current clinical practice". Final guidance awaits.

What have I learned about MCDA?

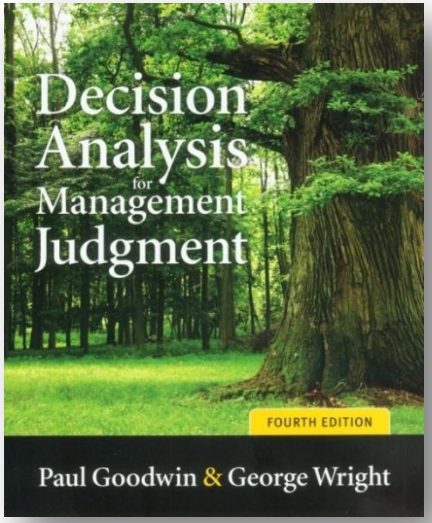
- Rational debate can be achieved within a deliberative discourse process.
- The process must provide structure for the debate: that is the role of MCDA.
- Technical processes are not sufficient; design of the social process is crucial.
- Values are constructed throughout the deliberative process, even with experts. MCDA is architecture, not archaeology.



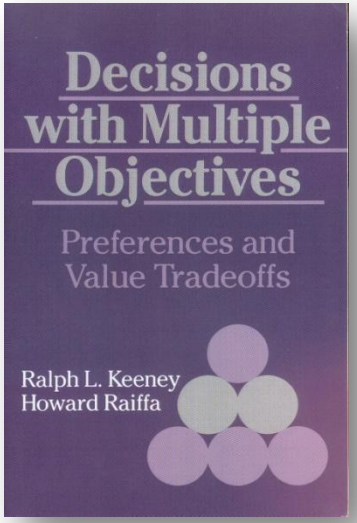
To sum up …

- MCDA does not give the ‘right’ answer, or a ‘scientifically correct’ answer. Nothing can.
- MCDA *does* provide a useful tool for thinking, and a serious guide to decision making.
- It is a model that ‘illuminates’; it provides clarity of decision making.
- MCDA enables rapid exploration of different perspectives on the issues.
- MCDA can be expanded with related model types
- However, MCDA requires careful design of social processes: engaging the right people in the right way at the right time.

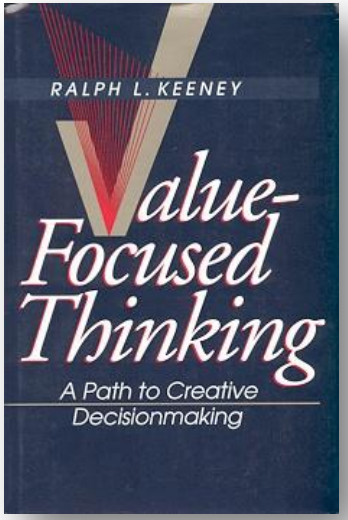
A guide to further reading



Wiley, 2009, 4th Ed.
MCDA in Chapter 3, prioritisation and resource allocation in Chapter 14.



Cambridge University Press, 1993
The book that introduced MCDA in 1976 (Wiley).



Harvard University Press, 1992.
Shows how to articulate values and make wise decisions.

Dodgson, J., Spackman, M., Pearman, A., & Phillips, L. (2000). *Multi-Criteria Analysis: A Manual*. London: Department of the Environment, Transport and the Regions, republished 2009 by the Department for Communities and Local Government. *Google the title to download a free copy. MCDA in Chapter 6.*