EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Quantitative Benefit-Risk: Determining values & assessing weights

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BBS Seminar
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Session Objectives

- *To demonstrate how quantitative modelling of benefit-risk, based on decision theory, can integrate data with clinical judgements.*
- *To suggest a framework for this integration*
- *To show how clinical judgements can be represented as value functions and criterion weights, assessed by groups of experts.*
- *To report the potential usefulness of this socio-technical process in research with five European Agencies.*

Current regulatory B-R assessment processes

Discussing

Voting

Defining ‘benefit’ and ‘risk’

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

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)

Available at ema.europa.eu. Click “Special topics” tab, scroll to “Benefit risk methodology” page

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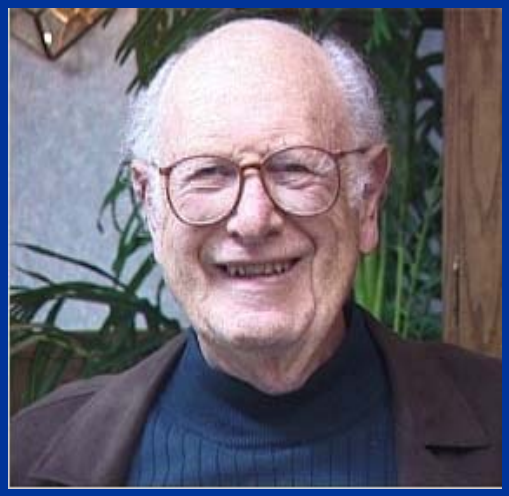


"The spirit of decision analysis is divide and conquer: decompose a complex problem into simpler problems, get one's thinking straight on these simpler problems, paste these analyses together with logical glue, and come out with a program of action for the complex problem"

(Howard Raiffa 1968, p. 271)

The PrOACT—URL process: Steps 1-5

PrOBLEM

1. Determine the nature of the problem and its context. Frame the problem.

OBJECTIVES

2. Establish objectives that indicate the overall purposes to be achieved and identify criteria of favourable and unfavourable effects.

ALTERNATIVES

3. Identify the options to be evaluated against the criteria.

CONSEQUENCES

4. Describe how the alternatives perform for each of the criteria, i.e., the magnitudes of all effects, and their desirability or severity, and the incidence of all effects. Create an Effects Table.

TRADE-OFFS

5. Assess the balance between favourable and unfavourable effects.

The PrOACT—URL process: Steps 6-8

At this point, only issues concerning the favourable and unfavourable effects, and their balance, have been considered. The next three steps are relevant in considering how the benefit-risk balance is affected by taking account of uncertainties.

UNCERTAINTY

6. Assess the uncertainty associated with the favourable and unfavourable effects. Consider how uncertainty affects the balance by conducting sensitivity analyses and scenario analyses on the model.

RISK TOLERANCE

7. Judge the relative importance of the decision maker's risk attitude for this product and indicate how this affects the balance reported in step 5.

LINKED DECISIONS

8. Consider the consistency of this decision with similar past decisions, and assess whether taking this decision could impact future decisions.

Decision Context for Drug X

Indication: Treatment of moderate to severe, active, rheumatoid arthritis in adult patients

Use: In combination with methotrexate (MTX) when the response to anti-rheumatic drugs (including MTX) has been inadequate

Efficacy: (2 clinical studies as add-on to MTX)

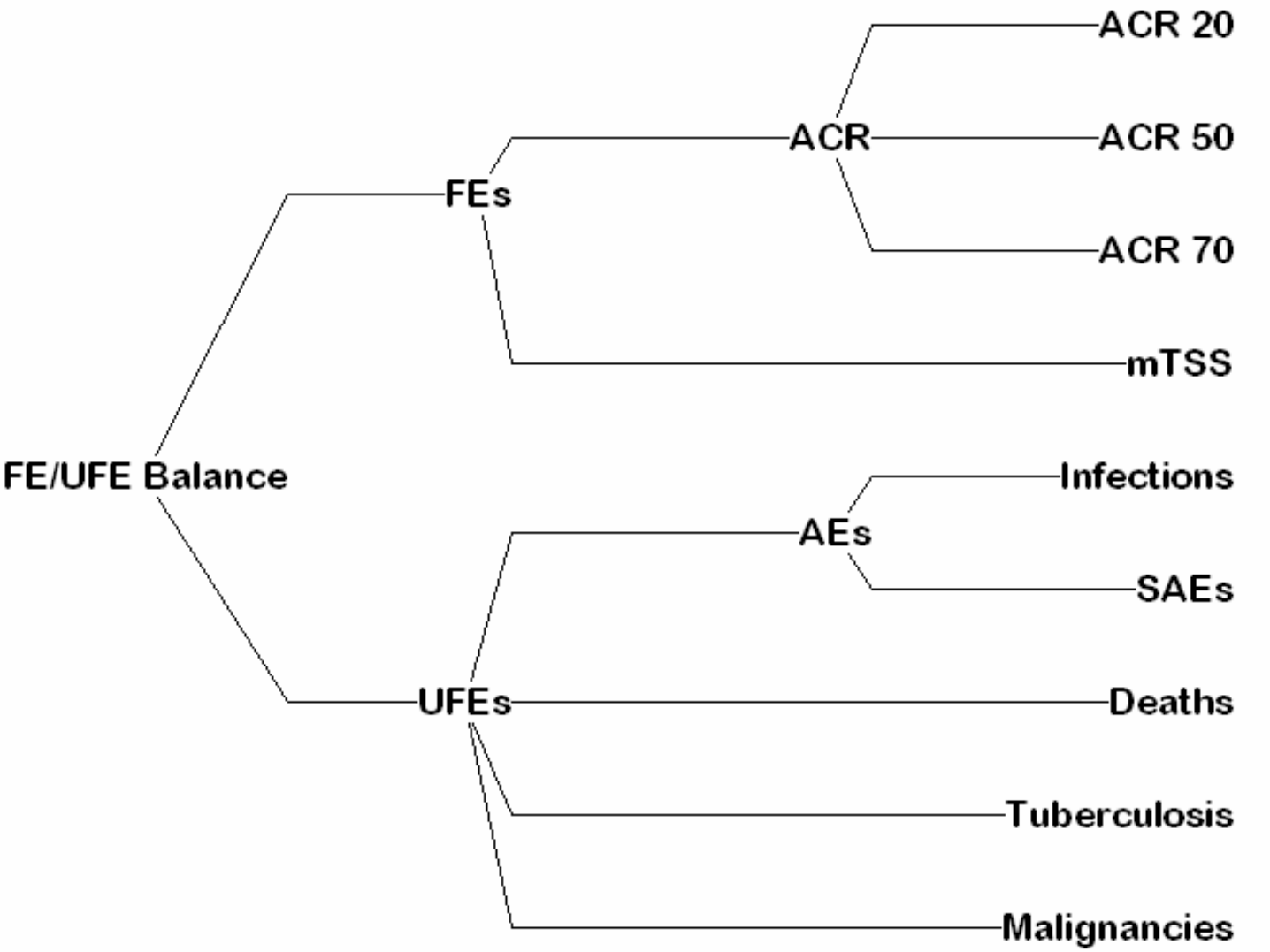
- Primary Endpoint: ACR 20 response at week 52
- Secondary Endpoints: ACR 50/70 & mTSS

