# Recommendations for Benefit-Risk Assessment

## Methodologies and Visual Representations

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| Keywords: | Benefit-risk, Drug development, Decision making, Regulation |
| Purpose | To draw on the practical experience from the PROTECT BR case studies and make recommendations regarding the application of a number of methodologies and visual representations for benefit-risk assessment. |
| Abstract: | Eight case studies based on the benefit-risk balance of real medicines were used to test various methodologies that had been identified from the literature as having potential applications in benefit-risk assessment. Recommendations were drawn up based on the results of the case studies. |

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Results
A general pathway through the case studies was evident, with various classes of methodologies having roles to play at different stages. Descriptive and quantitative frameworks were widely used throughout to structure problems, with other methods such as metrics, estimation techniques and elicitation techniques providing ways to incorporate technical or numerical data from various sources. Similarly, tree diagrams and effects tables were universally adopted, with other visualisations available to suit specific methodologies or tasks as required. Every assessment was found to follow five broad stages: 1) Planning, 2) Evidence gathering and data preparation, 3) Analysis, 4) Exploration, and 5) Conclusion and dissemination.

Conclusions
Adopting formal, structured approaches to benefit-risk assessment was feasible in real-world problems and facilitated clear, transparent decision making. Prior to this work, no extensive practical application and appraisal of methodologies had been conducted using real world case examples, leaving users with limited knowledge of their usefulness in the real world. The practical guidance provided here takes us one step closer to a harmonised approach to benefit-risk assessment from multiple perspectives.
Recommendations for Benefit-Risk Assessment Methodologies and Visual Representations

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Key messages

- Formal and transparent discussion of multiple viewpoints, interests and priorities facilitates mutual understanding of complex decision problems
- Benefit-risk assessments of treatments should be undertaken in a structured way so that it is clear how a decision on the overall balance of a treatment’s effects has been reached
- Various structured approaches and singular methodologies/visual representations are available to support benefit-risk assessment of medicines, but so far universal agreement as to the most suitable method for structured benefit-risk assessment has been lacking
- A team combining expertise from public and private institutions carried out a review of benefit-risk methods and visual representations, including application of the tools to case studies based on real regulatory scenarios
- The project produced a clear set of practical recommendations for undertaking benefit-risk assessments, organised around a generic, five stage benefit-risk assessment roadmap

Keywords: Benefit-risk, decision making, drug development, regulation
This manuscript contains material previously published in reports on the IMI PROTECT website at http://www.imi-protect.eu/benefitsRep.shtml and on the PROTECT BR website at http://protectbenefitrisk.eu/

Acknowledgements

The research leading to these results was conducted as part of the PROTECT consortium (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, www.imi-protect.eu) which is a public-private partnership coordinated by the European Medicines Agency. The PROTECT project has received support from the Innovative Medicines Initiative Joint Undertaking (www.imi.europa.eu) under Grant Agreement n° 115004, resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.

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The processes described and conclusions drawn from the work presented herein relate solely to the testing of methodologies and representations for the evaluation of benefit and risk of medicines. This report neither replaces nor is intended to replace or comment on any regulatory decisions made by national regulatory agencies, nor the European Medicines Agency.

The authors declare the following conflicts of interest: Dr Hughes has been employed by Pfizer Inc. for the duration of the project. Mr Downey reports that he is an employee of Amgen, a participant in the Innovative Medicines Initiative, which is a public-private partnership. The manuscript describes testing benefit-risk methodologies and visualizations using case studies of marketed products. No Amgen treatments were used in the work associated with this publication. Dr Juhaeri is an employee of Sanofi, the producer of rimonabant and telithromycin, which were used in the PROTECT project as case studies. Dr Juhaeri declares that he is an employee of Sanofi, the manufacturer of rimonabant which was studied in this project. Mr Lieftucht reports that he is an employee of GlaxoSmithKline, a participant in the Innovative Medicines Initiative, which is a public-private partnership. One of the case studies described in the manuscript is a GSK product but Mr Lieftucht did not work on that case study. Dr Metcalf reports that she is an employee of GlaxoSmithKline, a participant in the Innovative Medicines Initiative, which is a public-private partnership. One of the case studies described in the manuscript is a GSK product but Dr Metcalf did not work on that case study. Dr Noel is an employee and shareholder of Eli Lilly and Company. Professor Ashby reports grants from Innovative Medicines Initiative and EFPIA companies during the conduct of the study. Dr Micaleff was an employee of MerckSerono SA, the company which was the Marketing Authorisation holder of efalizumab, one of the case studies of PROTECT Work Package 5, until its withdrawal from the market in 2009. Mr Waddingham, Dr Mt-Isa, Dr Goginsky, Dr Chan, Dr Hallgreen, Dr Hockley, Professor Phillips and Professor Ashby have declared no conflicts.
Abstract

Purpose
To draw on the practical experience from the PROTECT BR case studies and make recommendations regarding the application of a number of methodologies and visual representations for benefit-risk assessment.

