Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium

IMI Work Package 5:

Report 1:b:i Benefit - Risk

Wave 1 Case Study Report: Rimonabant

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28th May 2013	Shahrul Mt-Isa	Reference to supplement was updated in Section 11.5.6

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Glossary

BMI	Body Mass Index
BRAT	Benefit Risk Action Team
BRR	Benefit Risk Ratio
CB1	Cannabinoid type I
CHMP	Committee for Medicinal Products for Human Use
CIN	Cases Impact Number
CNS	Central Nervous System
DCE	Discrete Choice Experiment
DIN	Disease Impact Number
ECIN	Exposed Cases Impact Number
EIN	Exposure Impact Number
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FDA	Food and Drug Administration
HDL	High Density Lipoprotein
INHB	Incremental Net Health Benefit
LDL	Low Density Lipoprotein
MAH	Marketing Authorization Holder
MCDA	Multi Criteria Decision Analysis
MTC	Mixed Treatment Comparison
NCB	Net Clinical Benefit
NCB*	Net Clinical Benefit metric calculated as $benefit - k \times risk$, where k is an arbitrary constant
NEPP	Number of Events Prevented in the Population
NNH	Number Needed to Harm
NNT	Number Needed to Treat
PhRMA	Pharmaceutical Research and Manufacturers of America
PIN	Population Impact Number
PIN-ER-t	Population Impact Number of Eliminating a Risk factor over time T
PROTECT	Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium
PSM	Probabilistic Simulation Methods
QALY	Quality-Adjusted Life-Years
Q-TWiST	Quality-adjusted Time Without Symptoms and Toxicity
RCT	Randomised Controlled Trial
SMAA	Stochastic Multicriteria Acceptability Analysis
WP5	Work Package 5 (of PROTECT)

1 Introduction and background

Rimonabant (Acomplia/Zimulti®) is a selective antagonist of cannabinoid type I (CB1) receptors. The cannabinoid system has been shown to be involved in the central regulation of food intake and the central nervous system (CNS) reward system. CB1 receptors were first found in the brain, and later in several human tissues, including adipocytes. [1]

Rimonabant is a new drug, the first in class, indicated for weight loss in obese or overweight patients with co-morbidities. Different trials have also shown that it could improve HbA1c and lipid profiles (increased HDL and reduced triglyceride) in overweight or obese patients. [2] It was not indicated for type 2 diabetes because, according to CHMP (Committee for Medicinal Products for Human Use), the effect size on HBA1C remained uncertain, although it was large enough to be clinically relevant. [3, 4] It was not indicated for dyslipidemia treatment because although rimonabant was associated with an improved HDL-C, its subfractions and triglycerides, its association cardiovascular complications, which, however was not proven (no outcome data available).[5]

The main safety issue was the psychiatric AEs, although most of the patients with various kinds of depressive symptoms did eventually recover with or without anti-depressants drugs.[3, 4] The most common adverse events were anxiety, insomnia, mood alterations with depressive symptoms, depressive disorders, dizziness nausea, diarrhoea, vomiting, and asthenia/ fatigue.

Rimonabant was approved in Europe in 2006 and first marketed in the UK. In July 2007, the CHMP recommended some changes to the prescribing information as follow: (1) upgrading to a contraindication the warning on the use of rimonabant in patients with ongoing major depression or taking antidepressants. This means that rimonabant must no longer be used in these patients, and (2) adding a warning that treatment with rimonabant should be stopped if a patient develops depression, including additional information on the psychiatric safety of rimonabant.

In November 2008, the marketing of rimonabant was suspended in all the Member States in which the product was being marketed and in December 2008, the marketing authorization holder (MAH) responsible for rimonabant, Sanofi-Aventis, voluntarily withdrew its marketing authorization. In January 2009, the European Commission withdrew the marketing authorization for rimonabant on the ground of negative benefit-risk balance based on post-marketing data. [3, 4] A benefit risk analysis using a quantitative method taking into account benefits, risks, as well as relative importance of benefit and risks according to patients or physicians has not been done.

2 Aim and objectives

The overall aim or this project is to evaluate the benefit-risk balance of rimonabant. The objectives are:

1. To compare different benefit-risk methods using rimonabant as a model
2. To evaluate benefit-risk profile of rimonabant based on data available during submission and around withdrawal period

3 Methods

PROTECT Work Stream B has recommended 13 approaches to be tested in the first wave of case studies. In this case study, we have considered the possibility of applying these approaches but it is not possible to apply every approach due to resources constraints – the main factor is time constraint.

3.1 Justifications for selection of benefit-risk approaches

Table 3-1 Benefit-risk approaches included for testing in rimonabant case study

Approach	Justification
1. **PrOACT-URL** 2. **PhRMA BRAT**	The purpose of applying descriptive guidelines in a benefit-risk assessment is to ensure transparency and to structure a benefit-risk decision problem. Two competing but very similar guidelines are tested in this case study to assess the usefulness and ease of use of each guideline.
3. **Multi-criteria decision analysis (MCDA)** 4. **Stochastic multi-criteria acceptability analysis (SMAA)**	MCDA is tested within its own framework since it provides a comprehensive approach to assessing benefit-risk balance. SMAA is regarded as an extension to MCDA with the added simulation, where the guidelines from MCDA are used to increase transparency and to aid the decision process.
5. **Number needed to treat and harm (NNT and NNH)**	NNT and NNH are tested because of their popularity and common use in the medical literature.
6. **Impact numbers**	Impact numbers are conceptually similar to NNT but give a public health perspective. Their applications have been promoted in a number of literature[6-10] and receive considerable attention for its simplicity.
7. **Benefit-risk ratio (BRR)**	BRR is conceptually simple and general. The concept of taking the ratio of the magnitude of benefits to risks is tested.
8. **Probabilistic simulation method (PSM)**	PSM allows more complex benefit-risk model to be constructed taking into account various uncertainties in input values. PSM is flexible and has great potential when it comes to benefit-risk assessment.
9. **Simple direct elicitation**	Simple direct elicitation is not part of the reviewed B-R approaches in PROTECT but due to time constraint, it is considered as the easiest way to obtain value preferences from stakeholders – in this case the regulators and physicians on the rimonabant team.

Table 3-2 Benefit-risk approaches excluded from testing in rimonabant case study

Approach	Justification
1. Quality-adjusted life-years (QALY)	There is no available QALYs research in the literature on rimonabant that is not conducted in economic settings.
2. Quality-adjusted time without symptoms and toxicity (Q-TWiST)	Q-TWiST is very specific to analysis within cancer domain. It is also not straightforward to define disease states as required by Q-TWiST for obesity.
3. Incremental net health benefit (INHB)	INHB by definition uses health indices like QALY in its derivation, therefore excluded here from testing due to the missing components required.
4. Mixed treatment comparison (MTC)	In this case study, the team has decided to focus on direct evidence. And since there are only two treatment options to be evaluated (rimonabant versus placebo), the complexity of having indirect evidence does not apply.
5. Discrete choice experiment (DCE)	Resources – time and money – constraint does not permit discrete choice experiment at this stage.

3.2 Overview and analysis approach

Below is the proposal on how to tackle the different analyses. Instead of regarding each approach as different method, they are regarded as groups. This highlights an important note made in the PROTECT WP5 methodology review that it may be necessary to implement more than one approach in combination in a benefit-risk assessment. The workload distribution is assumed to be similar in all three sub-teams.

3.3 Sub-teams organisation

(1) Sub-team 1: PrOACT-URL, MCDA (using Hiview 3), SMAA (using JSMAA)

Since PrOACT-URL is embedded as the steps in MCDA, these are tackled simultaneously with adjustments made to fit the steps in MCDA. SMAA is a variation of MCDA, therefore data and parameters obtained for MCDA are directly applicable to SMAA. SMAA has an added advantage that it can be modelled prior to having stakeholders' utilities by assuming them to be missing variables. Although, these may seem like the most complicated group of methodologies to be grouped together, the availability of specialist software, Hiview 3 and JSMAA, greatly simplify their implementations. A more details analysis plan is available in Appendix 11.3.

(2) Sub-team 2: BRAT, NNT, BRR

The PhRMA-BRAT guideline is quite labourious in the steps involved but NNT and BRR are simple metric indices. BRAT suggests odds ratios (OR) or relative risk (RR) for the communication of the results. To accomplish the use of BRR concept, the ratios of OR or RR for benefits to OR or RR for risks are calculated from the available data. The probability data are used to calculate NNT and NNH. The ratios of NNT to NNH can also

be regarded as BRR which are calculated for each pair of benefit and risk to be evaluated. A more detailed analysis plan is available in Appendix 11.4.

(3) Sub-team 3: PrOACT-URL, PSM, Impact numbers

Probabilistic simulation is a general estimation method. Since it involves probabilities, we can use PSM to estimate impact numbers in the population. Although, this may seem simple, there are several impact numbers and their purpose and interpretation are different. It would add more value if the model is fitted in a Bayesian framework to allow greater flexibility. A more detailed analysis plan is available in Appendix 11.5.

3.4 Collective tasks

(1) Utility elicitation from stakeholders

This is only relevant for MCDA and SMAA since the other approaches do not require utilities. A simple direct elicitation is used. This is done by listing all criteria in the MCDA model on a questionnaire through SurveyMonkey website (http://www.surveymonkey.com) using Likert scale 0-10. The average utility weight for each criterion is calculated by simply averaging the responses for that criterion received from responders (team members). The questionnaire used is available in Appendix 11.3.3.8.

(2) Final evaluation and comparison of methodologies

Once the analyses completed, the sub-teams discuss the results from their analyses. The important issue is to assess the consistency of the results, particularly if there were any aberrant findings. The final task is deciding the best method(s) for this case study should we have to do it again, or in the light of the prospect to extend this case study into a wave 2 case study. It is difficult to assess which method is the best because this might depend on the circumstances, but this is discussed thoroughly.

4 Evidence data

4.1 Objective data

Information will primarily be from European Public Assessment Reports (EPAR) as well as from the literature. Results from 6 randomised controlled trials were used to supplement data collected from EPAR. [2-5, 11-14]

4.1.1 Benefits (level 1 criterion)

The criteria for benefits identified from EPAR are listed in Table 4-1. The team in the first instance attempt to include all criteria into the benefit-risk models. Should including all benefits criteria prove to be too complicated given the time constraint, the focus is then on the main benefit criteria – weight loss at one year, improved total cholesterol, and improved HbA1c – as italicised in Table 4-1 below.

Table 4-1 Benefits criteria to be evaluated

Level 2 criteria	**Level 3 criteria**
Weight loss at 1 year	
Cholesterol changes	Total cholesterol
	HDL cholesterol
	LDL cholesterol
	HDL/LDL cholesterol ratio
Triglyceride control	
Waist circumference	
Diabetes control	Fasting glucose
	Fasting insulin
	Insulin resistance
	HbA1c
Blood pressure	Systolic control
	Diastolic control
Metabolic syndrome	

4.1.2 Risks (level 1 criterion)

The criteria for risks identified from EPAR are listed in Table 4-2. The team in the first instance attempt to include all criteria into the benefit-risk models. Should including all risk criteria prove to be too complicated given the time constraint, the focus is then on the severe adverse events – death, overall psychiatric disorder, severe depressive disorder, cardiac disorder, urinary disorder, and road traffic accident – as italicised in Table 4-2 below.

Table 4-2 Risks criteria to be evaluated

Level 2 criteria	Level 3 criteria
Infection and infestation	Upper respiratory tract infection
	Gastroenteritis viral
Psychiatric disorder	Anxiety
	Insomnia
	Mood alternation with depressive symptoms
	Depressive disorders
	Irritability
	Parasomnia
	Nervousness
	Sleep disorders
Nervous system disorders	Dizziness
	Memory loss
	Hypoesthesia
	Sciatica
Vascular disorders	Hot flushes
Gastrointestinal disorders	Nausea
	Diarrhoea
	Vomiting
Skin and Subcutaneous Tissue disorder	Pruritus
	Hyperhydrosis
Musculoskeletal and connective tissue disorder	Tendonitis
	Muscle cramp
	Muscle spasms
General disorder	Influenza
	Asthenia/Fatigue
Injury, Poisoning and Procedural complications	Joint sprain
	Contusion

	Fall
Severe Adverse Events	*Death*
	Overall Psychiatric disorder
	Severe Depressive disorder
	Cardiac disorder
	Urinary disorder
	Road traffic accident

4.2 Subjective data

Subjective data in this case study are collected from rimonabant team members with regulatory and medical background using direct elicitation method. These data are collected for each criterion in the MCDA model as previously described (Section 3.4).

5 Results

Please see individual sub sections for results on each methodology in Appendices 11.3 – 11.5.

6 Discussion

6.1 Methodology

6.1.1 Appropriate frame

Table 6-1 Assessment of appropriate frame for benefit-risk approaches through practical experience

	Comments	*Proposed improvements and/or extensions*
PrOACT-URL	PrOACT-URL is a useful framework when dealing with complicated problem with different alternatives. This framework divides complicated problems into smaller criteria and allowing objective and transparent approach on choosing the best alternative. The original framework introduced the concept of trade-offs, although not as sophisticated as the methodologies covered later in this report. This introduces the concept to align the criteria in the same scale for trade-offs. When used as the framework with PSM and Impact numbers, PrOACT-URL helped us focus on some of the issues to be addressed in the decision problem. We clarified beforehand the context of the problem, the decision-maker, the expected time required for analysis, and the expertise required. It also helped us consider the appropriate alternative for comparison, the study scenarios and the appropriate data having considered the complexity of the analysis. The guideline also forces us to plan how benefit-risk trade-off can be done, how to deal with uncertainty, which sensitivity analysis to be done and how decision-maker's risk attitude affects the balance, and to identify sources to benchmark the decisions from the analysis. By using PrOACT-URL as a structure of the report, the level of transparency is high providing sufficient audit trails but we feel that it is very demanding of what actually needs to be done. In effect, the application of PrOACT-URL can be very exhaustive and time-consuming. On the contrary, some difficulties encountered with the application of PrOACT-URL may be linked to the other benefit-risk assessment approach used within.	This framework provided a very useful frame for the problem to be used in other methodologies.

BRAT	The BRAT-approach is well documented in manuals and scientific journals. There is a software available CHECK that makes the implementation rather easy.	There are minor technical problems with the software that needs to be solved.
MCDA	MCDA is a natural progression of PrOACT, it divides difficult problems into manageable smaller criteria so to compare between alternatives. Software we used in this exercise, HiView3, was easy to use and made the MCDA analysis much efficient. MCDA methodology also allows addition of information easily, when more data become available. Comparing between alternatives is apparent in both visual and number output with current programme. This model requires criteria values and weights to be precisely known upfront. A detailed decision conference between stake holders is needed to discuss an agreed criteria function in each criteria and precise weight between each criterion; One would imagine it is often difficult and unrealistic to obtain an exact weighting score in real life situation, particularly when number of criteria for consideration is large. Besides, the decision maker's knowledge regarding to the question might not be sufficient to make an objective judgement in weighting. The result weighting and utility scale would be bias towards the stake holder's own experience or possibility influenced by other participants.	1) Stakeholders selected for the decision conference needed to be wide enough to accommodate views from different parties – regulators, physicians & patients 2) Information on criteria would need to be available for review prior to meeting. 3) Question regarding to criteria should be addressed by individual's independent to the decision conference.
SMAA	SMAA is very similar to MCDA. The process of decision making was based on PrOACT framework. Difference between MCDA and SMAA is that MCDA process data through simulation and also does not require any weight information on criteria from stake holder. Although preference between criteria or weight information in range or precise value can be incorporated in the model. Software used in this exercise, JSMAA, is free and easy to use. However, statistical/mathematical background is needed to explore the full potential of the programme but not crucial. SMAA methodology allows addition of information easily, when more data become available.	This approach is most useful in cases when precise weighting information is not available or inappropriate. This method allows the use of preference ranking between criteria, which would be much easier to elicit and replicable compared with the case of explicit weightings. This is a limitation of the current programme, further development is required to accommodate non linear utility function.

	Comparing between alternatives is apparent in both visual and numeric output with current programme. The benefit of this methodology is removing the need of precise weight information and utility function. In cases of no weight information, this programme will assume equal weighting between criteria during simulation. Weights are adjusted automatically in cases where either ranking on preference of criteria or individual criteria weight information (in range or precise point) is available. Benefit of this programme is that utility scales are determined automatically using 95% confidence interval from input data range. However, utility function is limited on a linear scale.	
PSM	There is no appropriate frame.	
Impact number	Does not consider framing to the problem very well on their own with the exceptions of justifying evidence data	
NNT	There is no appropriate frame.	
BRR	There is no appropriate frame.	
NCB	There is no appropriate frame.	

6.1.2 Meaningful reliable information

Table 6-2 Assessment of using meaningful reliable information for benefit-risk approaches through practical experience

	Comments	***Proposed improvements and/or extensions***
PrOACT-URL	Meaningful reliable information is emphasised in the guideline and must be documented throughout. In this case study, all benefit and risk criteria were included in this framework. Data source were reliable from published clinical trials.	
BRAT	There are two steps in the selection of outcomes. In the first step all potential outcomes should be presented. In the next step the number of outcomes should be reduced to those most relevant for the decision at hand. In this second step the stakeholders should be involved in the process.	
MCDA	All benefit and risk criteria listed in the EPAR were used in the MCDA model. Data source were reliable. However, transformation of data to utility score could be bias. As well as the final average weighted score. Both utility function and weighting were set based on stake holder's preference after decision conference meeting – which itself undoubtedly varies. Besides, the MCDA method only allows one value for every alternative in each criterion. However, medical data are often in range of mean with confidence interval so to account for the uncertainties and random error with the statistical estimates. This MCDA model would not able to take the uncertainty with data into account, this is crucial in making medical judgements especially in rare events where there is a intrinsically considerable degree of uncertainty with the statistics estimates.	Results range should be used in the model instead of one summary statistic value. Current programme we used in MCDA is not feasible for this type of input
SMAA	All benefit criteria and group risk criteria listed in EPAR were used in the model. Current JSMAA programme has a limitation when number of criteria large. In this case with rimonabant, EPAR listed 13 benefit and 34 risk criteria. As a result, our team generate the incidence rate over 10 overall group criteria (defined in EPAR) by	This is a limitation of the current programme, further development is required to accommodate a large amount of criteria. This makes this methodology very attractive to medical

	collapsing incidence of individual reported adverse event within the group, using the method of simulation. Data source is reliable. Benefit of the SMAA model is that it incorporates the uncertainties with the underlying statistics into the model. The data input can be in form of a precise value, a mathematical distribution or range.	applications.
PSM	Takes into account natural uncertainties of parameters based on binomial distributions of the data for proportions.	
Impact number	Only benefit and risk criteria with binary outcomes can be used in impact number calculations because they are based on probabilities of events. Any type of criteria may be considered but work best with criteria on safety. The benefit-risk evidence central to the problems are available from clinical trials conducted for rimonabant. Baseline rates of events were not obtained for our analysis but can be reliably estimated from longitudinal databases such as the GPRD. Impact numbers do not require any clinical judgments about the effects, and do not directly involve consumers in the decision process.	There is a need to establish the best method to trade off benefits and risks. We demonstrated the application of BRR and NCB to achieve this. Multiple benefits and risks criteria need to be integrated into a single measure to make comparison of benefit and risk more straightforward. Weighting the criteria may be an option but we have not demonstrated this suggestion forward in this case study.
NNT	Only binary criteria can be used as NNT is based on probabilities. Only efficacy (NNT) and safety (NNH) criteria may be used. Data required were available from clinical trials. NNT approach does not require clinical judgment.	
BRR	BRR can only be calculated for one benefit versus one risk. To obtain a complete set of BRRs in a decision problem, BRR needs to be calculated for every combination each benefit criterion to each risk criterion which is an exhaustive exercise both for analyst and decision-maker. BRR does not require clinical judgment.	
NCB	Same as BRR above.	

6.1.3 Clear values and trade-offs

Table 6-3 Assessment of the availability of clear values and trade-offs for benefit-risk approaches through practical experience

	Comments	***Proposed improvements and/or extensions***
PrOACT-URL	The original PrOACT-URL framework allows an explicit and transparent judgment in trade-offs between criteria. In the adopted version we used in this exercise, each steps were clearly defined in the framework. However, value judgments are not required for analysis using impact numbers in Sub-team 3.	
BRAT	It's optional if the outcomes should be explicitly compared with respect to relative importance or not. However, in the selection of outcomes to include in the final presentation there is an indirect judgement regarding importance. The approach assumes that all outcomes can be presented on a common scale to make them comparable. The final results are very clearly presented, but for many decision-makers the presentation might be difficult to comprehend.	An improvement would be if outcomes measured on different scales could be presented in the same graph. Many decision-makers need a more illustrative way to present the results. One option would be via value functions however this can add another layer of complexity.
MCDA	MCDA method allows a transparent judgement of value between risk and benefit. By transforming data into utility score using criteria function, this produce a common scale to allow comparison between risk and benefit Final results are easily interpretable in both graphical and numerical form.	
SMAA	SMAA method allows a transparent and objective judgement of value between risk and benefit. Data are transformed into utility score using linear criteria function. Instead of using the fixed scale defined by stakeholders, this method generates the fixed scales using the 95% confidence interval with the data. This produce a common scale to allow comparison between risk and	Further development is needed to incorporate non-linear utility function.

	benefit Final results are easily interpretable in both graphical and numerical form.	
PSM	Probabilistic simulation method allows uncertainties on the parameters to be incorporated into the model which are propagated to the final results.	
Impact number	Value judgments are not required. Benefit and risk criteria are defined by the outcomes in the trials. However, trial reporting can be inconsistent thus limit the amount of evidence that are comparable and can be used together. Impact numbers are measured on the same unit for both benefit and risk criteria, but the scale may not be directly comparable. Impact number for each criterion is presented individually and there is no trade-off method for benefit and risk. This results in final results which are difficult to digest to arrive at a clear decision. Since there are also several impact numbers with different interpretations and for slightly different purposes, it can be unclear as to which is required.	NEPP and PIN-ER-t are the two best impact numbers to use. Other impact numbers can be disregarded. Method to trade-off benefit and risk is required. We attempted the use of BRR and NCB in this study. Method to combine multiple criteria (benefits or risks) into a single measure prior to trade-off is also required. Importance weighting can be used but we have not attempted it here.
NNT	Similar to impact numbers and particularly equivalent to EIN. The problem with NNT is encountered with rare events.	
BRR	The approach itself is sound and provides clear values and trade-offs. Value judgments are not required. Consequently, for some benefit and risk criteria, the trade-off can be meaningless because the scales are not comparable. Simple adjustments such as multiplying by relative importance can be done to make the scales directly comparable. Furthermore, we found out that when BRR is used in combination with impact numbers, the values become difficult to interpret, and could potentially be misleading. By the end of the analysis, it is still difficult to see the overall benefit-risk balance and what is the decision to be made.	We can simply multiply the criteria by relative importance to produce impact numbers on the same scale for direct trade-off. However, the appropriate choice of relative importance is beyond the scope of this case study.
NCB	This is very similar to BRR with the exception that interpretations are more straightforward. However, it introduces values which are related to the number of people in the population which may be difficult to judge just by the face value.	Same as BRR.

6.1.4 Logically correct reasoning

Table 6-4 Assessment of the logically correct reasoning for benefit-risk approaches through practical experience

	Comments	***Proposed improvements and/or extensions***
PrOACT-URL	The adopted PrOACT-URL framework in our exercise was used to frame the problem not used as an analysis tool. In the original Pro-ACR-URL framework, benefit and risk data can be in any form. Uncertainties in the data are not addressed within the trade off, however, this is considered in the overall uncertainty of the result.	
BRAT	The approach can to some extend handle data on different scales. However, it's not possible to handle qualitative variables or subjective opinions. The uncertainty in the data is illustrated by confidence intervals. There were different opinions regarding which outcomes to keep in the final analyses. We did not have time to come to an agreement so the final selection of outcomes was arbitrary an done for illustrative purposes.	
MCDA	Each criterion can only hold one value, however in any form. However, uncertainties within the data range are not addressed as this framework only allows one value for each criterion. Whereas medical data are not distinct. We used random effect meta-analysis to combine results from different studies listed in our data source. This allows an objective approach to pooled data between studies before using the result in the MCDA model. As discussed earlier, results of this technique is dependent on precise weight information collected from stake holders. And these often changes dependent on the stakeholder involved and possibility not replicable with different stake holder groups.	We would recommend using meta-analysis to combine results from different studies for assessment.

	As a result, conclusion from each analysis is conditional to the precise weighting decided by the stake holding group. It is arguable if the result is applicable to the wider public.	
SMAA	Each criterion can hold data in any form. It can be input as a discrete value, range or the distribution of the data. Uncertainty with the data is handled by inputting data in range or the underlying distribution. We used random effect meta-analysis to combine results from different studies listed in our data source. This allows an objective approach to pooled data between studies before using the result in this model. It is often difficult to achieve agreed and explicit weight information between stakeholders. This method allows a simplified approach by bypassing the need of criteria weighting information completely or by seeking ranking of preference instead of precise weight between criteria from stakeholders.	Although precise weighting information is not needed. A decision conference would be useful to elicit the stakeholder preference between criteria to examine the sensitivity of the model.
PSM	Any numeric data can be handled. Uncertainties in the data are sampled from appropriate statistical distributions. Complex network of evidence can be handled where many other approaches would fail.	
Impact number	Only binary data can be handled. There is no method to accommodate uncertainties except to recalculate impact numbers for different rates assumptions. Criteria are not combined through impact numbers analysis. We had some difficulties in choosing the impact numbers to present but we resolved this by discussing them with the team and decided to make things as simple as possible. We also contacted the author of impact numbers to get his opinions on the choice of impact numbers and we have agreed on NEPP and PIN-ER-t. It was suggested that impact numbers should be calculated in the trial population	

	although this is not the usual scenario impact numbers are used for. We demonstrated in the first study scenario how impact numbers behave which to our experience is somewhat confusing and mismatched.	
NNT	Only binary data can be handled. Uncertainties are inherited from the uncertainties in the attributable risks. Criteria are not combined through NNT analysis. Technical flaws with NNT arise in the confidence intervals when there is no attributable risk which equates to confidence intervals including the point of infinity. There are methods to interpret, visualise and construct the empirical distribution for the confidence intervals in such situations [15].	
BRR	Any numeric data can be handled. There is no specific method to accommodate uncertainties. Benefit is divided by risk to obtain BRR on the assumption of the same relative importance. BRR is difficult to interpret when the denominator approaches zero.	An appropriate scaling factor can be used as the relative importance.
NCB	Any numeric data can be handled. There is no specific method to accommodate uncertainties. Risk is subtracted from benefit to obtain NCB on the assumption of the same relative importance.	An appropriate scaling factor can be used as the relative importance.

6.1.5 Commitment to action

Table 6-5 Assessment of the commitment to action for benefit-risk approaches through practical experience

	Comments	***Proposed improvements and/or extensions***
PrOACT-URL	It certainly develops insight and promotes learning by forcing related issues to be thought about carefully. It also ensures transparency and clear audit trails but the requirements are very exhaustive to meet in very short period of time. On the other hand, it may just be what is needed for regulatory decision-making.	
BRAT	The approach is very clear and it's possible to trace all decisions made. The approach is easy to understand and gives a clear structure of the problem. We do think that this is a useful approach that should be used. However, the fact that it's not possible to display outcomes measured in different scales in the same graph is a drawback.	
MCDA	MCDA method divides a complex problem into smaller criteria for assessment, this approach lead the decision makers to develop a deeper insight into the problem to be addressed as well as the alternatives to be considered. Final results from the MCDA method are displayed clearly in both numeric and graphical form. Graphical presentation of the results is clear and easy to comprehend. The results are stable and replicable, as long as auditor have the same data, identical utility function and exact precise weight used in the original model. MCDA is a very useful and transparent methodology into decision making. However, this method is not without limitation. Firstly, each criterion can only take one data at one time. Medical data are presented as an average with a range to describe the underlying uncertainties with the statistics. It would be inappropriate to ignore this issue, especially in	One major benefit of current MCDA software is that the results are clear and easy to comprehend. This is most useful when used to communicate with other users. We ought to extend this concise and simple minimalistic output to future reporting.

	cases with rare events which the estimates often associate with a large uncertainty. Secondly, this method requires precise weighting and utility function from decision makers up front. This is often unrealistic and difficult to obtain in real life, particularly when the number of criteria is large. Lastly, result from this method is conditional to the explicit weighting and utility function set by selected decision makers. This raises the question if the results can be applied in the wider population. This method allows decision maker to structure the problem and assess the alternatives objectively but it does have a few technical issues that makes it less suitable in medical decisions. There is an alternative approach- SMAA: with a similar decision making framework as well as able address the uncertainties raised. On balance, MCDA in its current form is less favourable compared to SMAA and should not be recommended forward.	
SMAA	SMAA method is very similar to MCDA, only SMAA has benefit of not requiring explicit weight information and more importantly ability to handle uncertainty with data – which is crucial with medical applications. SMAA method is objective and easy to apply. Graphical presentation from the programme is easy to interpret. The result from this methodology is reliable and easy to replicate by auditors. Current programme JSMAA used in this exercise is free and easy to use, but not without its limitation. On balance, the author would recommend this methodology forward for further testing and development.	

PSM	It ensures that uncertain events are dealt with properly. It also provides an overview of the true shape of the distributions of the parameters which may influence decisions.	
Impact number	The results from the analyses are directly applicable to the population of interest where the context can be placed immediately in terms of number of people who would be affected by the decisions. Impact numbers are easy to understand but do not mean very much when just benefit-risk balance is to be established for an active drug to placebo. Impact numbers are more useful when comparing active drugs to determine which drug has better benefit-risk profile. However, when an active drug is compared to placebo and the decision question is related to resource allocation or to foreseeable burden of a particular event, impact numbers can then be directly associated with the decisions and actions to be taken. Furthermore, in analyses involving many criteria, the results from impact numbers are difficult to communicate and do not readily lend to a conclusion.	
NNT	The results are the same as EIN but does not have population context as in impact numbers. The interpretation does not have direct implications on the decision to be made. Furthermore, in analyses involving many criteria, the results from NNT are difficult to communicate and do not readily lend to a conclusion.	
BRR	Easy to communicate as relative magnitude in most cases but do not perform well with impact numbers.	
NCB	Easy to communicate as number of people but the numbers have to be put in context with additional related information to complete the picture. Potentially a good combination with impact numbers.	

6.2 The assessment of benefit-risk balance

The authors would like to emphasise that benefit risk analysis results from this report should only be used for demonstration of methodologies only. Data used in this report was obtained from EMA EPAR and published literatures, however, stakeholder weighting are fictitious and therefore results from the analysis is not a realisation of decision context at the time of licence review.

Both PrOACT-URL and BRAT are frameworks to structure the benefit- risk assessment in a logical and transparent manner. Both frameworks allow a clear display of objectives and data for assessment. Neither PrOACT-URL nor BRAT was designed for decision analysis. The benefit risk balance assessment is dependent on stakeholder appreciation of the results and was not inbuilt within the framework.

Both MCDA (HiView) and SMAA belongs to a family of decision analysis model. Our results showed that the benefit risk profiles are very similar between rimonabant and placebo, and the benefit risk profile was highly sensitive to stakeholder preference information using MCDA. Whereas, SMAA model suggested risk benefit profile in rimonabant is better than placebo in both cases of rank preference and missing preference. MCDA (HiView) and SMAA models are the only methodologies tested in this study that combine all criteria by preference weighting to form a summary risk benefit profile.

NNT, NNH, Impact numbers, BRR and PSM are methods used to compare one benefit outcome to one risk criteria at a time. Furthermore, benefit risk balance in these comparisons are related to risk tolerance with stakeholders. Details of risk benefit balance on each combinations of criteria using these method is detailed in Section 9.5

6.3 Visual representation of benefit-risk assessment results

PrOACT-URL framework structures risk and benefit assessment in a table with minimal graphical output. BRAT framework structures risk and benefit assessment in both tabulated and graphical format (Forest plot); and both can be produced easily with the BRAT Framework Tool.

Visual presentation with benefit risk profile in MCDA (HiView) is clear. Total and detailed average score are displayed in both numeric and graphical form. Each criterion and risk/benefit is colour coded in the graphics as a bar chart. Presentation is clear and easily produced using current software – HiView3. Results from the analysis can be exported and used to create other form of graphical presentation with ease.

In contrast to MCDA (HiView), SMAA presents the probability of each option achieving rank 1,2 to n^{th} rank in n alternatives. Current programme, JSMAA, presents these results in a stacked column chart as well as numeric form. JSMAA programme also estimate the average weight combination which gives each alternatives be the superior option. Data regarding this weight distribution are presented in a line graph and can be exported easily and used to create other graphical presentation.

Probabilistic simulation, NNT and NNH present risk benefit assessment in numeric form. There are no standardised graphical presentations.

Impact number, BRR and NCB present risk benefit assessment in numeric form structured in a table, same information could be presented in a line graph or forest plot with 95% confidence interval. These graphical presentations are not standardised and was created during analysis using STATA.

7 Conclusion

The PrOACT-URL framework defined decision context into a transplant process and compare alternatives in a series of criteria assessment. This is very similar to BRAT guidelines, the BRAT guideline divide the decision context into identifiable outcomes (criteria) and summarise the performance of alternatives in both numeric form and graphical format as a forest plot. In contrary to PrOACT-URL, BRAT framework has a further step to simply the decision process with reducing number of outcomes to those most relevant. PrOACT-URL tables performance of each alternative in a effects table in form of crude data, whereas BRAT display results from each alternatives as relative performance compared to a fixed option, placebo in most cases, in form of odd/rate ratio for example. Stakeholder preference on criteria is not required in the both frameworks and neither PrOACT-URL nor BRAT is a decision analysis tool.

Both MCDA (HiView) and SMAA are decision analysis tools. Both methodologies starts by dividing decision context in a series of outcomes and compare performance of each alternatives on each outcome. This is done by scoring data into a utility function, which is set on a clinical ground, and an average weighted utility score for risks and benefits is then calculated after adjusted for stakeholders' preference. SMAA can be termed as a MCDA process with simulation. Compared to MCDA (HiView), SMAA is able to manage uncertainty within data range by using distribution of statistics instead of a precise result, which is more suitable for clinical data. Furthermore, MCDA (HiView) requires explicit preference information from stakeholders upfront. SMAA process is more flexible that stakeholder preference can be absent or alternatively in form of criteria ranking at start.

Whilst probabilistic simulation method and impact numbers are a good combination for benefit-risk assessment, there are still many unresolved issues related to the methods. The use of impact numbers is very specific to answer specific public health questions; that is the correct targeted population and the underlying concerns must be considered a priori otherwise the interpretations of the results become very difficult. Although the probabilistic simulation method is very flexible to account various possibilities, the combination with impact numbers lacks the much needed framework in a benefit-risk assessment of medicines. PrOACT-URL asks for great deal of details which feel very exhaustive particularly because there are no established method to integrate benefit and risk, to perform benefit-risk trade-off, to perform sensitivity analyses or to present results. These result in various possibilities to be explored and justified, which cost time.

Even after great deal of effort to quantify benefits and risks of rimonabant when compared to placebo, the benefit-risk balance is still unclear. Impact numbers approach to benefit-risk assessment may be more suitable for resource-allocation exercise or in epidemiological studies because they directly describe the impact on the populations of interest in terms of number of people affected. Impact numbers analysis may also be suitable as second line approach to provide an overview of the impact in a population following another approach to benefit-risk assessment. The simplicity of impact numbers thence requires any limitations and underlying assumptions to be clearly stated and discussed. Unfortunately, at this stage, even with combinations with other approaches, impact numbers are not matured enough for use in regulatory settings for the purpose of making decisions on marketing authorisation. Having said that, the impact numbers were not developed with that agenda in mind, hence the difficulties we encountered in the application of the impact numbers at the marketing authorisation stage especially with the hypothetical scenario of the trials population may indicate the applications of impact numbers outside its epidemiological roots should be used with care.

8 Recommendations

After testing and reviewing the methodology recommendations, our group would like to make the following recommendations for Wave 2 study.

1. Risk and Benefit assessment on medications should be assessed with an objective and transparent framework. Both PrOACT-URL and BRAT divided a large problem into manageable smaller criteria for assessment; there are little differences between the frameworks. Decision maker should use either of the frameworks at their preference

2. Data on risk and benefit criteria should be summarised using a systematic approach, either in form of meta-analysis in cases with multiple clinical trials of the same medication or using method of indirect comparison, e.g. multi treatment comparison method, in case with multiple comparators.

3. Decision should be supported by a decision analysis method, either Multi Criteria Decision Analysis (MCDA) or Stochastic Multi-Criteria Acceptability Analysis (SMAA). Both methodologies analyse available alternatives using on observed data and decision maker preference. We would recommend exploring the difference between the two methodologies further using more complex cases in Wave 2 study.

4. Most visualisation tools presented in this report is limited to graphical output from the software used for analysis. We would recommend further testing on alternative visualisation in Wave 2 study.

5. A number of criteria used for assessment in this case study are highly correlated (e.g. 10% weight lost and changes in waist circumference), we would recommend to examine the impact of these correlated variables on the final risk benefit profile.

6. We would also recommend to examine the changes in elicited preference weights and final risk/benefit profile in cases when different cut offs are used on the same criterion (e.g. Proportion of patient achieved >5% weight lost and Proportion of patient achieved >10% weight lost).

9 Acknowledgement

We are grateful and would like to thank Dr John Pears (AstraZeneca) and Dr Laurence Titeux (Sanofi) for the discussions and useful suggestions throughout the case study. We would also like to thank Ms Kimberley Hockley (Imperial College London) for her editorial contribution to the report.

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11 Appendix

11.1 Timeline

Task	Owner	Start	End
Develop study plan	JJ & Team	August 23	September 22
Define context and objectives	Team	August 23	August 30
Choose methods	Team	August 23	September 15
Data collection	Team	August 23	September 15
Analysis		September 15	November 15
Sub-team 1 (method 1)	Ed, Shahrul, Laurence, JJ		
Sub-team 2 (method 2)	Johan, Ian, JJ, another AZ colleague		
Sub-team 3 (method 3)	Shahrul, Ed, Johan, JJ		
Report	JJ & Team	1 November	December 15

11.2 Team members

Person	Email	Areas of expertise	Time available
Juhaeri Juhaeri	Juhaeri.Juhaeri@sanofi-aventis.com	Epidemiology, Statistics	25-40%
Shahrul Mt-Isa	s.mt-isa@imperial.ac.uk	Statistics	20%-40%
Edmond Chan	kk.chan@imperial.ac.uk	Statistics, Medical	40%
Georgy Genov	Georgy.Genov@ema.europa.eu	Regulatory	10%
John Pears	John.Pears@astrazeneca.com	Medical	<10%
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Ian Hirsh	Ian.Hirsch@astrazeneca.com	Statistics, Regulatory	~10%

11.3 Sub-team 1 specific findings report

11.3.1 PrOACT-URL

Authors: Edmond Chan, Shahrul Mt-Isa, John Pears, Laurence Titeux and Juhaeri Juhaeri

11.3.1.1 Introduction to PrOACT-URL

11.3.1.1.1 Description

PrOACT-URL is a generic framework which provides a generic problem structure to be considered when facing a decision problem. The acronym PrOACT-URL represents the steps of this framework:

(1) determine the decision context and frame the ***Pr****oblems*;

(2) establish ***O****bjectives* and identify criteria;

(3) identify options and ***A****lternatives*;

(4) evaluate the expected ***C****onsequences* of the options for each criterion;

(5) assess the ***T****rade-offs* of benefit and risk;

(6) report the ***U****ncertainty* in benefit and risk, and assess the impact of uncertainty on B-R balance;

(7) judge the relative importance and the ***R****isk* attitude of the decision maker and assess how this affect the B-R balance; and

(8) consider the decision's consistency with other ***L****inked decisions*, both in the past and its impact on future decisions.

11.3.1.1.2 Problem

To determine the context of the problem:

- 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 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).
- The factors to be considered in solving the problem (e.g., study design, sources and adequacy of data, disease epidemiology, and the presence of alternative treatments).

11.3.1.1.3 Objective

The aims are:

- to evaluate the benefit-risk balance
- to determine what additional information is required
- to assess change in the benefit-risk balance
- to recommend restrictions

  Based on a set of criteria

- covering the favourable
- 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.

11.3.1.1.4 Alternatives

What are the alternatives to proposed treatment?

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

11.3.1.1.5 Consequence

- The consequences separately for each alternative on each criterion (e.g., efficacy and safety effects that are clinically relevant, positive and negative health outcomes).
- Summarized in an 'Effects Table' with alternatives in tables.
- Qualitative and quantitative descriptions of the effects in each cell, including statistical summaries with confidence intervals, and references to source data, graphs and plots.

11.3.1.1.6 Trade-offs

The judgment about the benefit-risk balance, and the rationale for the judgment.

In the book "A Practical Guide to making better life decisions" [16] the authors proposed a method of making trade off using even swaps, by increasing the value of an alternative in terms of one criterion while decreasing its value by an equivalent amount in terms of another criterion – a form of bartering, so to allow elimination of criteria. As more criteria are eliminated, the final objective option would become more dominant and clear; similar to the concept that applied to the Multi Criteria Decision Analysis (MCDA) and Stochastic Multicriteria Acceptability Analysis (SMAA), we will apply this simple technique in this example.

11.3.1.1.7 Uncertainty

What are the uncertainties related to the decision?

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)

The extent to which the benefit-risk balance is reduced by considering all sources of uncertainty, to provide a benefit-risk balance, and the reasons for the reduction.

11.3.1.1.8 Risk

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).

The basis for the decision maker's decision as to how tolerable the benefit-risk balance is judged to be.

11.3.1.1.9 Linked decision

How this decision, and the value judgments and data on which it is based, might set a precedent or make similar decisions in the future easier or more difficult.

11.3.1.2 PrOACT-URL Rimonabant case study set up

Step	Description	Information source
Problem 1. Determine the nature of the problem and its context.	Should rimonabant be licensed to use in Europe? *1a. The medicinal product* Rimonabant (Acomplia/Zimulti®) is a selective antagonist of cannabinoid types I (CB1) receptors. The cannabinoid system has been shown to be involved in the central regulation of food intake and the central nervous system (CNS) reward system. CB1 receptors were first found in the brain, and later in several human tissues, including adipocytes Rimonabant is a new drug, the first in class, indicated for weight loss in obese or overweight patients with co-morbidities *1b. Indication(s) for use.* Weight lost *1c. The therapeutic area and disease epidemiology* Around two-third of the US population is overweight or obese (Hedley, Ogden et al. 2004). In Europe, there is also a high prevalence of overweight, around 50%, and obesity, up to 30% (James, Rigby et al. 2004; York, Rossner et al. 2004). As obesity is strongly associated with and increased risk of diabetes and cardiovascular diseases (Klein, Burke et al. 2004)and mortality, obesity remains a great public health problem(Solomon and Manson 1997) *1d. The unmet medical need, severity of condition, affected population, patients' and physicians' concerns, time frame for health outcomes*. With around 2.5 million deaths worldwide due to obesity, there is a large unmet medical need in obesity(Organisation 2002). The prevalence of obesity has been increasing not only in the US but also in other countries, in adults as well as children(Hedley, Ogden et al. 2004). Because diet and exercise has a limited long-term success in reducing weight (Loveman, Frampton et al. 2011), a more comprehensive approach to treating obesity with a long-term effect is needed. *1e. The decision problem (what is to be decided and by whom, e.g., industry, regulator, prescriber, patient)* Decision problem: Rimonabant should be licensed to be used in Europe. This decision should be carried out by regulators, physicians and patients. We have limited input from patient group at this stage of the project. Therefore, we will concentrate on the decision making process as regulators and physicians.	EPAR[3, 4]
2. Frame the problem.	*2a. 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).* Problem regarding safety and trade-offs of side effects for benefits in weight lost. We have limited input from patient group into the project at this stage, also with a limitation on time and resources to assess patients prospective. Our group had decided to use in house medical and regulators assessment. Apart from uncertainties with stakeholder prospective on trade-offs, in order to simplify the model for the trade off exercise, we had limited the total criteria for decision from 15 benefits and 34 adverse events to the 5 most important criteria. The 5 criteria were selected based on a separate ranking exercise performed for the MCDA model. Some other factors might contribute into the tradeoff which could affect the final results, this itself is an important uncertainty we need to consider when interpreting the results from this exercise.	

Step	Description	Information source
	2b. The factors to be considered in solving the problem (e.g., study design, sources and adequacy of data, disease epidemiology, presence of alternative treatments). There are 5 randomised controlled studies [2, 5, 11, 12, 14] of which 4 have final outcome at 12 months[2, 5, 11, 12] and the remaining study only presented outcomes at 6 months[14] Samples sizes were adequate in all 5 studies. We were interested in 12 months outcome in this exercise, therefore, we dropped study with only 6 months follow up. In the 4 remaining RCT. There are alternative treatment dosage , but for the purpose of this exercise, we only used rimonabant 20mg compared to placebo.	EPAR, literatures
Objectives 3. Establish objectives that indicate the overall purposes to be achieved. 4. Identify criteria for a) favourable effects b) unfavourable effects	3. *The aim* To assess the treatment related risk/health benefits of Rimonabant compared to placebo in obese people 4. For the purpose of this exercise Favourable effects: Proportion of patient achieved 10% weight lost at 1 year Waistline changes at 1 year Proportion reduction in metabolic syndrome Unfavourable effects: Incidence of psychiatric disorder Incidence of severe adverse events **All criteria listed in EPAR:** <u>Favourable/beneficial effects:</u> Weight lost at 12 months: Percentage of patient reached 10% weight lost Lipid control at 12 months: Total Cholesterol HDL Cholesterol LDL Cholesterol Ratio HDL Cholesterol/Total Cholesterol Triglyceride Waist Circumference at 12 months Diabetes control at 12 months Fasting glucose Fasting insulin Insulin resistance HbA1c Glucose intolerance Blood pressure control Systolic Blood Pressure Diastolic Blood Pressure Metabolic Syndrome at 12 months <u>Unfavourable effects/ risk</u> Infection and infestation: Upper respiratory tract infection Gastroenteritis viral Psychiatric disorder: Anxiety	EPAR, literatures

Step	Description	Information source
	Isonmia Mood alternation with depressive symptoms Depressive disorders Irritability Parasomnia Nervousness Sleep disorders Nervous system disorders: Dizziness Memory loss Hypoesthesia Sciatica Vascular disorders Hot flushes Gastrointestinal disorders Nausea Diarrhoea Vomiting Skin and Subcutaneous Tissue disorder Pruritus Hyperhydrosis Musculoskeletal and connective tissue disorder Tendonitis Muscle cramp Muscle spasms General disorder Influenza Asthenia/Fatigue Injury, Poisoning and Procedural complications Joint sprain Contusion Fall Severe Adverse Events Death Overall Psychiatric disorder Cardiac disorder Urinary disorder Road traffic accident	
Alternatives 5. Identify the options to be evaluated against the criteria.	*5a. Pre-approval:* Placebo *5b. Post-approval: N/A*	
Consequences 6. Describe how the alternatives perform for each of the criteria, i.e., the	See effects table attached	

<table>
<tr><th>Step</th><th>Description</th><th>Information source</th></tr>
<tr><td>magnitudes of all effects, and their desirability or severity, and the incidence of all effects.</td><td></td><td></td></tr>
<tr><td>Trade-offs
7. Assess the balance between favourable and unfavourable effects.</td><td>
There were 16 key criteria in the assessment of rimonabant. For the purpose of this exercise, we concentrated in the top 5 key criteria, ranking for the listed benefit and risk criteria were collected by previous weighting survey performed for MCDA (Details can be found in MCDA report):

1) Proportion of patient achieved 10% weight lost at 1 year
2) Changes in waist line at 1 year
3) Incidence of psychiatric events
4) Incidence of severe adverse events
5) Percentage reduction in metabolic syndrome

Note: Trade-offs scales between criteria used in this report were factitious, based on a team physician's prospective. Results from this analysis was intended for illustration of the technique only, formal assessment of benefit and risk of this medication would require established decision meeting with stakeholders to decide on agreeable trade-offs.

Results from these 5 criteria.
<table>
<tr><th>Objectives</th><th>Rimonabant 20mg</th><th>Placebo</th></tr>
<tr><td>10% weight lost at 1 year</td><td>25%</td><td>6%</td></tr>
<tr><td>Changes in waist line at 1 year</td><td>-6.2</td><td>-1.9</td></tr>
<tr><td>Incidence of psychiatric disorder</td><td>22.2%</td><td>11.1%</td></tr>
<tr><td>Incidence of severe adverse events</td><td>1.7%</td><td>0.8%</td></tr>
<tr><td>% Reduction in metabolic syndrome</td><td>42.9%</td><td>20.7%</td></tr>
</table>

Step 1: Assuming we were able to exchange proportion of reduction in metabolic syndrome with adverse events in the following exchange rate:
10% metabolic syndrome = 1% severe adverse events
<table>
<tr><th>Objectives</th><th>Rimonabant</th><th>Placebo</th></tr>
<tr><td>10% weight lost at 1 year</td><td>25%</td><td>6%</td></tr>
<tr><td>Changes in waist line at 1 year</td><td>-6.2</td><td>-1.9</td></tr>
<tr><td>Incidence of psychiatric disorder</td><td>22.2%</td><td>11.1%</td></tr>
<tr><td>Incidence of severe adverse events</td><td>1.7%</td><td><s>0.8%</s> 0.8% + (42.9%-20.7%)/10%x1%->3.02%</td></tr>
<tr><td><s>% Reduction in metabolic syndrome</s></td><td><s>42.9%</s></td><td><s>20.7%</s></td></tr>
</table>

Step 2: Assuming we were able to exchange proportion of psychiatric disorder with severe adverse events with the following exchange rate:
1% severe adverse events= 5% psychiatric disorder
<table>
<tr><th>Objectives</th><th>Rimonabant</th><th>Placebo</th></tr>
<tr><td>10% weight lost at 1 year</td><td>25%</td><td>6%</td></tr>
<tr><td>Changes in waist line at 1 year</td><td>-6.2</td><td>-1.9</td></tr>
<tr><td>Incidence of psychiatric disorder</td><td>22.2%</td><td><s>11.1%</s> 11.1%+(3.02%-1.7%)x5% ->17.7%</td></tr>
<tr><td><s>Incidence of severe adverse events</s></td><td><s>1.7%</s></td><td><s>3.02%</s></td></tr>
</table>

Step 3: Assuming we were able to exchange proportion of patient with 10% weight lost at 1 year and changes in waistline with the following exchange rate:
</td><td></td></tr>
</table>

<table>
<tr><th>Step</th><th>Description</th><th>Information source</th></tr>
<tr><td></td><td>1cm difference in waist line = 2% in proportion patient for every
<table>
<tr><th>Objectives</th><th>Rimonabant</th><th>Placebo</th></tr>
<tr><td>10% weight lost at 1 year</td><td>~~25%~~ 25%+(6.2-1.9)x2%->33.6%</td><td>6%</td></tr>
<tr><td>~~Changes in waist line at 1 year~~</td><td>~~6.2~~</td><td>~~1.9~~</td></tr>
<tr><td>Incidence of psychiatric disorder</td><td>22.2%</td><td>17.7%</td></tr>
</table>
<u>Final step:</u> Assuming we were able to exchange proportion of patient achieved 10% weight lost with incidence of psychiatric disorder with the following exchange rate:
0.20% psychiatric disorder = 1% of patients achieving 10% weight lost at 1 year
<table>
<tr><th>Objectives</th><th>Rimonabant</th><th>Placebo</th></tr>
<tr><td>10% weight lost at 1 year</td><td>33.6%</td><td>~~6%~~ 6%+(22.2%-17.7%)/0.2%-> 28.5%</td></tr>
<tr><td>~~Risk of psychiatric disorder~~</td><td>~~22.2%~~</td><td>~~17.7%~~</td></tr>
</table>
<u>Conclusion</u>: This trade off model suggesting rimonabant would be a superior option.</td><td></td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>Uncertainty
8. Report the uncertainty associated with the favourable and unfavourable effects.</td><td colspan="2">This model has the following limitations/uncertainties
1) Albeit these data were collected from well conducted randomised controlled studies. There were different restrictions in study inclusion criteria. For example, RIO-diabetes limited to participants who were diabetic at start; As well the uncertainties between patient populations in different catchment area. Some of these uncertainties were handled by using meta analysis to summarise the results before input into this model.
2) Data used in this framework were summary statistics. There are uncertainties in the natural variation in statistic.
3) In terms of nature of adverse events, there were possibilities of under reporting.</td></tr>
<tr><td>9. Consider how the balance between favourable and unfavourable effects is affected by uncertainty.</td><td colspan="2">It is inevitable that the risk benefit balance would be influenced by the uncertainties.
For example, if rimonabant should be more efficacious over patients with diabetes, this would change this balance towards improvement in benefit as the data collected are unbalanced.
Besides, data used in this model were summary statistics. Therefore, this is subjective to random error.</td></tr>
<tr><td>Risk tolerance
10. Judge the relative importance of the decision maker's risk attitude for this product.
11. Report how this affected the balance reported in step 9.</td><td colspan="2">The main benefit of rimonabant was for weight reduction, which there is a selection of licensed alternatives available; and the key concern with rimonabant was the increased incidence of depression and psychiatric disorder, which is not uncommon and could be severe in some cases.
Therefore, decision maker might have a lower tolerance of risk related to this medication.
Lower risk tolerance was reflected in the trade-offs. For the purpose of this exercise, trade-offs were factitious and decided by the group in house physician, and have no input from other stakeholders.</td></tr>
<tr><td>Linked decisions
12. Consider the consistency of this decision with similar past decisions, and assess whether taking this decision could impact future decisions.</td><td>Decision on this drug would certainly influence future application on medications targets cannabinoid type I (CB1)</td><td></td></tr>
</table>

Revision 5 (23 June 2011). Lawrence D. Phillips & Work Group members

Disclaimer: This table is an adaptation of the original PrOACT-URL for PROTECT and is a working document. Please forward suggested additions and improvements derived from its use to lawrence.phillips@ema.europa.eu.

Table 11-1. Effects table

	Effects	Description	Fixed Lower†	Fixed Upper†	Units*	Rimonabant 20mg	Placebo
Favourable Effect at 12 months	**Weight control**	Percentage patients reached 10% weight lost	0	100	%	25	6
	Lipid control	Total Cholesterol changes	-2	2	mmol/L	0.05	0.12
		HDL Cholesterol changes	-2	2	mmol/L	0.22	0.11
		LDL Cholesterol changes	-2	2	mmol/L	0.08	0.15
		Ratio HDL /Total Cholesterol changes	-2	2		-0.65	-0.33
		Triglyceride changes	-2	2	mmol/L	-0.26	0.01
	Waist Circumference	Waist circumference changes	-10	10	cm	-6.2	-1.87
	Diabetes control	Fasting glucose changes	-2	2	mmol/dL	-0.22	0.05
		Fasting insulin changes	-5	5	µIU/mL	-1.04	1.08
		Insulin resistance changes	-5	5	Compared to placebo	-0.8	
		HbA1c changes	-5	5	%	-0.6	0.1
		Glucose intolerance changes	-5	5	Compared to placebo	-0.89	
	Blood pressure control	Systolic blood pressure changes	-10	10	mmHg	-1.26	0.48
		Diastolic blood pressure changes	-10	10	mmHg	-1.45	-0.28

	Effects	Description	Fixed Lower†	Fixed Upper†	Units*	Rimonabant 20mg	Placebo
Unfavorable le effect at 12 months	Infection and infestation	Upper respiratory tract infection	0	15	%	11.4	12.4
		Gastroenteritis viral	0	10	%	2.9	3.6
	Psychiatric disorder	Anxiety	0	10	%	2.4	5.6
		Insomnia	0	10	%	3.2	5.4
		Mood alternation with depressive symptoms	0	10	%	3.1	4.8
		Depressive disorders	0	10	%	1.6	3.2
		Irritability	0	10	%	0.6	1.9
		Parasomnia	0	10	%	0.2	1.5
		Nervousness	0	10	%	0.2	1.2
		Sleep disorders	0	10	%	0.4	1
	Nervous system disorders	Dizziness	0	10	%	4.9	7.5
		Memory loss	0	10	%	0.9	1.6
		Hypoesthesia	0	10	%	0.6	1.6
		Sciatica	0	10	%	0.4	1
	Vascular disorders	Hot flushes	0	10	%	0.7	1.9
	Gastrointestinal disorders	Nausea	0	15	%	4.9	11.9
		Diarrhoea	0	10	%	4.8	6.3
		Vomiting	0	10	%	2.2	4

	Skin and Subcutaneous Tissue disorder	Pruritus	0	10	%	0.5	1.2
		Hyperhydrosis	0	10	%	0.5	1.2
	Musculoskeletal and connective tissue disorder	Tendonitis	0	10	%	1	2.1
		Muscle cramp	0	10	%	1	1.4
		Muscle spasms	0	10	%	0.5	1
	General disorder	Influenza	0	10	%	8.6	8.9
		Asthenia/Fatigue	0	10	%	5	6
	Injury, Poisoning and Procedural complications	Joint sprain	0	10	%	2.1	3
		Contusion	0	10	%	0.6	2.2
		Fall	0	10	%	1.4	1.9
	Severe Adverse Events	Death	0	10	%	0.25	0.16
		Overall Psychiatric disorder	0	10	%	0.12	0.48
		Severe Depressive disorder	0	10	%	n/a	0.24
		Cardiac disorder	0	10	%	0.25	0.48
		Urinary disorder	0	10	%	0.12	0.36
		Road traffic accident	0	10	%	0.00	0.24

† 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.

11.3.2 Multi Criteria Decision Analysis

Authors: Edmond Chan, Shahrul Mt-Isa, Laurence Titeux and Juhaeri Juhaeri

11.3.2.1 Aims

The overall aims of this case study analysis are:

a. To assess the feasibility and suitability of the approaches using Multi Criteria Decision Analysis (MCDA) model for benefit-risk assessment of drugs by the regulator, having considered other stakeholders' perspectives using rimonabant as a model;

b. To evaluate the benefit-risk balance of rimonabant 20mg at marketing authorisation approval using the MCDA method.

11.3.2.2 Data requirement and confidentiality

Data for analysis in this case study are obtained from published trials on rimonabant. Public data from the pivotal trials in EPAR[3, 4] and original publications (RIO-North America[11], RIO-Europe[5], RIO- Diabetes[12] and RIO-Lipids[2]) are soughed and summarized for the analysis.

No issue of confidentiality was noted.

11.3.2.3 MCDA model

11.3.2.3.1 Introduction

Multicriteria Decision Analysis (MCDA) is a useful methodology when decision maker faces a decision with different alternatives, complicated with multiple, often conflicting objectives. This methodology was first developed in 1970's by Zionts et al.

The principle of this model is to address the problem by structuring and solving the problem using different criteria. Conflicting components of the decisions making will become clear by dividing decisions into criteria and alternatives are scored in each criterion to form the criteria score, which then weighted according to decision maker preferences.

A weighted average for each alternatives then created by summing the weighted criteria score. The alternative with the highest weighted average is the most preferred option.

The framework of building MCDA model is similar to that of PrOACT, with addition of sensitivity testing to examine the effect of uncertainty in weighting with outcomes.

Step 1 : Determine the context of the problem

Step 2:Determine the objectives of assessment

Favourable and unfavourable criteria. The criteria are then depicted in a value tree, with nodes representing the objectives and branches from nodes represent different criteria.

Step 3: Determine the alternatives

Placebo, treatment dosage or alternative established treatments

Step 4: Effect table

Creating an effect table with the attainment of each alternative against the bottom level criterion in the value tree. A fixed upper and lower limit on each criterion is then fixed by decision makers. The upper and lower fixed limit reflects the best and worst performance that decision maker should expect from the alternatives in that criterion. Performances of each alternative then convert into criteria score between 0 and 100 using either a liner scale or piecewise scale within the range of the fixed limits. Alternatively, criteria score can be formed using a relative scale which the superiority alternative will score 100 whereas the inferior option will score 0 in that criterion.

Step 5: Weighting

Criteria score on one criterion is in equal value to another criterion because the difference in the fixed limits ranges. In order to combine the overall score and make the criteria score comparable, each criteria value is weighted for decision maker preferences. A decision making conference is organised with all stake holders and agreed weighting are elicited using swing weighting methods.

Step 6: Overall value

A weighted average on each alternative is then calculated by summing the weighted criteria scores. The alternative with highest weighted average is the most preferred option.

Step 7: Sensitivity testing

A key question for applying MCDA to the benefit-risk assessment of drugs is who does the scoring and weighting. Measurable data are usually available, but these must then be translated into preference scores through the use of value functions. Criterion weights are a matter of clinical judgement, and, , could be made differently by different constituents. MCDA modelling requires these judgements, and sensitivity testing can be used to examine the degree which these judgements affect the final result.

11.3.2.4 Development of MCDA model

Establishment **of decision context**

Rimonabant (Acomplia/Zimulti®) is a selective antagonist of cannabinoid type I (CB1) receptors. The cannabinoid system has been shown to be involved in the central regulation of food intake and the central nervous system (CNS) reward system. CB1 receptors were first found in the brain, and later in several human tissues, including adipocytes.

Rimonabant was approved in Europe in 2006 and first marketed in the UK. In July 2007, the CHMP recommended changes to the medicine's prescribing information as follow: 1) Upgrading to a contraindication the warning on the use of rimonabant in patients with ongoing major depression or taking antidepressants. This means that rimonabant must no longer be used in these patients and 2) Adding a warning that treatment with rimonabant should be stopped if a patient develops depression, including additional information on the psychiatric safety of rimonabant.

In November 2008, the marketing of rimonabant was suspended in all the Member States in which the product was being marketed and in December 2008, the marketing authorization holder (MAH) responsible for rimonabant, sanofi-aventis, voluntarily withdrew its marketing authorization. In January 2009, the European Commission withdrew the marketing authorization for rimonabant on the ground of negative benefit-risk balance based on post-marketing data (EPAR)[3, 4] .A benefit risk analysis using a quantitative

method taking into account benefits, risks, as well as relative importance of benefit and risks according to patients or physicians has not been done.

The purpose of this analysis is to establish benefit and risks in view of the regulators and layman.

Identification of options to be appraised

This model will be used to appraise rimonabant 20mg vesus placebo.

Identification of the benefit and risk criteria and organisation in a value tree

Rimonabant is a new drug, the first in class, indicated for weight loss in obese or overweight patients with co-morbidities. Different trials have also shown that it could improve HbA1c and lipid profiles (increased HDL and reduced triglyceride) in overweight or obese patients. It was not indicated for type 2 diabetes because, according to CHMP (Committee for Medicinal Products for Human Use), the effect size on HbA1C remained uncertain, although it was large enough to be clinically relevant (EPAR)[3, 4]. It was not indicated for dyslipidemia treatment because although rimonabant was associated with an improved HDL-C, its subfractions and triglycerides, its association cardiovascular complications, which, however was not proven (no outcome data available) (EPAR).[3, 4]

The main safety issue was the psychiatric AEs, although most of the patients with various kinds of depressive symptoms did eventually recover with or without anti-depressants drugs (EPAR)[3, 4]. The most common adverse events were anxiety, insomnia, mood alterations with depressive symptoms, depressive disorders, dizziness nausea, diarrhoea, vomiting, and asthenia/ fatigue.

Benefit criteria

The primary benefit of rimonabant was the effect on weight lost and maintenance of weight lost at 12 months. Other secondary benefits were divided into groups with different measurement criteria, listed below.

1) Percentage of patient reached 10% weight lost

2) Lipid control at 12 months:

- Total Cholesterol
- HDL Cholesterol
- LDL Cholesterol
- Ratio HDL Cholesterol/Total Cholesterol
- Triglyceride

3) Waist Circumference at 12 months

4) Diabetes control at 12 months

- Fasting glucose
- Fasting insulin
- Insulin resistance
- HbA1c

- Glucose intolerance

5) Blood pressure control

- Systolic Blood Pressure

- Diastolic Blood Pressure

6) Metabolic Syndrome at 12 months

Risk criteria

For the purpose of this analysis, we used data obtained from EPAR for risk assessment. The main concern was psychiatric disorder. And other reported adverse events were arranged in groups of body system.

1) Infection and infestation

- Upper respiratory tract infection

- Gastroenteritis viral

2) Psychiatric disorder

- Anxiety

- Insomnia

- Mood alternation with depressive symptoms

- Depressive disorders

- Irritability

- Parasomnia

- Nervousness

- Sleep disorders

3) Nervous system disorders

- Dizziness

- Memory loss

- Hypoesthesia

- Sciatica

4) Vascular disorders

- Hot flushes

5) Gastrointestinal disorders

- Nausea

- Diarrhoea

- Vomiting

6) Skin and Subcutaneous Tissue disorder

- Pruritus

- Hyperhydrosis

7) Musculoskeletal and connective tissue disorder

- Tendonitis

- Muscle cramp

- Muscle spasms

8) General disorder

- Influenza

- Asthenia/Fatigue

- Injury, Poisoning and Procedural complications

- Joint sprain

- Contusion

- Fall

7) Severe Adverse Events

- Death

- Overall Psychiatric disorder

- Cardiac disorder

- Urinary disorder

- Road traffic accident

Tree

The purpose of this model is to examine the risk and benefit of rimonabant. During the process of this analysis, a total of three trees were developed following PrOACT-URL framework. Conventionally, MCDA divides problem into decision trees or influence diagram. In our case, decision nodes compose of a large list of criteria and hence it would be clearer displaying the decision process with decision tree. Furthermore, the current programme, HiView3, supports only decision tree.

All three trees were based on identical first, second and third level criteria. Different trees were developed to accommodate variations in format of the input data.

Tree 1: Data Input were directly from individual studies.

Tree 2: Using pooled data. (Section 11.3.2.10)

Tree 3: Using results from random effect meta-analysis. (Section 11.3.2.10)

First level Criteria

Total Risks and Total Benefits of rimonabant

Second level criteria

The primary benefit in regards the use of rimonabant was 10% weight lost at 12 months.

Secondary benefits included diabetes, lipid, blood pressure control and reduction of metabolic syndrome. These factors contributed to overall benefit of rimonabant and were used as second level criteria towards benefit.

Risks associated with the use of rimonabant were grouped into body system in the EPAR, and second level criteria on risks were developed in similar structure in this model.

Third level criteria

Third level criteria were created for diabetes, lipid, blood pressure control and most risks criteria. These criteria were assessed with a composite of measures. Therefore, the incidence of observed event and different measurements were used as third level criteria contribute towards the final score.

Forth level criteria

Forth level criteria were created to accommodate data from individual studies in Tree 1.

Scoring options for each the criteria

Ideally, the scoring options should be discussed in details with stakeholders. The range of preference score and type of criterion value function would greatly affect the utility score, which will have substantial impact on final results.

In view that current exercise is to test the feasibility of the technique. Our group opted for a minimalist approach, all preference scores between rimonabant and placebo were established on a fixed scale based on a linear preference scoring. The range of preference scale was anchored according to clinical importance based on an in-group physician opinion.

Assignment of a weight to each criteria

The purpose of this exercise is to examine the feasibility of using MCDA model in medicine safety decision making; however, weighting on risk and benefit is subjective and varies between regulator and end-users.

In order to examine the sensitivity of the model with different weighting between user groups, our team took the approach to collect weighting opinions within our group consisting of physicians, regulators and statisticians. Medical and regulator members of the group provided medical/regulatory opinion, whereas, statisticians were acted as layman.

All three trees carry the same weighting between each criterion. Weighting data from members of the group were collected using online questionnaire (www.surveymonkey.com). The questionnaires were divided into Medical and regulator (http://www.surveymonkey.com/s/9FDP7NJ), and layman version (http://www.surveymonkey.com/s/9FLTQSG). Questions raised were based on criteria listed above and expressed in medical or layman terms depending on the version of questionnaire. Responders were asked to score importance of individual criteria between 0 and 10, from not important to extremely important.

Results from the two surveys then summarised as mean scoring between all responders and used this average score to calculate proportional weighting in each groups of criteria.

Apart from nominating specific numeric weighting between criteria, HiView3 is capable to generate numeric weighting function using a built in function MACBETH (Measuring Attractiveness by a Categorical Based Evaluation Technique), using a verbal assessment tool to transform a qualitative judgement into quantitative weighting.

In the MCDA working framework, a decision conference between stakeholders should be held to achieve agreed criteria utility functions, weightings and trade-offs between criteria after reviewing preference scores. This approach was not feasible at current work group setting, and we would address this with patient group involvement in Wave 2 studies.

Calculation of weighted score at each level and overall weighted average

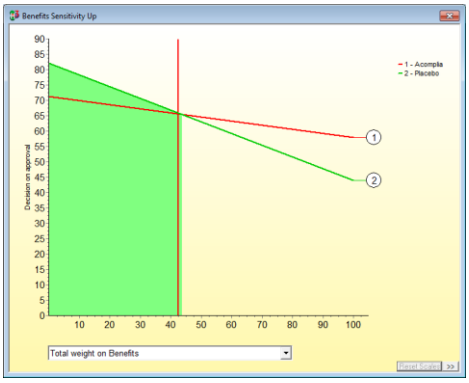
Results for criteria score will be discussed in results section.

11.3.2.5 Sensitivity analysis

Results for the sensitivity testing in each tree will be discussed more detail the individual analysis report in the appendix. In this section, we will explain briefly how to interpret the sensitivity testing report on weights from using HiView3. There is no inbuilt sensitivity testing tool for criteria scoring on using HiView3.

