Benefit-risk methodology project: work package 4 report: benefit-risk tools and processes

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Report by the EMA Benefit-Risk Methodology Project Team

1. Introduction

The main objective of the EMA Benefit-Risk Methodology Project [1] is the development and testing of tools and processes for balancing multiple benefits and risks, which can be used as an aid to informed, science-based regulatory decisions about medicinal products. The project consists of five consecutive work packages. The first work package reported on the current practice of benefit-risk assessment in the centralised procedure for medicinal products in the EU regulatory network [2]. The report of that work package described processes at the six participating agencies, all of which effectively serve the centralised procedure, but in different ways.

The second work package examined the applicability of three frameworks and 18 quantitative approaches for assessing the benefit-risk balance [3]. We found that decision analysis [4], the applied technology that arose from decision theory [5], can provide a theoretically-sound basis for quantifying favourable and unfavourable effects, including their clinical relevance and associated uncertainties, on a common scale that shows the balance between benefits and risks. We proposed taking forward an elaboration of one framework, PrOACT-URL [6], which is based on experience in applying decision analysis. We also recognised the potential for supplementing decision analysis modelling with five other approaches: probabilistic simulation, Markov processes, Kaplan-Meier estimators, QALYs and conjoint analysis.

Support for our view about combining methodologies came in the summer of 2010 when four post-graduate students from the London School of Economics studying operational research and decision sciences modelled four drugs previously approved by the EMA. A variety of model combinations were used, all were based on decision theory.

The experiences of the students contributed to work package 3, field testing of models for five drugs that were then under review by the CHMP [7]. Working with teams of four to six assessors in the National Competent Authorities (NCA), we found that multi-criteria decision analysis (MCDA) models were directly relevant to the issues faced by the teams. We completed a model for each team on-the-spot in less than one working day, as a separate exercise from the scientific assessment.

Participants were given a 20-item questionnaire at the start and end of each workshop to determine how the modelling approach compared to the usual process of preparing an assessment report. For all 20 questions, on average, the group modelling was rated higher. In particular, participants gave higher ratings for the modelling approach's ability to test easily the impact of different perspectives on the benefit-risk balance, provide a means to see the impact of uncertainty, provide a clear and overt structure, combine evidence with judgements of clinical relevance, and make assumptions, multiple objectives and trade-offs explicit.

Overall, the field trials demonstrated the feasibility of a workshop approach to assessing the benefit-risk balance of a medicinal product, guided by a framework and a quantitative model. The findings of

the Benefit-Risk Project through Work Package 3 were published in *Drug Discovery Today—Technology* [8].

2. Recommended Tools and Processes

The task of Work Package 4 was to synthesize information from the field test and develop a benefit-risk tool and process that can add value in other domains. At the start of the work package, it was clear that MCDA would be the most relevant tool (though occasionally a decision tree might be more appropriate, especially when the problem is dominated by uncertainty), and that the PrOACT-URL framework could provide a useful guide to the steps in determining the benefit-risk balance of a medicinal product.

The report for WP3 [7] recognised that a complete quantitative model might not be necessary to assist regulators in assessing a drug. That report suggested two gradations of assistance, assuming that the assessment is not so obvious that no help is needed: (1) applying the PrOACT-URL model with no quantitative modelling may be sufficient, or (2) developing a simple MCDA model following the eight steps (which are consistent with PrOACT-URL) explained in chapter 6 of *Multi-Criteria Analysis: A Manual* [9]; no special software other than Excel is required.

In short, a full MCDA model would be most useful for difficult or contentious cases. These could arise when the benefit-risk balance is marginal and could tip either way depending on judgements of the clinical relevance of the effects, favourable or unfavourable, and in the case of many conflicting attributes.

We also see a key role for quantitative modelling for European regulators as they devise plans for implementing the new European Community pharmacovigilance directive [10, 11]. The process of monitoring the benefit-risk balance of a medicinal product post-approval could be supported in complex or marginal cases if a quantitative model was available. As new data are received it would be possible to update the model with the new information to see if the benefit-risk balance has changed.

The remainder of this report explores the development of the PrOACT-URL framework since Work Package 3, discusses the importance of the Effects Table, and emphasises the value of the graphical displays as produced for the five models in WP3.

2.1. PrOACT-URL framework

This extends the work begun in the WP2 report from the EMA's Benefit-Risk Project. The current version, shown in Appendix 5.1, is useful as a framework for evaluating the benefit-risk profile, whether or not a quantitative model is created. Its use is illustrated in detail in the Appendix.