Safety: (from 4 well-controlled, double blind Ph III studies in adult patients with RA)

Alternatives (all injected)

1. Placebo - MTX only
2. Drug X – 200mg + MTX
3. Drug X - 400mg + MTX

Objectives shown in an Effects Tree



Effects Table: Criteria Definitions

	Name	Description	Fixed Lower†	Fixed Upper†	Units	Placebo	Drug X 200 mg+MTX	Drug X 400mg+MTX
Favourable Effects	ACR 20	Proportion of patients achieving ACR 20 at week 24	0	100	%	11.7	58.2	59.6
	ACR 50	Proportion of patients achieving ACR 50 at week 24	0	100	%	5.8	34.8	36.6
	ACR 70	Proportion of patients achieving ACR 70 at week 24	0	100	%	2.4	18.8	16.1
	mTSS	Mean amount of progression of joint damage in hands and feet at week 52	0	10	Change Score±SD	2.8±7.8	0.4±5.7	0.0±4.8
Unfavourable Effects	Infections	Proportion of patients experiencing infections & infestations	70	80	No. per 100 pt-yrs	72.13	79.88	76.62
	SAEs	Proportion of patients experiencing musculoskeletal & connective tissue disorders	25	60	No. per 100 pt-yrs	57.05	28.39	25.88
	Deaths	Proportion of patient deaths	0	3	%	0.15	0.42	0.97
	Tuberculosis	Number of patients contracting tuberculosis	0	30	Number	0	5	28
	Malignancies	Proportion of patients developing at least one malignancy	0	2	%	0.9	1.9	1.4

† Lower to Upper Limits define the range of a measurement scale that includes all the data for each criterion and is meaningful for assessing swing weights.

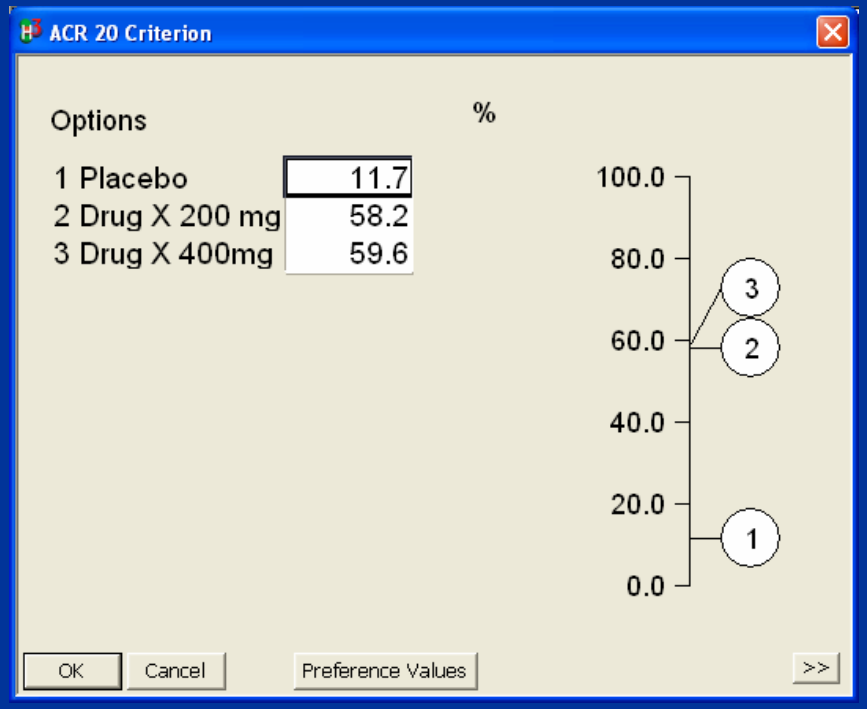
Decision Conference

- A one-to-three-day workshop
- To resolve important issues of concern
- Attended by key players who represent the diversity of perspectives on the issues
- 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

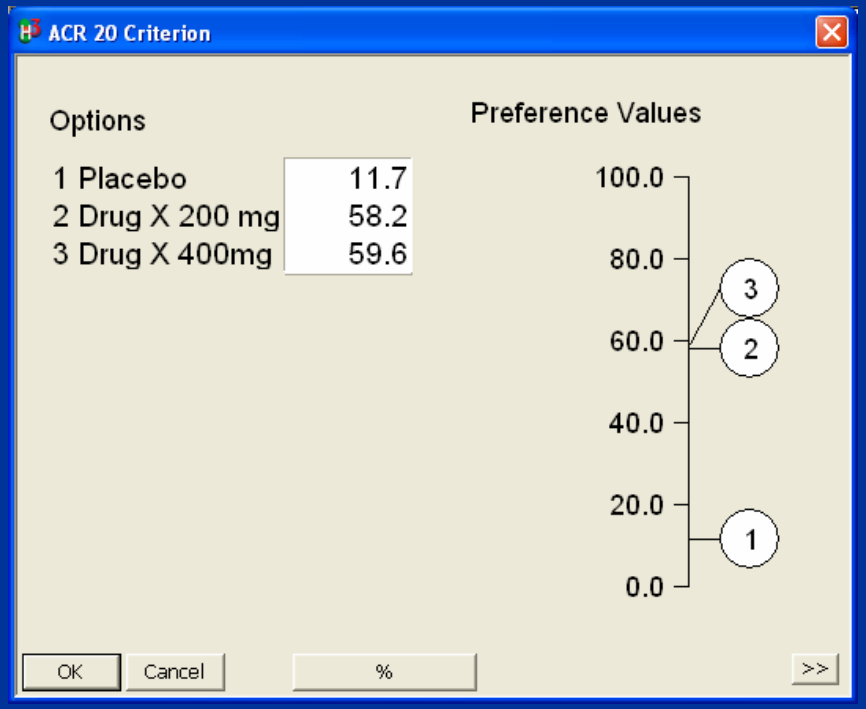
Ref: Phillips, L. D. (2007). Decision Conferencing. In W. Edwards, R. F. Miles & D. von Winterfeldt (Eds.), *Advances in Decision Analysis. Cambridge: Cambridge University Press.*