Sensitivity testing can be performed in 2 ways using HiView3:

First approach – sensitivity up; this approach displays the sensitivity testing on weights assigned on the node or criterion in full weighting range between 0 and 100.

(A) 

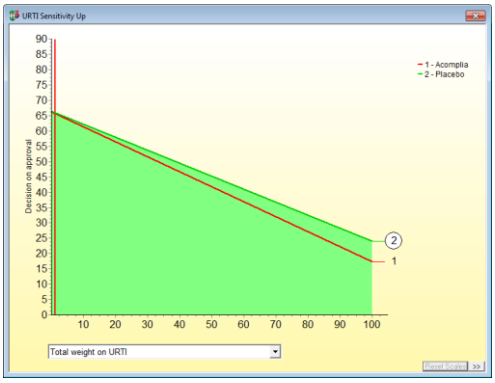
(B) 

Figure 11-1 Sensitivity up graph

Figure 11-1(A) is a graphical presentation of sensitivity up testing criteria. X axis is weights and Y axis is the final average weight score. The vertical red line shows the current assigned weight for the criteria. E.g, Figure 11-1(A) shows the weight assigned to benefit is 42.5. The red line, labelled 1, is the trend line of overall weight score related to weights assigned to rimonabant. The green line, labelled 2, is the trend line of overall weight score related to weights assigned to placebo. The point where the lines crosses elicit the critical point where the criteria weights value changes the results of the preferred alternative, the weights space below this point is shown in green for display. This allow a easy visual assessment the distance between current weight and the critical point, therefore to assess how sensitive is the conclusion to the swing in weight in that particular criterion.

Figure 11-1(B) shows a senario when the trend line between alternatives did not cross. This suggests changes of weight assigned would not alter the final results.

Second approach – sensitivity down; this approach displays the sensitivity testing on criteria below the selected node.

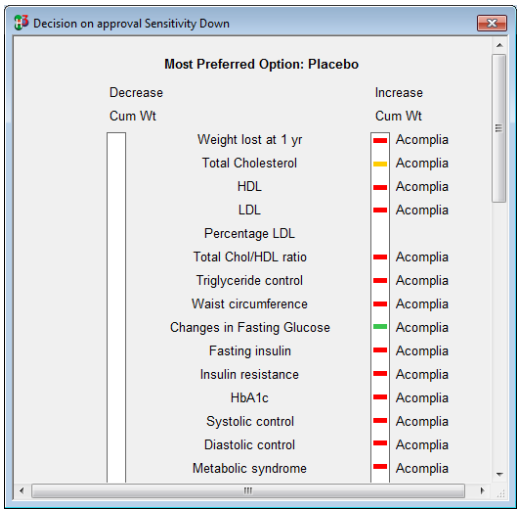


Figure 11-2 Sensitivity down graph

Figure 11-2 is a graphical display of sensitivity down testing with HiView3. The most preferred option is shown on the top the graph. Criteria below the node testing is listed in the middle, column on left showing the consequence of decreasing total weight on the selected criterion and vice versa on the right. Bars within the column are colour coded and reflects the sensitivity of the criterion by the range of cumulative weight changes required to alter the most preferred option in the model.

Red– Most preferred option would change by <5 points of cumulative weight.

Yellow – Most preferred option would change by 5-15 points of cumulative weight.

Green - Most preferred option would change by >15 points of cumulative weight.

Lack of colour bar within the column suggesting the results from the model is not sensitivity to changes to weights assigned to that criterion.

In this example, placebo is the most preferred option and this results is very sensitive to increase in cumulative weight on percentage of patients achieved 10% weight lost, changes in HDL, LDL, Total Chol/HDL ratio, Triglycerides control, waist circumference, fasting insulin, HbA1c, systolic blood pressure control, diastolic blood pressure control and metabolic syndrome. The result also moderately sensitivity to changes in total cholesterol controls. A large increment in weights assigned to fasting glucose will alter the most preferred option to rimonabant.

Both sensitivity testing techniques gives the same result. Sensitivity down method provides a quick review on all criteria and the effect on final result, whereas sensitivity up method allows a more detail review on sensitivity testing on individual criterion but more labour intensive.

We used sensitivity up method in this report.

11.3.2.6 Results

3 trees were developed for this analysis. Each tree was modelled using separate medical/regulator and layman weightings. Data from this analysis was collected from EPAR[3, 4] and the 4 randomised controlled trials [2, 5, 11, 12] completed prior to drug approval. Three trees were developed to examine the flexibility and practicality of source data input.

In tree 1, original reported data from individual studies were used as end criteria. This approach allows us to clearly specify results from individual studies within the tree. Also, increase the flexibility to change weighting of the particular study on individual outcome measure reflecting the recruitment specification and limitations of the study. Further, this approach has the feasibility of adding more data easily when new study emerges. For the purpose of the exercise, equal weights were assigned for the four RCT.

Results from tree 1 showed an equivocal weighted average score between rimonabant compared to placebo. Average benefit score were higher in rimonabant, but these were outweighed by the risk score.

This approach is intuitive when drawing up a decision tree. However, using individual trial data was inefficient and difficult for adjust weighting of decision criteria. Sensitivity down testing on higher level criteria was also proven to be difficult in this case.

Further, one would argue that the end criteria of decision tree should not be completed with individual trial, as the trial itself were not part of the decision criteria. In view of these issues, 2 further trees were developed and results from these two trees will be discussed in more detail.

In tree 2, individual criteria were used as end criteria and data from the RCTs were used as sub-criteria. Criterion scoring was then calculated from pooled results. Pooled results were weighted according to operator preference. For the purpose of this exercise, data between trials are given equal weighting. Benefits of this approach are similar to Tree 1, but allow a more succinct sensitivity testing on different criteria.

In tree 3, individual criteria were used as end criteria and data from the RCT were first summarised using random effects meta-analysis. Random effect methods were chosen to reflect the uncertainties and difference in underlying populations used in the trials. Data from different studies were pooled using method of inverse variance. Benefit of this method allows assessment of individual criteria in sensitivity testing, as well as providing a systematic and objective approach to combine results from different trials.

In this part of report, we will concentrate on discussing the results from tree 2 and tree 3 based on regulatory prospective and examine the difference in results with regulatory and layman weighting on tree 3 finally. Based on the following criteria:

- Overall result, level one criteria and overall weighted score
- Sensitivity analysis

Tree 2 - using pooled data with medical/regulatory weighting:

Figure 11-4 shows the final overall weighted scores between the two alternatives in tree 2 using medical and regulatory prospective. Total wieighted score in rimonabant was 65.7 compared to placebo scored 66.0 in this model. This analysis showed placebo was more flavourable to rimonabant by a small margin.

This preference result was highly sensitive to weighting assigned on benefit, in particular weight assigned on proportion of patients achieved 10% weight lost, change in waist circumference and Total cholesterol/HDL

cholesterol ratios. Besides beneficial effects, this model also highly sensitive to weighting assigned on incidence of overall psychiatric disorder.

Tree 3 – using data from meta analysis with medical/regulatory weighting:

Figure 11-38 shows the break down of the score between rimonabant and placebo in this model. Total wieighted score in rimonabant was 63.5 compared to placebo scored 63.9. This analysis showed placebo was more flavourable to rimonabant by a small margin.

This preference result was highly sensitive to weighting assigned on benefit, in particular weight assigned on proportion of patients achieved 10% weight lost, change in waist circumference and Total cholesterol/HDL cholesterol ratios. Besides beneficial effects, this model also highly sensitive to weighting assigned on incidence of overall psychiatric disorder.

Tree 3 – using data from meta analysis with layman weighting:

Figure 11-72 shows the final overall weighted scores between the two alternatives. Total weighted score in rimonabant was 61 compared to placebo scored 57.4. This analysis showed rimonabant was more flavourable option.

Sensitivity testing of this model showed this model was relatively stable with swings in weightings assigned in each criterion.

11.3.2.7 Assumptions

Criteria preferences are consistent and independent.

11.3.2.8 Summary

Multicriteria Decision Analysis (MCDA) is a useful methodology when decision maker faces a decision with different alternatives, complicated with multiple, often conflicting objectives.

The objective of this exercise is to examine the feasibility on applying this technique in Risk/Benefit assessment.

For the purpose of this exercise, our group used data on rimonabant 20mg compared to placebo. Data used in this model are real but weighting were factitious. In principle, a decision conference with stake holders should be held to explore an agreement in criteria function and weighting. Weighting we used in this exercise were built on a simplistic web survey designed collect personal opinion on the importance of each criteria within our group, therefore, *the risk and benefit result from this analysis should only be taken as an example of the technique.*

The first step of MCDA exercise is to establish utility function to convert performance on the alternatives in each criterion in a common scale for trade-offs using weights. We did not have end users involvement in this part of the study and the utility function and the scale were set to a hypothetical range. Author would like to emphasise that the setting of utility function and scale would greatly impact on the final risk benefit profile in the MCDA HiView model. However, for the purpose of this exercise, the utility function and scales were identical between all 3 trees. Therefore, allowing the team to compare the difference in tree setup.

This exercise showed that using individual study data as end criteria (Tree 1) was intuitive and convenient to incorporate new data when new study emerges. However, using individual study as end criteria greatly increases number of criteria and complicates the model.

Our second approach (Tree 2) was to pooled results from the RCTs and used criteria as end nodes. The software we used in this exercise allows the option of using sub-criteria within each end criteria to hold data from different trials and user required to assign weights between each sub criteria. This approach has the feasibility to add new data when available, as well as allowing sensitivity testing on criterion level easily. However, the weights between studies were subjective which could affect final results. For the purpose of this exercise, the 4 RCT's were assigned equal weightings.

Our third and final approach (Tree 3) was to use results from Meta-analysis method used to summarise data from different RCTs, as data. This was very similar to previous approach; however, using Meta-analysis allowed an objective approach in pooling data between trials and reduces bias. As well as adjusted for the uncertainties and difference in underlying populations used between the trials. However, a full set of Meta-analysis is needed if new data emerges.

Our results showed weighted pooled data approach with equal weightings and Meta-analysis approach produce a similar result in this model. Both model suggested placebo is the preferred choice by a very small margin. The author would flavour the use of Meta-analysis approach to avoid bias that might occur, particular when trial sizes are small.

Finally, we also explored the sensitivity of the model with different opinion weighting by collecting weighting opinion from medical/regulatory prospective and layman prospective. Albeit a very small number of participants in the survey, this survey showed a rather different in preference opinions between stake holders. Our experience with using SurveyMonkey also highlighted the importance of survey design, weight preference changes substantially depending on how the questions were asked.

Despite the using the same data and decision tree, our model suggested placebo would be the more preferable option by a small margin if we use medical/regulatory weighting. Whereas, using layman's weighting resulted a more favourable profile with rimonabant.

Although the weighting were factitious, this highlighted the issue that the results from this framework is sensitive to weight assigned and which often varies dependent on stake holder's interest and prospective.

11.3.2.9 Appraisal of technique

MCDA is a very useful tool for decision makers, especially when the decision is complex with multiple alternatives. This method divides decision making into different smaller and more objective criteria and each alternative is then compared and weighted. Decision maker can then conclude the preferred option objectively.

The software we used in this exercise, HiView3, is easy to use with a simple to use yet comprehensive interface. The built in MACBETH tool are also proven to be most useful in cases requiring to translate qualitative assessment into quantitative weights to be used in the model. Sensitivity testing with this approach also useful to assess the sensitive of the final results to weight swings.

However, there are a few concerns with HiView MCDA model.

1. The MCDA programme only allows one value for every alternative in each criterion. However, medical data are often in range of mean with confidence interval so to account for the uncertainties and random error with the statistical estimates. This MCDA programme would not able to take the uncertainty with data into account, this is crucial in making medical judgements especially in rare events where there is a intrinsically considerable degree of uncertainty with the statistics estimates.

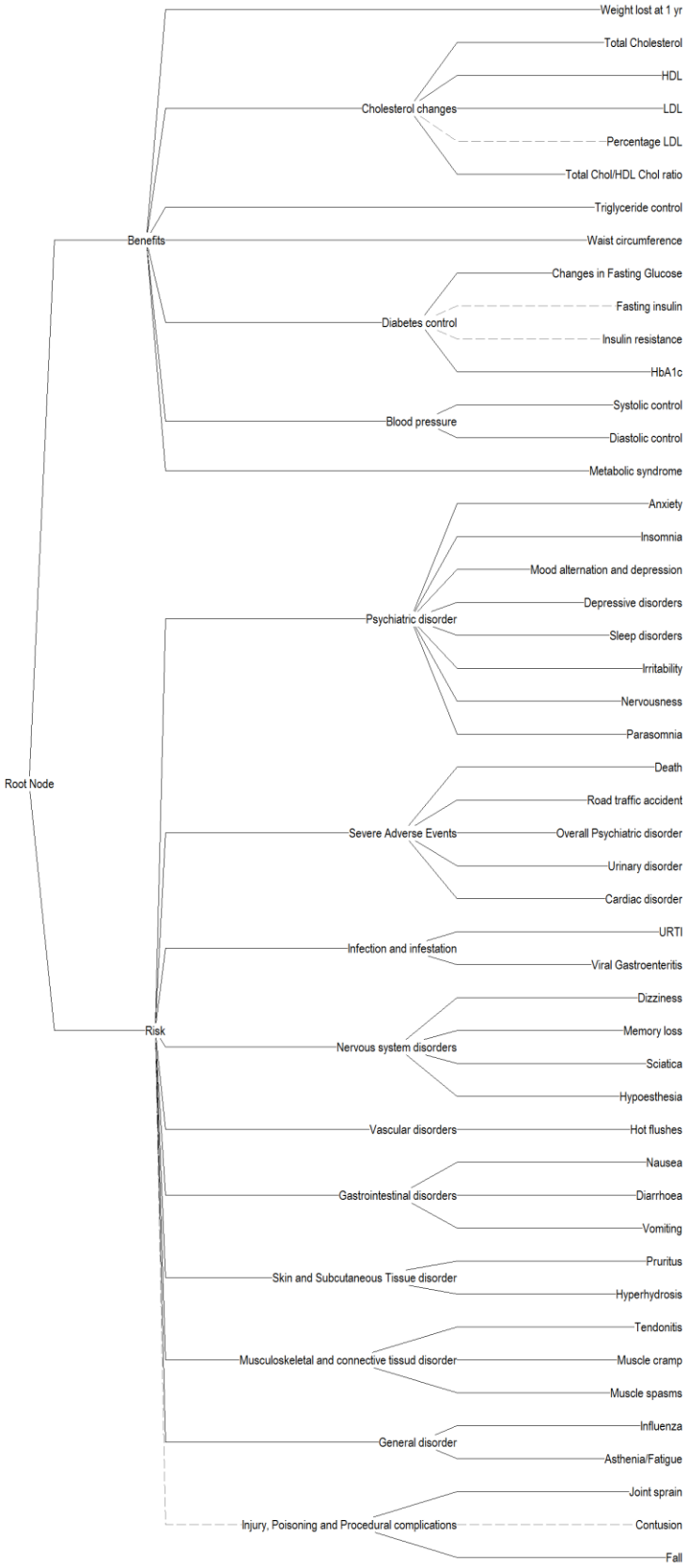
2. MCDA programme requires criteria values and weights to be precisely known upfront. It is often difficult and unrealistic to obtain an exact weighting score in real life situation. As well as the decision maker's knowledge regarding to the question might not be sufficient to make an objective judgement in weighting. As we demonstrated using Tree 3, results from framework are subjective to weighting assigned on criteria.

3. MCDA programme also require user to define utility function and scale in order to convert performance of each alternative on each criterion into a common scale for trade-offs. The final risk benefit profile is highly sensitive to the utility function. As with weight information, one would imagine it is difficult to obtain a consistent agreement on how much difference is important between experts in order to translate this into a utility function.

11.3.2.10Sub Appendix

11.3.2.10.1 Tree 2 –Medical/Regulatory prospective with weighted results from trials

Decision Tree



Overall results

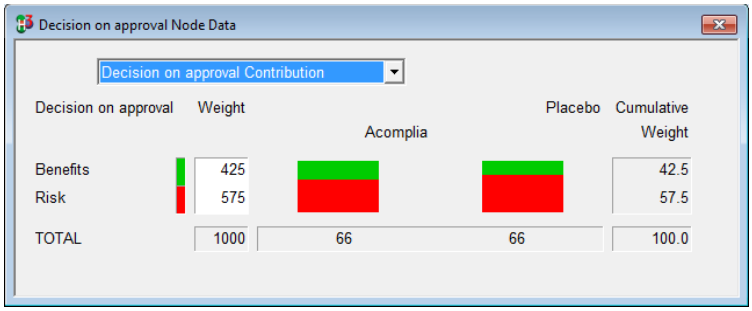


Figure 11-3 Overall results

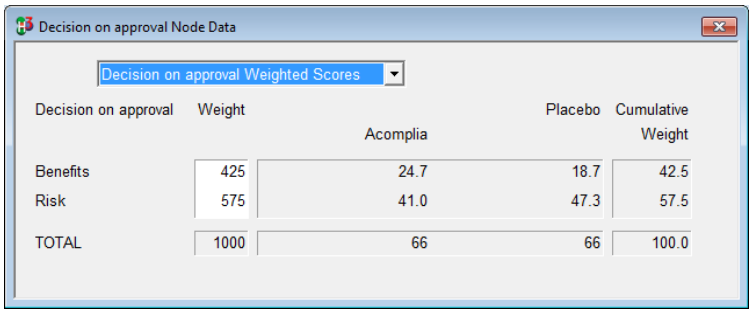
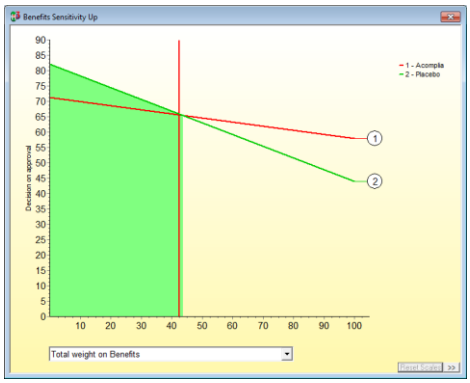


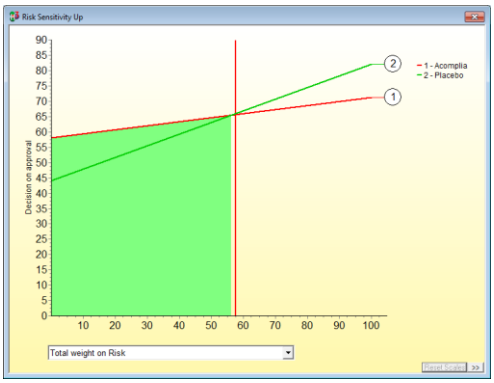
Figure 11-4 Overall scores

Overall results (Figure 11-4) showed the final overall weighted scores between the two alternatives. The green bar from Figure 9-1 shows the average overall weighted score on benefit, and the red bar is the average overall weighted score on risk. Risk criteria score were set in inverser order, i.e., alternatives rewarded higher score with lower risk. Figure 9-2 shows the break down of the score. Total wieighted score in rimonabant was 65.7 compared to placebo scored 66.0. This analysis showed placebo was more flavourable to rimonabant by a small margin.

Sensitivity testing



A) Benefits.



B) Risks

Figure 11-5 Sensitivity testing: a) Benefits b) Risk

In this case, it demonstrated the conclusion that placebo was the preferred option is sensitive to weights assigned to these two criteria, current weights between benefit and risk were set at 42.5 and 57.5. A small rise in weights assgned to rimonabant, approximately to 44, will result rimonabant becomng the more preferred alternative.

Benefit - Level 2 Criteria

Overall results

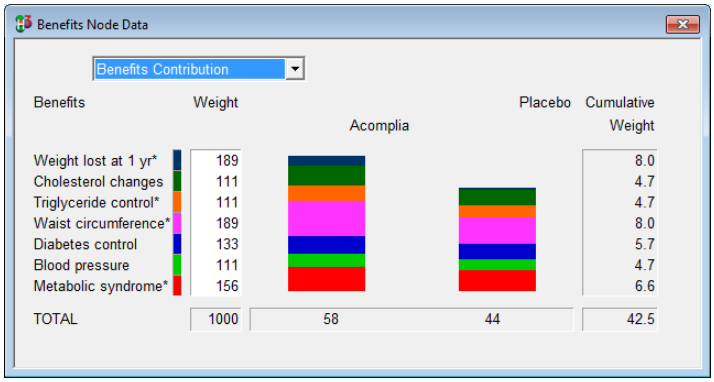
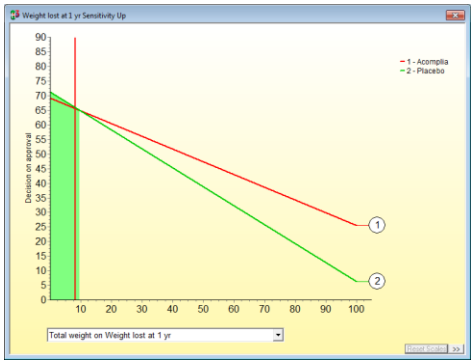


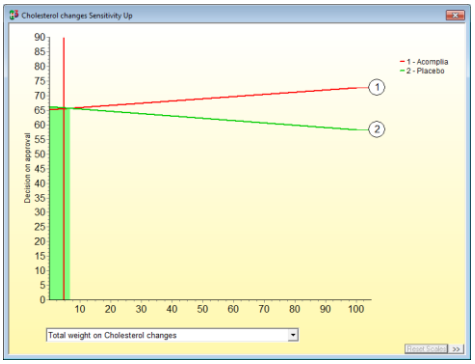
Figure 11-6 Overall results: Level 2 benefit criteria

In terms of benefit, rimonabant achieved higher score(58) compared to that of control (44) (Figure 11-6). Mainly related to benefit with reduction in waist circumference.

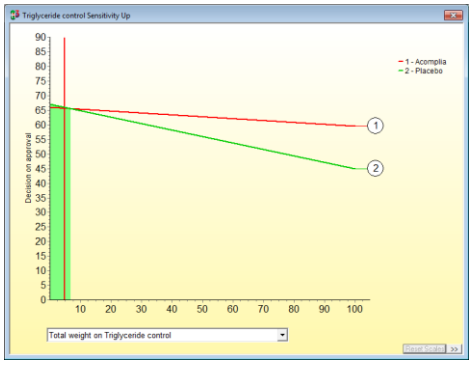
<u>Sensitivity testing</u>



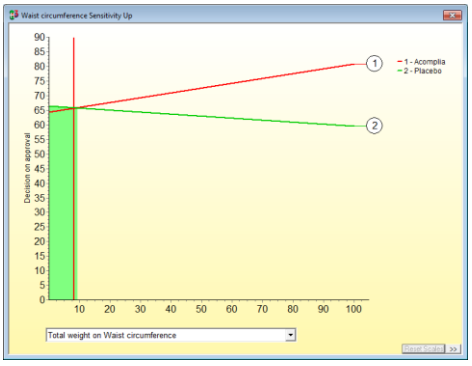
A) Weight lost



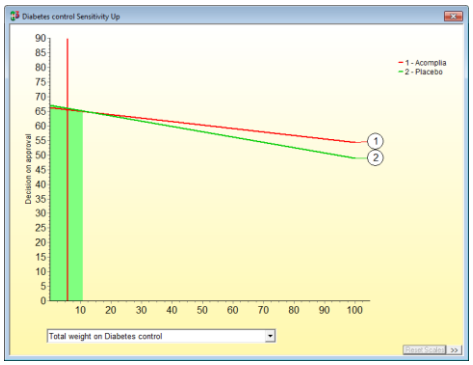
B) Cholesterol changes



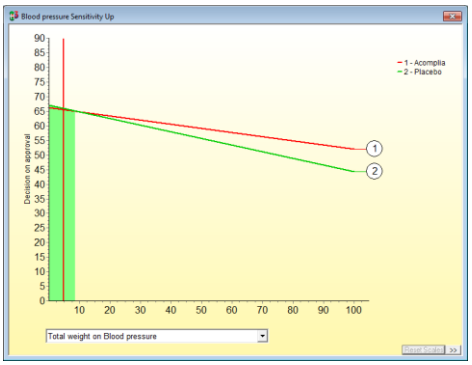
C) Triglyceride control



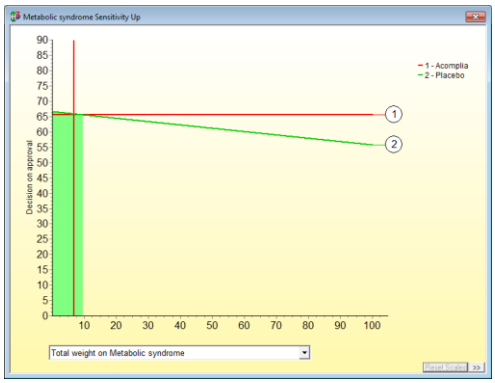
D) Waist circumference



E) Diabetes control



F) Blood pressure control



G) Reduction in metabolic syndrome

Figure 11-7 Sensitivity testing: Level 2 benefit criteria

Sensitivity testing on on level 2 criteria suggested that this model was highly sensitive to weight assigned to these criteria. A small change in weights assigned on percentage of patient achieved 10% weight lost, changes in waist circumference, changes in triglyceride and cholesterol control alters the final preference between placebo and rimonabant. (Figure 11-7)

Benefit – Level 3 Criteria

Cholesterol Control

Node results

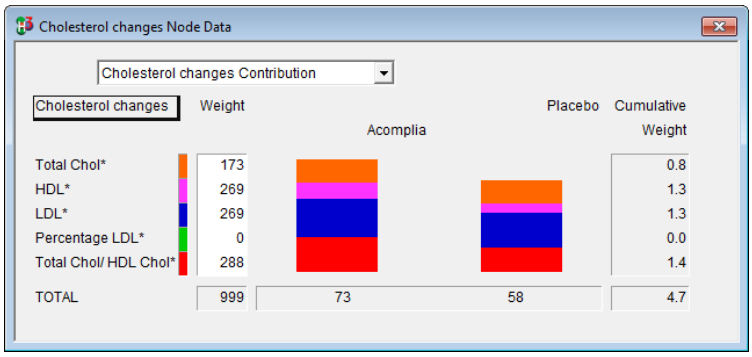
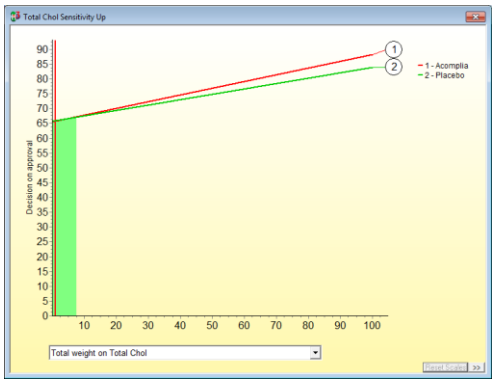
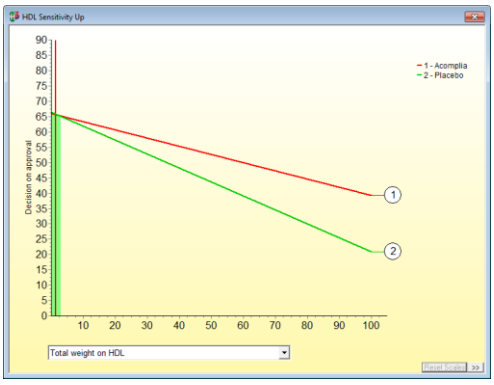


Figure 11-8 Weighted score on level 3 Cholesterol control criteria

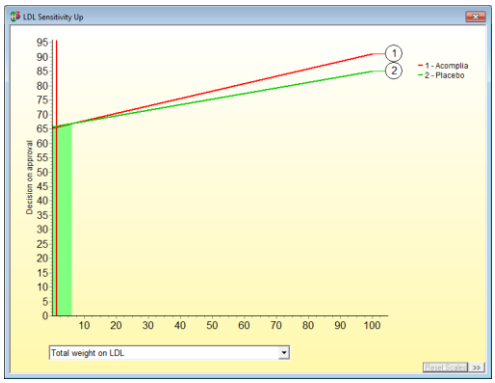
Sensitivity testing



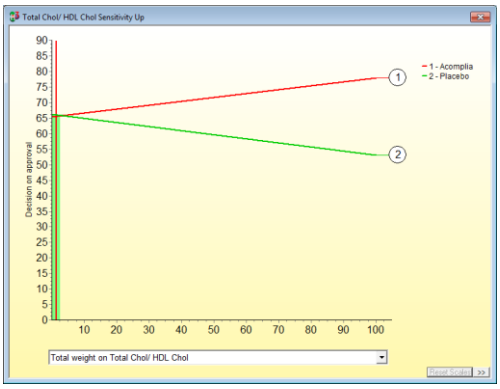
A) Total Cholesterol



B) HDL reduction



C) LDL cholesterol



D) Reduction in Total Cholesterol/HDL Cholesterol ratio

Figure 11-9 Sensitivity testing: Level 3 Cholesterol control

Rimonabant scored higher compared to placebo in cholesterol control (Figure 11-8). This final outcome was sensitive to weighting given to HDL cholesterol Total Cholesterol/HDL cholesterol ratios. (Figure 11-9)

Diabetes Control

Node results

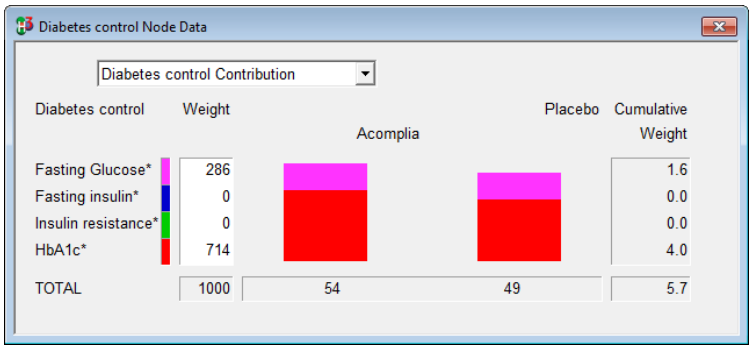
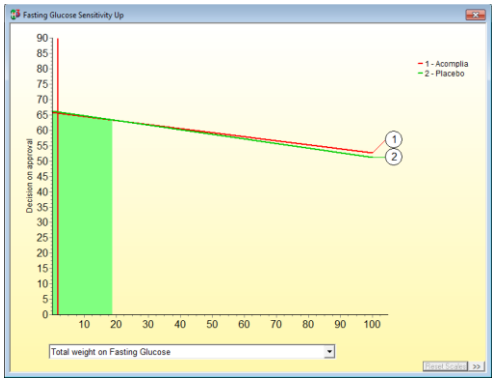
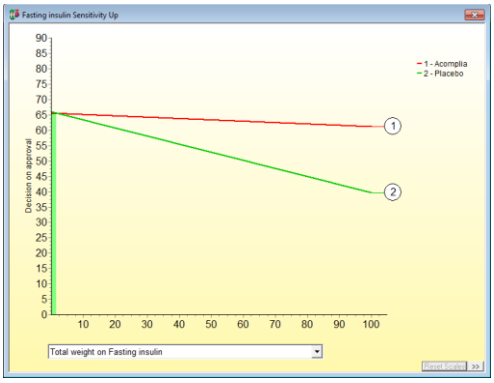


Figure 11-10 Weighted score on level 3 Diabetes control criteria

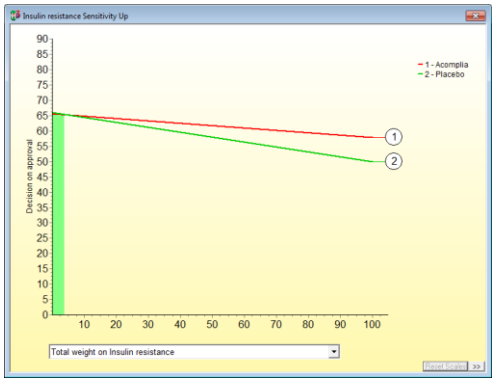
Sensitivity testing



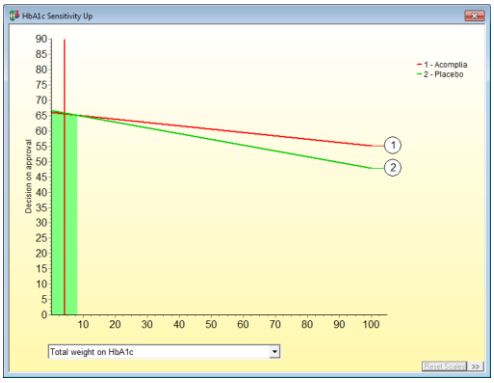
A) Fasting glucose



B) Fasting Insulin



C) Insulin Resistance



D) HbA1c Control

Figure 11-11 Sensitivity testing: Level 3 diabetes control

Results from this node suggesting rimonabant achieved higher score with diabetes control. (Figure 11-10) Interestingly, our group assigned 0 weighting over effect of fasting insulin - The sensitivity testing suggested the final results would change with a small weighting assigned to this criteria. (Figure 11-11)

Blood pressure control

Node result

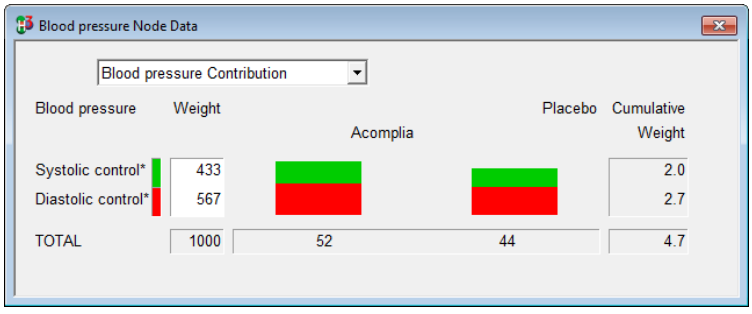
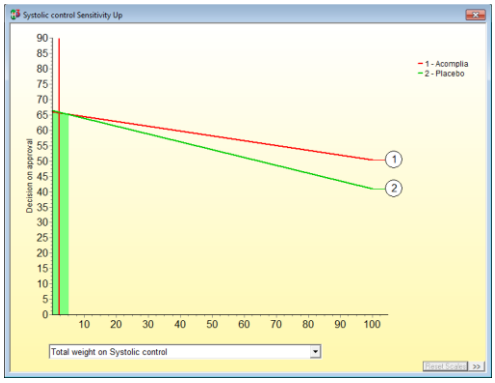
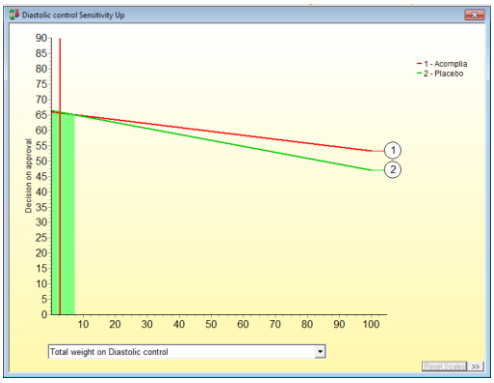


Figure 11-12 Weighted score on level 3 Blood pressure control criteria

Sensitivity testing





A) Systolic blood pressure

B) Diastolic blood pressure

Figure 11-13 Sensitivity testing: Level 3 blood pressure control

Rimonabant scored higher in perference with blood pressure control, compared to placebo (Figure 11-12). Despite of the higher preference score with blood pressure control, this had little impact on the final result. Changes over weighing on blood pressure control has little impact on final outcomes (Figure 11-13)

Risk - Level 2 criteria

Overall results

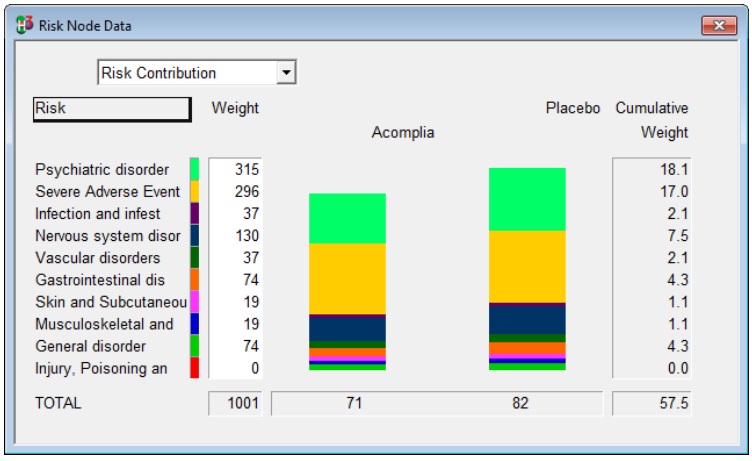
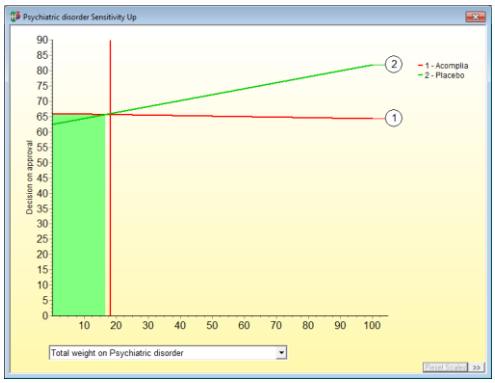


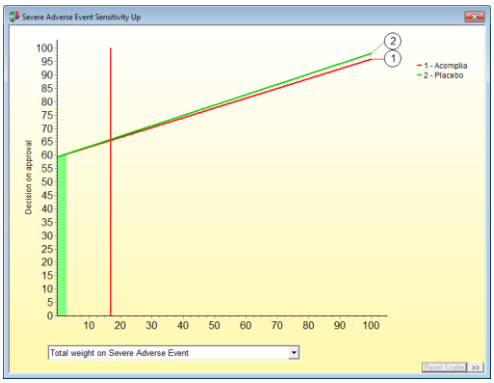
Figure 11-14 Weighted score on level 2 Risk criteria

Rimonabant scored lower in preference score in risk, in particular risk in psychiatric disorder and severe adverse events. (Figure 11-14)

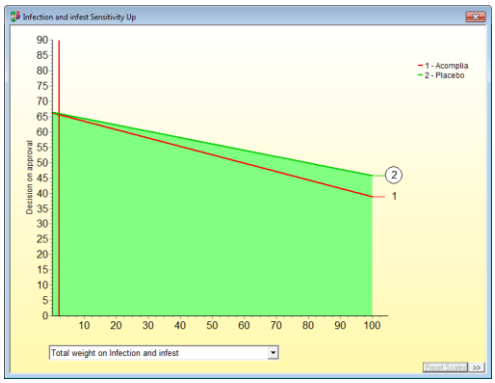
Sensitivity testing



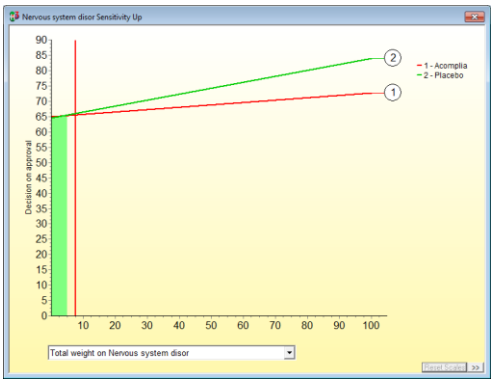
A) Psychiatric disorder



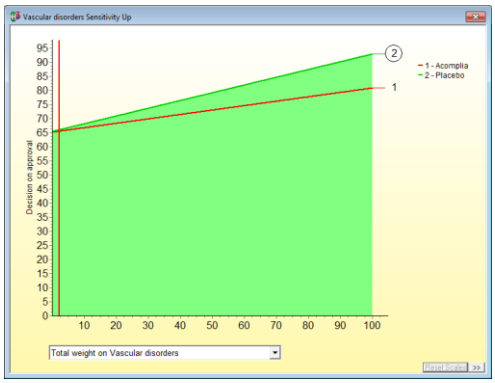
B) Severe Adverse Event



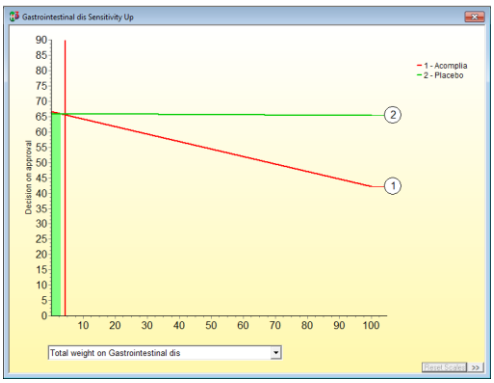
C) Infection and infestation



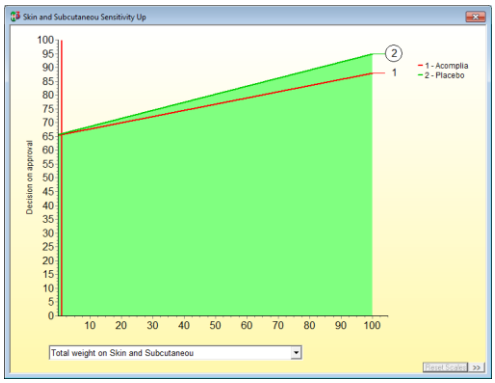
D) Nervous system disorder



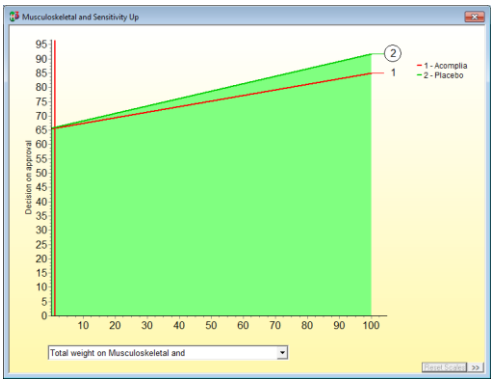
E) Vascular disorder



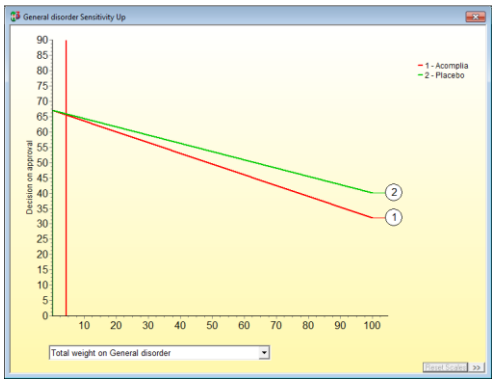
F) Gastrointestinal disorder



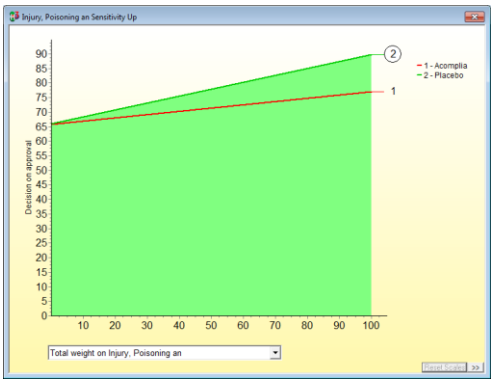
G) Skin and subcutaneous disorder



H) Musculoskeletal disorder



I) General disorder



J) Injury, poisoning and procedural complications

Figure 11-15 Sensitivity testing: Level 2 risk criteria

Sensitivity testing on level 2 risk criteria showed this model was reasonably stable to weighting assigned to different group criteria, apart from weighting on overall psychiatric disorder. A small reduction in weighting assigned to psychiatric disorder would suggest rimonabant be the prefered choice. (Figure 11-15)

Risk – Level 3 criteria

Overall result reflected that the higher incidence of psychiatric disorder following rimonabant resulted in lower total preference score (Figure 11-16). Sensitivity testing within this node suggesting that this model was sensitive to weighting assigned for anxiety and insomnia. (Figure 11-17)

The absolute incidences of severe adverse events between the 2 groups were small. The overall preference score suggesting placebo was slightly more preferable compared to rimonabant (Figure 11-18), results from this risk criteria was not sensitive to changes in weighting assigned to individual criterion. (Figure 11-19)

Rimonabant were associated with higher incidence of side effects and scored lower in infection and infestation (Figure 11-20), nervous system disorder Figure 11-22), vascular disorder (Figure 11-24), gastrointestinal disorder (Figure 11-26) , skin and subcutaneous tissue disorder (Figure 11-28), musculoskeletal and connective tissue disorder (Figure 11-30) , general disorder (Figure 11-32) and procedure related complications (Figure 11-34).

Sensitivity testing in these sub nodes showed the model was not sensitive to changes of weightings in these criteria.

Psychiatric disorder

Node results

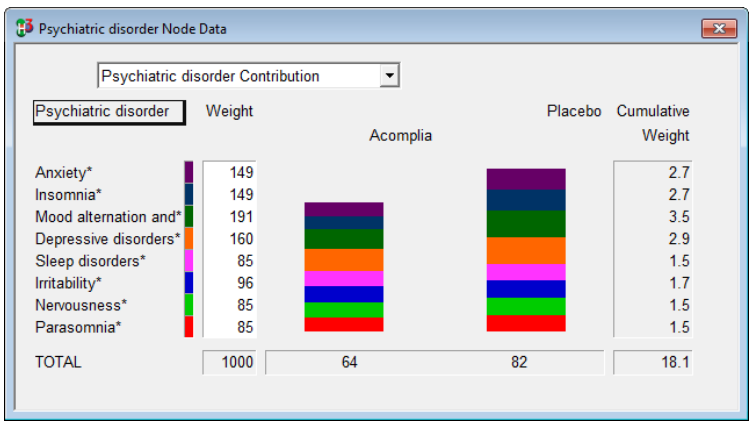
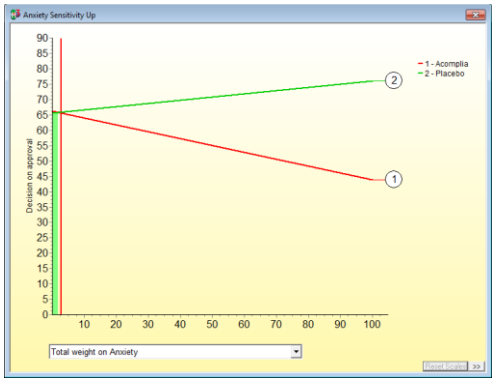
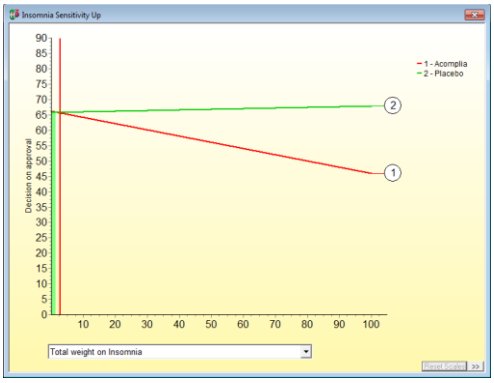


Figure 11-16 Weighted score on level 3 criteria: Psychiatric disorder

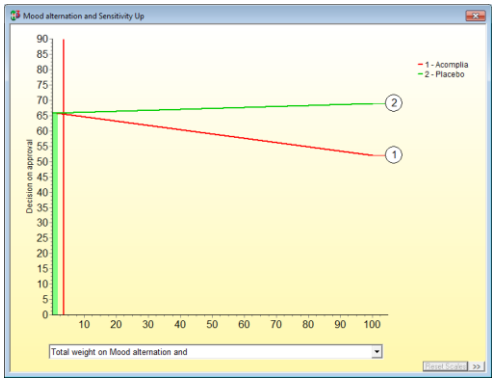
Sensitivity testing



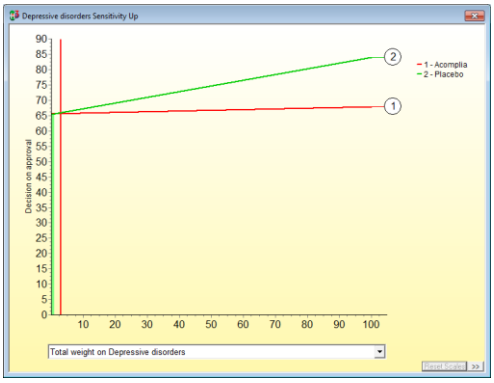
A) Anxiety



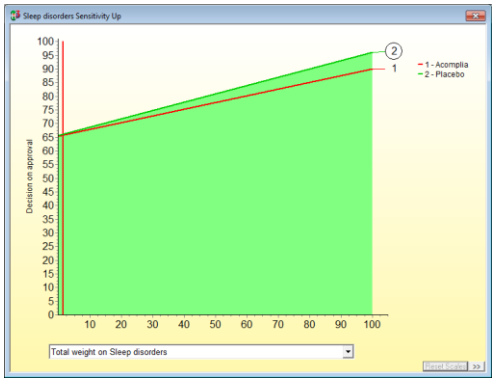
B) Insomnia



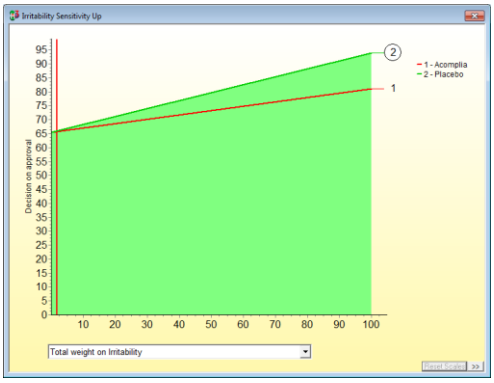
C) Mood alternation



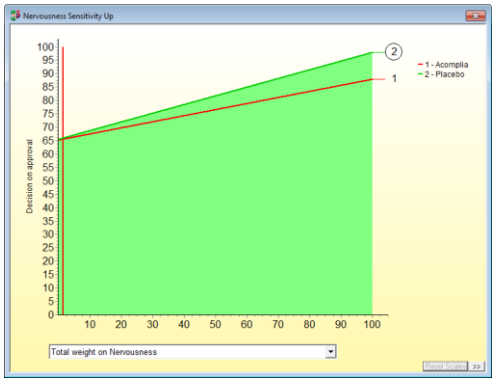
D) Depression



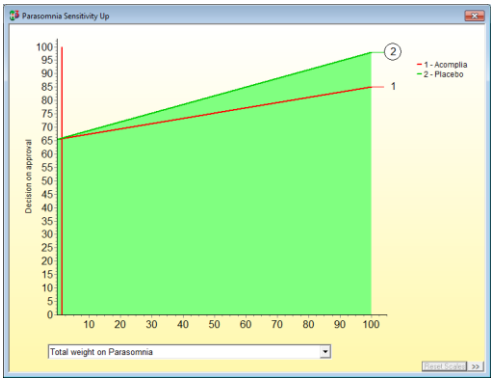
E) Sleep disorders



F) Irritability



G) Nervousness



H) Parasomnia

Figure 11-17 Sensitivity testing: Level 3 - Psychiatric disorder

Severe Adverse Events

Node result

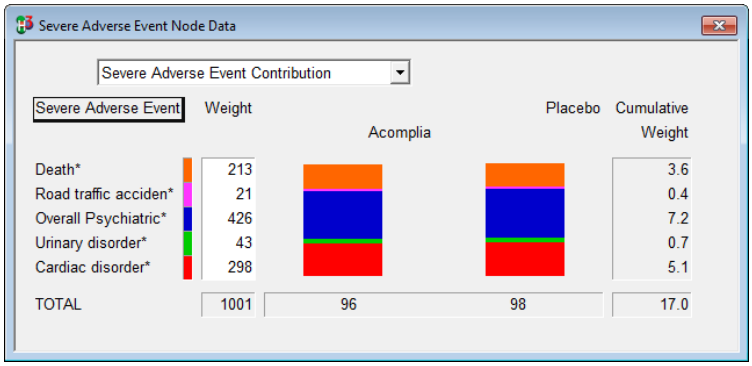
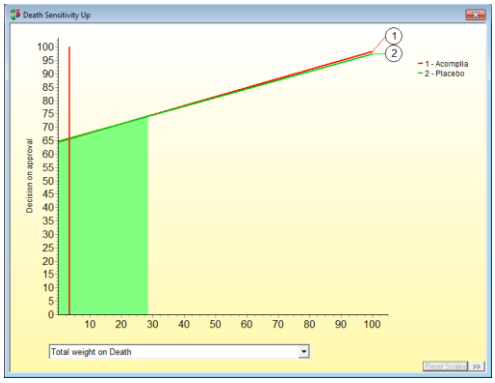
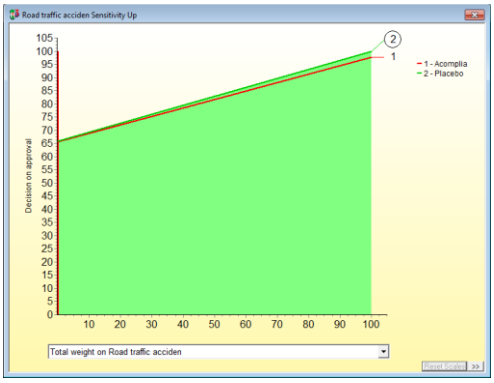


Figure 11-18 Weighted score on level 3 criteria: Severe adverse events

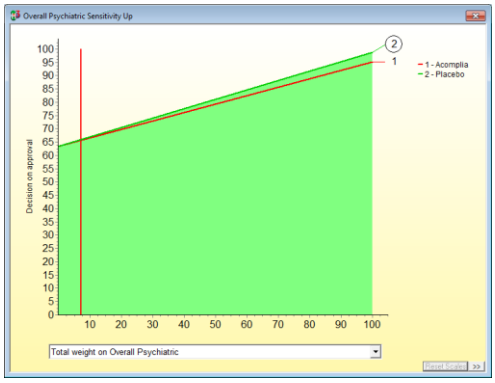
Sensitivity testing



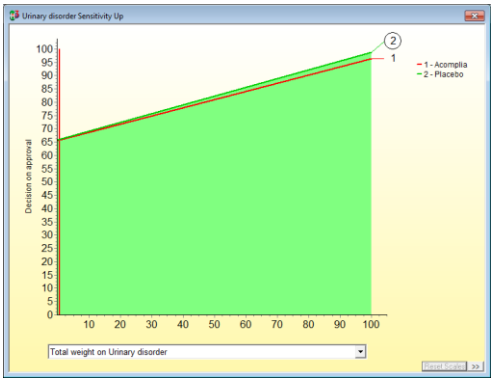
A) Death



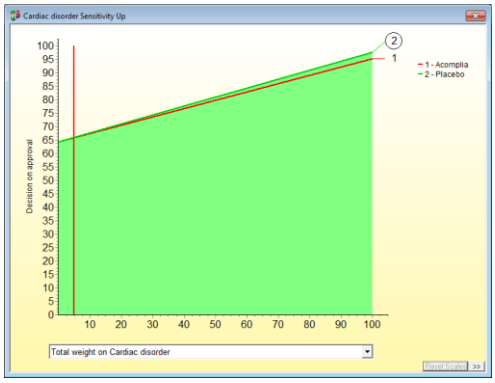
B) Road Traffic Accident



C) Overall psychiatric disorder



D) Urinary disorder



E) Cardiac disorder

Figure 11-19 Sensitivity testing: Level 3- Severe adverse events

Infection and infestation

Node results

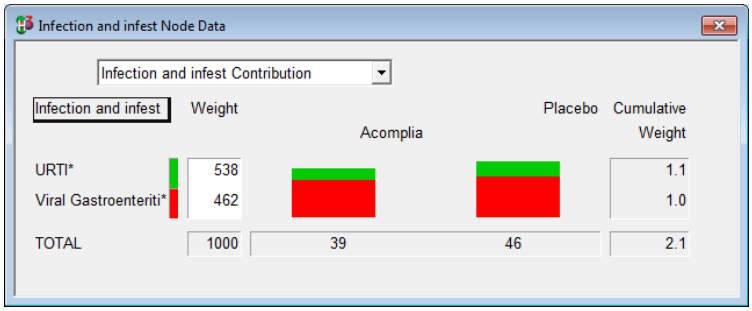
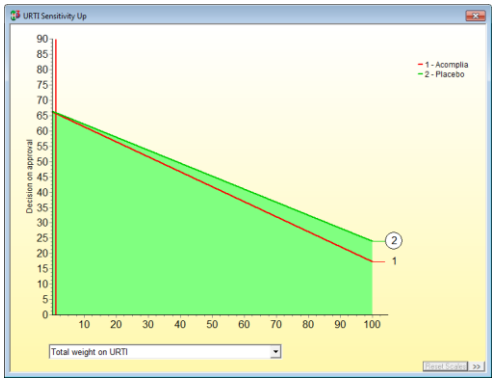
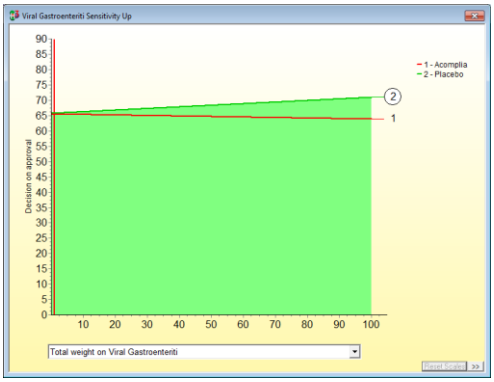


Figure 11-20 Weighted score on level 3 criteria: Infection and infestation

Sensitivity testing



A) Upper respiratory tract infection



B) Viral Gastroenteritis

Figure 11-21 Sensitivity testing: Level 3- Infection and infestation

Nervous system disorder

Node result

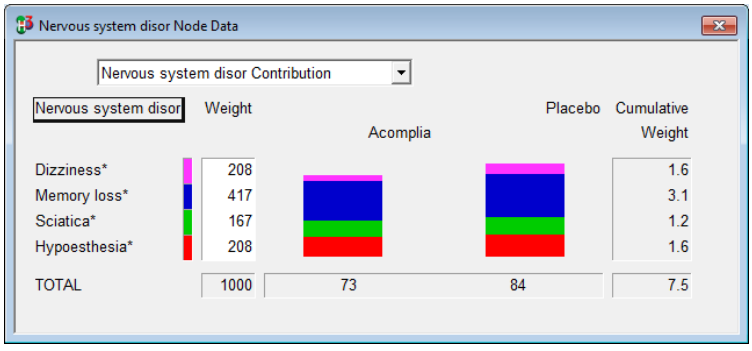
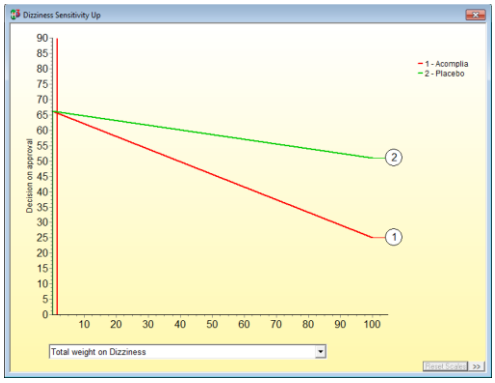
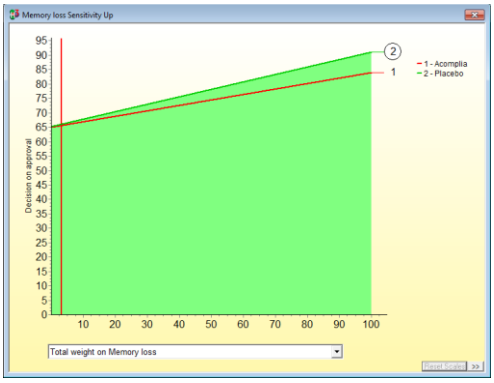


Figure 11-22 Weighted score on level 3 criteria: Nervous system disorder

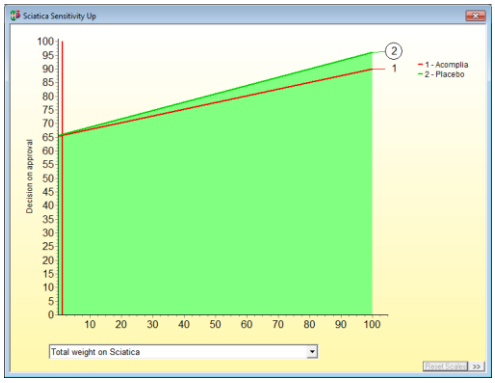
Sensitivity testing



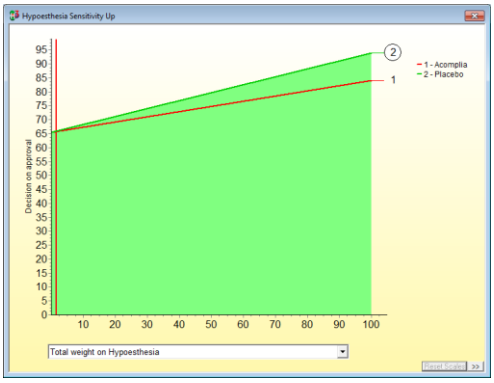
A) Dizziness



B) Memory loss



C) Sciatica



D) Hypoesthesia

Figure 11-23 Sensitivity testing: Level 3- Nervous system disorder

Vascular System disorders

Node results

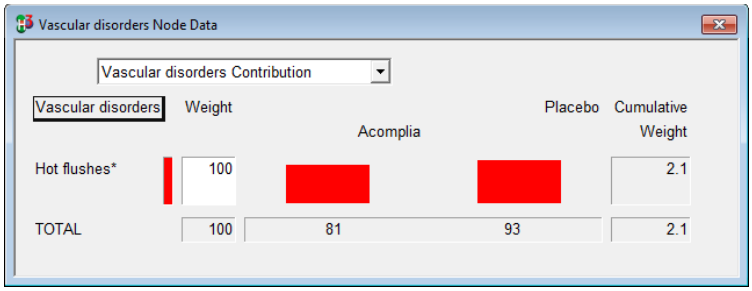


Figure 11-24 Weighted score on level 3 criteria: Vascular system disorder

Sensitivity testing

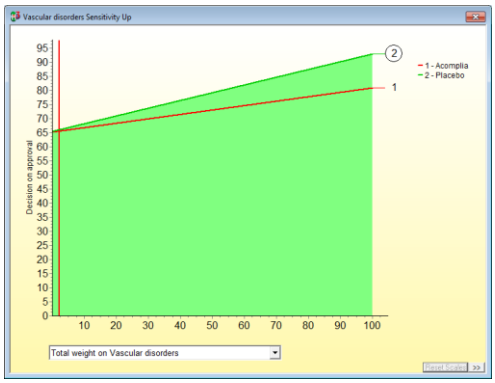


Figure 11-25 Sensitivity testing: Level 3- Vascular system disorder

Gastrointestinal disorder

Node results

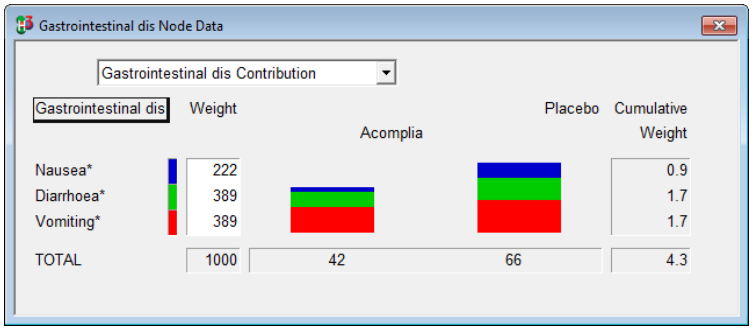
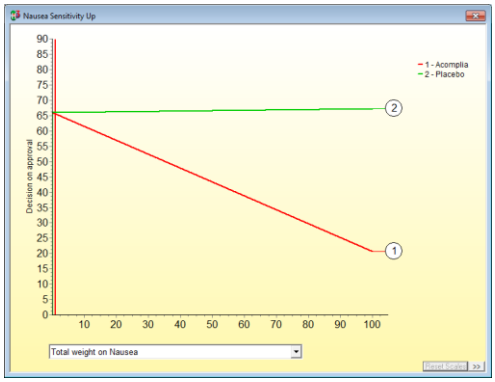
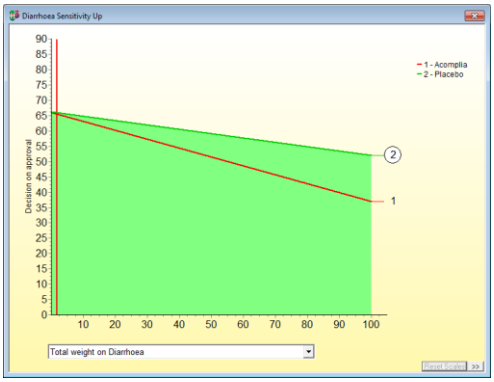


Figure 11-26 Weighted score on level 3 criteria: Gastrointestinal disorder

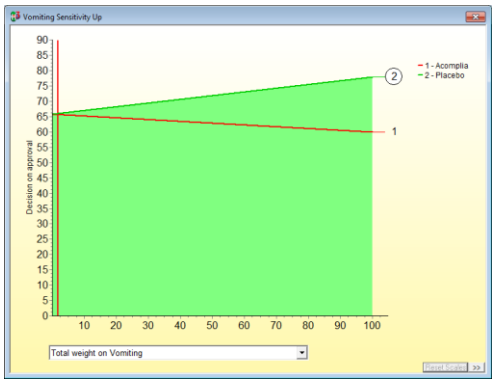
Sensitivity testing



A) Nausea



B) Diarrhoea



C) Vomiting

Figure 11-27 Sensitivity testing: Level 3- Gastrointestinal disorder

Skin and subcutaneous tissue disorder

Node results

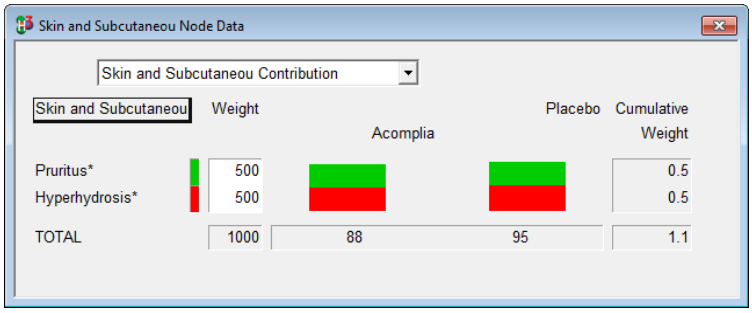
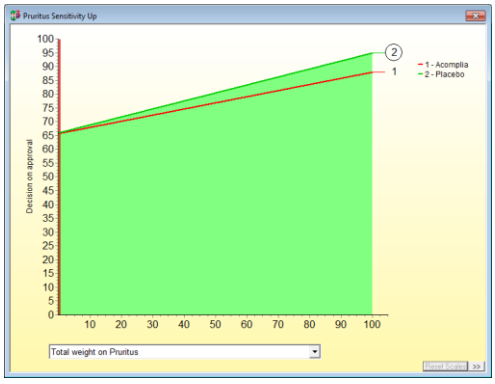
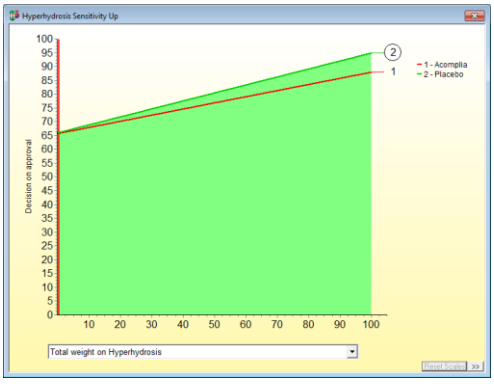


Figure 11-28 Weighted score on level 3 criteria: Skin and Subcutaneous tissue disorder

Sensitivity testing



A) Pruritis



B) Hyperhydrosis

Figure 11-29 Sensitivity testing: Level 3- Skin and Subcutaneous tissue disorder

Musculoskeletal and connective tissue disorder

Node result

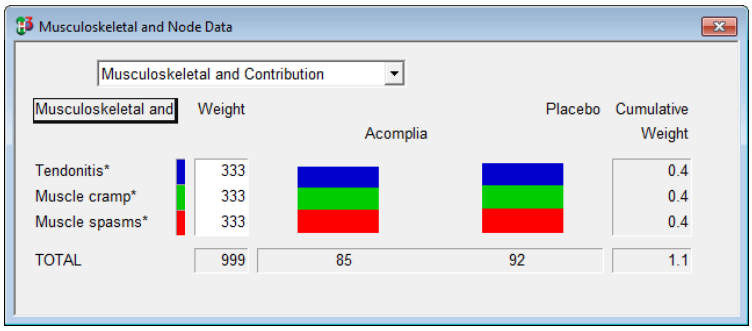
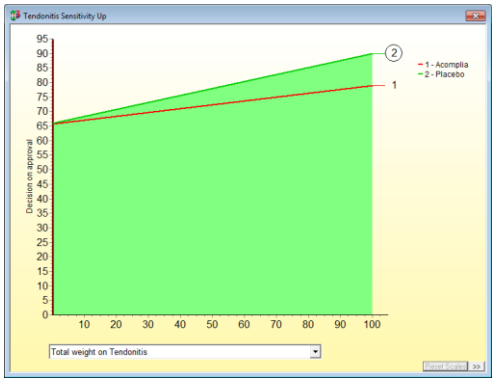
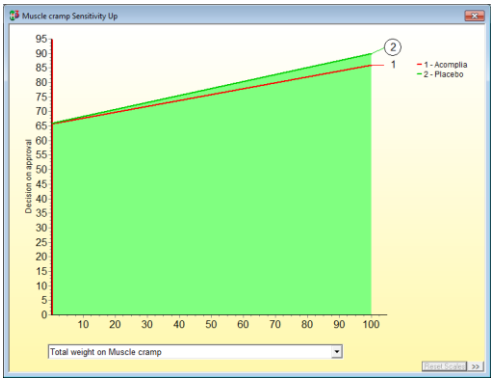


Figure 11-30 Weighted score on level 3 criteria: Musculoskeletal and connective tissue disorder

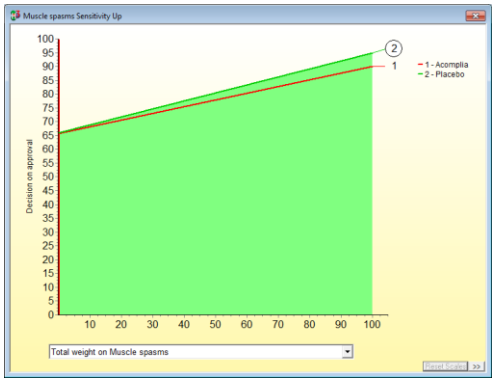
Sensitivity testing



A) Tendonitis



B) Muscle Cramp



C) Muscle spasm

Figure 11-31 Sensitivity testing: Level 3- Musculoskeletal and Connective tissue disorder

General disorder

Node results

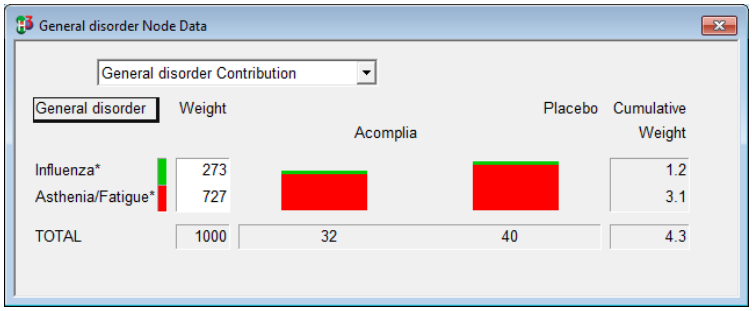
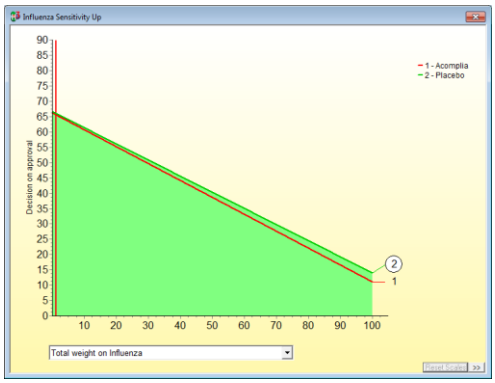
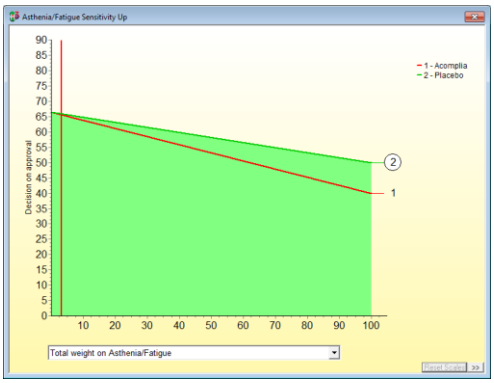


Figure 11-32 Weighted score on level 3 criteria: General disorder

Sensitivity testing



A) Influenza



B) Asthenia\Fatigue

Figure 11-33 Sensitivity testing: Level 3- General disorder

Injury, Poisoning and Procedural complications

Node results

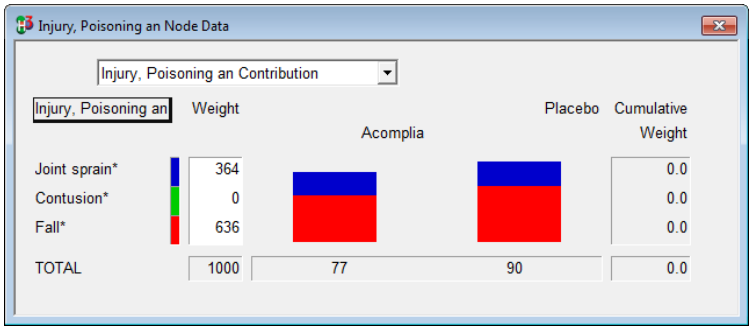
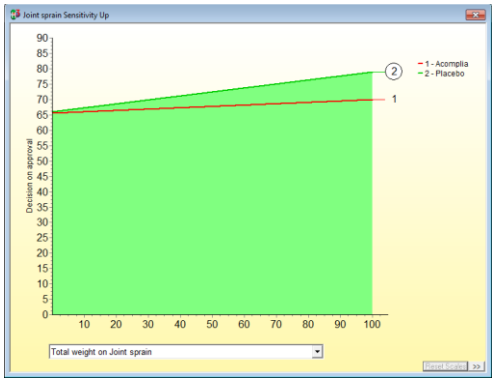
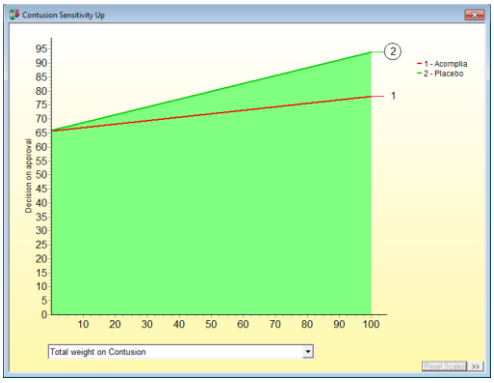


Figure 11-34 Weighted score on level 3 criteria: Injury, Poisoning and Procedural complication

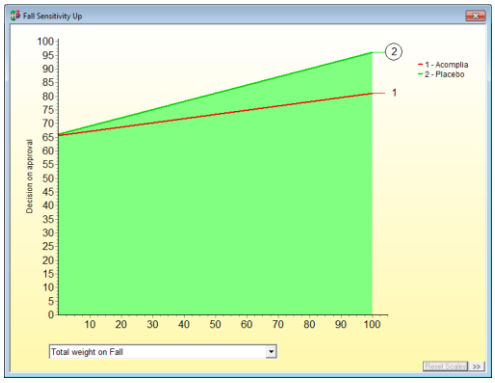
Sensitivity testing



A) Joint Sprain



B) Contusion



C) Fall

Figure 11-35 Sensitivity testing: Level 3 - Injury, Poisoning and Procedural Complication

Difference in Weighted score

Figure 11-36 demonstrated detailed difference in scores between rimonabant and placebo in all criteria listed. Detailed difference in score and cumulative weighting can be found in section 11.3.2.10.4 - Tree 2 Medical/Regulatory prospective.

