IMI Work Package 5: Report 2:b:i Benefit - Risk

Wave 2 Case Study Report: Rimonabant

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Glossary

BMI	Body Mass Index
BRAT	Benefit Risk Action Team
BRR	Benefit Risk Ratio
CHMP	Committee for Medicinal Products for Human Use
DCE	Discrete Choice Experiment
EMEA	European Medicines Agency
EPAR	European Public Assessment Report
FDA	Food and Drug Administration
ITC	Indirect Treatment Comparison
MAH	Marketing Authorization Holder
MCDA	Multi Criteria Decision Analysis
MTC	Mixed Treatment Comparison
NNH	Number Needed to Harm
NNT	Number Needed to Treat
PEM	Prescription Event Monitoring
PSM	Probabilistic Simulation Methods
RCT	Randomised Controlled Trial
SMAA	Stochastic Multicriteria Acceptability Analysis
T2DM	Type Two Diabetes Mellitus

1 Introduction

1.1 Epidemiology of obesity

Approximately two-thirds of the United States' population is overweight or obese, defined as having a body mass index (BMI) of 25 kg/m^2 and above (1). In Europe, there is also a high prevalence of overweight, estimated to affect approximately 50% of adults, and obesity, estimated to affect up to 30% of adults (2, 3). As obesity is strongly associated with an increased risk of type two diabetes mellitus (T2DM), cardiovascular diseases, and premature mortality (4), it is a major public health concern (5). With around 2.5 million deaths worldwide due to medical complications associated with obesity, there is a large unmet medical need for safe and effective treatments (6). The prevalence of obesity is increasing not only in the US but also in other countries, in adults as well as children (1). As diet and exercise have demonstrated limited success in weight reduction (7), alternative approaches to treat obesity are necessary.

1.2 Rimonabant for the treatment of obesity

Rimonabant (ACOMPLIA/ZIMULTI®) is a selective antagonist of cannabinoid type I (CB1) receptors. The cannabinoid system is involved in the central regulation of food intake and the central nervous system reward system. CB1 receptors were first found in the brain, and later in several human tissues, including adipocytes (fat cells) (8).

Rimonabant was a new drug, the first in class, indicated for weight loss in obese, and overweight patients with weight-related co-morbidities such as T2DM. Trials have also shown that the drug could also potentially improve HbA1c and lipid profiles (increased HDL cholesterol and reduced triglycerides) in overweight or obese patients (9-12). It should be noted that rimonabant was not indicated for T2DM alone—without the presence of overweight or obesity, because its effect size on HBA1C remained uncertain according to the Committee for Medicinal Products for Human Use (CHMP), despite being large enough to be clinically relevant (10, 13). Also, although associated with an improvement in HDL cholesterol, its subfractions, and triglycerides, rimonabant was not associated with a decrease in cardiovascular complications (outcome data not available). Hence, it was not indicated for the treatment of dyslipidaemia (10, 13).

In November 2008, rimonabant was suspended in all the Member States in which the product was marketed, and in December 2008, the marketing authorisation holder (MAH), Sanofi-Aventis, voluntarily withdrew its marketing authorisation. In January 2009, the European Commission withdrew the marketing authorization for rimonabant on the grounds of a perceived negative benefit-risk balance based on post-marketing data (10, 13). A benefit-risk analysis using quantitative methods which take into account the benefits and risks of rimonabant, and their perceived relative importance according to stakeholders was not performed.

1.3 Previous work from Wave 1

In PROTECT WP5 Wave 1, we performed an evaluation with the aim of comparing different benefit-risk methods using rimonabant as a model relative to placebo. Active treatment comparators were not used. Eight benefit-risk methods were tested: BRAT and PrOACT – URL frameworks, Multi-Criteria Decision Analysis (MCDA), SMAA, Number Needed to Treat (NNT) and Number Need to Harm (NNH), Benefit-risk Ratio (BRR), and Probabilistic Simulation Methods (PSM). Our team only used publically available pre-marketing data in the Wave 1 case study, with the exception of the

impact numbers analysis where the second time point included clinical trials data collected post-approval.

Results from Wave 1 demonstrated that, in general, rimonabant was better than placebo. BRAT and PrOACT-URL were observed to be very similar. MCDA and SMAA were considered the most suitable benefit-risk assessment methods when compared against all those evaluated due to their ability to synthesise benefits and risks within regulatory context. The main advantage of SMAA over MCDA was that SMAA allowed for flexibility in the uncertainty regarding the data range and criteria weight information. A disadvantage of SMAA is that the currently available software, JSMAA, is not able to analyse complex models with a complete number of criteria for multiple treatment comparators.

1.4 Structure of this report

The purpose of this report is to describe the experience our team gained during the rimonabant Wave 2 case study.

We firstly provide an introduction to the case study in Section 2, outline our aim and objectives, and describe the decision context. Also, the two active comparators to be used in Wave 2, sibutramine and orlistat, are detailed.

Section 3 lists all of the favourable and unfavourable effects for each treatment under consideration. In this section, potential publically available data sources for use within this case study are identified, the benefit and risk criteria are defined, and relevant data is extracted. In Section 4 this benefit and risk data are then synthesised with the use of an indirect treatment comparison (ITC).

The steps of the benefit-risk analysis methods adopted for use in Wave 2 are described in Section 5. The team explored the use of Discrete Choice Experiments (DCE) to elicit preference values from lay people; used Indirect Treatment Comparison (ITC) for data synthesis; developed Stata code for Stochastic Multicriteria Acceptability Analysis (SMAA) and investigated the use of dashboards as a visual presentation tool for benefit-risk assessment. DCE results are reported in Section 6, SMAA results in Section 7, and visual results are presented in Section 0.

Lastly, we discuss our experience with the Wave 2 case study in Section 9, and outline our recommendations for future work in Section 10.

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2 Introduction to Wave 2 rimonabant case study

From Wave 1, we learned that results from decision analysis models are highly dependent on criteria weighting and further work should investigate methods of preference elicitation. Additionally, the advantages of a decision analysis model are more prominent in cases of complex decision-making with multiple criteria and multiple alternative comparator treatments. Therefore, for Wave 2, we proposed to include two other alternatives in the assessment of medical treatments for obesity, sibutramine and orlistat. We set out to extend the work in Wave 1 and address the recommendations that were made in the case study report.

2.1 Aim and objectives

The aim of Wave 2 was to evaluate the benefit-risk balance of rimonabant 20mg, while comparing it against placebo and two active comparators: orlistat 120mg and sibutramine 15mg. This aim was met via the following objectives:

1. To estimate the treatment effects of rimonabant, placebo and two active comparators (sibutramine and orlistat) using a indirect treatment comparison (ITC)
2. To elicit lay preferences regarding the benefits and risks of obesity treatments
3. To explore the potential of performing SMAA outside of JSMAA
4. To apply and evaluate sophisticated graphical techniques that can be used in benefit-risk assessment

2.2 Team structure

To meet the objectives of the case study, we organised our team into three sub-teams:

1. Sub-team 1: Discrete choice experiment (Section 5.1)
2. Sub-team 2: ITC and SMAA (Sections 4 and 5.2)
3. Sub-team 3: Visual representation (Section 5.3)

2.3 Decision context

The decision context is described in Table 2-1 and a lay perspective of benefits and risks was adopted.

Table 2-1 the decision context/problem to address

Indication	**Medical treatment of obesity**
Drug	Rimonabant
Dosage	20mg
Comparator	Sibutramine, Orlistat, Placebo
Population	(a) For all, a BMI greater than or equal to 30 kg/m^2 AND (b) For rimonabant and sibutramine a BMI of 27.0 to 29.9 kg/m^2 with one or more major obesity-related co-morbidities (c) For orlistat, a BMI of 28.0 to 29.9 kg/m^2 with one or more major obesity-related co-morbidities
Time horizon for outcomes	One year

Stakeholder perspective	Patient

2.4 Alternative medical treatments for obesity

In Wave 2, two active comparators were used in the decision models in addition to placebo and rimonabant: sibutramine and orlistat.

2.4.1 Sibutramine

Sibutramine (MERIDIA®) is a serotonin and noradrenaline reuptake inhibitor. It was licensed as an adjunctive therapy indicated for weight loss and maintenance of weight loss in:

- Patients with nutritional obesity and a BMI of 30 kg/m^2 or higher
- Patients with a BMI of 27 kg/m^2 or higher, with co-morbid weight related risk factors (e.g. diabetes or dyslipidaemia)

Sibutramine was first licensed in the European Union in January 1999. Safety concerns over cardiovascular side effects were raised in 2002. However, the data available at that time did not provide any firm conclusion regarding the potential for cardiovascular side effects. Consequently, the MAH was requested to conduct a large randomised controlled study to investigate the effect of sibutramine on cardiovascular complications, particularly in presence of additional cardiovascular risk factors. As a result, the Sibutramine Cardiovascular OUTcome (SCOUT) study (14) was initiated in January 2003.

Data from the SCOUT study confirmed that sibutramine was associated with an increased risk of cardiovascular complications (non-fatal myocardial infarction, non-fatal stroke, cardiac arrest and cardiovascular death), particularly in high-risk patients. Therefore, the CHMP concluded that the benefit-risk balance was not favourable and recommended suspension of its marketing authorisation in 2009.

2.4.2 Orlistat

Orlistat (XENICAL®) is a potent, specific and long acting inhibitor of gastric and pancreatic lipases in the lumen of the stomach and small intestine, crucial for hydrolysis of dietary fat. Therefore, it reduces dietary fat absorption and induces weight loss.

Orlistat is indicated in conjunction with a mildly hypocaloric diet for weight loss in:

- Patients with nutritional obesity and a BMI of 30 kg/m^2 or higher
- Patients with a BMI of 28 kg/m^2 or higher, with co-morbid weight related risk factors

Gastrointestinal adverse events are common with orlistat. Additionally, cases of hypersensitivity, transaminitis, and bullous eruptions were reported in 1999 and 2001.

Orlistat was first authorised in the European Union in July 1998 and a 5-year marketing authorisation was granted in 2003 and 2008 (15).

3 Data availability, data extraction and criteria definitions

In this section we discuss all of the potential favourable and unfavourable outcomes for each treatment under consideration. Next, we describe how the benefit and risk criteria are defined, and the data that will be adopted for use to evaluate the benefits and risks in all subsequent ITC and SMAA analyses.

3.1 Favourable and unfavourable outcomes by treatment

3.1.1 Rimonabant

A complete value tree for rimonabant is shown in Figure 3-1. It presents all of the favourable and unfavourable outcomes for rimonabant using clinical trial data and data extracted from the EPAR (13, 16).

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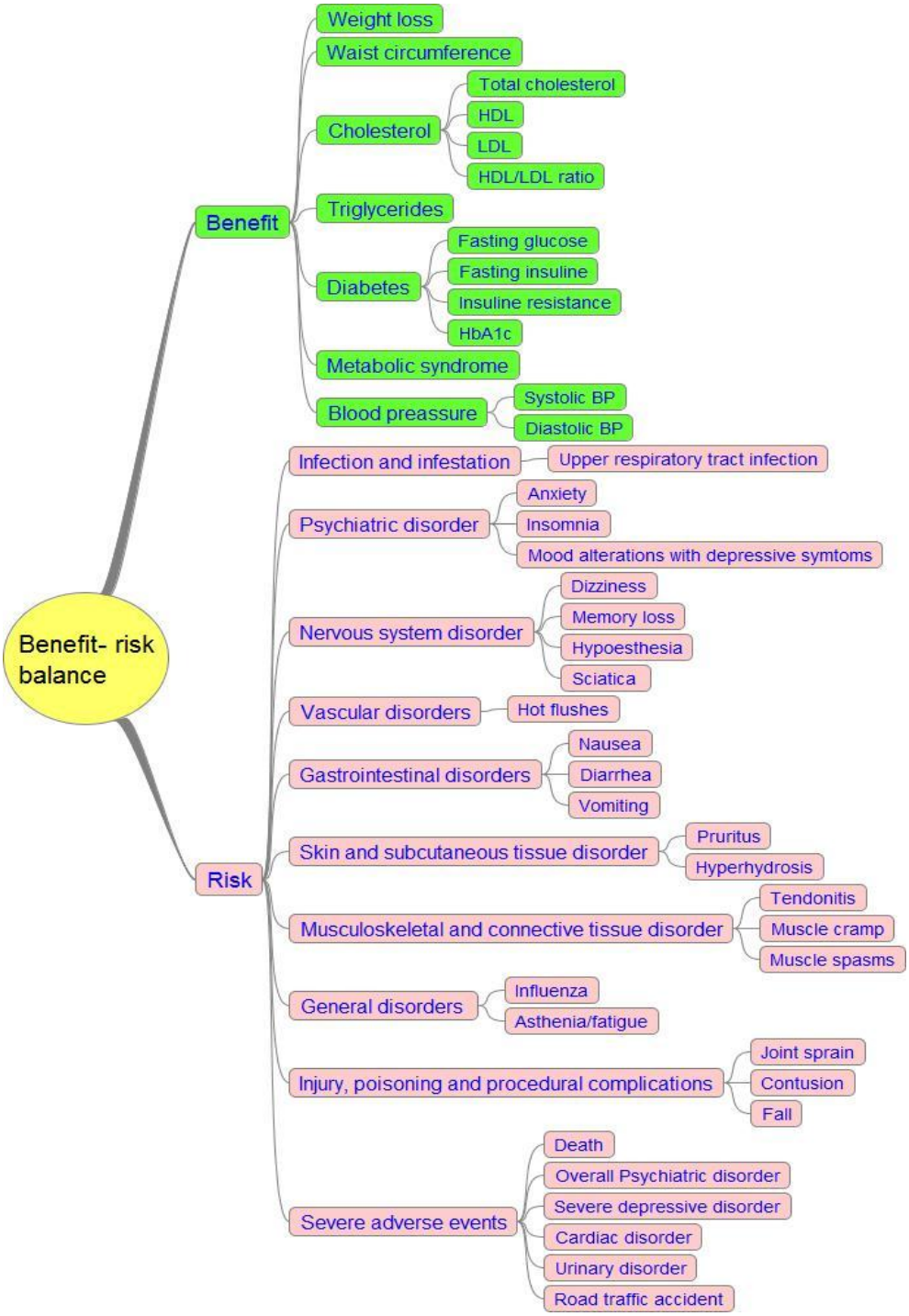

Figure 3-1 Complete value tree for rimonabant showing all favourable and unfavourable outcomes.

3.1.2 Sibutramine and Orlistat

Value trees which present all of the favourable and unfavourable outcomes identified via clinical trials and EPARs for sibutramine and orlistat are shown in Figure 3-2 and Figure 3-3 respectively.

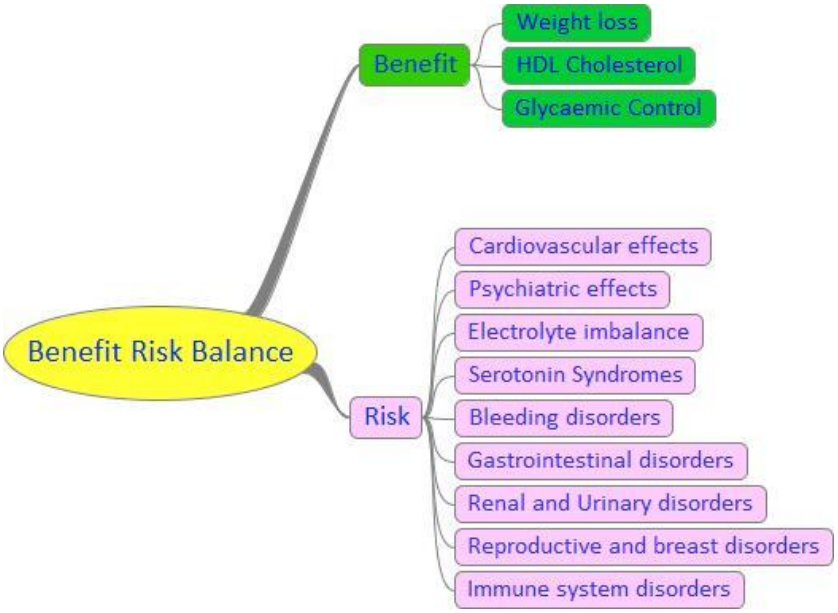

Figure 3-2 Value tree for sibutramine showing all favourable and unfavourable outcomes

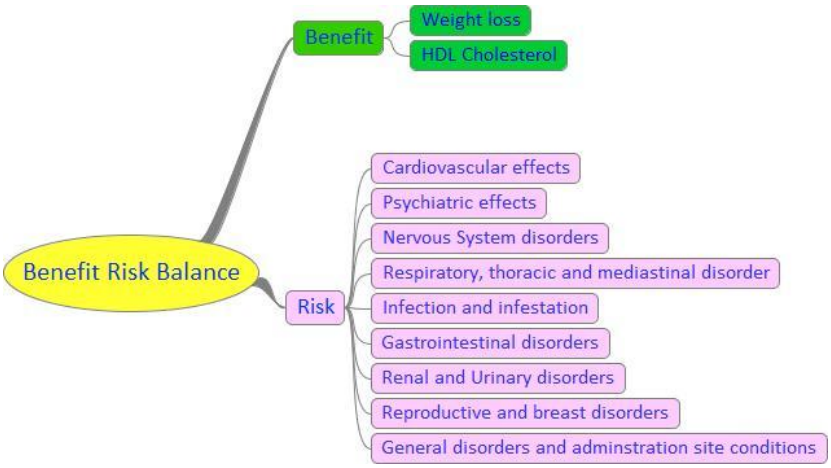

Figure 3-3 Value tree for orlistat showing all favourable and unfavourable outcomes

3.2 Selection of benefit and risk criteria

To include all of the favourable and unfavourable outcomes for all three drugs in the SMAA and DCE models was unfeasible. Therefore, it was necessary for the team to extract the benefit and risk outcomes considered to be of greatest importance to the regulator during decision-making. Five outcomes were extracted; two benefits, and three risks.

3.2.1 Benefits

In Wave 1, a total of 14 benefits were included in the analysis of rimonabant. Given that sibutramine and orlistat were now comparators and not all of the benefit outcomes used previously in Wave 1 apply to these treatments, only two benefit outcomes common across all three treatments were included in Wave 2: weight loss and HDL control.

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10% Weight loss: Weight loss is reported as either a reduction in weight (kg), or the proportion of patients who achieve a ≥10% loss in bodyweight. We chose to define weight loss as the proportion of those achieving a ≥10% loss in bodyweight. This was because the CHMP guideline on drugs used in weight control considers a ≥10% loss in bodyweight to be a valid primary efficacy endpoint in the treatment of obesity.

HDL Cholesterol: HDL cholesterol is reported as a proportional or absolute change of HDL cholesterol (mmol/mL or mg/mL). We chose to use absolute changes, due to the completeness of data available across all three treatments.

3.2.2 Risks

A total of 10 risks (33 preferred terms) were used in Wave 1. However, in Wave 2 risk outcomes were only considered if data was available for the same risk across all three treatments. Three risks remained: psychiatric disorders, cardiovascular disorders and gastrointestinal disorders.

Each weight loss treatment under consideration had a specific risk associated with it: sibutramine was withdrawn from the market due to the occurrence of cardiovascular events, rimonabant was withdrawn due to the occurrence of psychiatric events, and orlistat was associated with gastrointestinal events. These adverse events are described in more depth below:

Psychiatric disorders: Rimonabant was withdrawn as a result of psychiatric disorders. Psychiatric disorders were reported as the number of patients with new cases of adverse events observed in the study cohort.

Cardiovascular disorders: Sibutramine was withdrawn after a large randomised controlled study concluded that the proportion of patients experiencing a cardiovascular event was greater in high-risk patients. Post-marketing prescription event monitoring data were also available, and was reported as the incidence rate of cardiovascular disorders per 1000 patient years in the study cohort.

Gastrointestinal disorders: Orlistat was known to be associated with gastrointestinal disorders. Although a common adverse event, its severity did not warrant a withdrawal of license. The outcome was reported as the proportion of patients experiencing an event. Post-marketing prescription event monitoring data were also available, and was reported as the incidence rate of gastrointestinal disorders per 1000 patient years in the study cohort.