Methods
Eight case studies based on the benefit-risk balance of real medicines were used to test various methodologies that had been identified from the literature as having potential applications in benefit-risk assessment. Recommendations were drawn up based on the results of the case studies.

Results
A general pathway through the case studies was evident, with various classes of methodologies having roles to play at different stages. Descriptive and quantitative frameworks were widely used throughout to structure problems, with other methods such as metrics, estimation techniques and elicitation techniques providing ways to incorporate technical or numerical data from various sources. Similarly, tree diagrams and effects tables were universally adopted, with other visualisations available to suit specific methodologies or tasks as required. Every assessment was found to follow five broad stages: 1) Planning, 2) Evidence gathering and data preparation, 3) Analysis, 4) Exploration, and 5) Conclusion and dissemination.

Conclusions
Adopting formal, structured approaches to benefit-risk assessment was feasible in real-world problems and facilitated clear, transparent decision making. Prior to this work, no extensive practical application and appraisal of methodologies had been conducted using real world case examples, leaving users with limited knowledge of their usefulness in the real world. The practical guidance provided here takes us one step closer to a harmonised approach to benefit-risk assessment from multiple perspectives.
Introduction

Benefit-risk assessments play a critical role in bringing treatments to market, providing crucial information for decisions regarding (among others) drug development, licensing and reimbursement. In such situations, judgements by individuals or committees have traditionally been the main approach. However, without an explicit, systematic framework to capture the logic around these assessments, there has been increasing concern among companies and regulators about non-standardised, implicit and often qualitative approaches, with the Council for International Organizations of Medical Sciences (CIOMS) IV suggesting that explicit, quantitative statements would improve the transparency and consistency of decisions. It was this concern that led the European Medicines Agency to establish the three-year Benefit-Risk Methodology Project in 2009, and the ongoing testing of tools and processes for balancing the key benefits and risks of a new medicinal product. In the US since 2010, the Food and Drug Administration and industry worked together to introduce a formal framework for benefit-risk assessment into the reauthorization of the Prescription Drug User Fee Act.

Various structured approaches to decision-making have been developed and widely employed in other fields to address similar problems, and many could theoretically be applied in benefit-risk assessment to address concerns about the decision-making process. However, these have not traditionally been used in this field, and no single agreed method exists for integrating benefit-risk data or to determine the overall balance, and hence arrive at a treatment decision. Importantly, while several methodologies had been proposed prior to this project, a thorough appraisal of methodologies and practical applications in a large number of different real-life case studies had been missing, leaving practitioners with limited guidance.

The Innovative Medicines Initiative’s PROTECT project (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium) was established with the aim of strengthening the monitoring of the benefit-risk balance of medicines in Europe. This paper reports the findings of PROTECT’s Benefit-Risk Group (PROTECT BR) since inception in September 2009. The group’s objectives were to: “1) identify, characterise and test methods of collating data on benefits and risks from various data sources, parameters and strengths of evidence, and of integrating them with decision-criteria and formal assessment of values of patients, healthcare providers, regulators, the pharmaceutical industry and in benefit-risk assessment; 2) identify, test and compare modelling approaches that would allow continuous benefit-risk risk-modelling along the lifecycle of the product, and support decision-making; and 3) develop methods of graphical expression of the benefits and risks of the medicinal products for use by patients, healthcare providers, the pharmaceutical industry and regulators along the lifecycle of the product”. A variety of organisations from the public, private and academic sectors participated in the group.

A total of thirteen methodologies with features representative of their categories were selected for investigation in the case studies. This list was not intended to be exhaustive or restrictive, but it was believed that, taken together, the selected methodologies would be a sufficiently powerful toolbox for most benefit-risk assessments. The thirteen methodologies, their classification and the abbreviations used to refer to them are shown in Table 1.