Although overall results demonstrated that rimonabant was superior in waistline reduction, 10% weight lost at 1 year, triglyceride control and reduction in metabolic syndrome.

Rimonabant was inferior in association with insomnia, mood alternation and depression.

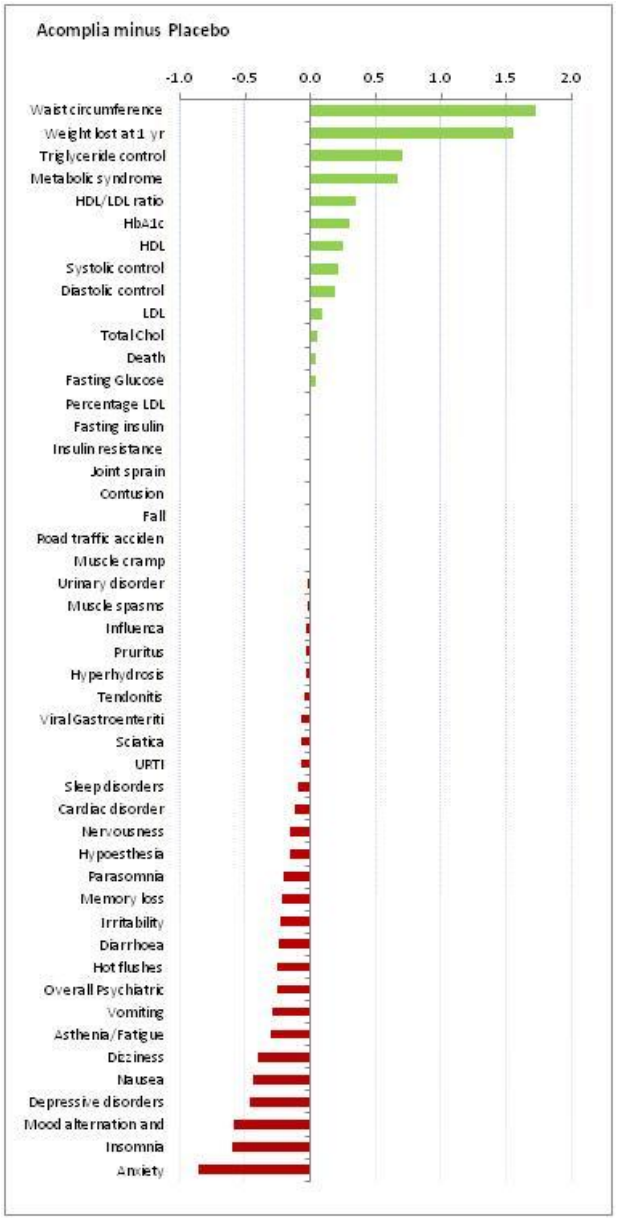
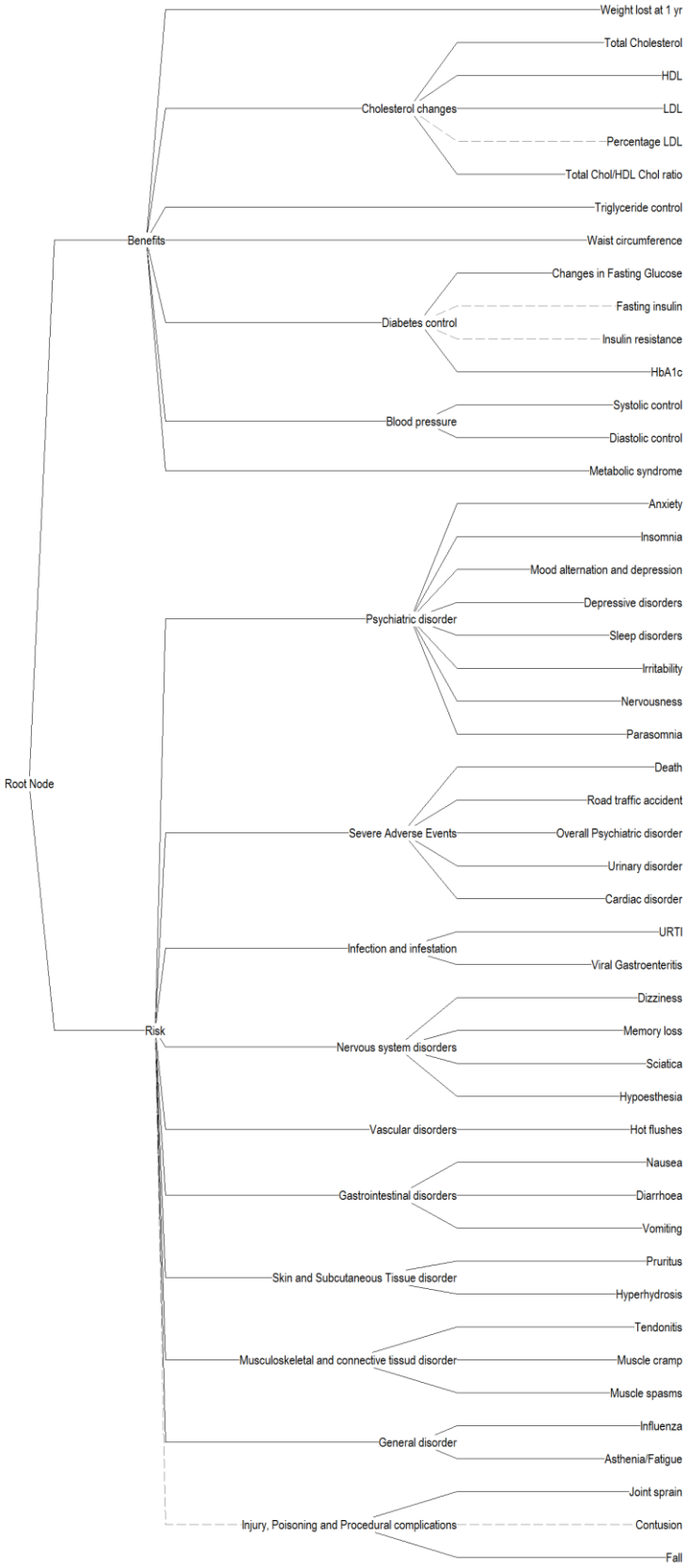


Figure 11-36 Difference in weighted score: Tree 2

11.3.2.10.2 Tree 3 – Medical/Regulatory Prospective using results from Meta Analysis

Decision tree



Overall results

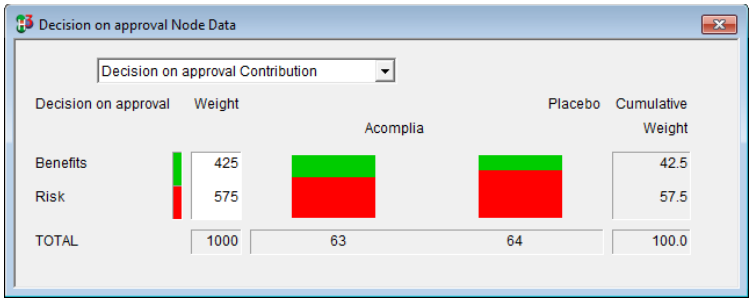


Figure 11-37 Overall results

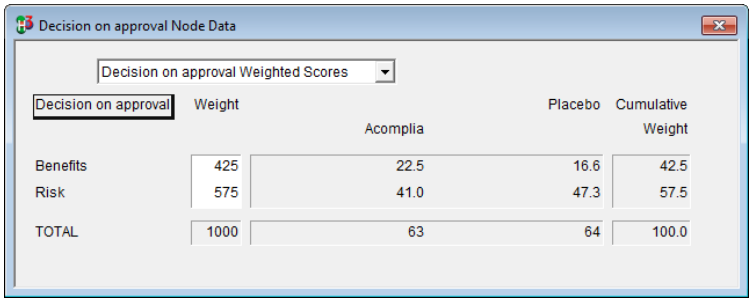
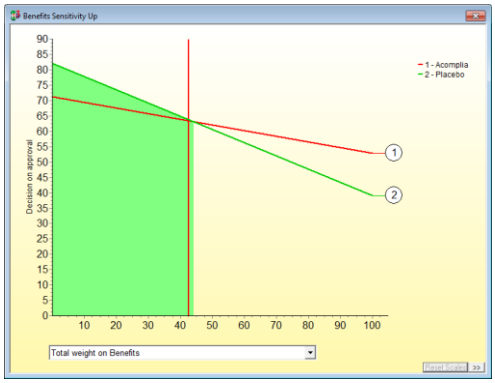


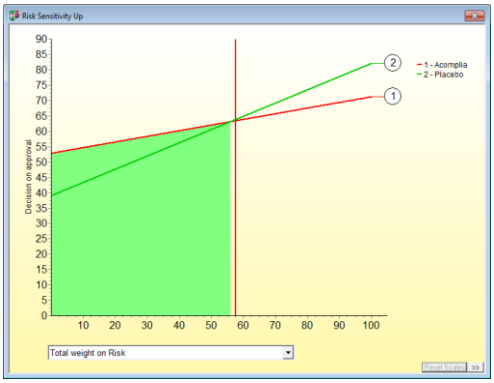
Figure 11-38 Overall scores

Overall results (Figure 11-38) showed the final overall weighted scores between the two alternatives. Figure 11-38 shows the break down of the score. Total wieighted score in rimonabant was 63.5 compared to Placebo scored 63.9. This analysis showed Placebo was more flavourable to rimonabant by a small margin.

Sensitivity testing



A) Benefits.



B) Risks

Figure 11-39 Sensitivity testing: a) Benefits b) Risk

In this case, it demonstrated the conclusion that Placebo was the preferred option is sensitive to weights assigned to these two criteria, current weights between benefit and risk were set at 42.5 and 57.5. A small rise in weights assgned to rimonabant, approximately to 44, will result rimonabant becoming the more preferred alternative.

Benefit - Level 2 Criteria

Overall results

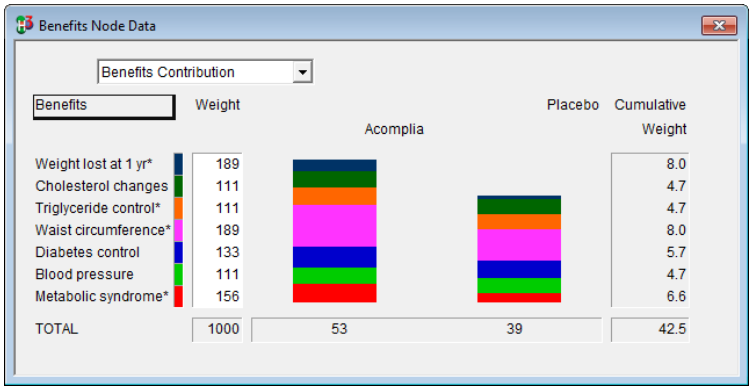
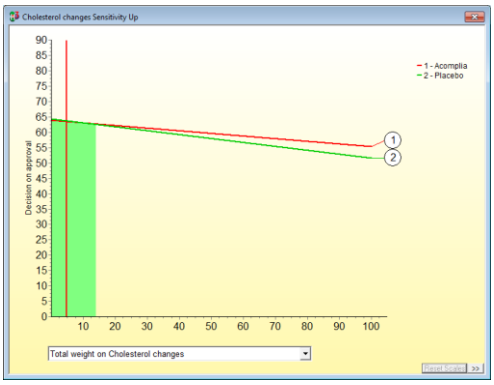


Figure 11-40 Overall results: Level 2 benefit criteria

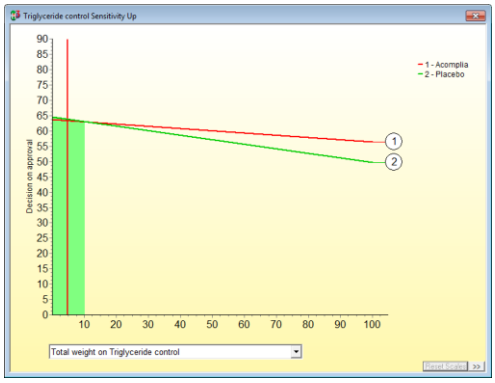
In terms of benefit, rimonabant achieved higher score(53) compared to that of control (39) (Figure 11-40). Mainly related to benefit with reduction in waist circumference.

Sensitivity testing

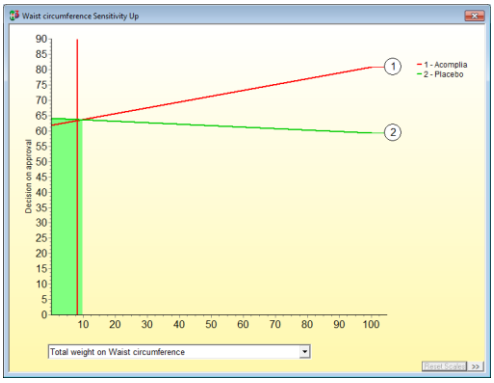
A) Weight lost



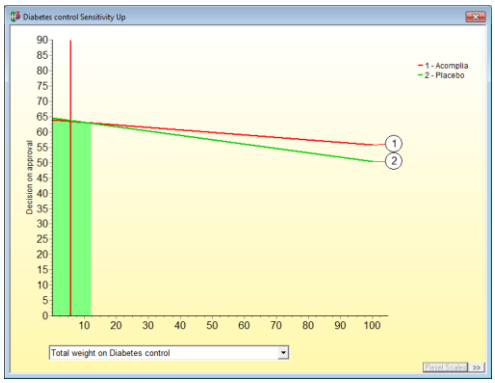
B) Cholesterol changes



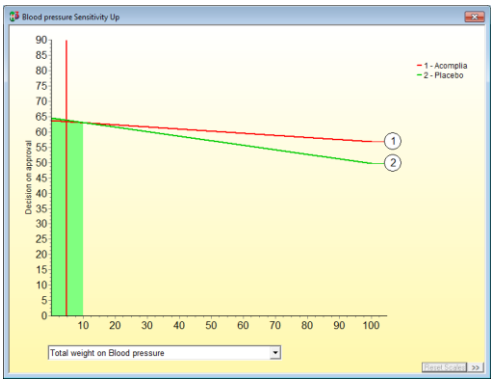
C) Triglyceride control



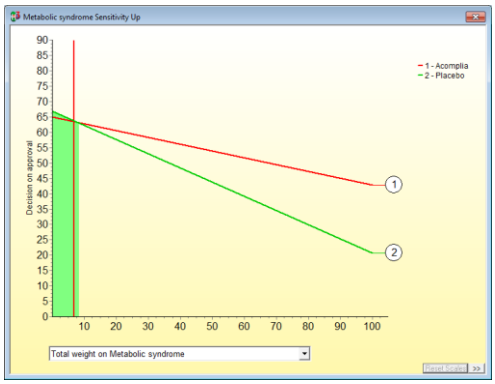
D) Waist circumference



E) Diabetes control



F) Blood pressure control



G) Reduction in metabolic syndrome

Figure 11-41 Sensitivity testing: Level 2 benefit criteria

Sensitivity testing on on level 2 criteria suggesting this model was highly sensitive to weight assigned to these criteria. A small change in weights assigned on percentage of patient achieved 10% weight lost, changes in waist circumference, changes in incidence of metabolic syndromes alters the final preference between placebo and rimonabant. (Figure 11-41)

Benefit – Level 3 Criteria

Cholesterol Control

Node results

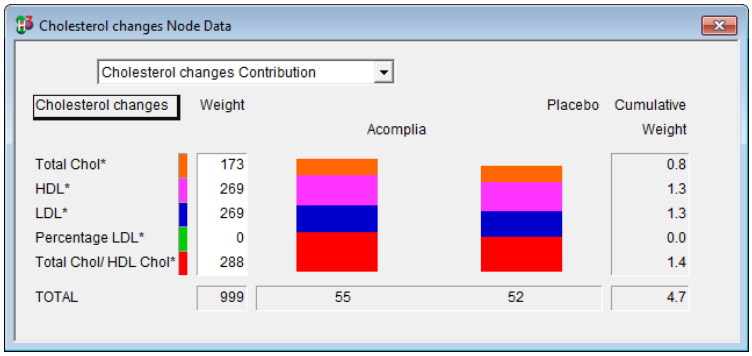
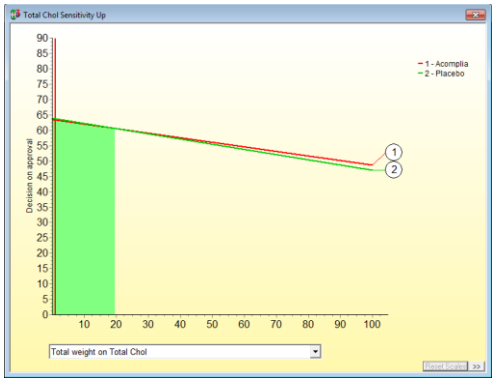
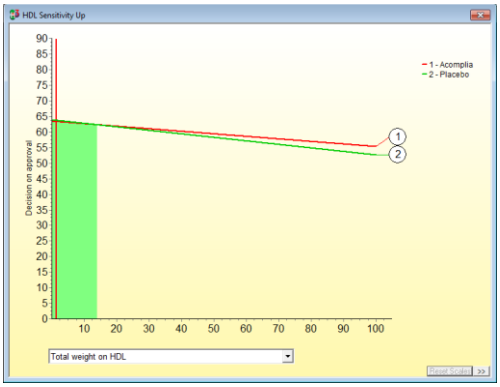


Figure 11-42 Weighted score on level 3 Cholesterol control criteria

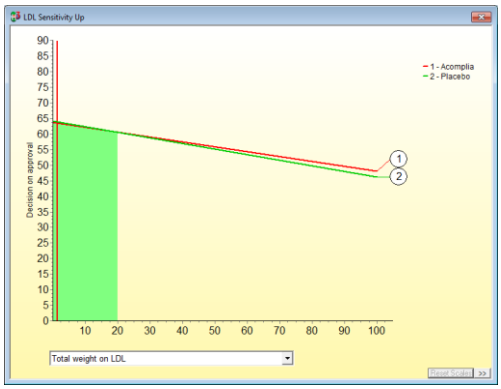
Sensitivity testing



A) Total Cholesterol



B) HDL reduction



C) LDL cholesterol

D) Reduction in Total Cholesterol/HDL Cholesterol ratio

Figure 11-43 Sensitivity testing: Level 3 Cholesterol control

Rimonabant scored higher compared to placebo in cholesterol control (Figure 11-42). This final outcome was moderately sensitive to weighting given to HDL cholesterol Total Cholesterol/HDL cholesterol ratios. (Figure 11-43)

Diabetes Control

Node results

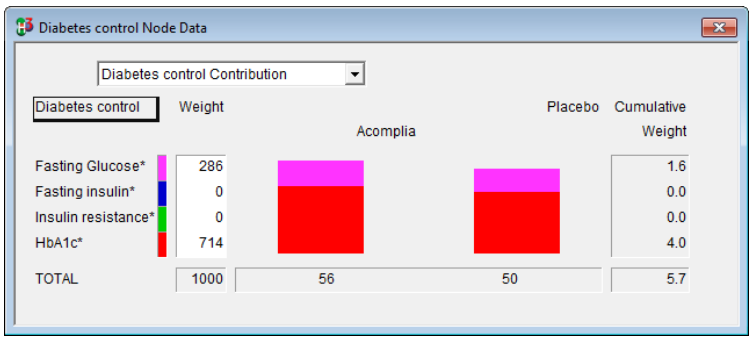
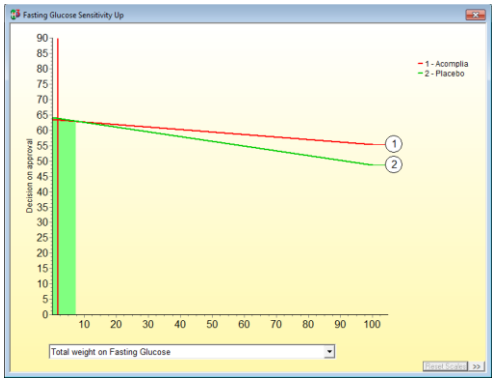
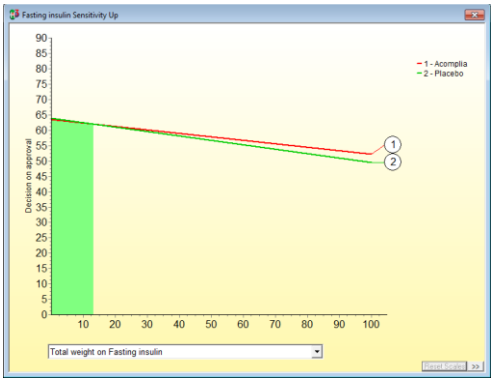


Figure 11-44 Weighted score on level 3 Diabetes control criteria

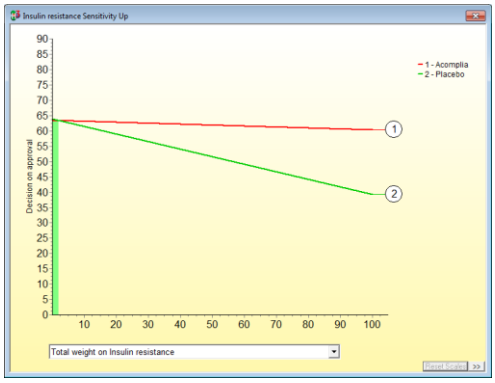
Sensitivity testing



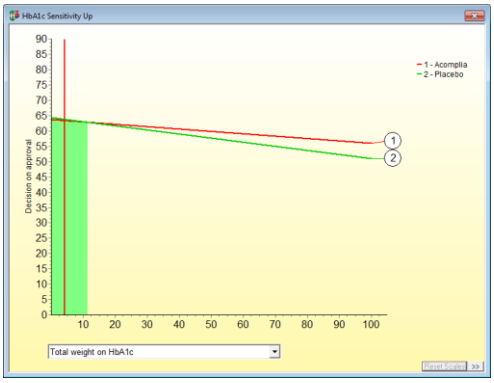
A) Fasting glucose



B) Fasting Insulin



C) Insulin Resistance



D) HbA1c Control

Figure 11-45 Sensitivity testing: Level 3 diabetes control

Results from this node suggesting rimonabant achieved higher score with diabetes control. (Figure 11-44) Interestingly, our group assigned 0 weight over effect of insulin resistance. The sensitivity testing suggested the final results would change with a small weighting assigned to this criteria. (Figure 11-45)

Blood pressure control

Node result

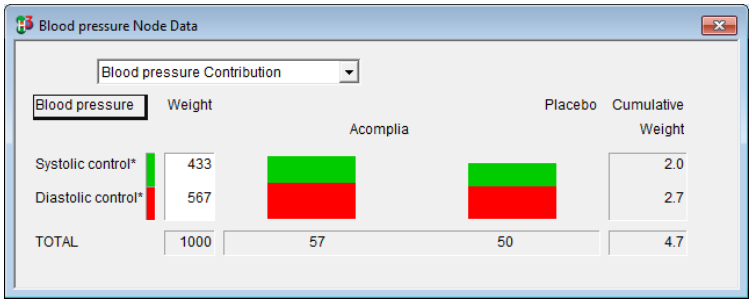
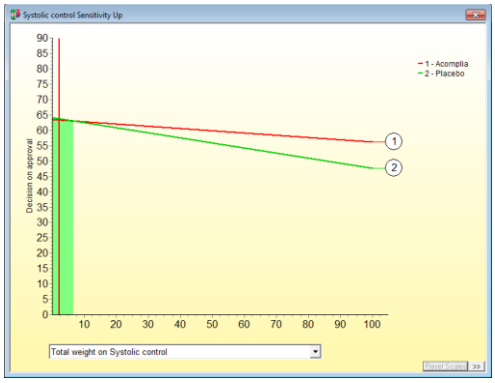
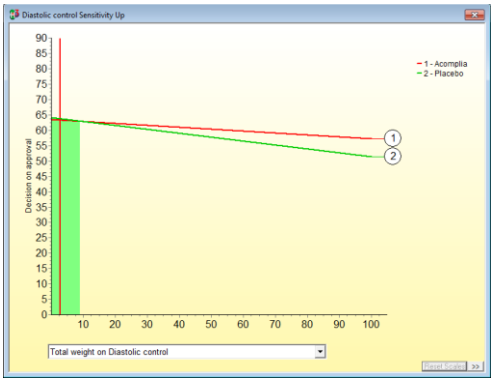


Figure 11-46 Weighted score on level 3 Blood pressure control criteria

Sensitivity testing



A) Systolic blood pressure



B) Diastolic blood pressure

Figure 11-47 Sensitivity testing: Level 3 blood pressure control

Rimonabant scored higher in perference with blood pressure control, compared to placebo (Figure 11-46). Despite of the higher preference score with blood pressure control, this had little impact on the final result. Changes over weighing on blood pressure control has little impact on final outcomes (Figure 11-47)

Risk - Level 2 criteria

Overall results

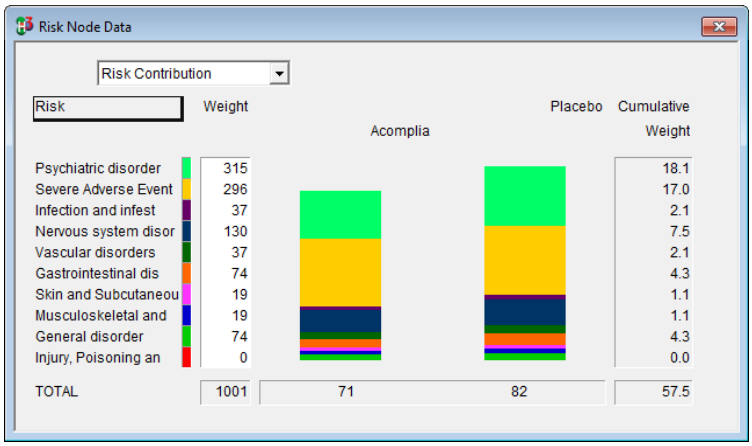
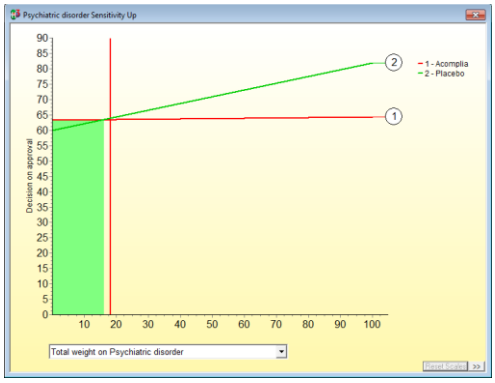


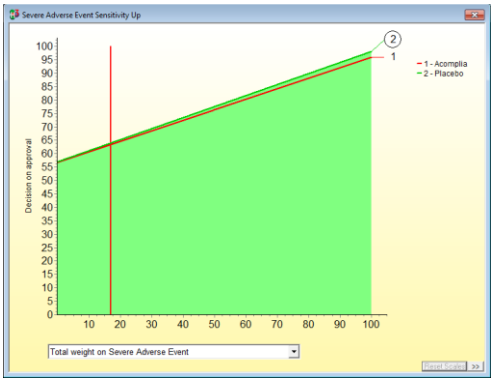
Figure 11-48 Weighted score on level 2 Risk criteria

Rimonabant scored lower in preference score in risk, in particular risk in psychiatric disorder and severe adverse events. (Figure 11-48)

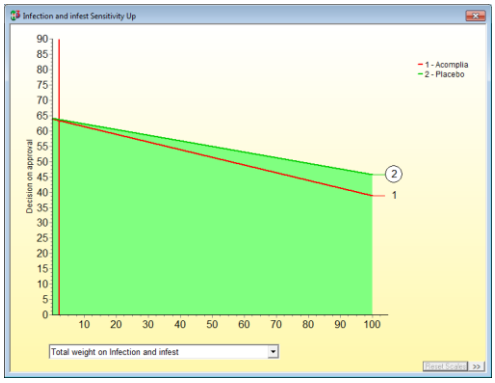
Sensitivity testing



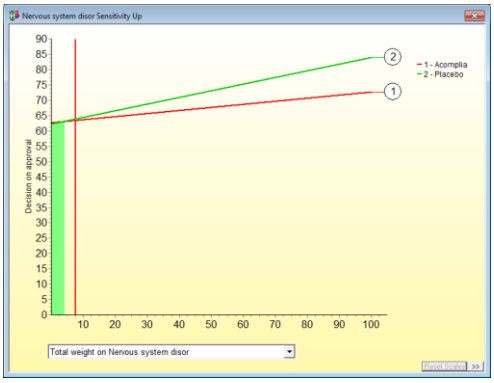
A) Psychiatric disorder



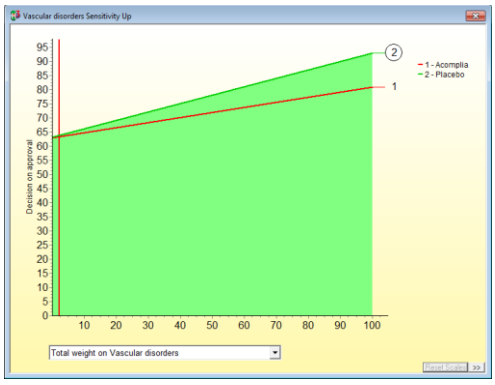
B) Severe Adverse Event



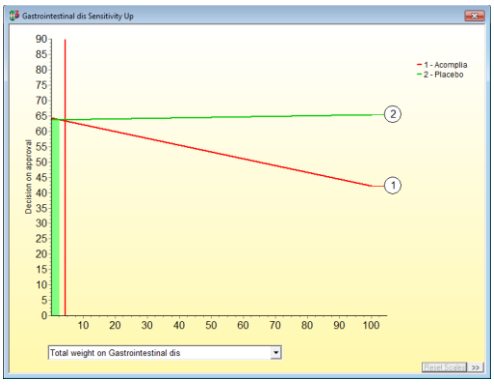
C) Infection and infestation



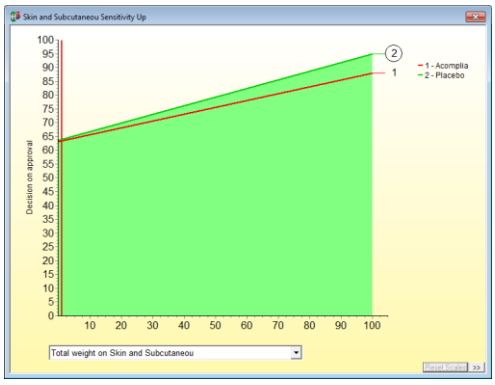
D) Nervous system disorder



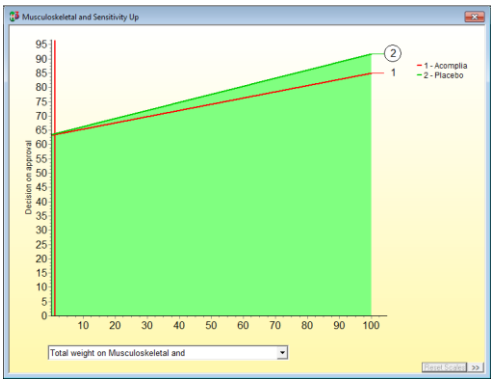
E) Vascular disorder



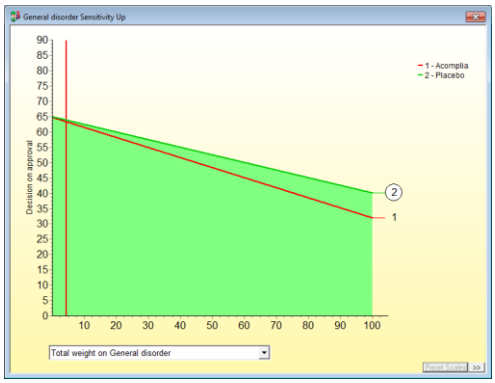
F) Gastrointestinal disorder



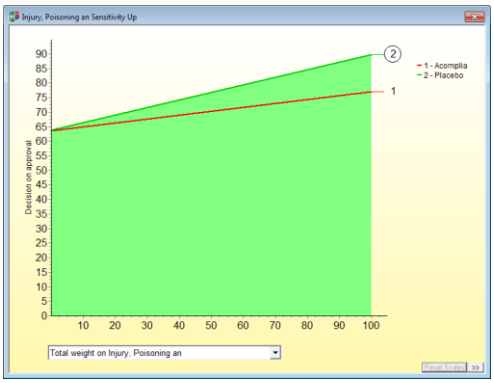
G) Skin and subcutaneous disorder



H) Musculoskeletal disorder



I) General disorder



J) Injury, poisoning and procedural complications

Figure 11-49 Sensitivity testing: Level 2 risk criteria

Sensitivity testing on level 2 risk criteria showed a small reduction in weighting assigned to psychiatric disorder, a moderate reduction in weights assigned in central nervous disorder and gastrointerestinal disorder would suggest rimonabant be the prefered. (Figure 11-49)

Risk – Level 3 criteria

Overall result reflects the higher incidence of psychiatric disorder following rimonabant resulted in lower total preference score (Figure 11-50). Sensitivity testing within this node suggesting that this model was sensitive to weighting assigned for anxiety and insomnia. (Figure 11-51) Depression is a major concern with rimonabant, model suggested the results is stable against weighting assigned on depression.

The absolute incidences of severe adverse events between the 2 groups were small. The overall preference score suggesting placebo was slightly more preferable compared to rimonabant (Figure 11-52), results from this risk criteria was not sensitive to changes in weighting assigned to individual criterion. (Figure 11-53)

Rimonabant were associated with higher incidence of side effects and scored lower in infection and infestation (Figure 11-54), nervous system disorder (Figure 11-56), vascular disorder (Figure 11-58), gastrointestinal disorder (Figure 11-60) , skin and subcutaneous tissue disorder (Figure 11-62), musculoskeletal and connective tissue disorder (Figure 11-64) , general disorder (Figure 11-66) and procedure related complications (Figure 11-68).

Sensitivity testing in these sub nodes showed the model was not sensitive to changes of weightings in these criteria.

Psychiatric disorder

Node results

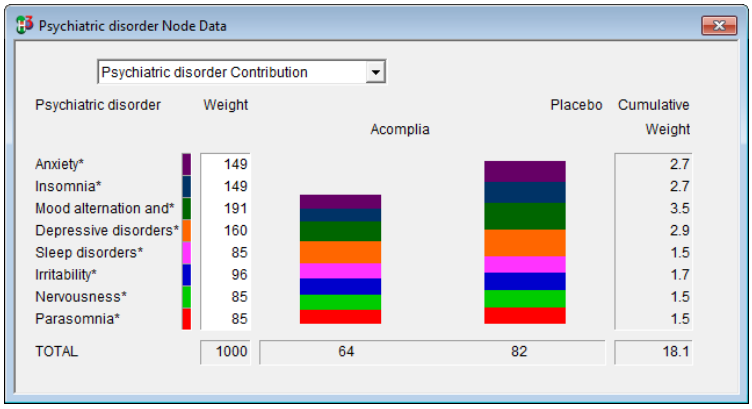
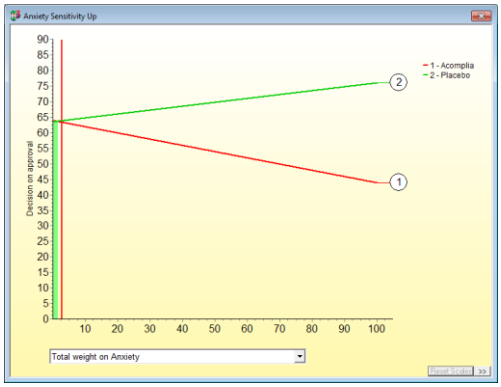
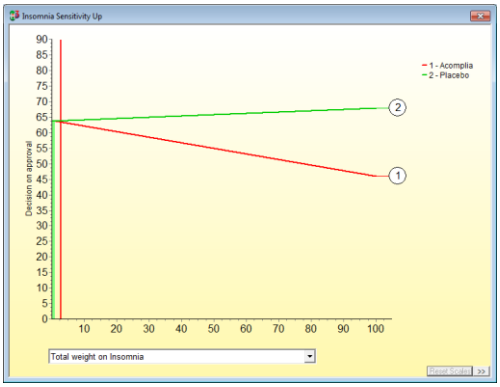


Figure 11-50 Weighted score on level 3 criteria: Psychiatric disorder

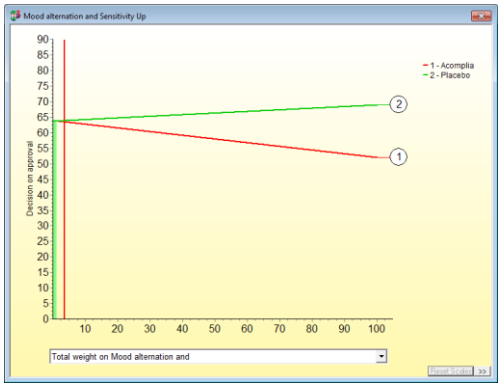
Sensitivity testing



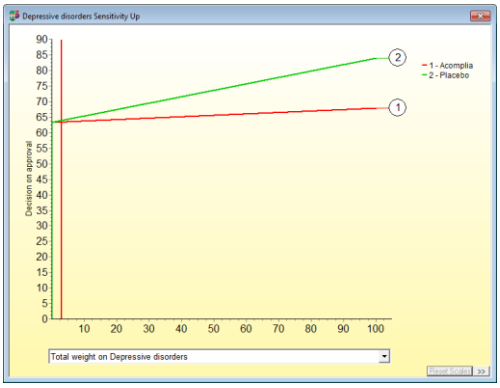
A) Anxiety



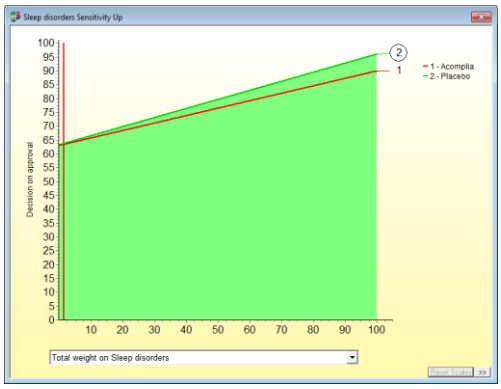
B) Insomnia



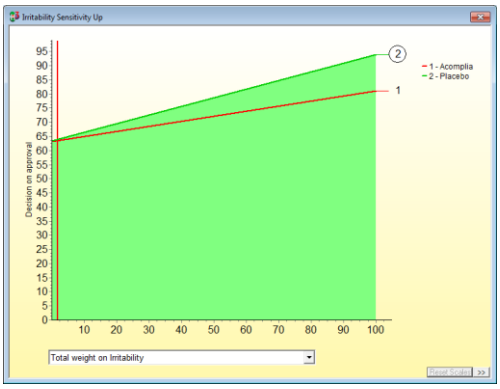
C) Mood alternation



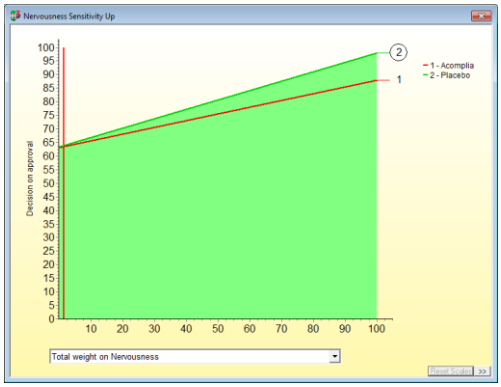
D) Depression



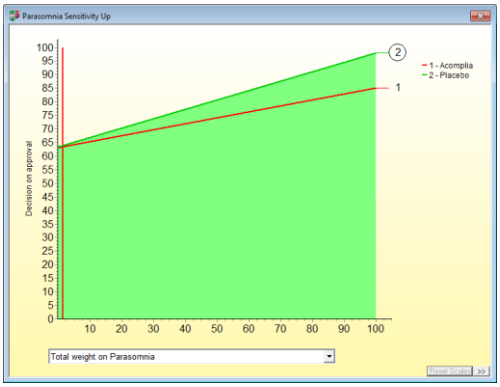
E) Sleep disorders



F) Irritability



G) Nervousness



H) Parasomnia

Figure 11-51 Sensitivity testing: Level 3 - Psychiatric disorder

Severe Adverse Events

Node result

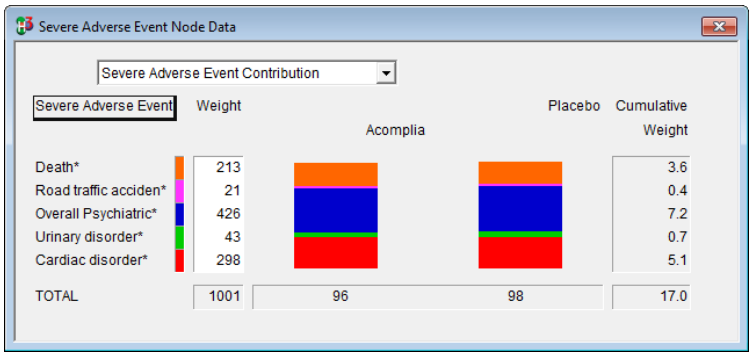
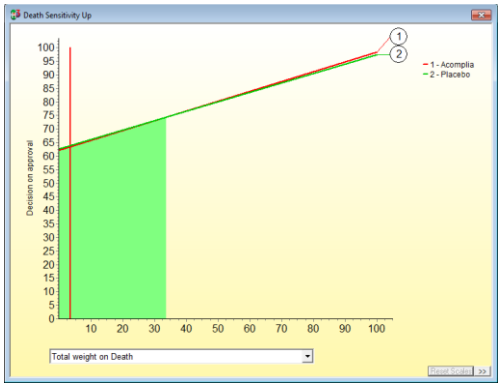
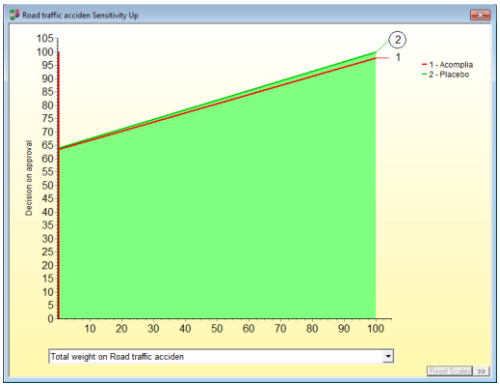


Figure 11-52 Weighted score on level 3 criteria: Severe adverse events

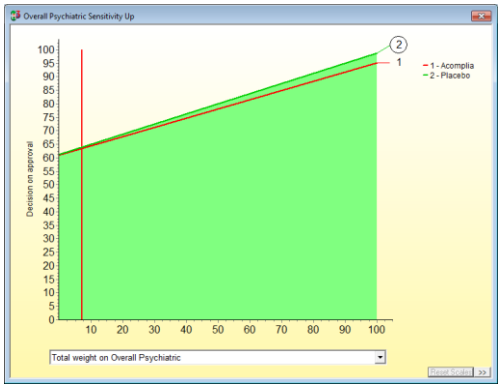
Sensitivity testing



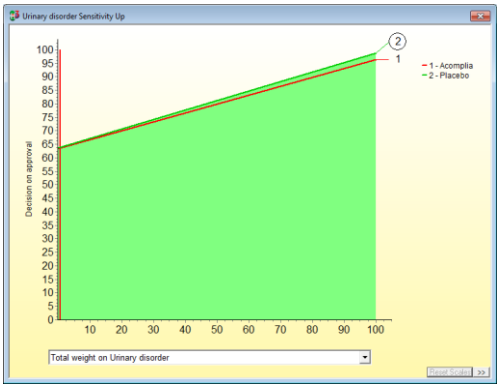
A) Death



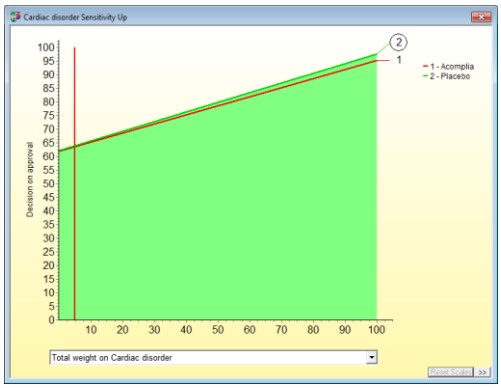
B) Road Traffic Accident



C) Overall psychiatric disorder



D) Urinary disorder



E) Cardiac disorder

Figure 11-53 Sensitivity testing: Level 3- Severe adverse events

Infection and infestation

Node results

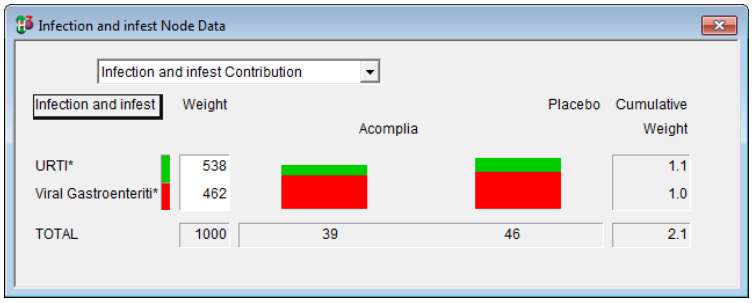
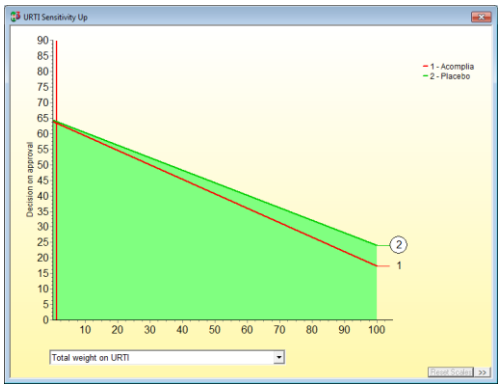
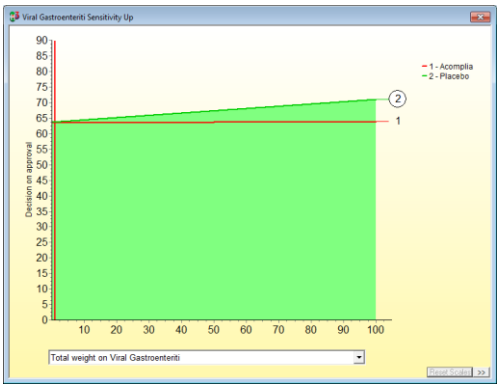


Figure 11-54 Weighted score on level 3 criteria: Infection and infestation

Sensitivity testing



A) Upper respiratory tract infection



B) Viral Gastroenteritis

Figure 11-55 Sensitivity testing: Level 3- Infection and infestation

Nervous system disorder

Node result

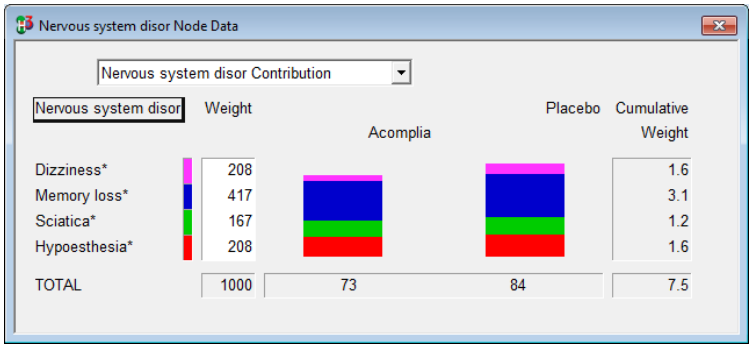
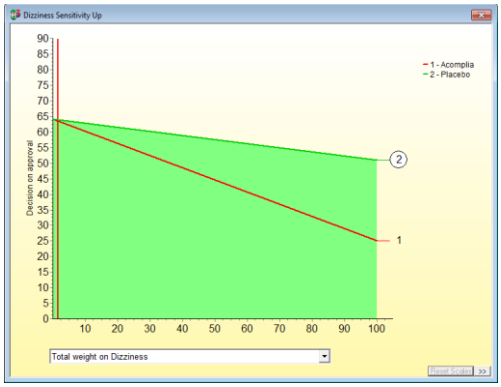
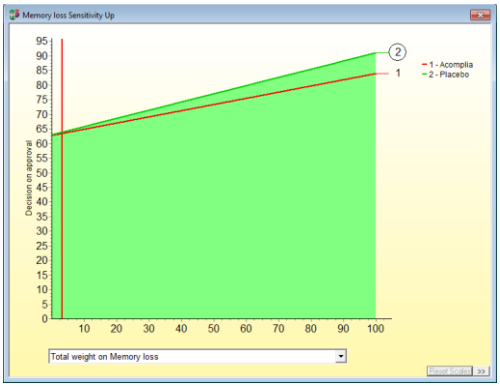


Figure 11-56 Weighted score on level 3 criteria: Nervous system disorder

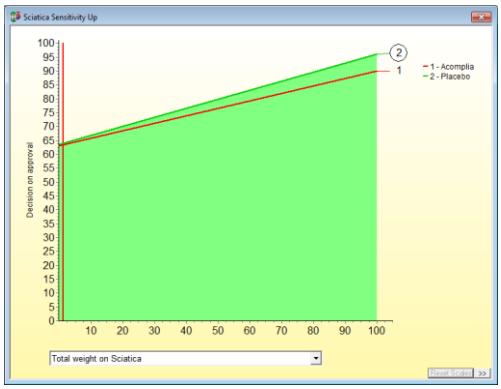
Sensitivity testing



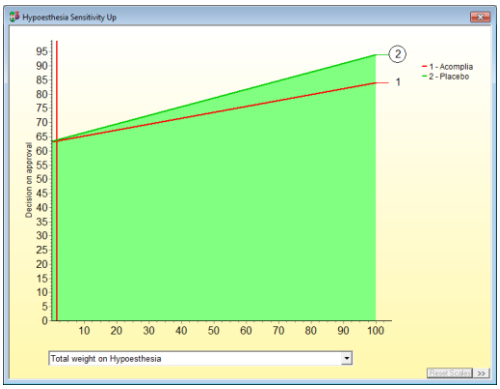
A) Dizziness



B) Memory loss



C) Sciatica



D) Hypoesthesia

Figure 11-57 Sensitivity testing: Level 3- Nervous system disorder

Vascular System disorders

Node results

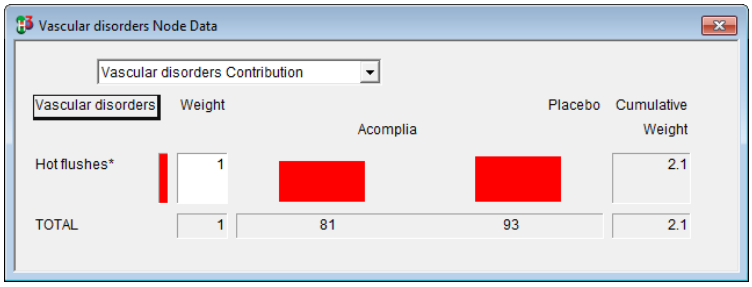


Figure 11-58 Weighted score on level 3 criteria: Vascular system disorder

Sensitivity testing

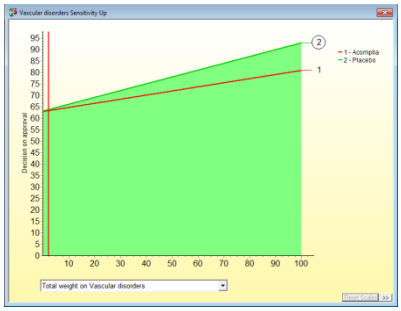


Figure 11-59 Sensitivity testing: Level 3- Vascular system disorder

Gastrointestinal disorder

Node results

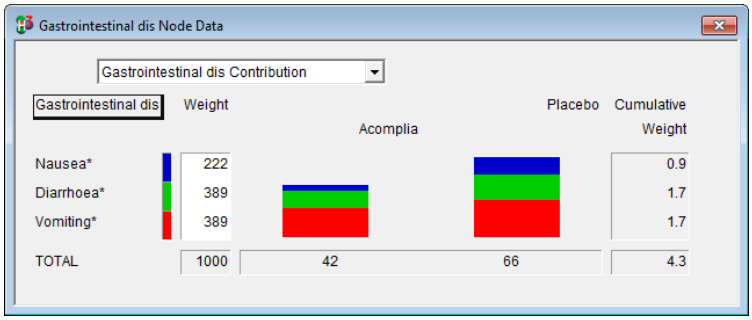
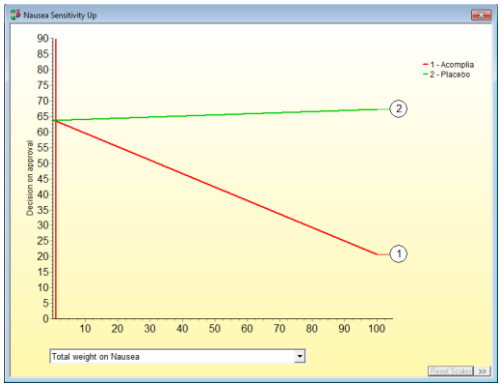
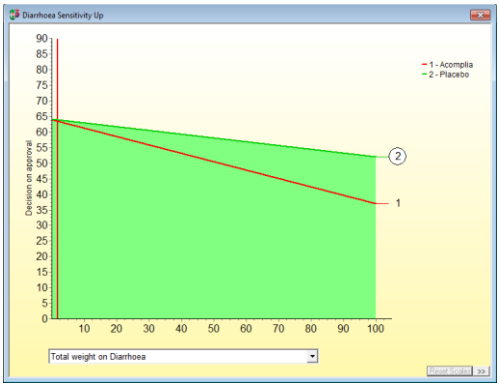


Figure 11-60 Weighted score on level 3 criteria: Gastrointestinal disorder

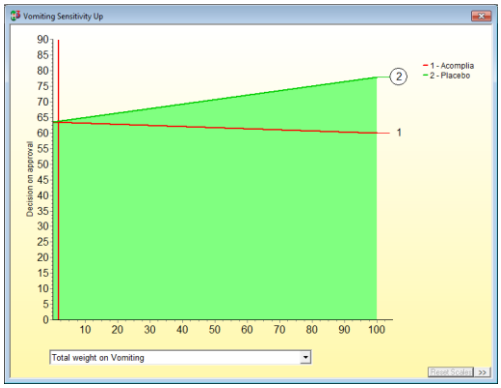
Sensitivity testing



A) Nausea



B) Diarrhoea



C) Vomiting

Figure 11-61 Sensitivity testing: Level 3- Gastrointestinal disorder

Skin and subcutaneous tissue disorder

Node results

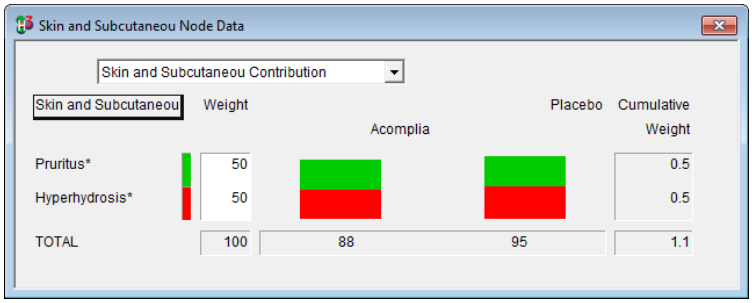
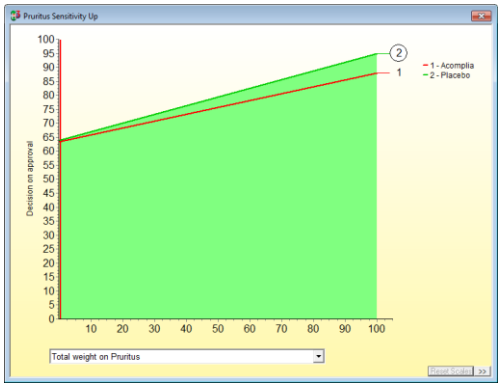
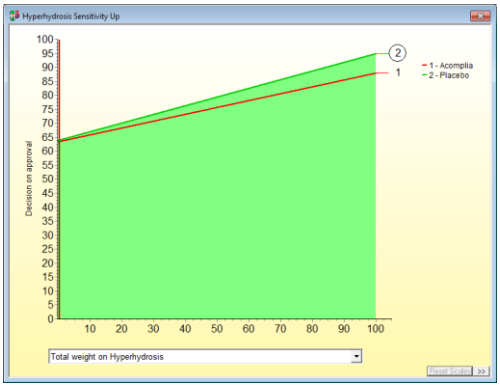


Figure 11-62 Weighted score on level 3 criteria: Skin and Subcutaneous tissue disorder

Sensitivity testing



A) Pruritis



B) Hyperhydrosis

Figure 11-63 Sensitivity testing: Level 3- Skin and Subcutaneous tissue disorder

Musculoskeletal and connective tissue disorder

Node result

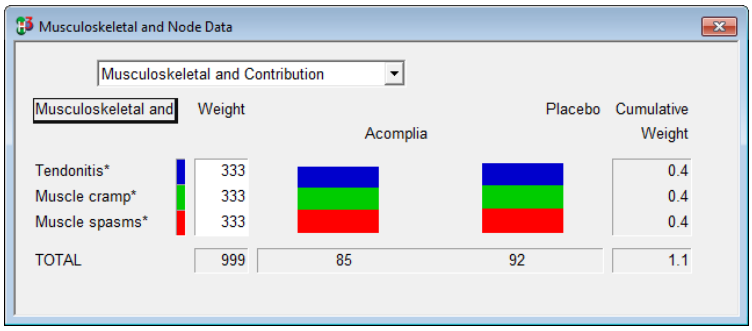
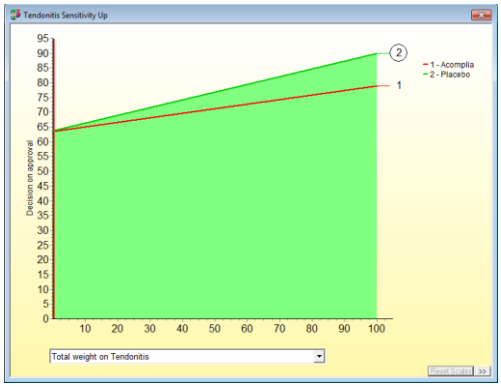
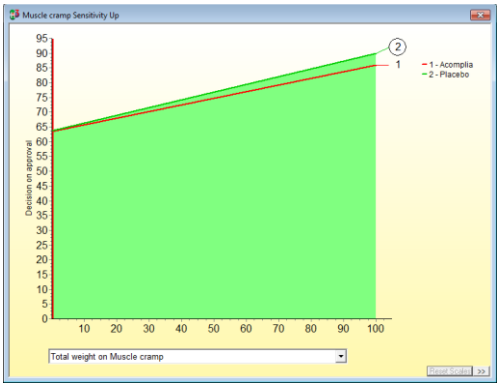


Figure 11-64 Weighted score on level 3 criteria: Musculoskeletal and connective tissue disorder

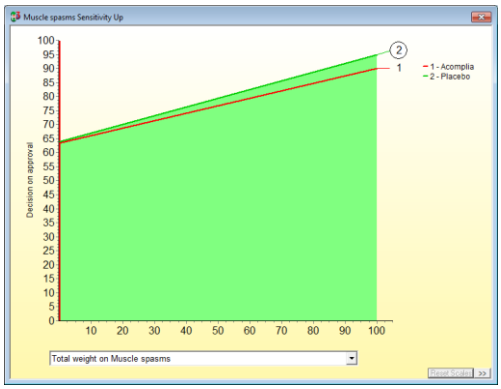
Sensitivity testing



A) Tendonitis



B) Muscle Cramp



C) Muscle spasm

Figure 11-65 Sensitivity testing: Level 3- Musculoskeletal and Connective tissue disorder

General disorder

Node results

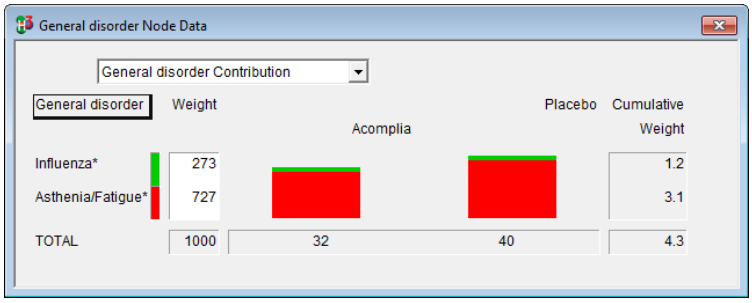
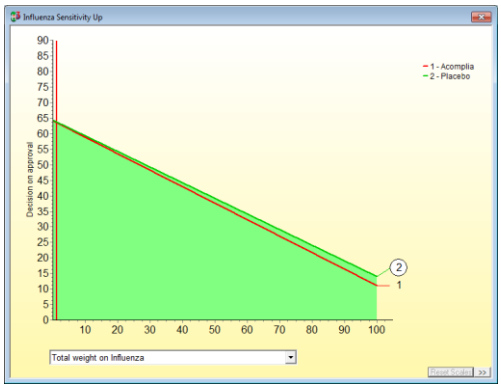
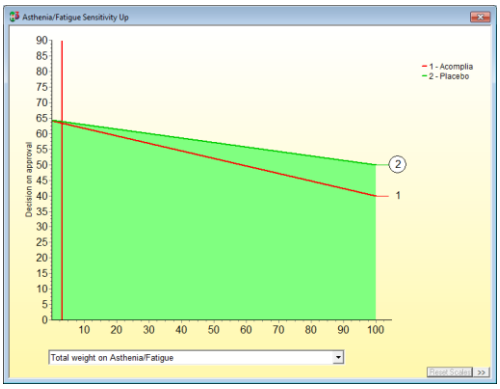


Figure 11-66 Weighted score on level 3 criteria: General disorder

Sensitivity testing



A) Influenza



B) Asthenia\Fatigue

Figure 11-67 Sensitivity testing: Level 3- General disorder

Injury, Poisoning and Procedural complications

Node results

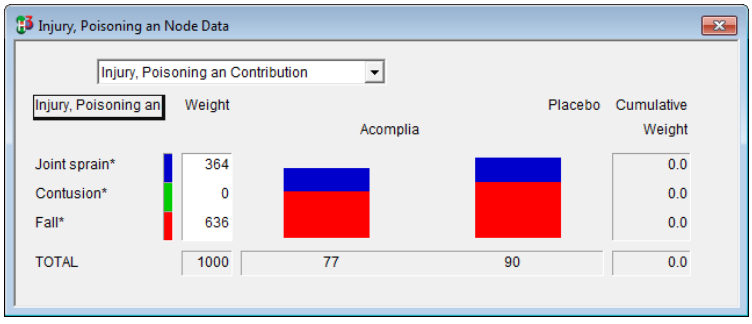
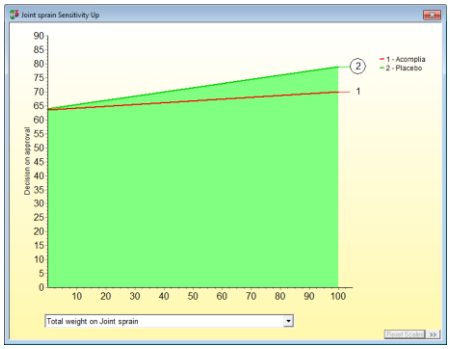
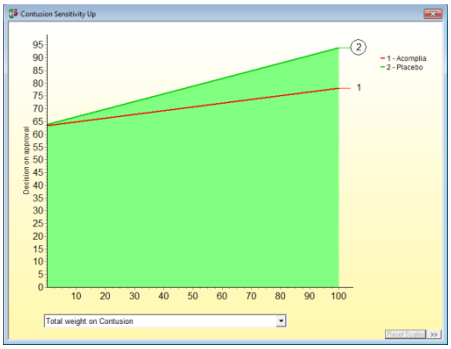


Figure 11-68 Weighted score on level 3 criteria: Injury, Poisoning and Procedural complication

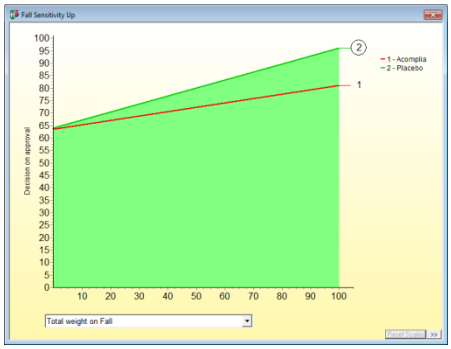
Sensitivity testing



A) Joint Sprain



B) Contusion



C) Fall

Figure 11-69 Sensitivity testing: Level 3 - Injury, Poisoning and Procedural Complication

Difference in Weighted score

Figure 11-70 demonstrated detailed difference in scores between rimonabant and placebo in all criteria listed. Detailed difference in score and cumulative weighting can be found in section 11.3.2.10.4 – Tree 3 Medical/Regulatory weightings.