3.2.3 Summary of the outcomes to be used in further analyses

Figure 3-4 below summarises the final value tree with the reduced number of criteria and measures.

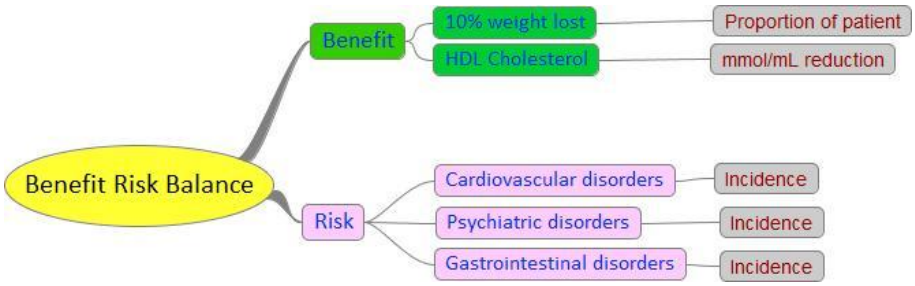

Figure 3-4 Final reduced tree

3.3 Data extraction

Data on the two benefit measures and three risk measures were considered for all three active treatments under consideration. Pre-marketing clinical trial data and post-marketing clinical trial and surveillance data were retrieved from EPARs, FDA documents and publicly available published literature. This section describes the data sources that were retrieved, and indicates which sources were included in the subsequent ITC, and benefit-risk analyses models.

3.3.1 Rimonabant

Five pre-marketing randomised controlled studies (9-12, 17), two meta-analysis reports (18, 19) and an EPAR (10) published in 2006 were considered. The Cochrane meta-analysis and EPAR were based on the four RIO randomised controlled trials (RCT). The RIO RCTs provided pre-marketing data on efficacy and safety. We included one RCT which investigated post-marketing efficacy and safety data (CRESCENDO) (20), and the UK post marketing prescription adverse events monitoring survey for post-marketing data.

Table 3-1 Data sources: Rimonabant

Study	Publication Year	Type	Placebo controlled	Data					
				10% Wt lost	HDL Cholesterol	Psychiatric disorders	Cardiovascular disorders	GI disorders	Included in ITC and SMAA models
EPAR	2006	EMEA report	Yes	Y	Y	Y	Y	Y	Y
FDA Briefing 4306	2007	FDA report	Yes	Y	Y	Y	Y	Y	
Cochrane	2009	Meta analysis	Yes	Y*	Y	Y	NA	NA	
Christensen	2007	Meta analysis	Yes	Y	N	Y*	Y*	Y*	
RIO North America	2004	RCT	Yes	Y	Y*	Y	Y	Y	Y
RIO Europe	2005	RCT	Yes	Y	Y	Y*	Y	Y	Y
RIO Lipid	2004	RCT	Yes	Y	Y*	Y	Y*	Y	Y
RIO Diabetes	2006	RCT	Yes	Y	Y	Y	NA	Y	Y
CRESCENDO	2010	RCT	Yes	Y	Y	Y	Y	Y	Y
Buggy	2011	Post Marketing survey	No	N	N	Y	NA	NA	Y

*Data available but not suitable for analysis

3.3.2 Sibutramine

EPARs were not available for sibutramine, although EMEA article 31 and 107 provided small amounts of information on efficacy and safety (21, 22). The FDA approval document package (1997) was found; it reported efficacy and pooled adverse event data.

There were seven RCTs relating to sibutramine, all published following marketing authorisation (23-29). One of these RCTs was conducted following the CHMP's concern with cardiovascular disorders

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(15), and subsequently led to the marketing authorisation withdrawal of sibutramine. A Cochrane review on efficacy data was published in 2009 (19), based on data from the six earlier RCTs.

Table 3-2 Data sources: Sibutramine

Study	Publication Year	Type	Placebo controlled	Data 10% Wt lost	HDL Cholesterol	Psychiatric disorders	Cardiovascular disorders	GI disorders	Included in ITC and SMAA models
EPAR	NA	EMEA report	NA	NA	NA	NA	NA	NA	Y
EMEA article 107	2010	EMEA report	Yes	NA	NA	NA	NA	NA	
EMEA article 31	2002	EMEA report	Yes	NA	NA	NA	Y*	Y*	
FDA Approval document	1997	FDA	Yes	Y	Y	Y	Y	Y	Y
Cochrane	2009	Meta analysis	Yes	Y*	Y*	NA	NA	NA	
Hauner	2004	RCT	Yes	Y	NA	NA	NA	NA	
McMahon	2000	RCT	Yes	Y	Y*	Y*	Y*	Y*	Y
McMahon	2002	RCT	Yes	Y	Y*	NA	NA	NA	Y
McNutty	2003	RCT	Yes	Y	Y	NA	NA	NA	Y
Sanchez Reyes	2004	RCT	Yes	Y	Y	NA	NA	NA	Y
Smith	2001	RCT	Yes	Y	NA	NA	NA	NA	Y
SCOUT	2010	RCT	Yes	Y*	NA	NA	Y	NA	
Perrio	2007	Post Marketing survey	No	NA	NA	Y	Y	Y	Y

*Data available but not suitable for analysis

3.3.3 Orlistat

Although we were unable to access the first EPAR released around time of marketing authorisation, we did have access to the updated EPAR published in 2003 (15).

16 RCTs were available (30-45), 3 of which were published around the time of market authorisation.

Table 3-3 Data sources: Orlistat

Study	Publication	Type	Placebo	Data

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	Year		controlled	10% Wt lost	HDL Cholesterol	Psychiatric disorders	Cardiovascular disorders	GI disorders	Included in ITC and SMAA models
EPAR	2003	EMEA report	Yes	Y	Y	Y*	NA	Y	Y
Approval document	1999	FDA	Yes	Y	Y	Y	Y	Y	Y
Cochrane	2009	Meta analysis	Yes	Y*	Y*	NA	NA	Y*	
Bakris	2002	RCT	Yes	NA	Y*	NA	Y	Y	
Berne	2004	RCT	Yes	Y	Y	NA	NA	Y	Y
Broom	2002	RCT	Yes	NA	NA	NA	NA	NA	
Davidson	1999	RCT	Yes	Y	NA	NA	NA	NA	
Derosa	2003	RCT	Yes	Y*	NA	NA	NA	NA	
Finer	2000	RCT	Yes	Y	Y	Y*	Y*	Y	Y
Hauptman	2000	RCT	Yes	Y	Y	NA	NA	Y	Y
Hollander	1998	RCT	Yes	Y	Y	NA	NA	NA	Y
Kelley	2002	RCT	Yes	Y	Y	NA	NA	NA	Y
Krempf	2003	RCT	Yes	Y	Y*	NA	NA	Y	Y
Lindgarde	2000	RCT	Yes	Y	Y	NA	NA	Y	Y
Miles	2002	RCT	Yes	Y	Y	NA	NA	Y	Y
Rossner	2000	RCT	Yes	Y	Y	NA	NA	Y	Y
Sjostrom	1998	RCT	Yes	Y	Y	NA	NA	Y	Y
Swingburn	2005	RCT	Yes	Y*	Y	NA	NA	Y	Y
XENDOS	2004	RCT	Yes	Y	Y*	NA	NA	Y	Y
Perrio	2007	Post-marketing survey	No	NA	NA	Y	Y	Y	Y

*Data available but not suitable for analysis

3.3.4 Data availability

There were plentiful randomised controlled study data regarding the two benefit criteria for all three of the active comparators. There were some data regarding the three risk criteria from the post marketing prescription survey studies and pooled data from the FDA documents. However, data from individual randomised controlled studies for risk criteria were scarce.

The sibutramine EPAR and pre-marketing EPAR assessment of orlistat was not available. The Scientific Discussion of of rimonabant was available (46). Furthermore, none of the studies used in the Cochrane review on sibutramine were published prior to marketing authorisation.

Asides from the lack of clear data which led to market authorisation, there were very little clear data related to post-marketing risk assessment. Therefore, our team agreed that it was not possible to

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accurately evaluate changes in risk and benefit profile following marketing authorisation on the three comparators. For the purposes of this case study, we therefore considered all the available data described in this section. However, not all sources are retained in the ITC and SMAA analyses.

3.3.5 Criteria definitions

Our team noted that the definition of medical conditions grouped as psychiatric conditions, cardiovascular conditions and gastrointestinal conditions were different between comparator study groups. In order to allow us to proceed, the team opted to only include specific adverse events within the groups of conditions with available data in the ITC and SMAA model. Data for cardiovascular death was used as cardiovascular disorder, data related to depression was used as psychiatric conditions and constipation or diarrhoea data were used as gastrointestinal conditions.

It should be noted that whereas the ITC and SMAA models used the adapted definitions, the DCE subteam retained the original definitions for the benefit and risk outcomes as they worked concurrently to the data extraction team; once the DCE subteam began it was not possible to amend the definitions within the given timeframe.

Table 3-4 Criteria definitions

Definition of original benefit or risk outcome*	Adapted definition of benefit or risk outcome** for use in ITC model and SMMA
Proportion of individuals achieving 10% weight loss	Proportion of individuals achieving 10% weight loss
HDL cholesterol levels	HDL cholesterol control
Psychiatric conditions	Depression
Cardiovascular conditions	Cardiovascular death
Gastrointestinal conditions	Constipation or diarrhoea

*Used in DCE; **Used in ITC and SMAA

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4 Data synthesis: Indirect treatment comparison

This section describes how all of the extracted benefit and risk data were combined using ITC. The data can be found in Section 12.

4.1 Methods

The origins of ITC and MTC can be traced back to Confidence Profile Method literature, with which they share the same principles.

ITC specifically compares two treatments 1 and 2 where direct evidence is unavailable. ITC exploits the networks of evidence to link the pieces of evidence when they have been compared directly to another same treatment, usually to placebo.

MTC is a generalisation of ITC using a larger network of evidence where both direct and indirect comparisons are available. MTC serves two purposes: to strengthen the inference on relative treatment effects by including both direct and indirect evidence; and to facilitate simultaneous inference for all treatments.

In the present case, ITC was used to summarise all studies available involving one of the three active competitors and placebo, for each of the five endpoints involved in the benefit-risk balance. ITC models with a random effect for inter-study variations were all fitted within a Bayesian framework using WinBUGS 1.4.3.

Weight loss benefit criterion as well as all three risk criteria were defined as dichotomous/binary outcomes, while HDL control was evaluated as a continuous outcome (change from baseline).

Dichotomous events were described using a binomial model:

$$n_{ik} \sim Bin(p_{ik}, N_{ik})$$

$$logit(p_{ik}) = \mu_i + \delta_{ik}$$

$$\delta_{ik} \sim Norm(d_{ik}, Var_{ik})$$

Where n_{ik} is the number of events observed among N_{ik} patients, and p_{ik} is the risk of events in study *i* for treatment *k*. Although it would have been more correct to account for study duration and to evaluate rates rather than risks, the quality of data was not found to be sufficient to provide such a rate-level analysis. Given the similar study durations, the proposed analysis should still provide a realistic order of magnitude but may require a refined analysis.

HDL cholesterol change was described using a meta-analytic random effect normal model accounting for study sample sizes and inter-study variations. If Y_{ikj} stands for a measurement of HDL change in patient *j*, study *i* for treatment *k*, then empirical means $\sum_j \frac{Y_{ikj}}{N_{ik}}$ and variances $S_{ik}^{\ 2}$ are assumed to follow the following statistical distributions of the normal model:

$$\sum_j \frac{Y_{ikj}}{N_{ik}} \sim Norm\left(\mu_i + \delta_{ik}, \frac{\sigma^2}{N_{ik}}\right)$$

$$S_{ik}^{\ 2} \sim \frac{\sigma^2}{N_{ik}} \chi^2 (N_{ik} - 1)$$

$$\delta_{ik} \sim Norm(d_{ik}, Var_{ik})$$

Given the sparse data of risk outcomes, post-marketing studies were used in addition to published RCTs. PEM studies for the three active compounds were considered as three arms of the same study. Furthermore, an attempt of adjusting for under-reporting of risk events in post-marketing studies was made by using a binary study-level variable to be estimated within the statistical inference. In case such effect was found significant, it was kept in the model.

As a main output from the Bayesian ITC analysis, posterior distributions were derived for each of the five outcomes and for each treatment.

4.2 Results

Data used in the Indirect Treatment Comparison is detailed in Section 12.

Using placebo as common comparator between all three active comparators, the model estimating the treatment effects of the three comparators are listed in Table 4-1.

Table 4-1 Indirect Treatment Comparison Results 1 (OR/Mean Difference [95%CI])

Criteria	Placebo	Orlistat	Sibutramine	Rimonabant
10% Weight lost [OR]	1	2.38 [1.93,2.95]	6.91 [3.66,13.02]	5.18 [3.61,7.44]
HDL Chol [Mean difference, mg/dL]	0	0.90 [0.64,1.26]	1.84 [1.00,3.40]	1.10 [0.53,2.30]
Cardiovascular death [OR]	1	6.09 [0.01,4,843.53]	2.34 [0.02,232.42]	1.50 [0.04,57.93]
Depression [OR]	1	0.30 [0.11,0.81]	1.64 [0.71,3.79]	1.69 [0.96,2.96]
Constipation/Diarrhoea [OR]	1	4.11 [2.30,7.32]	1.75 [0.94,3.27]	1.41 [1.02,1.94]

Results from the ITC model depict the estimated treatment effect of active comparators if all share the same comparator in a relative term. Therefore, these results required to be converted into rate and absolute measurement so to be analysed using the decision analysis models. The results are shown in Table 4-2 below.

Table 4-2 Simulation Results from Indirect Treatment Comparison (Median of probability distribution for event, [Range])

Criteria	Placebo	Orlistat	Sibutramine	Rimonabant
10% Weight lost	0.11 [0.10,0.14]	0.24 [0.15,0.34]	0.47 [0.16,0.80]	0.40 [0.22,0.62]
HDL Chol [Mean difference, mg/dL]	1.02 [0.95,1.10]	1.92 [1.12,2.75]	2.63 [1.19,4.11]	2.12 [0.26,3.93]
Cardiovascular death	0.02 [0.01,0.02]	0.11 [0.00,1.00]	0.04 [0.00,1.00]	0.03 [0.00,0.99]
Depression	0.01 [0.01,0.01]	0.00 [0.00,0.03]	0.02 [0.00,0.11]	0.02 [0.00,0.06]
Constipation/Diarrhoea	0.05 [0.05,0.06]	0.19 [0.06,0.50]	0.09 [0.02,0.35]	0.07 [0.04,0.15]

5 Methods

In addition to the estimation technique of ITC, two additional benefit-risk appraisal methods are investigated in Wave 2: DCE, and SMAA. This section of the report describes the application and steps taken when performing each method within the rimonabant case study.

5.1 Discrete choice experiment (Sub-team 1)

A large number of people strongly believe that members of the public should be involved in decisions which directly affect them. This includes deciding which drugs should be licensed for the treatment of obesity. Several methods have been proposed to elicit benefit and risk preferences within a regulatory setting. Subteam 1 will investigate the use of one of the recommended methods—DCEs, within a lay population. The DCE will evaluate the attractiveness of obesity treatments by observing how people choose between treatments while comparing and trading off specified levels of benefits and risks.

Four steps were used to guide the application of DCE to the case study:

1. Identify attributes and assign levels
2. Experimental design and construction of choice sets
3. Questionnaire design
4. Analysis of responses

5.1.1 Identify attributes and assign levels

In a DCE, individuals are shown a specific number of choice sets, where each of them presents a hypothetical choice scenario. The scenario involves the presentation of a decision-making situation, with two or more possible actions that can be taken. The individual is required to make a decision, and select the action that they consider to be most preferable. In this case study, the hypothetical scenario is to receive a treatment for weight loss, and two different options are presented, each with a unique benefit and risk profile.

The two treatment options are presented by levels of specific attributes. Attributes are characteristics used to describe options within choice sets. In this case study, the characteristics were the benefits and risks of the treatments under consideration. After deciding which benefits and risks should be included in the DCE, levels—i.e. measurement units, must be assigned to each attribute.

It should be noted that attributes were determined prior to data extraction and synthesis, and thus instead of comparing measures of specific conditions within outcome groupings (as with ITC, and SMAA in this report), entire ranges of outcome groupings are represented and compared against one another.

When determining the inclusion or exclusion of attributes, it is important to retain the most realistic and plausible attributes that will most greatly impact the attractiveness of an option. After reviewing publically available regulatory literature and published studies, it was decided that attributes which most greatly impact the attractiveness of rimonabant from a regulator's perspective would be represented in the DCE. These were: (1) high-density lipoprotein cholesterol

levels, (2) ten percent weight loss, (3) psychiatric conditions, (4) cardiovascular conditions, and (5) gastrointestinal conditions. As a pre-requisite before engaging in a DCE, correlation and interaction was deemed to be minimal between the attributes.

Each attribute is described by levels in the choice sets. It is important to note that the results of the DCE were initially to evaluate not only rimonabant, but also placebo, orlistat and sibutramine. Consequently, the efficacy and safety outcomes obtained during clinical trial and post-marketing surveillance had to be succinctly characterised into corresponding levels that overlap the outcome data ranges. This would enable later representation of the four treatments under consideration.

Details of the attributes and levels used in the DCE are provided in Table 5-1.

Table 5-1 Treatment attributes, definitions, and levels		
Treatment attribute	**Definition**	**Attribute levels**
Physician's view on HDL cholesterol levels	A high overall cholesterol level can cause a chance of heart attacks and stroke. However, there are different types of cholesterol and not all cholesterol is bad. High density lipoprotein (HDL) is a good cholesterol and is associated with a lower chance of heart attack or stroke.	• Moderate improvement • Mild improvement • No change • Got worse
Number of people who experience a 10% weight loss	Obesity is associated with an increased risk of diabetes, heart disease and stroke. If a person is obese, by losing ten percent of their bodyweight they can lower the chance of these conditions.	• 10 out of 1000 • 150 out of 1000 • 300 out of 1000 • 450 out of 1000
Number of people who experience psychiatric conditions	Psychiatric disorders is a broad term used to describe mild anxiety to severe depression. The scenarios mainly refer to mild psychiatric events, for example anxiety attacks and depression that can be managed by your family doctor. These disorders occur during the course of treatment. Anxiety is a common condition and describes a state of worry, nervousness or unease. Depression can be described as feeling sad all time, finding it difficult to fall asleep and waking up early, feeling unenergetic, and individuals may lose interest in activities. In a small number of cases, those with severe depression may contemplate self harm or suicidal thoughts.	• None • 1 person out of 1000 • 10 people out of 1000 • 100 people out of 1000
Number of people who experience cardiovascular conditions	Cardiovascular diseases are illnesses that involve the heart and blood vessels where not enough blood flows to vital organs. The scenarios in the following questions refer to severe, disabling or potentially fatal illnesses, such as heart attacks and stroke that happen during treatment.	• None • 1 person out of 1000 • 10 people out of 1000 • 100 people out of 1000
Number of people who experience gastrointestinal conditions	Gastrointestinal disorders affect the bowel and stomach. The following scenarios mainly refer to mild types of side effects that cause discomfort or inconvenience, e.g. diarrhoea or constipation, stool spotting, heart burn and flatulence that happen during treatment period.	• None • 1 person out of 1000 • 10 people out of 1000 • 100 people out of 1000

5.1.2 Experimental design and construction of choice sets

The total number of possible profiles in a full factorial design, i.e. combinations of attributes into profiles for a given number of levels (L) and number of attributes (A) is calculated using the formula L^A (47). To present five attributes, each with four levels in a survey would produce a total of 1024 (i.e. 4^5) treatment scenarios. Using this number of scenarios is unrealistic due to the high cognitive demand it would place on participants. Therefore a fractional factorial design was used.