Due to the limited space available for the main text of this paper, a degree of familiarity with the names and basic features of the methods and visualisations is assumed on the part of the reader. For those with no knowledge of the methods, a description of each method and visual type is provided in the Appendices. The purpose of this paper is to augment the existing descriptions and theoretical appraisals of these benefit-risk assessment methods and visual representations with practical experience and recommendations from the PROTECT BR case studies.
Methods

The case studies were selected based on real world scenarios involving medicines where the publicly available data suggested a marginal benefit-risk balance and which presented various practical challenges to stress-test candidate methods. The drugs and indications that formed the focus of the case studies are shown in Table 2. The methods were tested in two ‘waves’ comprising four case studies each. The first wave established the feasibility of many candidate methods by applying them to a straightforward benefit-risk assessment problem, while the second explored more complex scenarios or methods, and applied selected visual representation techniques. Each case study was highly collaborative in nature, with participants drawn from the range of public and private organisations within PROTECT BR. The case study teams worked independently of each other, but some individuals worked on more than one case study.

<<Table 2 here>>

The case study teams used only publicly available evidence on treatment effects. The qualitative and quantitative methods applied throughout the case studies drew heavily on the principles of decision analysis, which provided the foundations for both the BRAT and ProACT-URL frameworks, and the theory underlying the most frequently used quantitative approach, MCDA, was used in some form in all of our case studies.

Following the case studies, the key findings and lessons learnt from the reviews and case studies were organised according to five stages representing an approximate chronological order of activities to be undertaken for a benefit-risk assessment (the Recommendations Roadmap), which aims to provide an overarching view of benefit-risk assessment for those who are new to the process, while also allowing more experienced readers to hone in on technical aspects or methodologies of interest.41

The efalizumab study has been chosen to provide the illustrations in this paper as it has features that were shared by many of the case studies, is comprehensive enough to illustrate a range of approaches and provides visual examples that are relatively simple.
Results

Case studies

Each of the eight case studies applied several methodologies in combination or in parallel, as shown in Table 1. In total, ten of the thirteen methodologies recommended by Mt-Isa et al. were tested; no suitable data could be found for the QALY, Q-TWiST or INHB methodologies in any case study. Two additional quantitative frameworks were also tested: weighted Net Clinical Benefit (wNCB) in the natalizumab case study and Sarac’s Benefit-Risk Assessment Method (SBRAM) in the telithromycin case study. wNCB is a utility-weighted extension of NNT/NNH, and can be seen as a special case of MCDA that is simpler to apply in some situations. SBRAM has a similar structure to the other frameworks but with a unique way of scoring the data on each treatment effect.

Methods were chosen according to their suitability for the underlying decision problem and compatibility with the available data (for example, some methods such as NNT/NNH only work with binary outcome data). Methods were selected by group consensus within the case study teams; it is acknowledged that individuals may have proposed methods based on their own experience or research interests. In the first wave of case studies, teams were required to use as many methods as possible, giving reasons for any excluded methods, in order to encourage a comprehensive evaluation. The reasons given for selecting or excluding each method at this stage are set out in Appendix 2 and summarised in Table 1. Each case study in the second wave, by contrast, was aimed at testing a particular method or subset of methods as indicated in Appendix 3.

A common structure to the case studies emerged, with each team using a descriptive (i.e. qualitative) framework to document key contextual aspects of the benefit-risk assessment and to act as a foundation and a guide for the application of formal methods for specific subtasks, namely: measuring/expressing outcomes (metrics), extracting data (estimation techniques), eliciting preferences (utility survey techniques) and integrating effects data with preferences (quantitative frameworks). This common structure is shown in Figure 1.

<<Figure 1 here>>

A common pathway through each case study also emerged, with each team proceeding in broadly the following order:

1. select a descriptive framework
2. consider and document basic aspects of the decision context, beginning with a statement of the decision question itself in fairly general terms and moving towards more specific practical aspects of the problem such as establishing what alternative treatments exist and what data are available
3. examine the data and establish what metrics could be used to express the favourable and unfavourable effects
4. extract the data in the desired form using estimation techniques
5. optionally, elicit preference information using utility survey techniques and integrate this with the effects data using a quantitative framework
6. bring the results of the previous step back into the descriptive framework and proceed to conduct sensitivity analyses and communicate the findings.

This critical path is shown on Figure 1 by the curved arrow. It is important to note that, although this indicates the general order in which to proceed, the teams often found that it was necessary to look a few steps ahead during the process and/or to revisit earlier tasks in the light of what was uncovered later (for example, the choice of quantitative framework could in some cases limit the range of metrics that could be adopted). The next few paragraphs deal with each step of the path in turn.
The descriptive frameworks PrOACT-URL and BRAT were found to be useful guides for planning and executing a benefit-risk assessment and are considered suitable for use at any stage of a medicinal product’s life cycle. Each was used in six out of the eight case studies, with the first wave of four case studies employing both frameworks in parallel. The frameworks provide a structure for breaking down a benefit-risk problem into a stepwise thought process. The list of steps is somewhat similar in both frameworks, although they do not perfectly map onto one another. At the time of the initial methodology review, PrOACT-URL and BRAT were the two most promising descriptive frameworks; other frameworks may have since emerged, but we have not reviewed these and are unable to comment on their suitability.