2.2. Effects Table

Step 6 of the PrOACT-URL model suggests creating an Effects Table, detailed in Appendix 5.2. The table displays all the favourable and unfavourable effects that assessors consider as influencing the benefit-risk balance, along with definitions of the effects, the unit of measurement for each effect with the plausible range of data, and the measured data (pooled or separately for each clinical trial) associated with the medicinal product and any comparators, including confidence intervals where appropriate. A final column in the table is reserved for brief comments about uncertainties remaining in the minds of assessors.

The table provides a compact display which enables a reader quickly to see what effects and accompanying information were taken into account in evaluating the benefit-risk balance of the drug.

2.3. MCDA modelling

The theory of modelling decisions with multiple objectives was introduced in 1976 by Keeney and Raiffa [12], who extended decision theory to allow consideration of decision outcomes that are multi-attributed. It is this theory that admirably serves the multiple criteria that must be considered in judging the benefit-risk balance of a medicinal product.

In its additive form, which is suitable for most drug-approval decisions, it is fairly easy to create an MCDA model in Excel, particularly for the simpler representations as mentioned above. However, providing good sensitivity analysis capabilities allied to effective graphical displays of results is usually best accomplished using specialised software, such as V·I·S·A[1], Logical Decisions[2] or Hiview3[3].

2.4. Graphical displays

The five models reported in WP3 were created using Hiview3, software that was originally developed at the London School of Economics in the early 1980s. It was designed to be used in a group setting, and provides extensive graphical displays of results.

Appendix 5.4 shows three graphical displays based on the five drugs modelled in WP3. The first display gives overall scores for the alternatives, with stacked bar graphs showing the separate contribution of benefit and safety. The second display shows how the overall benefit-risk difference between two alternatives, e.g. a drug and the placebo, is made up of the separate weighted differences on the effects. For example, if the drug scores overall five points higher than the placebo, then that difference is broken down into the 'part score differences' contributed separately by each effect. The third graph indicates how robust the overall result is to changes in the weights on each of the individual effects. The computer changes the current cumulative weight on each effect over its entire possible range from 0 to 100, and notes whether at any stage a different overall result occurs. A red bar shows that a slight change of less than 5 points can change the result; a yellow bar, 5 to 15 points results in a change; while a green bar requires a change of more than 15 points. No coloured bar indicates that the overall result is unaffected by any weight from 0 to 100. Thus, a display that shows just a few green bars provides a robust result; substantial shifts in the data or in the judged clinical relevance of the effects would be required before the overall benefit-risk balance would favour a different option. At the other extreme, many red bars would indicate a delicately-balanced result.

We believe that these three types of graphs could greatly increase the transparency and communicability of results to non-technical and technical readers.

These graphs can be created in a similar way with any specialised software.

3. Future Applications

After adoption of the current WP, the project will enter into WP 5 in the form of a pilot/training phase focused on the Effects Table (ET). In this context, the project team will produce a template/guidance in preparing an ET to be incorporated under the benefit-risk section of the Rapporteur's and CHMP

[1] Available at http://www.visadecisions.com/
[2] Available at http://www.logicaldecisions.com/home.htm
[3] Available at http://www.catalyze.co.uk

assessment reports. This initial pilot phase will last for six months and upon completion the ET will be revised based on the experience gained from this period.

Depending on the outcome of the pilot phase and with the agreement of the CHMP, a public consultation phase will be initiated that will be concluded with a workshop. A final methodology will be agreed by EMA based on the received feedback.

4. References

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5. Appendix

5.1. PrOACT-URL Framework

The 12-step PROACT-URL framework shown here is based on a generic framework for decision making, as explained in Hammond JS, Keeney RL, Raiffa H, *Smart Choices: A Practical Guide to making Better Decisions*, Boston, MA: Harvard Business School Press; 1999.

The first two columns below show how the generic framework can be adapted to drug decision making. The third column has been completed to show where the information is currently available in the EPAR. The key document accessed here for measurable data was the EPAR (additional data would be available to regulators from the Application). However, different judgments and sources could be used for different stakeholders, e.g., drug developers, regulators, health technology assessors, prescribers, patients.