Fractional factorial designs reduce the total number of profiles from a full factorial design into a subset from all possible combinations of attribute levels (47). A fractional factorial design with choice sets was created using SAS, which maintained the important principles of level balance, minimal overlap, and orthogonality. The choice sets were "forced", whereby individuals had to choose between Treatment A or Treatment B for each choice set. The smallest design that could be used to estimate all main effects for the number of attributes and levels was 16. An additional choice set was added to the 16, where one treatment clearly performed more beneficially than the other. This choice set acts as a consistency test, to evaluate comprehension of the task and reliability of responses.

5.1.3 Questionnaire design

During the pilot, it was found that 17 choice sets were too many for an individual to consider and evaluate in a single questionnaire. This was due to high amounts of cognitive burden and fatigue, which could potentially compromise the validity of the DCE. As a result, the 17 choice sets were randomly split into two halves to create two separate questionnaires, each containing 9 choice sets (i.e. 8 fractional factorial designed choice sets and one test for consistency).

The visualisation of choice sets underwent numerous changes from conception to launch. Help was provided by the visualisation subteam, who suggested the labelling and segregation of outcomes into benefits and risks, colour coding, and a carefully aligning the numerical denominator for risks. An example of a choice set can be found below.

Two treatments for obesity are described in the table below.
Please imagine that you have an option of receiving one of the treatments, and consider which one you would prefer to receive.

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

***6. After considering them, please answer the following question:**

	Treatment A	Treatment B
Which treatment would you prefer to receive?	○	○

Figure 5-1 Example of a choice set

The discrete choice questionnaires were then circulated via the obesity organization Weight Concern, established in 1997 to address the raising obesity-related issues in the United Kingdom (http://www.weightconcern.org.uk/). The membership list received an email informing them about the study, with a link to a questionnaire. The list was randomised, so that one half received a link to the first questionnaire, and the second half received a link to the second questionnaire in the format of an online survey.

5.1.4 Analysis

The utility derived by an individual (u) has an observable systematic component (v), with an unobservable random component (ε). I.e. $u = v + \varepsilon$ (47). With this, and the data that has been collected from the DCE, it is possible to estimate the importance and relative importance of each attribute via the utility function:

$$V = \propto + \underbrace{\beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_K X_K}_{\text{systematic component of the utility function}} + \varepsilon$$

α – alternative specific constant (ASC)

X – attributes

β – parameters

ε – random component of the utility function

For rimonabant, the equation that describes the observable systematic component is:

$$V = \propto + \beta_1(WL) + \beta_2(HDL) + \beta_3(GI) + + \beta_4(PSY) + \beta_5(CV)$$

WL – 10% weight loss

HDL – physician's perception of HDL cholesterol levels

GI – gastrointestinal conditions

PSY – psychiatric conditions

CV – cardiovascular conditions

5.2 Stochastic multi-criteria acceptability analysis (Sub-team 2)

SMAA is a type of Multi-Criteria Decision Analysis (MCDA). The principle of MCDA is to address the decision problem by dividing decisions into a set of criteria, which helps separate conflicting components in the decision-making process. Alternatives are scored in each criterion according to performance to form the criteria score, which is then weighted according to decision maker preferences. A weighted average for each alternative is then created by summing the weighted criteria score. The alternative with the highest weighted average is the most preferred option.

In contrast to other MCDAs, which require the specification of criteria values and weights upfront, SMAA supports imprecise, uncertain, and missing information by making distributional assumptions.

SMAA can be seen as an extension of MCDA with the added advantage of being able to characterise typical benefit-risk trade-offs so that they include uncertainty due to sampling variations, and uncertainty due to variations in weight preferences. 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 are estimated through simulations for combinations of weights in hypothetical scenarios assigning a rank 1 to r to each alternative, for a decision problem with r number of alternatives.

The difference between MCDA and SMAA is that SMAA processes data through simulations. This means that SMAA allows for models: (a) without any weights, (b) using ranges of weight information, (c) using rank of preferences, or (d) using precise weight values. Most importantly, SMAA allows input data in the form of distributions, accounting for uncertainty in clinical data.

Our team had a positive experience using JSMAA as a decision analysis model in Wave 1. However, JSMAA was unable to handle complex models with large numbers of alternatives and criteria, and only allowed for a linear utility function. Therefore, our team set out to develop SMAA programme code using Stata. This would allow users to set any number of comparators and criteria, and would also accommodate non-linear utility functions. Furthermore, the programme code could also be applied in cases where individual level data is available. Codes were developed using Stata to transform observed or simulated data into utility values using (a) a linear utility function, or (b) a stepwise utility function. Additionally, codes were developed for preference weight simulation with (a) missing weight information, (b) range weight information, (c) preference rank, and (d) specific weights.

5.2.1 Transforming observed data distribution into utility value distribution

We developed SMAA simulation code in Stata to transform continuous data as well as dichotomous data into utility. All simulations for this analysis were performed with 50,000 iterations. This process of data simulation will generate the distribution of data based on descriptive information available from source documents and the distribution then transformed into distribution of utility value using a linear utility function or a stepwise utility function. The utility

function is created dependent on the relationship between clinical importance and data value. A linear utility function was used in this case study for demonstration.

The utility value distribution is then weighted by the criterion weight distribution generated dependent on the weight information available.

5.2.2 The effects of preference weights

The conventional SMAA model is able to perform decision analyses by combining uncertainty in data via data distributions and uncertainty in preference weights based on the following scenarios:

- Missing weights
- Range weights
- Rank weights
- Specific weights

A SMAA programme was developed in Stata for each of these weight scenarios.

5.2.3 The influence of uncertainty on the benefit-risk model

The SMAA model determines the benefit-risk balance between comparators by ranking their final average weighted utility in each simulated scenarios and summarise the results of all simulation to calculate a "ranking profile" of each comparator.

Similar to other decision analysis models, data used in the model and the criteria preference information provided have a large impact on the final average weighted utility. Hence, uncertainty with the distribution of the observed data and the precision of criteria preference can potentially induce a large degree of uncertainty in the final ranking results.

For this section, the uncertainty of observed data in the model was demonstrated with the underlying distribution of the data and the distribution of the utility value, whereas the precision of the criteria preference was reflected in the distribution of the weight. For example, the distribution of simulated weights is substantially platykurtic ("flatter" and more spread out) in the case with absent weight information (**Error! Reference source not found.**) compared to hat of the ones with range criteria preference information (**Error! Reference source not found.**).

Furthermore, the uncertainty of the final benefit-risk assessment was reflected in the distribution of the average weighted utility. A platykurtic utility distribution depicts a larger uncertainty with the final benefit-risk assessment. Apart from studying the degree of kurtosis utility distribution, uncertainty with the final benefit-risk assessment can also be seen by examining the degree of overlaps between comparator utility distributions.

The SMAA model reports the probability in which one option outranks the alternatives, but it does not quantify the absolute differences between comparators. By examining the level of overlap between distributions of the average weighted utility, we can visually assess the difference in benefit-risk assessment between comparators that resulted in the difference in ranking.

Alternatively, the difference can be assessed by calculating the differences between options in their final average utility and we have developed a dashboard to demonstrate this point. Details of this dashboard can be found in Section 8.5.

5.3 Visual presentations (Sub-team 3)

The aim of sub-team 3 is to develop a selection of interactive visual tools to present the results from benefit-risk assessment specific to the SMAA model built by Sub-team 2. We developed prototypes of interactive dashboards

jointly with Sub-team 2 to better communicate the results. We have also sought some assistance on good practices in dashboard design from the PROTECT Visual Review team when designing our dashboards.

Interactive visual representation of the benefit-risk results is the primary interest in this case study. Interactive visualisation allows the intended message to be communicated and understood easily by giving users control of the information being displayed on the visuals. In order to judge and decide on the benefit-risk balance of drug alternatives, it may be necessary to represent the information as a series of graphs. Representing information in a series of graphs in separate pages, either as static or dynamic format, could increase the time required to make comparison and judgment as well as requiring more cognitive effort since the decision-makers need to tap into their short-term memory to make the comparison. Presenting all the required visuals to be compared on the same page is the most efficient for the task. This could be achieved via building dashboards.

A dashboard is a visual display of the most important information needed to achieve one or more objectives; consolidated and arranged on a single screen so the information can be monitored at a glance (48). In this case study, we applied the best practice in dashboard design to our benefit-risk assessment using common graphic types for the data. In designing the dashboards, we paid attention to avoid the thirteen common mistakes in information dashboard design (49):

i. exceeding the boundaries of a single screen
ii. supplying inadequate context for the data
iii. displaying excessive detail or precision
iv. choosing a deficient measure
v. choosing inappropriate graphic types
vi. introducing meaningless variety
vii. using poorly designed graphics
viii. encoding quantitative data inaccurately
ix. arranging the data poorly
x. highlighting important data ineffectively or not at all
xi. cluttering the display with useless decorations
xii. misusing or overusing colour
xiii. designing an unattractive visual display

Additionally, we also assumed that the intended users have low or no technical knowledge of the benefit-risk of the drugs. Therefore, the dashboards are enhanced with text descriptions on the interpretations of the entities on the graphs and are mainly aimed at patients or the general public.

We used the Tableau Public software package (http://www.tableausoftware.com/public) to design the online dashboards in this case study. We show the snapshots of the online dashboards and describe the interactive features that were incorporated into their functions (Section 0). Live links to the online dashboards are also given for readers to experiment with the interactivity features. The experience in using Tableau Public from the designer's and user's perspective is also discussed in Section 9.4.

6 Results: Discrete choice experiment

6.1 Demographic information

In total, 191 individuals responded to the questionnaires (100 responded to questionnaire one and 91 responded to questionnaire two). Of all those who responded, one individual did not pass the consistency test. All of the responses provided by this individual were excluded from all further analyses. 24 individuals did not complete all of the nine choice sets. However, any responses they did provide were still retained in the analyses. The most frequently reported age groups were age 40 to 49 and 50 to 59 years old, and 90% of the respondents were female.

Table 6-1 Characteristics of respondents

	Respondents	
	n	%
All responses	191	
Incomplete	24	12.6
Failed consistency	1	0.5
Included in analysis	166	
Age group	n	%
21 to 29	9	5.4
30 to 39	26	15.7
40 to 49	56	33.7
50 to 59	55	33.1
60 and over	20	12.0
	166	
Gender		
Male	15	9.0
Female	150	90.4
Unknown	1	0.6
	166	

6.2 Benefit and risk coefficients

Table 6-2 Regression results from probit modelshows the coefficients estimated using a probit regression model. Asides from HDL cholesterol levels, the coefficient for each attribute reflects the impact on choice for a 1% increment in the level of that attribute. The coefficient for HDL cholesterol level reflects the change of preference for each increase in attribute level. Hence, the change in preference is assumed to be equal between each level.

The coefficients were all statistically significant different when compared to baseline, indicating that all two benefits and three risks were important factors affecting treatment preference. The two benefits, HDL improvement and 10% weight loss have positive coefficients. This means that as the level of each benefit increases, a respondent is more likely to select the treatment in the choice set. Conversely, the three risks, psychological, cardiovascular and gastrointestinal disorders all have negative coefficients. This indicates that as the levels of each risk increases, a respondent is less likely to select the treatment in the choice set.

Table 6-2 Regression results from probit model

	All respondents (n=166)	
Attribute	**Coefficient**	**95% CI**
10% Weight loss (%)	0.034 **	(0.030 , 0.039)
Psychological conditions (%)	-0.134 **	(-0.158 , -0.110)
Cardiovascular conditions (%)	-0.097 **	(-0.114 , -0.080)
Gastrointestinal conditions (%)	-0.035 **	(-0.053 , -0.018)
Cholesterol level (per level)	0.306 **	(0.224 , 0.387)
Constant	-0.149 *	(-0.288 , -0.011)

* p≤0.05, ** p≤0.001
Log-likelihood = -577.88

From the results, it is possible to determine the ranking of benefits and risks by importance for a one per hundred incremental change, although HDL cholesterol levels are excluded from this ranking as the attribute does not use the same scale. The most important outcome with the largest coefficient is psychological conditions, followed by cardiovascular conditions, weight loss, and lastly gastrointestinal conditions.

6.3 Combining coefficient estimates with efficacy and safety data

By combining coefficient estimates from this analysis with the efficacy and safety data for placebo and rimonabant, preference between placebo or rimonabant can be calculated using,

$$V(Rimonabant) = \beta_1 RD(1) + \beta_2 RD(2) + \beta_3 RD(3) + \beta_4 RD(4) + \beta_5 RD(5),$$
$$V(Placebo) = 0,$$
$$P(Rimonabant) = e^{V(Acomplia)}/(e^{V(Rimonabant)} + e^{V(Placebo)}),$$
$$P(Placebo) = e^{V(Placebo)}/(e^{V(Rimonabant)} + e^{V(Placebo)}),$$

where $RD(x)$ is the risk difference between rimonabant and placebo and β_1 is the coefficient for attribute x.

Estimates of choice probabilities were derived through 100,000 simulations. Model coefficients were assigned normal distributions with mean and standard deviation as estimated by the DCE model. Safety and efficacy estimates for placebo and rimonabant were assigned approximated normal distributions based on Wave 1 meta-analysis results. As HDL cholesterol levels were expressed categorically, simulated changes in HDL cholesterol levels from treatment were categorised to match those specified in the DCE model (got worse, <0 mg/dL; no change, 0-2.5mg/dL; mild improvement, 2.5-5 mg/dL; moderate improvement, >5mg/dL).

Table 6-3 Results of preference analysis for placebo and rimonabant using DCE results

	Mean	**2.50%**	**97.50%**
Preference for Rimonabant (%)	56	50	66
Preference for Placebo (%)	44	34	51
Rimonabant preferred (%)	67	Not applicable	
Placebo preferred (%)	33	Not applicable	

The distribution of the probability of preferring rimonabant or placebo was not significantly different. Throughout simulation sets, the average probability of choosing rimonabant was 56%, whereas that of placebo was 44%. However, rimonabant was the preferred option 67% of the time. This means that in 67% of the 100,000 iterations, the probability of choosing rimonobant was higher than the probability of choosing placebo.

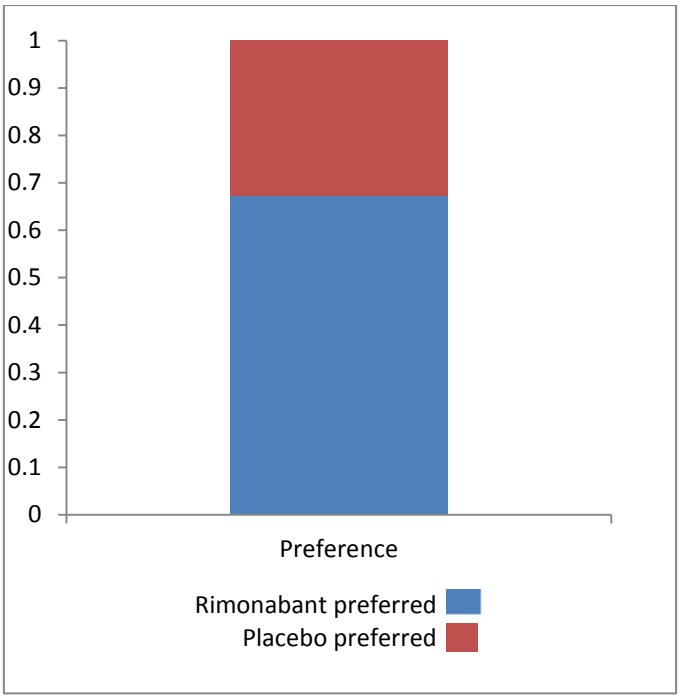


Figure 6-1 Probability of selecting rimonabant or placebo

6.4 Marginal rates of substitution

Using the results from the probit model, it is possible to calculate the marginal rates of substitution between the two benefits, i.e. number of individuals achieving a 10% weight loss and HDL level, and the three risks, i.e. psychological, gastrointestinal, cardiovascular conditions. Essentially, this calculates how much of a benefit a respondent is willing to trade off in order to avoid a specified amount of risk. The results are shown in the table below.

Table 6-4 Marginal rates of substitution

Risk attribute	Description	Willingness to forgo a % reduction in the number of those achieving 10% weight loss (95% CI)		Willingness to forgo a level improvement in HDL cholesterol (95% CI)	
Psychological conditions (%)	1% reduction in risk of psychological conditions	3.9	(2.8 - 5.3)	0.44	(0.28 - 0.71)
Cardiovascular conditions (%)	1% reduction in risk of cardiovascular conditions	2.8	(2.1 - 3.8)	0.32	(0.21 - 0.51)
Gastrointestinal conditions (%)	1% reduction in risk of gastrointestinal conditions	1.0	(0.5 - 1.8)	0.12	(0.05 - 0.24)

The table shows that in order to avoid one percent of psychological conditions, respondents would be willing to forgo a 3.9% (95% CI: 2.8% to 5.3%) reduction in the number of those achieving a 10% weight loss, or forgo a 0.44 (95% CI: 0.28 to 0.71) level improvement in HDL cholesterol. The respondents would be willing to forgo a smaller reduction of the two benefits for each of the other two risks.

7 Results: SMAA

7.1 Transforming observed or simulated data into utility values

7.1.1 Continuous data

HDL cholesterol was the only criterion in our case study presented as a continuous variable. The effect of HDL cholesterol changes from placebo and the three active comparators were simulated based on results from the ITC. Results from the ITC analysis are presented in Section 4. Effects of the placebo were set as the baseline comparator estimated using a random effects meta-analysis model.

Graphical presentation of the results from ITC is demonstrated in Figure 7-1 below; this figure demonstrates the estimated distribution of effects for each of the four comparators on cholesterol changes.

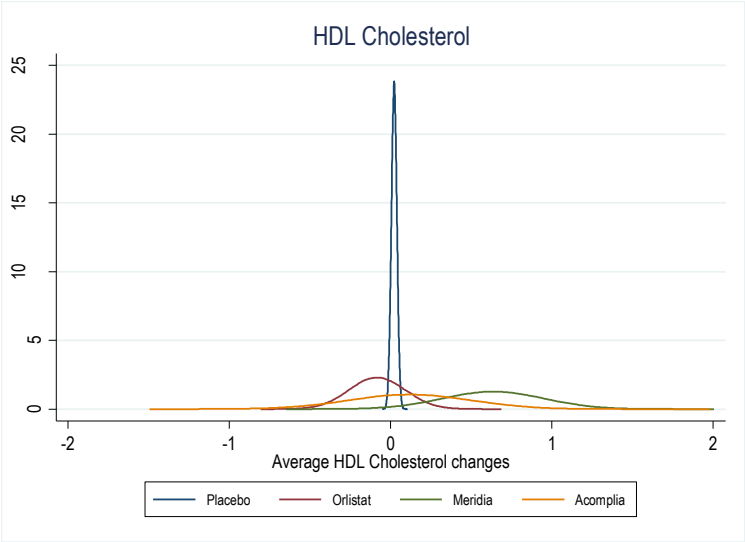


Figure 7-1 Distribution of net effect on HDL Cholesterol changes between placebo and 3 active comparators

Simulated data on HDL cholesterol change for each treatment was then converted into utility value using a linear utility function. The main disadvantage of the SMAA analysis using JSMAA is that is utility function is restricted to linear form in the JSMAA programme. However, Stata programming can allow for a stepwise function which is more appropriate for clinical indications.

For the purpose of the programme development, a linear utility function with fixed base on the value range from simulated data was used (Figure 7-2).