Measured data ⇨ 0-100 values: direct

ACR 20 measures

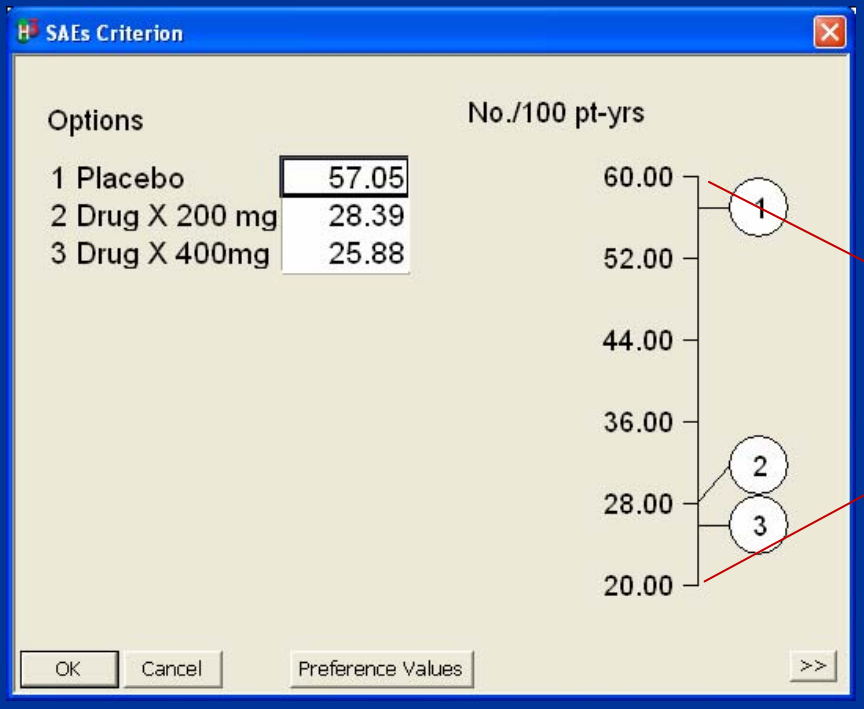


Preference values

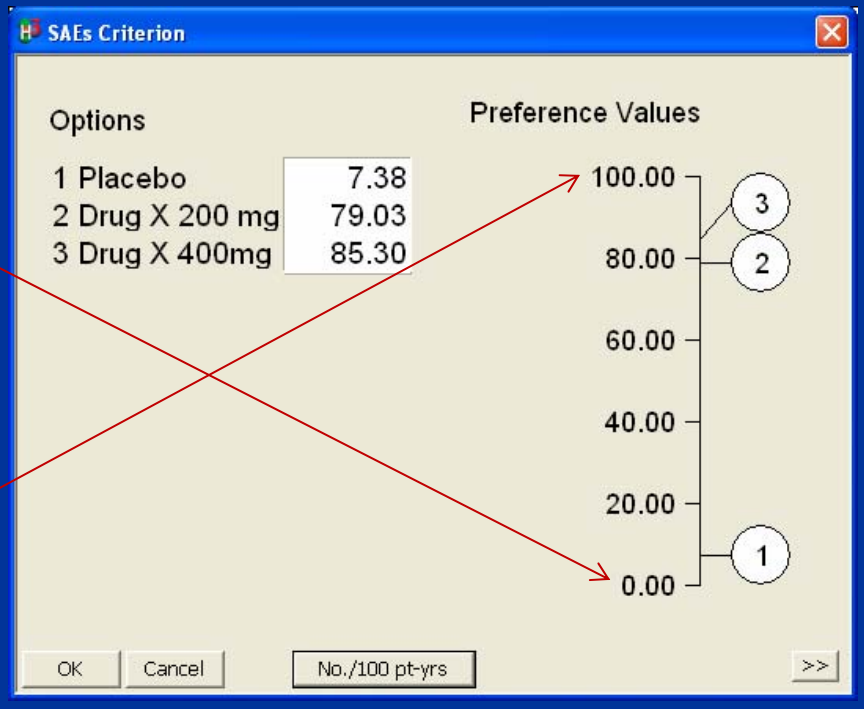


Measured data ⇨ 0-100 values: inverse

SAEs*

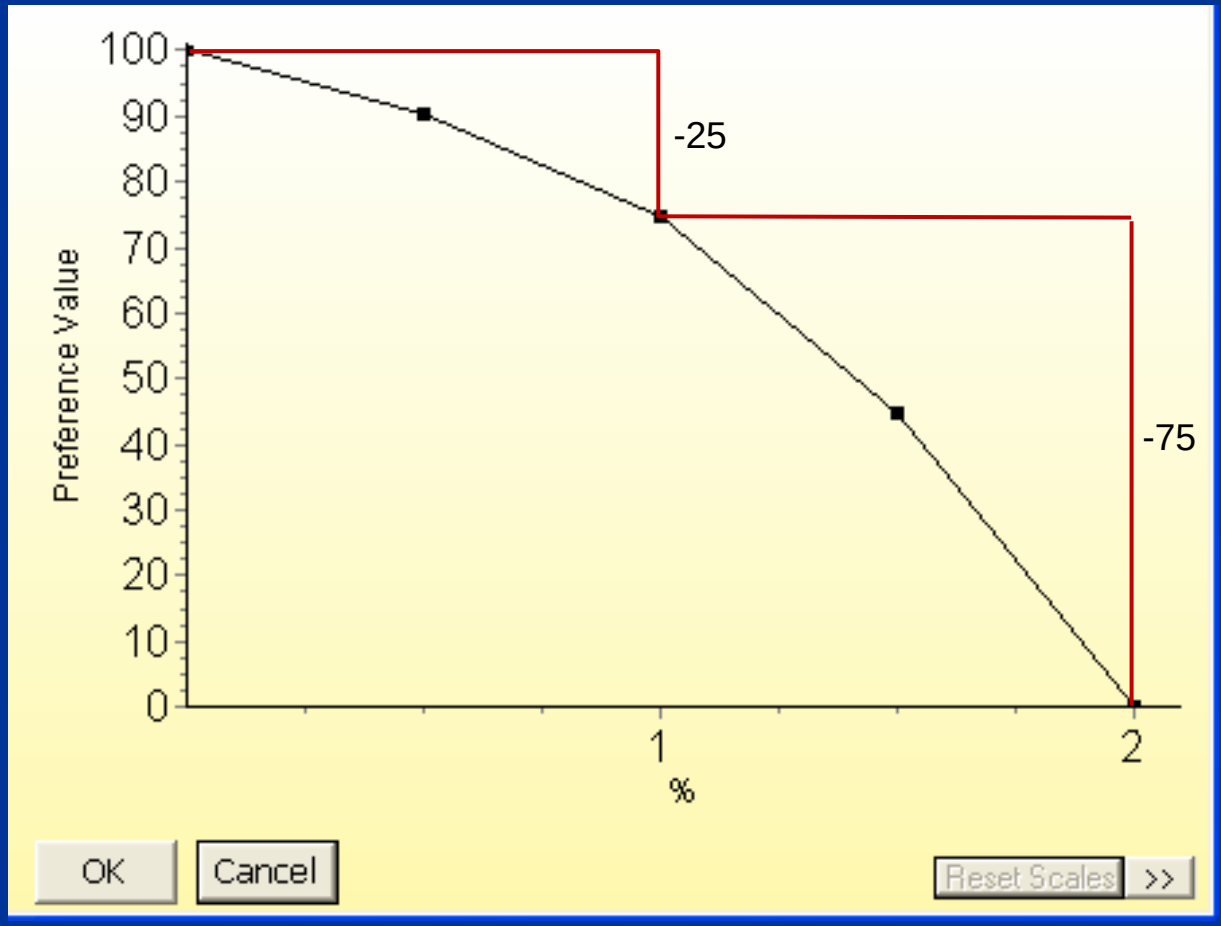


Preference values

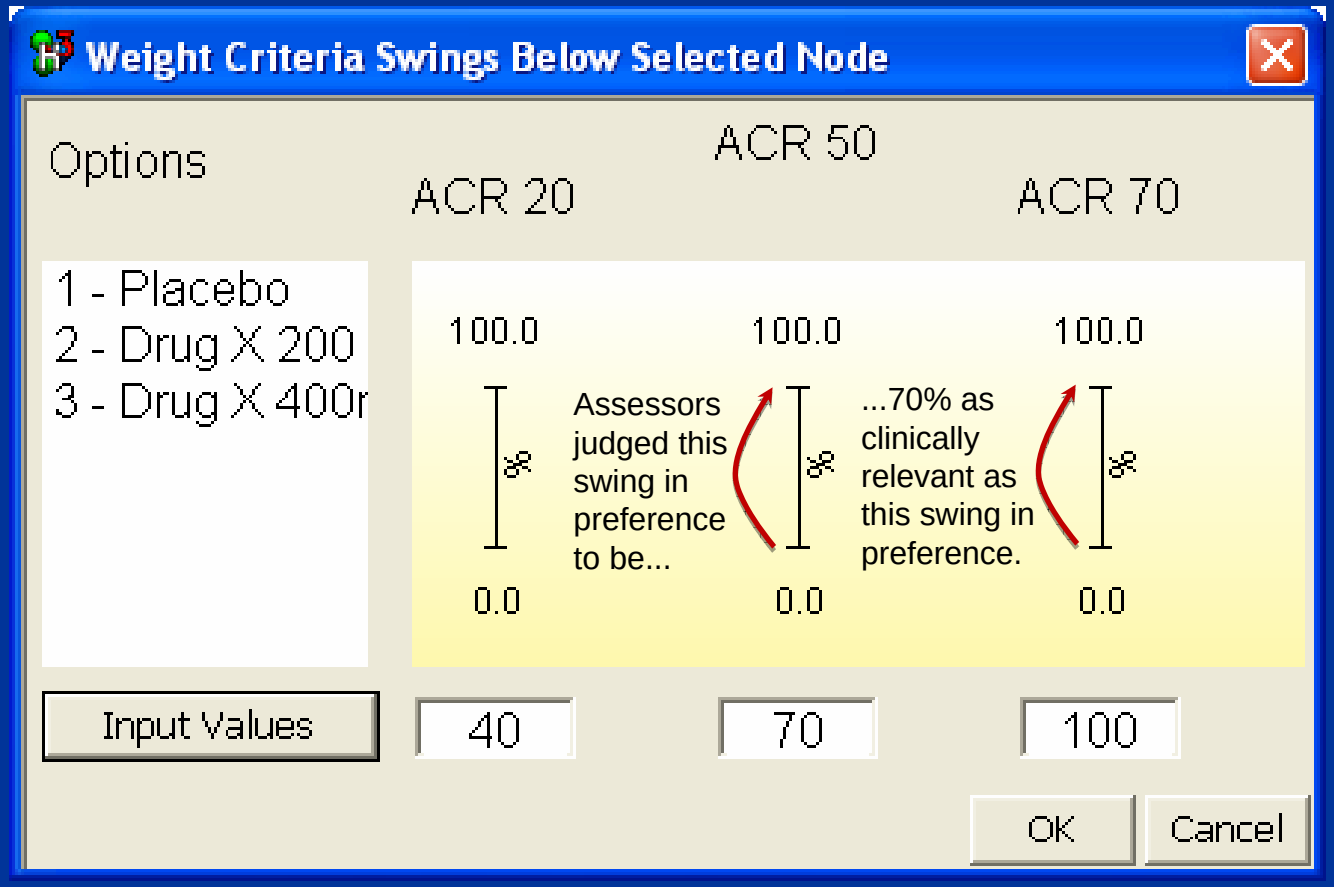


* Musculoskeletal & connective tissue disorders