STEP	DESCRIBE	Notes
PROBLEM 1. Determine the nature of the problem and its context.	The medicinal product (e.g., new or marketed chemical or biological entity, device, generic). Indication(s) for use. The therapeutic area and disease epidemiology The unmet medical need, severity and morbidity of condition, affected population, patients' and physicians' concerns, time frame for health outcomes. The decision problem (what is to be decided and by whom, e.g., industry, regulator, prescriber, patient)	
	Whether this is mainly a problem of uncertainty, or of multiple conflicting objectives, or some combination of the two, or something else (e.g., health states' time progression).	Usually it is a mixture of favourable effect size, unfavourable effect seriousness and their uncertainties.
2. Frame the problem.	The factors to be considered in solving the problem (e.g., study design, sources and adequacy of data, disease epidemiology, presence of alternative treatments).	Ideally, only factors that make a difference to a decision need be included.

STEP	DESCRIBE	Notes
OBJECTIVES 3. Establish objectives that indicate the overall purposes to be achieved. 4. Identify criteria for a) favourable effects b) unfavourable effects	The aim (e.g., to evaluate the benefit-risk balance, to determine what additional information is required, to assess change in the benefit-risk balance, to recommend restrictions). A full set of criteria covering the favourable and unfavourable effects (e.g., endpoints, relevant health states, clinical outcomes). An operational definition for each criterion along with a measurement scale with two points defined to encompass the range of performance of the alternatives (not just reported measures of central tendency, but also confidence intervals). Considerations of the clinical relevance of the criteria—some are of more concern to decision makers than others.	Establishing two points on each measurement criterion facilitates scaling of the alternatives. Usually, data are reported only for the alternatives considered, but quantitative modelling requires definitions of two points on each measurement scale: e.g., lowest and highest practically-realisable measures. Quantitative weights assigned to the scales are based on considerations of relevance, which may not be documented, in which case the relevant stakeholders or key players can provide the information.
ALTERNATIVES 5. Identify the options to be evaluated against the criteria.	Pre-approval: dosage, timing of treatment, drug vs. placebo and/or active comparator; the decision or recommendation required (e.g., approve/disapprove, restrict, withdraw). Post-approval: do nothing, limit duration, restrict indication, suspend.	Provide a clear definition of each option.
CONSEQUENCES 6. 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.	The consequences separately for each alternative on each criterion (e.g., efficacy and safety effects that are clinically relevant, positive and negative health outcomes), summarised in an 'Effects Table' with alternatives in columns and criteria in rows. Qualitative and quantitative descriptions of the effects in each cell, including statistical summaries with confidence intervals, and references to source data, graphs and plots.	This information rarely appears in one place, so it is necessary to search for the information. If more than one study is reported, are decisions to be based on a single 'best' study or on combined data? Is a meta-analysis available? Can the effects table be populated with the results from several studies? Head-to-head comparisons are not necessarily needed for quantitative modelling. Report missing data. A quantitative model will require judgements of value functions, which express the clinical relevance of the data.
TRADE-OFFS 7. Assess the balance between favourable and unfavourable effects.	The judgement about the benefit-risk balance, and the rationale for the judgement.	A quantitative model will also require judgements of weights associated with the criteria.

STEP	DESCRIBE	Notes
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 8. Report the uncertainty associated with the favourable and unfavourable effects.	The basis for and extent of uncertainty in addition to statistical probabilities (e.g., possible biases in the data, soundness and representativeness of the clinical trials, potential for unobserved adverse effects)	Incidence data, reported at step 6 in the effects table, provide information relevant to the probabilities of realising the effects.
9. Consider how the balance between favourable and unfavourable effects is affected by uncertainty.	The extent to which the benefit-risk balance in step 7 is reduced by considering all sources of uncertainty, to provide a benefit-risk balance, and the reasons for the reduction.	Judgement plays a key role. A quantitative model will explore in sensitivity analyses and scenario analyses (or by explicitly incorporating probability distributions in the model) the effects on the overall benefit-risk balance of all sources of uncertainty.
RISK TOLERANCE 10. Judge the relative importance of the decision maker's risk attitude for this product.	Any considerations that could or should affect the decision maker's attitude toward risk for this product (e.g., orphan drug status, special population, unmet medical need, risk management plan).	Some idea of the risk tolerance can be inferred from any report of step 9—how the favourable-unfavourable effects balance was affected by uncertainty. Another key role for judgement.
11. Report how this affected the balance reported in step 9.	The basis for the decision maker's decision as to how tolerable the benefit-risk balance is judged to be (taking into account stakeholders' views of risk?).	
LINKED DECISIONS 12. Consider the consistency of this decision with similar past decisions, and assess whether taking this decision could impact future decisions.	How this decision, and the value judgements and data on which it is based, might set a precedent or make similar decisions in the future easier or more difficult.	As all decisions are based not only on evidence, but also interpretations of that evidence that invoke value judgements and beliefs about uncertainty, decision makers may wish to reflect on whether those judgements and beliefs are consistent across similar past decisions, allow future changes and can be defended.