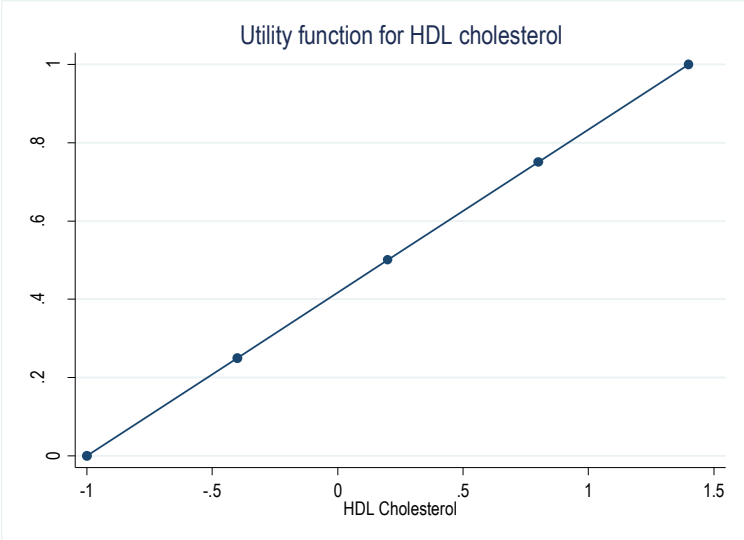


Figure 7-2 Utility function for HDL Cholesterol

Figure 7-3 below shows the distribution of utility values on the four comparators after transforming simulated data using the specified utility function.

These utilities were then weighted in accordance with available preference weight information and a distribution of the average weighted utility for each comparator.

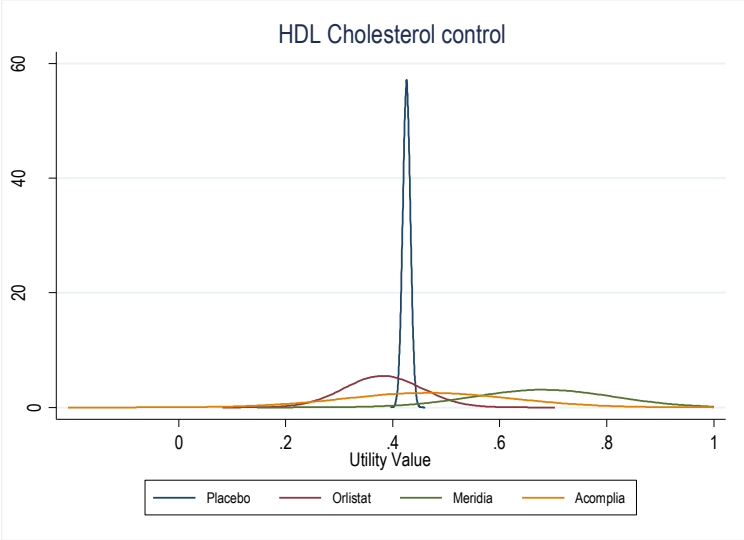


Figure 7-3 Distribution of HDL Cholesterol Utility

7.1.2 Data with dichotomous outcomes

The proportion of subjects achieving a 10% weight loss, incidence of associated psychiatric illness (depression), incidence of associated gastrointestinal disorder (constipation/diarrhoea) and incidence of cardiovascular events (cardiovascular death) are all presented as binomial variables in this case study. The odds ratio for each of these events in the active comparator group when compared to placebo was estimated using ITC (Section 4). Our team opted to use the incidence of depression to represent psychiatric illness, incidence of constipation or diarrhoea to represent rate of gastrointestinal disorder and incidence of cardiovascular death to represent the incidence of cardiovascular disorder. Conventional meta-analysis on event rates normally presents the results in the rate and the standard deviation of the pooled average rate of events. In our case study, some of the observed events were rare and therefore it could result in a negative event rate while simulated. In order to avoid this, our team proposed to

simulate the rate of the events based on a beta distribution model. Under the assumption of ITC that all placebo team are interchangeable, we proposed to estimate the rate of events in the placebo group using a summation of beta distribution from individual studies and were set as the baseline. The rates in comparator groups were estimated using the odd ratio estimated from the ITC model.

We used the rate of subjects achieved 10% weight loss as an example to demonstrate the results from the simulations.

Figure 7-4 below demonstrates the distribution of probability participants achieving 10% weight loss between placebo and the three active comparators.

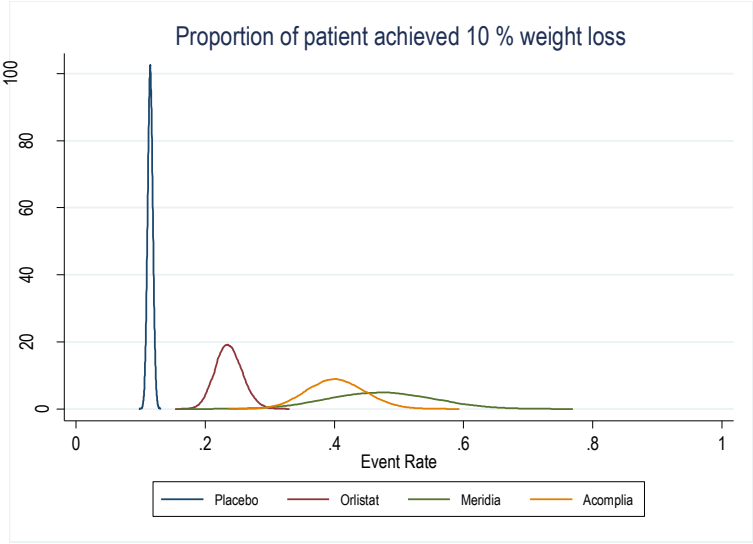


Figure 7-4 Distribution of the proportion of patients achieved 10% weight loss

Data generated from the simulation was then converted into utility value using a linear utility function generated with the data range.

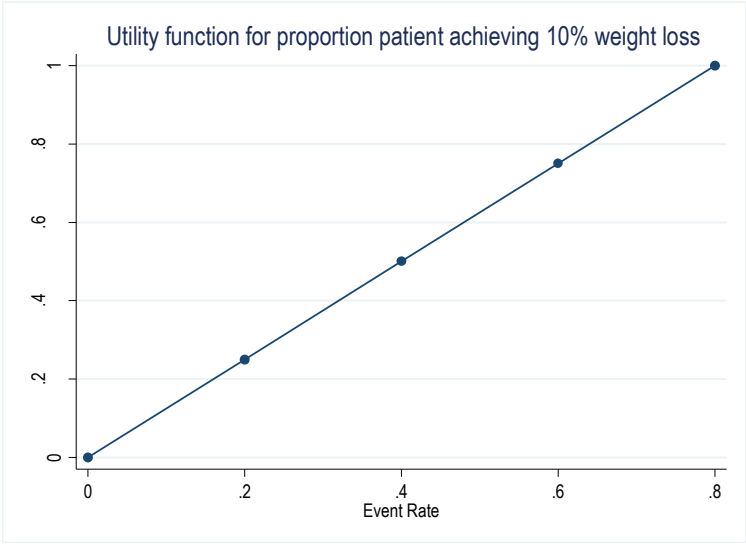


Figure 7-5 Utility function for proportion of patients achieved 10% weight loss

The result utility value after conversion is shown in Figure 7-6.

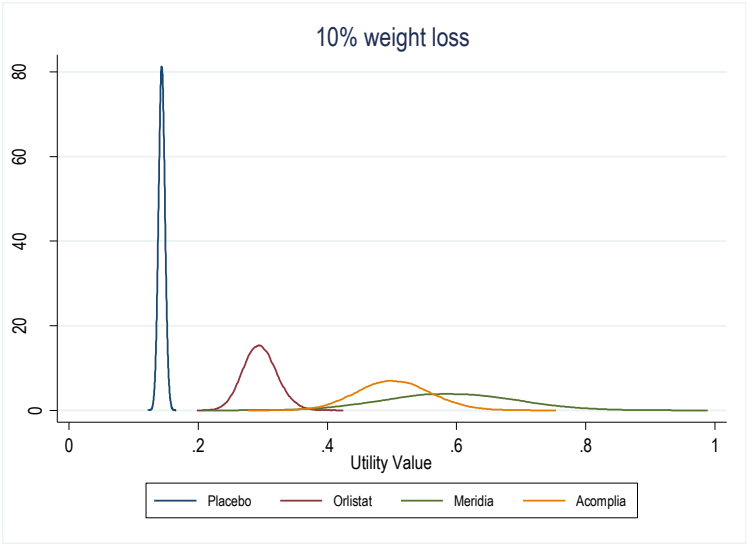


Figure 7-6 Distribution of utility value on proportion of participants achieved 10% weight loss

7.2 Utility value distribution

7.2.1 Missing Weights

In this scenario, we assumed that there was no prior information available regarding criteria weights. Hence, the model explored potential weight combinations of criteria. The weight information for each of the five criteria was simulated using a uniform distribution between 0 and 1, and rescaled to reach total of 1.

Figure 7-7 below shows the distribution of the simulated weights on the three criteria, showing average weights were 0.33 between the five criteria.

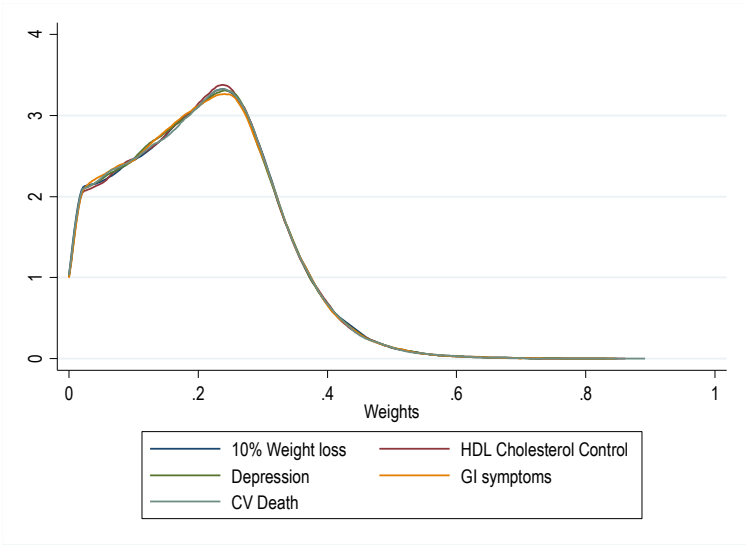


Figure 7-7 Weights distribution - Absent weight information

Utility value transformed from simulated data from each criterion was then weighted by the simulated weight to calculate the weighted utility. This is best demonstrated using the 10% weight loss example. The primary utility value (Figure 7-6) is weighted with simulated weight (**Error! Reference source not found.**) to generate the weighted utility alues. The distribution of the resultant weighted utility values of the four comparators is shown in Figure 7-8 below.

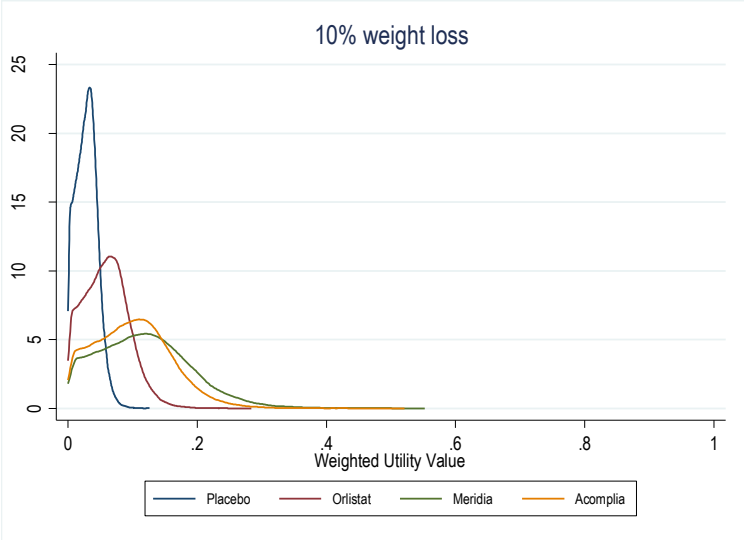


Figure 7-8 Distribution of weighted utility value on Criterion "10% Weight Loss" with missing weight preference

7.2.2 Range weights

In this scenario, we assumed that the stakeholders did not place a specific weight on criteria preference and instead provided a range of weights. Hence, the model explores all possible weight combinations between preference ranges across all criteria.

We used the following hypothetical criteria preferences in this example.

Criterion	Weight range [0 – no importance, 1- very important]
Achieving 10% weight loss	0.5 – 1
Effect on HDL Cholesterol Control	0.2 – 0.5
Side effect of depression	0.3 - 0.7
Side effect of Cardiovascular death	0.1 – 0.4
Side effect of Gastrointestinal symptoms	0 – 0.4

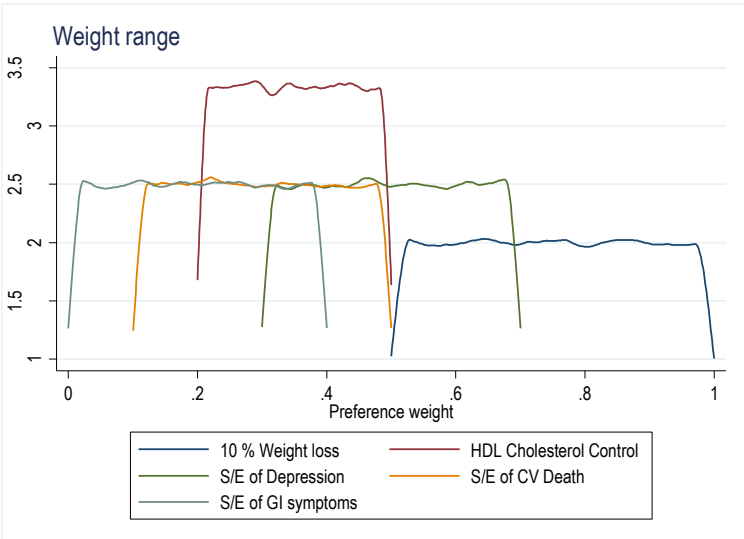


Figure 7-9 Example on weight range in criteria preference

Weight information on the five criteria was simulated using a uniform distribution between the upper and lower range weight preference, and rescaled to reach a total of 1. Distribution of the scaled preference weight is shown in Figure 7-10 below.

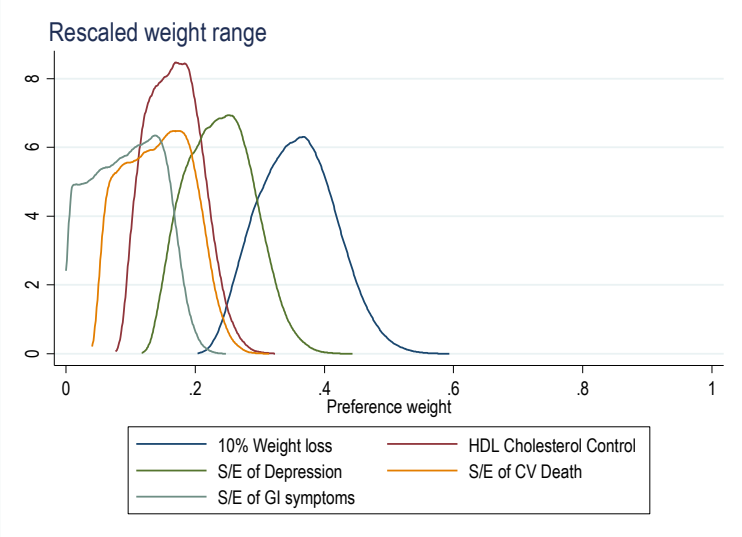


Figure 7-10 Weight Distribution - Range weight

Utility value transformed from simulated data for each criterion was then weighted by the simulated weight to calculate the weighted utility. By using the 10% weight loss example, the primary utility value (Figure 7-6) is weighted with simulated weight (Figure 7-10) to generate the weighted utility values. The distribution of the resultant weighted utility value between the four comparators is demonstrated in Figure 7-11.

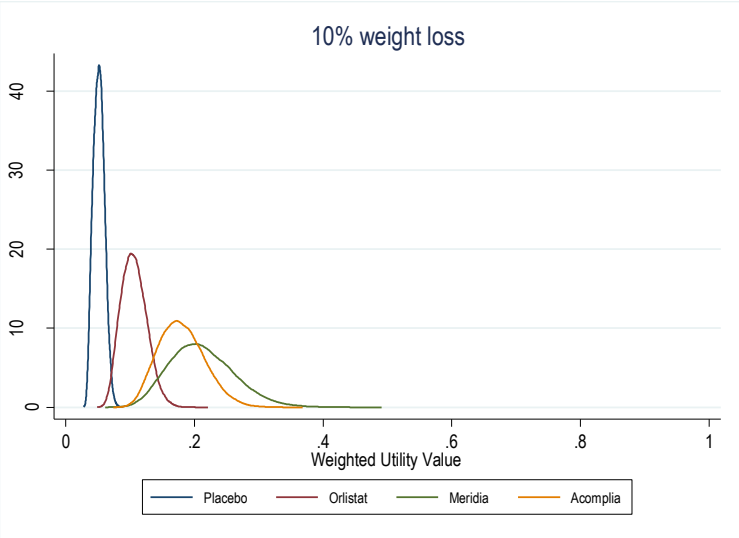


Figure 7-11 Distribution of weighted utility value on Criterion "10% Weight Loss" with sample weight range preference

7.2.3 Rank Weight

In this scenario, we assumed that precise information on criteria weights was not available. Instead, we assumed prior information on rank preference on all criteria from stakeholders [Criterion 1>Criterion2>Criterion3].

We used the following hypothetical criteria preferences ranking in this example.

Criterion	Ranking 1 – most important 5 – least important
Achieving 10% weight loss	1
Effect on HDL Cholesterol Control	2
Side effect of depression	3
Side effect of Cardiovascular death	4
Side effect of Gastrointestinal symptoms	5

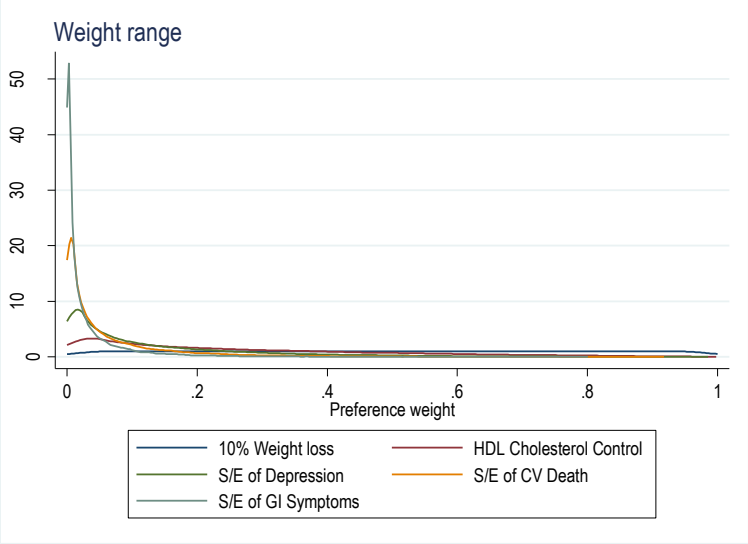


Figure 7-12 Example on rank criteria preference

Therefore, weight information on the most favoured criteria was simulated using a uniform distribution between 0 and 1, followed by weight simulation on the r^{th} favoured criteria using a uniform distribution between 0 to the simulated weights from the $r+1^{th}$ criteria, and the same process repeated until all criteria in the model are covered. This method of simulation ensures preservation of ranking form simulation. All weight simulations were then rescaled to reach total of 1. Distribution of the scaled preference weight is shown in Figure 7-13 below.

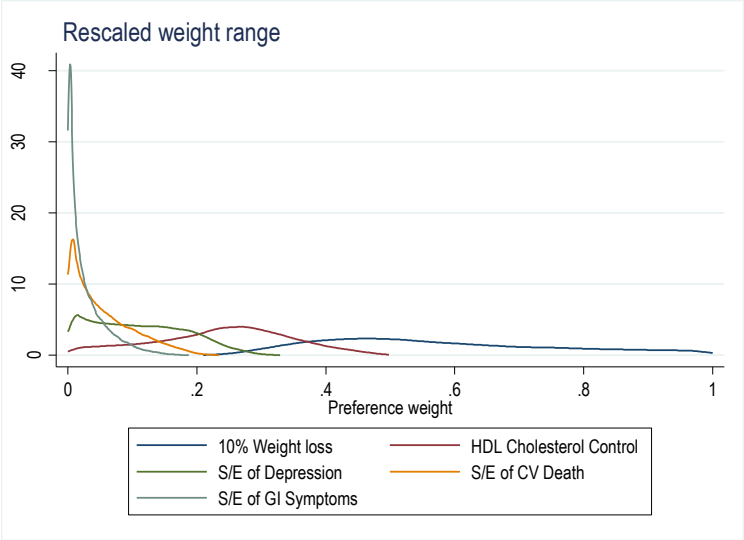


Figure 7-13 Weight Distribution - Rank weight preference

Utility value transformed from simulated data from each criterion was then weighted by the simulated weight to calculate the weighted utility. By using the 10% weight loss example, the primary utility value (Figure 7-6) was weighted with simulated weight (Figure 7-13) to generate the weighted utility values. The distribution of result weighted utility value between 4 comparators is demonstrated in Figure 7-14 below.