Value Function for Malignancies



Swing Weighting



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

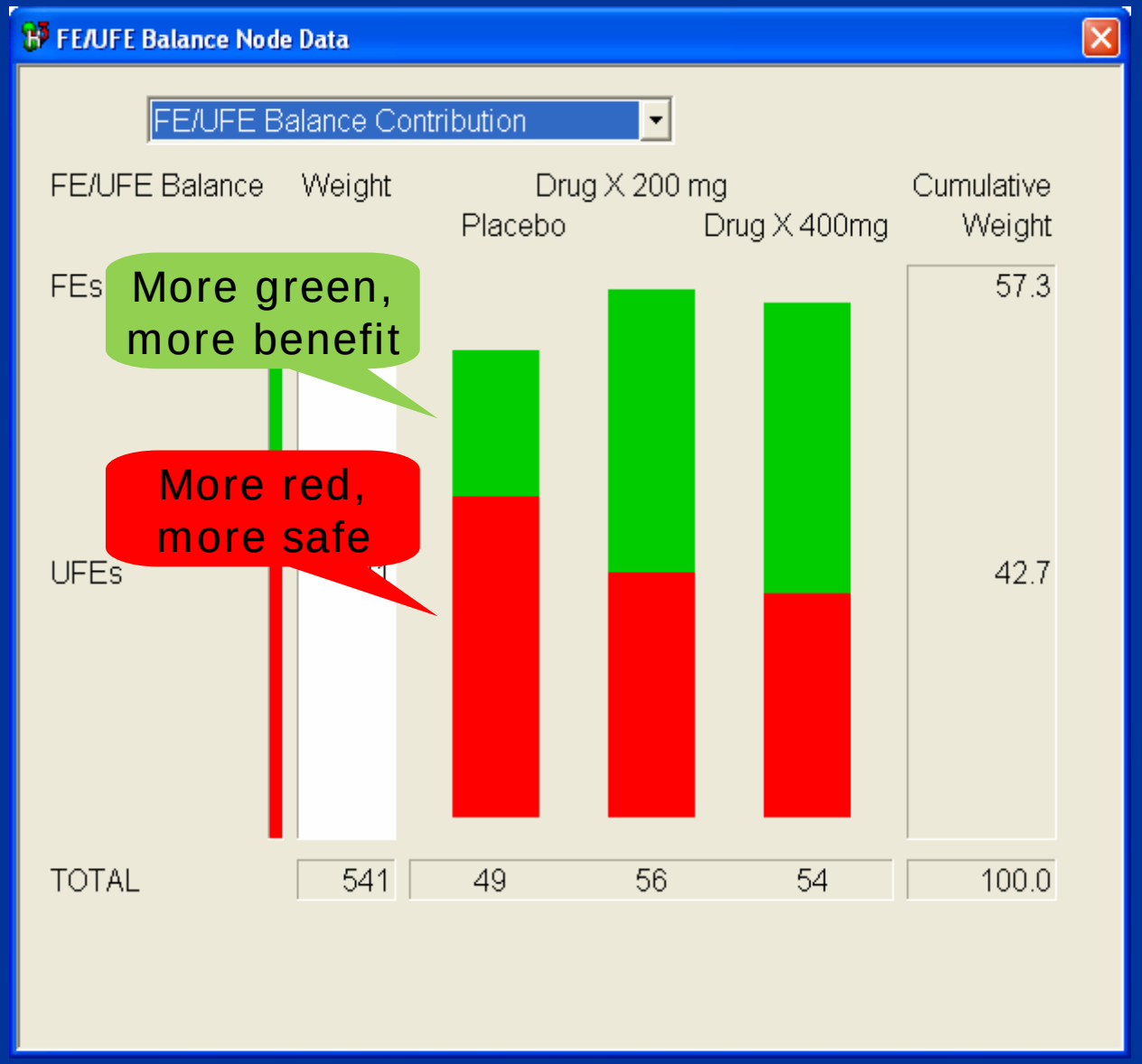
Calculate overall results

- Normalise the weights so they sum to 100 over the nine effects (which retains their ratios)
- Multiply the preference values by their corresponding weights
- Sum the products for each option