5.2. Effects Table: Examples

In the modelling of five drugs in WP3, a major problem was establishing what favourable and unfavourable effects should be modelled. The guideline to decide what to include is simple: include only those effects that have an appreciable effect on the benefit-risk balance. Clinical judgement is required to apply the guideline, and even then it may be necessary to be over-inclusive initially so that the effects can be explored, and those that don't affect the benefit-risk balance can then be ignored in making the final judgement.

Each effect requires a precise definition, but this may not be reported in assessment reports. Making these explicit facilitates interpretation of the data, and enables non-specialists to understand what was being measured. Establishing measurement scales and defining their units provides a context that further aids interpretation of the data by providing an indication of the expected range of measured data. Thermometers in offices and homes are restricted in their range, in part so that a meaningful change in temperature can be observed. An increase in a favourable effect might be interpreted differently if a change of 3 points occurred on a 10-point scale rather than a 100-point scale.

Another reason for establishing ranges is to facilitate quantitative modelling. The relative importance of effects is judged by comparing effect swings from worst to best on these scales, which is easier than comparing differences between the effects of a drug and a comparator.

With the effects and their measurement scales defined, it follows that the data for all the options can then be identified. Options will include the target drug, and at least one comparison, often a placebo and/or other treatments. An option might include more than one dose of the drug, restricting an indication of the drug, limiting the duration of administering the drug, or any other action.

Finally, the Effects Table provides a place to summarise the remaining uncertainties about how effects might influence the benefit-risk balance.

The following steps are illustrated for Benlysta and Caprelsa.

1. Identify only those favourable and un-favourable effects relevant to the B-R balance. It may be helpful to cluster the favourable effects under the headings of Primary and Secondary Endpoints, and unfavourable effects under Adverse Events and Serious Adverse Events. Criteria within a cluster are typically more similar to each other than criteria between clusters.

2. Provide descriptions of the effects. These should include footnotes and references to documents that elaborate the descriptions sufficiently that they could be understood by a non-expert.

3. Define the measurement scales. The range should encompass measured values that could realistically be expected to extend from worst to best. This is explained in footnote (1) under each table.

4. Identify the options. These can include the drug with different doses, a placebo, a comparator, and actions to restrict or limit.

5. Display the data. Multiple studies could be displayed as separate rows, but it would be more helpful to provide some sort of statistical summary (e.g., pooled data or a simple weighted average with weights proportional to each study's sample size, but reduced for poor studies or possible

biases in the data). Show confidence intervals, if available. Data from different sources could be flagged with footnotes if the extra information is relevant to the overall benefit-risk judgement.

6. Note remaining effect uncertainties. A short description of the reason for each uncertainty, accompanied by a reference to a relevant source document if available, is sufficient.

Table 1. Hypothetical example of an Effects Table for Benlysta (belimumab, treatment of systemic lupus erythematosus) / Based on the EPAR EMEA/H/C/002015 published on 09/08/2011

Effects		Name	Description	Best[1]	Worst	Units	Placebo[2]	10 mg[2]	1 mg[2]	Uncertainties (See EPAR ¶2.8)
Favourable Effects (pooled data based on the EPAR)	**SLE Responder Index (SRI)**	SLEDAI % Improved ≥ 4	Percentage of patients with at least 4 points' reduction in SLEDAI[3]	100	0	%	41	53	48	Approved only for patients with high disease activity. Uncertainties remain about optimal treatment duration, maintenance doses, treatment holidays and rebound phenomenon.
		PGA % no worse	Percentage of patients with no worsening in Physician's Global Assessment[4] (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	Difference	0.44	0.48	0.45	
		BILAG A/B	Percentage of patients with no new BILAG[3] 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	Support from the analyses of the secondary endpoints is weak for the overall population
		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	Difference	3.5	3.4	3.7	
Unfavourable Effects		Potential SAEs	Potential for developing tumour, opportunistic infections or PML	100	0	Judgement	100	0	90	The mechanism of action could increase potential for developing infections.
		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	0.30	

(1) Best and Worst: For similar scales, the most preferred and least preferred values that would be realistically realisable (e.g., 0 to 100% for both SLEDAI and PGA scales). For dissimilar scales, a range that facilitates comparing the relative importance of the scales (e.g., Infections 0-10%, and Sensitivity Reaction 0-2%).