Although overall results demonstrated that rimonabant was superior in waistline reduction, 10% weight lost at 1 year, triglyceride control and reduction in metabolic syndrome.

Rimonabant was inferior in association with insomnia, mood alternation, depression and anxiety.

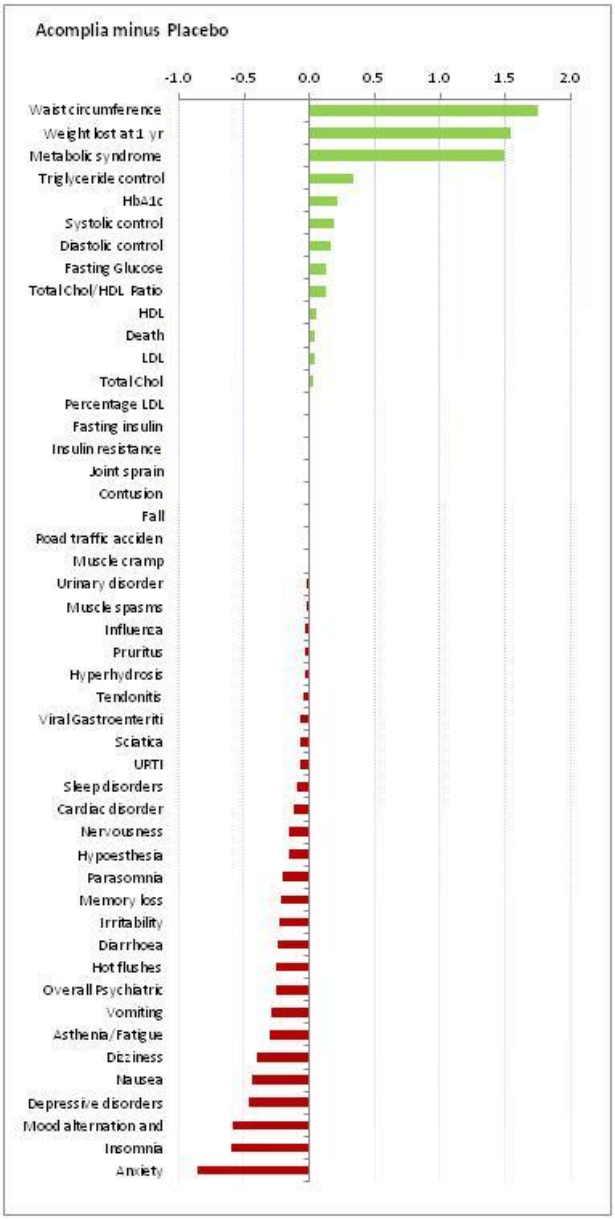
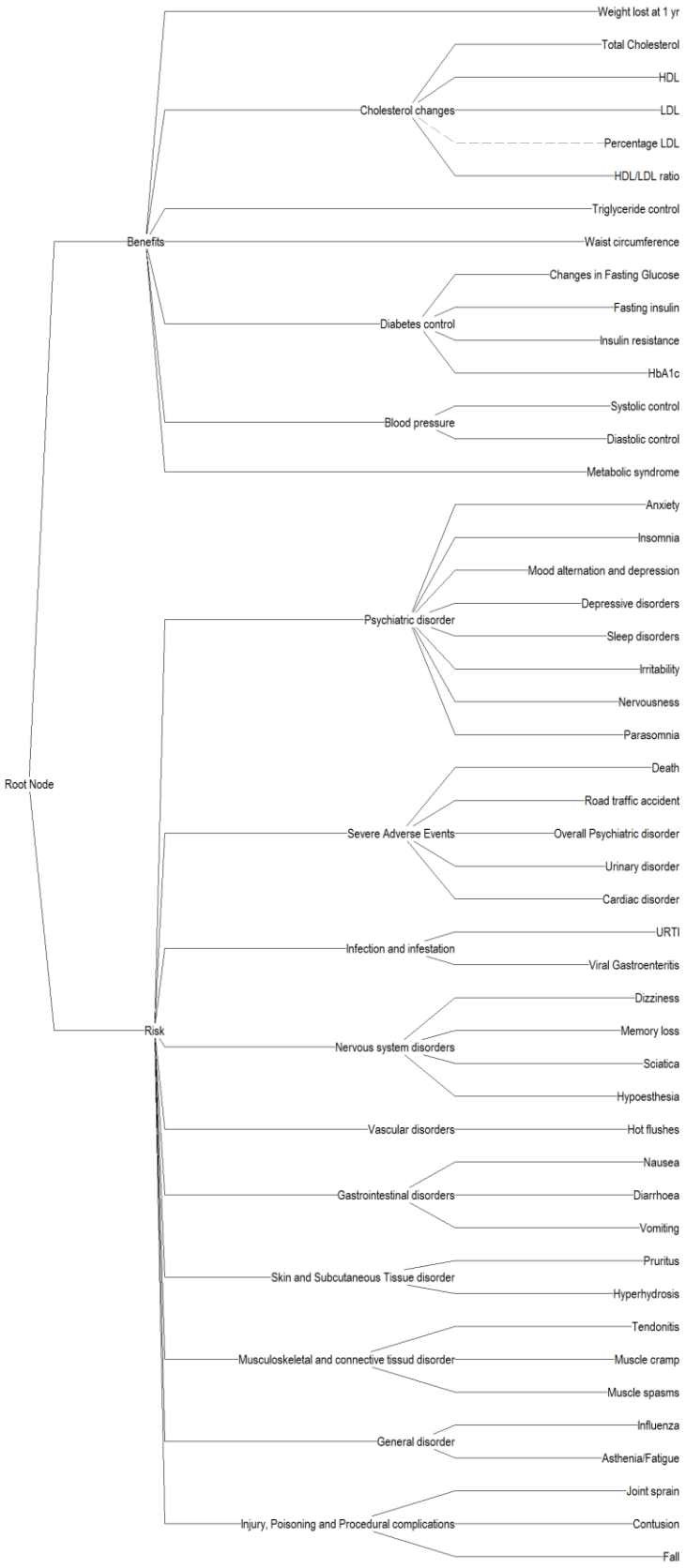


Figure 11-70 Difference in weighted score: Tree 3

11.3.2.10.3 Tree 3 – Layman Prospective using results from Meta Analysis

Decision tree



Overall results

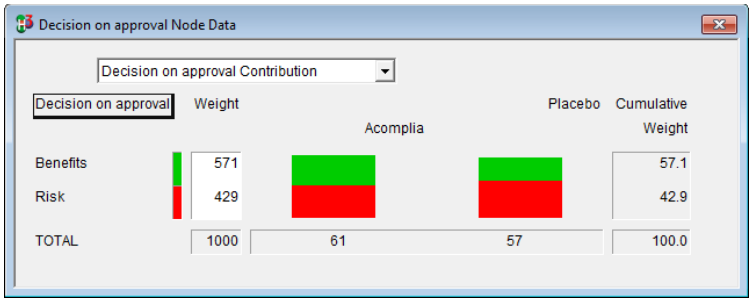


Figure 11-71 Overall results

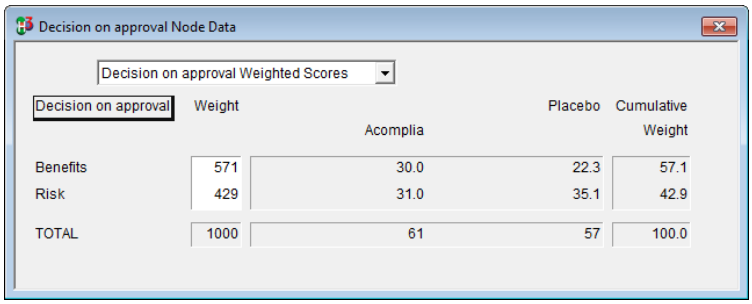
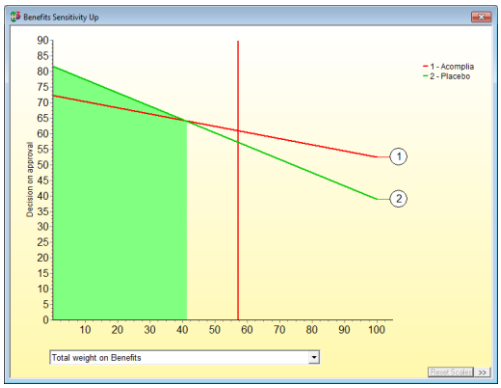


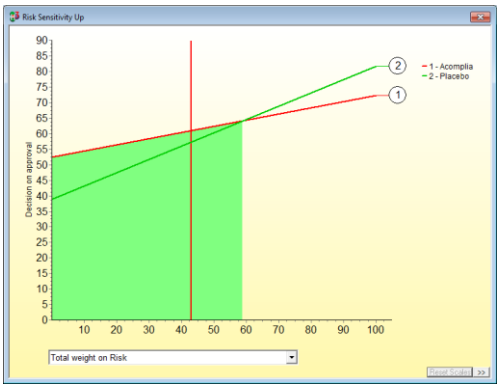
Figure 11-72 Overall scores

Overall results (Figure 11-72) showed the final overall weighted scores between the two alternatives. The green bar from Figure 11-71 shows the average overall weighted score on benefit, and the red bar is the average overall weighted score on risk. Risk utility score were set in inverser order, i.e., alternatives rewarded higher score with lower risk. Figure 11-72 shows the break down of the score. Total weighted score in rimonabant was 61 compared to placebo scored 57.4. This analysis showed rimonabant was more flavourable option.

Sensitivity testing



A) Benefits.



B) Risks

Figure 11-73 Sensitivity testing: a) Benefits b) Risk

In this case, it demonstrated the conclusion that rimonabant was the preferred option was not sensitive to weights assigned to these two criteria.

Benefit - Level 2 Criteria

Overall results

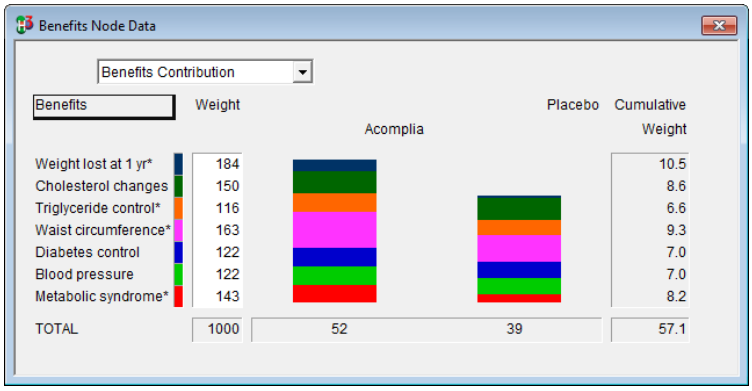
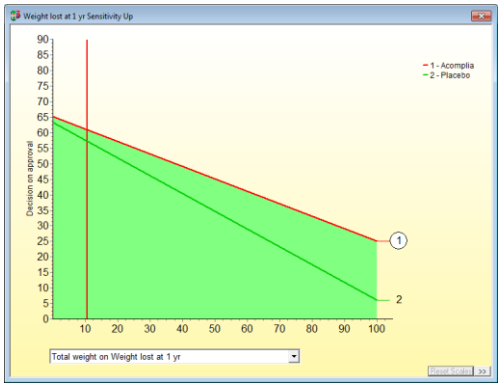


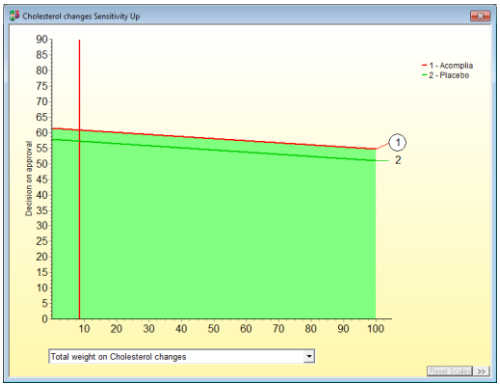
Figure 11-74 Overall results: Level 2 benefit criteria

In terms of benefit, rimonabant achieved higher score(52) compared to that of control (39) (Figure 11-40). Mainly related to benefit with reduction in waist circumference.

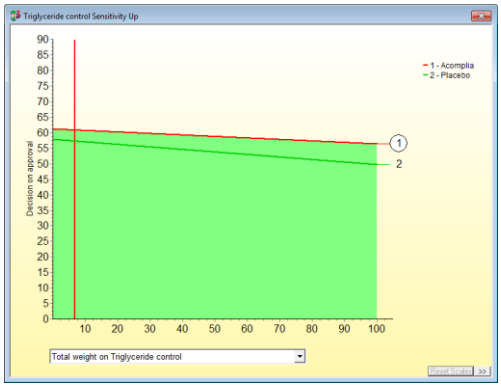
Sensitivity testing



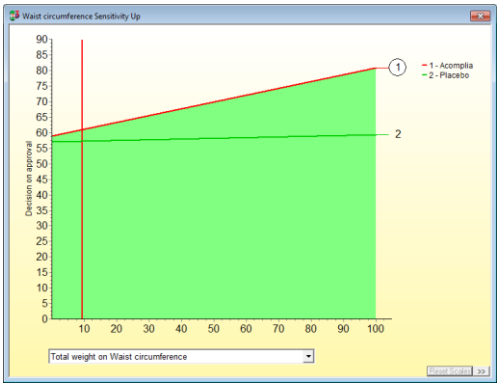
A) Weight lost



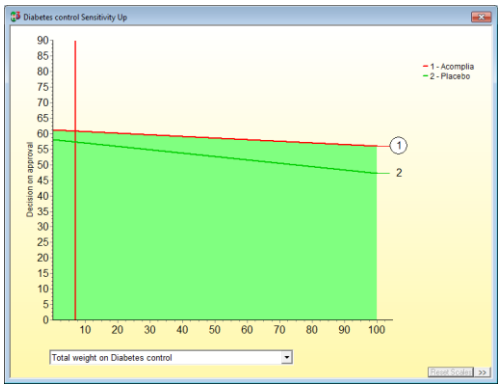
B) Cholesterol changes



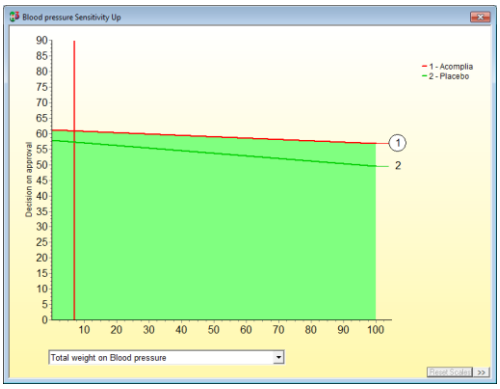
C) Triglyceride control



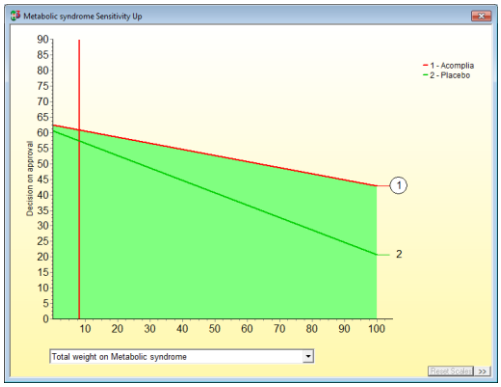
D) Waist circumference



E) Diabetes control



F) Blood pressure control



G) Reduction in metabolic syndrome

Figure 11-75 Sensitivity testing: Level 2 benefit criteria

Sensitivity testing on on level 2 criteria suggesting this model was not sensitive to weight assigned to these criteria. (Figure 11-75)

Benefit – Level 3 Criteria

Cholesterol Control

Node results

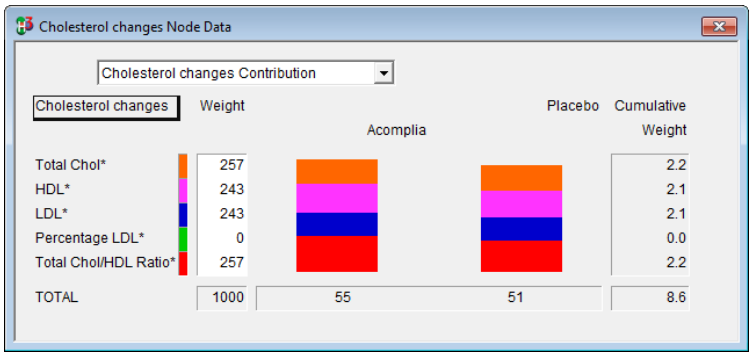
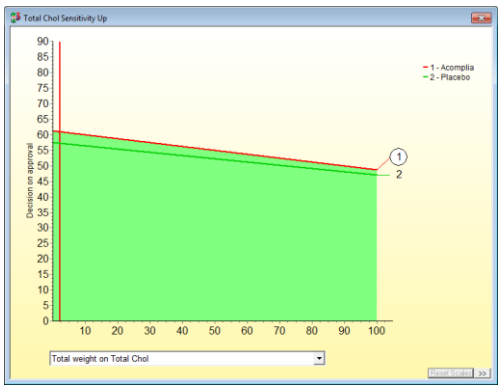
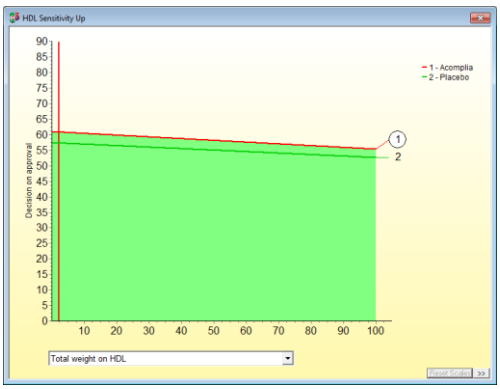


Figure 11-76 Weighted score on level 3 Cholesterol control criteria

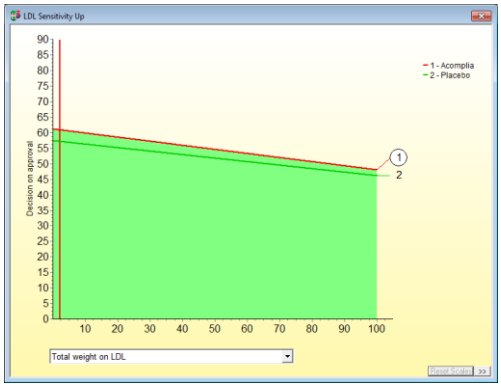
Sensitivity testing



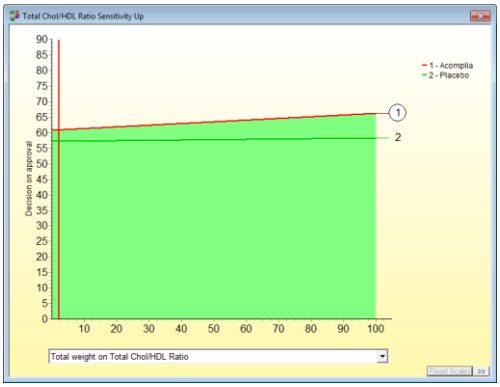
A) Total Cholesterol



B) HDL reduction



C) LDL cholesterol



D) Reduction in Total Cholesterol/HDL Cholesterol ratio

Figure 11-77 Sensitivity testing: Level 3 Cholesterol control

Rimonabant scored higher compared to placebo in cholesterol control (Figure 11-76). This final outcome was not sensitive to weighting given to any of the sub criteria. (Figure 11-77)

Diabetes Control

Node results

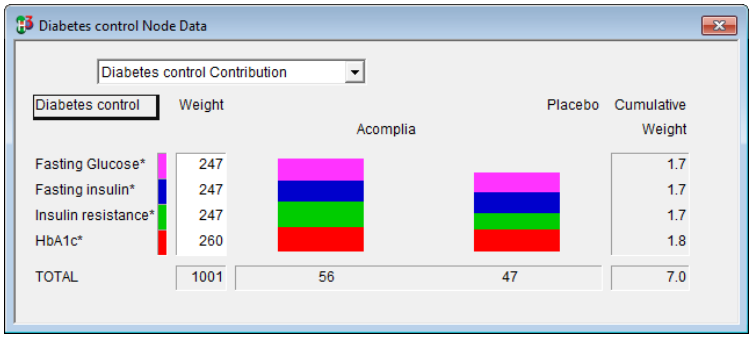
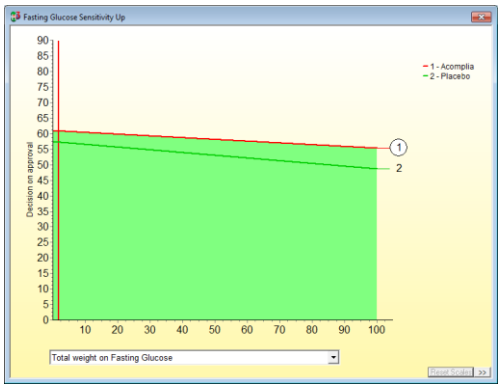
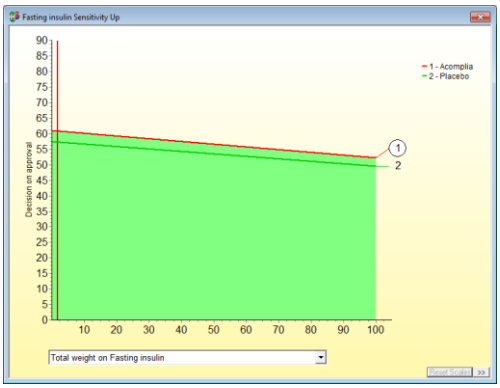


Figure 11-78 Weighted score on level 3 Diabetes control criteria

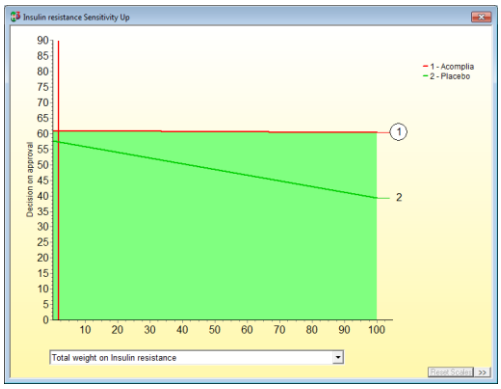
Sensitivity testing



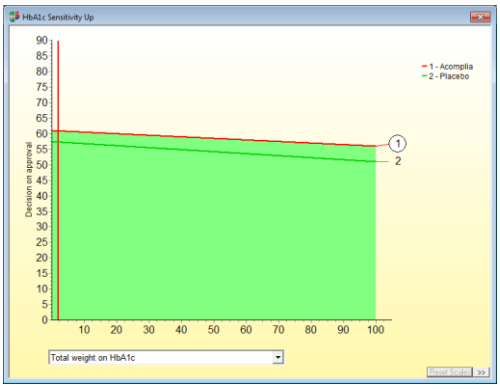
A) Fasting glucose



B) Fasting Insulin



C) Insulin Resistance



D) HbA1c Control

Figure 11-79 Sensitivity testing: Level 3 diabetes control

Results from this node suggesting rimonabant achieved higher score with diabetes control.(Figure 11-78) Once again, the results were not sensitive to weighting changes in this node. (Figure 11-79)

Blood pressure control

Node result

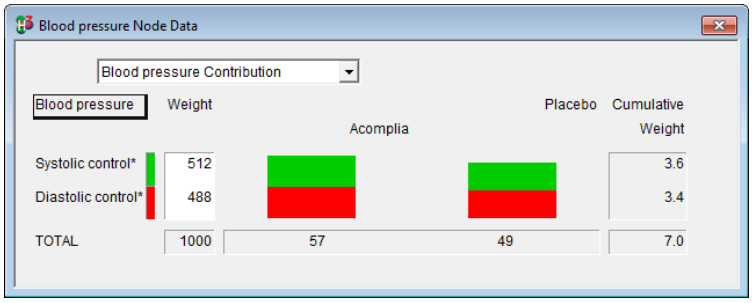
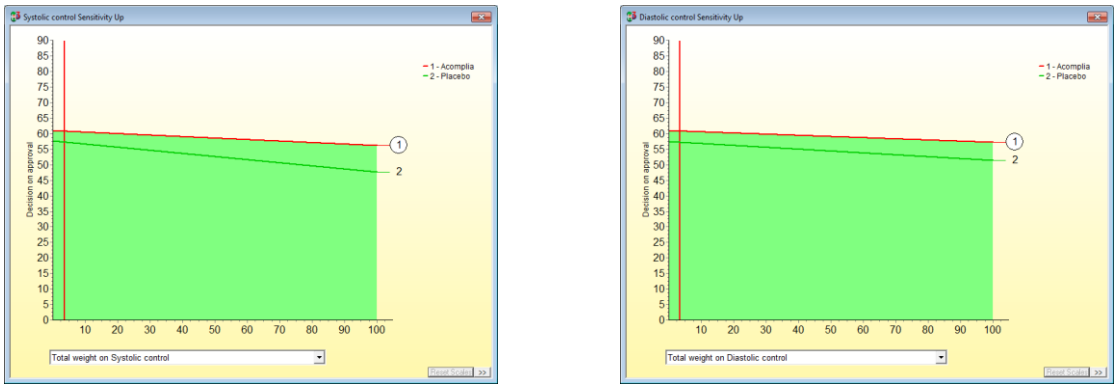


Figure 11-80 Weighted score on level 3 Blood pressure control criteria

Sensitivity testing



A) Systolic blood pressure

B) Diastolic blood pressure

Figure 11-81 Sensitivity testing: Level 3 blood pressure control

Rimonabant scored higher in perference with blood pressure control, compared to placebo (Figure 11-80). Despite of the higher preference score with blood pressure control, this had little impact on the final result. Changes over weighing on blood pressure control has little impact on final outcomes (Figure 11-81)

Risk - Level 2 criteria

Overall results

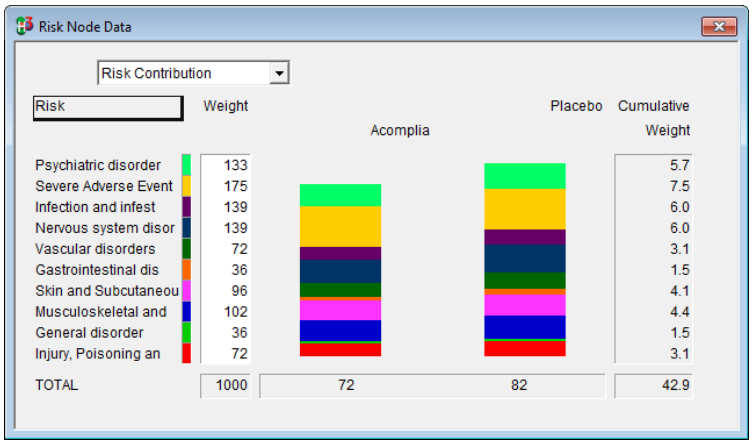
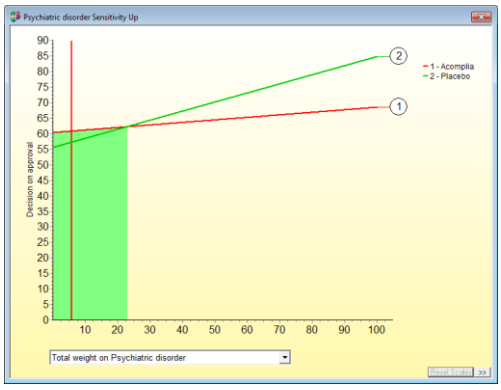


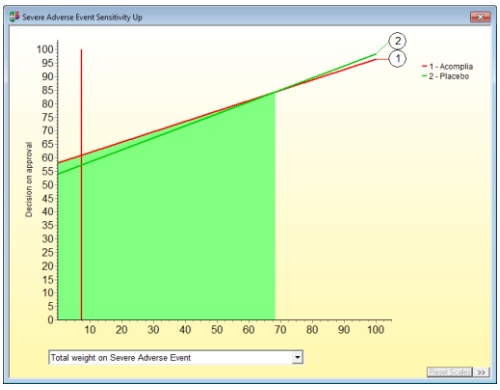
Figure 11-82 Weighted score on level 2 Risk criteria

Rimonabant scored lower in preference score in risk, in particular risk in psychiatric disorder and severe adverse events. (Figure 11-82)

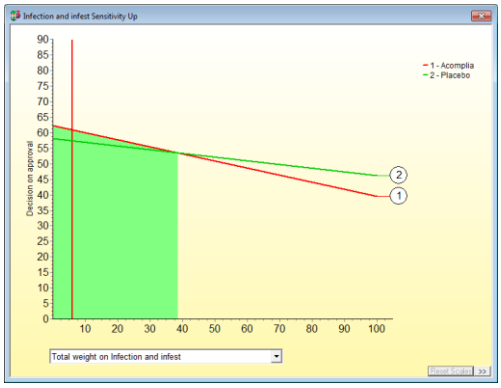
<u>Sensitivity testing</u>



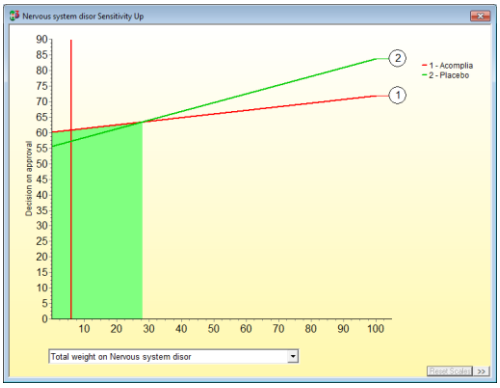
A) Psychiatric disorder



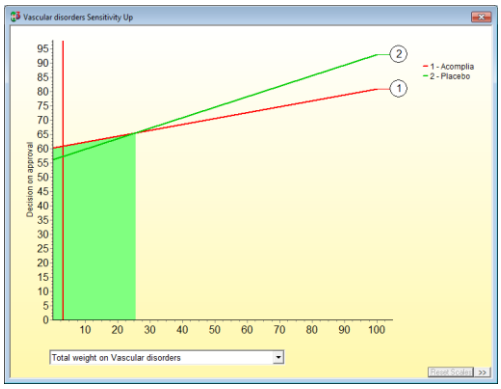
B) Severe Adverse Event



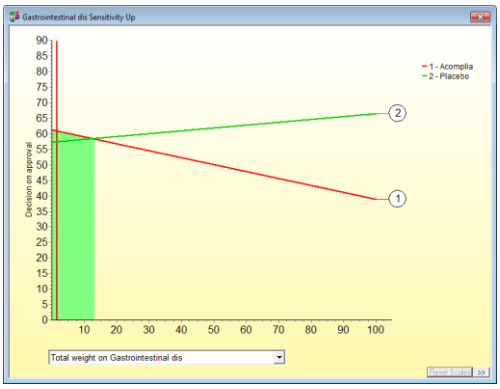
C) Infection and infestation



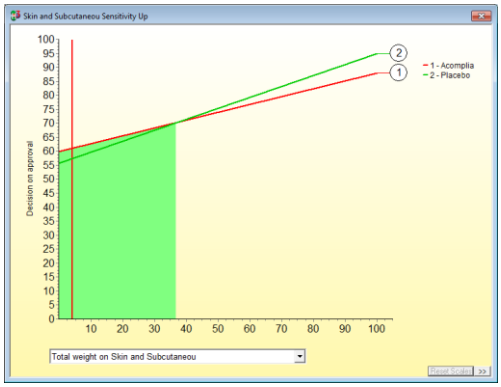
D) Nervous system disorder



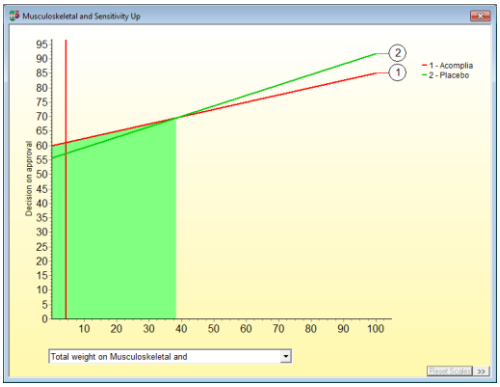
E) Vascular disorder



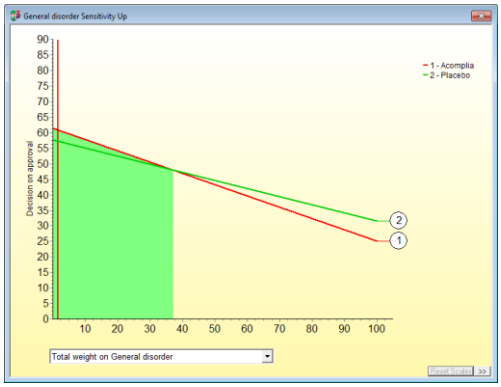
F) Gastrointestinal disorder



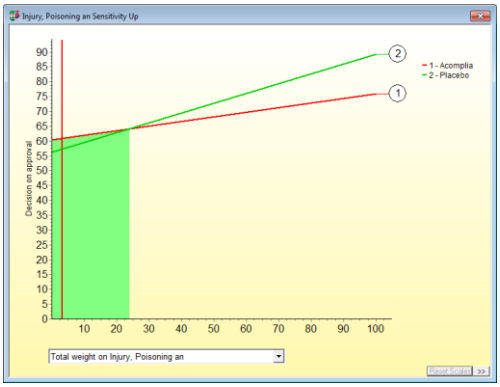
G) Skin and subcutaneous disorder



H) Musculoskeletal disorder



I) General disorder



J) Injury, poisoning and procedural complications

Figure 11-83 Sensitivity testing: Level 2 risk criteria

Sensitivity testing on level 2 risk criteria showed this model is not senstivie to changes to level 2 criteria (Figure 11-83)

Risk – Level 3 criteria

Overall result reflects the higher incidence of psychiatric disorder following rimonabant resulted in lower total preference score (Figure 11-84). Sensitivity testing within this node suggesting that this model was not sensitive to weighting assigned. (Figure 11-85)

The absolute incidences of severe adverse events between the 2 groups were small. The overall preference score suggesting placebo was slightly more preferable compared to rimonabant (Figure 11-86), results from this risk criteria was not sensitive to changes in weighting assigned to individual criterion. (Figure 11-87)

Rimonabant were associated with higher incidence of side effects and scored lower in infection and infestation (Figure 11-88), nervous system disorder (Figure 11-90), vascular disorder (Figure 11-92), gastrointestinal disorder (Figure 11-94) , skin and subcutaneous tissue disorder (Figure 11-96), musculoskeletal and connective tissue disorder (Figure 11-98) , general disorder (Figure 11-100) and procedure related complications (Figure 11-102).

Sensitivity testing in these sub nodes showed the model was not sensitive to changes of weightings in these criteria.

Psychiatric disorder

Node results

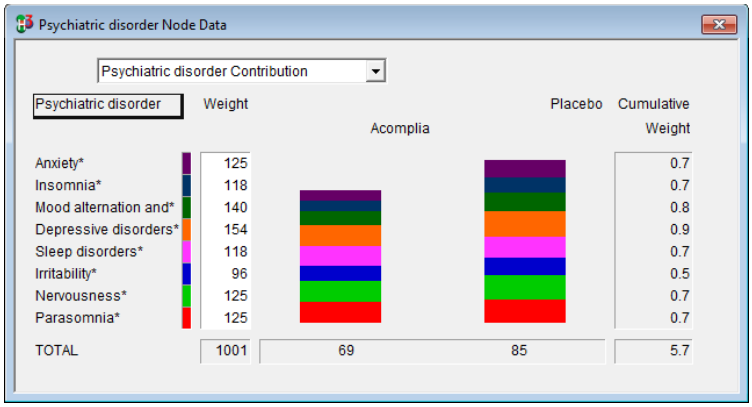
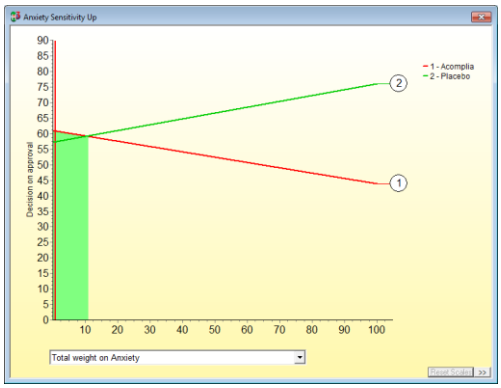
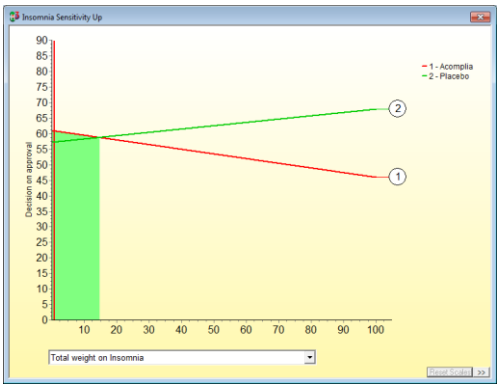


Figure 11-84 Weighted score on level 3 criteria: Psychiatric disorder

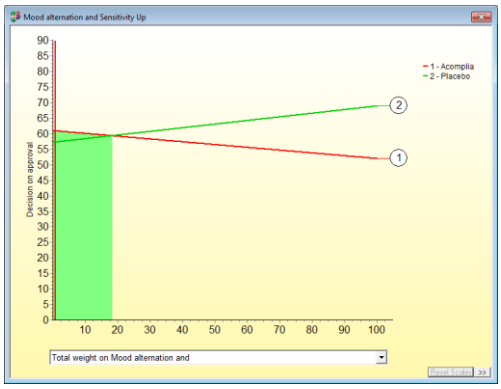
Sensitivity testing



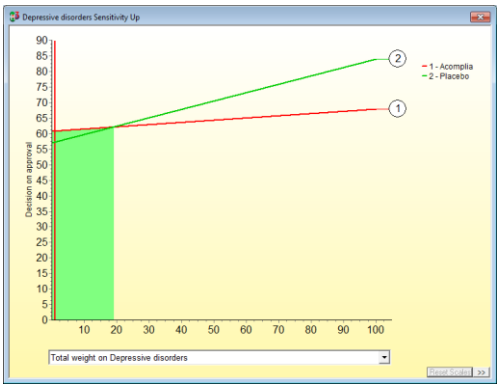
A) Anxiety



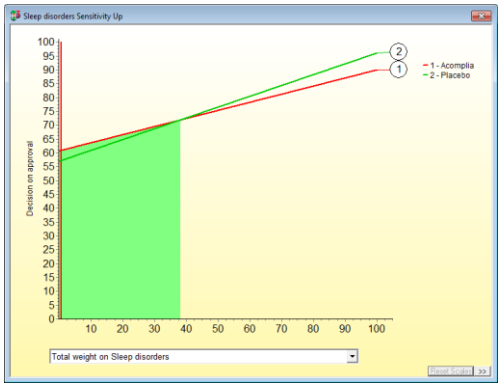
B) Insomnia



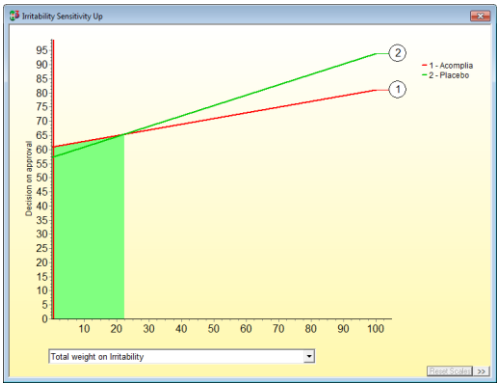
C) Mood alternation



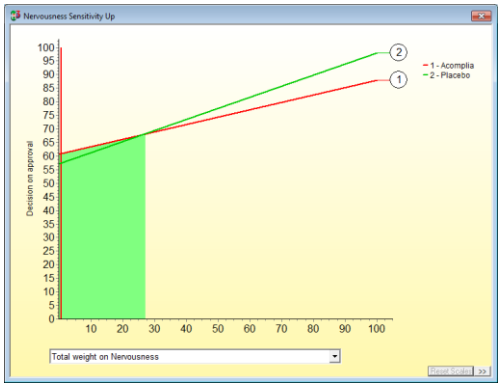
D) Depression



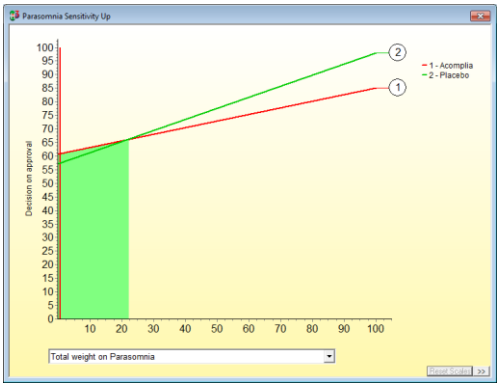
E) Sleep disorders



F) Irritability



G) Nervousness



H) Parasomnia

Figure 11-85 Sensitivity testing: Level 3 - Psychiatric disorder

Severe Adverse Events

Node result

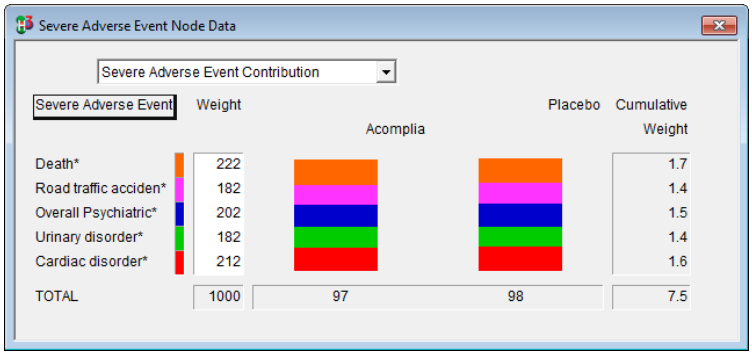
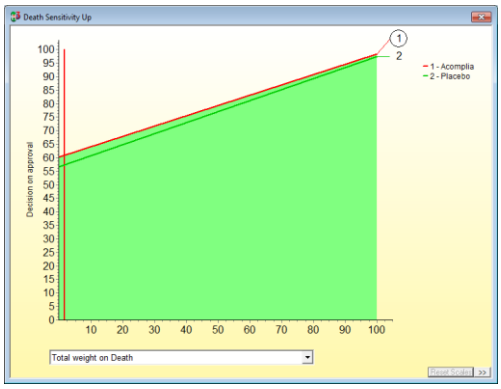
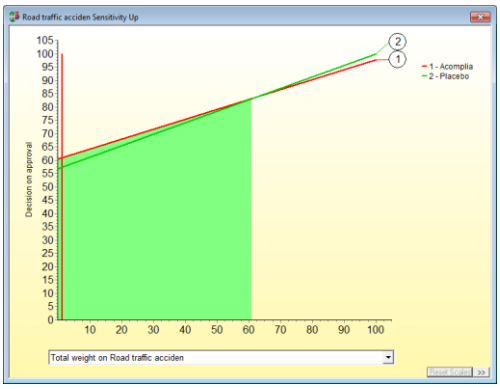


Figure 11-86 Weighted score on level 3 criteria: Severe adverse events

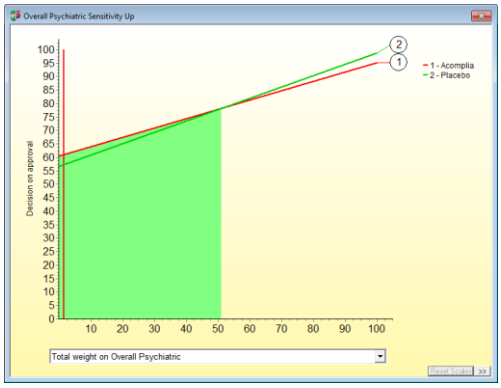
Sensitivity testing



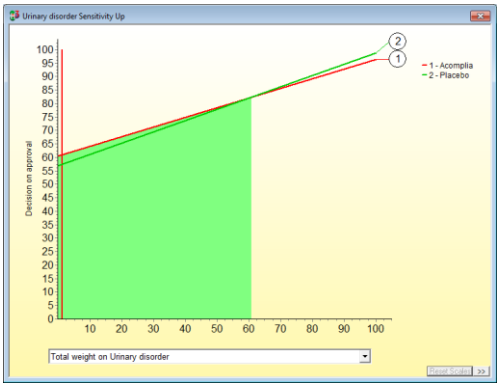
A) Death



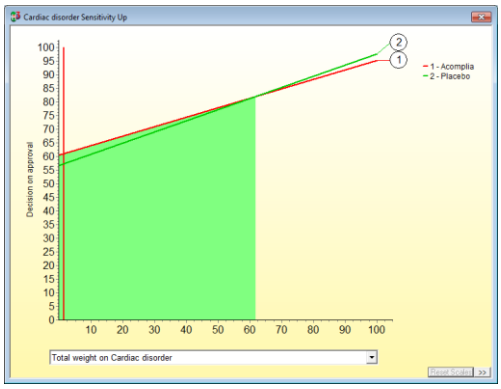
B) Road Traffic Accident



C) Overall psychiatric disorder



D) Urinary disorder



E) Cardiac disorder

Figure 11-87 Sensitivity testing: Level 3- Severe adverse events

Infection and infestation

Node results

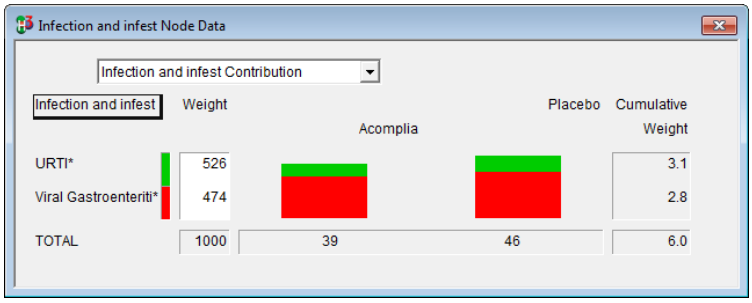
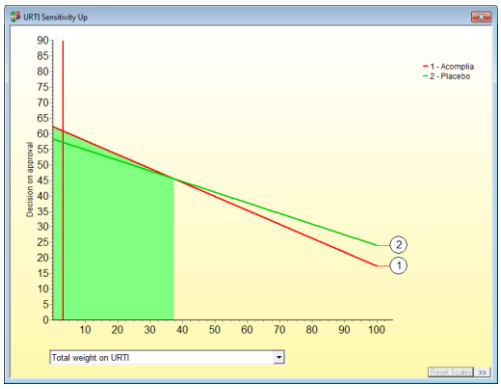
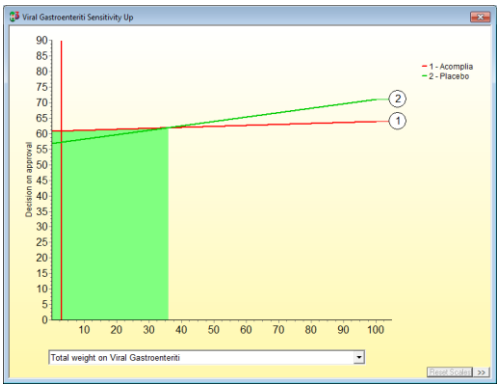


Figure 11-88 Weighted score on level 3 criteria: Infection and infestation

Sensitivity testing



A) Upper respiratory tract infection



B) Viral Gastroenteritis

Figure 11-89 Sensitivity testing: Level 3- Infection and infestation

Nervous system disorder

Node result

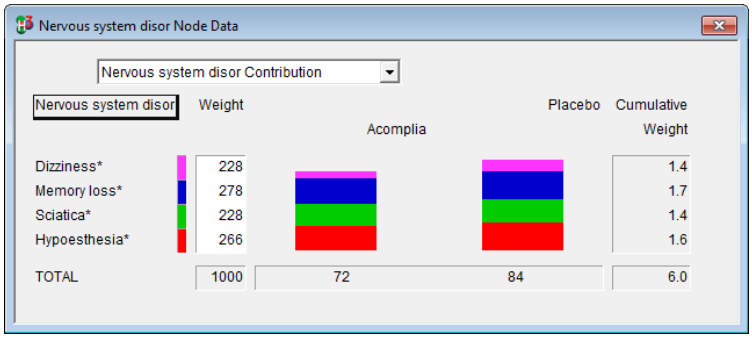
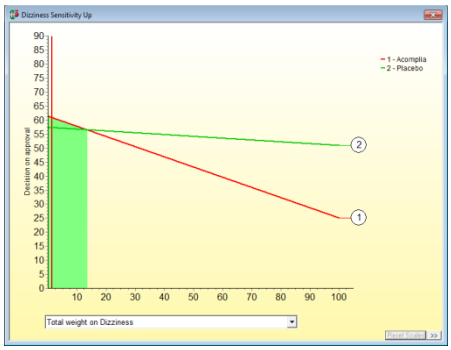
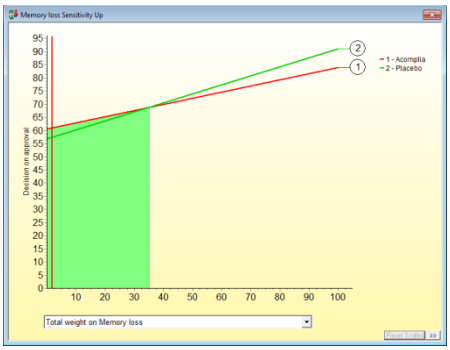


Figure 11-90 Weighted score on level 3 criteria: Nervous system disorder

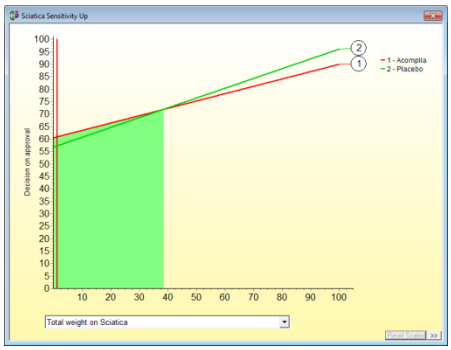
Sensitivity testing



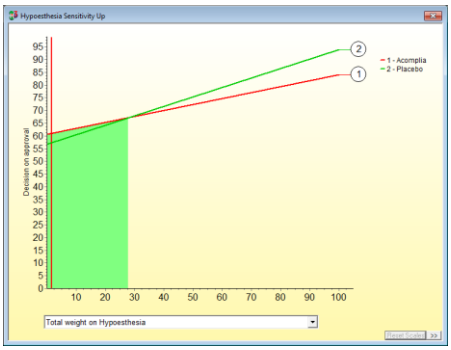
A) Dizziness



B) Memory loss



C) Sciatica



D) Hypoesthesia

Figure 11-91 Sensitivity testing: Level 3- Nervous system disorder

Vascular System disorders

Node results

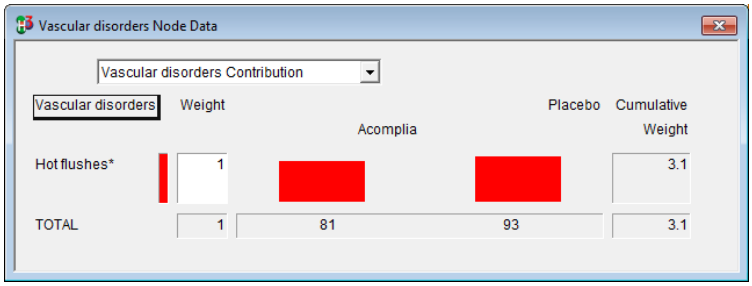


Figure 11-92 Weighted score on level 3 criteria: Vascular system disorder

Sensitivity testing

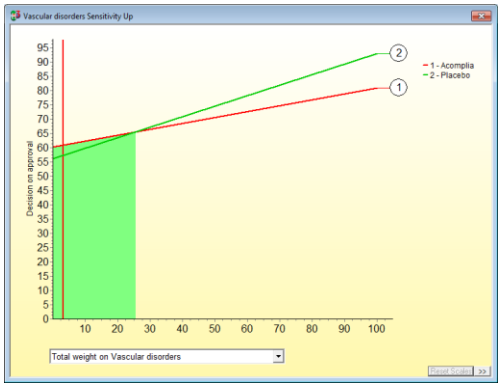


Figure 11-93 Sensitivity testing: Level 3- Vascular system disorder

Gastrointestinal disorder

Node results

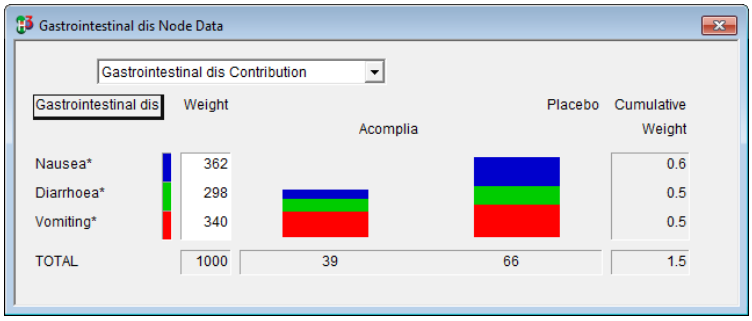
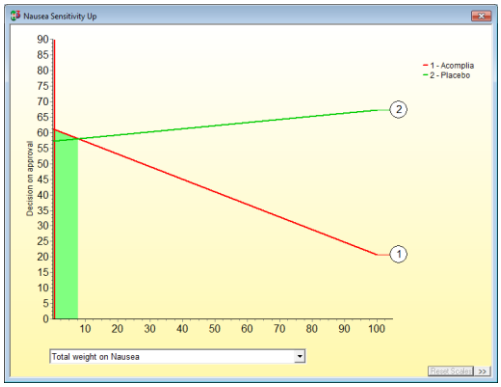
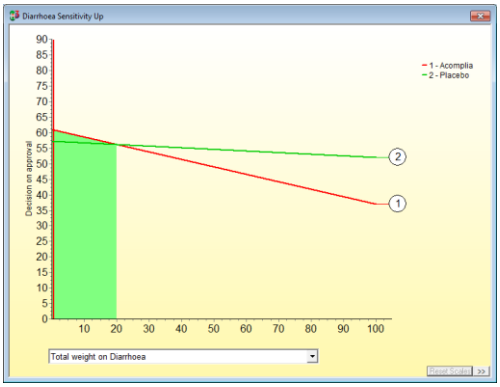


Figure 11-94 Weighted score on level 3 criteria: Gastrointestinal disorder

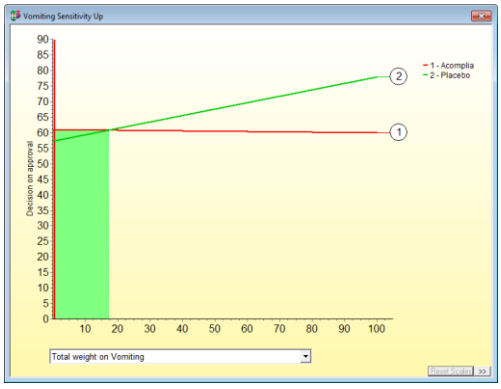
Sensitivity testing



A) Nausea



B) Diarrhoea



C) Vomiting

Figure 11-95 Sensitivity testing: Level 3- Gastrointestinal disorder

Skin and subcutaneous tissue disorder

Node results

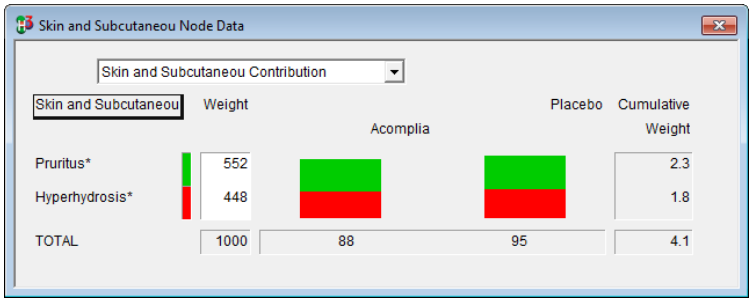
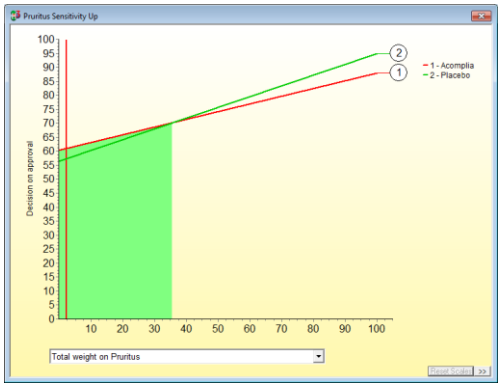
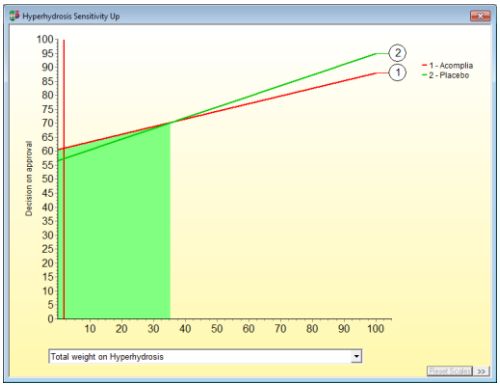


Figure 11-96 Weighted score on level 3 criteria: Skin and Subcutaneous tissue disorder

Sensitivity testing



A) Pruritis



B) Hyperhydrosis

Figure 11-97 Sensitivity testing: Level 3- Skin and Subcutaneous tissue disorder

Musculoskeletal and connective tissue disorder

Node result

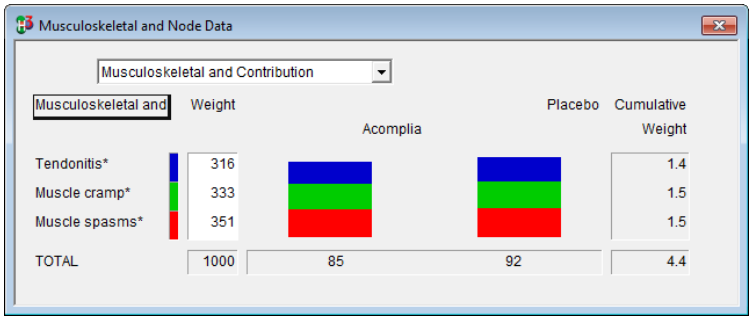
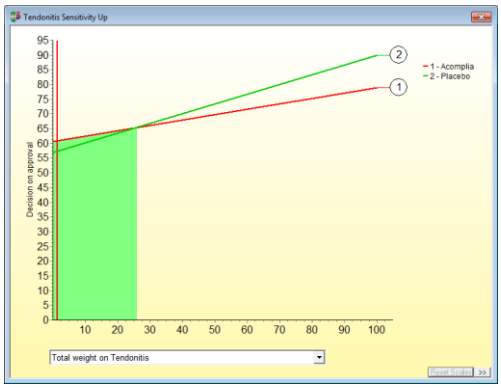
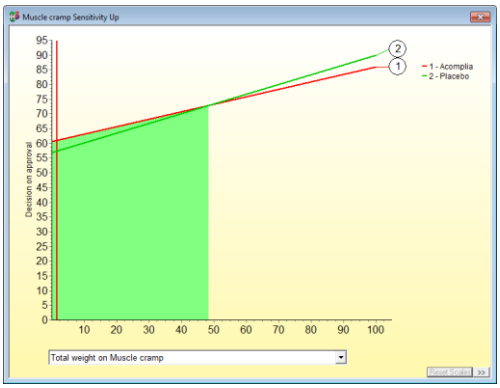


Figure 11-98 Weighted score on level 3 criteria: Musculoskeletal and connective tissue disorder

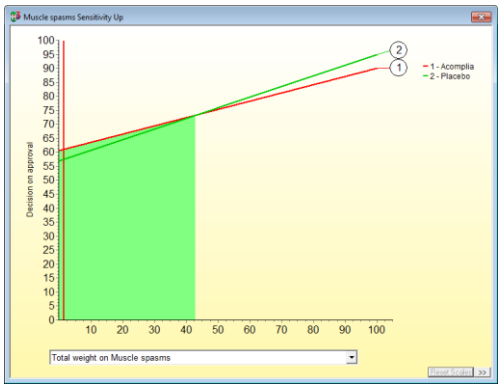
Sensitivity testing



A) Tendonitis



B) Muscle Cramp



C) Muscle spasm

Figure 11-99 Sensitivity testing: Level 3- Musculoskeletal and Connective tissue disorder

General disorder

Node results

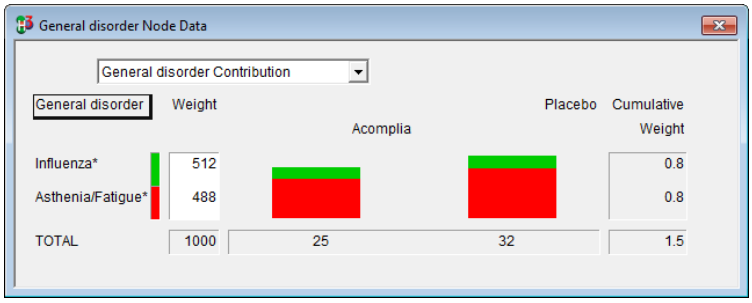
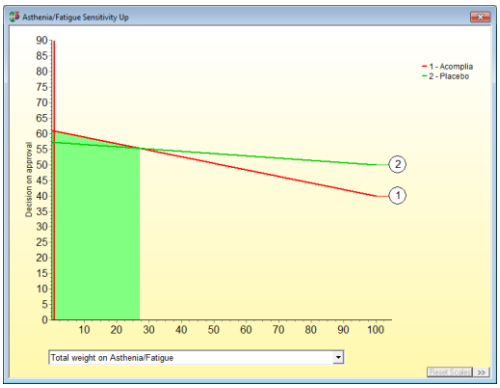


Figure 11-100 Weighted score on level 3 criteria: General disorder

Sensitivity testing

A) Influenza



B) Asthenia\Fatigue

Figure 11-101 Sensitivity testing: Level 3- General disorder

Injury, Poisoning and Procedural complications

Node results

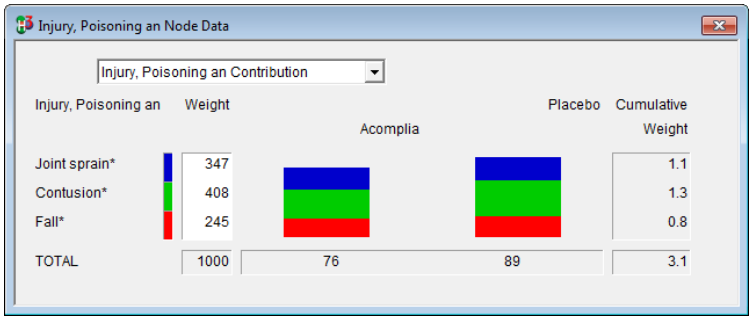
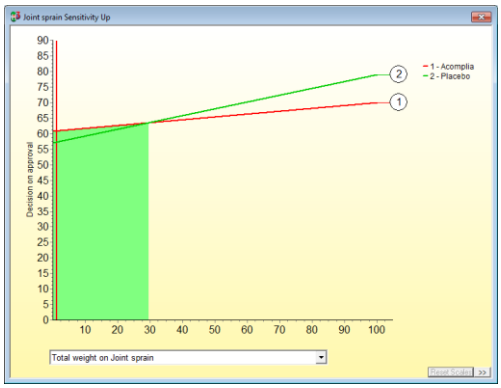
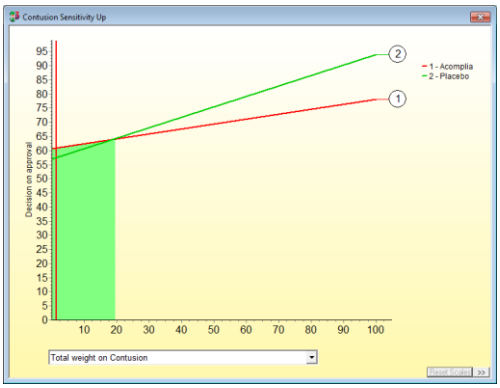


Figure 11-102 Weighted score on level 3 criteria: Injury, Poisoning and Procedural complication

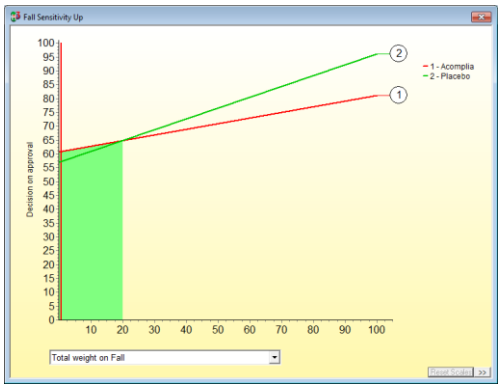
Sensitivity testing



A) Joint Sprain



B) Contusion



C) Fall

Figure 11-103 Sensitivity testing: Level 3 - Injury, Poisoning and Procedural Complication

Difference in Weighted score

Figure 11-104 demonstrated detailed difference in scores between rimonabant and placebo in all criteria listed. Detailed difference in score and cumulative weighting can be found in section 11.3.2.10.4 – Tree 3 Layman weightings

Although overall results demonstrated that rimonabant was superior in waistline reduction, 10% weight lost at 1 year, triglyceride control and reduction in metabolic syndrome.

Rimonabant was inferior in association with anxiety, nausea, dizziness and hot flushes.