The descriptive frameworks encourage clear delineation of the decision problem, which in the benefit-risk context means setting out the treatment under investigation, the indication and target population of interest, and any specific efficacy or safety concerns that have prompted the assessment. Clinical expertise can then guide the choice of appropriate comparators, i.e. existing alternative treatments that act as benchmarks for the benefit-risk balance.

The favourable and unfavourable effects in the assessment should include, at a minimum, key efficacy measures, any adverse events that may have prompted the assessment, and the key side effects of the treatment under investigation and of all the comparators. In practice, our case study teams found selecting a complete set of relevant effects to be a surprisingly difficult task. The assessor typically starts with an exhaustive list of clinical outcomes for a given treatment and indication, and must attempt to narrow this down to those benefits and risks that have a substantial impact on the benefit-risk balance, aiming to represent the range of treatment effects as fully as possible while avoiding problems such as double-counting of endpoints. The effects are often displayed in a tree diagram or value tree such as that shown in Figure 2, which is a simplified version of the final tree from the efalizumab case study. Such tree diagrams can be used with any methodology that handles multiple outcomes in order to aid understanding of the structure of the problem, and are typically drawn up in the early stages of the PrOACT-URL or BRAT frameworks and/or used to guide the weighting process in quantitative methods such as MCDA. To avoid bias, decision-makers should establish a common understanding and state the assumptions underlying the selection of benefits and risks. This allows for a transparent and auditable selection process. Ideally, both clinical expertise and patients’ views inform selection of the most relevant benefits and risks, and sufficient time should be allowed to resolve any disagreements through group discussion.

Our case studies were retrospective in nature and used publicly available data, principally from published trial reports and public registration documents (such as European public assessment reports and periodic safety update reports in the European Union, or periodic adverse drug experience reports in the United States), which are a convenient summary of the data from pivotal studies allowing replication and further exploration by others. However, these documents have clear limitations for benefit-risk assessment. They are low on detail, and reporting standards and outcome definitions frequently vary. In some cases, to facilitate testing of the more complex methods, the teams made strong modelling assumptions on an ad hoc basis to align the data (for example, to convert between related outcome measures where the same measure was not reported for all comparators). We recognise that this may have introduced bias in some instances and that real-world assessors would need to proceed more carefully with any data manipulations, or to use more qualitative methods and avoid the problem altogether. Nevertheless, we feel our approach was justified for the purpose of this project, which was to test methodologies rather than comment on the benefit-risk balance of medicines.

Metrics are measures used to numerically express the absolute or relative value of treatment effects. This includes everyday outcome measures such as incidence rates, which were not specifically reviewed by PROTECT-BR owing to their familiarity and ubiquity in medical reporting, but were nevertheless indispensable in the case studies. The
group of metrics known as Impact Numbers go further in describing the numbers of people affected by (binary) events in a population, but were not found to be particularly useful for making benefit-risk decisions. The NNT/NNH and BRR metrics were developed to compare multiple effects for benefit-risk assessment, but in their standard form they suffer from being able to compare only one favourable and one unfavourable effect, and from not explicitly acknowledging any difference in importance between the effects (even, arguably, implying they are of equal importance). To address these shortcomings, extensions to NNT/NNH have been developed, effectively resulting in the wNCB quantitative framework which is discussed below.

Estimation techniques are designed to facilitate the extraction and/or synthesis of appropriate values for the chosen metrics. Again, widely known epidemiological/biostatistical methods such as 2x2 tables or meta-analyses can be seen to fall within this class but have not been evaluated by PROTECT BR owing to their familiarity. The two specific estimation techniques evaluated were ITC/MTC and PSM, and both were found particularly useful in the case studies as they lend themselves naturally to benefit-risk assessments. ITC/MTC is designed to bring together evidence on several treatments where each source study does not compare all treatments simultaneously, a situation that arose in both the natalizumab and rimonabant case studies. PSM is used to propagate uncertainty through complex multi-variable models, and as such was the only tool capable of quantifying the uncertainty of the overall benefit-risk balance in many of the case studies.