(2) Treatment effect estimates

(3) Scales defined in Grossman, J. and C. P. Gordon (2007). Clinical Indices in the Assessment of Lupus. Dubois' Lupus Erythematosus, 7th Ed. D. J. Wallace and B. H. Hahn. Philadelphia, PA, Lippincott Williams & Wilkins: 920-932. SLEDAI (Systematic Lupus Erythematosus Disease Activity Index) is a score that represents disease activity as judged by physicians for 24 items associated with standard weightings that are summed to give an overall score ranging from 1 to 105. BILAG (British Isles Lupus Assessment Group) consists of 86 items that represent a physician's judged or measured activity in eight organ-based systems. A weighted scoring system based on intent to treat provides an overall score ranging from 0 to 72. BILAG A is associated with severe disease, BILAG B with less active disease.

(4) The PGA scale used here is a 0-10 scale with 10 being worst. However, the scale is reported to range from 0 to 3 in some publications.

Table 2. Hypothetical example of an Effects Table for Caprelsa (vandetanib, treatment of inoperable thyroid cancer) / Based on the EPAR EMEA/H/C/002315 published on 02/03/2012

		Name	Description	Best[1]	Worst	Units	Placebo[2]	300 mg[2]	Uncertainties
Favourable Effects	Primary Endpoint	Progression-free survival Hazard Ratio	Date of randomization to the date of objective progression or death (blinded independent review)	0	1	unitless	1	0.46	Only a very low number of patients with definite RET negative status at baseline
	Secondary Endpoints	Progression-free survival (median)	Date of randomization to the date of objective progression or death (Weibull model)	60	0	months	19.3	30.5	
		Objective Response (RECIST)	Proportion of complete or partial responders (at least a 30% decrease in the sum of the longest diameter of target lesions compared to baseline)	100	0	%	13	45	
Unfavourable Effects		Diarrhoea CTC3 Grade 3-4	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with activities of daily living; Life-threatening consequences (e.g., hemodynamic collapse)	0	100	%	2.0	10.8	Duration of follow up in the pivotal study is quite short with regard to the need for long duration of treatment and therefore the risk of developing further major Cardiac SAEs including Torsades de pointe.
		QTc related events CTC[3] Grade 3-4	QTc >0.50 second; life threatening signs or symptoms (e.g., arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes	0	100	%	1.0	13.4	
		Infections CTC[3] Grade 3-4	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated; Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	0	100	%	36.4	49.8	

(1) Best and Worst: For similar scales, the most preferred and least preferred values that would be realistically realisable. For dissimilar scales, a range that facilitates comparing the relative importance of the scales.

(2) Treatment effect estimates

(3) NCI Common Terminology Criteria for Adverse Events v3.0; Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS March 31, 2003 (http://ctep.cancer.gov), Publish Date: August 9, 2006

5.3. Hypothetical examples of graphical displays from the MCDA models in WP3

The left column gives information about the drug.

The 'Added-value bars' column shows a stacked bar graph of the final results, with the overall score for the alternatives given just below each bar graph. Longer green bars indicate more benefit, while longer red bars show more safety. The white Weight column give the sum of the weights on the favourable effects and the unfavourable effects, while the Cumulative Weight column shows those same weights normalised so their sum is 100.

The 'Difference display' gives the weighted differences between the preference scores for the two alternatives above each display. The figures are shown graphically, the green bars giving the advantages of the first-named alternative, and the red bars the advantages of the other alternative.

The 'Sensitivity analysis' display shows how the results might change if more or less weight is assigned to each of the effects individually. The display gives the overall most preferred alternative (option), while the left white field identifies criteria for which a decrease in the associated effect might change the result, and the right white field shows changes resulting from an increase in weight. A green bar shows that a change in cumulative weight of more than 15 points would be required for a different result; a yellow bar, a change between 5 and 15 points; a red bar, less than 5 points; and no bars, same result whatever the weight.