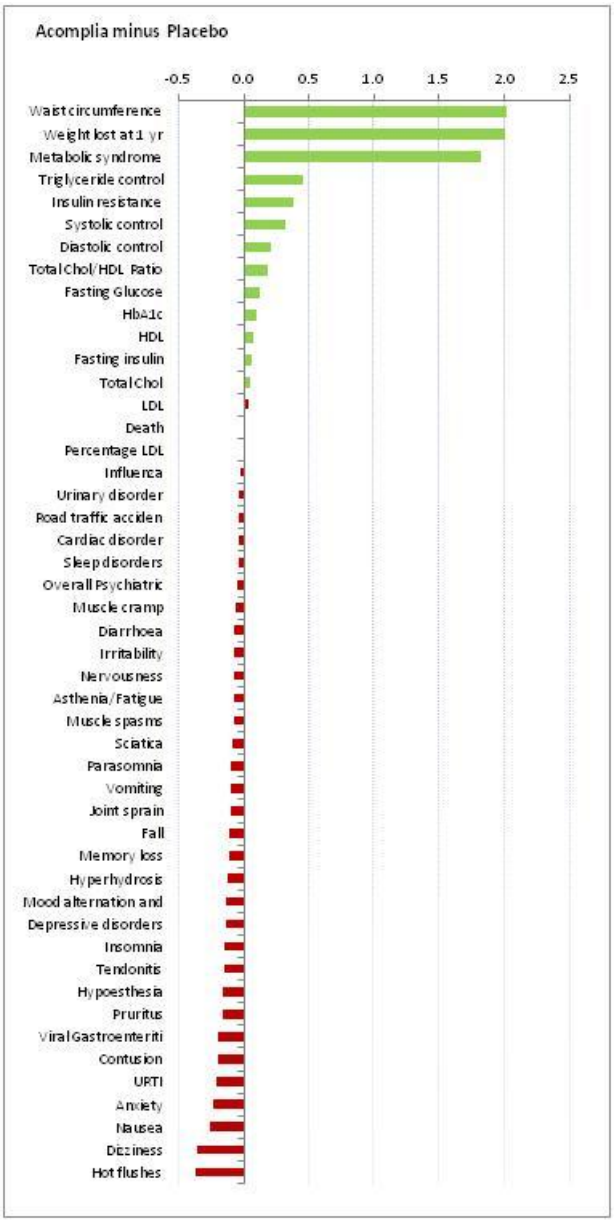
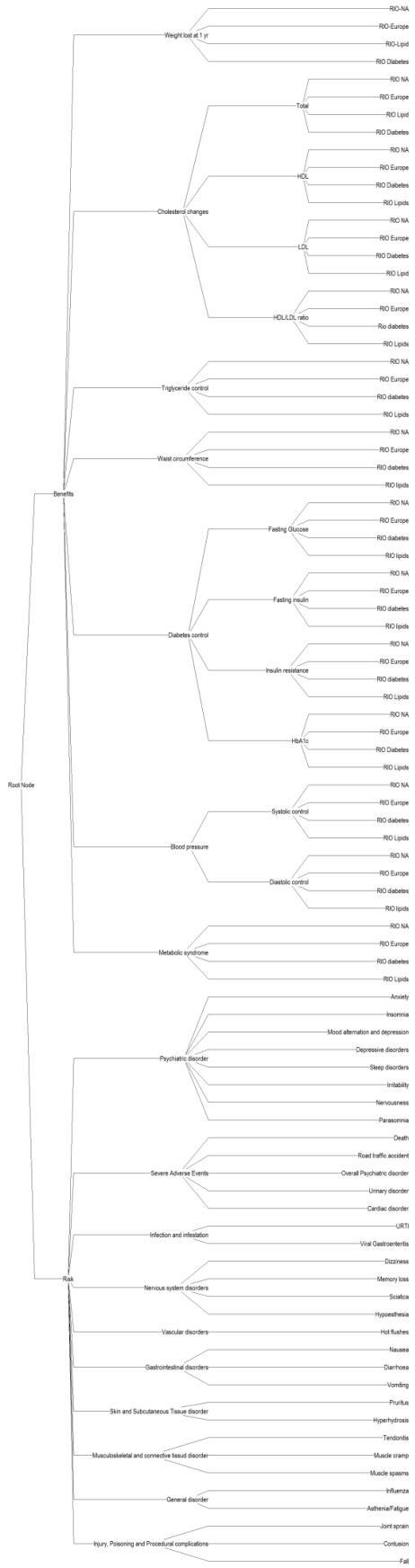


Figure 11-104 Difference in weighted score: Tree 3

11.3.2.10.4 Decision Tree

Tree 1



Tree 2 Medical/Regulatory prospective

11-2 Difference in weighted score in tree 2 with Medical/Regulatory prospective

Criteria	Cum wt	Diff	Wt diff	Sub total
Waist circumference	8.0	21	1.7	1.7
Weight lost at 1 yr	8.0	19	1.5	3.3
Triglyceride control	4.7	15	0.7	3.9
Metabolic syndrome	6.6	10	0.7	4.6
Total Chol/HDL Chol ratio	1.4	25	0.3	4.9
HbA1c	4.0	7	0.3	5.2
HDL	1.3	18	0.2	5.5
Systolic control	2.0	10	0.2	5.7
Diastolic control	2.7	6	0.2	5.8
LDL	1.3	6	0.1	5.9
Total Chol	0.8	4	0.0	5.9
Death	3.6	1	0.0	6.0
Fasting Glucose	1.6	2	0.0	6.0
Percentage LDL	0.0	0	0.0	6.0
Fasting insulin	0.0	22	0.0	6.0
Insulin resistance	0.0	8	0.0	6.0
Joint sprain	0.0	-9	0.0	6.0
Contusion	0.0	-16	0.0	6.0
Fall	0.0	-15	0.0	6.0
Road traffic accident	0.4	-2	0.0	6.0
Muscle cramp	0.4	-4	0.0	6.0
Urinary disorder	0.7	-2	0.0	6.0
Muscle spasms	0.4	-5	0.0	5.9
Influenza	1.2	-3	0.0	5.9
Pruritus	0.5	-7	0.0	5.9
Hyperhydrosis	0.5	-7	0.0	5.8
Tendonitis	0.4	-11	0.0	5.8
Viral Gastroenteritis	1.0	-7	-0.1	5.7
Sciatica	1.2	-6	-0.1	5.6
URTI	1.1	-7	-0.1	5.6
Sleep disorders	1.5	-6	-0.1	5.5
Cardiac disorder	5.1	-2	-0.1	5.4
Nervousness	1.5	-10	-0.2	5.2
Hypoesthesia	1.6	-10	-0.2	5.0
Parasomnia	1.5	-13	-0.2	4.8
Memory loss	3.1	-7	-0.2	4.6
Irritability	1.7	-13	-0.2	4.4
Diarrhoea	1.7	-15	-0.2	4.2
Hot flushes	2.1	-12	-0.3	3.9
Overall Psychiatric	7.2	-4	-0.3	3.6
Vomiting	1.7	-18	-0.3	3.3
Asthenia/Fatigue	3.1	-10	-0.3	3.0
Dizziness	1.6	-26	-0.4	2.6
Nausea	0.9	-47	-0.4	2.2
Depressive disorders	2.9	-16	-0.5	1.7
Mood alternation and	3.5	-17	-0.6	1.1
Insomnia	2.7	-22	-0.6	0.5
Anxiety	2.7	-32	-0.9	-0.3

Tree 3 Medical/Regulatory weightings

11-3 Difference in weighted score in tree 3 with Medical/Regulatory prospective

Criteria	Cum wt	Diff	Wt diff	Sub total
Waist circumference	8.0	22	1.7	1.7
Weight lost at 1 yr	8.0	19	1.5	3.3
Metabolic syndrome	6.6	22	1.5	4.7
Triglyceride control	4.7	7	0.3	5.0
HbA1c	4.0	5	0.2	5.2
Systolic control	2.0	9	0.2	5.4
Diastolic control	2.7	6	0.2	5.6
Fasting Glucose	1.6	7	0.1	5.7
HDL/LDL ratio	1.4	8	0.1	5.8
HDL	1.3	3	0.0	5.8
Death	3.6	1	0.0	5.9
LDL	1.3	2	0.0	5.9
Total Chol	0.8	2	0.0	5.9
Percentage LDL	0.0	0	0.0	5.9
Fasting insulin	0.0	3	0.0	5.9
Insulin resistance	0.0	21	0.0	5.9
Joint sprain	0.0	-9	0.0	5.9
Contusion	0.0	-16	0.0	5.9
Fall	0.0	-15	0.0	5.9
Road traffic accident	0.4	-2	0.0	5.9
Muscle cramp	0.4	-4	0.0	5.9
Urinary disorder	0.7	-2	0.0	5.9
Muscle spasms	0.4	-5	0.0	5.8
Influenza	1.2	-3	0.0	5.8
Pruritus	0.5	-7	0.0	5.8
Hyperhydrosis	0.5	-7	0.0	5.7
Tendonitis	0.4	-11	0.0	5.7
Viral Gastroenteritis	1.0	-7	-0.1	5.6
Sciatica	1.2	-6	-0.1	5.6
URTI	1.1	-7	-0.1	5.5
Sleep disorders	1.5	-6	-0.1	5.4
Cardiac disorder	5.1	-2	-0.1	5.3
Nervousness	1.5	-10	-0.2	5.1
Hypoesthesia	1.6	-10	-0.2	5.0
Parasomnia	1.5	-13	-0.2	4.8
Memory loss	3.1	-7	-0.2	4.5
Irritability	1.7	-13	-0.2	4.3
Diarrhoea	1.7	-15	-0.2	4.1
Hot flushes	2.1	-12	-0.3	3.8
Overall Psychiatric	7.2	-4	-0.3	3.6
Vomiting	1.7	-18	-0.3	3.3
Asthenia/Fatigue	3.1	-10	-0.3	2.9
Dizziness	1.6	-26	-0.4	2.5
Nausea	0.9	-47	-0.4	2.1
Depressive disorders	2.9	-16	-0.5	1.6
Mood alternation and	3.5	-17	-0.6	1.0
Insomnia	2.7	-22	-0.6	0.5
Anxiety	2.7	-32	-0.9	-0.4

Tree 3 Layman weightings

11-4 Difference in weighted score in tree 3 with Layman prospective

Criteria	Cum wt	Diff	Wt diff	Sub total
Waist circumference	9.3	22	2.0	2.0
Weight lost at 1 yr	10.5	19	2.0	4.0
Metabolic syndrome	8.2	22	1.8	5.8
Triglyceride control	6.6	7	0.4	6.3
Insulin resistance	1.7	21	0.4	6.6
Systolic control	3.6	9	0.3	6.9
Diastolic control	3.4	6	0.2	7.1
Total Chol/HDL Ratio	2.2	8	0.2	7.3
Fasting Glucose	1.7	7	0.1	7.4
HbA1c	1.8	5	0.1	7.5
HDL	2.1	3	0.1	7.6
Fasting insulin	1.7	3	0.0	7.6
Total Chol	2.2	2	0.0	7.7
LDL	2.1	2	0.0	7.7
Death	1.7	1	0.0	7.7
Percentage LDL	0.0	0	0.0	7.7
Influenza	0.8	-3	0.0	7.7
Urinary disorder	1.4	-2	0.0	7.7
Road traffic accident	1.4	-2	0.0	7.6
Cardiac disorder	1.6	-2	0.0	7.6
Sleep disorders	0.7	-6	0.0	7.5
Overall Psychiatric	1.5	-4	-0.1	7.5
Muscle cramp	1.5	-4	-0.1	7.4
Diarrhoea	0.5	-15	-0.1	7.4
Irritability	0.5	-13	-0.1	7.3
Nervousness	0.7	-10	-0.1	7.2
Asthenia/Fatigue	0.8	-10	-0.1	7.1
Muscle spasms	1.5	-5	-0.1	7.1
Sciatica	1.4	-6	-0.1	7.0
Parasomnia	0.7	-13	-0.1	6.9
Vomiting	0.5	-18	-0.1	6.8
Joint sprain	1.1	-9	-0.1	6.7
Fall	0.8	-15	-0.1	6.6
Memory loss	1.7	-7	-0.1	6.5
Hyperhydrosis	1.8	-7	-0.1	6.3
Mood alternation and	0.8	-17	-0.1	6.2
Depressive disorders	0.9	-16	-0.1	6.1
Insomnia	0.7	-22	-0.1	5.9
Tendonitis	1.4	-11	-0.2	5.8
Hypoesthesia	1.6	-10	-0.2	5.6
Pruritus	2.3	-7	-0.2	5.5
Viral Gastroenteritis	2.8	-7	-0.2	5.3
Contusion	1.3	-16	-0.2	5.1
URTI	3.1	-7	-0.2	4.8
Anxiety	0.7	-32	-0.2	4.6
Nausea	0.6	-47	-0.3	4.4
Dizziness	1.4	-26	-0.4	4.0
Hot flushes	3.1	-12	-0.4	3.6

Effects table

11-5 Effects table

Short Name	Description	Scale Type	Fixed Upper	Fixed Lower	Units	Value Function
Weight lost at 1 yr	Net Percentage difference in patient reached 10% weight lost at 1 year	Fixed	100	0	Percentage	Linear
Total Chol	Net Measured difference compared to placebo	Fixed	2	-2	mmol/L	Linear
HDL	Net Measured difference compare to placebo	Fixed	2	-2	mmol/L	Linear
LDL	Net Measured difference compare to placebo	Fixed	2	-2	mmol/L	Linear
Percentage LDL	Not available	Fixed	100	0	Data	Linear
Total Chol/HDL Ratio	net difference compare to placebo	Fixed	2	-2		Linear
Triglyceride control	Net difference in compare to control	Fixed	2	-2	absolute changes	Linear
Waist circumference	Net difference in waist circumference compared to placebo	Fixed	10	-10	cm	Linear
Fasting Glucose	Net difference in fasting Glucose	Fixed	2	-2	mmol/L	Linear
Fasting insulin	net difference compare to placebo	Fixed	5	-5	nanoIU/mL	Linear
Insulin resistance		Fixed	5	-5		Linear
HbA1c	HbA1c difference	Fixed	5	-5	%	Linear
Systolic control	Net Systolic BP difference	Fixed	10	-10	mmHg	Linear
Diastolic control	net difference	Fixed	10	-10	mmHg	Linear
Metabolic syndrome	net difference	Fixed	100	0	%	Linear
Anxiety	Pool rate	Fixed	10	0	%	Linear
Insomnia	Pool rate	Fixed	10	0	%	Linear
Mood alternation and	Pool rate	Fixed	10	0	%	Linear
Depressive disorders	Pool rate	Fixed	10	0	%	Linear
Sleep disorders	Pool rate	Fixed	10	0	%	Linear
Irritability	Pool rate	Fixed	10	0	%	Linear
Nervousness	Pool rate	Fixed	10	0	%	Linear
Parasomnia	Pool rate	Fixed	10	0	%	Linear
Death	Pool rate	Fixed	10	0	%	Linear
Road traffic acciden	Pool rate	Fixed	10	0	%	Linear
Overall Psychiatric	Pool rate	Fixed	10	0	%	Linear
Urinary disorder	Pool rate	Fixed	10	0	%	Linear
Cardiac disorder	Pool rate	Fixed	10	0	%	Linear
URTI	Pool rate	Fixed	15	0	%	Linear
Viral Gastroenteriti	Pool rate	Fixed	10	0	%	Linear
Dizziness	Pool rate	Fixed	10	0	%	Linear
Memory loss	Pool rate	Fixed	10	0	%	Linear
Sciatica	Pool rate	Fixed	10	0	%	Linear
Hypoesthesia	Pool rate	Fixed	10	0	%	Linear
Hot flushes	Pool rate	Fixed	10	0	%	Linear
Nausea	Pool rate	Fixed	15	0	%	Linear
Diarrhoea	Pool rate	Fixed	10	0	%	Linear
Vomiting	Pool rate	Fixed	10	0	%	Linear
Pruritus	Pool rate	Fixed	10	0	%	Linear
Hyperhydrosis	Pool rate	Fixed	10	0	%	Linear
Tendonitis	Pool rate	Fixed	10	0	%	Linear
Muscle cramp	Pool rate	Fixed	10	0	%	Linear
Muscle spasms	Pool rate	Fixed	10	0	%	Linear
Influenza	Pool rate	Fixed	10	0	%	Linear
Asthenia/Fatigue	Pool rate	Fixed	10	0	%	Linear
Joint sprain	Pool rate	Fixed	10	0	%	Linear
Contusion	Pool rate	Fixed	10	0	%	Linear
Fall	Pool rate	Fixed	10	0	%	Linear

Weightings questionnaires

Medical/Regulator version

1 In case of weight losing medication, how would you rate the importance benefit and risk?												
	0 (Not important)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (Very important)**	**Response Count**
Benefit	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	66.7% (2)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	3
Risk	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	3
2. In the use of rimonabant, a drug designed for weight lost, how important are the following benefits?												
	0 (Not important)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (Very important)**	**Response Count**
Success in losing and maintained 10% lost of bodyweight	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	50.0% (1)	2
Improvement in cholesterol control	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	100.0% (2)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Reduce triglyceride levels	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	100.0% (2)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Reducing waist circumference	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	50.0% (1)	2
Improvement in diabetes control	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	2
Lowering blood pressure	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	100.0% (2)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Reducing incidence of metabolic syndrome	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	100.0% (2)	0.0% (0)	0.0% (0)	0.0% (0)	2
3. With regards to cholesterol control, how important is the following markers of cholesterol?												
	0 (Not important)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (Very important)**	**Response Count**
Total Cholesterol (Sum of Cholesterol level)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	2
HDL cholesterol ("Good Cholesterol")	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	2
LDL cholesterol ("Bad Cholesterol")	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	2
HDL/LDL cholesterol ratio	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	2
4. With regards to measurements of diabetes control, how would you rate the importance of the following markers?												
	0 (Not important)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (Very important)**	**Response Count**
Fasting Glucose (Use in diagnosis of diabetes)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	2
Fasting Insulin (Measurement of Insulin production)	100.0% (2)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Insulin resistance	100.0% (2)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Changes in HbA1C (Overall Diabetes control over 120 days)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	100.0% (2)	2
5 With regards to blood pressure control. How would you rate the importance of the following?												
	0 (Not important)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (Very important)**	**Response Count**
Systolic blood pressure (Top measurement)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	2
Diastolic blood pressure (Bottom measurement)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	50.0% (1)	2
6. With regards to weight losing medication, rimonabant, independent to its benefit. How would you rate the importance of avoiding potential negative effect in following body system?												
	0 (Not important)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (Very important)**	**Response Count**
Infection and Infestation	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2

Psychiatric disorder	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	50.0% (1)	0.0% (0)	2
Nervous system disorder, for example dizziness or neuralgia	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Vascular disorder, e.g. hot flushes	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Skin and subcutaneous tissue disorder	50.0% (1)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Musculoskeletal disorder	50.0% (1)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Injury, poising or procedure related complication	100.0% (2)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Severe adverse events (i.e. events that caused irreversible damage or require hospitalization)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	100.0% (2)	0.0% (0)	0.0% (0)	2

7. How would you rate the importance of the following reported side effects associated with rimonabant?

	0 (Not important)	1	2	3	4	5	6	7	8	9	10 (Very important)	Response Count
Upper respiratory tract infection	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	2
Gastroenteritis viral	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Anxiety	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	2
Insomnia	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	2
Mood alternation with depressive symptoms	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	2
Depressive disorders	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	2
Irritability	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Parasomnia	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Nervousness	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Sleep disorders	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Dizziness	0.0% (0)	0.0% (0)	50.0% (1)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Memory loss	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	2
Hypoesthesia	0.0% (0)	0.0% (0)	50.0% (1)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Sciatica	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Hot flushes	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Nausea	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Diarrhoea	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Vomiting	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2

Pruritus	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Hyperhydrosis	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Tendonitis	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Muscle cramp	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Muscle spasms	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Influenza	50.0% (1)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Asthenia/Fatigue	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Joint sprain	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Contusion	100.0% (2)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Fall	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Death	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	2
Overall Psychiatric disorder	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	100.0% (2)	2
Cardiac disorder	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	2
Urinary disorder	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Road traffic accident	50.0% (1)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2

Layman version

1. In case of weight losing medication, how would you rate the importance benefit and risk?												
	0 (Not important)	1	2	3	4	5	6	7	8	9	10 (Very important)	Response Count
Benefit	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	33.3% (1)	3
Risk	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	33.3% (1)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	3

2. In the use of rimonabant, a drug designed for weight lost, in your opinion - how important are the following benefits?												
	0 (Not important)	1	2	3	4	5	6	7	8	9	10 (Very important)	Response Count
Success in losing 10% bodyweight and maintenance	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	33.3% (1)	33.3% (1)	3
Improvement in cholesterol levels	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	66.7% (2)	0.0% (0)	0.0% (0)	3
Reduce triglyceride levels	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	33.3% (1)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	3
Reducing waist circumference	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	33.3% (1)	3
Improvement in diabetes control	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	3
Lowering blood pressure	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	33.3% (1)	0.0% (0)	3
Lessen risk of developing metabolic syndrome (A group of factors that increase risk of heart disease and stroke)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	66.7% (2)	0.0% (0)	0.0% (0)	3

3. With regards to cholesterol control, how important is the following markers of cholesterol?												
	0 (Not important)	1	2	3	4	5	6	7	8	9	10 (Very important)	Response Count
Total Cholesterol (Sum of All measured cholesterol level, what your GP uses)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	3
HDL cholesterol ("Good Cholesterol" - more the better)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	66.7% (2)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	3
LDL cholesterol ("Bad Cholesterol" - lower the better)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	66.7% (2)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	3
HDL/LDL cholesterol ratio	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	3

4. With regards to measurements of diabetes control, how would you rate the importance of the following markers?												
	0 (Not important)	1	2	3	4	5	6	7	8	9	10 (Very important)	Response Count
Fasting Glucose (Use in diagnosis of diabetes, little information about diabetes control)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	66.7% (2)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	3
Fasting Insulin (Measurement of Insulin production, little use in clinical setting)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	66.7% (2)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	3
Insulin resistance (How effective is insulin produced, little use	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	66.7%	0.0% (0)	0.0% (0)	33.3%	0.0% (0)	0.0% (0)	3

in clinical setting)						(2)			(1)			
Changes in HbA1C (Overall Diabetes control over 120 days, a common marker used by doctors)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	3
5. With regards to blood pressure control measurement, doctors routinely measure blood pressure with 2 figures. The top figure (Systolic) and lower figure (diastolic). Systolic pressure implies blood pressure during your heart beat and diastolic pressure implies blood pressure between heart beats. In general, your doctor considers both figures together when reviewing blood pressure control. In your opinion, how would you rate the importance of the following measurement?												
	0 (Not important)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (Very important)**	**Response Count**
Systolic blood pressure (Top measurement)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	3
Diastolic blood pressure (Bottom measurement)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	33.3% (1)	0.0% (0)	0.0% (0)	3
6. With regards to weight losing medication - rimonabant, independent to its benefit. How would you rate the importance of avoiding potential side effects from the medication on the following body system?												
	0 (Not important)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (Very important)**	**Response Count**
Severe adverse events (Events that caused irreversible damage or require admission to hospital. e.g. Death)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	66.7% (2)	3
Infection caused by medication (e.g. chest infection)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	3
Psychiatric disorder (e.g. Depression, anxiety)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	66.7% (2)	33.3% (1)	0.0% (0)	0.0% (0)	3
Nervous system disorder, (e.g. example dizziness, trapped nerve)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	66.7% (2)	0.0% (0)	33.3% (1)	0.0% (0)	3
Vascular disorder (e.g. hot flushes)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	3
Skin disorder (e.g. itchiness, rash)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	3
Musculoskeletal disorder (e.g. joint pain, arthritis)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	66.7% (2)	0.0% (0)	0.0% (0)	0.0% (0)	3
Procedure related complications (e.g. Fall, poisoning)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	66.7% (2)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	3
7. The following side effects are ones that had been reported associated with the use of rimonabant, how would you rate the importance of the these side effects?												
	0 (Not important)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (Very important)**	**Response Count**
Chest infection	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	33.3% (1)	0.0% (0)	0.0% (0)	3
Gastroenteritis	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	33.3% (1)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	3
Anxiety	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	66.7% (2)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	3
Trouble falling asleep	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	3
Mood alternation with depressive symptoms	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	3
Depression	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	66.7% (2)	0.0% (0)	0.0% (0)	3

Being easily irritated	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	3
Nightmare and/or sleep walking	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	33.3% (1)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	3
Nervousness	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	33.3% (1)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	3
Other sleep disorders (e.g. early wakening)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	3
Dizziness	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	33.3% (1)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	3
Memory loss (Minor)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	33.3% (1)	3
Reduced sense of touch or sensation	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	3
Trapped nerve	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	33.3% (1)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	3
Hot flushes	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	33.3% (1)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	3
Nausea	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	66.7% (2)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	3
Diarrhoea	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	3
Vomiting	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	3
itchiness	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	3
Excessive sweat	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	3
Inflammation of tendon	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	33.3% (1)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	3
Muscle cramp	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	66.7% (2)	0.0% (0)	0.0% (0)	0.0% (0)	3
Muscle spasms	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	33.3% (1)	0.0% (0)	0.0% (0)	3
Flu	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	33.3% (1)	3
Tiredness	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	3
Joint sprain	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	66.7% (2)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	3
Contusion	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	33.3% (1)	0.0% (0)	0.0% (0)	3
Fall	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	3
Death	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	33.3% (1)	3

Overall severe psychiatric disorder (e.g. depression require hospital admission)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	33.3% (1)	0.0% (0)	0.0% (0)	3
Heart disorder (e.g. Heart attack)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	0.0% (0)	3
Disorder of kidney and bladder	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	33.3% (1)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	3
Road traffic accident	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	33.3% (1)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	3

11.3.3 Stochastic multicriteria acceptability analysis

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11.3.3.1 Aims

The overall aims of this case study analysis are:

To assess the feasibility and suitability of the approaches using stochastic multicriteria acceptability analysis (SMAA) model for benefit-risk assessment of drugs by the regulator.

To evaluate the benefit-risk balance of rimonabant 20mg at marketing authorisation approval using the SMAA method.

11.3.3.2 Data requirement and confidentiality

Data for analysis in this case study are obtained from published trials on rimonabant. Public data from the pivotal trials in EPAR [3, 4] and original publications (RIO-North America[11], RIO-Europe[5], RIO- Diabetes[12] and RIO-Lipids[2]) are soughed and summarized for the analysis.

No issue of confidentiality was noted.

11.3.3.3 Overview of SMAA model

The stochastic multicriteria acceptability analysis (SMAA) is a type of Multi Criteria Decision Analysis (MCDA). In contrast to MCDA which requires criteria values and weights to be precisely known upfront, SMAA supports imprecise, uncertain, and missing information by making appropriate distributional assumptions. SMAA can be seen as an extension of MCDA with an added advantage of being able to characterise typical benefit-risk trade-offs to include uncertainties due to sampling variations, and to deal with incomplete or missing data. With the exception of not having to elicit precise value preferences from stakeholders beforehand, SMAA closely follows the framework of MCDA. The benefit-risk trade-offs in SMAA is estimated through simulations for combinations of weights in the hypothetical scenarios of assigning a rank 1 to r to each alternative in turn in a decision problem with r number of alternatives.

In other words, the SMAA can be interpreted as a MCDA process with simulation; A brief explanation of simulations of data and weights will be discussed later in this report.

The criteria can be ranked according stakeholders preference in an SMAA model. In this case, the simulations in weights are adjusted to reflect the ranking in criteria preferences.

11.3.3.4 Development of SMAA model

Establishment of decision context

Rimonabant (ACOMPLIA/ZIMULTI®) is a selective antagonist of cannabinoid type I (CB1) receptors. The cannabinoid system has been shown to be involved in the central regulation of food intake and the central nervous system (CNS) reward system. CB1 receptors were first found in the brain, and later in several human tissues, including adipocytes.

Rimonabant was approved in Europe in 2006 and first marketed in the UK. In July 2007, the CHMP recommended changes to the medicine's prescribing information as follow: 1) Upgrading to a contraindication the warning on the use of rimonabant in patients with ongoing major depression or taking antidepressants. This means that rimonabant

must no longer be used in these patients and 2) Adding a warning that treatment with rimonabant should be stopped if a patient develops depression, including additional information on the psychiatric safety of rimonabant.

In November 2008, the marketing of rimonabant was suspended in all the Member States in which the product was being marketed and in December 2008, the marketing authorization holder (MAH) responsible for rimonabant, sanofi-aventis, voluntarily withdrew its marketing authorization. In January 2009, the European Commission withdrew the marketing authorization for rimonabant on the ground of negative benefit-risk balance based on post-marketing data (EPAR)[3, 4]. A benefit risk analysis using a quantitative method taking into account benefits, risks, as well as relative importance of benefit and risks according to patients or physicians has not been done.

The purpose of this analysis is to establish benefit and risks with medical and regulatory opinions.

Identification of options to be appraised

This model will be used to appraise rimonabant 20mg vesus Placebo.

Identification of the benefit and risk criteria and organisation in a value tree

Rimonabant is a new drug, the first in class, indicated for weight loss in obese or overweight patients with co-morbidities. Different trials have also shown that it could improve HbA1c and lipid profiles (increased HDL and reduced triglyceride) in overweight or obese patients (RIO-North America[11], RIO-Europe[5], RIO- Diabetes[12] and RIO-Lipids[2]). It was not indicated for type 2 diabetes because, according to CHMP (Committee for Medicinal Products for Human Use), the effect size on HBA1C remained uncertain, although it was large enough to be clinically relevant (EPAR)[3, 4]. It was not indicated for dyslipidemia treatment because although Rimonabant was associated with an improved HDL-C, its subfractions and triglycerides, its association cardiovascular complications, which, however was not proven (no outcome data available) (EPAR)[3, 4].

The main safety issue was the psychiatric AEs, although most of the patients with various kinds of depressive symptoms did eventually recover with or without anti-depressants drugs (EPAR)[3, 4]. The most common adverse events were anxiety, insomnia, mood alterations with depressive symptoms, depressive disorders, dizziness nausea, diarrhea, vomiting, and asthenia/ fatigue.

Benefit criteria

The primary benefit of rimonabant is effect on weight lost and maintenance of weight lost at 12 months. Other secondary benefits are divided into groups with different measurement criteria, listed below.

1) Percentage of patient reached 10% weight lost

2) Lipid control at 12 months:

- Total Cholesterol
- HDL Cholesterol
- LDL Cholesterol
- Ratio Total Cholesterol/HDL Cholesterol
- Triglyceride

3) Waist Circumference at 12 months

4) Diabetes control at 12 months

- Fasting glucose
- Fasting insulin
- Insulin resistance
- HbA1c
- Glucose intolerance

5) Blood pressure control

- Systolic Blood Pressure
- Diastolic Blood Pressure

6) Metabolic Syndrome at 12 months

Risk criteria

For the purpose of this analysis, we used data obtained from EPAR for risk assessment. The main concern was psychiatric disorder. And other reported adverse events were arranged in groups of body system.

1) Infection and infestation

- Upper respiratory tract infection
- Gastroenteritis viral

2) Psychiatric disorder

- Anxiety
- Insomnia
- Mood alternation with depressive symptoms
- Depressive disorders
- Irritability
- Parasomnia
- Nervousness
- Sleep disorders

3) Nervous system disorders

- Dizziness
- Memory loss
- Hypoesthesia
- Sciatica

4) Vascular disorders

- Hot flushes

5) Gastrointestinal disorders

- Nausea
- Diarrhoea
- Vomiting

6) Skin and Subcutaneous Tissue disorder

- Pruritus
- Hyperhydrosis

7) Musculoskeletal and connective tissue disorder

- Tendonitis
- Muscle cramp
- Muscle spasms

8) General disorder

- Influenza
- Asthenia/Fatigue
- Injury, Poisoning and Procedural complications
- Joint sprain
- Contusion
- Fall

7) Severe Adverse Events

- Death
- Overall Psychiatric disorder
- Cardiac disorder
- Urinary disorder
- Road traffic accident

Tree

The purpose of this model is to examine the risk and benefit of the use of rimonabant.

Current free software[17] we used in the SMAA model is restricted on one level criteria. Therefore, we changed all 2nd and 3rd level nodes in the tree to 1st level nodes in order to fit into the programme. Unfortunately, this approach

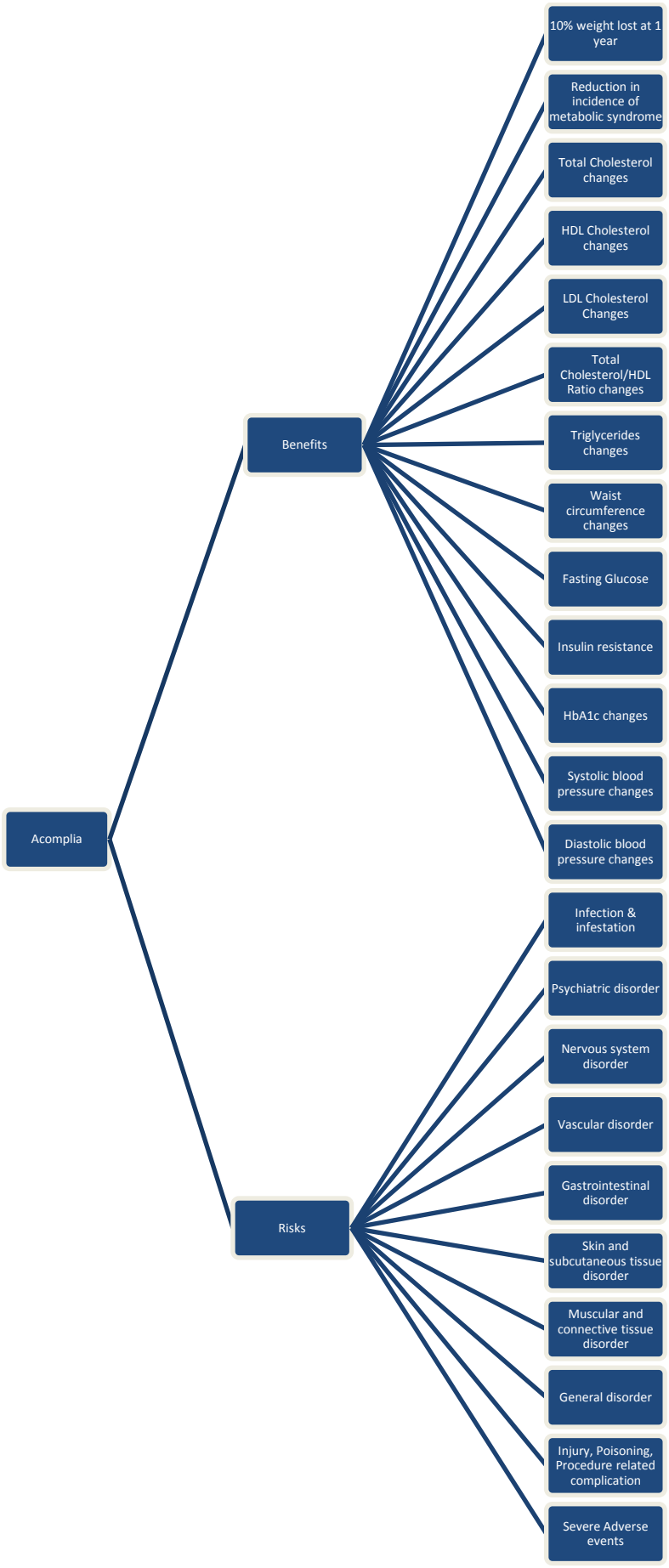
highlighted a problem with this software that it was not able to process complex model consisting of too many criteria, each with a different function.

In order to reduce number of criteria in the model; we collapsed the risk tree by combining total incidence of adverse events into bodily system groups as described in the EPAR by simulation using STATA.

Incidence of each adverse event was obtained from EPAR and used to formulate the beta distribution to describe the underling incidence rate function for that event. Under an assumption that the events within a group were independent, we created a sample of 1000 individual for each bodily group and simulate the episodes of adverse events based on the rate randomly sampled from the incidence rate distribution created. A total rate of adverse events within the group was then calculated. The same process then reiterated for 10000 times and total rate of adverse event within the group were estimated using results of the iterations.

An example of this simulation can be found in section in appendix

Albeit this simulation method offers an estimation of total adverse events using data described, this was built on an assumption that individual events are not correlated and likely over estimated the total incidences of adverse events within group. Our subgroup agreed this would be an acceptable pragmatic approach when primary patient level data regarding treatment event and risks were not available.


Acomplia
Benefits
10% weight lost at 1 year
Reduction in incidence of metabolic syndrome
Total Cholesterol changes
HDL Cholesterol changes
LDL Cholesterol Changes
Total Cholesterol/HDL Ratio changes
Triglycerides changes
Waist circumference changes
Fasting Glucose
Insulin resistance
HbA1c changes
Systolic blood pressure changes
Diastolic blood pressure changes
Risks
Infection & infestation
Psychiatric disorder
Nervous system disorder
Vascular disorder
Gastrointestinal disorder
Skin and subcutaneous tissue disorder
Muscular and connective tissue disorder
General disorder
Injury, Poisoning, Procedure related complication
Severe Adverse events

Criteria evaluation

Data regarding benefits were based a meta-analysis on benefit data from 4 RCTs which contributed into EPAR. Confidence interval of mean benefit measured were used in the model input, except HbA1c, which we only have data from one trial and it was reported as mean reading with 95%CI.

Risk data were generated using simulation by combining reported incidence of adverse events into groups specified in EPAR, as described above.

Benefits

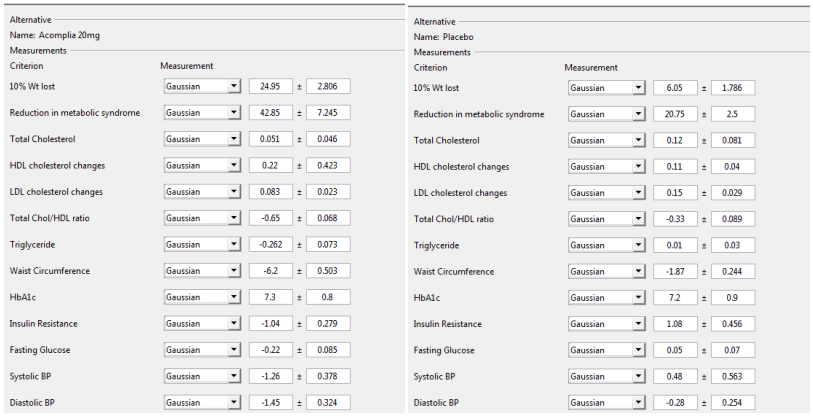


Figure 11-105 Criteria- Benefit

Risks

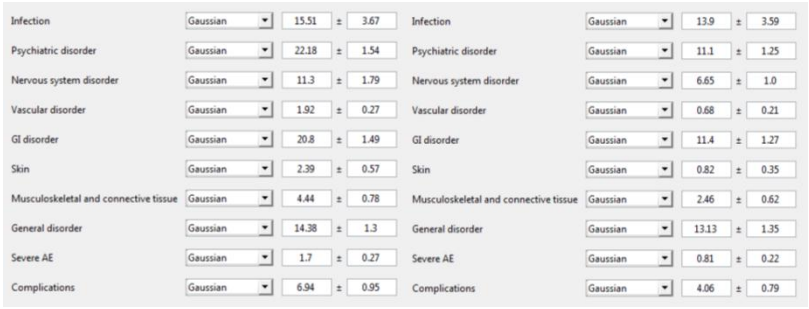


Figure 11-106 Criteria - Risk

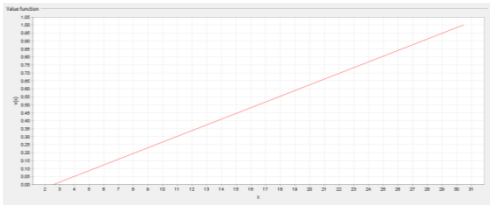
Scoring options for each the criteria

In contrary to MCDA model which require stakeholders to define the criteria function. In this SMAA software, criteria functions were created automatically based on a liner function with fixed preference scale generated by the programme. The fixed limits were the upper 95%CI of the higher result and lower 95% CI of the lower result.

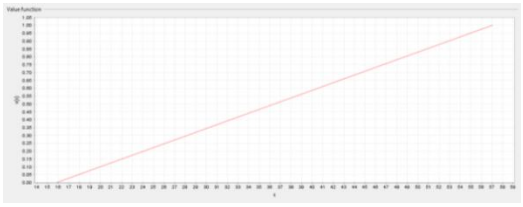
Figures below showed the value function of all criteria included in this model. The Y-axis is the utility score and X-axis is the data range. The red line shows the direction of the utility score, an ascending line reflects an increase in criteria score with higher data value and vice versa.

Random samples were then drawn from the joint distribution between alternatives in each criterion and used in the simulations.

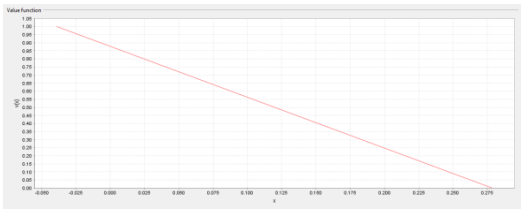
Value function



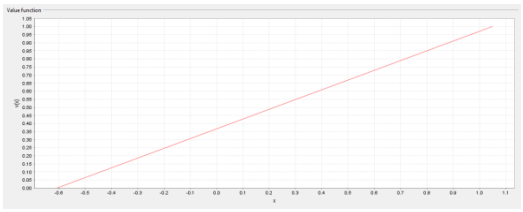
A) 10% weight lost at 1 year



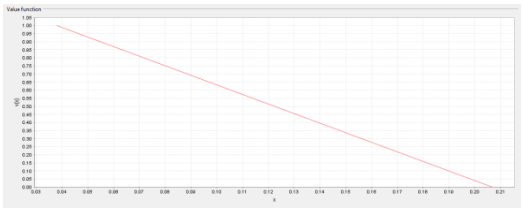
B) Reduction in metabolic syndrome



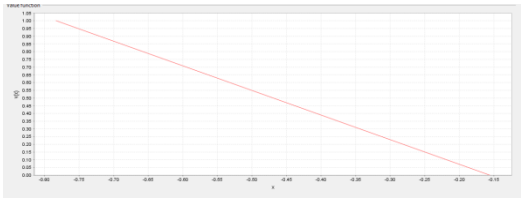
C) Difference in Cholesterol changes



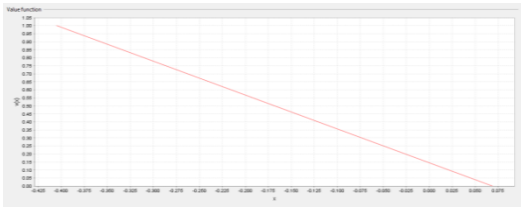
D) HDL Cholesterol changes



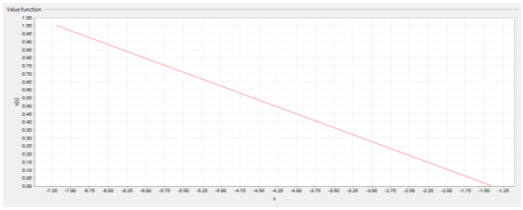
E) LDL Cholesterol Changes



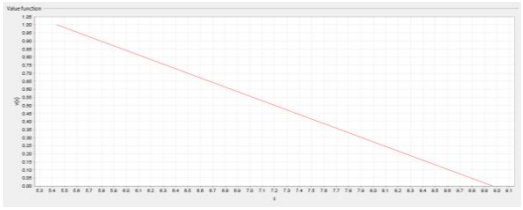
F) Total Chol/HDL Chol ratio changes



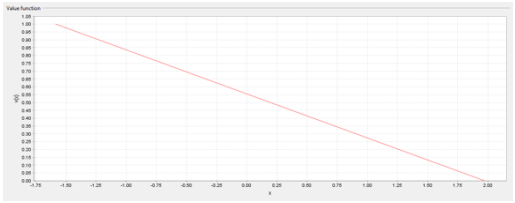
G) Triglyceride changes



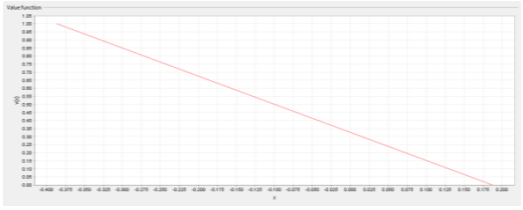
H) Waist line changes



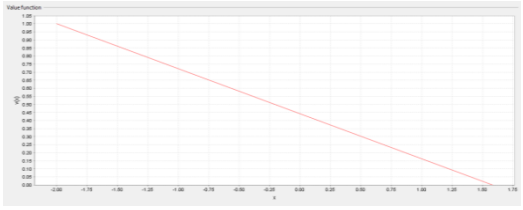
I) HbA1c changes



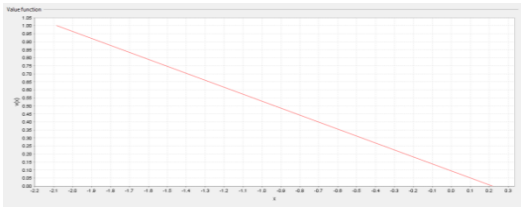
J) Insulin resistance changes



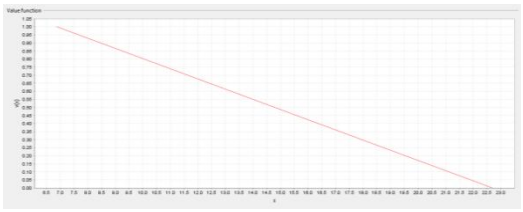
K) Fasting Glucose changes



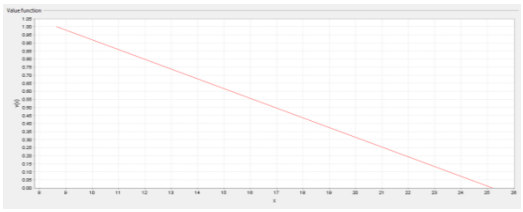
L) Systolic blood pressure changes



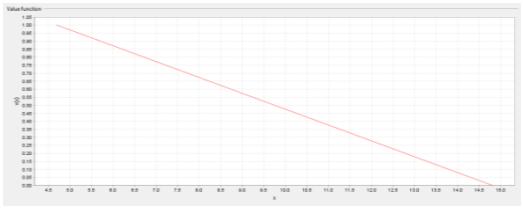
M) Diastolic blood pressure changes



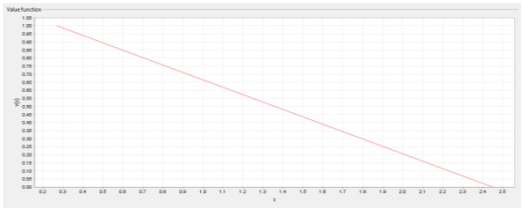
N) Incidence of Infection & infestation



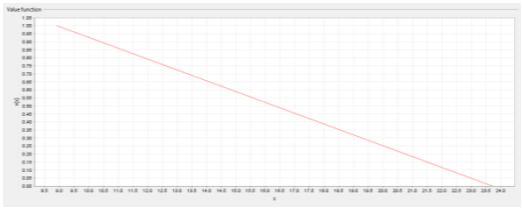
O) Incidence of psychiatric disorder



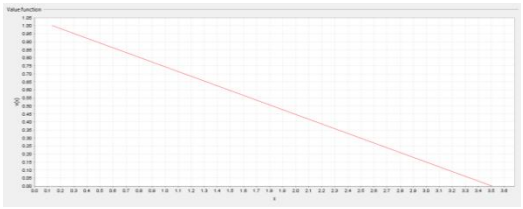
P) Incidence of nervous system disorder



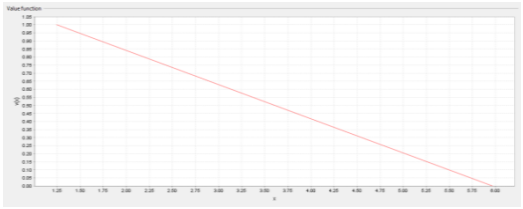
Q) Incidence of Vascular disorder



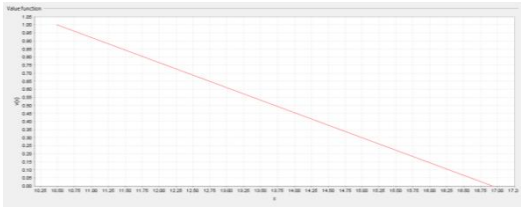
R) Incidence of Gastrointestinal disorder



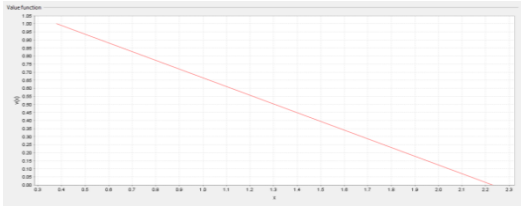
S) Incidence of Skin and subcutaneous tissue disorder



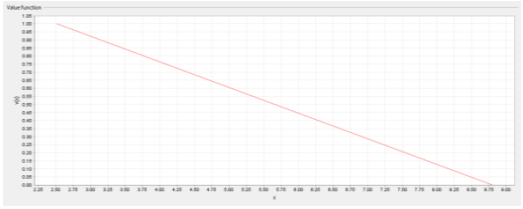
T) Incidence of Muscle and connective tissue disorder



U) Incidence of General disorders



V) Incidence of Severe adverse events



W) Incidence of Injury, Poisoning and procedure related complications

Figure 11-107 Value function of all criteria

Assignment of a weights to each criteria

It is often difficult and unrealistic to obtain a consensus on weights scores between stakeholders in real life situation, as well as the decision maker's knowledge regarding to the question might not be sufficient to make an objective judgement in weights.

The benefit of the SMAA model is replacing the need to assign specific weights on criteria with simulation. In the case of total lack of preference information, the model will assume a uniform weights distribution between criteria. [18]

During each iteration of the simulations, the SMAA model sample weights from the weightings distribution. (The model assumes weights function follows a uniform distribution with a density function in the case with no prior criteria preference). The model then determines a set of *favourable weights vectors* for each alternative, defined as the weights vector that makes the overall utility of this option greater to the utility of others in achieving the target rank of 1^{st} to r^{th} ranking in *r* alternatives.

A descriptive measure of *acceptability index* is then measured using the total weights space formed by the favourable weights vectors and the sample space of utility function, this index representing the probability of the option achieving the target rank.

The central weights vector is then calculated using the expected centre of gravity of the favourable weights space. The central weights vector can be interpreted as the best single vector representing the weights of which will support that option as the preferred choice.

Although specific criteria weighting is not required for the model, SMAA-2 does allow the model to incorporate ranking preference between criteria from decision maker. The model will adjust weights assigned by restricting the feasibility of weights space according to ranking given [18]. We will therefore examine if the model result changes as a result of extra information regarding criteria preference ranking.

We have previously collected weighting data from members of the group using an online questionnaire (www.surveymonkey.com). The questionnaires were divided into Medical and regulator (http://www.surveymonkey.com/s/9FDP7NJ), and layman version (http://www.surveymonkey.com/s/9FLTQSG). Questions raised were based on criteria listed above and expressed in medical or layman terms depending on the version of questionnaire. Responders were asked to score importance of individual criteria between 0 and 10, from not important to extremely important.

Results from the two surveys then summarised as mean scoring between all responders and used this average score to calculate proportional weighting in each groups of criteria.

11.3.3.5 Results

In this model, data from the RCT [2, 5, 11, 12] on benefits were first summarised using random effects meta-analysis. Random effect methods were chosen to reflect the uncertainties and difference in underlying populations used in the trials. Data from different studies were pooled using method of inverse variance. Benefits of this method allow a systematic and objective approach to combine results from different trials.

Model without pre-assigned weights preference

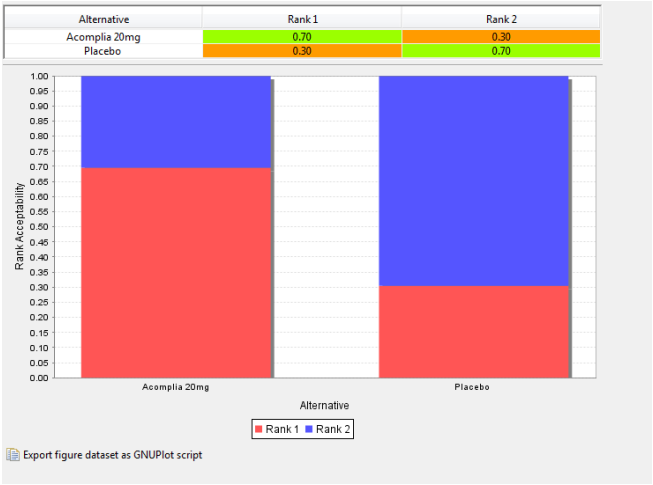


Figure 11-108 Results from model without pre-assigned weighting

Figure 5-1 above is a standard visualisation of the output from this software. The colour bar represents the probability of ranking of the option (Acceptability index). In this simple example of two alternatives; the red bar represents the probability of the given option being the Rank 1 choice, and the blue bar represent the probability of the option being the Rank 2 choice.

This model suggested a higher probability of rimonabant be ranked first compared to placebo (0.70 versus 0.30) and central weighting generated by the model is listed below.

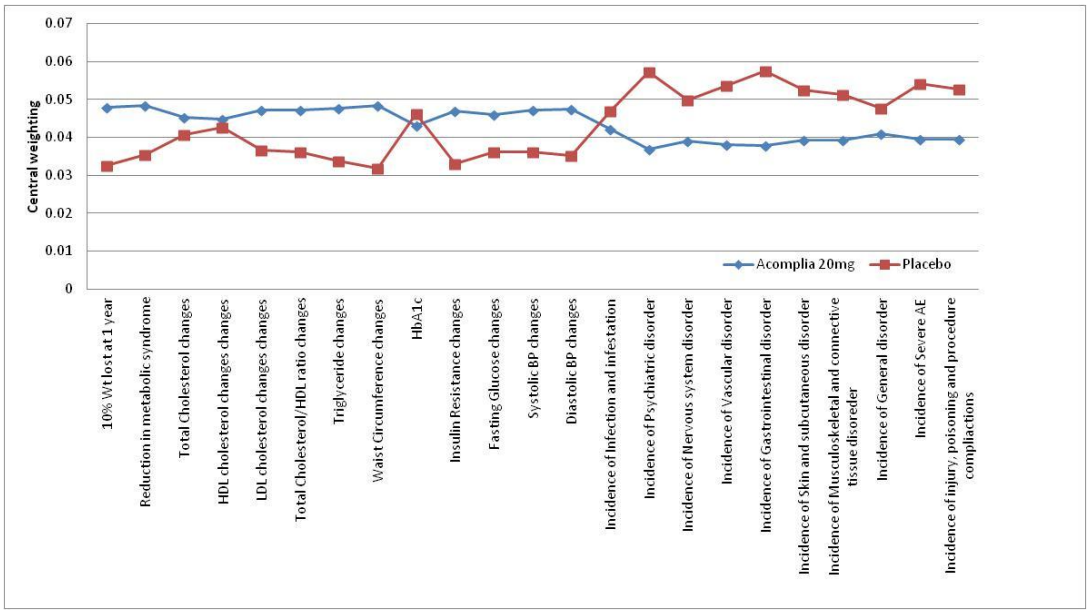


Figure 11-109 Central weighting between criteria

Figure 10-109 above showing central weighting of the 2 options. X axis listed all criteria, Y axis is weights. This demonstrates the weights combination of the criteria which will typically support the option as the preferred choice.

Model with pre-assigned weights preference

This model was calculated based on the criteria preference from results collected from the questionnaires, as shown below Figure 5-3. Interestingly, by assigning preference ranking, result from this model suggested a high preference over rimonabant (1.0 vs 0.00 Figure 10-111)

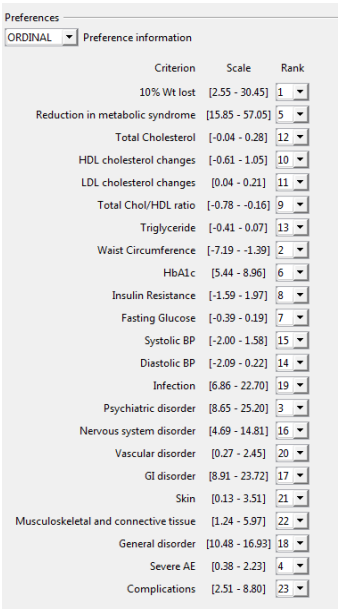


Figure 11-110 Ranking in criteria preferences

Figure 11-111 Results from model with pre-assigned weightings

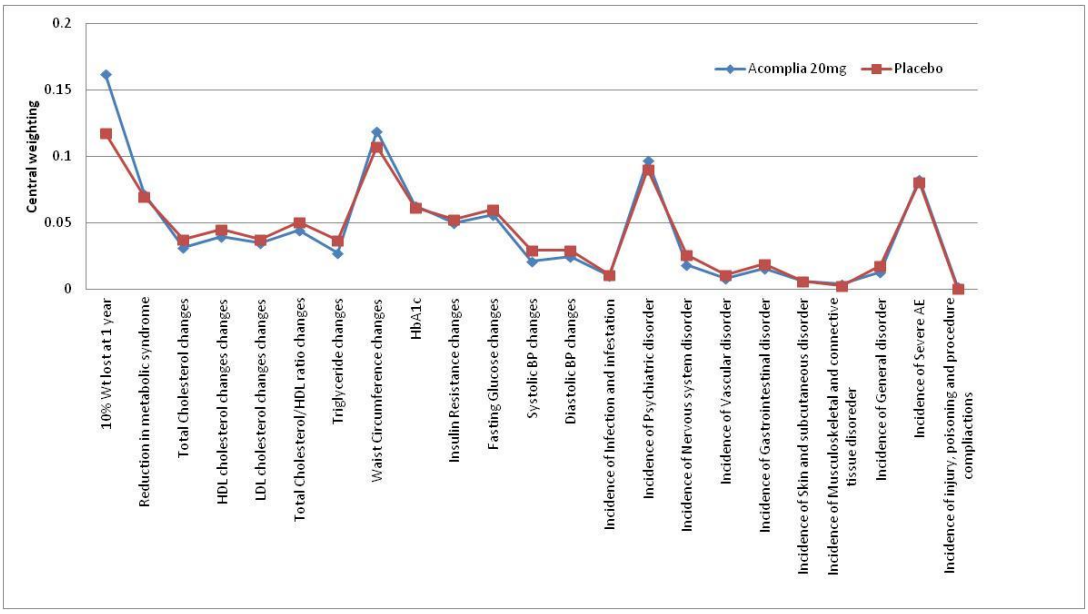


Figure 11-112 Central weightings between criteria

Figure 10-112 above showing central weightings in the 2 options. This demonstrates the combination in weights of the criteria which will typically support the option as the preferred choice. Weighting in this model were adjusted with the criteria ranking preference.

Interpretation of results

Interpretation of SMAA model is different to the MCDA model discussed in the report.

SMAA model calculates an acceptability index, which represents the proportion that the alternative achieved 1st rank in the simulations. The same process repeats for n-1 iterations for n alternatives to calculate the acceptability index of each alternative achieving the nth rank.

One benefit of SMAA is that it reports the probability of each option achieving the 1-nth rank of all alternatives. This allows decision maker to judge each alternatives not only on the probability it achieve the 1st rank but also probability which the alternative achieving the 2nd to kth rank. (kbr – k best ranks acceptability).

In this case with 2 alternatives, the interpretation of the results is intuitive. The benefit of kbr acceptability becomes more apparent when there are more than 2 alternatives. kbr acceptability helps to clarify the acceptability index when two options performs very similarly in the 1st rank, as well as avoiding bias in extreme case when one of the options outperformed other alternatives in the most preferred criterion in a large scale but not in other criteria.

It had been proposed that weight on ranking can be added to the kbr to form a holistic acceptability index to aid decision making if decision maker should decide ranking should be weighted. [25]

The central weight is an example of a set weight on criteria a typical decision maker would choose when the alternative becomes the most preferred option, depending on any preference information given by decision maker beforehand.

11.3.3.6 Assumptions

Model

Criteria value can are random variable with a joint distribution between range of data input

Criteria are independent.

Data

Events and sub criteria within different risk group are independent

11.3.3.7 Summary

Result from this SMAA model suggesting that rimonabant would be a preferred option compared to placebo. Rimonabant is associated with more beneficial effects and high risks of adverse events; this reflected in the central weighting that placebo would be the preferred option if lower weights were placed on benefits and higher weights were placed on risks.

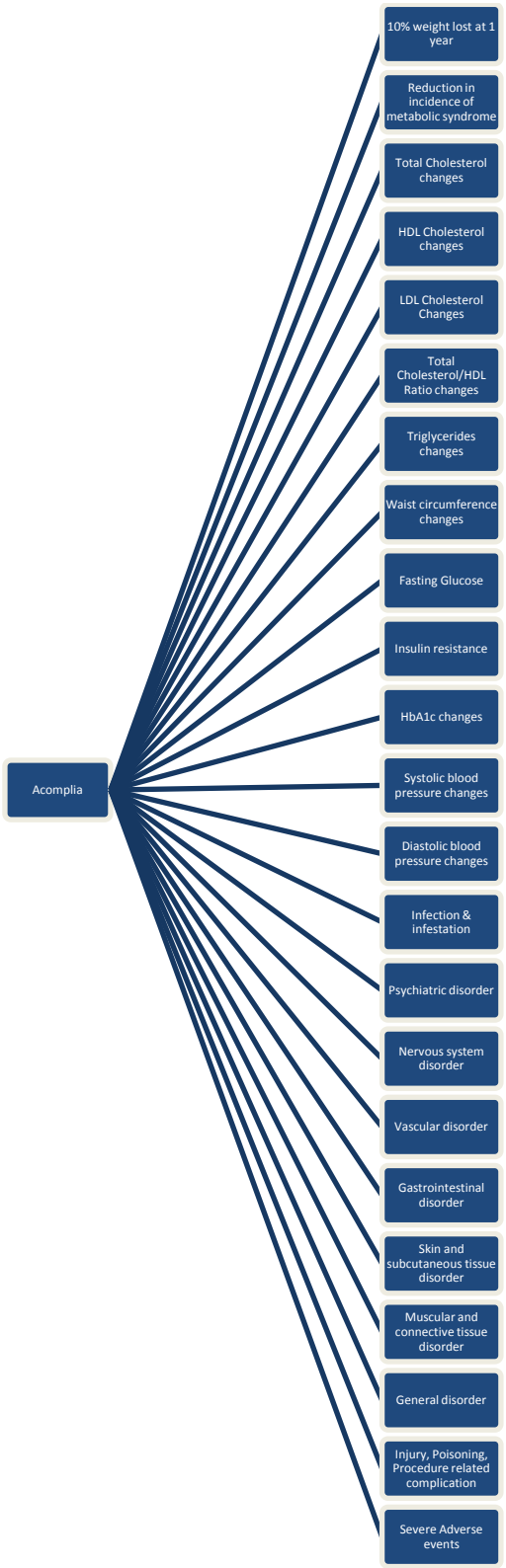
The results were more striking when ranking on criteria preference were included in the model. This model estimated acceptability index of 100% with rimonabant using the preference ranking obtained in our survey exercise. This might because of the large difference between rimonabant and placebo in these benefits reported. Within the restriction of the criteria ranking, a moderate change in weights assigned on benefits in weight lost and waist line changes and a small change in weighting on psychiatric disorder will result in Placebo to be the preferred option.

There are several advantages and disadvantages of the SMAA method.

SMAA method is able to handle uncertainties with the data, e.g. sampling variation and missing data. Also, this method does not require precise value preference from stakeholders, either in form of value function or weighting, prior to the analysis. These functions are often difficult to obtain in real life. Furthermore, SMAA is easily accessible using open software.

However, understanding the principles of SMAA require mathematical understanding of stochastic phenomena and uncertainty. The open software we used in this exercise had a limitation on number of criteria or alternatives that can be included in the model

Tree used in SMAA model



Simulation example

```
log using psychiatric.log, replace

program define acomplia_psy, rclass
syntax (, obs(integer 1) )

drop _all
 set obs `obs'

local acomplia_anxiety_rate=rbeta(140,2362)
local acomplia_insomnia_rate=rbeta(135,2367)
local acomplia_mood_alternation_rate=rbeta(120,2382)
local acomplia_depression_rate=rbeta(80,2423)
local acomplia_irritability_rate=rbeta(47,2455)
local acomplia_parasomnia_rate=rbeta(37,2465)
local acomplia_nerviousness_rate=rbeta(30,2473)
local acomplia_sleep_disorder_rate=rbeta(25,2477)

local control_anxiety_rate=rbeta(38,1563)
local control_insomnia_rate=rbeta(51,1551)
local control_mood_alternation_rate=rbeta(50,1552)
local control_depression_rate=rbeta(26,1576)
local control_irritability_rate=rbeta(10,1592)
local control_parasomnia_rate=rbeta(3,1599)
local control_nerviousness_rate=rbeta(3,1599)
local control_sleep_disorder_rate=rbeta(6,1596)

gen acomplia_anxiety = (rbinomial(1,`acomplia_anxiety_rate'))
gen acomplia_insomnia=(rbinomial(1,`acomplia_insomnia_rate'))
gen acomplia_mood_alternation=(rbinomial(1,`acomplia_mood_alternation_rate'))
gen acomplia_depression=(rbinomial(1,`acomplia_depression_rate'))
gen acomplia_irritability=(rbinomial(1,`acomplia_irritability_rate'))
gen acomplia_parasomnia=(rbinomial(1,`acomplia_parasomnia_rate'))
gen acomplia_nerviousness=(rbinomial(1,`acomplia_nerviousness_rate'))
gen acomplia_sleep_disorder=(rbinomial(1,`acomplia_sleep_disorder_rate'))

gen control_anxiety = (rbinomial(1,`control_anxiety_rate'))
gen control_insomnia=(rbinomial(1,`control_insomnia_rate'))
gen control_mood_alternation = (rbinomial(1,`control_mood_alternation_rate'))
gen control_depression=(rbinomial(1,`control_depression_rate'))
gen control_irritability = (rbinomial(1,`control_irritability_rate'))
gen control_parasomnia=(rbinomial(1,`control_parasomnia_rate'))
gen control_nerviousness = (rbinomial(1,`control_nerviousness_rate'))
gen control_sleep_disorder=(rbinomial(1,`control_sleep_disorder_rate'))

gen cond_free_acomplia=1 if acomplia_anxiety==0 ///
        & acomplia_insomnia==0 ///
        & acomplia_mood_alternation==0 ///
        & acomplia_depression==0 ///
        & acomplia_irritability==0 ///
        & acomplia_parasomnia==0 ///
        & acomplia_nerviousness==0 ///
        & acomplia_sleep_disorder==0

replace cond_free_acomplia=0 if cond_free_acomplia==.
gen cond_free_control=1 if control_anxiety==0 ///
        & control_insomnia==0 ///
        & control_mood_alternation==0 ///
```

```
        & control_depression==0 ///
        & control_irritability==0 ///
        & control_parasomnia==0 ///
        & control_nerviousness==0 ///
        & control_sleep_disorder==0

replace cond_free_control=0 if cond_free_control==.
sum cond_free_acomplia if cond_free_acomplia==0
return  scalar ave_rate_acomplia=r(N)/`obs'
sum cond_free_control if cond_free_control==0
return  scalar ave_rate_control=r(N)/`obs'

end

simulate acomplia_rate=r(ave_rate_acomplia) ///
        control_rate=r(ave_rate_control) ///
        , nodots reps(10000): ///
        acomplia_psy, obs(1000)
gen diff_rate=acomplia_rate-control_rate
sum acomplia_rate
di r(mean) - 1.96* r(sd)
di r(mean) +1.96*r(sd)
sum control_rate
di r(mean) - 1.96* r(sd)
di r(mean) +1.96*r(sd)
sum diff_rate
di r(mean) - 1.96* r(sd)
di r(mean) +1.96*r(sd)
log close
```

11.3.3.8 Weightings questionnaires

Medical/Regulator version

1 In case of weight losing medication, how would you rate the importance benefit and risk?												
	0 (Not important)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (Very important)**	**Count**
Benefit	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	66.7% (2)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	0.0% (0)	3
Risk	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	0.0% (0)	33.3% (1)	0.0% (0)	33.3% (1)	3
2. In the use of rimonabant, a drug designed for weight lost, how important are the following benefits?												
	0 (Not important)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (Very important)**	**Count**
Success in losing and maintained 10% lost of bodyweight	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	50.0% (1)	2
Improvement in cholesterol control	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	100.0% (2)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Reduce triglyceride levels	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	100.0% (2)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Reducing waist circumference	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	50.0% (1)	2
Improvement in diabetes control	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	2
Lowering blood pressure	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	100.0% (2)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Reducing incidence of metabolic syndrome	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	100.0% (2)	0.0% (0)	0.0% (0)	0.0% (0)	2
3. With regards to cholesterol control, how important is the following markers of cholesterol?												
	0 (Not important)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (Very important)**	**Count**
Total Cholesterol (Sum of Cholesterol level)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	2
HDL cholesterol ("Good Cholesterol")	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	2
LDL cholesterol ("Bad Cholesterol")	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	2
HDL/LDL cholesterol ratio	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	2
4. With regards to measurements of diabetes control, how would you rate the importance of the following markers?												
	0 (Not important)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (Very important)**	**Count**
Fasting Glucose (Use in diagnosis of diabetes)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	2
Fasting Insulin (Measurement of Insulin production)	100.0% (2)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Insulin resistance	100.0% (2)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Changes in HbA1C (Overall Diabetes control over 120 days)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	100.0% (2)	2
5 With regards to blood pressure control. How would you rate the importance of the following?												
	0 (Not important)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (Very important)**	**Count**
Systolic blood pressure (Top measurement)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	2
Diastolic blood pressure (Bottom measurement)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	50.0% (1)	2
6. With regards to weight losing medication, rimonabant, independent to its benefit. How would you rate the importance of avoiding potential negative effect in following body system?												
	0 (Not important)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (Very important)**	**Count**
Infection and Infestation	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2

Psychiatric disorder	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	50.0% (1)	0.0% (0)	2
Nervous system disorder, for example dizziness or neuralgia	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Vascular disorder, e.g. hot flushes	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Skin and subcutaneous tissue disorder	50.0% (1)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Musculoskeletal disorder	50.0% (1)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Injury, poising or procedure related complication	100.0% (2)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Severe adverse events (i.e. events that caused irreversible damage or require hospitalization)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	100.0% (2)	0.0% (0)	0.0% (0)	2

7. How would you rate the importance of the following reported side effects associated with rimonabant?

	0 (Not important)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (Very important)**	**Count**
Upper respiratory tract infection	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	2
Gastroenteritis viral	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Anxiety	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	2
Insomnia	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	2
Mood alternation with depressive symptoms	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	2
Depressive disorders	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	2
Irritability	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Parasomnia	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Nervousness	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Sleep disorders	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Dizziness	0.0% (0)	0.0% (0)	50.0% (1)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Memory loss	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	2
Hypoesthesia	0.0% (0)	0.0% (0)	50.0% (1)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Sciatica	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Hot flushes	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Nausea	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Diarrhoea	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Vomiting	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Pruritus	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Hyperhydrosis	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Tendonitis	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Muscle cramp	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Muscle spasms	0.0% (0)	50.0%	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2

		(1)										
Influenza	50.0% (1)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Asthenia/Fatigue	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Joint sprain	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Contusion	100.0% (2)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Fall	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Death	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	2
Overall Psychiatric disorder	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	100.0% (2)	2
Cardiac disorder	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	2
Urinary disorder	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2
Road traffic accident	50.0% (1)	50.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	2

11.4 Sub-team 2 specific findings report

Authors: Johan Bring, Ian Hirsch, John Pears

11.4.1 BRAT Benefit Risk Action Team (BRAT) guidelines

The framework is developed by Pharmaceutical Research and Manufacturers of America (PhRMA) Benefit-Risk Action Team (BRAT), which aims to guide decision-makers in selecting, organizing, understanding and summarizing the evidence relevant to benefit-risk decisions. The guidelines consciously proposed avoiding integration of benefits and risks evidence, but instead advocates assessing them separately in order to make it more accessible and transparent to those not familiar with complex statistical models. The BRAT framework emphasis the value tree (criteria tree) build-up, data selection, data preparation and summarization. It focuses on the comparison of new drug and a comparator. The benefits and risks are not integrated for assessment in this framework, but are assessed separately. It is primarily a framework for pharmaceutical companies to collect all available and relevant evidences of a new drug in a standard way to facilitate communication with regulatory authorities. The use of such framework can increase the transparency, predictability and consistency with which benefit-risk assessments are conducted. The tabular output delivers benefit-risk information to patients, healthcare professionals and regulators as a basis for their own decisions based on individual preferences. Figure 11-113 illustrates the six steps to be completed in the process. In the following sections we'll go through each step for the rimonabant case-study. As a guidance we have used the articles by Levitan et al [19], Coplan et al [20] and the User's Guide [21].