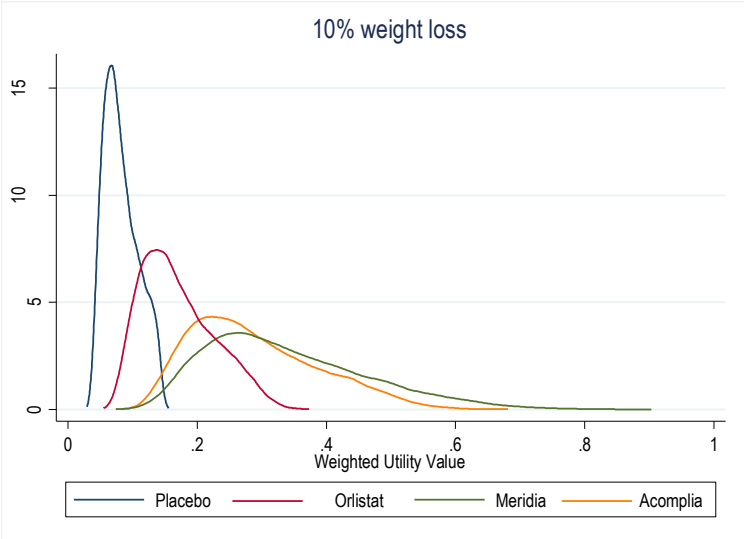


Figure 7-14 Distribution of weighted utility value on Criterion "10% Weight Loss" with sample Rank preference weight

7.2.4 Specified Weight

In this scenario, specific weights on criteria preference are assumed to be available. Hence, weight information on the five criteria was then rescaled to reach total of 1. Utility value on each simulation was then adjusted according to the weight information.

We used the following hypothetical criteria preferences ranking in this example. A full preference range model has been developed and can be found in the visual review result section (Section 0).

Criterion	Weights 0- No importance 1- Most important
Achieving 10% weight loss	0.8
Effect on HDL Cholesterol Control	0.4
Side effect of depression	0.5
Side effect of Cardiovascular death	0.2
Side effect of Gastrointestinal symptoms	0.6

Utility value transformed from simulated data from each criterion was then weighted by the specific weight to calculate the weighted utility. By using the 10% weight loss example, the primary utility value (Figure 7-6) was weighted to generate the weighted utility values. The distribution of result weighted utility value between 4 comparators is demonstrated in Figure 7-15 below.

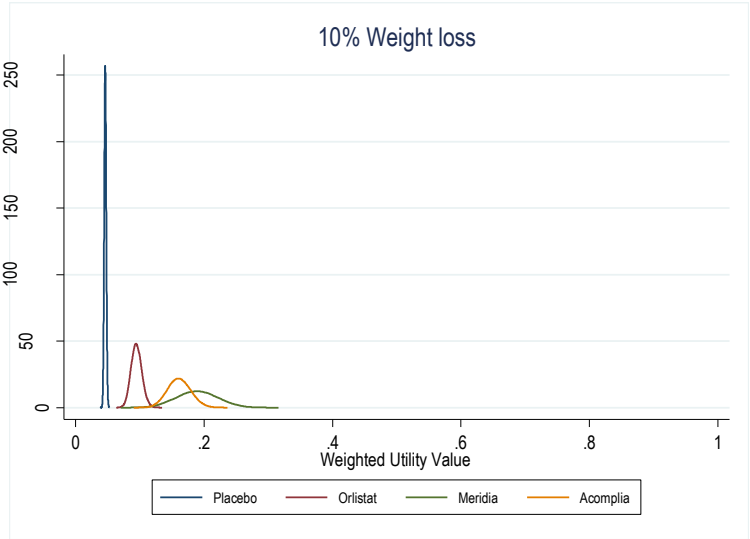


Figure 7-15 Distribution of weighted utility value on Criterion "10% Weight Loss" specific preference weight

7.3 Visualisation of results from the SMAA model

Results from the SMAA model can be depicted in two forms:

As distribution of average of weighted utility. A superior risk benefit balance is reflected by a higher average weighted utility and uncertainty of the risk benefit balance is by the distribution of the average utility value. In this exercise, average weighted utility were generated by summing weighted utility value following the principles from our previous experience with MCDA and SMAA. This implies the higher the weighted average utility, the better the risk benefit balance.

Alternatively, the average weighted utility value can be calculated by difference between total benefit utility and total risk utility. A positive average weighted utility depicts a positive benefit risk balance and uncertainty of benefit risk balance is reflected by the distribution of results.

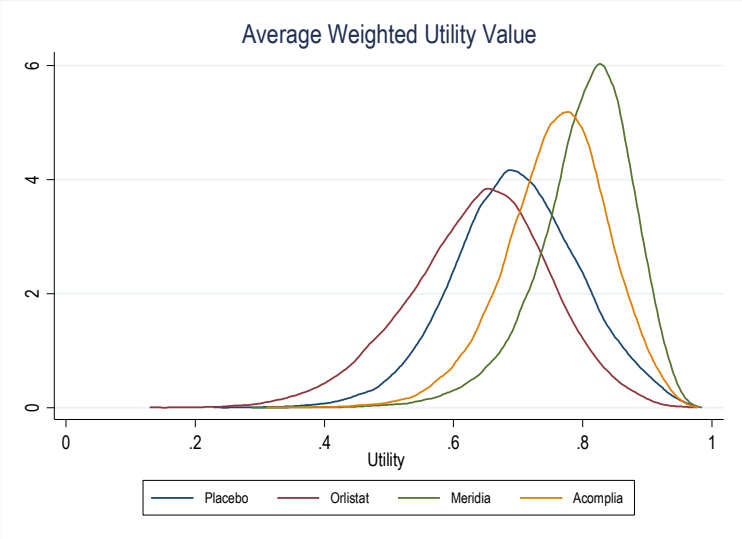


Figure 7-16 SMAA results - Average weighted utility distribution

As Utility ranking. In this case, the rank of each alternative in every simulation is ranked. The proportion of r alternative achieved 1st - rth rank is estimated and show on a stacked bar chart. This method is easy to read but ignore the magnitudes of differences in benefit risk balance between each alternative.

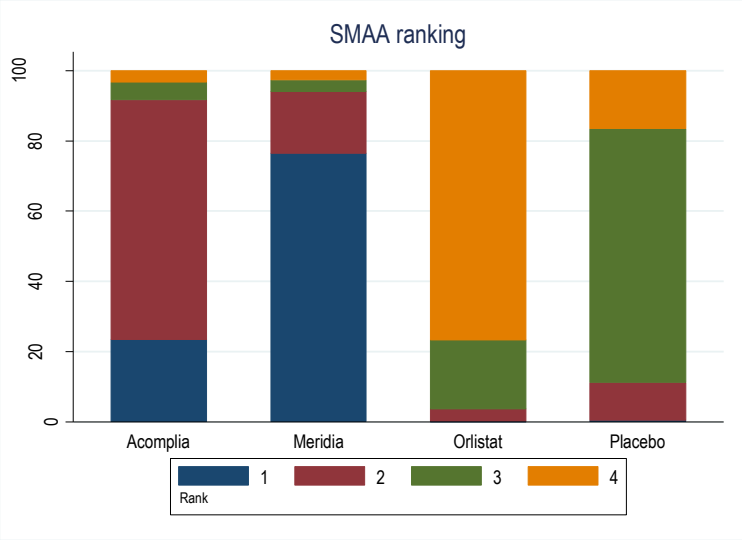


Figure 7-17 SMAA results – Utility ranking

7.4 The effects of preference weights

7.4.1 Missing weights

In this scenario, we assume that there was no prior information available regarding to preference on criteria. Therefore, the model required to explore all possible weight combinations between criteria. Figure 7-10 shows the distribution of criteria weights in the simulated scenarios.

SMAA simulations demonstrated that sibutramine became the most favourable choice in 66% of simulated scenarios and rimonabant achieved the first rank in 30% of cases, when there were no weight preference criteria given. [Figure 7-18]

It has been suggested that one should take a more holistic approach when interpreting results in the SMAA model, instead of concentrating on probability on achieving the first rank, one ought to review the ranking profile of individual options (50).

In this case, both sibutramine and rimonabant achieved first two ranks in similar proportion and their ranking profiles were substantially more favourable compared to either orlistat or placebo. It appeared the chance of sibutramine achieved first rank was higher than rimonabant, although there was a degree of uncertainty and a large overlap in performance between the two options (Figure 7-22).

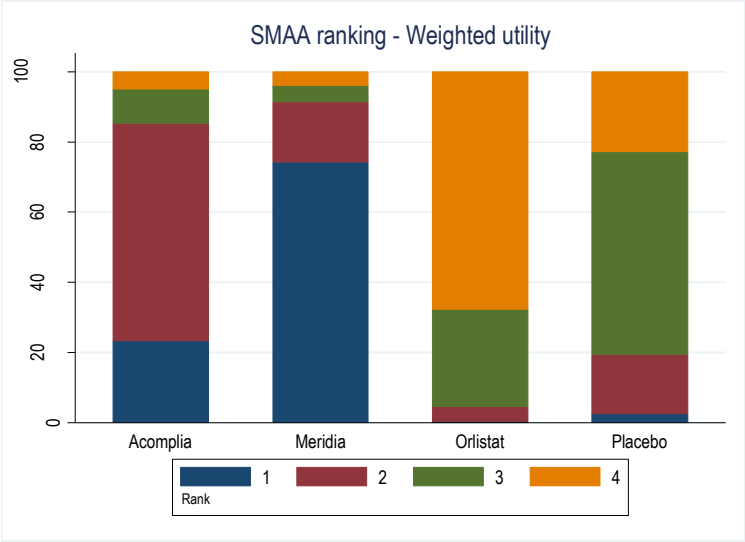


Figure 7-18 SMAA results: Missing weights example

7.4.2 Range weights

In this scenario, we assumed that the exact weights of criteria preference were unknown; instead, we used a range (Table 7-1). Thus, weights were drawn from weight space as specified in the ranges in order to calculate weighted utility.

Table 7-1 Hypothetical weight range for SMAA

Criterion	Weight range [0 – no importance, 1- very important]
Achieving 10% weight loss	0.5 – 1
Effect on HDL Cholesterol Control	0.2 – 0.5
Side effect of depression	0.3 - 0.7
Side effect of Cardiovascular death	0.1 – 0.4
Side effect of Gastrointestinal symptoms	0 – 0.4

The distributions of criteria weights in the simulated scenarios are shown in Figure 7-10.

SMAA simulations demonstrated that sibutramine was the most favourable option in 82% of simulated scenarios and rimonabant achieved the first rank in 18% of cases (Figure 7-19).

In this case, sibutramine and rimonabant achieved one of the first two ranks in similar proportions and their ranking profiles were substantially more favourable compared to orlistat and placebo.

There was a degree of uncertainty and large overlap in performance between the two options, albeit much lower than the previous example (Figure 7-23).

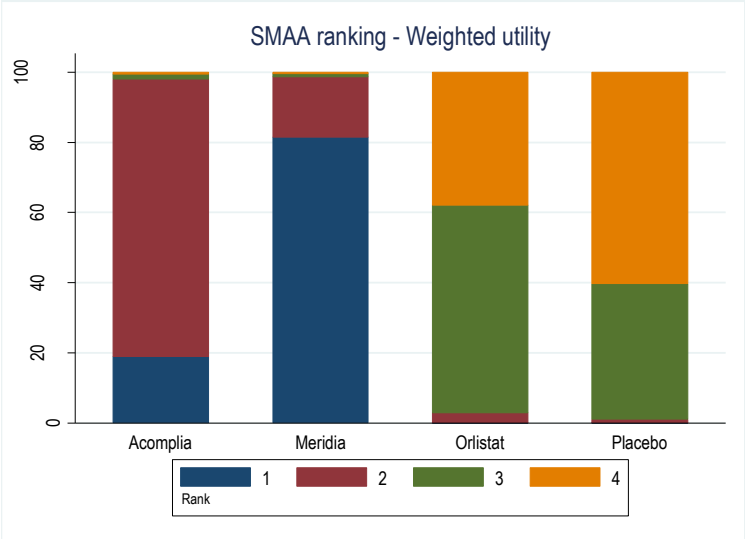


Figure 7-19 SMAA results: Range weights example

7.4.3 Rank Weight

In this scenario, we assumed that the exact weights of criteria preference were unknown; instead, we used prior information on rank preference for criteria from stakeholders (Criterion 1>Criterion2>Criterion3) (Table 7-2). Thus, any weight distribution that respected the ranking could be selected in simulations.

Table 7-2. Hypothetical ranking for SMAA

Criterion	Ranking 1 – most important 5 – least important
Achieving 10% weight loss	1
Effect on HDL Cholesterol Control	2
Side effect of depression	3
Side effect of Cardiovascular death	4
Side effect of Gastrointestinal symptoms	5

The distribution of criteria weights in the simulated scenarios are shown in Figure 7-13.

Ranking from SMAA simulations showed that sibutramine was the most favourable option in 82% of simulated scenarios and rimonabant achieved the first rank in 18% of cases. Also, all three active comparators outperformed placebo (Figure 7-20).

In this exercise, sibutramine and rimonabant achieved any of the first two ranks in similar proportions and their ranking profiles were substantially more favourable compared to orlistat or placebo in almost all of the simulated scenarios. It appeared the chance of sibutramine achieved first rank was much higher than rimonabant, although there was a degree of uncertainty and because of the degree of possible combinations, the uncertainty in utility value is increased compare to that of the previous example (**Error! Reference source not found.**).

Figure 7-20 SMAA results: Rank weight example

7.4.4 Specified Weights

In this scenario, specific weights for criteria preference were available. For all simulations, criteria weights were therefore fixed.

We used the following hypothetical criteria preferences ranking in this example (Table 7-3). A full preference range model has been developed and can be found in the visual review result section (Section 0).

Table 7-3. Hypothetical weights for SMAA

Criterion	Weights 0- No importance 1- Most important
Achieving 10% weight loss	0.8
Effect on HDL Cholesterol Control	0.4
Side effect of depression	0.5
Side effect of Cardiovascular death	0.2
Side effect of Gastrointestinal symptoms	0.6

As with previous examples, sibutramine was the most favourable option in 83% of simulations, whereas rimonabant achieved the first rank in 17% of cases. sibutramine and rimonabant achieved any of the first two ranks in similar proportions and their ranking profiles were substantially more favourable compared to either orlistat or placebo in almost all of the simulated scenarios (Figure 7-21).

The degree of uncertainty in utility value was lowest compared to other examples due to fixed criteria weights. Hence, the uncertainty in weighted utility reflected the uncertainty in the underlying benefit-risk data (Figure 7-25).

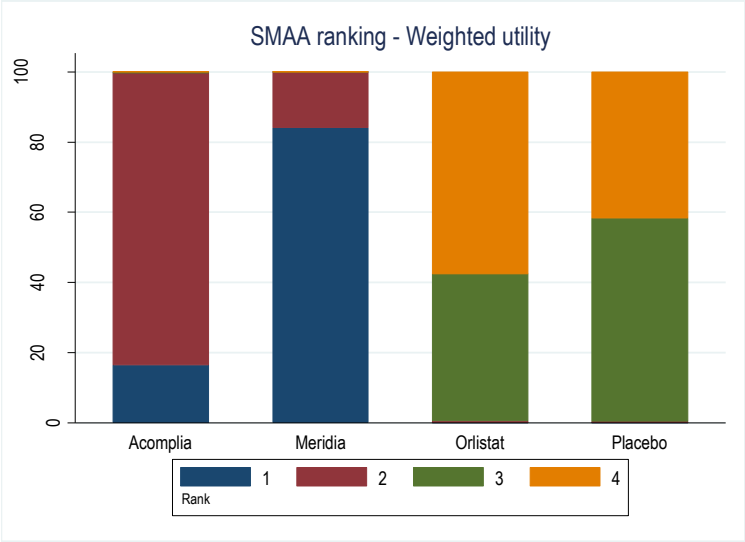


Figure 7-21 SMAA results: Specific weights example

7.5 The influence of uncertainty on benefit-risk model

The following figures show the distributions of average weighted utility between the four comparators in different criteria preference setting. Unsurprisingly, the model with the specific criteria preference information demonstrated least uncertainty compared to the other models.

7.5.1.1 Missing weights

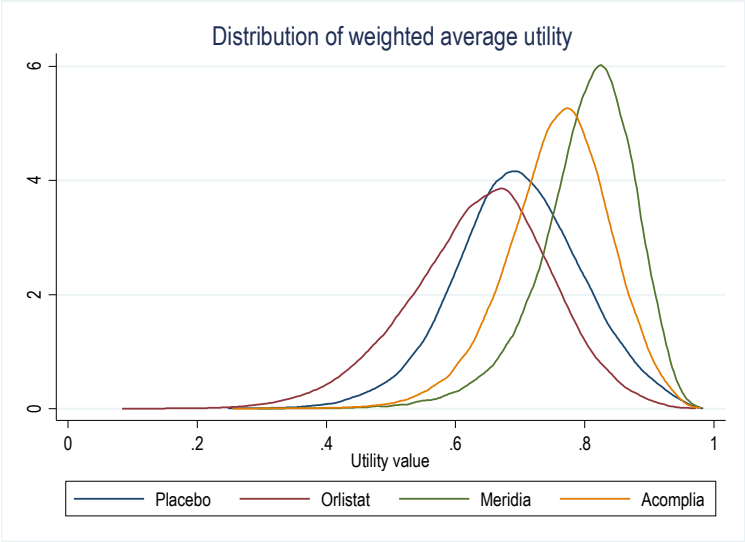


Figure 7-22 Distribution of weighted average utility - missing weight preference

7.5.1.2 Range weights

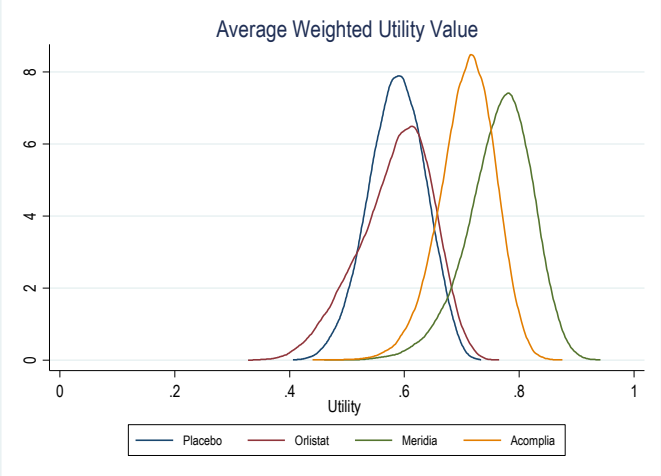


Figure 7-23 Distribution of weighted average utility - range weight preference

7.5.1.3 Rank Weight

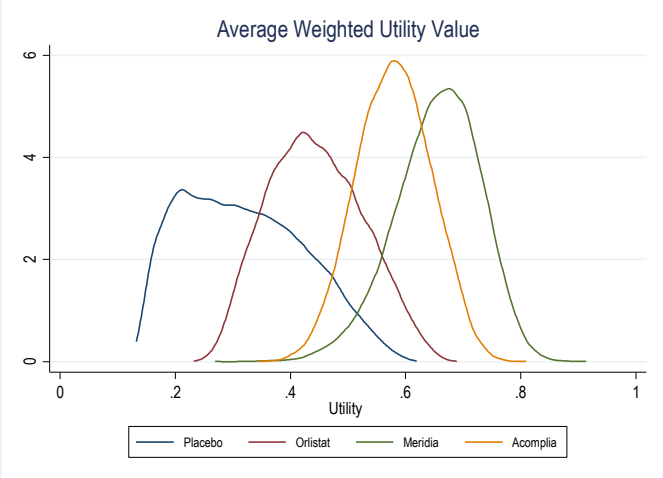
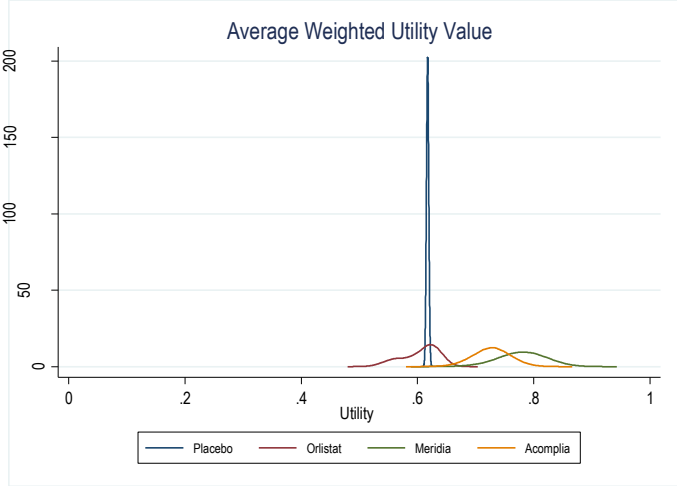