Note: The examples of graphical displays presented here were done in a research context with the input from the relevant Product Team and do not reflect the views of the Committee for Medicinal Products for Human Use.

Table 1: Hypothetical example of graphical displays for Vyndaqel (tafamidis meglumine)

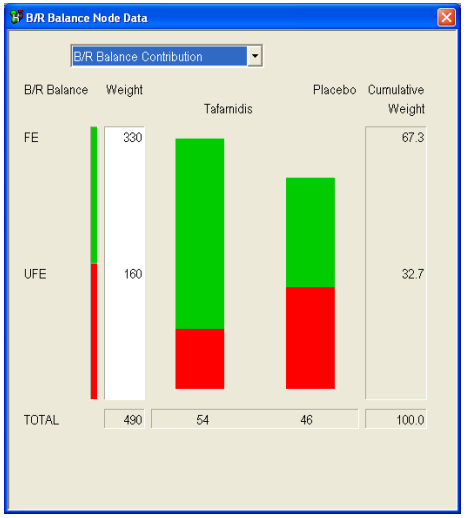
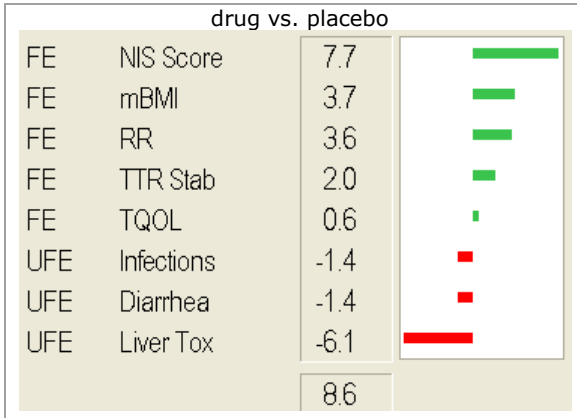
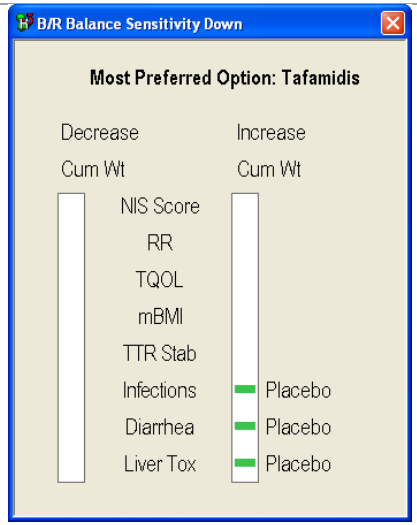
Drug Information	Added-value bars* (more green, more benefit; more red, safer)	Difference display	Sensitivity analysis (green: robust; yellow: fairly robust; red: not robust)
Tafamidis meglumine **Indication:** transthyretin amyloid polyneuropathy			
Abbreviations:	FE: Favourable Effects, UFE: Unfavourable Effects, NIS: Neuropathic Impairment Score, mBMI: Modified Body Mass Index, RR: Percentage of patients with less than 2 points increase in NIS score, TTR: Transthyretin stabilasation, TQOL: Total Quality of Life, Cum Wt: Cumulative Weight		

Table 2: Hypothetical example of graphical displays for Caprelsa/Zictifa (vandetanib)