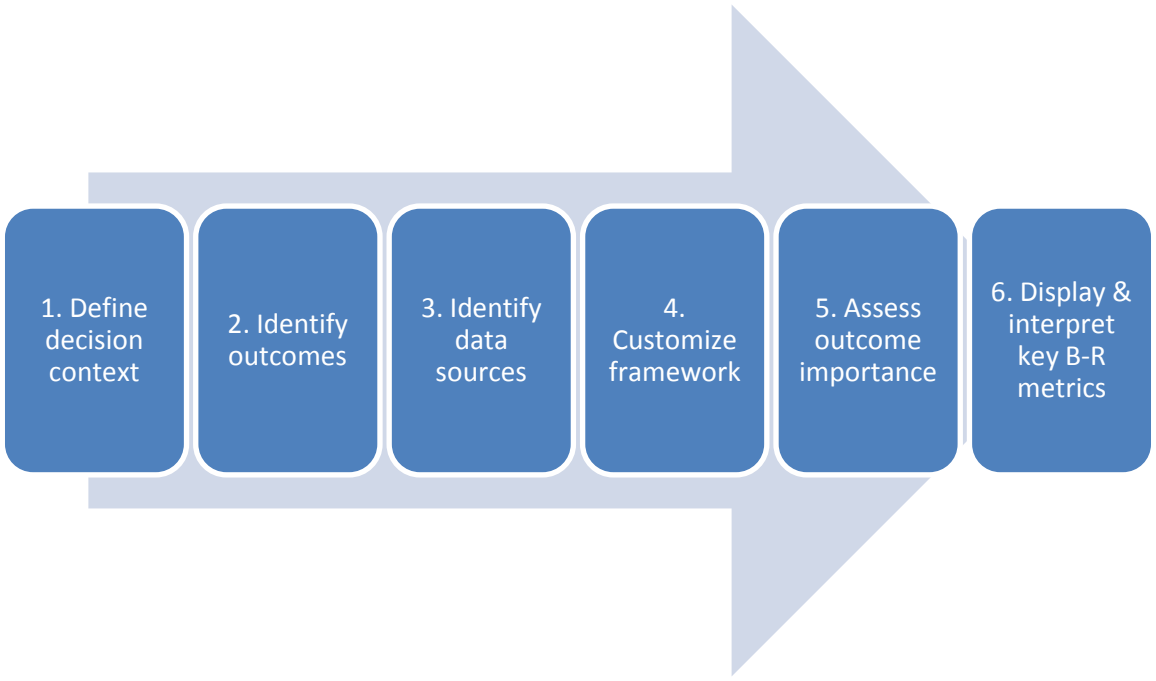


Figure 11-113 The steps in the BRAT assessment framework

11.4.2 Objectives

The objectives of this case study are:

a. To assess the feasibility and suitability of the approaches using BRAT model for benefit-risk assessment of drugs by the regulator, having considered other stakeholders' perspectives using rimonabant as a model;

b. To evaluate the benefit-risk balance of rimonabant 20mg at marketing authorization approval using the BRAT model.

11.4.3 Define the decision context

In Table 11-6 we have summarized the key information regarding the context. The most important decision for us was the choice to use the regulators perspective. Plausible alternatives could have been the perspectives from patients, payers, the company or from physicians. We did not choose patient's perspective because of time limitation to collect data from patients or from pharmaceutical companies.

Table 11-6 The decision context

Indication	Overweight
Drug	Rimonabant
Dosage	20mg
Comparator	Placebo
Population	Body-mass index (BMI) greater than or equal to 30 kg/m2, or a BMI of 27.0‑29.9 kg/m2 with one or more major obesity-related comorbidities.
Time horizon for outcomes	One year
Stakeholder perspective	Regulatory

11.4.4 Identify outcomes

In the User's guide it state that:

All possible outcomes that are likely to have a substantial impact on the benefit risk balance should be considered. (Users Guide, p. 12)

In the IMI group we decided to include all outcomes from the EPAR. A value tree based on all outcomes becomes rather extensive. Figure 11-114 is drawn with the software FreeMind[1] and Figure 11-115 with the ´BRAT-software'[2].

[1] http://freemind.sourceforge.net/wiki/index.php/Download

[2] Provided by The Benefit-Risk Action Team, PhRMA 950 F St. N.W. Suite 300, Washington DC 20004

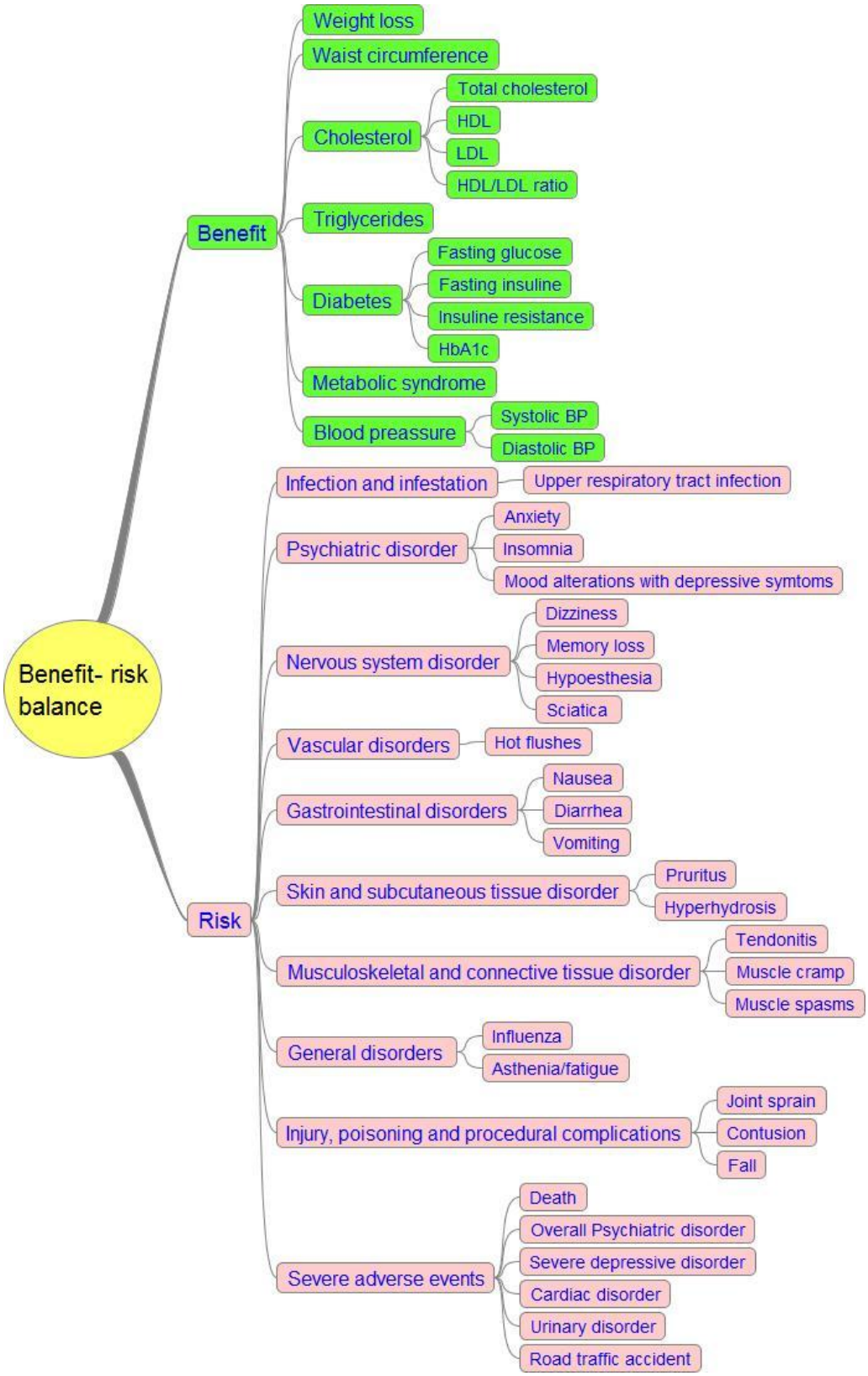


Figure 11-114 Value tree for possible risks and benefits. (using the FreeMind software)

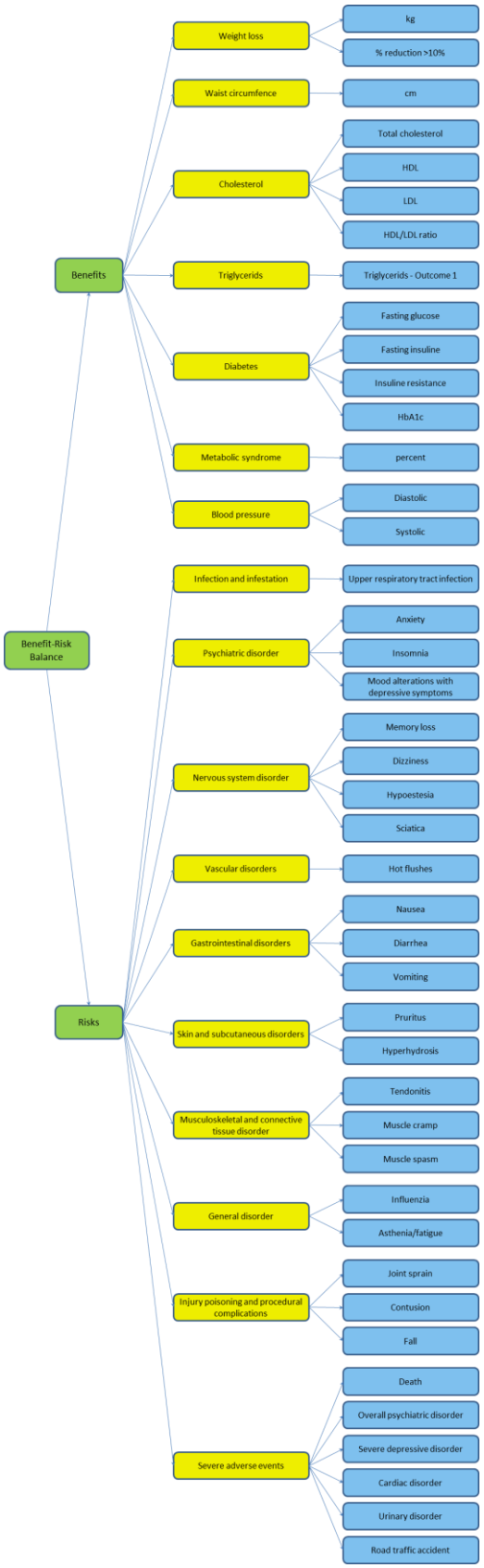


Figure 11-115 Value tree for possible risks and benefits. (using the BRAT-software)

NOTE 1:

Since we decided to use the outcomes listed in EPAR this step became rather straightforward. Otherwise it could be tricky to decide which outcomes to include in this step. However, in this step it's better to include too many rather than too few outcomes. In step 4 the number of outcomes is reduced and in that step it's more crucial to not miss an important outcome.

NOTE 2:

In the User's Guide (page 17-20) they differentiate in the value tree between 'known benefit or risk outcomes' and 'potential benefit or risk outcomes'. It's unclear how to decide which outcomes that should be considered as 'known' and which should be considered as 'potential'. One option would be to use statistically significance as a criterion for this classification. 'Potential benefit or risk outcomes' could include outcomes that were not significant but numerically suggestive or could include important outcomes without enough data to assess statistically.

NOTE 3:

In the User's Guide they select measures for the outcomes in this step. We think it's better to do this in step 4 instead. First, all variables in the tree will not be used in the end and it's then a waste of time to work on finding appropriate measures for these outcomes. Moreover, in step 3 the data sources are selected and it seems more natural to select outcome measures when the data sources have been identified so we know which measures are available.

11.4.5 Identify and extract source data

We decided to mainly use the EPAR-data plus additional data published in the literature because there is limited information available at EMA website after submission. The EPAR data is primarily based on the four RIO-studies. The reason for only using data from these studies is…CHECK …In Table 11-7 there is a summary of the four trials.

Table 11-7 Summary of the four RIO-studies (table taken from Christensen et al 2007[22])

	Year	ITT* individuals	Women	Age (years)	BMI (kg/m²)	Weight (kg)	Glucose (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	Metabolic syndrome	Smokers	Definite sample size (ITT)	
												n_E	n_C
RIO-Europe[10]	2005	904	722 (80%)	44·7 (11·8)	36·0 (5·8)	101·1 (19·8)	5·27 (0·70)	1·45 (0·86)	1·27 (0·33)	372 (41%)	162 (18%)	599	305
RIO-Lipids[11]	2005	688	411 (60%)	47·7 (10·0)	33·9 (3·4)	96·1 (15·2)	5·29 (0·62)	2·08 (1·18)	1·11 (0·25)	361 (52%)	114 (17%)	346	342
RIO-North America[12]	2006	1826	1483 (81%)	45·3 (11·7)	37·3 (6·3)	103·7 (20·8)	5·11 (0·61)	1·53 (0·88)	1·27 (0·33)	611 (33%)	182 (10%)	1219	607
RIO-Diabetes[13]	2006	687	360 (52%)	55·4 (8·6)	34·2 (3·6)	97·3 (14·8)	8·35 (2·20)	2·02 (1·17)	1·16 (0·26)	538 (78%)	81 (12%)	339	348

Data are number (%) or mean (SD). ITT=intention to treat. BMI=body-mass index. TG=triglycerides. HDL-C=high-density lipoprotein cholesterol. *The number of ITT individuals is based on patients allocated to the rimonabant 20 mg and placebo groups, respectively; patients receiving rimonabant 5 mg were excluded. n_E and n_C are the number of individuals in the exposed and control group (ie, rimonabant and placebo), respectively.

Table 1: **Summary of baseline characteristics of all participants in the eligible trials**

All relevant data has been compiled in an Excel file ("Acomplia_data_111007.xls") Table 11-8 shows the basic data structure of the file.

Table 11-8 Basic structure of the data file for relevant data.

Criteria (benefit)	End point	Study	Treatment	N enrolled	N completed at exit	5% Responded n	5 % Responded Rate(%)	10% responded n	10% Responde Rate(%)
Weight lost 10% and maintainence at year 1	Primary	RIO-North America Yr 1 EFC4743	Rimonabant 5mg	1214	620	317	26.1	129	10.6
			Rimonabant 20mg	1219	673	578	48.6	300	25.2
			Placebo	607	309	118	20.0	50	8.5
		RIO - Europe EFC 4733	Rimonabant 5mg	603	379	126	33.2	38	10.1
			Rimonabant 20mg	599	363	303	50.9	163	27.4
			Placebo	305	178	58	19.2	22	7.3
		RIO - Lipids EFC4735	Rimonabant 5mg	345	208	N/A	N/A	N/A	N/A
			Rimonabant 20mg	346	221	201	58.4	112	32.6
			Placebo	342	214	65	19.5	24	7.2
		RIO - Diabetes	Rimonabant 5mg	359	232	77	21.7	22	6.2
			Rimonabant 20mg	339	229	166	49.4	55	16.4
			Placebo	348	231	50	14.5	7	2.0
						Baseline	sd	Exit	sd
Total Cholesterol [mmol/L]	Secondary	RIO - Europe EFC 4733	Rimonabant 5mg	603	379	5.37	0.92	5.43	0.86
			Rimonabant 20mg	599	363	5.37	1.00	5.42	0.98
			Placebo	305	178	5.29	1.00	5.37	1.01
		RIO - Diabetes	Rimonabant 5mg	359	232	4.99	0.49		
			Rimonabant 20mg	339	229	5.06	0.97		
			Placebo	348	231	5.00	0.96		
		RIO - Lipids EFC4735	Rimonabant 5mg	345	208	6.03	0.81		
			Rimonabant 20mg	346	221	5.91	0.91		
			Placebo	342	214	6.01	0.86		
Total Cholesterol [%]		RIO - Lipids EFC4735	Rimonabant 5mg	345	208				
			Rimonabant 20mg	346	221				
			Placebo	342	214				

NOTE 4:

The data from the RIO-studies have been analysed and summarised by Christensen et al 2007.

FDA has also summarized these data (FDA 2007). This saved us a lot of time.

11.4.6 Customize framework

In this step we'll 'tune' the value tree and select which outcomes to use. We'll also decide which measures to use for each outcome. This task was accomplished by a telephone conference[3]. Even though the participants had no experience with the BRAT framework they rapidly were able to immerse themselves in the discussion in a useful way.

NOTE 5: A general conclusion was that it was very difficult to exclude outcomes. For most outcomes there were arguments why the particular outcome was relevant to keep. A general impression was that the participants really wanted to see 'the whole picture' and not just a summary of the key outcomes. Another issues that came out of the discussion was that we were doing it with the benefit of hindsight; especially an issue for the risks around CNS/psychiatry.

NOTE 6: Johan Bring argued for excluding outcomes where there was no difference between the treatments. Johan's argument was that if there is no difference between the two treatments with respect to a specific outcome this outcome should not influence a risk-benefit analysis. The other participants were not convinced and preferred to keep even these outcomes. This was based on the fact that having no difference for key outcomes could help in interpreting the risk-benefit of the drug.

[3] Johan Bring, Dr. Björn Carlsson, Dr. Jan Eriksson, Ian Hirsch, John Pears

NOTE 7: Some outcomes could be seen as both benefits and risks. E.g. a reduced blood pressure could be a benefit but an increased blood pressure could be a risk. Hence, it's not obvious if some outcomes should be classified as benefits or risks.

NOTE 8: A question raised was if the selection of outcomes should be influenced by the data or if the selection should be done independent of the data. We agreed that the decision at this step should be guided by the data while the selection of outcomes in step 2 of the process should be independent of the data.

11.4.6.1 Reduction of the benefits in the value tree

A telephone conference was held to discuss how to reduce the number of outcomes. Table 11-9 and Table 11-11 (Section 11.4.11.1) summarizes part of our decisions.

Table 11-9 Benefits criteria evaluated at the telephone conference

Level 2 criteria	Level 3 criteria	Keep	Exclude	Comment
Weight loss at 1 year		X (A)		Key readout
Cholesterol changes	Total cholesterol		X	
	HDL cholesterol		X	Nice to have
	LDL cholesterol	X (B)		Key readout for CV-risk assessment
	HDL/LDL cholesterol ratio		X	
Triglyceride control		X (C)		
Waist circumference		X (A)		
Diabetes control	Fasting glucose		X	Nice to have
	Fasting insulin		X	Emerging CV-risk factor
	Insulin resistance		X	Nice to have. Expected to improve if HbA1c lowering seen.
	HbA1c	*X (*)*		Key readout
Blood pressure	Systolic control	X (A)		Key readout for CV-risk assessment
	Diastolic control	X (C)		Key readout for CV-risk assessment
Metabolic syndrome			X	Several definitions

** relevant for diabetics*

The majority of the participants in the telephone conference voted for keeping all the outcomes in the 'keep' column. However, for illustrative purposes we'll only use the three outcomes marked with an A in the 'keep' column.

11.4.6.2 Selection of measures for the chosen benefits

Weight loss: Here we have the choice between weight reduction in kg or the proportion of patients with a reduction greater than 10% (responders). To use responders is more convenient but it's not using as much information as the actual weight reduction. We choose the proportion responders/non-responders for convenience and illustrative purposes.

Waist circumference: For this variable the only measure we have is average reduction in centimeters.

Systolic blood pressure: For this outcome we only have the average change in mmHg per group.

11.4.6.3 Reduction of the risks in the value tree

The table with risk outcomes and the selection is given in Sub-appendix 1 (Section 11.4.11.1). The same problem occurred as with the benefits that it was very difficult to exclude any outcome. The participants had good arguments why most of the risks were interesting to evaluate in a risk- benefit analysis. For illustrative purposes we will focus on three level 2 outcomes: psychiatric disorders, nervous system disorders and severe adverse events.

NOTE 9: To only get information about a few risks at level 2 will not be sufficient to make a reasonable risk- benefit assessment. Information at level 2 is too coarse to really be informative. An increased risk for e.g. psychiatric disorder can have very different implications if it's 'irritability' or 'depressive disorder'.

11.4.6.4 Summary of the outcomes used for further analysis

In Figure 11-116 a reduced value tree is presented. However, as mentioned before, most participants were not content with this reduction arguing for keeping many more outcomes. We compromised on the reduced value tree for this case study for illustration and due to limited time available.

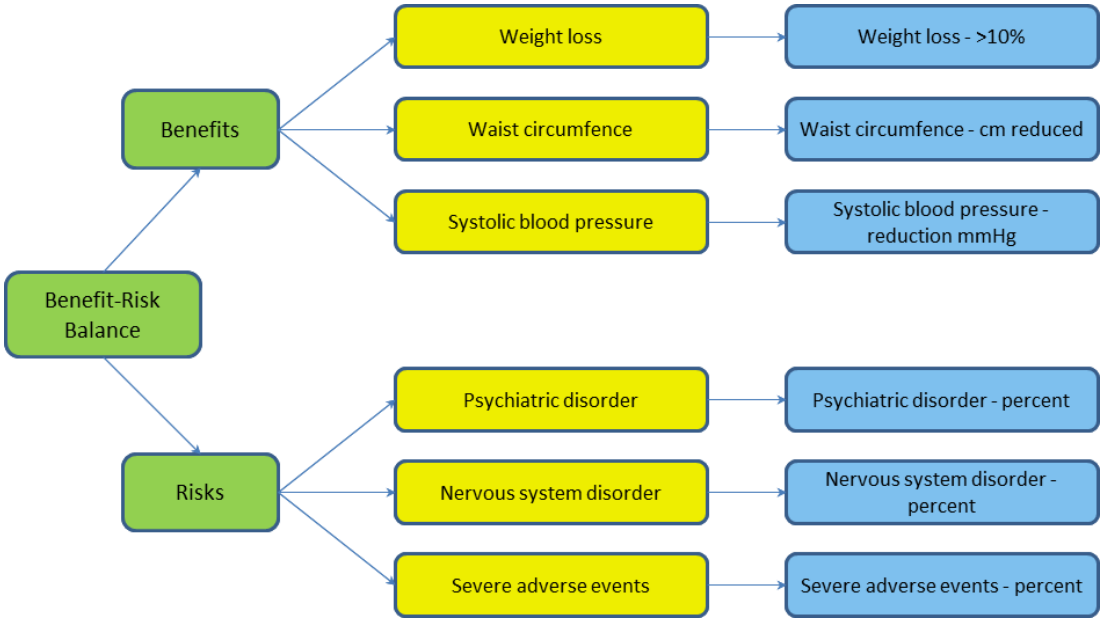


Figure 11-116 A reduced value tree

NOTE 10: If this had been a real application there would be a need for much better documentation regarding all decisions made. Why do we choose to keep some outcomes and exclude others. In this study we had 1.5 hour telephone conference to discuss these issues which was not sufficient to be able to get good documentation. In a real application this step must be given much more time. Time for face-to-face discussions would also be needed because we found telephone conference might not be sufficient to disentangle any disagreement.

11.4.7 Assess outcome importance

To be able to assess the importance of different outcomes they have to be studied in more detail. Especially when we chose to present the risks at level 2. The importance of a psychiatric adverse event is of course dependent on the type of event and the severity of the event. Since this step is not a prerequisite for the BRAT method we decided to not assess any ranking of the outcomes chosen. However, a kind of importance assessment is done when you trim the tree in step 4.

11.4.8 Display & interpret key B-R metrics

In the final step the results are displayed to give the decision-maker a good overview of the results. There are two main modes of presentation: the summary table and the forest plot. In Table 11-10 the main results are summarized.

Table 11-10 The estimated treatment effect for different outcomes (95% confidence intervals)

	Outcome	Rimonabant	Placebo	Difference
Benefits	Weight loss (kg) [a]	-6.3 kg	-1.6 kg	4.7 kg (4.1-5.3)
	Weight loss >10% [a]	25.5% (23.8 , 27.3)	6.6% (5.5 , 7.9)	19% (17 , 22) OR=5.1 (3.6 – 7.3)
	Waist circumference changes (cm) [b]	-6.2 (-7.2 , -5.2))	-1.9 (-2.3 , -1.4))	-4.3 (-5.5 , -3.0)
	Systolic blood pressure [b]	-1.3 (-2.0 , -0.5)	0.5 (-0.6 , 1.6)	-1.8 (-2.8 , -0.8)
Risks	Psychiatric adverse event [c]	26.2% (24.5 , 28.0)	14.1% (12.4 , 15.9)	12.1% (10 , 15) OR=1.9 (1.5 , 2.3)
	Neurological Adverse Event [c]	27.4% (25.7 , 29.2)	24.4% (22.3 , 26.6)	3.0% (0.5 , 5.5) OR=1.7 (1.1 , 2.7)*
	Serious adverse event [a]	5.9% (5.0 , 6.9)	4.2% (3.3, 5.3)	1.7% (0.4 , 3.0) OR=1.43 (1.03 , 1.98)

[a] Christensen (2007)
[b] Chan Edmond simulations
[c] FDA Briefing document
* The proportion of subjects with an adverse event (27.4 and 24.4% respectively) is not compatible with an odds ratio of 1.7.

The other important display within the BRAT-framework is the forest plot. The two options available in the BRAT-software are to present the results as risk differences or relative risks (or odds ratios). However, two of our outcomes are measured in centimetres and mmHg. The treatment effects for these outcomes are not naturally presented as either risk differences or relative risks. Hence, in Figure 11-117 there is no output for two of the outcomes. In Figure 11-118 the forest for odds ratios we have excluded these two outcomes. This could be seen as a key limitation of the current software.[4] In both Figure 11-117 and Figure 11-118, orange rectangles represent confidence intervals for benefits and blue boxes confidence intervals for risks.

[4] The next version of the software intends to address the issue of commonly used "change from baseline" measurements such as we have here with centimeters and mmHg.

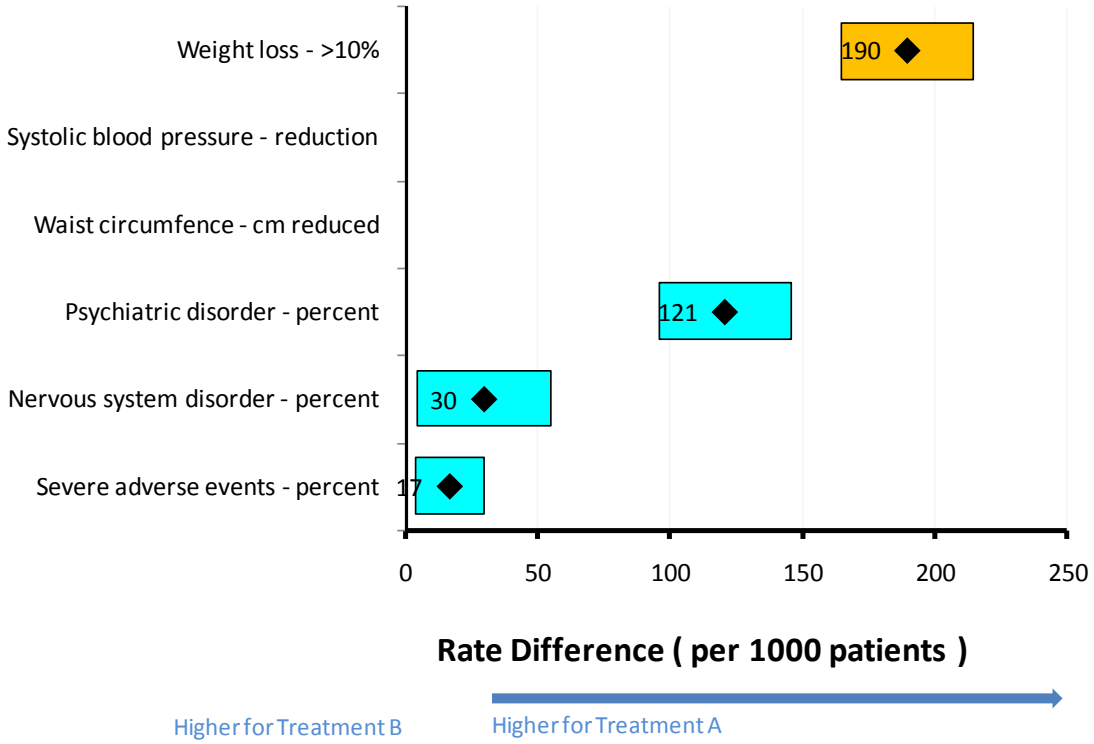


Figure 11-117 Forest plot for risk differences between rimonabant (treatment A) and placebo (treatment B) (The number in the box is a point estimate and the width of the box is the confidence interval. Yellow is Benefit, blue is Risk)

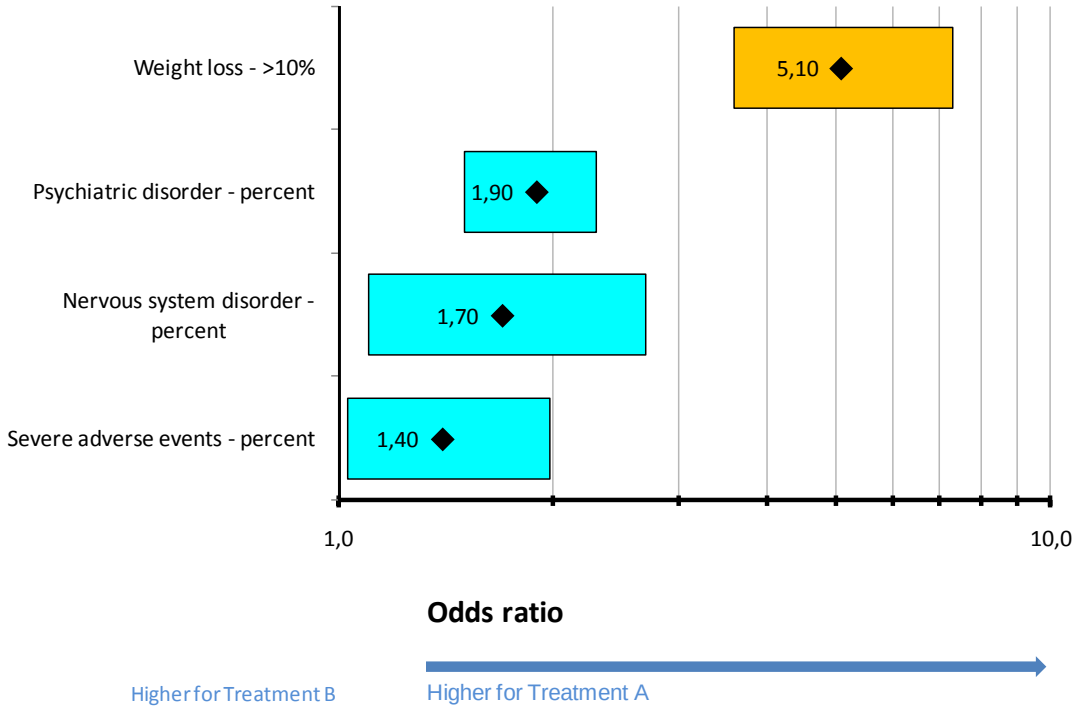


Figure 11-118 Forest plot for odds ratios between rimonabant (treatment A) and placebo (treatment B). (The number in the box is a point estimate and the width of the box is the confidence interval. Yellow is Benefit, blue is Risk)

NOTE 10: The forest plot is most suitable when all outcomes can be measured in the same metric, e.g. percent. Even if it's possible to categorize all outcomes this will not be the natural way to present some types of outcomes (e.g. reduction in waist circumference) and a lot of information will be lost.

11.4.9 Software

Value tree

One important characteristic of the BRAT-method is the construction of a value tree to display possible outcomes. In the Users's Guide they refer to the software BRAT Framework tool. We had problems getting the program to work properly. It's probably a language problem since we used the Swedish language in the Excel installation. (See sub-appendix 2 in Section 11.4.11.2 for the error message received.)

Before we managed to get the software working we produced a value tree using the Open Source software FreeMind[5]. There is no big difference between the two softwares with respect to creating value trees. However the BRAT-software is designed specifically for this type of applications and by creating the value tree in this software many other useful outputs become available.

Summary table

The BRAT-method is also associated with a summary table summarizing all the risks and benefits. This is nicely produced in the software but could also easily be produced in Microsoft Word.

Forest plot

Another characteristic of the BRAT-method is to display the outcomes in a forest plot. This graphical presentation is common in meta-analyses and can rather easily be produced in standard statistical softwares.

11.4.10 Summary

The BRAT framework is a very well structured approach to address a benefit-risk task. The first three steps in the process are rather straight forward. However, during steps 4-6 several issues have arisen.

Step 4: How to reduce the number of outcomes to a manageable size.

The participants in our working group were eager to keep many outcomes both regarding risks and benefits. They felt a need to see 'the whole picture' and were not comfortable by reducing the number of outcomes to just a few. This underscores one of the purposes of the Framework – its ability to indicate where discussion is needed by helping identify areas of non-agreement There is nothing in the method that prevents the user from keeping many outcomes but in the way the method is presented in papers and guidelines one advantage with the method is to get a condensed summary based on a few outcomes.

Step 5: Assess outcome importance.

[5] A software to create MindMaps.

If outcomes are presented at a coarse level (level 2) it is very difficult to assess their importance since it is unclear what they are actually measuring. If we had more time to spend on this case-study it would have been useful to choose risks at a more detailed level (level 3).

Step 6: Display the results.

The BRAT framework uses summary tables and forest plots as the primary output. However, for this output to be comparable it requires that all outcomes are measured using the same metric. In our case it was e.g. difficult to compare the average reduction in waist circumference with proportion of subjects getting a specific adverse event.

11.4.11 Sub Appendix

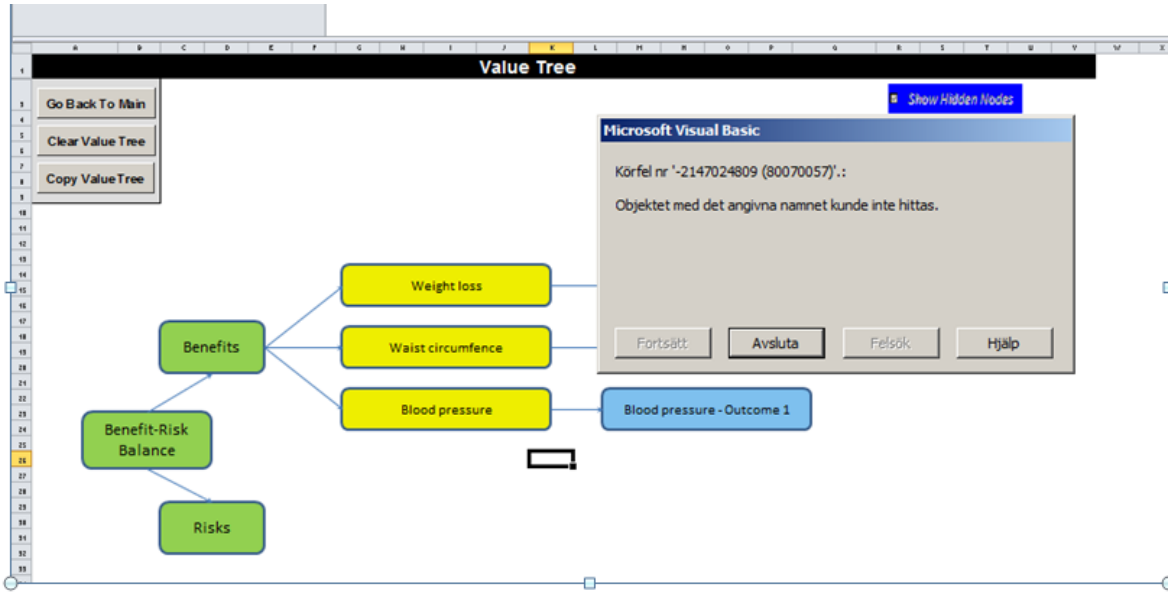
11.4.11.1 Sub Appendix 1

Table 11-11 Risks criteria to be evaluated

Level 2 criteria	Level 3 criteria	Keep	Exclude	Comment
Infection and infestation	Upper respiratory tract infection		x	
	Gastroenteritis viral		x	
Psychiatric disorder	Anxiety (A)	X		Signal and need to evaluate CNS safety based on experience from CNS acting weight loss drugs
	Insomnia	X		Signal and need to evaluate CNS safety based on experience from CNS acting weight loss drugs
	Mood alternation with depressive symptoms(B)	X		Signal and need to evaluate CNS safety based on experience from CNS acting weight loss drugs
	Depressive disorders(A)	X		Signal and need to evaluate CNS safety based on experience from CNS acting weight loss drugs. (same comment for all CNS related AEs below
	Irritability	X		
	Parasomnia	X		
	Nervousness	X		
	Sleep disorders	X		
Nervous system disorders	Dizziness	X		
	Memory loss	X		
	Hypoesthesia	X		
	Sciatica	X		
Vascular disorders	Hot flushes			

Gastrointestinal disorders	Nausea	X		Common issue with weight loss drugs
	Diarrhoea	X		
	Vomiting	X		
Skin and Subcutaneous Tissue disorder	Pruritus		x	
	Hyperhydrosis		x	
Musculoskeletal and connective tissue disorder	Tendonitis		x	
	Muscle cramp		x	
	Muscle spasms		x	
General disorder	Influenza		x	
	Asthenia/Fatigue	X		
Injury, Poisoning and Procedural complications	Joint sprain		x	
	Contusion		x	
	Fall		x	
Severe Adverse Events	*Death*	*x*		
	Overall Psychiatric disorder	*x*		
	Severe Depressive disorder	*x*		
	Cardiac disorder	*x*		
	Urinary disorder		*x*	
	Road traffic accident		*x*	

11.4.11.2 Sub Appendix 2



Translation of the error message: *"Runerror nr ……. The object with the given name could not be found"*

11.5 Sub-team 3 specific findings report

Author: Shahrul Mt-Isa, Ed Chan, Georgy Genov, Juhaeri Juhaeri

11.5.1 Introduction

11.5.1.1 Background

The details of the clinical problems and the decision frame for rimonabant have been described in the main body of the report (Section 1). Sub-team 3 investigates the performance of a group of recommended approaches to quantify benefit-risk assessment.

The main task of sub-team 3 is to evaluate the recently proposed metric indices, the impact numbers . [6, 8-10, 23] Impact numbers are a family of metric indices based on rates of events. Probabilistic simulations method is used to estimate impact numbers to take into account uncertainties in the parameters. PrOACT-URL is used to frame the problems and to guide the process. Trade-offs between benefits and risks are also considered using the benefit-risk ratio and net clinical benefit metrics. This is because impact numbers, probabilistic simulation method and PrOACT-URL do not explicitly warrant benefit-risk trade-off. The net clinical benefit used in this case study does not directly correspond to the NCB framework in the PROTECT methodology report but only the NCB metric described within the framework, which the functional form is herewith established.

11.5.1.2 Objectives

The objectives of sub-team 3 are to evaluate the potential use of:

(i) PrOACT-URL as the guideline to conducting benefit-risk assessment in the absence of a structured framework;

(ii) impact numbers to quantify benefits and risks; and

(iii) probabilistic simulation to take into account statistical uncertainties in the outcome

11.5.1.3 Alternatives

In this case study, rimonabant is compared to placebo as the alternative treatment for weight loss. The choice of placebo as an alternative was discussed and agreed in the kick-off meeting on 23rd August 2011 via teleconference. This decision was made on several grounds:

(i) the first line of treatment for weight loss is lifestyle intervention such as diet changes and exercise there are no data or very limited data directly comparing rimonabant to lifestyle interventions;

(ii) Orlistat and sibutramine were also considered as alternatives but the time limit for wave 1 case study does not allow us to pursue in that direction;

(iii) placebo is a simpler and more straightforward alternative;

(iv) placebo is the obvious alternative for regulatory perspective

11.5.1.4 Report structure

Section 11.5.2 describes the benefit-risk approaches in more detail. It also describes and presents the evidence data to be used. The analyses strategy including hypothetical scenarios and planned sensitivity analyses are defined.

Section 11.5.3 presents the benefit-risk assessment results separately by hypothetical scenarios in the first instance followed by a comparison of the results from all scenarios. The results are organised into the consequences of choosing an alternative by criteria, the trade-offs between criteria, and the effect of uncertainties on the trade-offs.

Section 11.5.4 discusses the results in terms of the benefit-risk profiles of rimonabant obtained from the impact numbers simulation analyses. The effects of uncertainties and changing assumptions are also discussed. The risk tolerance as might be judged by the relevant decision-maker and its effect on the balance is then discussed. Previous decisions on rimonabant are briefly discussed and compared. Finally, the use of chosen approaches are discussed and evaluated as a combined benefit-risk assessment strategy.

Section 11.5.5 concludes the findings from sub-team 3. Stata programmes developed to facilitate impact numbers simulations are given in file “Rimonabant Case Study Final Report Supplement”

11.5.2 Methods

11.5.2.1 Foreword

This section first introduces the case study scenarios we have chosen for the application of impact numbers simulation (Section 11.5.2.2). Evidence data available and required for impact numbers analysis and probabilistic simulation are listed in relation to the hypothetical scenarios (Section 11.5.2.3). More details on the benefit-risk approaches to be tested in this case study are discussed in Sections 11.5.2.4 – 11.5.2.6. We also discuss how benefit-risk trade-off could be carried out (Section 11.5.2.7) and the planned sensitivity analyses (Section 11.5.2.8). To help facilitate the application of impact numbers through probabilistic simulations, we developed computer programmes and are briefly described in Section 11.5.2.9.

11.5.2.2 Hypothetical case study scenarios

We consider two populations for which the impact numbers are to be calculated:

(i) Trials population at the marketing authorisation application time point

In this scenario, we seek to estimate the impact of exposing the trial participants to rimonabant 20mg intervention. The choice of this scenario is made to assess whether impact numbers can be used to characterise benefits and risks experienced by clinical trials' participants (under trial's conditions).

(ii) The population of England and Wales

In this scenario, we seek to estimate the public health impact in the year following marketing authorisation of rimonabant in the UK. The choice of this scenario is made to assess whether impact numbers can be used in real life regulatory activities such as for marketing authorisation approval or withdrawal in this case study.

For both scenarios, we run impact number analysis for year 2006 when rimonabant just came on the market, where evidence of benefits and risks were only from the four pivotal trials. [2, 5, 11, 12]Additional evidence from another trial [14] was available in 2008. We rerun impact number analysis for England and Wales for year 2008 with the additional evidence.

11.5.2.3 Evidence data

Benefit and risk criteria data

We considered data from EPAR on four trials. [2, 5, 11, 12]Since impact numbers only deal with rates of events, we have not considered reported continuous endpoints in the analysis. It is possible to categorise continuous endpoints but we have not done this due to the difficulty in establishing appropriate cut points.

We performed random effect meta-analysis on benefit outcomes to estimate the relative risk from the four trials, and used the pooled rates of adverse events reported on EPAR for risks for which we calculated their relative risks. The relative risks and their corresponding baseline risk in the placebo group are listed in Table 11-12 by criterion.

Table 11-12 Benefit and risk criteria from RIO trials

	Criterion	Placebo rates (%)	Relative risk (95% CI)
Benefits	10% weight loss at 1 year	6.11	3.75 (3.08,4.57)
	Reduction in metabolic syndrome	21.17	1.96 (1.67,2.29)
Risks	Upper respiratory tract infection	11.45	1.08 (0.91,1.29)
	Gastroenteritis viral	2.90	1.25 (0.88,1.78)
	Anxiety	2.40	2.36 (1.66,3.36)
	Insomnia	3.21	1.69 (1.24,2.32)
	Mood alterations with depressive symptom	3.15	1.54 (1.11,2.12)
	Depressive disorders	1.65	1.97 (1.27,3.05)
	Irritability	0.66	3.07 (1.56,6.05)
	Parasomnia	0.22	8.11 (2.51,26.22)
	Nervousness	0.22	6.40 (1.96,20.94)
	Sleep disorders	0.41	2.67 (1.10,6.49)
	Dizziness	4.90	1.54 (1.19,1.99)
	Memory loss	0.90	1.83 (1.00,3.35)
	Hypoesthesia	0.66	2.56 (1.28,5.10)
	Sciatica	0.41	2.67 (1.10,6.49)
	Hot flushes	0.72	2.79 (1.45,5.36)
	Nausea	4.90	2.45 (1.92,3.11)
	Diarrhoea	4.83	1.31 (1.01,1.71)
	Vomiting	2.21	1.83 (1.25,2.67)
	Pruritus	0.53	2.40 (1.10,5.22)
	Hyperhydrosis	0.53	2.40 (1.10,5.22)
	Tendonitis	1.03	2.12 (1.22,3.70)
	Muscle cramp	1.03	1.40 (0.78,2.52)
	Muscle spasms	0.53	2.00 (0.90,4.42)
	Influenza	8.64	1.03 (0.84,1.27)
	Asthenia/Fatigue	5.02	1.20 (0.92,1.56)
	Joint sprain	2.15	1.41 (0.95,2.11)
	Confusion	0.66	3.52 (1.80,6.89)
	Fall	1.40	1.40 (0.85,2.30)
	Death	0.28	0.64 (0.16,2.56)
	All Psychiatric disorder	0.16	3.84 (0.86,17.14)
	Severe Depressive disorder	0.03	8.32 (0.47,147.63)
	Cardiac disorder	0.28	1.92 (0.62,5.94)
	Urinary disorder	0.16	2.88 (0.62,13.31)
	RTA	0.03	8.32 (0.47,147.63)

Population of interest data

Data from the population of interest where intervention is targeted is required in the application of impact numbers analysis. This ensures that the results from the analysis are directly transferrable to the intended population and therefore allows any decision made to be carried out more efficiently and within context of the analysis.

The following data are required:

i. baseline risk of the events in the population (I_u)

ii. proportion of people eligible for rimonabant (P_e)

iii. prevalence of overweight and obesity in the population (P_d)

iv. the size of the population of interest (n_s)

v. the size of the sample (ν_1, ν_2, ν_3) where i-iii were estimated from

In this exercise, we were unable to obtain baseline risks I_u data for the criteria. For this reason, we made the assumption that the baseline risks for all criteria are similar to those seen in the trials for those who did not receive rimonabant. Because of this assumption, the impact numbers would not be perfectly tailored for the intended population. ν_1 is the number of people in the placebo group estimated from the trials.

In the hypothetical scenario with the trial populations in 2006, we estimated $P_e$from the proportion of people who were exposed to rimonabant in all four trials. This was 2503 participants from 4105 eligible for the intervention, giving $P_e = 0.6097$ and $\nu_2 = 4105$. In 2008 with additional evidence from Stradivarius Trial, P_e is estimated from a total of 2925 out of 4944 eligible participants. giving $P_e = 0.5916$ and $\nu_2 = 4944$.

For hypothetical scenario with population of England and Wales, we estimated P_e from the proportion of people who were eligible for randomisation in RIO-Europe trial [5]. Of the 2168 screened, 1508 were eligible for randomisation giving $P_e = 0.6956$. ν_2 is then 2168 which is the number of people who were screened in RIO-Europe trial. This gives the P_e of people in England and Wales who could receive the intervention. P_e and ν_2 are assumed to be the same in both 2006 and 2008.

The proportions of people who were overweight and obese in the general population P_d were estimated from the Epidemiological survey in England data [24]. We used the proportion of people at least 16 years old whose BMI were at least 25. We were unable to get better estimate of proportions on overweight and obese adults over 18 years old but we feel that the proportions shown in Table 11-13 are on the right ballpark. ν_3 is the total number of people over 16 years old in the survey, as also given in Table 11-13.

Table 11-13 Proportions of people with BMI at least 25 by year

	% people ≥ 25 BMI (P_d)	Total number of people ≥ 16 (ν_3)
2006	*61.6*	*12088*
2008	*61.4*	*12835*

Finally the size of the population n_s was estimated from the four pivotal plus one trials, and the population estimates for Middle Layer Super Output Area (MSOA) in England and Wales data. Because the trial population and the marketing authorisation were for adults over 18 years old but the MSOA population data were reported in different age group, we only included people from 20 years old. The trials populations correspond to hypothetical scenario (i) and the MSOA populations (England and Wales) correspond to hypothetical scenario (ii). Table 11-14 lists the number of people in each population of interest by year.

Table 11-14 Total number of people n_s in each population by year

	Trials (18+)‡	England and Wales (20+)
2006	4,105	40,665,471
2008	4,944	41,377,066

‡ The numbers of people in trials population are limited to those receiving placebo and 20mg rimonabant

11.5.2.4 PrOACT-URL

The acronym "PrOACT-URL" refers to the eight steps in the descriptive framework [16] Decision-makers applying the framework are firstly required to determine the context and frame ***pr***oblems. Then the ***o***bjectives and criteria for the analysis must be established before identifying suitable ***a***lternatives to perform the comparison. The expected ***c***onsequences for choosing an alternative must then be evaluated for each criterion. Then the benefit-risk ***t***rade-offs for the alternatives are to be established. Any associated ***u***ncertainties, the decision-makers' relative importance and ***r***isk tolerance, the changes to benefit-risk balanced are to be assessed. Finally, the decisions made should be assessed for consistency with any ***l***inked decisions in the past and its impact on the future.

Sub-team 3 works closely with sub-team 1 to evaluate the potential use of PrOACT-URL in three different settings:

(i) to use in its own right

(ii) to use as part of multi-criteria decision analysis framework

(iii) to use as guideline for planning and reporting of benefit-risk assessment

We do not discuss points (i) and (ii) in this report since their applications are reported elsewhere (Sections 11.3.1 and 11.3.2 respectively). We follow PrOACT-URL steps throughout this report; and discuss the third setting in Section 11.5.4.4.

11.5.2.5 Impact numbers as metric indices for benefits and risks

Five impact numbers are described in the PROTECT benefit-risk methodology review. The disease impact number *(DIN)* and population impact number *(PIN)* were the first two to be introduced [6], followed by case impact number *(CIN)*, exposure impact number *(EIN)* and exposed cases impact number *(ECIN)* in the same issue [10]. In the following year,

the number of events prevented in the population *(NEPP)* and the population impact number of eliminating a risk factor over time t *(PIN-ER-t)* were introduced.

The definitions and formulae for the impact numbers are given in Table 11-15. In reality like their predecessor, the number needed to treat (NNT), the impact numbers evolved and are closely associated to the traditional epidemiological metrics; which are also given for completeness. Table 11-15 only shows the specific formulae which are used in this study to calculate the metrics, but there are various other expressions for the same formulae. The formulae calculate impact numbers (and the associated measures) in a study population of size n_s with baseline risk for the event of interest I_u using the estimates of relative risks RR of the event in the patients who received rimonabant against those who did not; on the assumption that in the population, there are a proportion of P_d people who are overweight and obese, and a proportion of P_e people who are eligible (or are exposed) for the intervention.

Table 11-15 Impact numbers and other associated epidemiological metrics

Metric index	Definition	Formula
Attributable risk (AR)	the difference in risk between exposed and unexposed cases	$I_u \times (RR - 1)$
Population attributable risk (PAR)	the attributable risk in the whole population	$\frac{P_e \times (RR - 1)}{1 + P_e \times (RR - 1)}$
Attributable fraction among exposed (AFE)	the attributable risk of exposure among exposed cases	$\frac{RR - 1}{RR}$
Disease impact number (DIN)	the number of people with the medical condition in question amongst whom one event is attributable to exposure to the risk factor	$\frac{1}{\mathrm{AR} \times P_e}$
Population impact number (PIN)	the number of people in the whole population amongst whom one case is attributable to exposure to the risk factor	$\mathrm{DIN} \times \frac{1}{P_d}$
Case impact number (CIN)	the number of people with the case for whom one case will be attributable to the exposure or risk factor	$\frac{1}{\mathrm{PAR}}$
Exposure impact number (EIN) or NNT	the number of people with the exposure amongst whom one excess case is due to the exposure	$\frac{1}{\mathrm{AR}}$
Exposed cases impact number (ECIN)	the number of exposed cases amongst whom one case is due to the exposure	$\frac{1}{\mathrm{AFE}}$
Population impact number of eliminating a risk factor	the potential number of cases prevented in the study population over the next t years by	$n_S \times I_u \times \mathrm{PAR}$

Metric index	Definition	Formula
over time *t* (PIN-ER-*t*)	eliminating a risk factor	
Number of events prevented in a population (NEPP)	the number of cases prevented by the intervention in the study population	$n_S \times P_e \times P_d \times I_u \times (RR - 1)$

Observant readers may notice that the formula for EIN is exactly the same as that for NNT. In fact, the two metrics are equivalent when the baseline risk in EIN is estimated from the study data. We report EIN as NNT in this case study and only for hypothetical scenario 1 because the baseline risks are estimated from the pivotal trials data hence would be equivalent in all three scenarios. Figure 11-119 shows the relationship among the metrics indicating which metrics are readily calculable from other existing metrics, or conversely which parameters are required to calculate certain metrics.

The two metrics *NEPP* and *PIN-ER-t* are the most favourable of the impact numbers. They are preferred and more recommended for use in benefit-risk assessment from the population health perspective (Heller, personal communication). Therefore, we only report *NEPP* and *PIN-ER-t* in this case study, whilst acknowledging that the other impact numbers may be useful but may not be as intuitive as they were originally claimed to be.

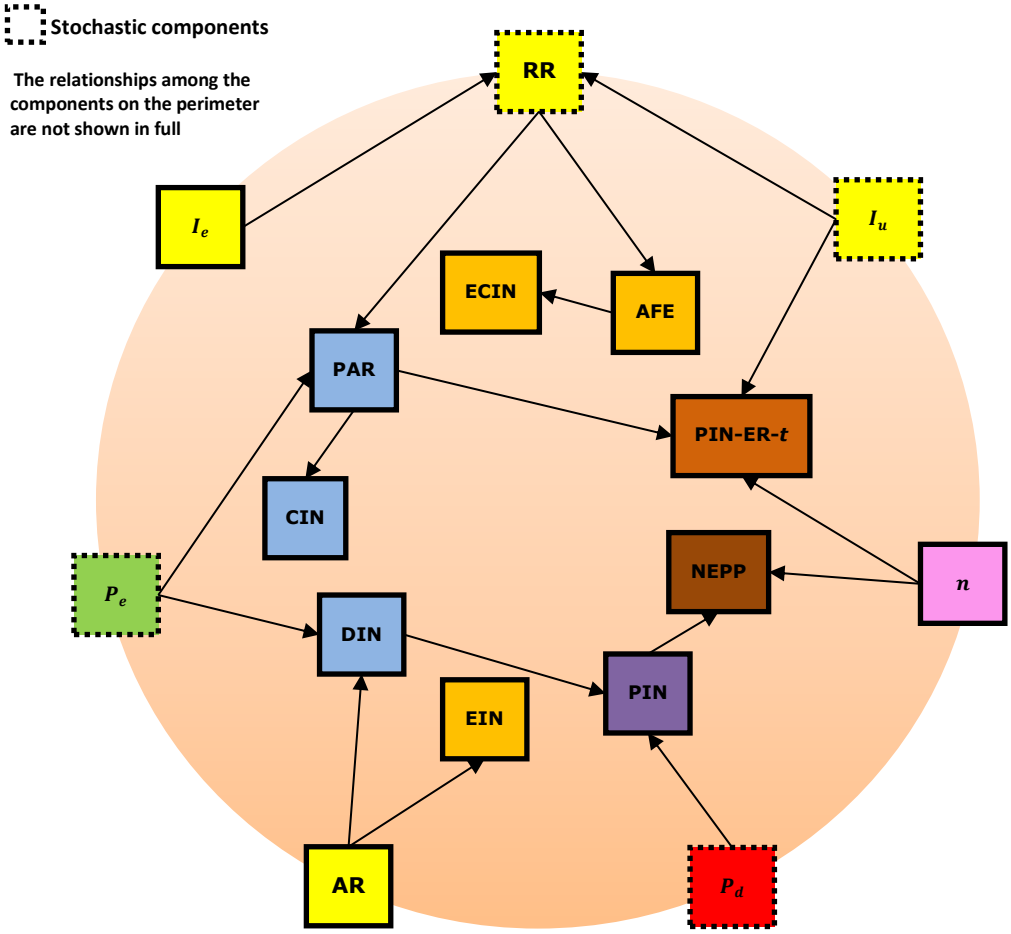


Figure 11-119 The relationship among impact numbers and other epidemiological metrics, coded as parameters for probabilistic simulation

11.5.2.6 Probabilistic simulation method

Probabilistic simulation method is an estimation technique which can flexibly incorporate statistical uncertainties in the simulated parameters. The uncertainties are then taken into account and reflected in the final results. In this case study, probabilistic simulation method is used to calculate the impact numbers described in Section 11.5.2.5. Figure 11-119 shows the parameters in the simulation models which are treated as being stochastic, represented by serrated boxes. That is, these parameters are sampled randomly from some appropriate probability distributions based on available data. The distributions we used in our models are listed in Table 11-16. The sampling on each parameter was repeated 100,000 times to capture the natural variations in the impact numbers (Monte Carlo) which were calculated deterministically (without incorporating additional variability) using the respective formulae. The 95% confidence intervals for the impact numbers were constructed from the 2.5th and 97.5th percentiles of the simulated values.

Table 11-16 Distributional assumptions for impact numbers benefit-risk assessment by hypothetical scenarios

Parameter	Trials	MSOA
Baseline risk I_u	These are different for each criterion and are based on the baseline rates in Table 11-12. In general, $I_{u,j}$ for criteria j is formulated as follows: $$x_{u,j} \sim Bin(\nu_{1,j}, I_{u,j})$$ $$r_{u,j} = x_{u,j}/\nu_{1,j}$$ $r_{u,j}$ is then the simulated proportion with Binomial errors. This two-stage parameterisation is to accommodate evidence data more directly as they are often reported as percentages. The same parameterisation are also used for P_e and P_d, so we only show the first line.	
Relative risk RR	RRs correspond to the criteria, and sampled as follows for each criterion j: $$lrr_j = \log(RR_j)$$ $$\sigma_{lrr,j} = \frac{\log(RR_{uci,j}) - \log(RR_{lci,j})}{2 \times \phi^{-1}(0.975)}$$ $$\Lambda_{lrr,j} \sim Normal(lrr_j, \sigma^2_{lrr,j})$$ $$\rho_j = e^{\Lambda_{lrr,j}}$$ ρ_j is then the simulated relative risk with the specified log-normal errors.	
Proportion eligible for Rimonabant P_e	2006: $x_e \sim Bin(0.6097, 4105)$ 2008: $x_e \sim Bin(0.5916, 4944)$	$x_e \sim Bin(2168, 0.6956)$
Proportion of overweight and obese P_d	2006: $x_d \sim Bin(12088, 0.616)$ 2008: $x_d \sim Bin(12835, 0.614)$	
Size of population n_s	as constants in Table 11-14	

11.5.2.7 Assessment of benefit-risk trade-offs

Neither the impact numbers approach nor the probabilistic simulation method provides a strategy to combine multiple criteria or to trade off benefits and risks. In this case study, we calculate benefit-risk ratio (BRR) and net clinical benefit (NCB) trade-off metric for each benefit criterion against each risk criterion for the purpose of directly comparing benefits and risks. Because the decision-maker's relative importance between benefit and risk criteria are unknown, we estimated BRR and NCB over a range of k values. In this setting, k is the scaling factor such that $\text{benefit} = k \times \text{risk}$, that is, how much more important is the benefit when compared to risk.

The benefit-risk ratio of NEPP for benefit criterion i and risk criterion j is calculated as

$$BRR_{i,j} = \frac{NEPP_{benefit,i}}{k \times NEPP_{risk,j}}$$

The net clinical benefit of NEPP for benefit criterion i and risk criterion j is calculated as

$$NCB_{i,j} = NEPP_{benefit,i} - k \times NEPP_{risk,j}$$

The BRR and NCB for PIN-ER-*t* are calculated in the same way.

11.5.2.8 Sensitivity analysis

We performed simple sensitivity analyses by varying the baseline risks in the situation when the actual baseline risk is halved, or doubled. The effect on the impact numbers were assessed in the England and Wales population since this is the population with unknown baseline risks which we assumed to be similar to those of trials population. Baseline rates in the trials population were observed thus eliminating the need for such sensitivity analyses.

11.5.2.9 Development of computer programme to facilitate implementation

We developed Stata programmes to facilitate the simulations of impact numbers (StataCorp). When writing these programmes, we took into account common data structure users have. Although we decided only to present *EIN, NEPP* and *PIN-ER-t*, we wrote the programmes to estimate all ten metric indices described in Table 11-15 for more general use and interest.

It is our goal to create user-friendly programmes so that users without in depth knowledge of probabilistic simulations and statistical distributions may use them without difficulties. In order to achieve that, some basic knowledge of Stata is assumed, and more importantly some assumptions are made by default in the programmes to account for unavailable data which are mostly related to the samples sizes from which the parameters are estimated from.

Details of these programmes and the assumptions are given in Section 11.5.6

11.5.3 Results

11.5.3.1 Foreword

In this section, the results of EIN (or the NNT and NNH), NEPP and PIN-ER-1 are presented for the two hypothetical scenarios in Sections 11.5.3.2.1 and 11.5.3.3.1. In general the impact number are not normally distributed, hence the medians give better estimate of the "average" impact of rimonabant than the means. We present both means and medians in the tables but only present visual results of the medians plus the 95% confidence intervals. EINs are only presented for the first hypothetical scenario (Table 11-17 and Figure 11-120 – Figure 11-123) because we have not made changes to the baseline rates and so they are the same in both populations. NEPP and PIN-ER-1 are presented for both hypothetical scenarios (Table 11-18 – Table 11-21 and Figure 11-124 – Figure 11-131).

Benefits and risks are traded off using benefit-risk ratio and net clinical benefit methods because neither impact numbers nor probabilistic simulations perform benefit-risk trade-off. The number of pairs to be compared for the different benefit and risk criteria, year and hypothetical scenarios are overwhelming. Therefore, we only do present selected cases to highlight the advantages and the disadvantages of the two trade-off methods for impact numbers. These are presented visually for a range of relative importance of benefit to risk criteria in Sections 11.5.3.2.2 and 11.5.3.3.2.

Statistical uncertainties are dealt with throughout the analysis through probabilistic simulations and are presented as 95% confidence intervals. Sections 11.5.3.2.3 and 11.5.3.3.3 present the uncertainties in the baseline event rates with sensitivity analyses of halving and doubling the rates for investigative purposes. For simplicity, we demonstrate the effects of halving and doubling baseline rates for events within the psychiatric disorders class.

Section 11.5.3.4 discusses the overall results presented in previous sections.