Total preference value =
Σ weight $\times$ preference value

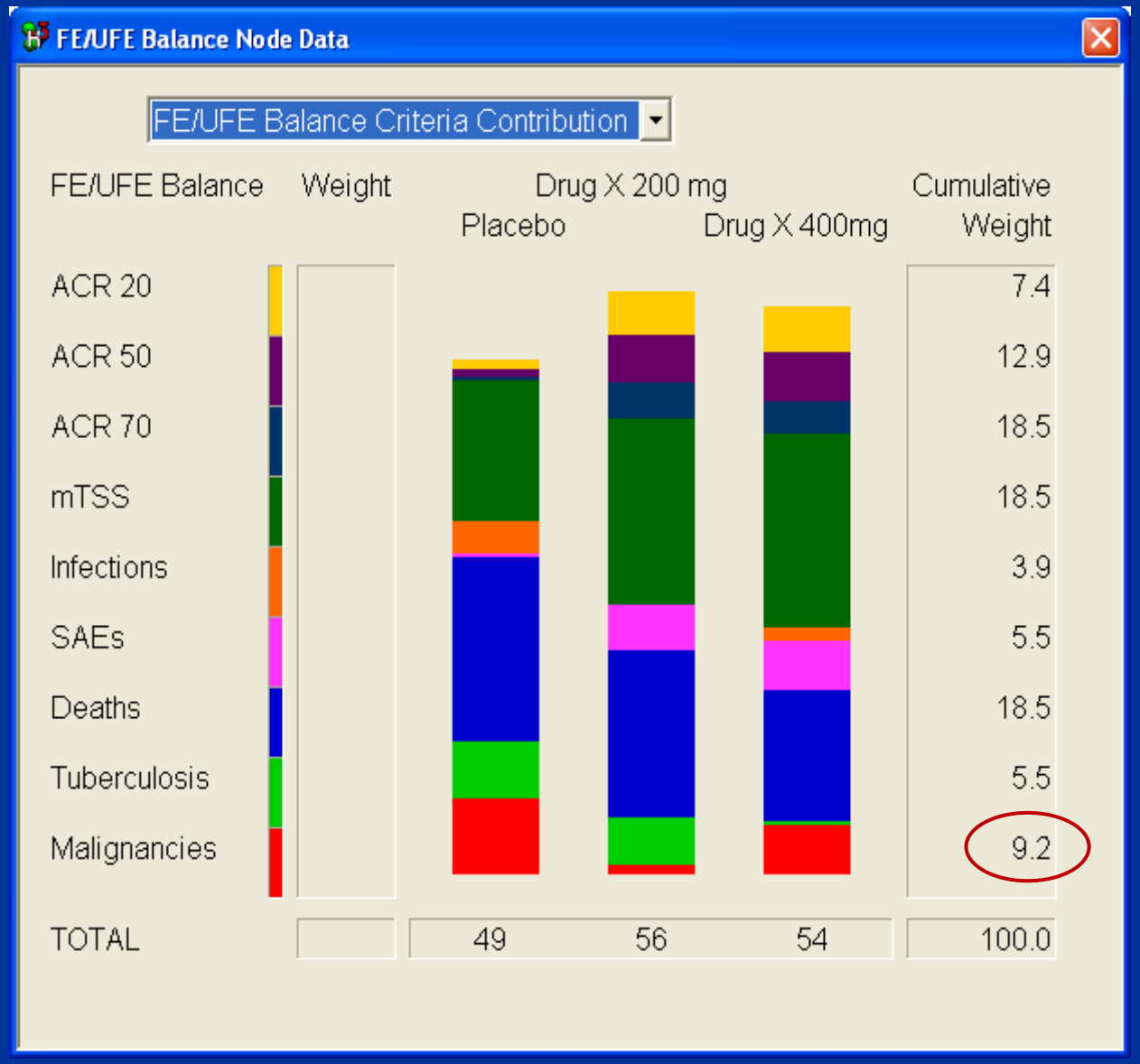
Added-value bars for FEs & UFEs

Base Case

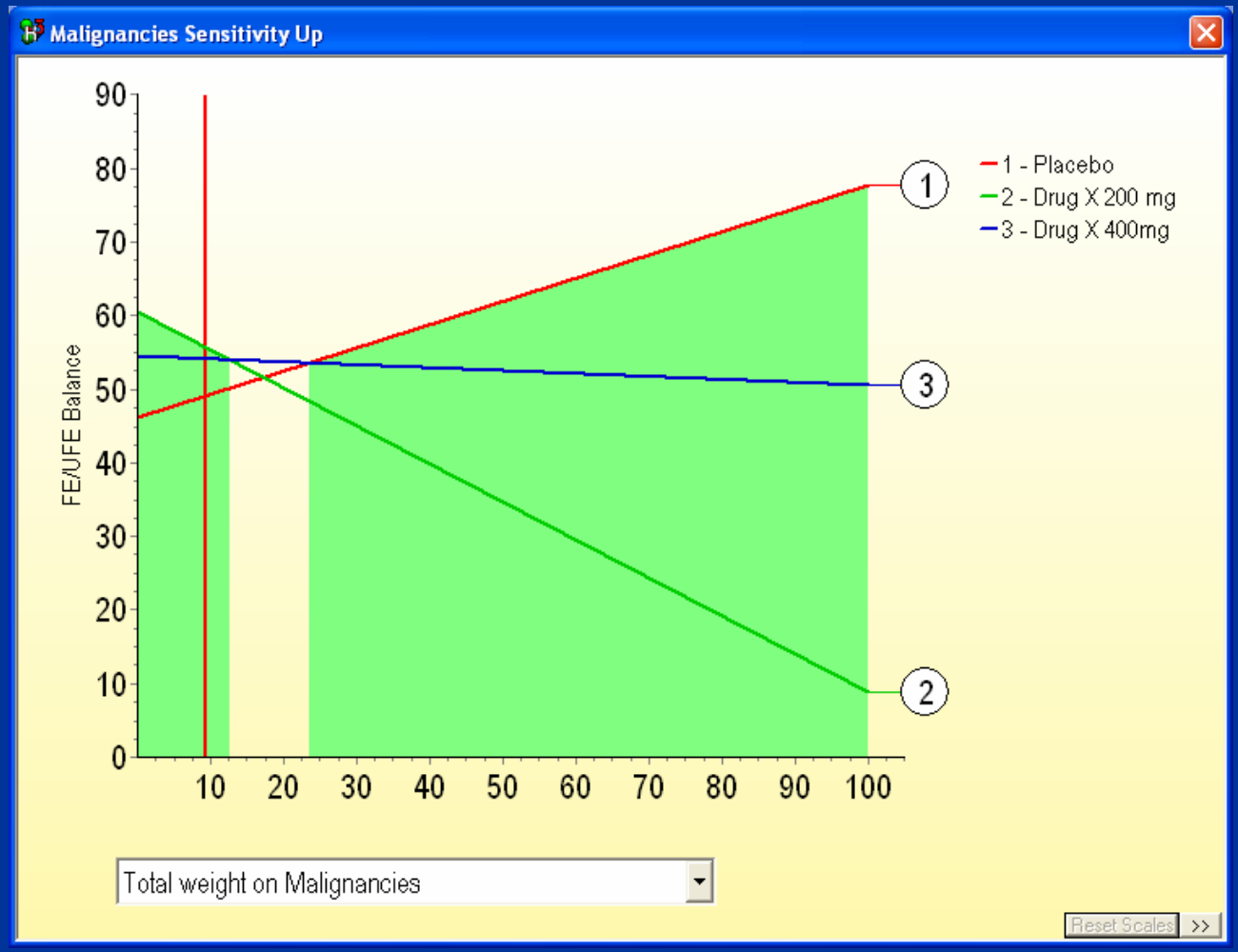


Added-value bars for each effect