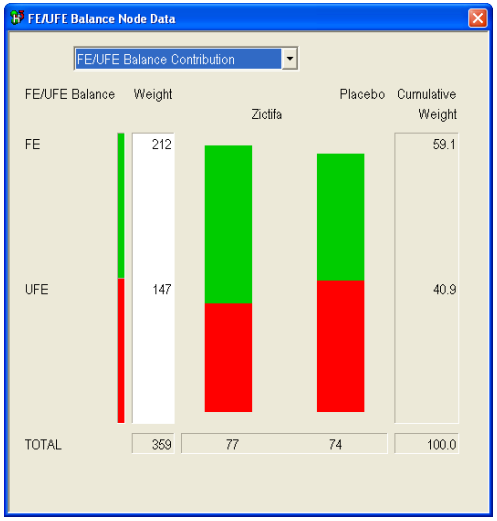
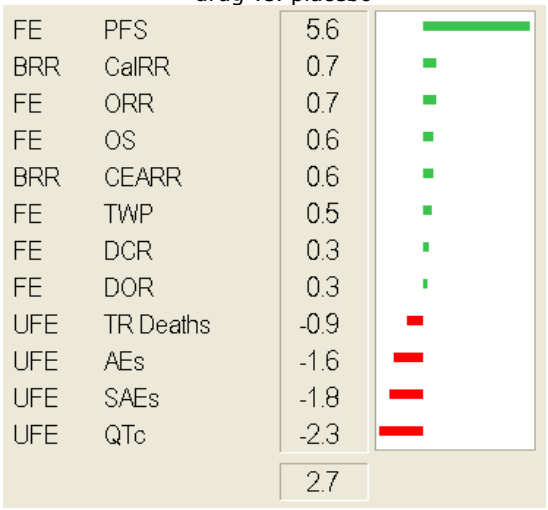
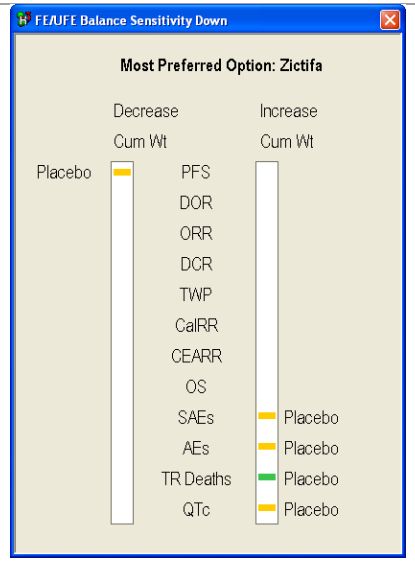
Drug Information	Added-value bars* (more green, more benefit; more red, safer)	Difference display	Sensitivity analysis (green: robust; yellow: fairly robust; red: not robust)
Vandetanib **Indication:** inoperable thyroid cancer			
Abbreviations:	FE: Favourable Effects, UFE: Unfavourable Effects, BRR: Biological Response Rate, PFS: Progression Free Survival, CalRR: Calcitonin Response Rate, ORR: Objective Response Rate, OS: Overall Survival, CEARR: Carcino-Embryonic Antigen Response Rate, TWP: Time to Worsening of Pain, DCR: Disease Control Rate, DOR: Duration of Response, TR: Treatment Related, AEs: Adverse Events, SAEs: Serious Adverse Events, QTc: QTc prolongation, Cum Wt: Cumulative Weight		

Table 3: Hypothetical example of graphical displays for RoActemra (tocilizumab)