Figure 7-24 Distribution of weighted average utility - rank weight preference

7.5.1.4 Specified Weights



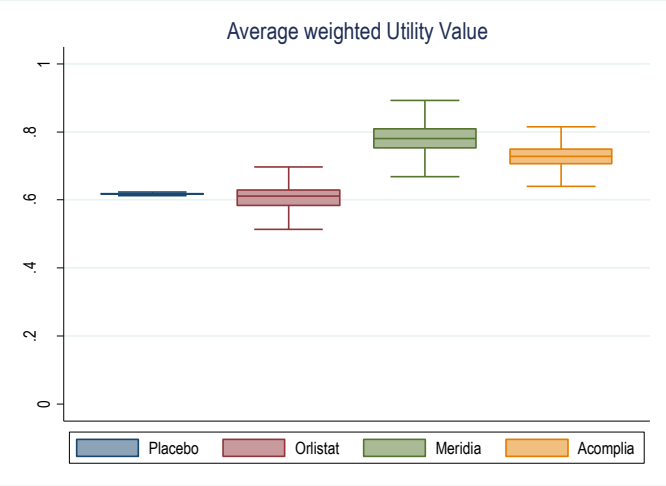


Figure 7-25 Distribution of weighted average utility - specific weight preference

8 Visual Results

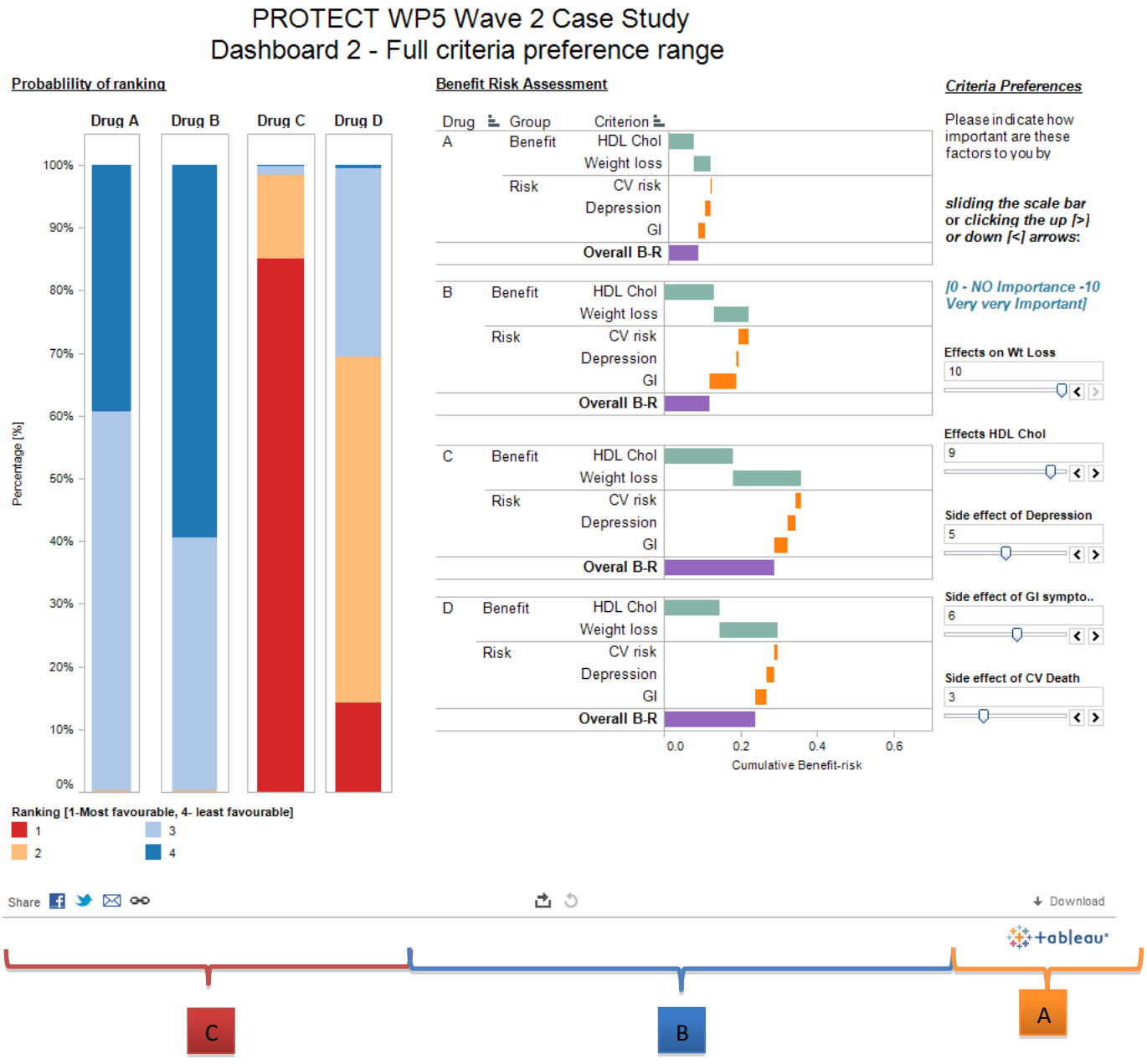
8.1 Introduction

We have developed five dashboards in Tableau Public to accompany the SMAA models in Section 5.2. These dashboards are designed for usability to help users to understand the consequences of their decisions when choosing drugs for weight loss.

8.2 Dashboard 1: Full criteria preference range SMAA with waterfall plot

Web link:

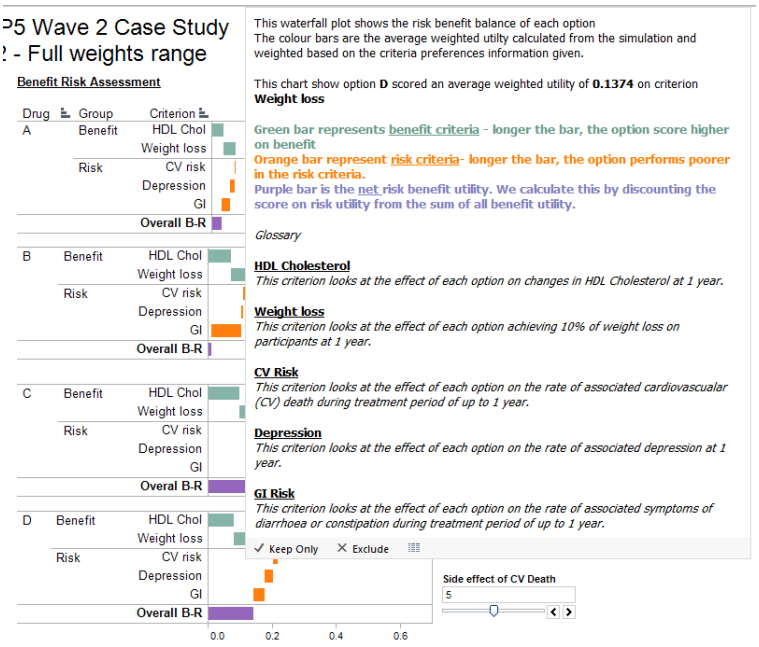
http://public.tableausoftware.com/views/Finalwave2dashboard-fullrangeweight/DashboardWaterfallplot?:embed=y



There are 3 main components in this dashboard

Component A: Component A is the criteria preference panel. Stakeholders are asked to select their criteria preference between 0 and 10 on all criteria. 0 refers to no importance whereas 10 refers to upmost important to the user. User can change it by pressing the direction arrows or by moving the pointer on the sliding bar.

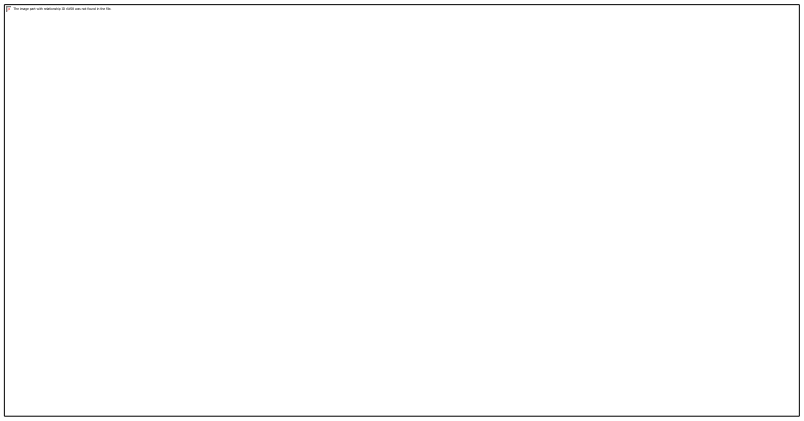
Component B: Component B is the Waterfall plot result panel. Following stakeholder indicated their criteria preference, the dashboard will update the weighted utility value on all criteria and re calculate the mean weighted utility on each criterion and the average weighted utility from the simulations and display the results in form of a waterfall plot.



Green bar represents benefit criteria - longer the bar, the option score higher on benefit
Orange bar represent risk criteria- longer the bar, the option performs poorer in the risk criteria.
Purple bar is the net risk benefit utility. We calculate this by discounting the score on risk utility from the sum of all benefit utility

Either hovering above or clicking the waterfall plot will openup an new tooltip window showing the explaination of waterfall plot and glossary.

Component C: Component C is the results of the SMAA simulations. This demonstrates the probability of each comparator rank 1st, 2nd, 3rd or 4th during the simulations. Results from this panel updates with the criteria preference information given in the criteria preference panel.

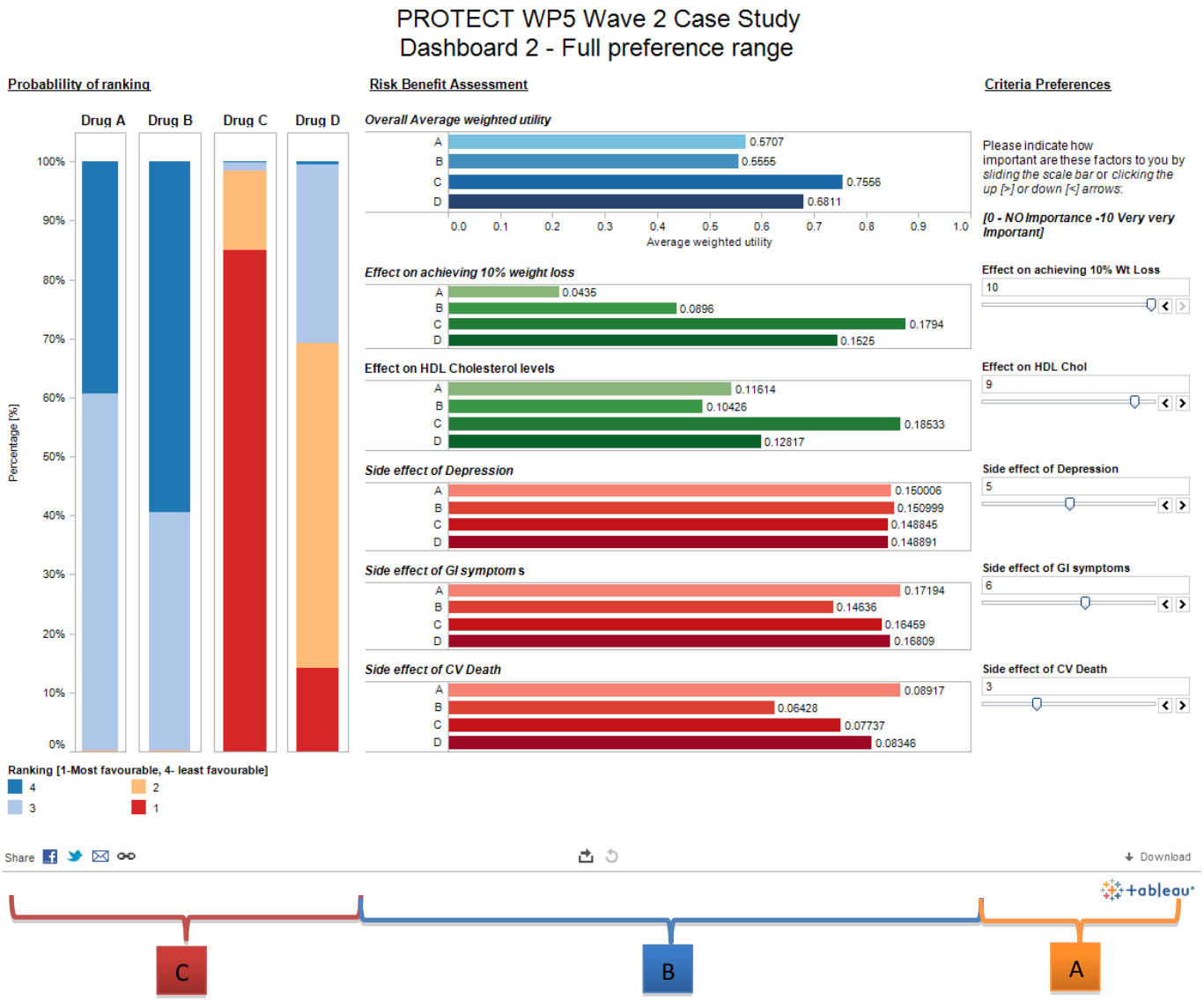


Either hovering above or clicking the stacked bar plot will openup an new tooltip window showing the explaination of SMAA result plot and detail results on the probability of each rank.

8.3 Dashboard 2: Full criteria preference range SMAA with Average Utility value

Web link:

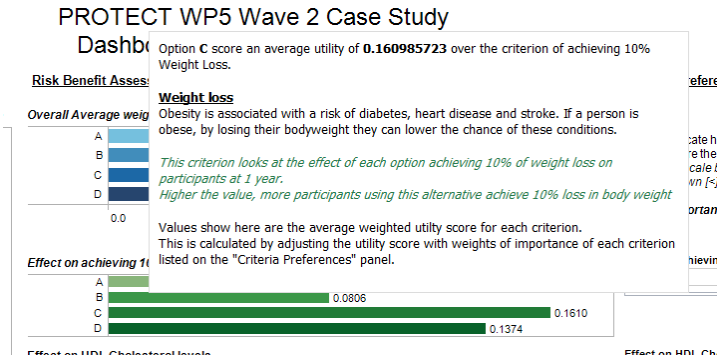
http://public.tableausoftware.com/views/Finalwave2dashboard-fullrangeweight/DashboardUtility?:embed=y



There are 3 main components in this dashboard

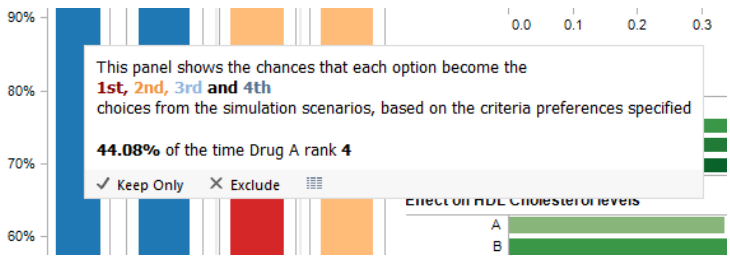
Component A: Component A is the criteria preference panel. Stakeholders are asked to select their criteria preference between 0 and 10 on all criteria. 0 refers to no importance whereas 10 refers to upmost important to the user. User can change it by pressing the direction arrows or by moving the pointer on the sliding bar.

Component B: Component B is the bar chart result panel. Following stakeholder indicated their criteria preference, the dashboard will update the weighted utility value on all criteria and re calculate the mean weighted utility on each criterion and the average weighted utility from the simulations and display the results in form of a bar chart.



Either hovering above or clicking the plot will openup an new tooltip window showing the numeric results and glossary.

Component C: Component C is the results of the SMAA simulations. This demonstrates the probability of each comparator rank 1st, 2nd, 3rd or 4th during the simulations. Results from this panel updates with the criteria preference information given in the criteria preference panel.

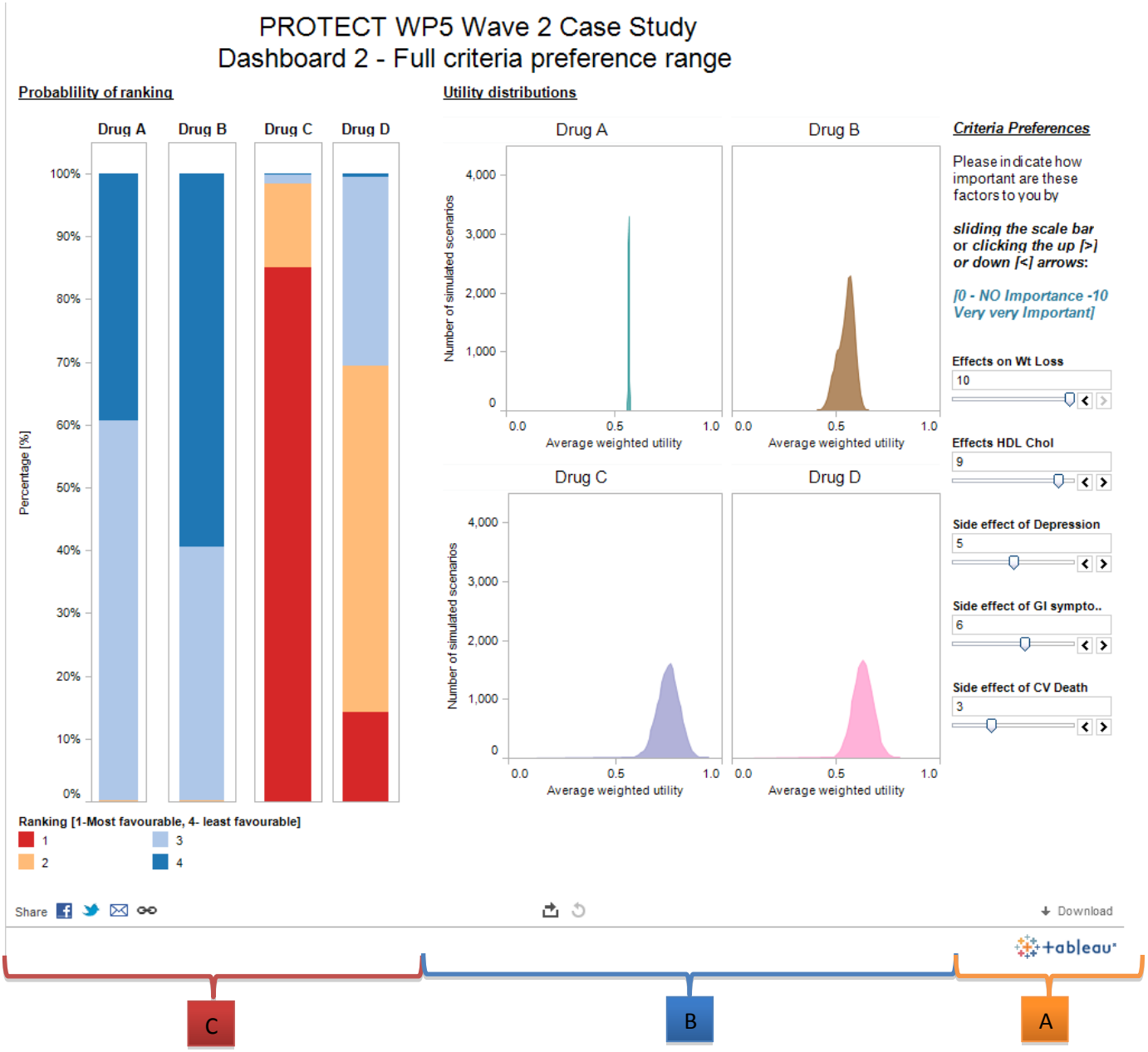


Either hovering above or clicking the stacked bar plot will openup an new tooltip window showing the explaination of SMAA result plot and detail results on the probability of each rank.