Base Case

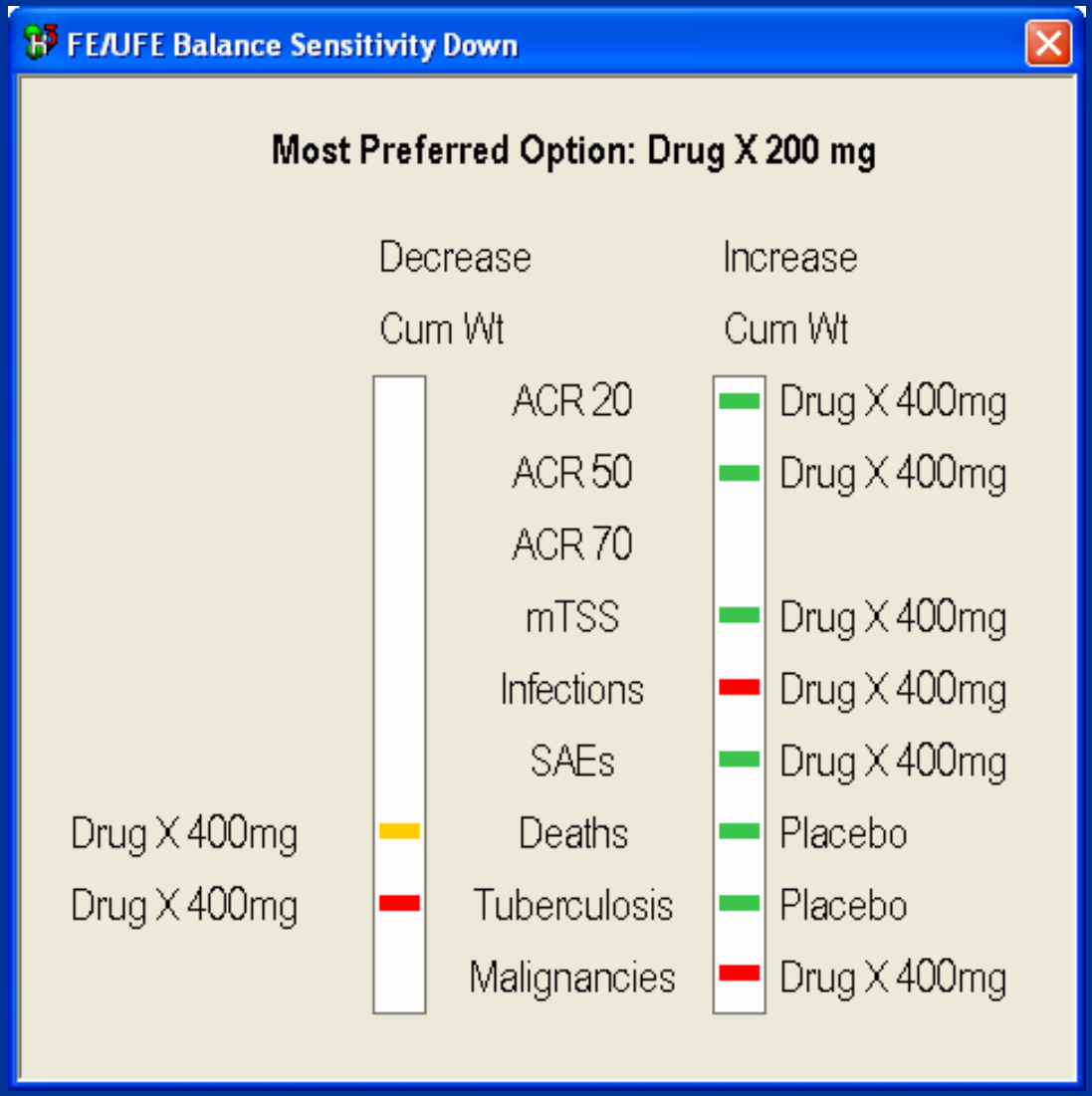


Sensitivity Analysis on Malignancies



Sensitivity Analyses on each Effect

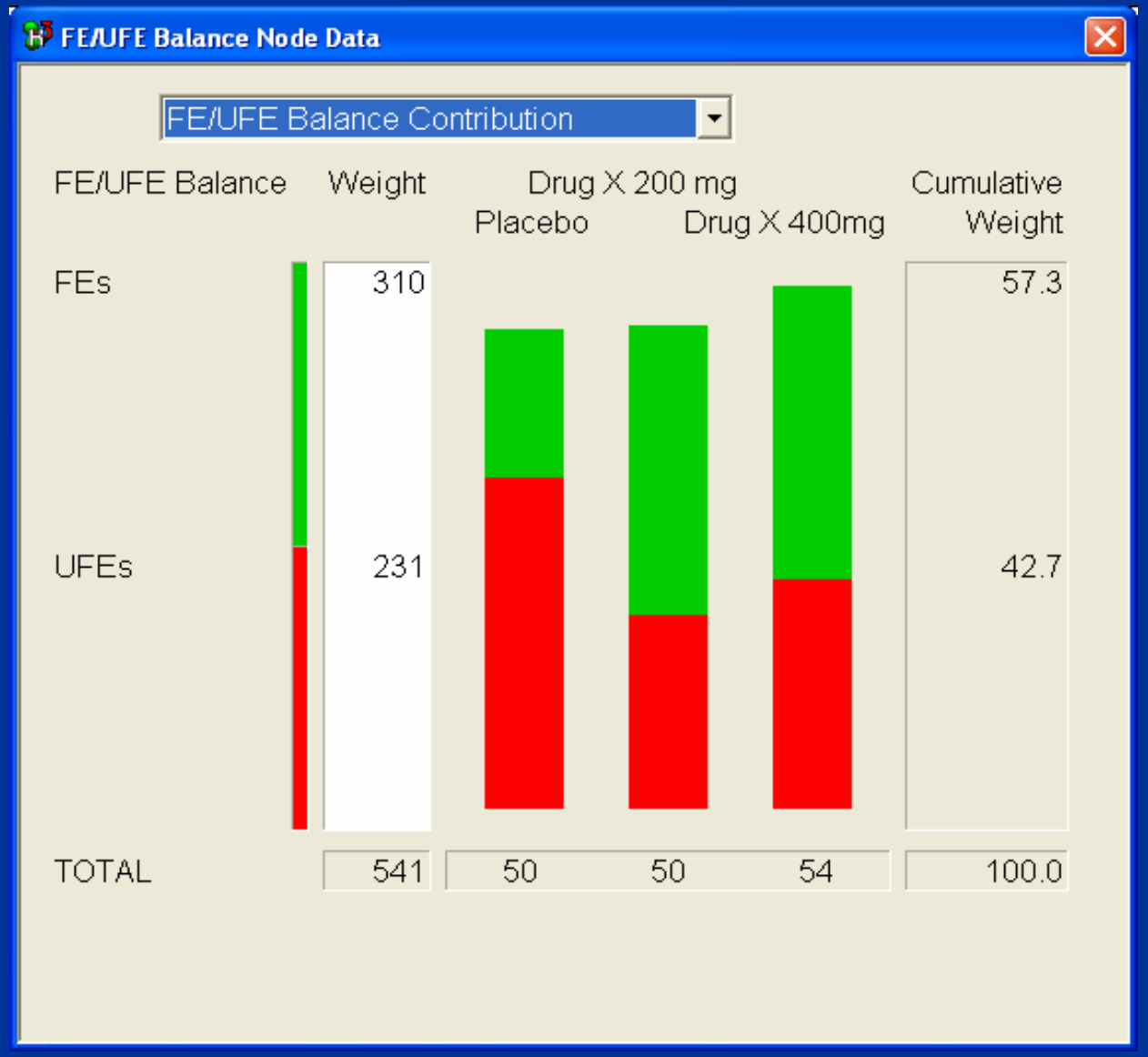