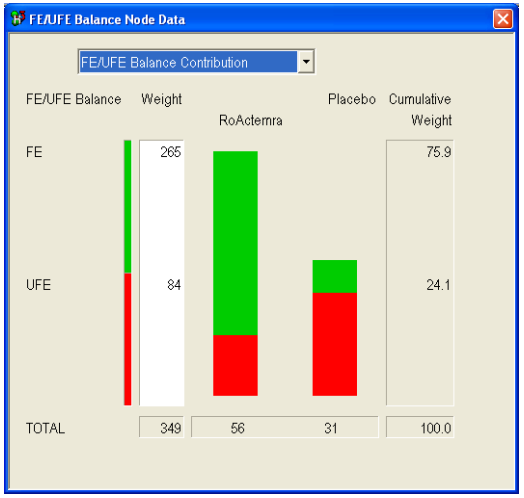
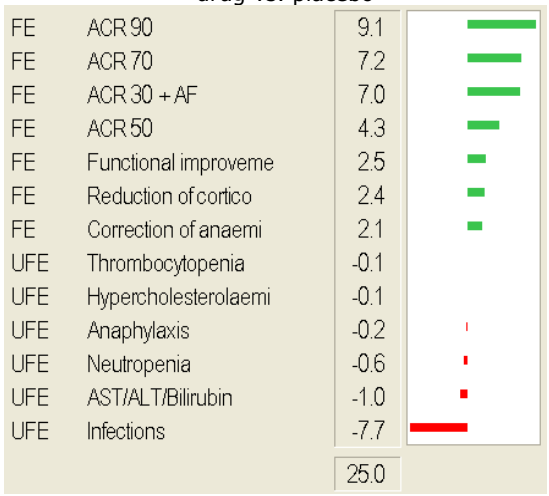
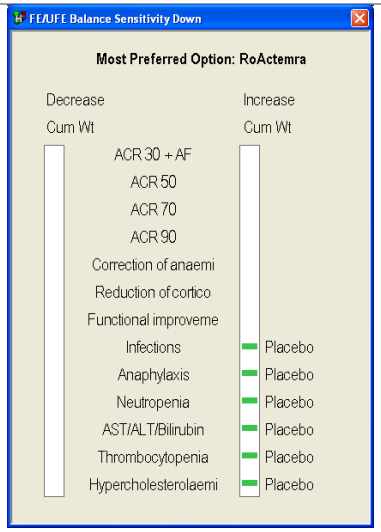
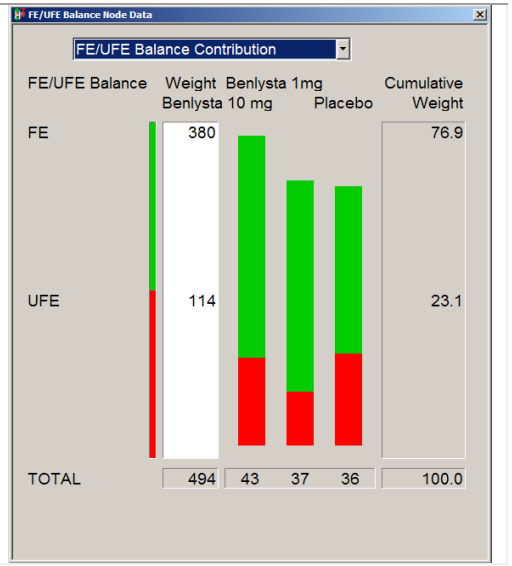
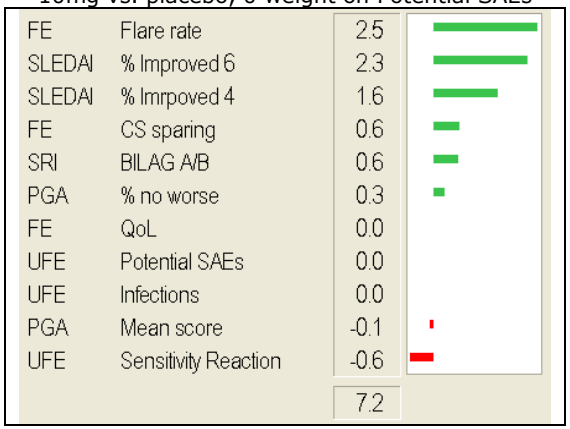
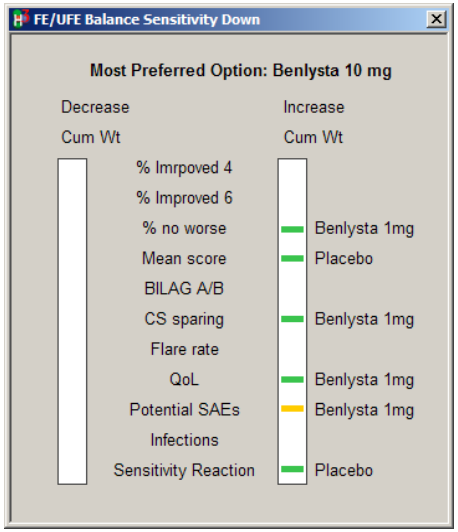
Drug Information	Added-value bars* (more green, more benefit; more red, safer)	Difference display	Sensitivity analysis (green: robust; yellow: fairly robust; red: not robust)
Tocilizumab **Extension of indication:** systemic idiopathic juvenile arthritis			
Abbreviations:	FE: Favourable Effects, UFE: Unfavourable Effects, ACR: American College of Rheumatology score, AST/ALT: Aspartate/Alanine Transaminas, Cum Wt: Cumulative Weight		

Table 4: Hypothetical example of graphical displays for Benlysta (belimumab)

Drug Information	Added-value bars* (more green, more benefit; more red, safer)	Difference display	Sensitivity analysis (green: robust; yellow: fairly robust; red: not robust)
Belimumab **Indication:** systemic lupus erythematosus			
Abbreviations:	FE: Favourable Effects, UFE: Unfavourable Effects, SLE: Systemic Lupus Erythematosus, SLEDAI: SLE Disease Activity Index, CS: Corticosteroids, SRI: SLE Responder Index, BILAG: British Isles Lupus Assessment Group score, PGA: Physician's Global Assessment, QoL: Quality of Life, SAEs: Serious Adverse Events, Cum Wt: Cumulative Weight		

* Out of a possible 100 points (score of 100 on all effects, i.e., all beneficial and completely safe).