11.5.3.2 Trials population

11.5.3.2.1 Consequences

Table 11-17 EIN (or NNT for benefit or NNH for risk) in trial population by year: the number of people who received rimonabant among whom one excess case of the events described by the criteria was due to rimonabant

	2006			2008		
Criterion	**Mean**	**Median**	**95% CI**	**Mean**	**Median**	**95% CI**
10% weight loss at 1 year	6.07	5.97	(4.34, 8.37)	6.07	5.97	(4.34, 8.37)
Reduction in metabolic syndrome	5.06	4.94	(3.56, 7.21)	5.06	4.94	(3.56, 7.21)
Diarrhoea	98.29	64.68	(22.19, 438.26)	61.96	49.52	(25.22, 159.72)
Nausea	14.77	14.22	(9.20, 23.48)	14.02	13.64	(9.29, 20.98)
Vomiting	113.97	55.50	(25.29, 186.33)	54.87	48.32	(24.66, 122.03)
Asthenia/Fatigue	121.74	85.55	(-830.07, 1045.60)	100.15	65.53	(26.81, 379.62)
Influenza	47.46	71.37	(-1664.83, 1718.06)	47.46	71.37	(-1664.83, 1718.06)
Gastroenteritis viral	223.74	112.73	(-1260.49, 1555.44)	223.74	112.73	(-1260.49, 1555.44)
Upper respiratory tract infections	-39.65	68.05	(-1000.15, 1072.40)	-39.65	68.05	(-1000.15, 1072.40)
Confusion	84.93	63.55	(22.58, 244.04)	84.93	63.55	(22.58, 244.04)
Fall	94.34	152.10	(-1741.48, 2170.51)	94.34	152.10	(-1741.48, 2170.51)
Joint sprain	144.63	106.80	(-659.85, 1039.35)	144.63	106.80	(-659.85, 1039.35)
Muscle cramps	2692.31	184.95	(-2780.97, 3194.08)	2692.31	184.95	(-2780.97, 3194.08)
Muscle spasms	100426.00	186.21	(-1368.78, 2347.66)	100426.00	186.21	(-1368.78, 2347.66)
Tendonitis	131.68	89.52	(31.79, 442.83)	131.68	89.52	(31.79, 442.83)
Dizziness	45.76	37.96	(19.90, 107.26)	61.04	49.17	(24.18, 197.89)
Hypoesthesia	168.87	102.85	(31.76, 588.36)	281.70	114.91	(36.97, 587.04)

Memory loss	336.53	133.85	(-204.45, 1170.85)	336.53	133.85	(-204.45, 1170.85)
Sciatica	4631.59	156.90	(30.67, 1623.38)	4631.59	156.90	(30.67, 1623.38)
Anxiety	34.05	31.11	(16.56, 68.44)	35.46	32.57	(18.89, 68.84)
Depressive disorders	80.22	63.84	(27.18, 234.39)	43.55	39.53	(21.40, 89.00)
Insomnia	53.54	45.40	(22.43, 136.11)	19.81	50.48	(25.51, 165.11)
Irritability	122.98	77.43	(26.32, 338.80)	34.34	112.34	(39.90, 605.51)
Mood alterations with depressive symptoms	54.01	59.75	(26.34, 258.57)	84.93	61.47	(28.96, 238.90)
Nervousness	271936.69	96.57	(18.29, 8.96e+06)	14985.26	107.08	(20.71, 489522.31)
Parasomnia	6119.54	73.18	(14.56, 198045.09)	968.54	89.22	(21.14, 720.18)
Sleep disorder	4631.59	156.90	(30.67, 1623.38)	4631.59	156.90	(30.67, 1623.38)
All psychiatric disorders	7.05e+07	253.08	(-1911.40, 8.47e+08)	1005.70	232.16	(-4989.88, 5040.10)
Cardiac disorder	89196.34	304.70	(-6320.05, 12529.14)	89196.34	304.70	(-6320.05, 12529.14)
Death	770811.19	-598.21	(-9289.47, 14171.14)	-288.55	-262.04	(-1075.86, -126.57)
Road traffic accident	1.98e+06	1255.09	(-2559.81, 4.41e+06)	1.98e+06	1255.09	(-2559.81, 4.41e+06)
Severe depression	1.98e+06	1255.09	(-2559.81, 4.41e+06)	1663.83	301.01	(-5949.62, 6425.22)
Urinary disorder	301871.41	330.44	(-5295.35, 4.38e+06)	301871.41	330.44	(-5295.35, 4.38e+06)
Hyperhydrosis	534.40	141.20	(32.62, 1203.00)	534.40	141.20	(32.62, 1203.00)
Pruritus	534.40	141.20	(32.62, 1203.00)	534.40	141.20	(32.62, 1203.00)
Hot flushes	103.55	81.50	(28.04, 364.55)	103.55	81.50	(28.04, 364.55)
Constipation	n/a	n/a	n/a	3136.97	60.54	(-1592.72, 1605.64)
Erectile dysfunction	n/a	n/a	n/a	65744.90	55.77	(-75.01, 790906.69)
Suicidal ideation	n/a	n/a	n/a	-121.25	-86.59	(-1146.90, 1016.53)

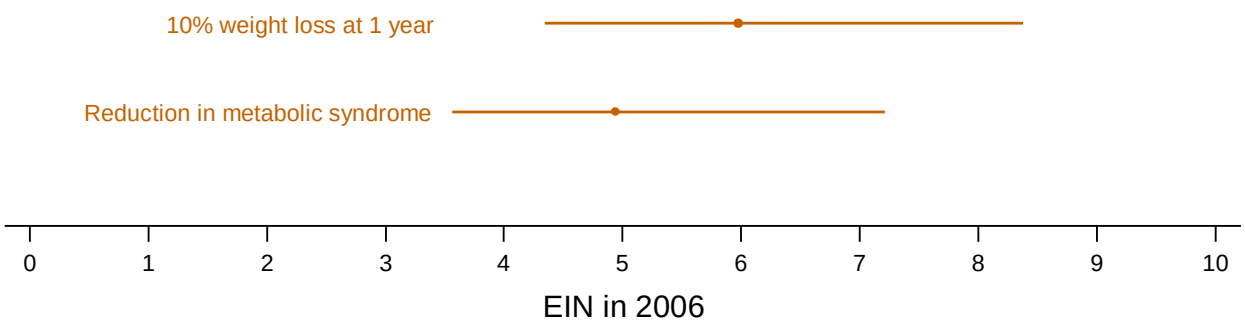


Figure 11-120 Exposure impact numbers (EIN) and 95% confidence intervals for benefits (equivalent to NNT) in 2006 in trials population

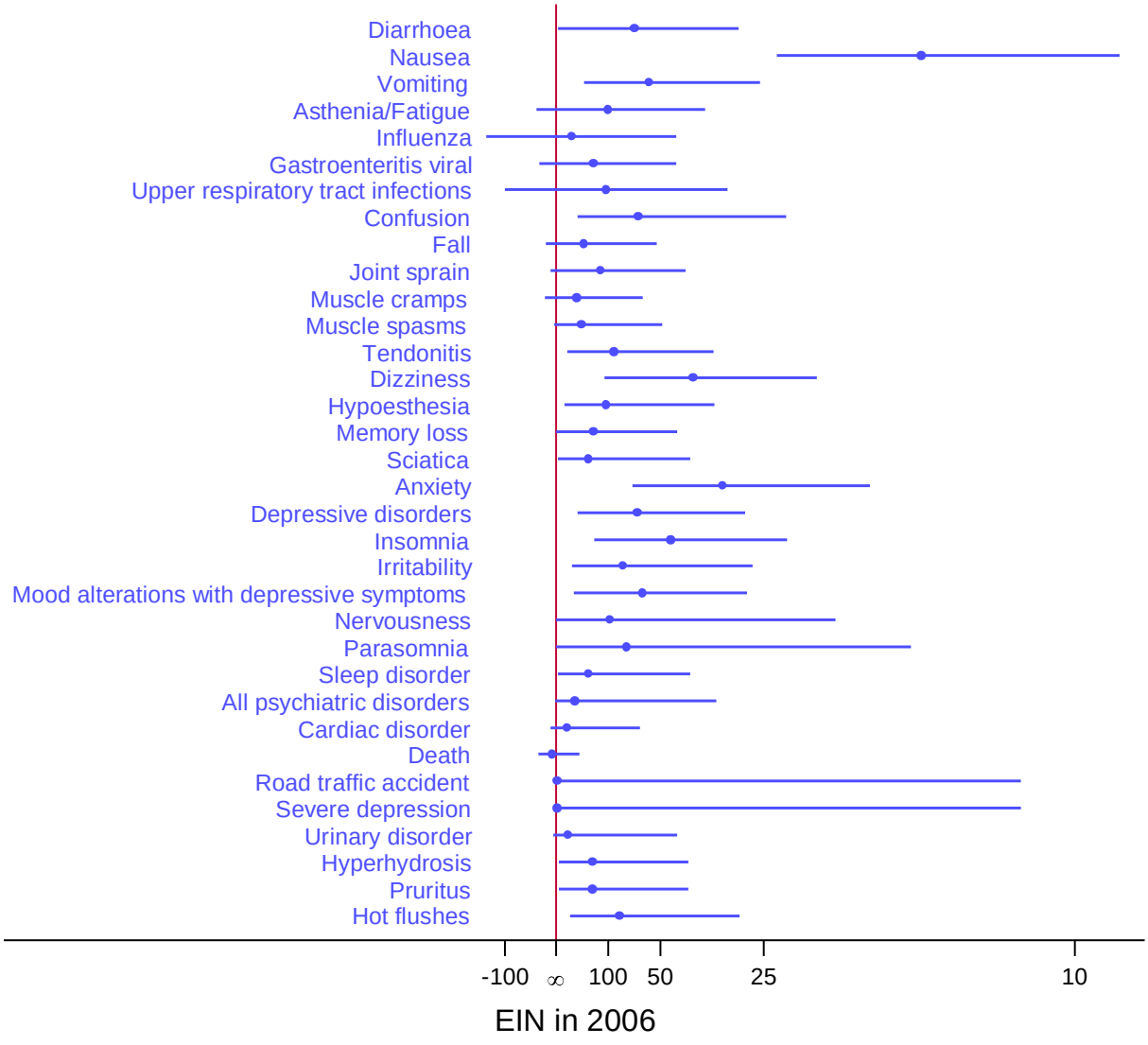


Figure 11-121 Exposure impact numbers (EIN) and 95% confidence intervals for risks (equivalent to NNH) in 2006 in trials population

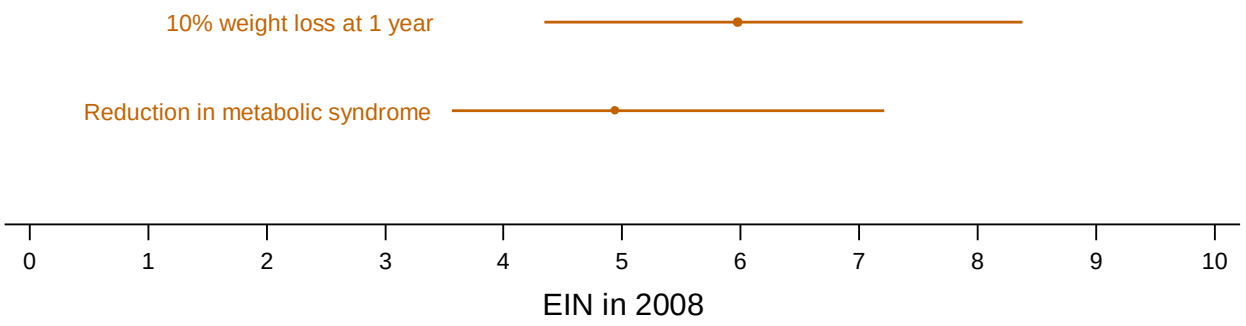


Figure 11-122 Exposure impact numbers (EIN) and 95% confidence intervals for benefits (equivalent to NNT) in 2008 in trials population

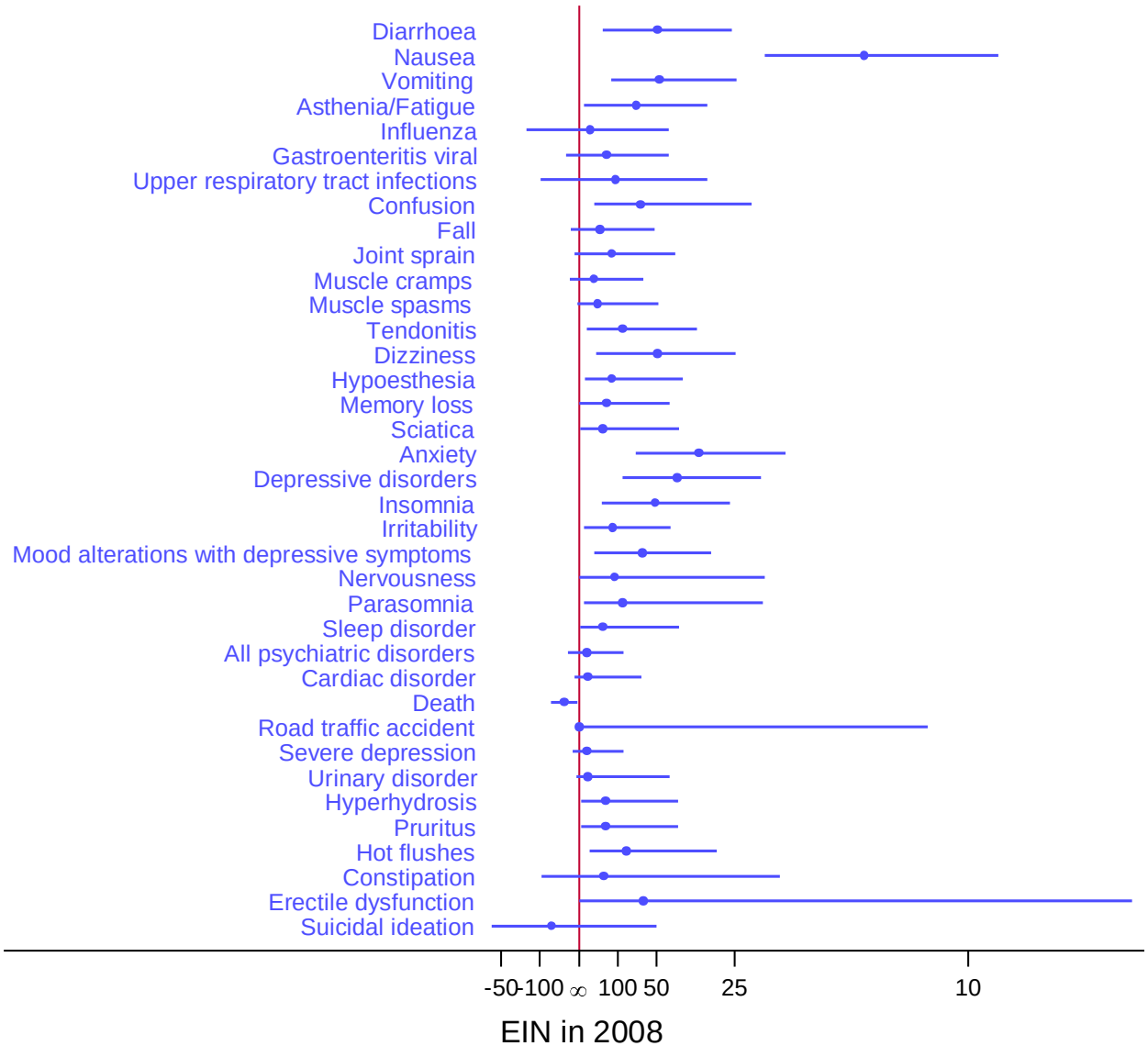


Figure 11-123 Exposure impact numbers (EIN) and 95% confidence intervals for risks (equivalent to NNH) in 2008 in trials population

Table 11-18 NEPP in trial population: the number of people in the pivotal trials in whom the events described by the criteria would have been prevented if everybody had received placebo

	2006			2008		
Criterion	**Mean**	**Median**	**95% CI**	**Mean**	**Median**	**95% CI**
10% weight loss at 1 year	424.04	418.98	(298.27, 577.43)	495.55	489.55	(348.54, 674.59)
Reduction in metabolic syndrome	511.26	506.14	(346.40, 704.03)	597.47	591.40	(404.75, 822.47)
Diarrhoea	39.36	37.51	(0.98, 88.13)	60.93	58.96	(17.83, 115.24)
Nausea	179.36	176.08	(106.46, 271.99)	217.80	214.47	(139.31, 315.06)
Vomiting	47.82	45.06	(13.21, 98.32)	63.31	60.54	(23.94, 118.76)
Asthenia/Fatigue	26.53	24.86	(-9.65, 71.85)	45.46	43.73	(3.67, 96.79)
Influenza	8.62	7.45	(-33.73, 57.86)	10.08	8.70	(-39.35, 67.64)
Gastroenteritis viral	19.76	17.98	(-8.35, 57.91)	23.09	20.99	(-9.77, 67.66)
Upper respiratory tract infections	25.35	24.10	(-24.89, 82.52)	29.63	28.17	(-29.06, 96.47)
Confusion	44.74	39.39	(10.24, 110.64)	52.28	46.01	(11.97, 129.55)
Fall	15.55	13.38	(-5.27, 48.46)	18.17	15.65	(-6.15, 56.65)
Joint sprain	23.77	21.66	(-2.75, 62.29)	27.78	25.31	(-3.22, 72.77)
Muscle cramps	11.97	9.79	(-5.68, 41.77)	13.99	11.45	(-6.64, 48.82)
Muscle spasms	15.51	12.22	(-1.12, 51.10)	18.12	14.27	(-1.31, 59.67)
Tendonitis	31.11	27.78	(5.10, 76.07)	36.36	32.46	(5.95, 88.78)
Dizziness	68.12	65.91	(23.31, 125.61)	60.80	59.13	(13.17, 117.92)
Hypoesthesia	28.22	24.19	(3.87, 76.12)	29.42	25.37	(4.76, 77.78)
Memory loss	20.76	17.86	(-0.00, 58.03)	24.26	20.85	(-0.01, 67.94)
Sciatica	19.80	15.43	(0.68, 64.63)	23.14	18.04	(0.79, 75.55)

Anxiety	83.87	80.42	(36.57, 151.17)	92.12	89.81	(42.42, 154.94)
Depressive disorders	42.17	39.12	(10.43, 91.13)	76.80	73.99	(32.83, 136.74)
Insomnia	57.60	55.09	(18.25, 111.34)	59.87	57.81	(17.21, 113.89)
Irritability	37.03	32.29	(7.31, 94.51)	28.56	25.77	(3.94, 68.99)
Mood alterations with depressive symptoms	43.92	41.64	(8.57, 92.18)	49.43	47.38	(11.37, 99.14)
Nervousness	36.42	25.81	(0.00, 134.69)	38.20	27.25	(0.00, 139.80)
Parasomnia	47.41	34.20	(0.00, 171.35)	42.44	32.75	(4.05, 138.48)
Sleep disorder	19.80	15.43	(0.68, 64.63)	23.14	18.04	(0.79, 75.55)
All psychiatric disorders	16.08	8.81	(-0.36, 77.03)	7.53	5.78	(-8.39, 33.22)
Cardiac disorder	8.88	5.45	(-2.66, 40.22)	10.37	6.37	(-3.10, 47.04)
Death	-1.26	-1.91	(-8.46, 11.24)	-11.03	-10.97	(-20.82, -1.38)
Road traffic accident	29.32	0.40	(-0.57, 223.74)	34.25	0.46	(-0.67, 261.12)
Severe depression	29.32	0.40	(-0.57, 223.74)	7.97	5.71	(-4.72, 33.28)
Urinary disorder	11.29	5.64	(-1.36, 58.15)	13.20	6.59	(-1.59, 67.90)
Hyperhydrosis	21.15	17.27	(1.15, 63.79)	24.71	20.17	(1.35, 74.46)
Pruritus	21.15	17.27	(1.15, 63.79)	24.71	20.17	(1.35, 74.46)
Hot flushes	35.00	30.67	(6.73, 88.47)	40.90	35.81	(7.86, 103.42)
Constipation	n/a	n/a	n/a	30.22	19.01	(-28.09, 150.72)
Erectile dysfunction	n/a	n/a	n/a	87.46	48.29	(-0.00, 415.19)
Suicidal ideation	n/a	n/a	n/a	-16.28	-20.12	(-65.36, 58.51)

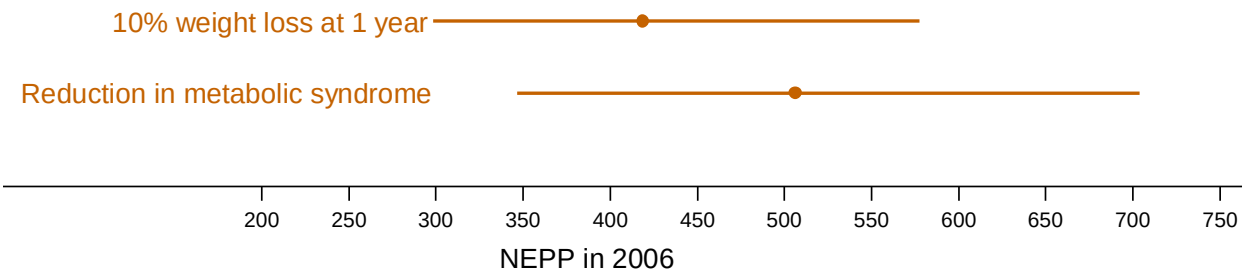


Figure 11-124 Number of events prevented in population (NEPP) and 95% confidence intervals for benefits in 2006 in trials population

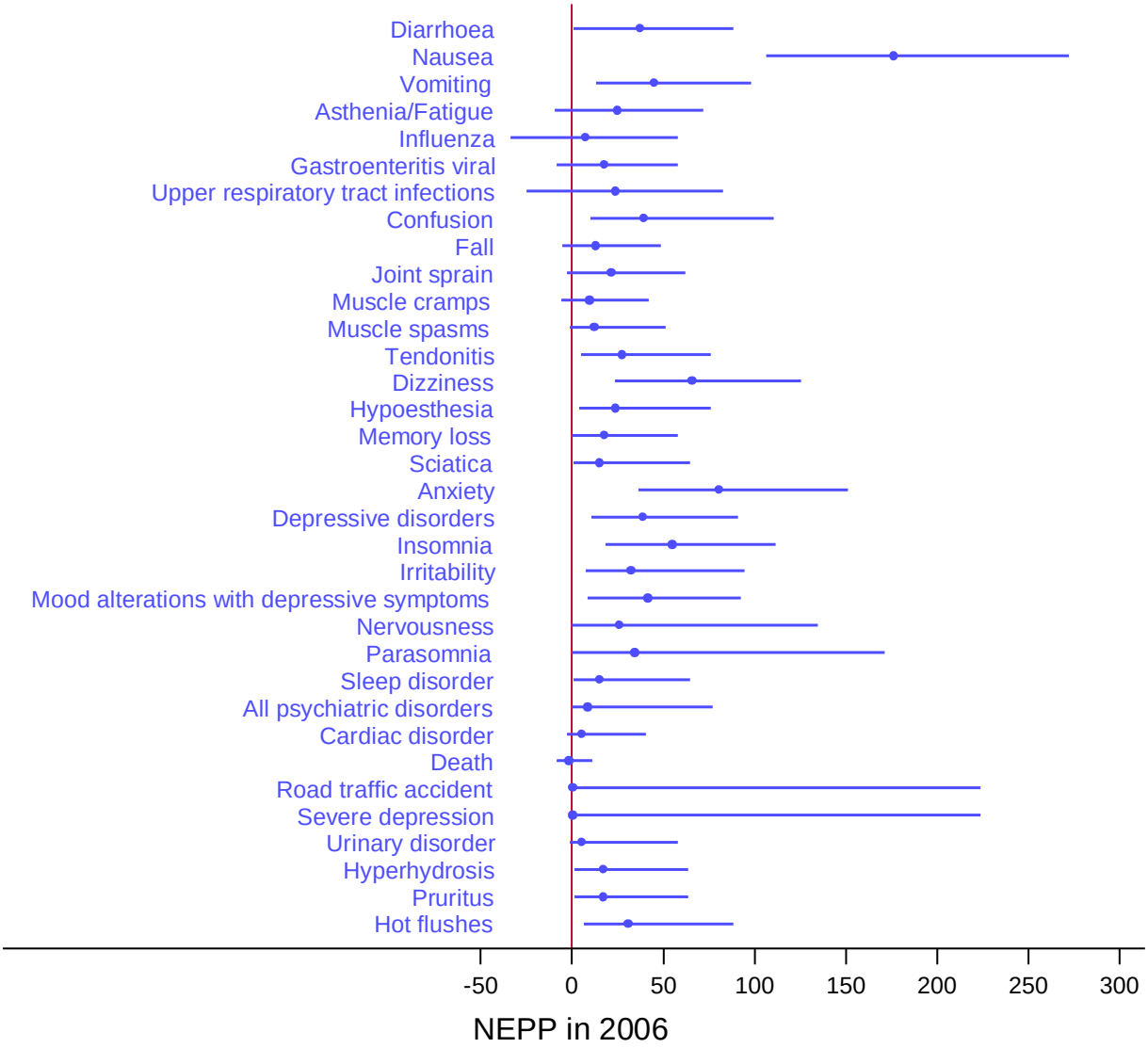


Figure 11-125 Number of events prevented in population (NEPP) and 95% confidence intervals for risks in 2006 in trials population

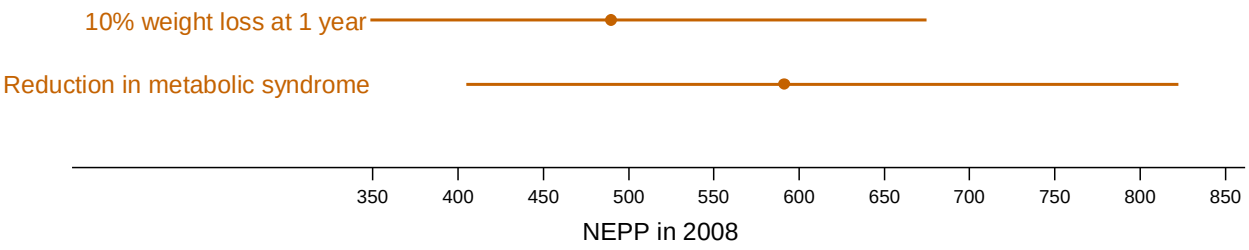


Figure 11-126 Number of events prevented in population and 95% confidence intervals for benefits in 2008 in trials population

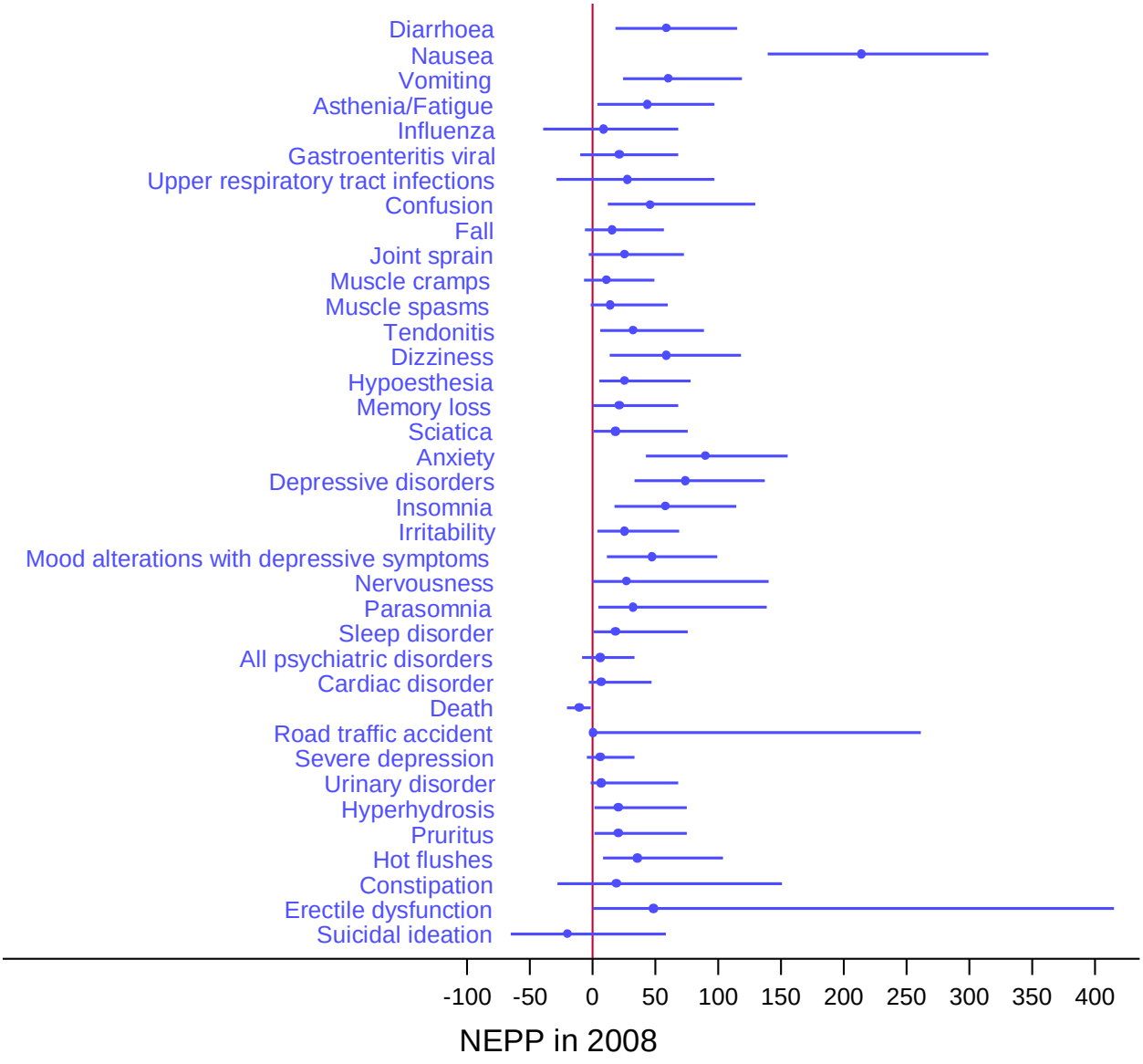


Figure 11-127 Number of events prevented in population and 95% confidence intervals for risks in 2008 in trials population

Table 11-19 PIN-ER-1 in the trial population: the number of people in the pivotal trials in whom the events described by the criteria due to rimonabant would have been prevented over the one year period if everybody had received placebo

	2006			2008		
Criterion	**Mean**	**Median**	**95% CI**	**Mean**	**Median**	**95% CI**
10% weight loss at 1 year	156.94	156.46	(124.55, 192.20)	186.89	186.32	(148.12, 229.03)
Reduction in metabolic syndrome	319.82	319.21	(243.05, 400.00)	377.93	377.13	(286.68, 473.51)
Diarrhoea	31.49	31.44	(0.98, 62.11)	46.67	46.52	(16.46, 77.67)
Nausea	93.76	93.34	(66.22, 123.95)	115.11	114.63	(85.33, 147.55)
Vomiting	30.11	29.76	(11.36, 50.88)	38.59	38.18	(19.04, 60.34)
Asthenia/Fatigue	22.10	22.13	(-10.12, 53.95)	37.38	37.32	(3.62, 71.28)
Influenza	7.01	7.30	(-37.26, 49.81)	8.24	8.52	(-43.29, 58.53)
Gastroenteritis viral	15.53	15.52	(-8.97, 39.90)	18.26	18.23	(-10.50, 47.10)
Upper respiratory tract infections	22.71	22.91	(-26.26, 70.33)	26.62	26.83	(-30.62, 82.60)
Confusion	15.92	15.43	(5.90, 28.75)	18.95	18.36	(6.98, 34.29)
Fall	10.85	10.70	(-5.82, 28.04)	12.79	12.57	(-6.77, 33.18)
Joint sprain	17.36	17.23	(-2.85, 38.16)	20.44	20.26	(-3.33, 45.11)
Muscle cramps	7.92	7.78	(-6.56, 22.83)	9.35	9.15	(-7.63, 27.02)
Muscle spasms	7.83	7.44	(-1.19, 18.91)	9.28	8.79	(-1.39, 22.51)
Tendonitis	16.76	16.32	(4.40, 31.61)	19.85	19.31	(5.16, 37.56)
Dizziness	49.60	49.44	(20.68, 79.65)	49.89	49.84	(12.65, 87.28)
Hypoesthesia	12.70	12.23	(3.09, 25.05)	12.74	12.26	(3.57, 24.60)
Memory loss	12.06	11.71	(-0.00, 26.02)	14.26	13.83	(-0.01, 30.89)

Sciatica	7.98	7.51	(0.62, 18.08)	9.49	8.90	(0.72, 21.57)
Anxiety	44.23	43.77	(25.12, 65.97)	63.26	63.00	(35.02, 93.14)
Depressive disorders	24.82	24.39	(8.82, 43.06)	47.30	46.89	(25.52, 71.19)
Insomnia	38.83	38.56	(15.84, 63.36)	45.79	45.60	(15.91, 76.53)
Irritability	14.62	14.12	(4.85, 27.23)	17.03	16.64	(3.59, 32.44)
Mood alterations with depressive symptoms	31.48	31.27	(8.02, 56.05)	37.18	37.01	(10.62, 64.72)
Nervousness	6.59	6.21	(0.00, 15.25)	6.46	6.08	(0.00, 14.82)
Parasomnia	7.04	6.61	(0.00, 15.94)	8.18	7.81	(1.67, 17.36)
Sleep disorder	7.98	7.51	(0.62, 18.08)	9.49	8.90	(0.72, 21.57)
All psychiatric disorders	3.67	3.26	(-0.39, 10.86)	5.08	5.06	(-10.22, 20.23)
Cardiac disorder	3.72	3.36	(-3.43, 12.31)	4.42	3.97	(-3.97, 14.66)
Death	-3.24	-2.51	(-15.70, 6.17)	-18.72	-18.01	(-39.90, -1.47)
Road traffic accident	1.37	0.35	(-0.72, 6.34)	1.65	0.41	(-0.83, 7.59)
Severe depression	1.37	0.35	(-0.72, 6.34)	4.61	4.41	(-5.87, 15.72)
Urinary disorder	3.00	2.46	(-1.72, 10.01)	3.57	2.91	(-1.99, 11.95)
Hyperhydrosis	9.61	9.15	(1.04, 20.83)	11.41	10.85	(1.22, 24.81)
Pruritus	9.61	9.15	(1.04, 20.83)	11.41	10.85	(1.22, 24.81)
Hot flushes	14.99	14.50	(4.82, 27.97)	17.80	17.21	(5.67, 33.33)
Constipation	n/a	n/a	n/a	15.85	15.36	(-37.41, 69.52)
Erectile dysfunction	n/a	n/a	n/a	18.09	16.33	(-0.00, 51.66)
Suicidal ideation	n/a	n/a	n/a	-27.71	-25.08	(-108.83, 40.42)

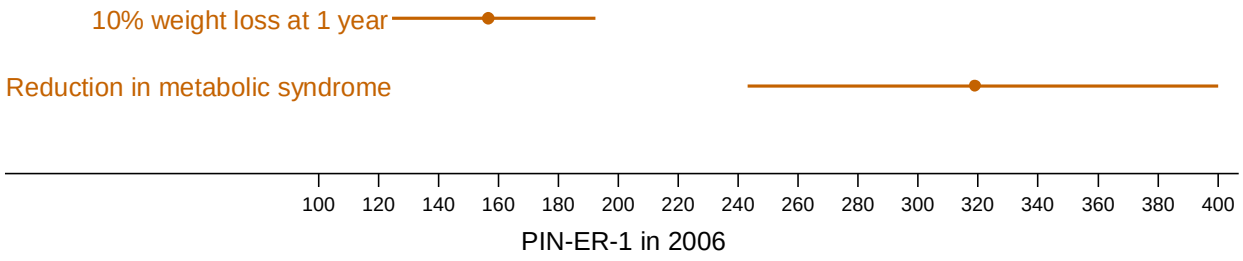


Figure 11-128 Population impact number of eliminating a risk factor over one year (PIN-ER-1) and 95% confidence intervals for benefits in 2006 in trials population

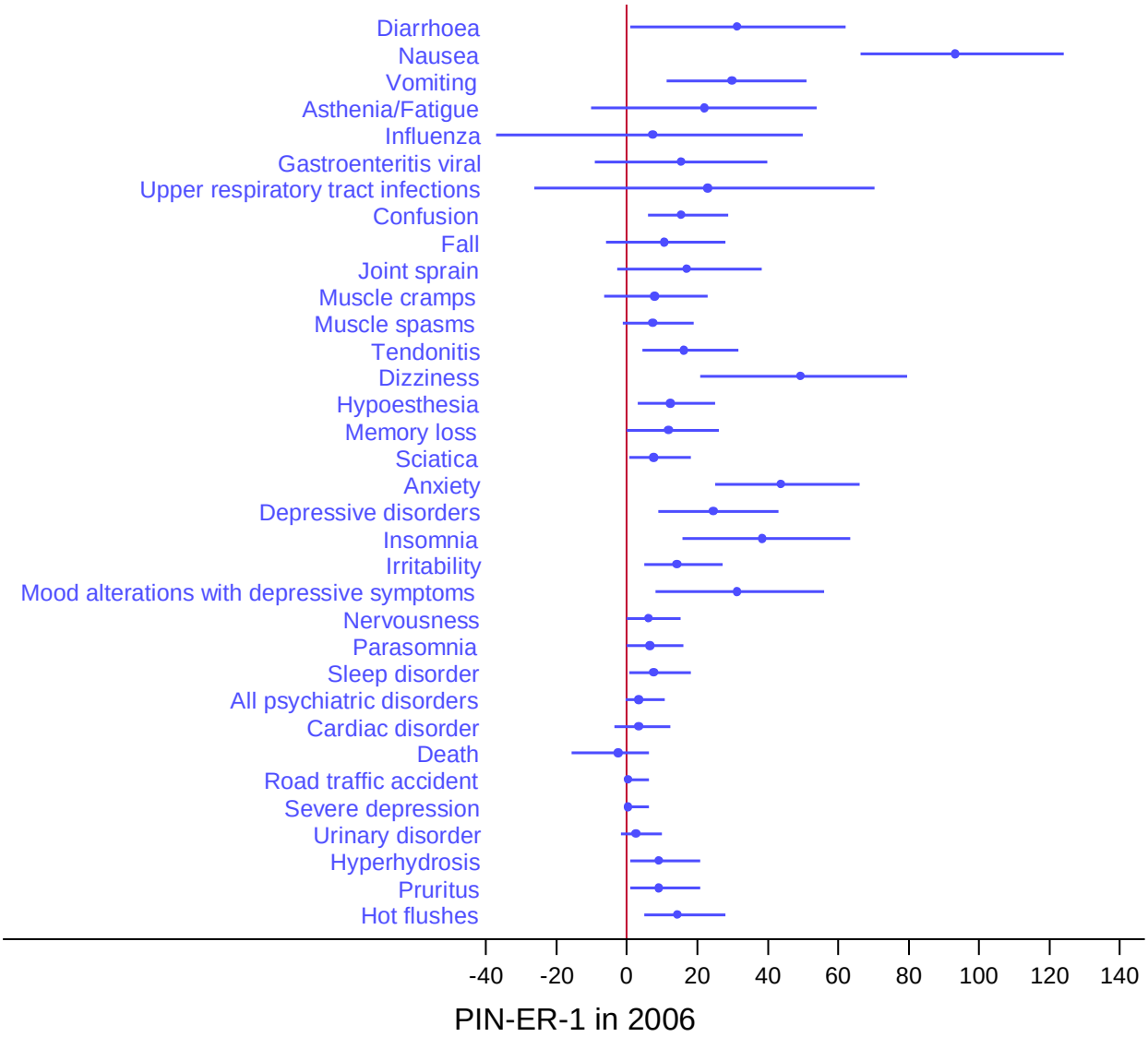


Figure 11-129 Population impact number of eliminating a risk factor over one year (PIN-ER-1) and 95% confidence intervals for risks in 2006 in trials population

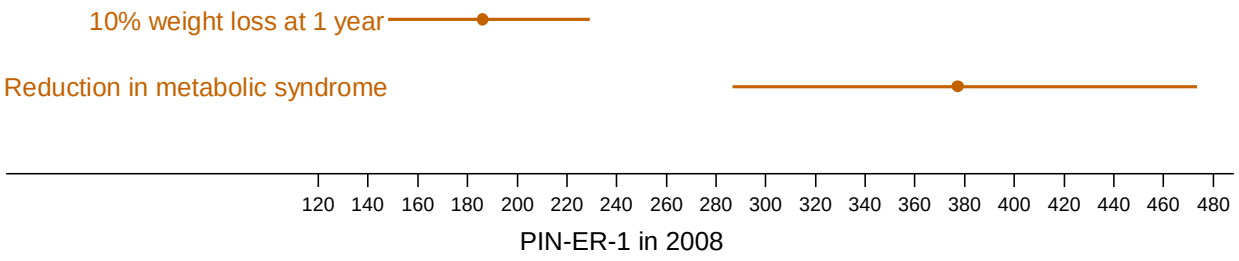


Figure 11-130 Population impact number of eliminating a risk factor over one year (PIN-ER-1) and 95% confidence intervals for benefits in 2008 in trials population

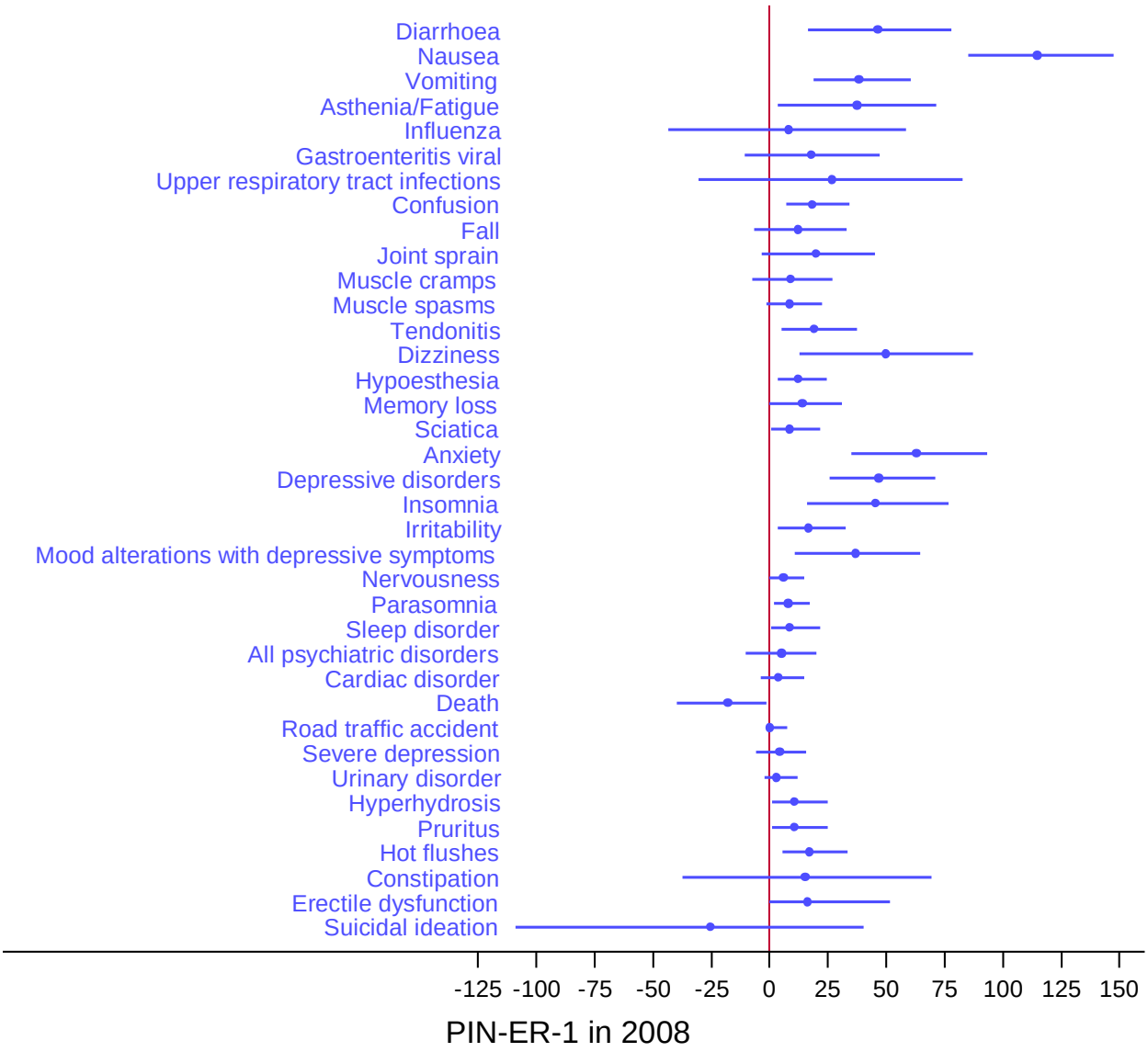


Figure 11-131 Population impact number of eliminating a risk factor over one year (PIN-ER-1) and 95% confidence intervals for risks in 2008 in trials population

11.5.3.2.2 Trade-offs

Impact numbers analysis does not trade off benefits and risks. It is possible that other approaches can be used in combination to achieve this task. We have not performed trade-off analysis in this hypothetical scenario to show where impact numbers analysis stops. Section 11.5.3.3.2 presents some examples on how we could tackle benefit-risk trade-off.

11.5.3.2.3 Uncertainty

Uncertainty analyses due changing baseline rates are not carried out here since the rates in this hypothetical scenario were observed rates. Statistical uncertainties in the parameters have been dealt with probabilistic simulations throughout.

11.5.3.3 England and Wales population

11.5.3.3.1 Consequences

Table 11-20 NEPP in England and Wales population: the number of people in England and Wales among whom the events described by the criteria would have been prevented if rimonabant were not prescribed

	2006			2008		
Criterion	**Mean**	**Median**	**95% CI**	**Mean**	**Median**	**95% CI**
10% weight loss at 1 year	2952200	2917808	(2076566, 4021742)	2994092	2959670	(2104870, 4079592)
Reduction in metabolic syndrome	3559377	3522975	(2409210, 4900704)	3609942	3573617	(2440849, 4970888)
Diarrhoea	274048	261184	(6879, 613107)	368158	356149	(107721, 695261)
Nausea	1248726	1225033	(742294, 1893343)	1315919	1295780	(841140, 1904120)
Vomiting	332942	313585	(92050, 684374)	382525	365669	(144719, 717755)
Asthenia/Fatigue	184677	173027	(-67150, 499882)	274649	264085	(22185, 585643)
Influenza	60024	51865	(-234802, 402877)	60883	52631	(-237831, 408687)
Gastroenteritis viral	137570	125015	(-58238, 402523)	139522	126826	(-58990, 408579)
Upper respiratory tract infections	176517	167705	(-172867, 574378)	179022	170124	(-175277, 582392)
Confusion	311477	274348	(71188, 770879)	315894	278166	(72142, 780736)
Fall	108274	93228	(-36598, 337520)	109808	94510	(-37210, 342001)
Joint sprain	165491	150795	(-19156, 433524)	167839	152920	(-19461, 439293)
Muscle cramps	83345	68140	(-39506, 290514)	84527	69160	(-40114, 295082)
Muscle spasms	107964	85071	(-7784, 355130)	109494	86303	(-7875, 360409)
Tendonitis	216625	193453	(35482, 529248)	219700	196241	(35982, 536855)
Dizziness	474242	458797	(161731, 874828)	367331	357251	(79767, 711962)
Hypoesthesia	196468	168324	(26847, 529684)	177756	153215	(28712, 469668)
Memory loss	144525	124288	(-31, 404302)	146574	126093	(-31, 410643)
Sciatica	137881	107479	(4731, 449497)	139835	109000	(4767, 455856)
Anxiety	583882	559475	(254316, 1052201)	556590	542619	(256538, 937358)
Depressive disorders	293602	272440	(72476, 635242)	464015	446864	(198229, 826110)
Insomnia	400991	383470	(127037, 774249)	361744	349377	(103800, 687229)

	2006			2008		
Criterion	**Mean**	**Median**	**95% CI**	**Mean**	**Median**	**95% CI**
Irritability	257806	224803	(50811, 658729)	172551	155641	(23791, 417242)
Mood alterations with depressive symptoms	305773	289951	(59596, 641210)	298680	286230	(68478, 599202)
Nervousness	253586	179908	(0, 935373)	230820	164898	(0, 844022)
Parasomnia	330061	238224	(0, 1190975)	256411	198001	(24528, 833661)
Sleep disorder	137881	107479	(4731, 449497)	139835	109000	(4767, 455856)
All psychiatric disorders	111946	61399	(-2466, 536742)	45497	34877	(-50722, 200764)
Cardiac disorder	61803	37944	(-18510, 280074)	62679	38479	(-18744, 284003)
Death	-8798	-13296	(-58896, 78216)	-66627	-66305	(-125952, -8316)
Road traffic accident	204064	2764	(-3996, 1552570)	206949	2794	(-4048, 1575188)
Severe depression	204064	2764	(-3996, 1552570)	48153	34488	(-28501, 200791)
Urinary disorder	78623	39258	(-9410, 404347)	79736	39814	(-9557, 410284)
Hyperhydrosis	147230	120179	(8006, 443395)	149317	121840	(8105, 449545)
Pruritus	147230	120179	(8006, 443395)	149317	121840	(8105, 449545)
Hot flushes	243673	213420	(46753, 616217)	247129	216487	(47508, 624566)
Constipation	n/a	n/a	n/a	182607	114874	(-170082, 911131)
Erectile dysfunction	n/a	n/a	n/a	528449	291994	(-17, 2508292)
Suicidal ideation	n/a	n/a	n/a	-98340	-121574	(-394865, 353534)

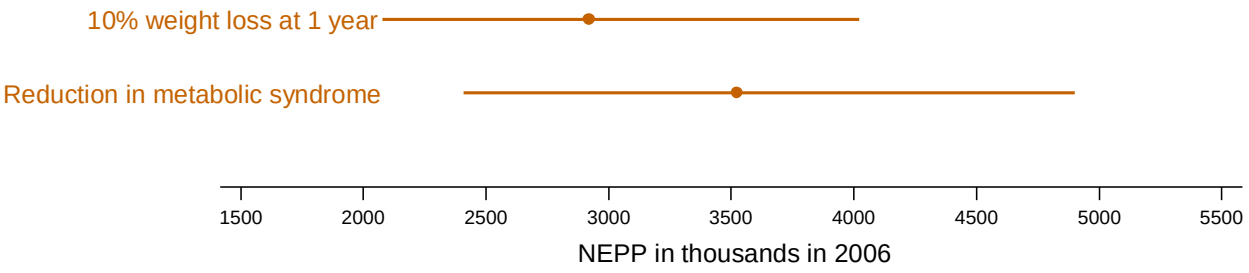


Figure 11-132 Number of events prevented in population (NEPP) and 95% confidence intervals for benefits in 2006 in England and Wales population

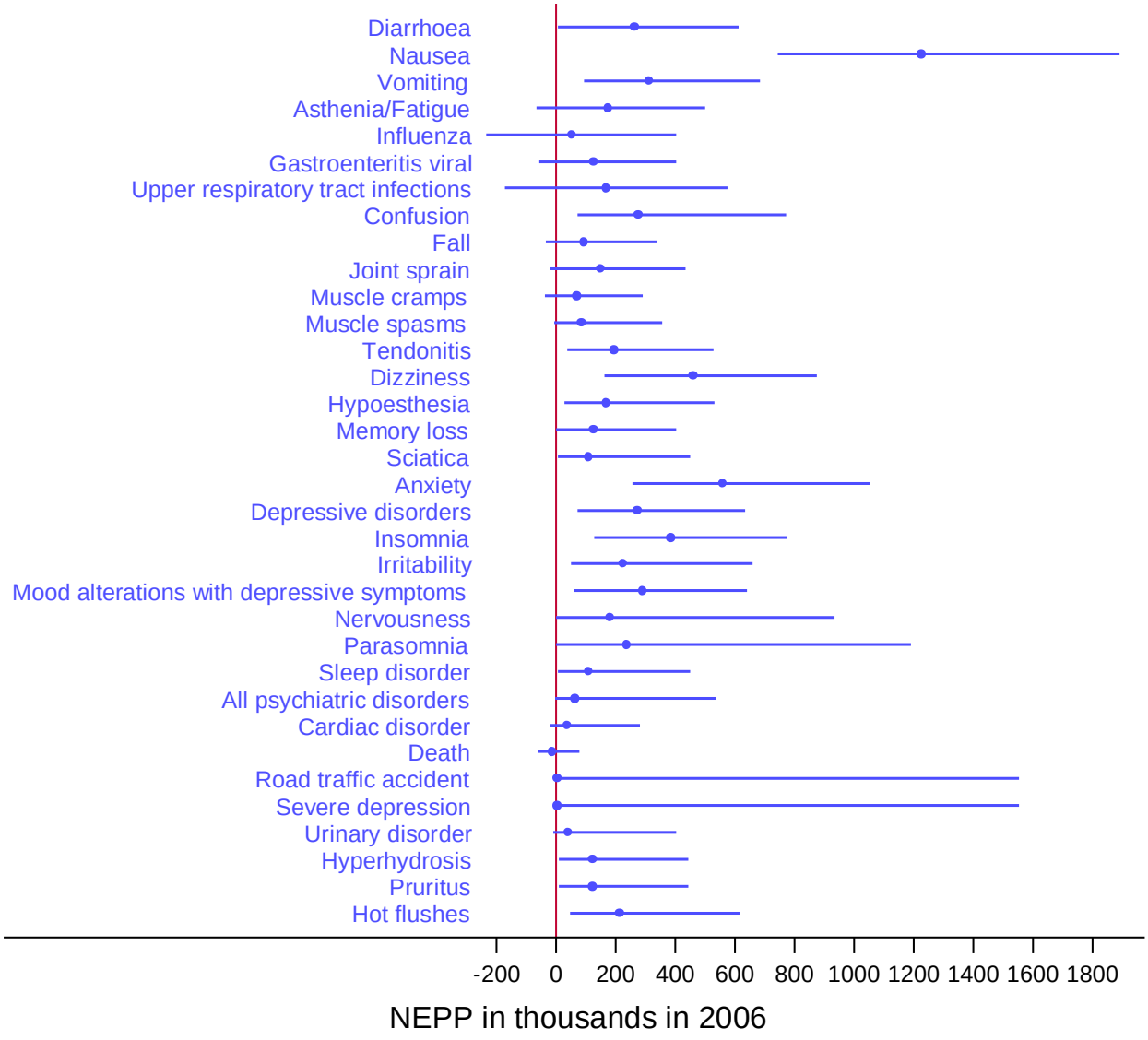


Figure 11-133 Number of events prevented in population and 95% confidence intervals for risks in 2006 in England and Wales population

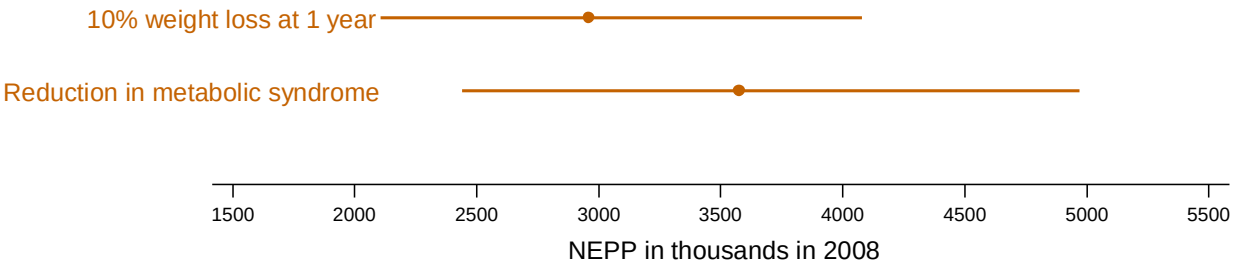


Figure 11-134 Number of events prevented in population (NEPP) and 95% confidence intervals for benefits in 2008 in England and Wales population

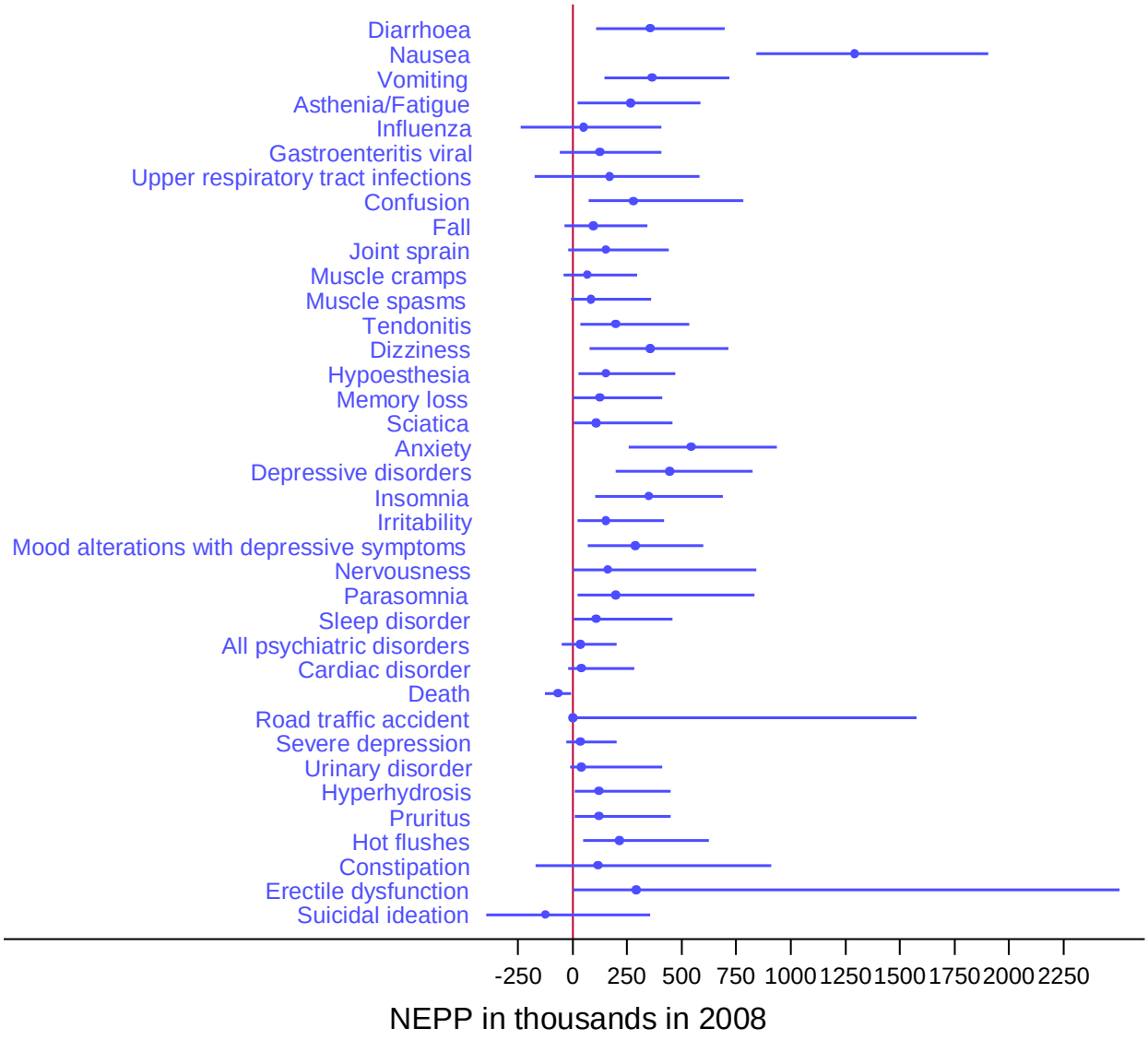


Figure 11-135 Number of events prevented in population and 95% confidence intervals for risks in 2008 in England and Wales population

Table 11-21 PIN-ER-1 in the England and Wales population: the number of people in England and Wales among whom the events described by the criteria due to rimonabant would have been prevented over one year period if rimonabant were eliminated

	2006			2008		
Criterion	**Mean**	**Median**	**95% CI**	**Mean**	**Median**	**95% CI**
10% weight loss at 1 year	1629754	1625149	(1298561, 1989220)	1658273	1653587	(1321284, 2024029)
Reduction in metabolic syndrome	3434538	3428339	(2633121, 4266218)	3494639	3488331	(2679197, 4340871)
Diarrhoea	346367	347412	(11091, 674122)	441457	441120	(159905, 723069)
Nausea	993624	989317	(709560, 1303356)	1046641	1042764	(785551, 1330061)
Vomiting	323967	320820	(125780, 539394)	355985	352736	(180660, 548248)
Asthenia/Fatigue	244176	246100	(-115305, 589773)	356950	357845	(35616, 670670)
Influenza	76830	82266	(-427213, 551862)	78174	83706	(-434688, 561519)
Gastroenteritis viral	170502	172150	(-102764, 432250)	173486	175163	(-104563, 439814)
Upper respiratory tract infections	252940	257111	(-299216, 778725)	257366	261610	(-304452, 792351)
Confusion	165633	160774	(62739, 296022)	168531	163587	(63837, 301202)
Fall	117810	117552	(-66463, 299544)	119871	119609	(-67626, 304786)
Joint sprain	189295	189270	(-32299, 409863)	192607	192582	(-32865, 417035)
Muscle cramps	85554	85461	(-75839, 242930)	87051	86957	(-77166, 247181)
Muscle spasms	83118	79697	(-13589, 197659)	84573	81091	(-13827, 201118)
Tendonitis	178463	174278	(48806, 331198)	181585	177328	(49660, 336994)
Dizziness	540324	539694	(230013, 856973)	476185	477250	(123783, 820780)
Hypoesthesia	133861	129214	(33812, 260225)	114653	110811	(33634, 217576)
Memory loss	129097	126224	(-49, 273872)	131356	128433	(-50, 278664)
Sciatica	83767	79175	(6858, 186864)	85233	80561	(6978, 190134)

Anxiety	469402	464861	(271540, 693047)	590576	589058	(334166, 856999)
Depressive disorders	265705	261786	(97722, 454331)	436632	433621	(241744, 647710)
Insomnia	420170	417947	(175805, 676080)	433094	432465	(154310, 712188)
Irritability	152943	148049	(52219, 281232)	157060	154202	(34871, 293196)
Mood alterations with depressive symptoms	342509	341444	(89464, 600313)	351033	350602	(103222, 600250)
Nervousness	67231	63360	(0, 154553)	55912	52581	(0, 127316)
Parasomnia	71439	66900	(0, 160960)	71015	67936	(14675, 149221)
Sleep disorder	83767	79175	(6858, 186864)	85233	80561	(6978, 190134)
All psychiatric disorders	37777	34166	(-4465, 110268)	47069	48645	(-104721, 186628)
Cardiac disorder	39013	35956	(-40280, 127679)	39696	36585	(-40985, 129914)
Death	-41585	-29857	(-203331, 65718)	-211512	-200052	(-473327, -14590)
Road traffic accident	13753	3891	(-8345, 64233)	13993	3959	(-8491, 65356)
Severe depression	13753	3891	(-8345, 64233)	42198	41659	(-60171, 142094)
Urinary disorder	30916	26252	(-20231, 102548)	31457	26712	(-20585, 104343)
Hyperhydrosis	101430	97034	(11499, 216371)	103205	98732	(11701, 220157)
Pruritus	101430	97034	(11499, 216371)	103205	98732	(11701, 220157)
Hot flushes	157370	152610	(52263, 289965)	160124	155280	(53178, 295039)
Constipation	n/a	n/a	n/a	142110	146193	(-391582, 626657)
Erectile dysfunction	n/a	n/a	n/a	158248	144967	(-27, 444588)
Suicidal ideation	n/a	n/a	n/a	-303163	-257864	(-1220096, 377604)

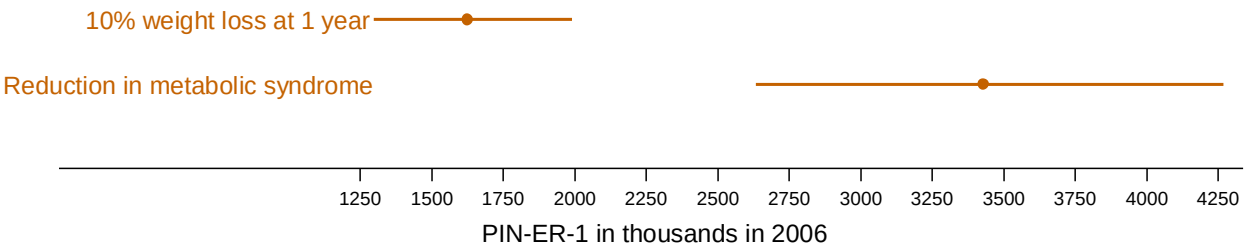


Figure 11-136 Population impact number of eliminating a risk factor over one year (PIN-ER-1) and 95% confidence intervals for benefits in 2006 in England and Wales population

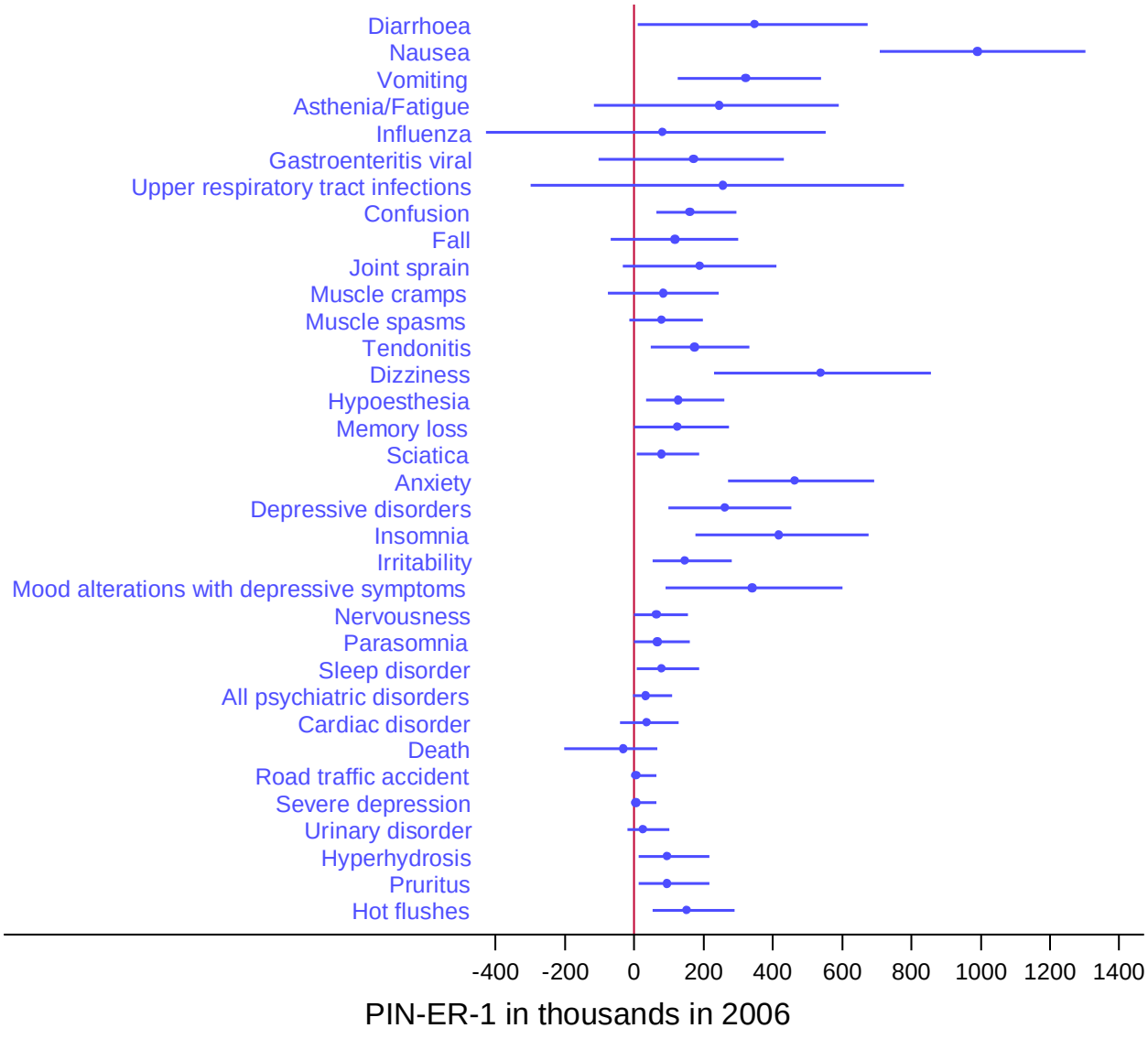


Figure 11-137 Population impact number of eliminating a risk factor over one year (PIN-ER-1) and 95% confidence intervals for risks in 2006 in England and Wales population

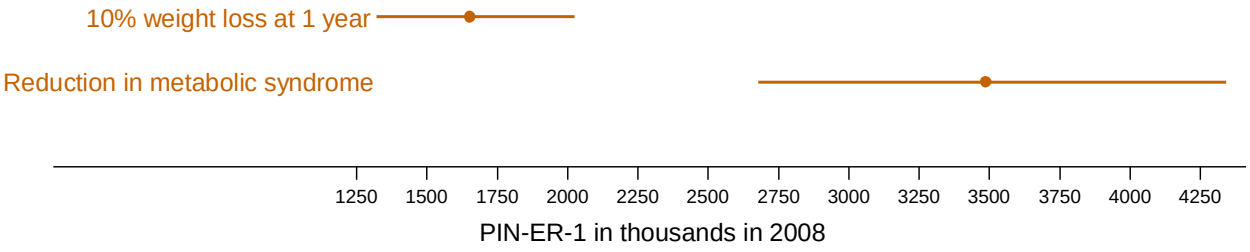


Figure 11-138 Population impact number of eliminating a risk factor over one year (PIN-ER-1) and 95% confidence intervals for benefits in 2008 in England and Wales population

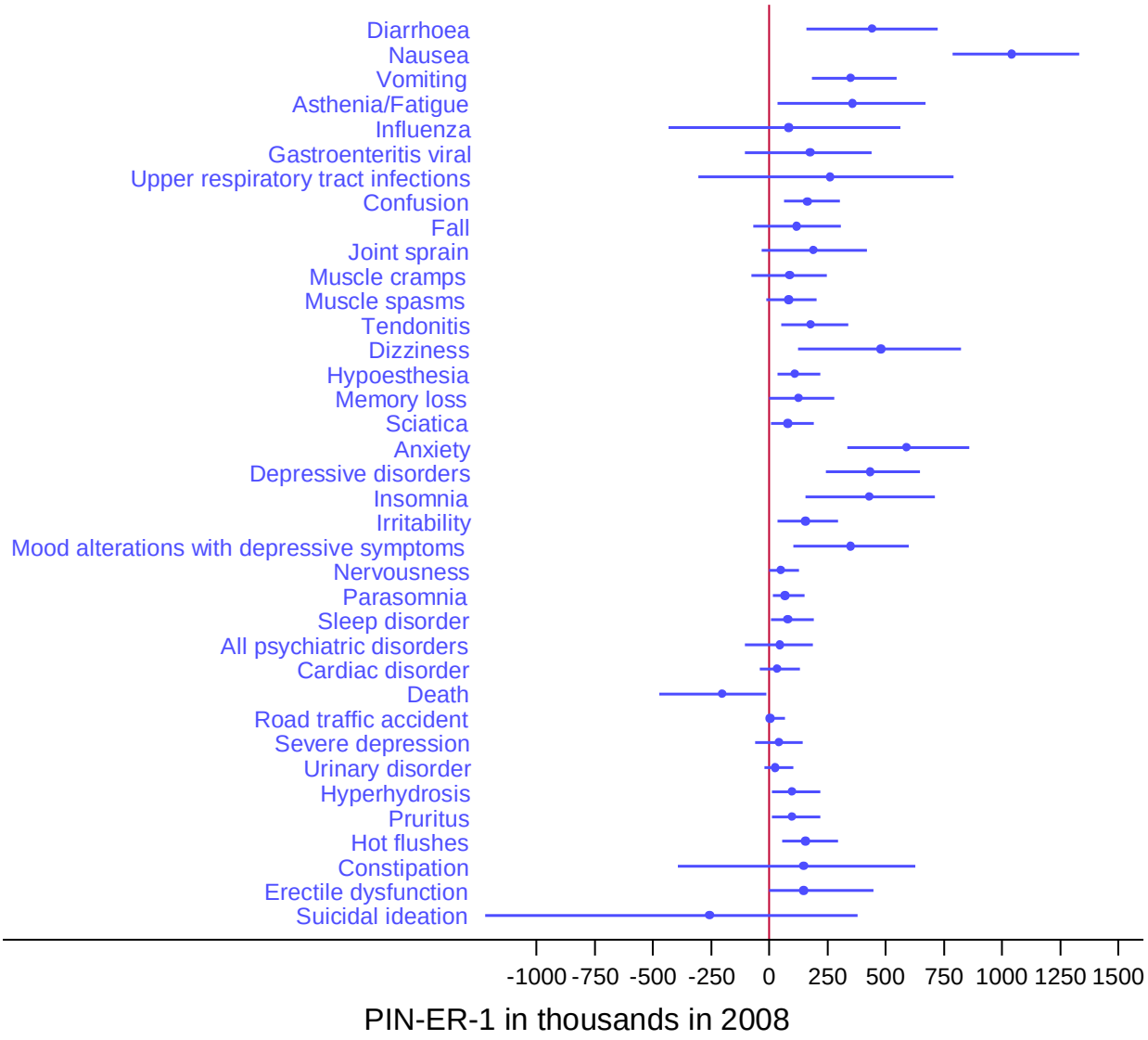


Figure 11-139 Population impact number of eliminating a risk factor over one year (PIN-ER-1) and 95% confidence intervals for risks in 2008 in England and Wales population

11.5.3.3.2 Trade-offs

11.5.3.3.2.1 Benefit-risk ratio (BRR)

We present the results for events in psychiatric disorders and severe psychiatric disorder for illustrations. The benefit-risk ratios for each event (criterion) are plotted against the relative importance of benefit to risk where the larger relative values refer to putting more weight on risks. This is equivalent to saying that a decision-maker prefers to avoid the risk more than gaining the benefit. The benefit-risk balance is achieved when BRR equals one that is when benefit equals risk.

For example in Figure 11-140 in the year 2008 with all available evidence from trials, when a DM prefer to lose weight twice as much than avoiding anxiety i.e. relative importance of 0.5, the ratio of benefit to risk is 5.6 (95% CI 3.8 – 9.5). This means 6 people would have lost weight by taking rimonabant for every person who experienced anxiety due to rimonabant. When weight loss is valued as important as avoiding anxiety, the BRR drops to 2.8 (95% CI 1.9 – 4.7). On the other hand, if a DM greatly preferred to avoid anxiety, say with an extreme relative importance of 10, the BRR drops to 0.3 (95% CI 0.2 – 0.5) suggesting that rimonabant should be avoided. The benefit-risk balance of rimonabant in this situation reverses when the relative importance of benefit to risk is between 2.9 and 3.0.

Figure 11-140 – Figure 11-148 show the benefit-risk ratio of weight loss to psychiatric-related events which should be interpreted with caution within the context of analysis. We discuss the effect of decision-makers' risk tolerance and the application of benefit-risk ratio on impact numbers in Section 11.5.4.2.