Most preferred option changes if cumulative weight changes by...
...>15 points
...5 to 15 points
...< 5 points



Scenario Analysis

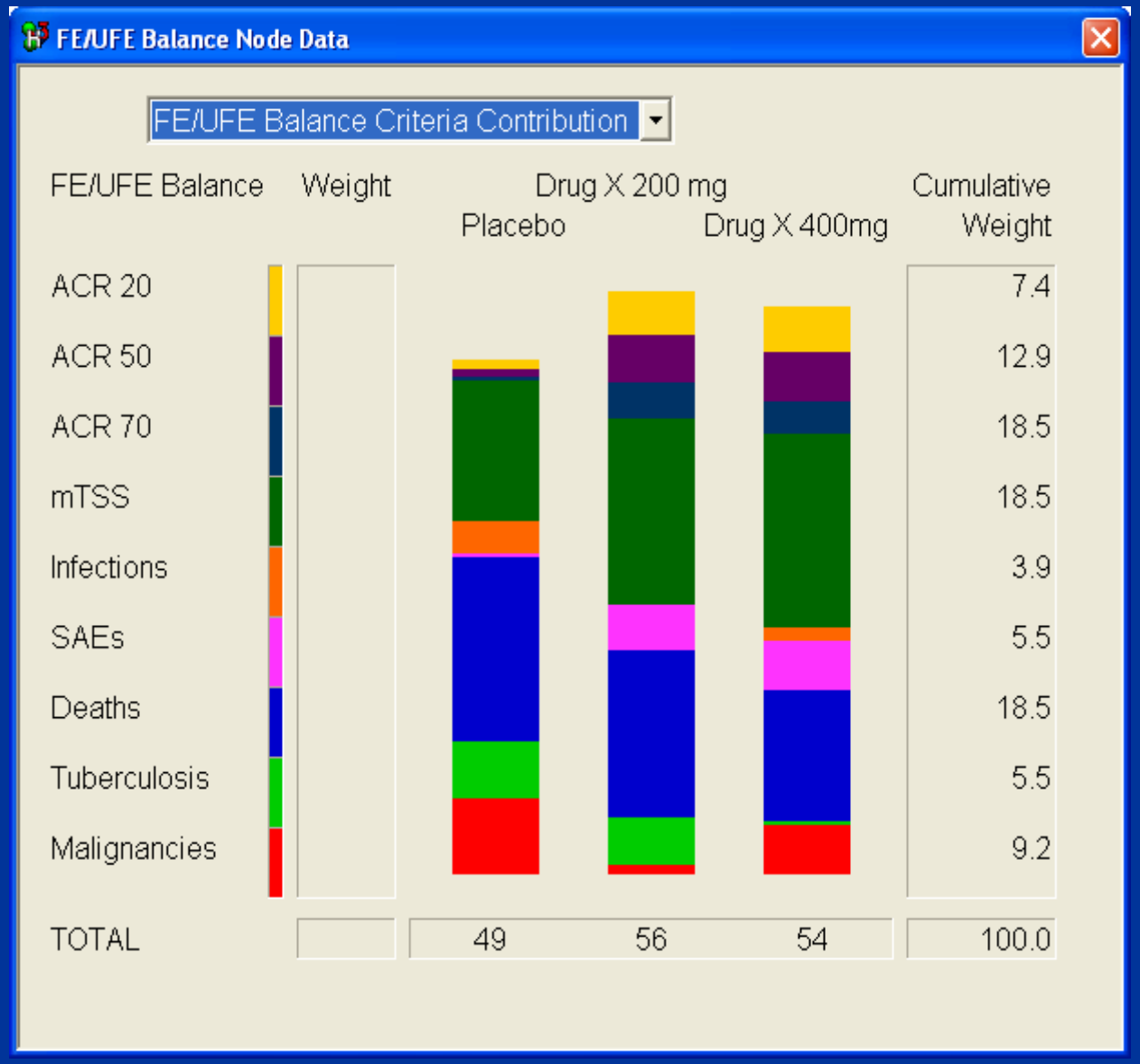
Less concern for Tuberculosis, more for Infections and Malignancies:

Tuberculosis wt ÷ 2
Infections wt × 2
Malignancies wt × 2

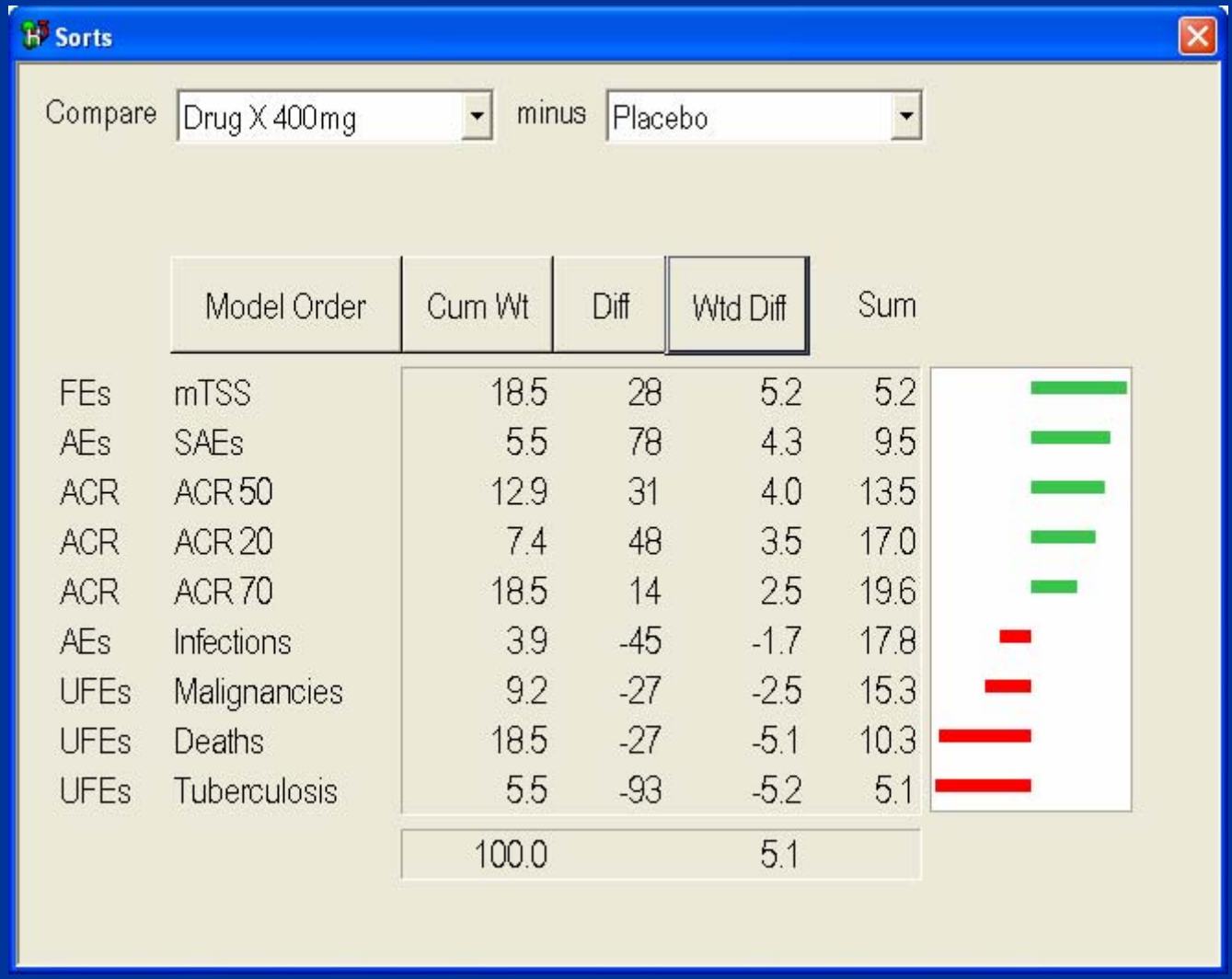


Added-value bars for each effect

Base Case



Difference Display, 400mg vs. Placebo

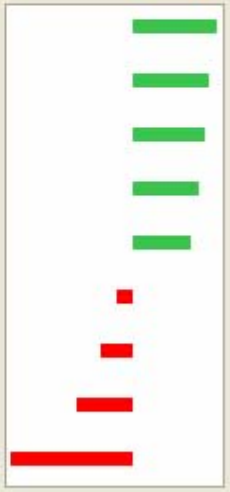


Difference Display, 200 mg vs. Placebo

Sorts

Compare: Drug X 200 mg — minus: Placebo

	Model Order	Cum Wt	Diff	Wtd Diff	Sum
FEs	mTSS	18.5	24	4.4	4.4
AEs	SAEs	5.5	72	4.0	8.4
ACR	ACR 50	12.9	29	3.8	12.2
ACR	ACR 20	7.4	47	3.4	15.6
ACR	ACR 70	18.5	16	3.0	18.6
UFEs	Tuberculosis	5.5	-17	-0.9	17.7
UFEs	Deaths	18.5	-9	-1.7	16.0
AEs	Infections	3.9	-78	-3.0	13.0
UFEs	Malignancies	9.2	-69	-6.4	6.7
		100.0		6.7	



Difference Display, 200mg vs. 400mg

Sorts

Compare: Drug X 200 mg — minus: Drug X 400mg

	Model Order	Cum Wt	Diff	Wtd Diff	Sum
UFEs	Tuberculosis	5.5	77	4.3	4.3
UFEs	Deaths	18.5	18	3.4	7.6
ACR	ACR 70	18.5	3	0.5	8.1
ACR	ACR 20	7.4	-1	-0.1	8.0
ACR	ACR 50	12.9	-2	-0.2	7.8
AEs	SAEs	5.5	-6	-0.3	7.5
FEs	mTSS	18.5	-4	-0.7	6.7
AEs	Infections	3.9	-33	-1.3	5.5
UFEs	Malignancies	9.2	-42	-3.9	1.6
		100.0		1.6	

Magic number seven, plus or minus two


George A Miller

1956: Short-term memory is limited to 7 ± 2 items

Similar items are 'chunked' into memorable items

Chunks are organised in hierarchies

Miller, G. A. (1956). The magical number seven, plus or minus two: some limits on our capacity for processing information. *Psychological Review, 63(2), 81-97.*

EMA B-R Project Field Tests

- Five Agencies participated
- 4-6 participants, including assessors, for every facilitated workshop (decision conference)
- Decision analysis model created for each in one day—6 hours or less
- Separate report for every workshop summarised the exercise and identified those processes, tools and organisational structures that were found in differences between post- and pre-questionnaires to add value to the process of benefit-risk assessment

Questionnaire findings: The modelling process...

- can easily test different perspectives for their impact on the results (*average change on 7-point scale:* 2.95),
- helps us explore how the overall balance is affected by a reduction or increase in uncertainty (2.47),
- helps me to see the impact of uncertainties on the benefit-risk balance (1.84),
- has an overt and clear structure (1.42),
- helps us combine data about value and uncertainty into an overall balance between favourable and unfavourable events (1.42), and
- helps us make our assumptions, multiple objectives and trade-offs explicit (1.37).

Ref: Phillips, L. D., Fasolo, B., Zafiropoulos, N., & Beyer, A. (2011). Is quantitative benefit-risk modelling of drugs desirable or possible? *Drug Discovery Today: Technologies, doi:10.1016/jddtec.2011.03.001.*

DA modelling + Social Process

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THANK YOU!