8.4 Dashboard 3: Full criteria preference range SMAA with distribution of average weighted utility

Web link:

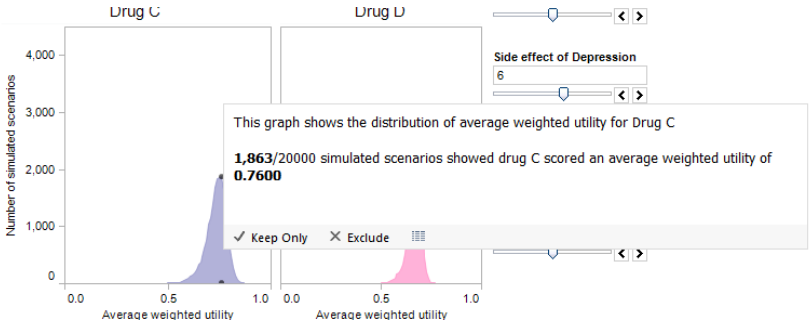
http://public.tableausoftware.com/views/Finalwave2dashboard-fullrangeweight/Dashboardutilitydensity?:embed=y



There are 3 main components in this dashboard

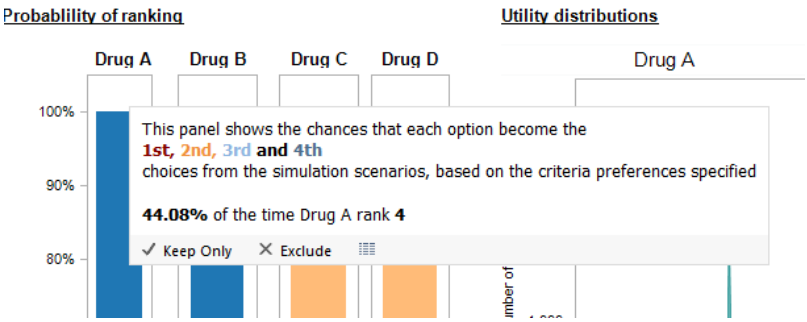
Component A: Component A is the criteria preference panel. Stakeholders are asked to select their criteria preference between 0 and 10 on all criteria. 0 refers to no importance whereas 10 refers to upmost important to the user. User change it by pressing the direction arrows or by moving the pointer on the sliding bar.

Component B: Component B are the histogarms of the average weighted utility of all 4 options. Following stakeholder indicated their criteria preference, the dashboard will update the weighted utility value on all criteria and re calculate the mean weighted utility on each criterion and the average weighted utility from the simulations and display the results in form of a histogram chart. The X Axis showing the average weighted utility value, Y Axis showing the frequency of the selected average utility during the 20000 simulations.



Either hovering above or clicking the plot will openup an new tooltip window showing the numeric results and glossary.

Component C: Component C is the results of the SMAA simulations. This demonstrates the probability of each comparator rank 1st, 2nd, 3rd or 4th during the simulations. Results from this panel updates with the criteria preference information given in the criteria preference panel.

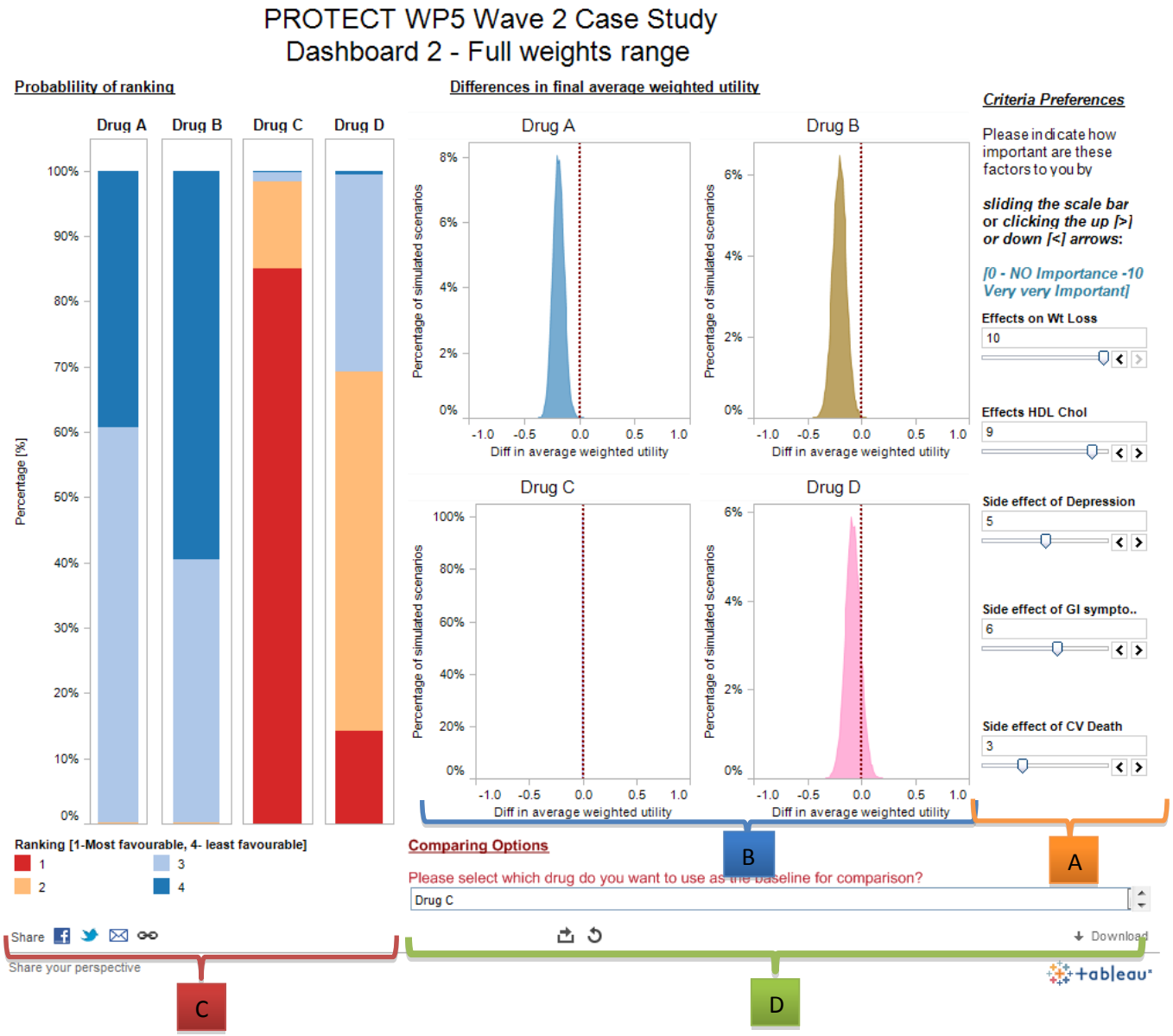


Either hovering above or clicking the stacked bar plot will openup an new tooltip window showing the explaination of SMAA result plot and detail results on the probability of each rank.

8.5 Dashboard 4: Full criteria preference range SMAA with comparison in utility value between options

Web link:

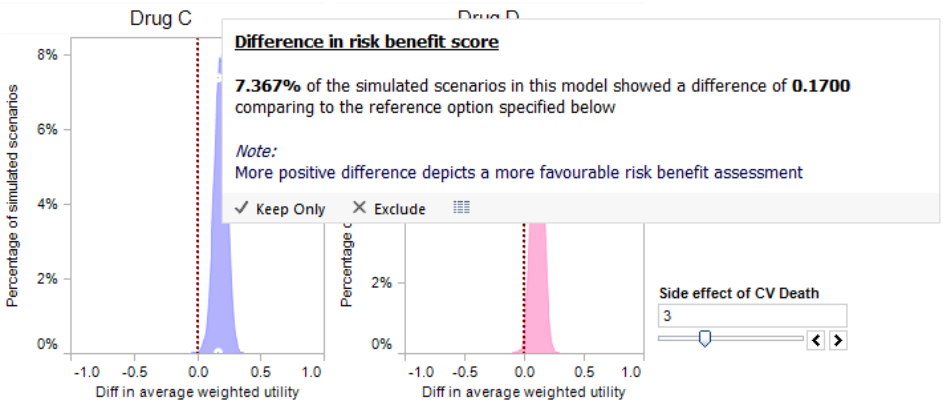
http://public.tableausoftware.com/views/Finalwave2dashboard-fullrangeweight/Uncertainty?:embed=y



There are 4 main components in this dashboard

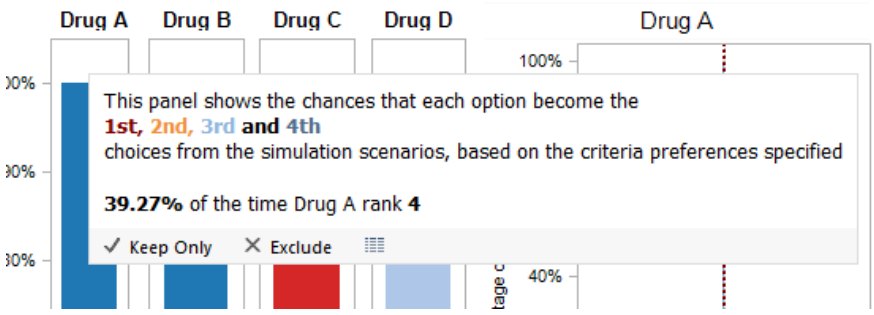
Component A: Component A is the criteria preference panel. Stakeholders are asked to select their criteria preference between 0 and 10 on all criteria. 0 refers to no importance whereas 10 refers to upmost important to the user. User can change it by pressing the direction arrows or by moving the pointer on the sliding bar.

Component B: Component B are the histogarms of the **difference** in average weighted utility of all 4 options. The aim of this dashboard is to explore the difference in average weighted utility between options, so to provide an additional piece of information for risk benefit assessment when interpreting the ranking results from SMAA model. The SMAA model produce the ranking whereas this panel allows user to examine differences between options by setting the baseline option in component D.



Following stakeholder indicated their criteria preference and the reference option, the dashboard will update the weighted utility value on all criteria and re calculate the weighted utility on each criterion and the average weighted utility from the simulations and display the results in form of a histogram chart. The X Axis showing the difference in average weighted utility value, Y Axis showing the percentage of the selected differences average utility during the 20000 simulations. The dotted red line act as the reference line to refer to point 0 [no difference].

Component C: Component C is the results of the SMAA simulations. This demonstrates the probability of each comparator rank 1st, 2nd, 3rd or 4th during the simulations. Results from this panel updates with the criteria preference information given in the criteria preference panel.



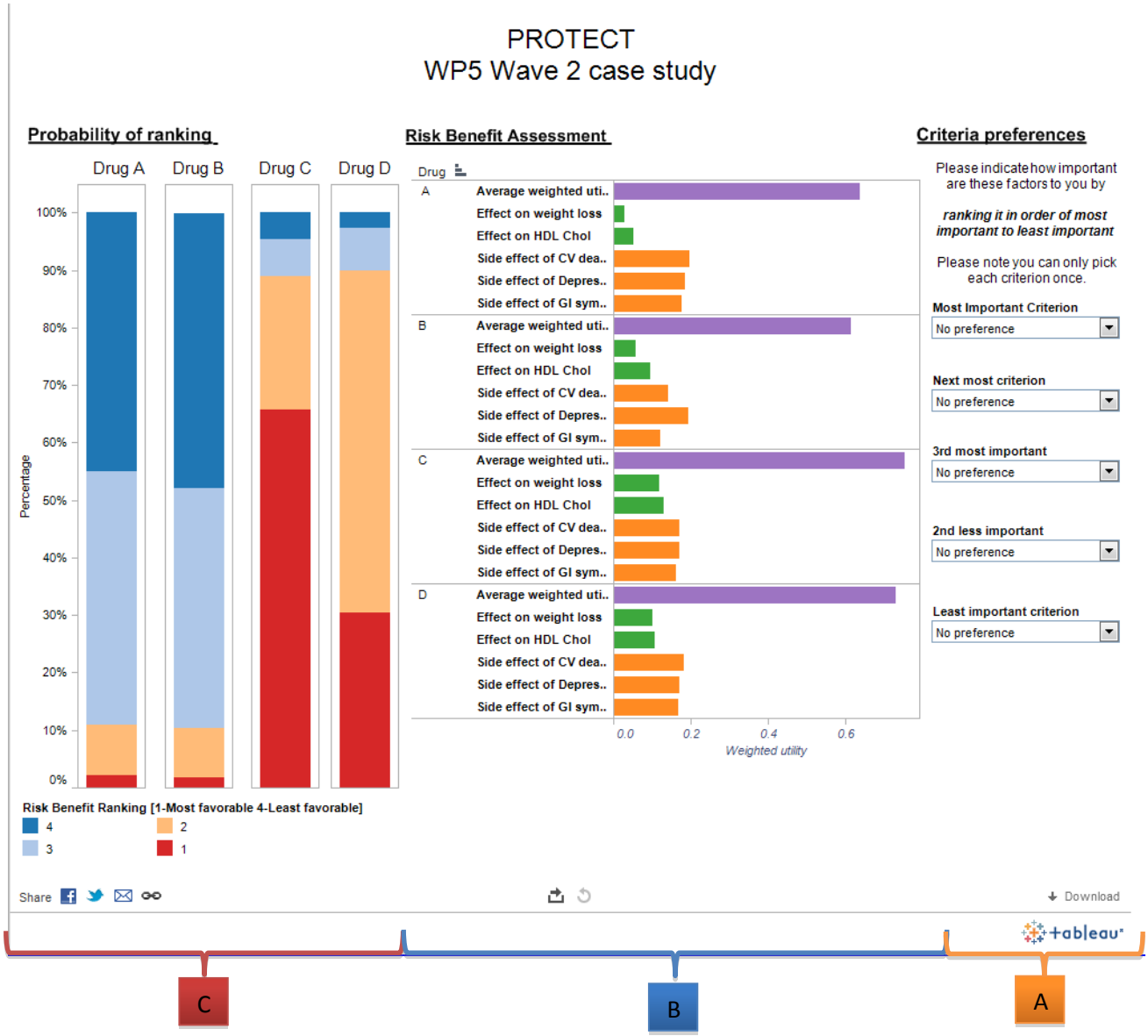
Either hovering above or clicking the stacked bar plot will openup an new tooltip window showing the explaination of SMAA result plot and detail results on the probability of each rank.

Component D: Component D is the reference baseline panel for comparison

8.6 Dashboard 5: Rank criteria preference with SMAA

Web link:

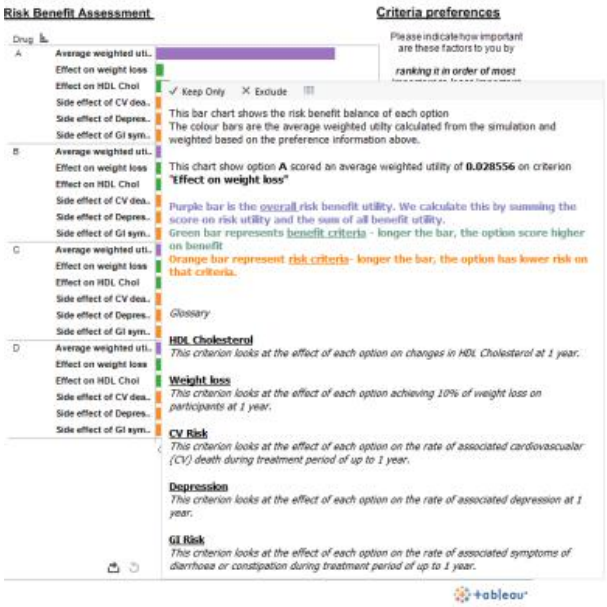
http://public.tableausoftware.com/views/FinalWave2dashboard-rankweight/Dashboardrankpreference?:embed=y



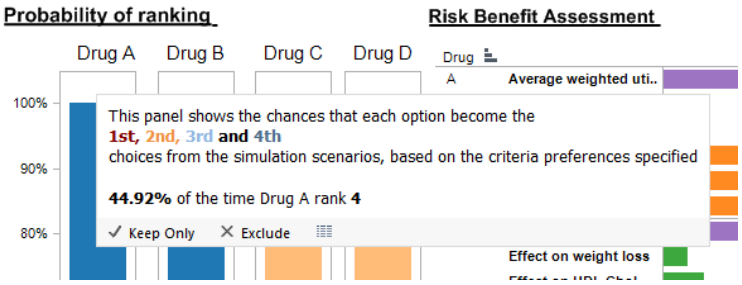
There are 3 main components in this dashboard

Component A: Component A is the criteria preference panel. Stakeholders are asked to rank their criteria preference between on all criteria from most favourable to least favourable. User also given an option to choose no preference in all criteria to demonstrate the "missing weights" model.

Component B: Component B is the bar chart result panel. Following stakeholder indicated their criteria preference, the dashboard will update the weighted utility value on all criteria and re calculate the mean weighted utility on each criterion and the average weighted utility from the simulations and display the results in form of a bar chart.



Component C: Component C is the results of the SMAA simulations. This demonstrates the probability of each comparator rank 1st, 2nd, 3rd or 4th during the simulations. Results from this panel updates with the criteria preference information given in the criteria preference panel.



Either hovering above or clicking the stacked bar plot will openup an new tooltip window showing the explaination of SMAA result plot and detail results on the probability of each rank.

9 Discussion

Later EPARs on rimonabant and sibutramine recommended the withdrawal of market approval for both medications based on the post-marketing safety signals associated with the side effect of depression and cardiovascular risk respectively. Results from the SMAA decision analyses in this report suggest both options had a favourable benefit-risk profile when compared to placebo or orlistat. This may have impact in future assessment on weight loss drug from similar class.

However, reader ought to remember that the process and conclusion drawn from this analysis are aimed to demonstrate the methodologies and visualisation only. The decision analysis result from this case study was based on a hypothetical setting with reduced criteria.

9.1 DCE

The DCE was implemented with relative ease, although a significant amount of time was required to understand the construction of a fractional factorial design, and potential methods of analysis. Once learned, the software commands on SAS and STATA were fairly straight forward to apply.

It should be noted that it is not an ideal scenario for the design of the DCE to take place concurrently alongside data extraction and ITC analysis. Ideally, data extraction and analysis should take place before design begins, and the results should feed into the DCE design. One consequence of the concurrent work within this case study is that data extraction yielded different outcomes and measurements to those used in the DCE, so that the DCE did not sufficiently cover the data, i.e. the outcomes and ranges of the data under consideration in the DCE did not represent the treatment, placebo or active comparators.

The number of attributes and levels that can be investigated with a DCE is limited. As the number of criteria and levels increase, the number of hypothetical scenarios required for each participant to complete escalates substantially. An increased number of choice sets may result in cognitive and time burden, and negatively affect the validity of responses. Therefore, within a regulatory setting, the number of benefit and risk criteria must be limited to only the most important criteria affecting the assessment.