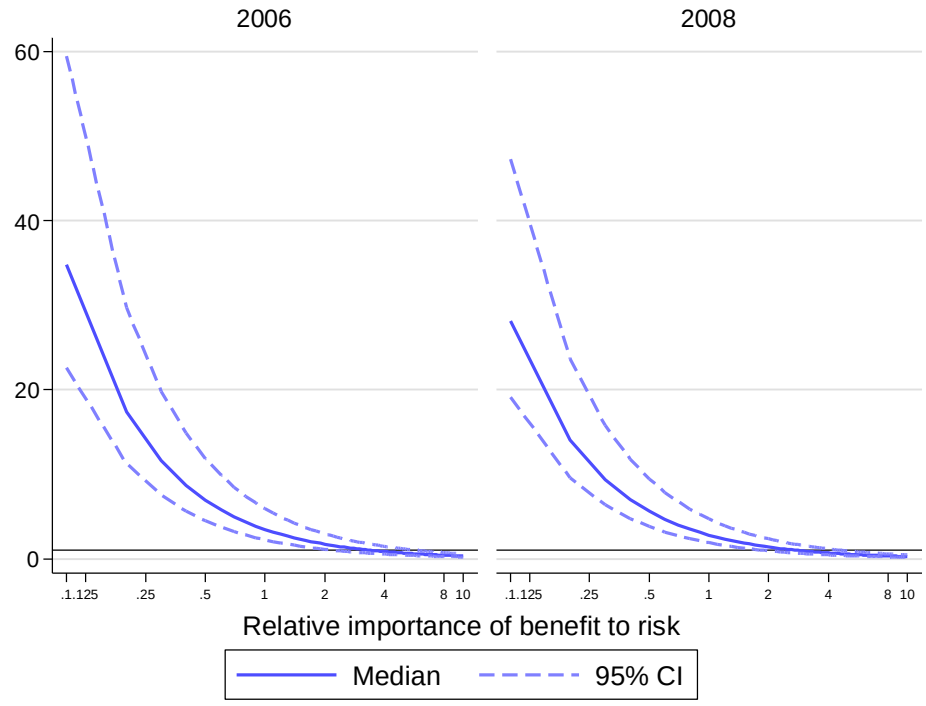


Figure 11-140 The ratio of number of people in the population whose weight loss were attributable to rimonabant to the number of people who experienced anxiety as a result of taking rimonabant over one year (BRR of PIN-ER-1)

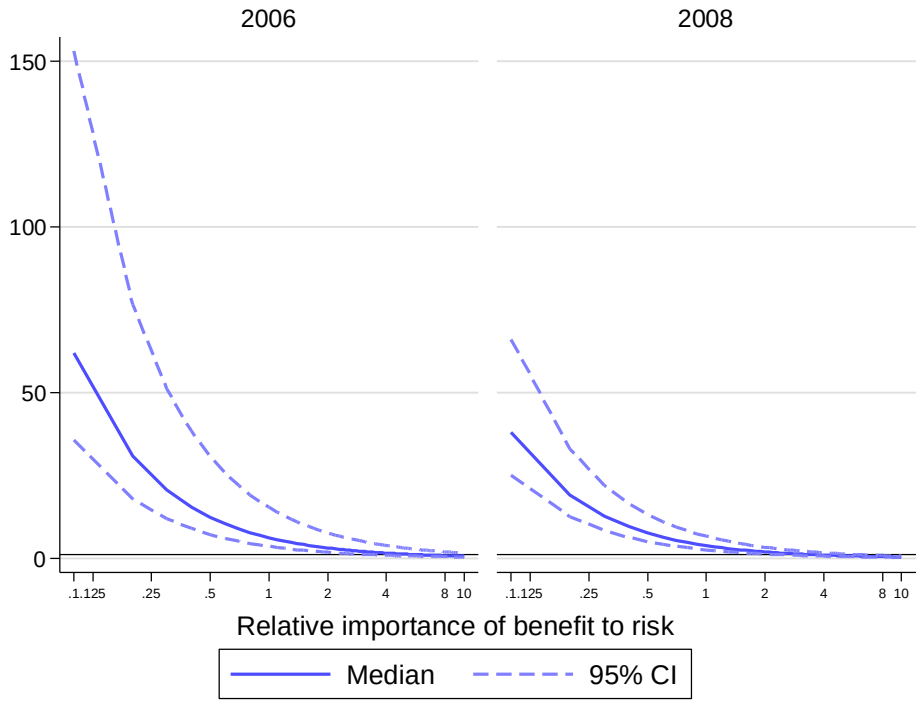


Figure 11-141 The ratio of number of people in the population whose weight loss were attributable to rimonabant to the number of people who experienced depressive disorders as a result of taking rimonabant over one year (BRR of PIN-ER-1)

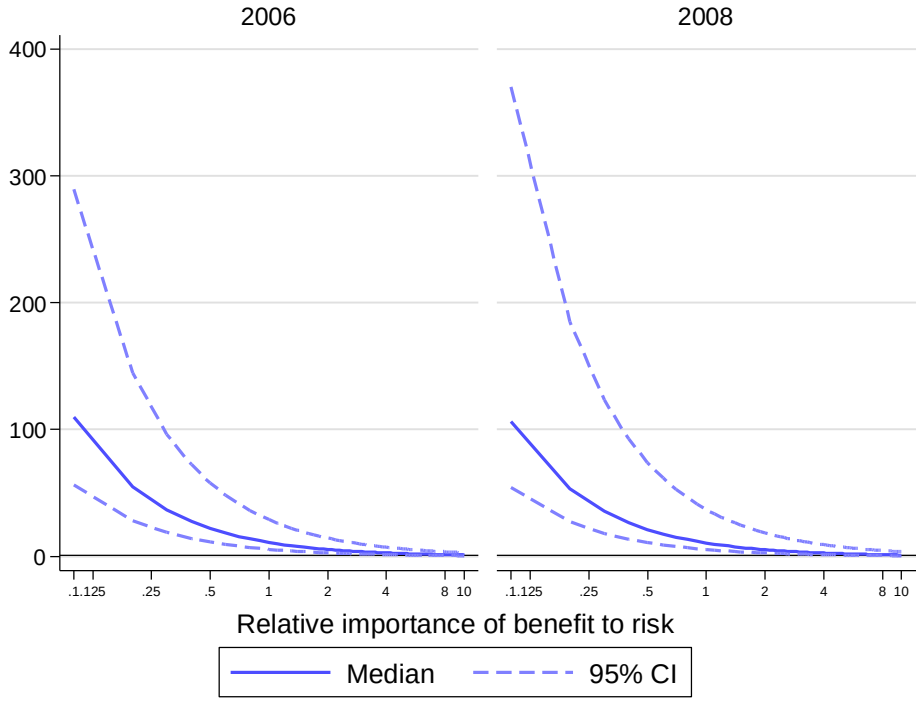


Figure 11-142 The ratio of number of people in the population whose weight loss were attributable to rimonabant to the number of people who experienced insomnia as a result of taking rimonabant over one year (BRR of PIN-ER-1)

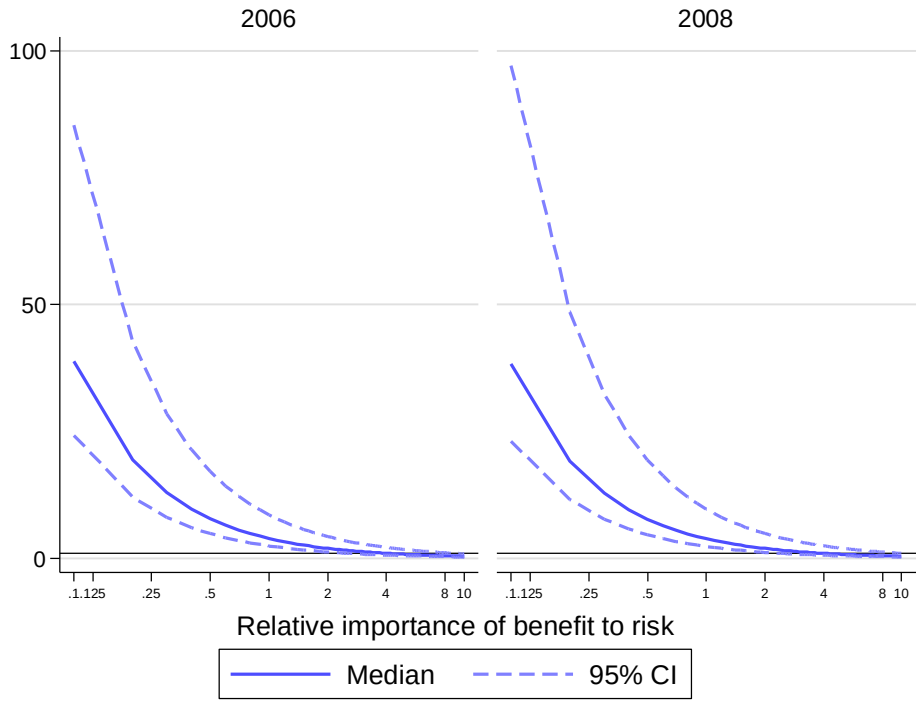


Figure 11-143 The ratio of number of people in the population whose weight loss were attributable to rimonabant to the number of people who experienced irritability as a result of taking rimonabant over one year (BRR of PIN-ER-1)

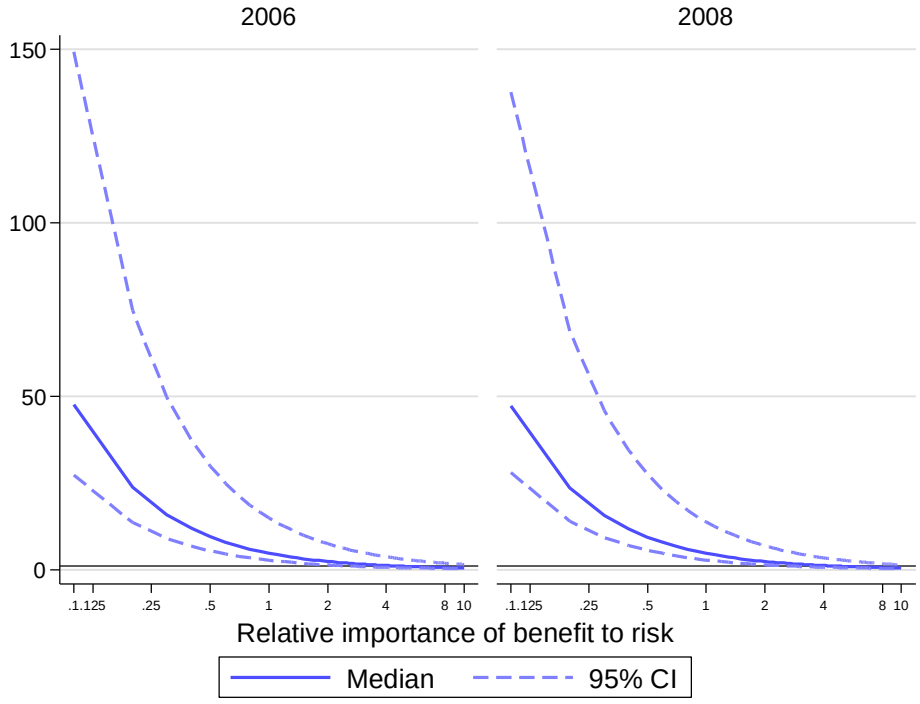


Figure 11-144 The ratio of number of people in the population whose weight loss were attributable to rimonabant to the number of people who experienced mood alterations with depressive symptoms as a result of taking rimonabant over one year (BRR of PIN-ER-1)

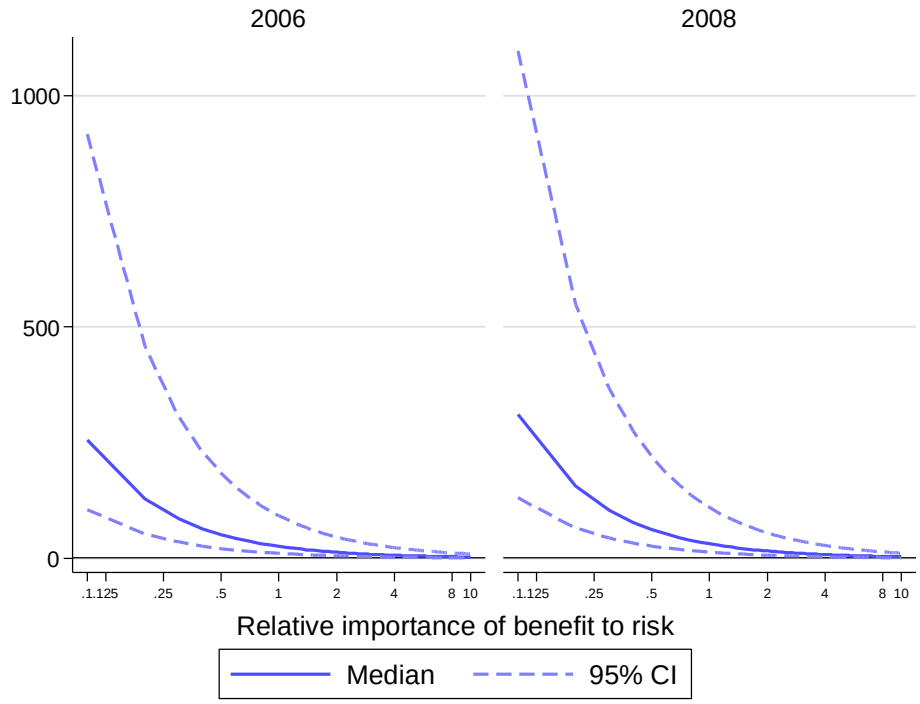


Figure 11-145 The ratio of number of people in the population whose weight loss were attributable to rimonabant to the number of people who experienced nervousness as a result of taking rimonabant over one year (BRR of PIN-ER-1)

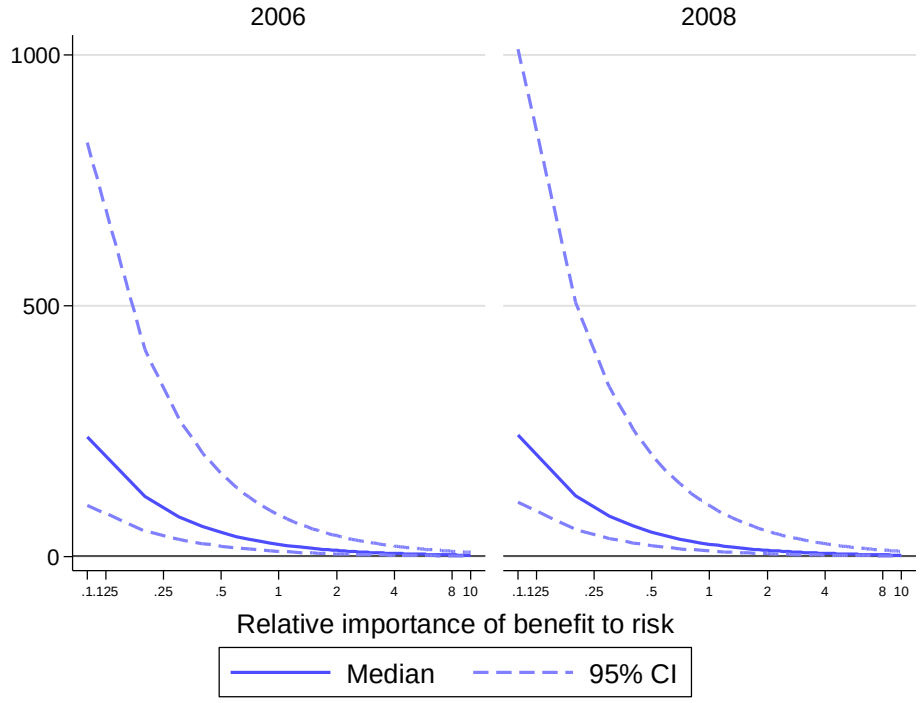


Figure 11-146 The ratio of number of people in the population whose weight loss were attributable to rimonabant to the number of people who experienced parasomnia as a result of taking rimonabant over one year (BRR of PIN-ER-1)

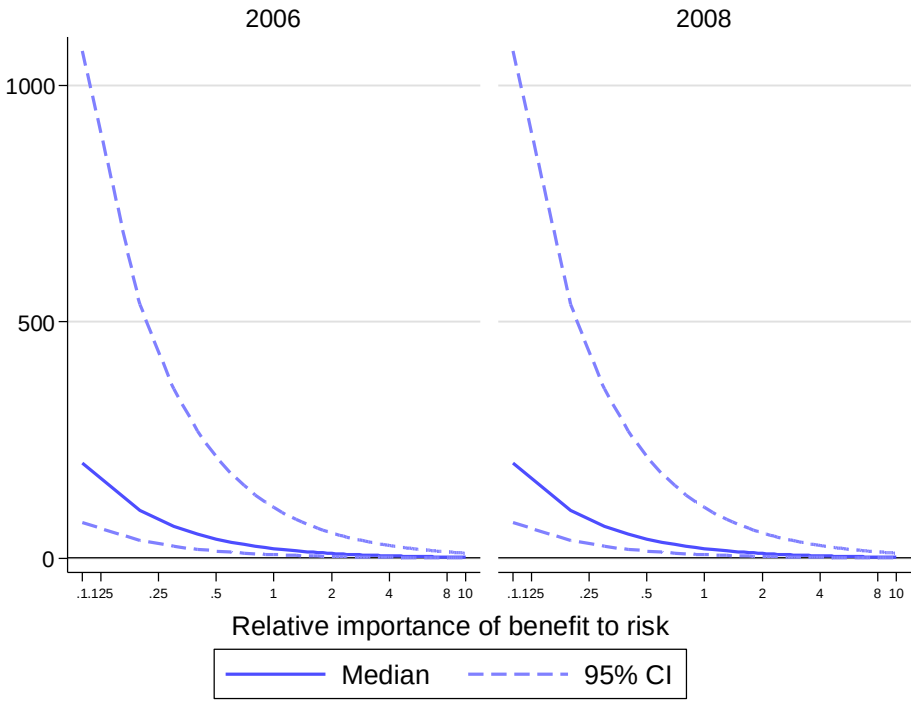


Figure 11-147 The ratio of number of people in the population whose weight loss were attributable to rimonabant to the number of people who experienced sleep disorder as a result of taking rimonabant over one year (BRR of PIN-ER-1)

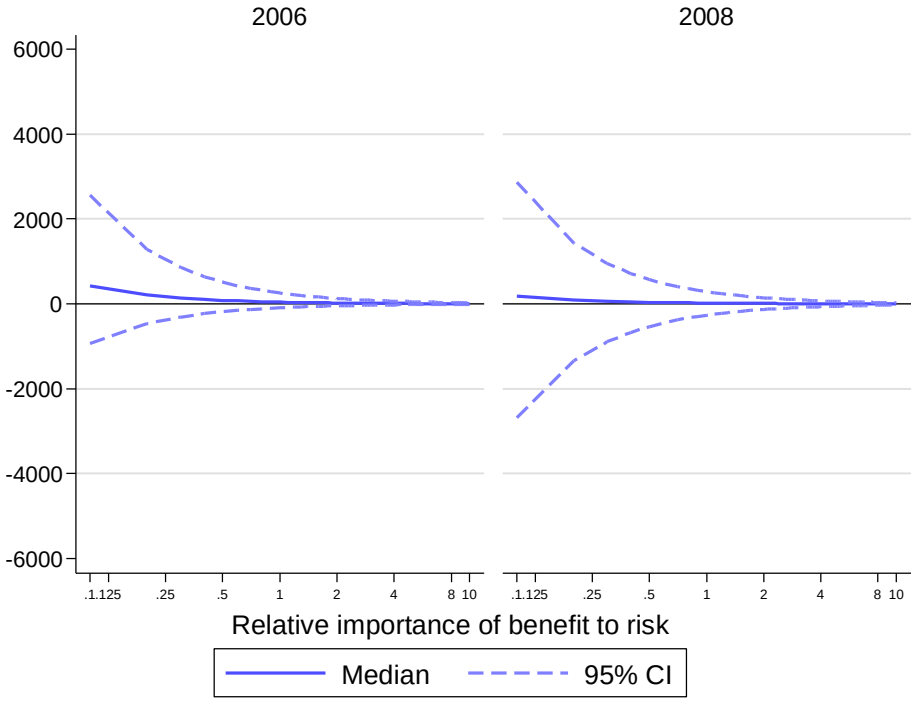


Figure 11-148 The ratio of number of people in the population whose weight loss were attributable to rimonabant to the number of people who experienced any severe psychiatric disorders as a result of taking rimonabant over one year (BRR of PIN-ER-1)

11.5.3.3.2.2 Net clinical benefit (NCB)

We present the results for events in psychiatric disorders and severe psychiatric disorder for illustrations. The net clinical benefits for each event (criterion) are plotted against the relative importance of benefit to risk where the larger relative values refer to putting more weight on risks. This is equivalent to saying that a decision-maker prefers to avoid the risk more than gaining the benefit. The benefit-risk balance is achieved when NCB equals zero that is when benefit equals risk.

For example in Figure 11-149 in the year 2008 with all available evidence from trials, when achieving weight loss is valued twice as important than avoiding anxiety i.e. relative importance of 0.5, the net clinical benefit is 1,360,066 (95% CI 1,064,064 – 1,669,787) persons over one year (PIN-ER-1). This means that rimonabant could benefit 1,360,066 people in the population. When weight loss is valued as important as avoiding anxiety, the NCB drops to 1,065,371 (95% CI 710,236 – 1,393,566) persons over one year. On the other hand, if it is in the utmost interest to avoid anxiety, say with an extreme relative importance of 10, the NCB drops to -4,229,102(95% CI -6,800,980 – -1,791,491) persons per year suggesting that rimonabant should be avoided. The benefit-risk balance of rimonabant in this situation reverses when the relative importance of benefit to risk is between 2.8 and 2.9.

Figure 11-149 – Figure 11-157 show the net clinical benefit of weight loss to psychiatric-related events which should be interpreted with caution within the context of analysis. We discuss the effect of decision-makers' risk tolerance and the application of net clinical benefit on impact numbers in Section 11.5.4.2. in comparison to BRR

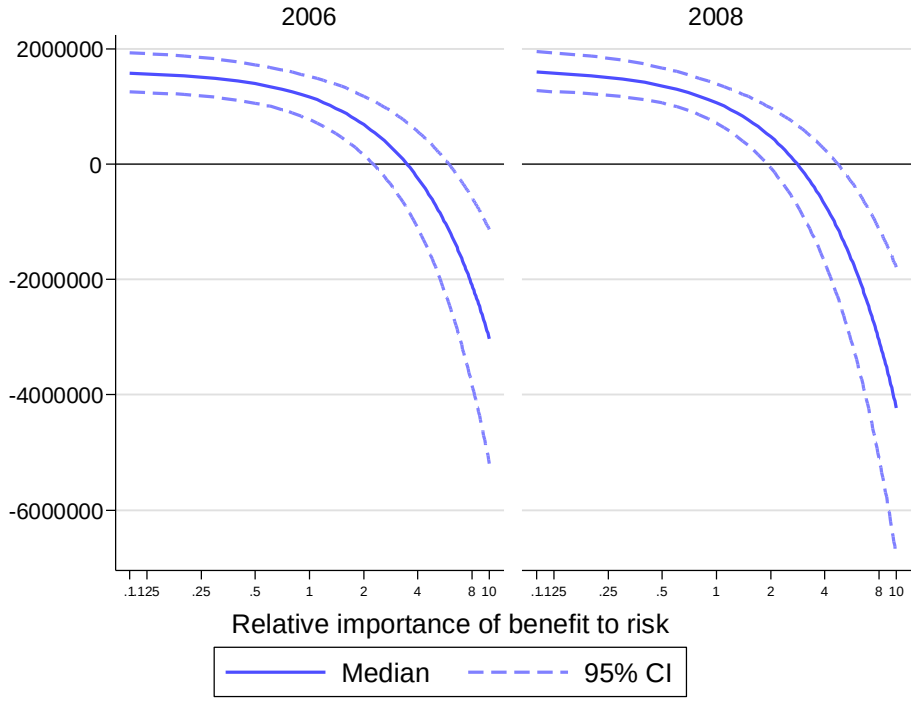


Figure 11-149 The total number of people in the population whose weight loss were attributable to rimonabant after the number of people who experienced anxiety as a result of taking rimonabant over one year had been discounted (NCB of PIN-ER-1)

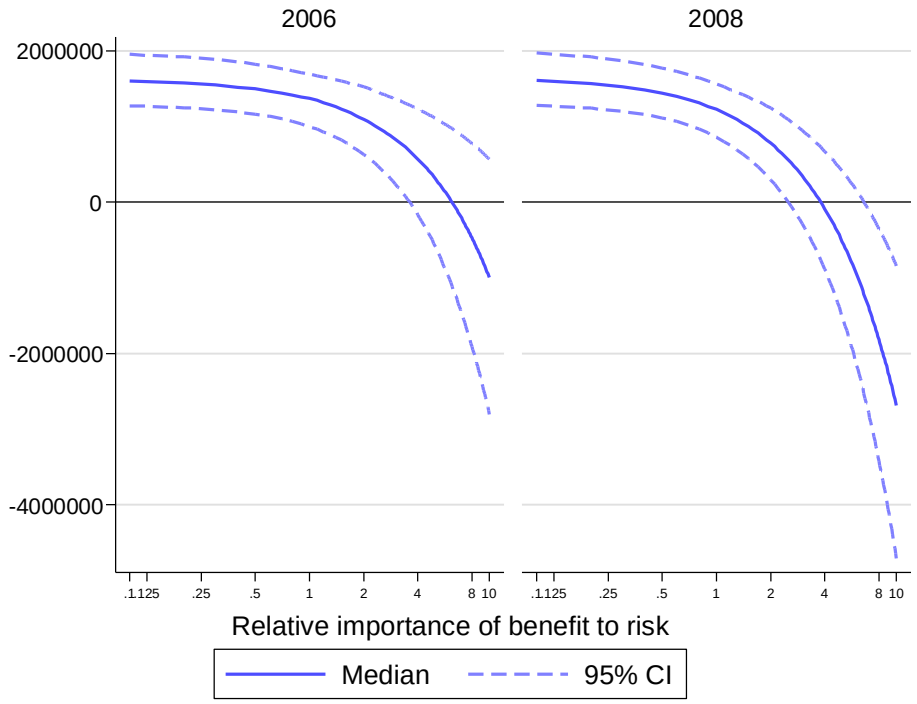


Figure 11-150 The total number of people in the population whose weight loss were attributable to rimonabant after the number of people who experienced depressive disorders as a result of taking rimonabant over one year had been discounted (NCB of PIN-ER-1)

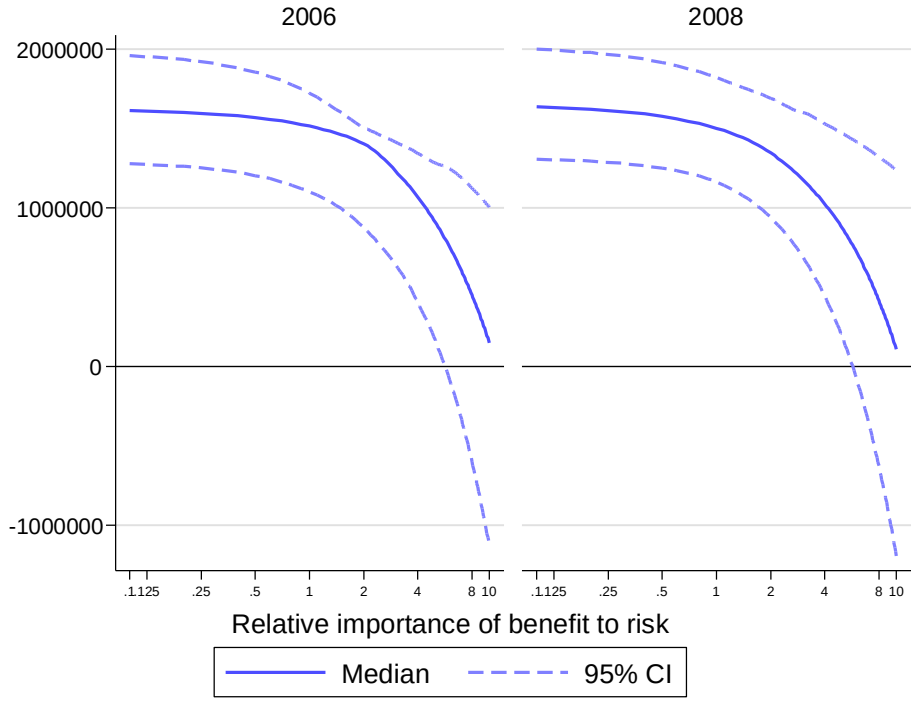


Figure 11-151 The total number of people in the population whose weight loss were attributable to rimonabant after the number of people who experienced insomnia as a result of taking rimonabant over one year had been discounted (NCB of PIN-ER-1)

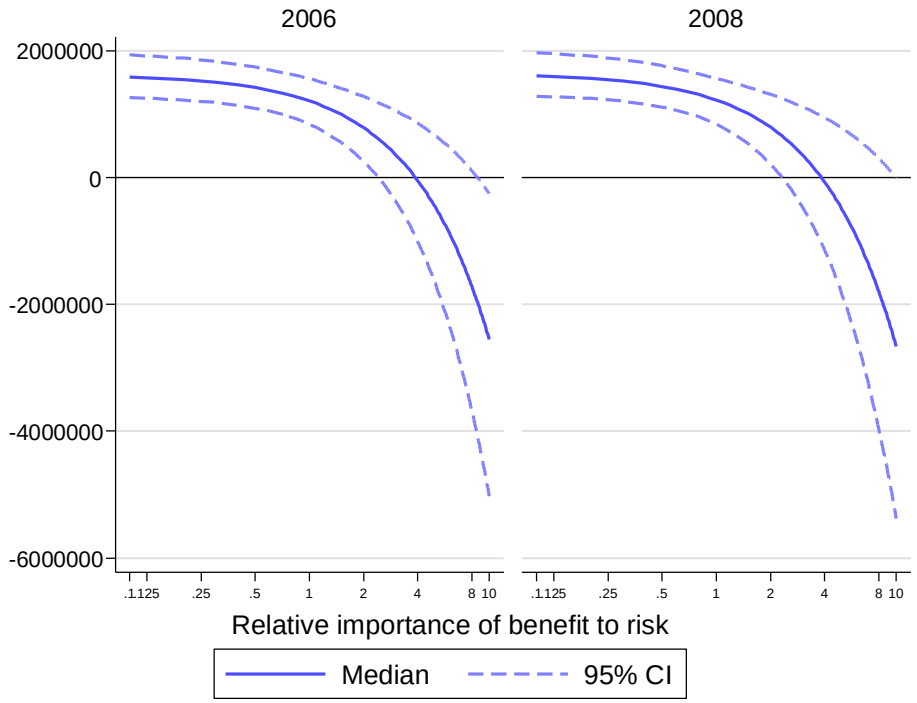


Figure 11-152 The total number of people in the population whose weight loss were attributable to rimonabant after the number of people who experienced irritability as a result of taking rimonabant over one year had been discounted (NCB of PIN-ER-1)

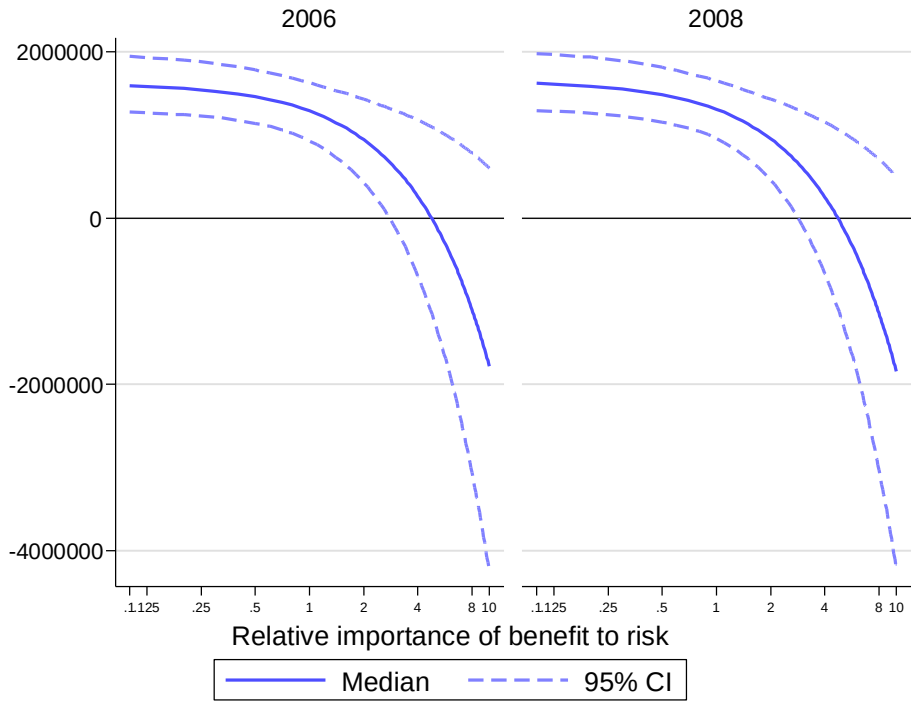


Figure 11-153 The total number of people in the population whose weight loss were attributable to rimonabant after the number of people who experienced mood alterations with depressive symptoms as a result of taking rimonabant over one year had been discounted (NCB of PIN-ER-1)

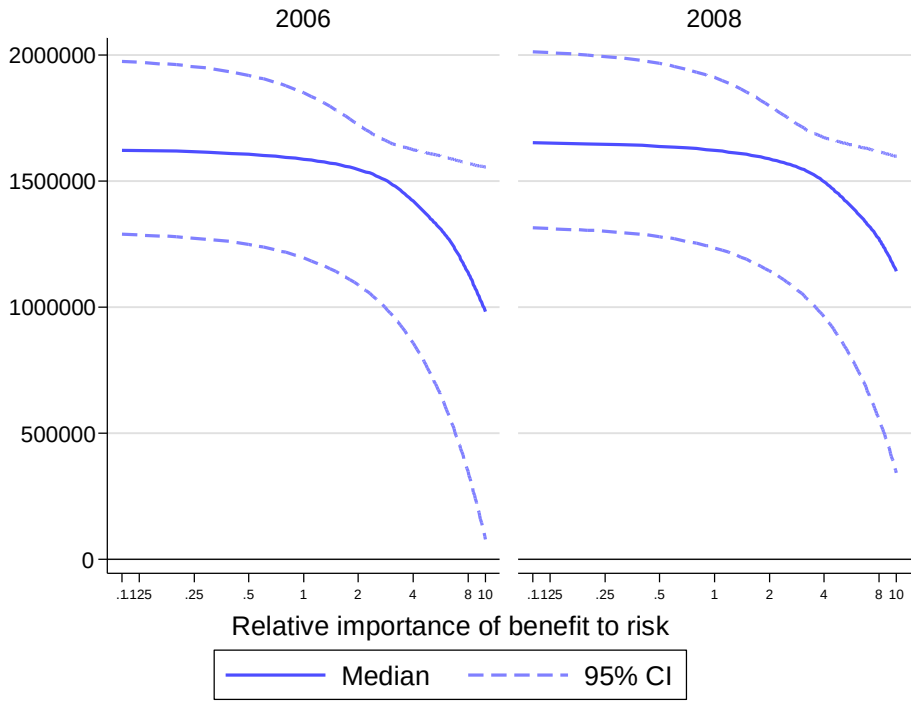


Figure 11-154 The total number of people in the population whose weight loss were attributable to rimonabant after the number of people who experienced nervousness as a result of taking rimonabant over one year had been discounted (NCB of PIN-ER-1)

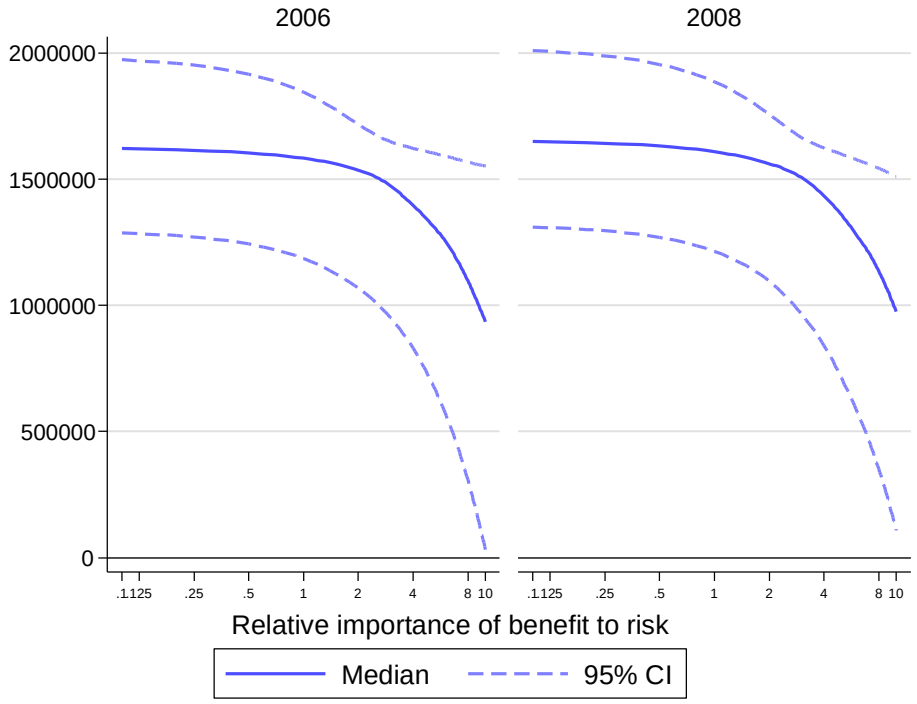


Figure 11-155 The total number of people in the population whose weight loss were attributable to rimonabant after the number of people who experienced parasomnia as a result of taking rimonabant over one year had been discounted (NCB of PIN-ER-1)

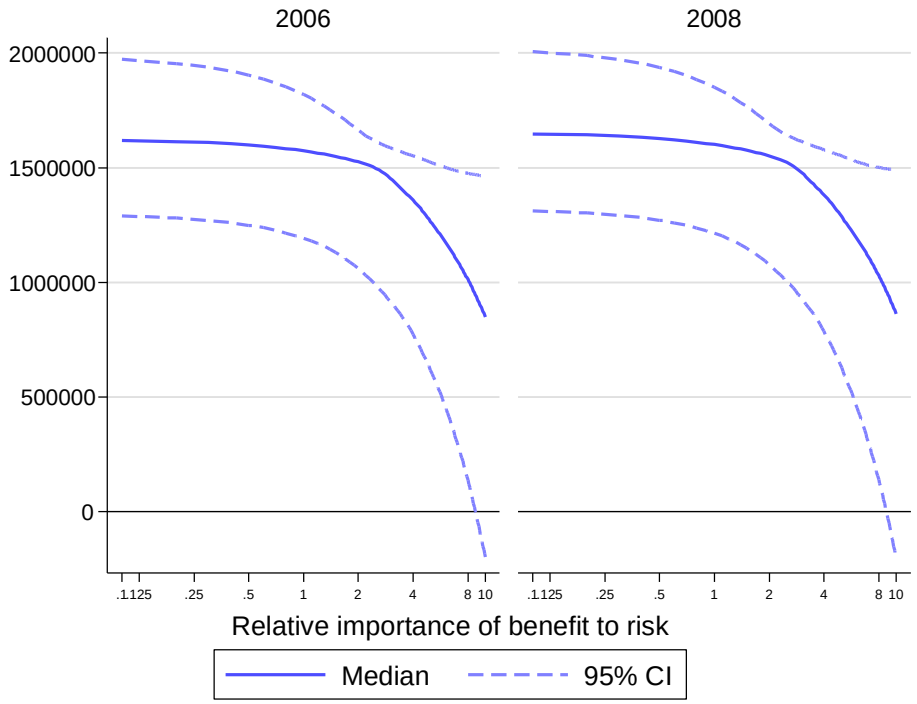


Figure 11-156 The total number of people in the population whose weight loss were attributable to rimonabant after the number of people who experienced sleep disorder as a result of taking rimonabant over one year had been discounted (NCB of PIN-ER-1)

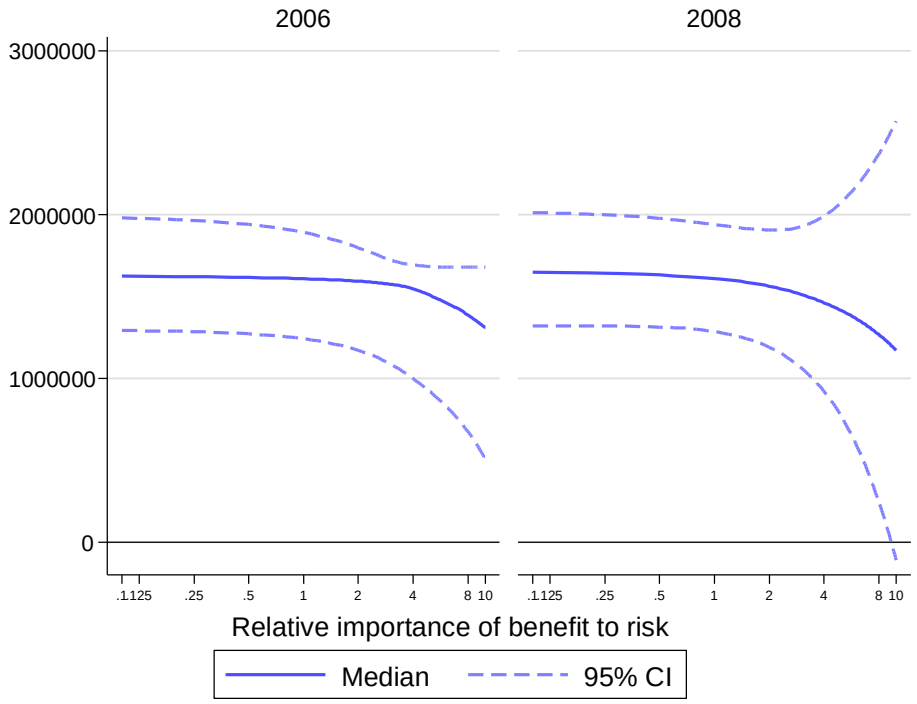


Figure 11-157 The total number of people in the population whose weight loss were attributable to rimonabant after the number of people who experienced any severe psychiatric disorder as a result of taking rimonabant over one year had been discounted (NCB of PIN-ER-1)

11.5.3.3.3 Uncertainty

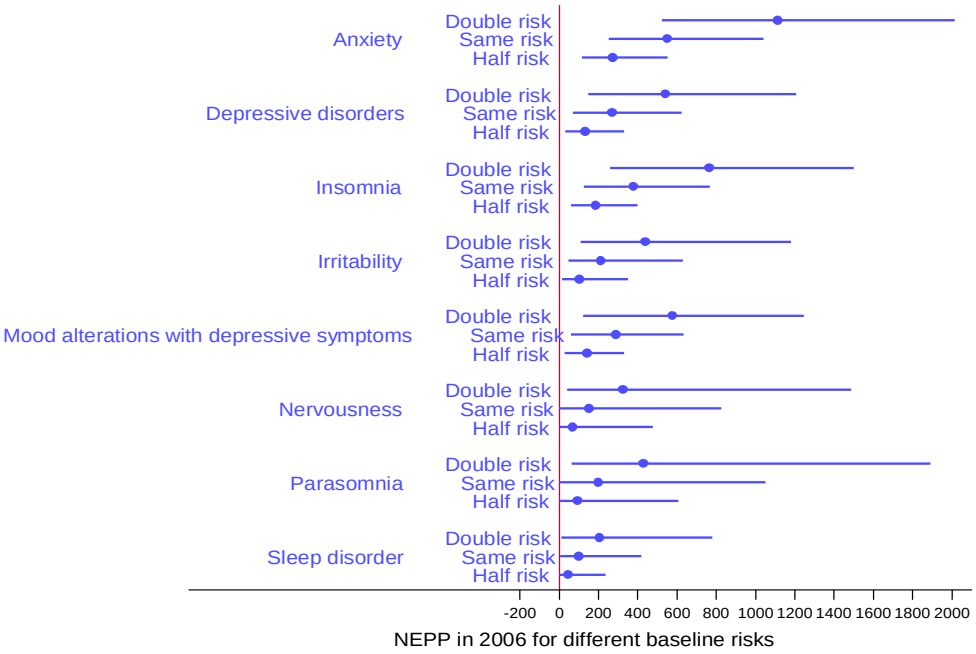


Figure 11-158 The effect of halving and doubling baseline rates for psychiatric adverse events on the NEPP in 2006

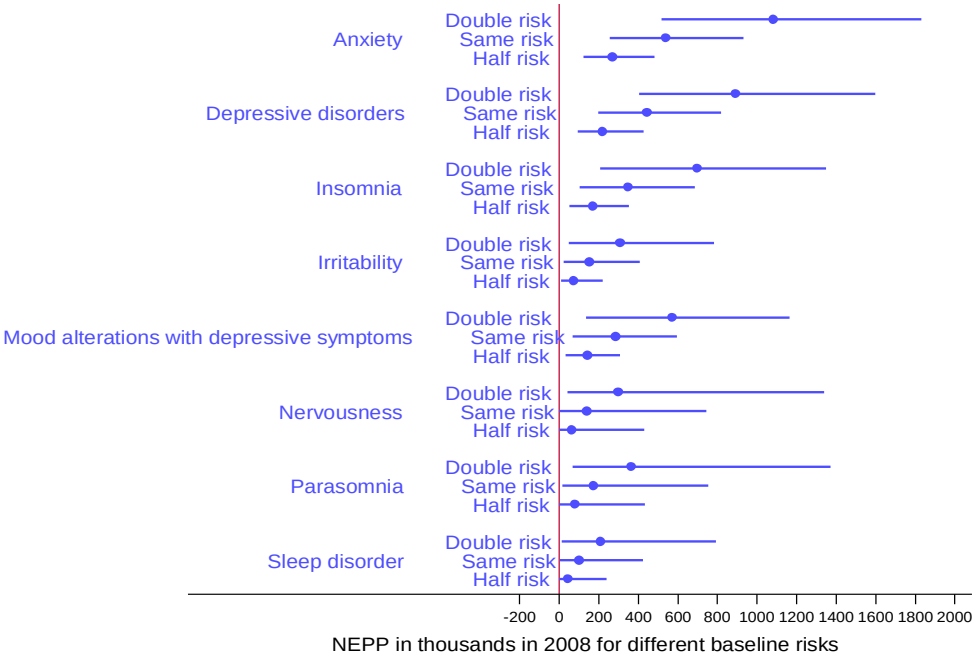


Figure 11-159 The effect of halving and doubling baseline rates for psychiatric adverse events on the NEPP in 2008

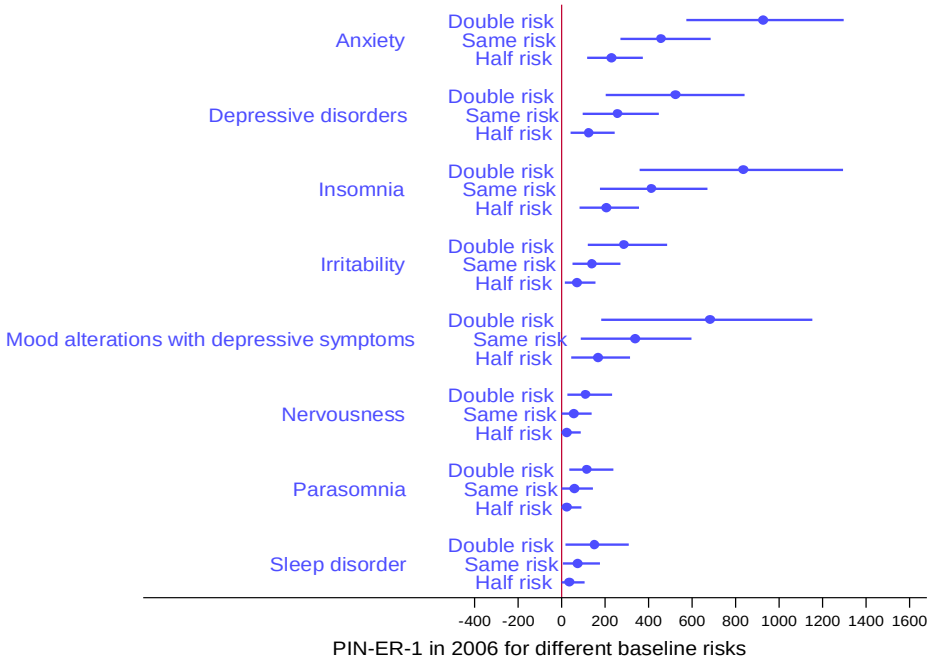


Figure 11-160 The effect of halving and doubling baseline rates for psychiatric adverse events on the PIN-ER-1 in 2006

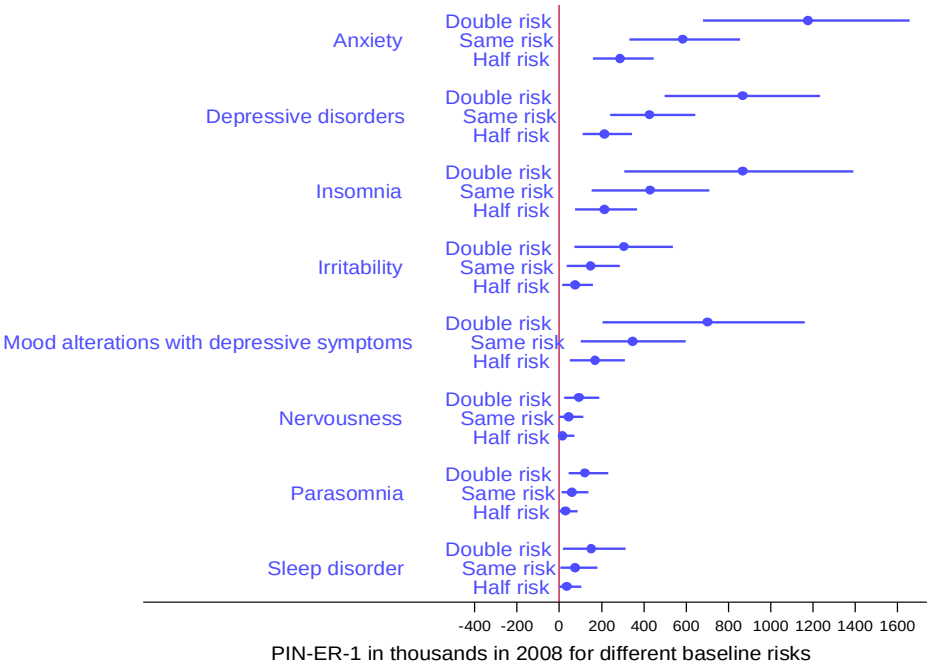


Figure 11-161 The effect of halving and doubling baseline rates for psychiatric adverse events on the PIN-ER-1 in 2008

11.5.3.4 Remarks

From the analyses, the benefit-risk balance appears to favour rimonabant. It is difficult to tell by how much since there is no overall metric to characterise the balance. We expect that benefits trump risks by a small margin overall because the trade-offs performed in Section 11.5.3.3.2 on achieving 10% weight loss in one year versus risks in psychiatric disorders and any severe psychiatric disorder suggest that heavy weight needs to be put on risks to overturn the positive balance.

11.5.4 Discussion

11.5.4.1 Benefit-risk balance and effects of uncertainty

Criteria analysis

In general, the benefits were considerably larger than risks and were also statistically significant at 5% level as suggested by EIN, NEPP and PIN-ER-1. Therefore the benefit almost always outweighs a risk when they are traded with equal weights. Of course this is not always true because although both benefit and risk are expressed in the same unit, they do not represent equal scale to allow direct trade-off.

The 95% confidence intervals on the criteria represent the amount of statistical uncertainties of the effect. For NEPP and PIN-ER-1, the width of the confidence intervals may be deceiving because they are already very large numbers. As in the NNT approach, EIN also suffers the small values problems when taking reciprocals of the attributable risks. This forced the confidence intervals for EIN to include $\pm\infty$ when the confidence intervals for the attributable risk includes zero. In Section 11.5.3.2.1 we showed how such phenomenon can be visualised [15]. Although wide, the confidence intervals give an idea of the uncertainties related to the effect size for a criterion, and allow decision-maker to make the conventional statistical judgments on based on hypothesis testing of equality.

The impact numbers in 2008 were largely greater than those in 2006. In most cases, these can be explained by the fact that the population size was larger in 2008. From a statistical point of view, this is not an issue and was expected. On the contrary, from a public health perspective, this means exposing more people to a potential risk factor, which may be problematic. Trial evidence in 2008 did not alter the conclusion for most criteria when combined with previous evidence. However, with all evidence, the association between rimonabant and risk of asthenia/fatigue became statistically significant from about 173,027 (95% CI -67,150 to 499,882) preventable events (NEPP) in 2006 to about 264,085 (95% CI 22,185 to 585,643) preventable events (NEPP) in England and Wales in 2008. Additionally, all trials evidence up to 2008 point to rimonabant being protective (indicated by negative NEPP for risks) of death from any causes with median NEPP of -66,305 (95% CI -125,952 to -8,316), which was statistically significant. The results were similar for PIN-ER-1 hence they are not discussed further here to avoid being repetitive.

Interpretations of impact numbers

EIN is interpreted in the same way as NNT that is the number of people who were exposed to rimonabant of whom one person would benefit or would experience adverse event.

The interpretations of NEPP and PIN-ER-*t* can be very tricky when applied to the clinical trials population where the evidence of benefits and risks came from. We attempted to calculate them for the trials population in the first hypothetical scenario where the issues of interpreting the NEPP and PIN-ER-1 became apparent. The number of events prevented in population or NEPP appears to be counter-intuitive since the events have already occurred and known. In fact, NEPP describing benefit criteria is also counter-intuitive because rimonabant does not prevent benefits. In hypothetical scenario with trials population, we have chosen to interpret NEPP as *"the number of people in the pivotal trials in whom the events would have been prevented if everybody in the trials had received placebo".* The interpretation can then be applied to both benefits and risks criteria, and also respects the terminology. PIN-ER-1 is easier to interpret for this population in the context if we were to eliminate the risk factor, which is simply *"the number of people in the pivotal trials in whom the events were due to rimonabant would have been prevented over the one year trial period if everybody in the trials had received placebo"*.

NEPP and PIN-ER-1 as applied in England and Wales population in the second hypothetical scenario are not free from interpretation problems. We have interpreted NEPP as *"the number of people in England and Wales in whom the*

events would have been prevented if rimonabant were not prescribed in the population" for the general interpretation and to avoid confusion with the terminology. We interpreted PIN-ER-1 as *"the number of people in England and Wales in whom the events were due to rimonabant would have been prevented over one year period if rimonabant were eliminated"* which suggests the effect of removing rimonabant from the population. However the more precise interpretation would be in the context of the analysis question. In our view, NEPP and PIN-ER-*t* should be redefined if they were to be used as a metric at the marketing authorisation stage simply because its current meaning and usefulness would have been lost. We would support renaming the impact numbers to "the number of events expected in the population" and "the population impact number of introducing a risk factor over time *t*" for NEPP and PIN-ER-*t* respectively when applied at marketing authorisation stage.

NEPP and PIN-ER-*t* as used for the population estimates data in 2008 demonstrated the best scenario for their application because rimonabant is already available on the market, and there were safety concerns relating to rimonabant. Their interpretations then immediately concur with the standard definitions in Table 11-15.

Sensitivity analysis

In our analyses, we assumed that the baseline rates of events in England and Wales in the second hypothetical scenario were similar to those observed in the trials. This may not always be true because trial populations are selective of group of people, and baseline rates of events also vary by populations e.g. by age, gender, ethnicity, geographical areas etc. The strength of impact numbers then come forth when interventions are truly targeted.

The uncertainty in baseline rates of events were dealt in two ways: by allowing for natural uncertainty in baseline rates parameter through probabilistic simulation and by running the simulations based on the effect of halving and doubling the baseline rates. Since NEPP and PIN-ER-*t* are proportional to the baseline rates, varying them is simply linear scaling of the impact numbers which are halving and doubling NEPP. However, such sensitivity analysis provide better perspective in terms of number of people affected where in a small population it might not matter but in a large population, if the true baseline rate of an adverse event is doubled, the number of people affected would be significantly larger.

11.5.4.2 Risk tolerance

11.5.4.2.1 Benefit-risk trade-off

We investigated how trade-off can be done on impact numbers in two ways: the benefit-risk ratio (BRR) approach, and the net clinical benefit (NCB) approach.

BRR trade-off metric is less favourable in this case since it also suffers small value problems when risks are rare as in NNT. We demonstrated in Figure 11-148 that confidence intervals may span across positive and negative values of BRR and could lead to infinity when the risk in the ratio does not matter the decision-maker. With the current visual representation of the BRR, it is difficult to interpret BRR. Table 11-22 shows the possible combinations of benefit and risk impact numbers and their interpretations. A better way to represent BRR of impact numbers is to plot the BRR against risk impact number and perhaps reversing the scale on the BRR axis as proposed for the presentation of NNT when encountered with similar issues. At this point, we found BRR for impact numbers can lead to many difficulties and is prone to misinterpretations.

Table 11-22 Various possible interpretations of BRR when the benefit or risk impact numbers are unknown

Benefit	Risk	BRR	Interpretation of BRR metric
$+ve$	$+ve$	$+ve$	>1: Benefit outweighs risk <1: Risk outweighs benefit
$+ve$	$-ve$	$-ve$	<0: Benefit outweighs risk (or more correctly, there is no risk)
$-ve$	$+ve$	$-ve$	<0: Risk outweighs benefit (or more correctly, there is no benefit)
$-ve$	$-ve$	$+ve$	>1: Risk outweighs benefit <1: Benefit outweighs risk

NCB performs better than BRR as trade-off metrics for impact numbers because positive NCB values always refer to benefit outweighing risk, and negative NCB values always refer to risk outweighing benefit. However, NCB produces a trade-off metric equivalent to the net number of people who benefit or at risk which may be difficult to be placed into context for inexperience decision-makers. Decision-makers are likely to require extensive knowledge about the population in order to make decisions based on NCB of impact numbers.

11.5.4.2.2 Relative importance

When BRR and NCB are used as trade-off metrics for impact numbers, the point of equilibrium in its simplest form is when BRR=1 or NCB=0. However, this is assuming that the benefit and risk in question are measured on the same scale. To some extent this may be true as they are both measured as the number of people but clinically some benefits and risks are more important than others. We dealt with this issue by transforming the scale of risk on to the scale of benefit by the relative importance k described in Section 11.5.2.7. The balance now is very dependent on the decision-maker. Therefore a consensus on the value of k needs to be established before any decision could be made. The relative importance k does not only depend on the seriousness of a risk, but is also dependent on the severity of the risk. The suitable choice of k is beyond the scope of this case study but is an important question for future research.

11.5.4.3 Linked decisions

There may be similar decisions have been made in the past on drugs with similar benefit-risk profiles to rimonabant but we only acknowledge it here but we have not carried it out as this case study is only for illustrations. Overall, the benefit-risk balance of rimonabant seems positive by a small margin. We arrive at this conclusion because the benefits were statistically significant and there were many associated risks but they were relatively low with about 10 times lower in magnitude compared to benefits. There was also no marked evidence suggesting the balance was unfavourable.

Link to future decisions of say to withdraw rimonabant from the market in 2008, given the underlying assumptions were correct, may mean conclusions along the line of “1,653,587 cases of weight loss attributable to the use of

rimonabant were prevented over one year" can be drawn from the analysis. Additionally, from the perspective of public health, there is likely to be other medical problems related to obesity that could have been prevented in the following year but are now needed to be dealt with. However, this case study could not justify such conclusions because several important factors such as patients' compliance, concomitant illnesses, concomitant medications, and market share of rimonabant have not been considered in the simulations of impact numbers in this case study.

11.5.4.4 Methodology evaluations

Appropriate frame

Table 11-23 Assessment of appropriate frame for benefit-risk approaches through practical experience

	Comments	Proposed improvements and/or extensions
PrOACT-URL	PrOACT-URL helped us focus on some of the issues to be addressed in the decision problem. We clarified beforehand the context of the problem, the decision-maker, the expected time required for analysis, and the expertise required. It also helped us consider the appropriate alternative for comparison, the study scenarios and the appropriate data having considered the complexity of the analysis. The guideline also forces us to plan how benefit-risk trade-off can be done, how to deal with uncertainty, which sensitivity analysis to be done and how decision-maker's risk attitude affects the balance, and to identify sources to benchmark the decisions from the analysis. By using PrOACT-URL as a structure of the report, the level of transparency is high providing sufficient audit trails but we feel that it is very demanding of what actually needs to be done. In effect, the application of PrOACT-URL can be very exhaustive and time-consuming. On the contrary, some difficulties encountered with the application of PrOACT-URL may be linked to the other benefit-risk assessment approach used within.	
Probabilistic simulations	n/a	
Impact numbers	Does not consider framing to the problem very well on their own with the exceptions of justifying evidence data.	
NNT	n/a	
BRR	n/a	
NCB*	n/a	

Meaningful reliable information

Table 11-24 Assessment of using meaningful reliable information for benefit-risk approaches through practical experience

	Comments	Proposed improvements and/or extensions
PrOACT-URL	Meaningful reliable information is emphasised in the guideline and must be documented throughout.	
Probabilistic simulations	Takes into account natural uncertainties of parameters.	
Impact numbers	Only benefit and risk criteria with binary outcomes can be used in impact number calculations because they are based on probabilities of events. Any type of criteria may be considered but work best with criteria on safety. The benefit-risk evidence central to the problems are available from clinical trials conducted for rimonabant. Baseline rates of events were not obtained for our analysis but can be reliably estimated from longitudinal databases such as the GPRD. Impact numbers do not require any clinical judgments about the effects, and do not directly involve consumers in the decision process.	There is a need to establish the best method to trade off benefits and risks. We demonstrated the application of BRR and NCB to achieve this. Multiple benefits and risks criteria need to be integrated into a single measure to make comparison of benefit and risk more straightforward. Weighting the criteria may be an option but we have not demonstrated this suggestion forward in this case study.
NNT	Only binary criteria can be used as NNT is based on probabilities. Only efficacy (NNT) and safety (NNH) criteria may be used. Data required were available from clinical trials. NNT approach does not require clinical judgment.	
BRR	BRR can only be calculated for one benefit versus one risk. To obtain a complete set of BRRs in a decision problem, BRR needs to be calculated for every combination each benefit criterion to each risk criterion which is an exhaustive exercise both for analyst and decision-maker. BRR does not require clinical judgment.	
NCB*	The same as BRR above.	

Clear values and trade-offs

Table 11-25 Assessment of the availability of clear values and trade-offs for benefit-risk approaches through practical experience

	Comments	Proposed improvements and/or extensions
PrOACT-URL	It emphasises making explicit value judgments on criteria but value judgments are not required for the analysis we performed.	
Probabilistic simulations	Probabilistic simulation method allows uncertainties on the parameters to be incorporated into the model which are propagated to the final results.	
Impact numbers	Value judgments are not required. Benefit and risk criteria are defined by the outcomes in the trials. However, trial reporting can be inconsistent thus limit the amount of evidence that are comparable and can be used together. Impact numbers are measured on the same unit for both benefit and risk criteria, but the scale may not be directly comparable. Impact number for each criterion is presented individually and there is no trade-off method for benefit and risk. This results in final results which are difficult to digest to arrive at a clear decision. Since there are also several impact numbers with different interpretations and for slightly different purposes, it can be unclear as to which is required.	NEPP and PIN-ER-t are the two best impact numbers to use. Other impact numbers can be disregarded. Method to trade-off benefit and risk is required. We attempted the use of BRR and NCB in this study. Method to combine multiple criteria (benefits or risks) into a single measure prior to trade-off is also required. Importance weighting can be used but we have not attempted it here.
NNT	Similar to impact numbers and particularly equivalent to EIN. The problem with NNT is encountered with rare events.	
BRR	The approach itself is sound and provides clear values and trade-offs. Value judgments are not required. Consequently, for some benefit and risk criteria, the trade-off can be meaningless because the scales are not comparable. Simple adjustments such as multiplying by relative importance can be done to make the scales directly comparable. Furthermore, we found out that when BRR is used in combination with impact numbers, the values become difficult to interpret, and could potentially be misleading (see discussion in Section 11.5.3.3.2.1). By the end of the analysis, it is still	We can simply multiply the criteria by relative importance to produce impact numbers on the same scale for direct trade-off. However, the appropriate choice of relative importance is beyond the scope of this case study.

	difficult to see the overall benefit-risk balance and what is the decision to be made.	
NCB*	This is very similar to BRR with the exception that interpretations are more straightforward. However, it introduces values which are related to the number of people in the population which may be difficult to judge just by the face value.	Same as BRR.

Logically correct reasoning

Table 11-26 Assessment of the logically correct reasoning for benefit-risk approaches through practical experience

	Comments	Proposed improvements and/or extensions
PrOACT-URL	n/a	
Probabilistic simulations	Any numeric data can be handled. Uncertainties in the data are sampled from appropriate statistical distributions. Complex network of evidence can be handled where many other approaches would fail.	
Impact numbers	Only binary data can be handled. There is no method to accommodate uncertainties except to recalculate impact numbers for different rates assumptions. Criteria are not combined through impact numbers analysis. We had some difficulties in choosing the impact numbers to present but we resolved this by discussing them with the team and decided to make things as simple as possible. We also contacted the author of impact numbers to get his opinions on the choice of impact numbers and we have agreed on NEPP and PIN-ER-t. It was suggested that impact numbers should be calculated in the trial population although this is not the usual scenario impact numbers are used for. We demonstrated in the first study scenario how impact numbers behave which to our experience is somewhat confusing and mismatched.	
NNT	Only binary data can be handled. Uncertainties are inherited from the uncertainties in the attributable risks. Criteria are not combined through NNT analysis. Technical flaws with NNT arise in the confidence intervals when there is no attributable risk which equates to confidence intervals including the point of infinity. There are methods to interpret, visualise and construct the empirical distribution for the confidence intervals in such situations [15]	

BRR	Any numeric data can be handled. There is no specific method to accommodate uncertainties. Benefit is divided by risk to obtain BRR on the assumption of the same relative importance. BRR is difficult to interpret when the denominator approaches zero.	An appropriate scaling factor can be used as the relative importance.
NCB*	Any numeric data can be handled. There is no specific method to accommodate uncertainties. Risk is subtracted from benefit to obtain NCB on the assumption of the same relative importance.	An appropriate scaling factor can be used as the relative importance.

Commitment to action

Table 11-27 Assessment of the commitment to action for benefit-risk approaches through practical experience

	Comments	Proposed improvements and/or extensions
PrOACT-URL	It certainly develops insight and promotes learning by forcing related issues to be thought about carefully. It also ensures transparency and clear audit trails but the requirements are very exhaustive to meet in very short period of time. On the other hand, it may just be what is needed for regulatory decision-making.	
Probabilistic simulations	It ensures that uncertain events are dealt with properly. It also provides an overview of the true shape of the distributions of the parameters which may influence decisions.	
Impact numbers	The results from the analyses are directly applicable to the population of interest where the context can be placed immediately in terms of number of people who would be affected by the decisions. Impact numbers are easy to understand but do not mean very much when just benefit-risk balance is to be established for an active drug to placebo. Impact numbers are more useful when comparing active drugs to determine which drug has better benefit-risk profile. However, when an active drug is compared to placebo and the decision question is related to resource allocation or to foreseeable burden of a particular event, impact numbers can then be directly associated with the decisions and actions to be taken. Furthermore, in analyses involving many criteria, the results from impact numbers are difficult to communicate and do not readily lend to a conclusion.	
NNT	The results are the same as EIN but does not have population context as in impact numbers. The interpretation does not have direct implications on the decision to be made. Furthermore, in analyses involving many criteria, the results from NNT are difficult to communicate and do not readily lend to a conclusion.	

BRR	Easy to communicate as relative magnitude in most cases but do not perform well with impact numbers.	
NCB*	Easy to communicate as number of people but the numbers have to be put in context with additional related information to complete the picture. Potentially a good combination with impact numbers.	

11.5.5 Conclusion

Whilst probabilistic simulation method and impact numbers are a good combination for benefit-risk assessment, there are still many unresolved issues related to the methods. The use of impact numbers is very specific to answer specific public health questions; that is the correct targeted population and the underlying concerns must be considered a priori otherwise the interpretations of the results become very difficult. Although the probabilistic simulation method is very flexible to account various possibilities, the combination with impact numbers lacks the much needed framework in a benefit-risk assessment of medicines. PrOACT-URL asks for great deal of details which feel very exhaustive particularly because there are no established method to integrate benefit and risk, to perform benefit-risk trade-off, to perform sensitivity analyses or to present results. These result in various possibilities to be explored and justified, which cost time.

Even after great deal of effort to quantify benefits and risks of rimonabant when compared to placebo, the benefit-risk balance is still unclear. Impact numbers approach to benefit-risk assessment may be more suitable for resource-allocation exercise or in epidemiological studies because they directly describe the impact on the populations of interest in terms of number of people affected. Impact numbers analysis may also be suitable as second line approach to provide an overview of the impact in a population following another approach to benefit-risk assessment. The simplicity of impact numbers thence requires any limitations and underlying assumptions to be clearly stated and discussed. Unfortunately, at this stage, even with combinations with other approaches, impact numbers are not matured enough for use in regulatory settings for the purpose of making decisions on marketing authorisation. Having said that, the impact numbers were not developed with that agenda in mind, hence the difficulties we encountered in the application of the impact numbers at the marketing authorisation stage especially with the hypothetical scenario of the trials population may indicate the applications of impact numbers outside its epidemiological roots should be used with care.

11.5.6 Supplements

Please see “Supplement to Rimonabant Wave 1 Case study Report, Oct 2011”