For this case study, a probit model was used to analyse the results of the DCE based on academic literature. However, there are alternate methods of evaluating the responses, including conditional logit. Additionally, although the model assumed HDL was categorical, it too could have been considered as linear. Although DCEs are frequently used within a marketing context, there is a lack of information that can be used to guide the analysis of DCEs within a benefit-risk assessment and regulatory setting. Further work should examine the multiple methods of analyses, stating the differing assumptions of each model and subsequent impact upon the results.

9.2 Indirect Treatment Comparison

In this case study, we proposed the use of ITC for data synthesis so to allow a levelled comparison between options in the decision analysis model.

Our experience with ITC is generally encouraging. Technically, the execution of this method of data synthesis required a moderate level of understanding of mathematics and Bayesian modelling. Although a software, GeMTC, has been developed by University of Groningen [http://drugis.org/gemtc]. This GeMTC software does not perform analysis, but will generate the required programme code and data file to be used in WinBUGS.

Our team had tried this software and found this is software is easy to use and the result codes are easy to follow. However, the result codes were restricted to a non-informative normal prior. Furthermore, this software only able to build models limited to a normally distributed continuous outcomes or binary outcomes in a logistic model.

Therefore, our team developed the codes further so it can potential handle other outcomes measures for example rate of events.

The choice of prior in the model can potentially has a substantial impact on the results, we learnt from our experience with ITC that the final results are subjective on the quality of the data and like other Bayesian models; it is dependent of prior distribution used in the model.

We found this method is extremely useful in estimating the relative response between comparators when direct comparisons are not available. Moreover, ITC was has shown to be crucial in data synthesis to prepare data for the decision analysis where the all alternatives are compared on the same level.

However, MTC/ITC works by analysis the difference in relative effects of each comparator against a common baseline option between comparator pairs, the placebo in our case study. Results were generated under an assumption that the common [pivot] option between different comparisons pairs is identical. One would argue that is not always clinically plausible.

9.3 SMAA

We viewed SMAA positively as a decision analysis from our case 1 experience, mainly because of its ability to cope with uncertainty with medical data and more importantly, uncertainty with criteria preference weight. However, the original SMAA software [JSMAA] used in wave 1 study is not able to handle problems with multiple alternatives and/or with multiple criteria. Furthermore, the original JSMAA software is also restricted to a linear utility function – which one would argue this is not appropriate for clinical scenarios as most utility function in clinical measurements are non-linear.

SMAA presents results as the probability of r options achieved the 1 – r^{th} rank, as well as the "Central weights" between criteria on each alternative, these can be seen as a set of "typical" weight combinations that results in the option become the most favourable choice. These result presentations do not quantify the differences between the options and the uncertainty with the rankings.

Therefore, we set out to extend the use of SMAA in decision analysis using Stata programming. We developed Stata code that can be used for binary or continuous outcomes. Our team also developed Stata code which can simulate preference weights in cases with missing weight preference (Appendix 11.1.4), in cases with a range of criteria preference (Appendix 11.1.5) and in cases with only criteria rank preference are available (Appendix 11.1.6), as well as, the cases where specific weights. We used data generated from these simulations to build the 5 dashboards in visual presentations.

Our experience of using the simulation approach of SMAA is encouraging. This approach greatly increases the flexibility on SMAA analysis from the original model. Not only it minimise the restrictions of number of alternatives or criteria, it would also allow the use of non-linear utility function which is more clinically relevant. Furthermore, this approach allowed user to evaluate the risk benefit using other data generated from the simulations.

In order to improve the visual presentation of risk benefit assessment using SMAA model, our team created further graphical representations on the final average weighted utility so to compare the risk benefit balance (bar chart showing the mean of average weighted utility in Section 8.2,8.3), the uncertainty of the rank results (in form of distribution of average weighted utility showing that a platykurtic distribution of weighted utility suggest a higher

level of uncertainty in Section 8.4) and the net difference in risk benefit balance between comparators (show in form of distribution of the net difference in Section 8.5).

We have also created a function dashboard to allow sensitivity testing of the final risk benefit balance, allowing user to test the robustness of risk benefit balance by adjusting the criteria preference.

Our experience with SMAA model was encouraging and we demonstrated the analysis can be done using Stata programming. The final results of the SMAA are not only dependent on weights assigned, but also the quality of data input into the model. We attempted to simulate data using the summary statistics and ideally patient level data should be used in the model to maximise the robustness of the results.

9.4 Visual presentations

The choices of visual types presented in this case study are to reflect the best practice in terms of visual perception and comprehension. They are designed with simplicity in mind and as priortity than aesthetics. We have taken some care to ensure that the information is projected clearly and accurately, but we acknowledge that the designs may not be suitable for everybody.

Most of the texts used on the dashboards are by Tableau's default, but some changes have been made where necessary such as bolding, underlining, resizing and colouring to make them more visible and distinguishable. In particular, we have taken into account that the dashboards may be projected to a screen where texts may need to appear slightly larger or bolder. The choice of colours were made through palettes on Color Brewer website (http://colorbrewer2.org) where we went for colour schemes that do not hinder people with colour-blindness from using the dashboard, as well ensuring that the colours would appear well when printed (these are the options on the website).

The dashboards contain large number of data points from the SMAA simulations. Where possible we have used Tableau's built-in mathematical functions to accomplish the view and interactivity features required. This includes generating sufficient data points from the analysis to allow data extrapolation in Tableau to avoid generating all data combinations for every scenario. We created variables called the "parameters" to be used with the sliders to allow weights to be varied more efficiently. We found the drag and drop features of building the graphics very easy to use and intuitive. However, we encountered some problems when creating bins for histograms where we were unable to match the bin sizes across multiple histograms. We resort to calculating the bins manually through the built-in mathematical function and plotting the distributions of the variables as two-way area graphs.

We performed group testing of the dashboards through email communications, face-to-face meetings and teleconferences. The members of the rimonabant case study team were initially concern that the dashboards do not convey meaningful message to lay users. We also addressed the issues of unaligned axes across graphs making comparison more difficult and less accurate. The positioning of graphs, legends and colour choices were also brought up in the discussions. Taking all the considerations into account, we revised the dashboards as proposed. This demonstrates that designing dashboard is not a one-step process and may require revisions before a final usable version is reached. The key to a usable dashboard design is in knowing the audience and testing.

We hope that the prototypes generated in this case study would be useful and encourage many more similar applications in the future.

10 Recommendations

After our reviewing our experience with the Wave 2 rimonabant case study, our group would like to make the following recommendations for future work:

1. ***Design DCE questionnaire with attributes and levels within the limits of observed data range***. DCE is a valuable tool to elicit opinion data from lay person and levels of attributes used should be matching the confines of data range, instead of using possible data range in this case study, in order to maximise the power of the experiment.
2. ***Testing participants understanding of the questions in the DCE questionnaires***. Although we endeavoured to use a clear and simple language in the DCE questionnaire, we would recommend further work to examine how participants understand the tasks required of them and context of the questions.
3. ***SMAA modelling using patient level data to examine the effects of demographics covariates on BR assessment***. Our SMAA models were developed in this case study were based on summary statistics collected from published literatures. As a result, we lose vital information on distributions of the observed effects, as well as any information on potential interactions between treatment outcomes and patient demographics. Therefore, we recommend applying SMAA modelling on patient level data to examine if the benefit risk assessment changes with patient demographics.
4. ***Further development of SMAA programme code into Stata add-on package***. The Stata codes developed for this exercise were aimed for users who are proficient in Stata programming. Our team would recommend developing this code further into a Stata add-on package so to improve its applications.
5. ***Testing dashboards with stakeholders***. Our dashboards were developed based on recommendations made by the visual review team. We would recommend further testing with and critique from stakeholders to improve the clarity of the message we try to convey using the dashboards.

11 Stata Codes

11.1.1 Continuous Data

```
gen comp_1_norm=rnormal(x,y)                    * Generate baseline data using normal dist
gen comp_2_norm=comp_1_norm+ rnormal(a,b)        * Generate comparator using baseline and estimate difference compare to base
```

11.1.2 Binomial Data

```
gen comp_1_rate=rbeta(x,y)                      *Generate baseline rate using beta(x,y)
gen odd_1=comp_1_rate/(1-comp_1_rate)           *Generate baseline odds
gen or_comp2=exp(rnormal(a,b))                  *Generate OR of event on each simulation
gen comp_2_rate=(odd_1*or_comp2t)/(1+odd_1*or_comp2)   *Convert odds to rate
```

11.1.3 Utility function

```
local bin_lowest=0                              *Set local criteria cut off
local bin_1=0.40
local bin_2=0.55
local bin_3=0.7
local bin_highest=1

local utility_lowest=0                          * Set utility value at cut off
local utility_1=0.2
local utility_2=0.3
local utility_3=0.4
local utility_highest=1

gen comp_1_data=comp_1_rate
gen utility_comp_1=.
replace utility_comp_1=`utility_lowest'+`utility_1'*(comp_1_data-`bin_lowest')/(`bin_1'-`bin_lowest') if comp_1_data<`bin_1'
replace utility_comp_1=`utility_1'+(`utility_2'-`utility_1')*(comp_1_data-`bin_1')/(`bin_2'-`bin_1') if comp_1_data<`bin_2' & utility_comp_1==.
replace utility_comp_1=`utility_2'+(`utility_3'-`utility_2')*(comp_1_data-`bin_2')/(`bin_3'-`bin_2') if comp_1_data<`bin_3' & utility_comp_1==.
replace utility_comp_1=`utility_3'+(`utility_highest'-`utility_3')*(comp_1_data-`bin_3')/(`bin_highest'-`bin_3') if comp_1_data<`bin_highest' & utility_comp_1==.
```

11.1.4 Missing Weights

```
gen criterion_1_wt=runiform()                   *Generate weight between 0-1
gen criterion_2_wt=runiform()
gen criterion_3_wt=runiform()
 gen total_wt=criterion_1_wt+criterion_2_wt+criterion_3_wt
replace criterion_1_wt=criterion_1_wt/total_wt  *Rescale weights to a total of 1
replace criterion_2_wt=criterion_2_wt/total_wt
replace criterion_3_wt=criterion_3_wt/total_wt
```

11.1.5 Range Weights

```
/* Assume
Criterion 1 range 0.4-0.9
Criteiron 2 range 0.05-0.6
Criterion 3 range 0.05-0.3
*/

gen criterion_1_wt=0.4+0.5*uniform()            * Generate random criteria weight within the specified range above
gen criterion_2_wt=0.05+0.55*uniform()
gen criterion_3_wt=0.05+0.25*uniform()

 gen total_wt=criterion_1_wt+criterion_2_wt+criterion_3_wt
replace criterion_1_wt=criterion_1_wt/total_wt  * Rescale all weights to a total of 1
replace criterion_2_wt=criterion_2_wt/total_wt
replace criterion_3_wt=criterion_3_wt/total_wt
```

11.1.6 Rank Weights

/* Assign simulated weight values for criteria 1 - 3
Assuming ranking as follows criterion 1>Criterion2 > criterion 3
Therefore, start simulating weight for criterion 1 using uniform distribution between 0 -1
followed by simulating weight for criterion 2 using usinform distribution between 0- weight assigned for criteria 1

followed by simulating weight for criterion 2 using usinform distribution between 0- weight assigned for criteria 2
This will ensure random number assigned are uniformed and with specified ranking
We can use the same logic for range - use formula criterion_wt=Lower range + (difference between ranges) * runiform
or unspecified ranking - use formula criterion_wt=runiform
*/

```
gen criterion_1_wt=runiform()
gen criterion_2_wt=criterion_1_wt*runiform()
gen criterion_3_wt=criterion_2_wt*runiform()

gen total_wt=criterion_1_wt+criterion_2_wt+criterion_3_wt          *Rescale to a total of 1
replace criterion_1_wt=criterion_1_wt/total_wt
replace criterion_2_wt=criterion_2_wt/total_wt
replace criterion_3_wt=criterion_3_wt/total_wt
```

11.1.7 Ranking

```
reshape long wt_overall_utility_comp_,i (id) j(comp)               *Reshape data from wide to long
rename wt_overall_utility_comp_ utility
sort id
bysort id: egen rank=rank(utility), field                          * rank weighted average utility in each simulation
tab rank comp, col
gen comp_name="Drug A" if comp==11
replace comp_name="Drug B" if comp==12
replace comp_name="Drug C" if comp==13
replace comp_name="Drug D" if comp==14
graph bar (count) id ,  over(rank) over(comp_name) stack asyvars percent title(SMAA ranking - Weighted utility) legend(note("Rank") row(1))
ytitle("Percentage")
```

12 ITC Data

12.1.1 10% Weight loss

Trials	N	Option	Result	
Pre Marketing				*Post Marketing*
RIO-North America Yr 1 EFC4743	607	Placebo	8.50%	No data
	1219	Rimonabant 20mg	25.20%	
RIO - Europe EFC 4733	305	Placebo	7.30%	
	599	Rimonabant 20mg	27.40%	
RIO - LIPID	342	Placebo	7.20%	
	346	Rimonabant 20mg	32.60%	
RIO - Diabetes	348	Placebo	2.00%	
	339	Rimonabant 20mg	16.40%	
Berne	109	Placebo	2.75% [3/109]	
	111	Orlistat 120mg	13.51% [15/111]	
Finer	114	Placebo	17%	
	114	Orlistat 120mg	28%	
Hauptman	212	Placebo	11.30%	
	210	Orlistat 120mg	28.60%	
Hollander	159	Placebo	8.80%	
	162	Orlistat 120mg	17.90%	
Kelley	269	Placebo	3.70%	
	266	Orlistat 120mg	10.20%	
Krempf	350	Placebo	24.50%	
	346	Orlistat 120mg	32.90%	
Lindgarde	186	Placebo	14.60%	
	190	Orlistat 120mg	19.20%	
Miles	254	Placebo	3.90%	
	250	Orlistat 120mg	14.10%	
Rossner	243	Placebo	18.80%	
	244	Orlistat 120mg	38.30%	
Sjostrom	340	Placebo	17.70%	
	343	Orlistat 120mg	38.80%	
XENDOS	1637	Placebo	20.80%	
	1640	Orlistat 120mg	41.00%	
McMahon	150	Sibutramine 15mg	13.40%	
	74	Placebo	4.30%	
McMahon	146	Sibutramine 20mg	13.10%	
	74	Placebo	2.80%	
McNutty	68	Sibutramine 15mg	14%	
	64	Placebo	0%	
Sanchez Reyes	44	Sibutramine 15mg	25.00%	
	42	Placebo	4.80%	

Smith	153	Sibutramine 15mg	34%
	157	Placebo	7%

12.1.2 HDL Chol Control

Trials	N	Option	Result	
Pre Marketing				*Post marketing*
RIO - Europe EFC 4733	305	Placebo	0.15 mmol/L [0.12, 0.18 95%CI]	No data
	599	Rimonabant 20mg	0.26mmol/L [0.15. 0.23 95%CI]	
RIO - Diabetes	348	Placebo	0.07+0.15 [SD]	
	339	Rimonabant 20mg	0.17+0.2 [SD]	
Berne	109	Placebo	"0.07+0.23 [SD]"	
	111	Orlistat 120mg	"-0.01+0.17 [SD]"	
Finer	114	Placebo	"0.3+0.68 [SD]"	
	114	Orlistat 120mg	"-0.05+0.76 [SD]	
Hauptman	212	Placebo	"0.3+?0.07 SEM"	
	210	Orlistat 120mg	"-0.04+?0.08 [SEM]	
Hollander	159	Placebo	0.08+0.01 [SEM]	
	162	Orlistat 120mg	0.06 + 0.01 [SEM]	
Kelley	269	Placebo	0.05+0.01 [SEM]	
	266	Orlistat 120mg	0.02+0.01 [SEM]	
Lindgarde	186	Placebo	0.02+0.2 [SD]	
	190	Orlistat 120mg	0.00+0.22 [SD]	
Miles	254	Placebo	0.1+0.02 [SEM]	
	250	Orlistat 120mg	0.09 + 0.02 [SEM]	
Rossner	243	Placebo	0.2 +?0.35 [SD]	
	244	Orlistat 120mg	0.04 + ?0.30 [SD]	
Sjostrom	340	Placebo	0.1+0.01 [SEM]	
	343	Orlistat 120mg	0.1+0.01 [SEM]	
Swingburn	169	Placebo	0.08+0.19 [SD]	
	170	Orlistat 120mg	0.04+0.18 [SD]	
McMahon	150	Sibutramine 15mg	0.14mmol/L [NO SD]	
	74	Placebo	0.06mmol/L [NO SD]	
McMahon	146	Sibutramine 20mg	4.8 mg/dL [No SD]	
	74	Placebo	1.3 mg/dL [no SD]	
McNutty	68	Sibutramine 15mg	`-0.1 (-0.14 to 0.6 RANGE) mmol/L	
	64	Placebo	0.0 (-4.9 to 0.3 Range)	
Sanchez Reyes	44	Sibutramine 15mg	0.6 +?6.4 [SD]	
	42	Placebo	`-1.3 + ?5.3 [SD]	

12.1.3 Side effect of Depression

Trials	N	Option	Result	*Trials*	N	Option	Result
Pre Marketing				*Post marketing*			
RIO-North America Yr 1 EFC4743	607	Placebo	3.10%	PEM		Rimonabant	Overall 829/10011
	1219	Rimonabant 20mg	5.20%				13.8 per 1000 patient months [Depression]
RIO - Europe EFC 4733	305	Placebo	<5%	CRESENDO trial [RCT]	9314	Placebo	424 [4.6%]
	599	Rimonabant 20mg	<5%		9381	Rimonabant 20mg	902 [9.6%]
RIO - LIPID	342	Placebo	<5%				
	346	Rimonabant 20mg	<5%	PEM		Orlistat	234/16021
RIO - Diabetes	348	Placebo	<5%				2.76 per 1000 patient monthss
	339	Rimonabant 20mg	<5%				
EPAR		Placebo	1.60%	PEM		Sibutramine	222/13418
		Rimonabant 20mg	3.20%				4.36 per 1000 patient months
Finer	114	Placebo	<3%				
	114	Orlistat 120mg	<3%				
FDA documents	2068	Sibutramine	4.30%				
	884	Placebo	2.50%				
McMahon	150	Sibutramine 15mg	<10%				
	74	Placebo	<10%				

12.1.4 Side effect of CV Death

Trials	Option	N	Results	Trials	N	Options	Results
Pre marketing				Post Marketing			
EPAR	Placebo	1602	0.20%	CRESENDO RCT	9314	Placebo	123 [1.3%]
	Rimonabant	2503	0.50%		9381	Rimonabant 20mg	122 [1.3%]
FDA documents	Placebo	1466	0%	PEM	16021	Orlistat	0
	Orlistat	1913	0.05%	SCOUT	4898	Placebo	4.70%
FDA documents	Placebo	884	0.00%		4906	Sibutramine 15mg	4.50%
	Sibutramine	2068	0.05%	PEM	13418	Sibutramine 15mg	0 cases

12.1.5 Side effect of GI Symptoms

Trials	Option	N	Results	Trials	N	Options	Results
Pre Marketing				Post Marketing			
RIO-North America Yr 1 EFC4743	607	Placebo	5.10%	CRESENDO RCT	9314	Placebo	5.60%
	1219	Rimonabant 20mg	5.30%		9381	Rimonabant 20mg	8.10%
RIO - Europe EFC 4733	305	Placebo	4.90%	PEM		Rimonabant 20mg	No data
	599	Rimonabant 20mg	8.70%				
RIO - LIPID	342	Placebo	4.10%	PEM	16021	Orlistat	789/16021

	346	Rimonabant 20mg	7.20%				8.29 per 1000 patient months
RIO - Diabetes	348	Placebo	7%				
	339	Rimonabant 20mg	7%	PEM	13418	Sibutramine	184/13418
FDA	1466	placebo	7%				3.61 per 1000 patient yr
	1913	Orlistat 120mg	22%				
FDA	884	Placebo	6%				
	2068	Sibutramine	11%				

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