Quantitative frameworks integrate objective treatment effects data with subjective preference data, i.e. utilities and/or weights that give information regarding the relative importance of the treatment effects. MCDA was the most commonly used quantitative framework in the case studies, owing partly to its comprehensiveness, flexibility (unlike some other methods it is not restricted in the types of outcome metrics it can handle) and its natural link with the PrOACT-URL descriptive framework. SMAA was also used widely in the case studies; this method is an extension of MCDA that explores all possible weightings in the event that utility/preference information is missing or limited, essentially applying PSM to the weights in an MCDA model. This is certainly a useful tool, but we would not recommend it as the default approach; it would be a shame if most benefit-risk assessments employed quantitative decision models and yet made no attempt to understand the underlying trade-offs. Also evaluated were wNCB, a weighted extension of the NNT/NNH metric and which is similar to MCDA but limited to binary outcomes, and SBRAM, which is again similar to MCDA but uses a simplified scoring system that does not always discriminate well between different options.

Utility survey techniques are used to obtain utility/preference information for use in a quantitative framework. MCDA is usually implemented via a simple pairwise weighting process whereby stakeholders directly quantify the importance of outcomes (“swing weighting”), but the rimonabant case study also combined MCDA with DCE, a utility survey technique that presents participants with a set of binary choice scenarios in which the outcomes take different values. For simple problems, a well-designed DCE with a sufficiently large number of responses can arguably provide the most comprehensive preference information, but DCEs require significant resources to design, and it has been argued that they do not work well when more than seven outcomes are to be considered simultaneously (a limit that was exceeded in most of our case studies). Swing weighting is more easily adaptable to different problems and was therefore favoured in the case studies.

The reports available at http://www.imi-protect.eu/benefitsRep provide detailed accounts of the application of the methods to the case study problems. This paper includes several examples from the efalizumab case study which asked, hypothetically, whether the overall benefit-risk balance of the drug as a treatment for chronic plaque psoriasis was favourable based on publicly available data at the time of regulatory review. However, this work was intended to test methodologies and representations for the evaluation of benefit and risk of medicines. It neither replaces nor is intended to replace or comment on any regulatory decisions made by national regulatory agencies, nor the European Medicines Agency.
Appraisal of visual representations
Among the variety of visual representations applied throughout the case studies, two visual types stood out as playing a fundamental role in every assessment. These are the value tree (or tree diagram) (Figure 2) and effects table (or data table) (Table 3) (examples taken from the efalizumab case study). The value tree is a simple visual hierarchy that displays the favourable and unfavourable effects (with clear definitions provided) and organises them into smaller groups to aid understanding (by adopting a logical structure based on, say, body systems) and/or facilitate elicitation of preferences (by grouping together outcomes according to seriousness, duration or any other factor that aids comparison).

The effects table also lists the favourable and unfavourable effects, not necessarily grouped this time but with the numerical values of the outcome metrics for each comparator and other key data clearly displayed in each row. The data shown in the effects table is purely descriptive, i.e. it does not incorporate any in-depth analysis or preference information. The effects table is an important milestone in a benefit-risk balance because it summarises all the objective data and prompts the assessor to consider what more is required. The data may clearly show that one treatment has a superior benefit-risk balance than all its comparators. If, alternatively, the data in the effects table shows no clear advantage for any one treatment then quantitative modelling of the benefit-risk balance (i.e. assigning preferences to the treatment effects) may be considered, either on a fully quantitative basis (with explicit utilities) or a partially quantitative one (a complete or partial ranking of the treatment effects that eliminates any doubt as to the overall balance). Figure 3 is a flowchart showing the possible ways in which a benefit-risk assessment may proceed at this point.

Besides the value tree and effects table, a variety of other visual types were used in the case studies. Figures 4 and 5 are a difference display and a line graph from the efalizumab case study, showing, respectively, the results of a quantitative analysis using MCDA and a sensitivity analysis on a key preference parameter.

PROTECT BR’s visual review workstream investigated visuals in greater depth, identifying 14 visual types. The team made recommendations on how to create these visuals by considering four audience-visual compatibility criteria, and how to determine appropriate visuals for benefit-risk information through a series of key benefit-risk questions. Further recommendations on visuals, including their style and design, were published in a full report and in another article. More details, including interactive visual displays created within PROTECT BR’s case studies, are available at http://protectbenefitrisk.eu/visualisations.html.

Recommendations and Conclusions
The critical path through a benefit-risk assessment shown in Figure 1 can be organised according to five broad stages common to all benefit-risk assessments: Planning, Evidence Gathering and Data Preparation, Analysis, Exploration and Conclusion and Dissemination, as shown in Figure 6 with key recommendations for each stage.
Regulators, such as the European Medicines Agency, and pharmaceutical companies have begun implementing structured approaches to benefit-risk assessments, but each organisation has adopted its own set of frameworks and tools, leading some commenters to propose a harmonisation initiative.\(^1,47,48\) It is clear that many of the frameworks and methods have common elements; identifying these and finding a shared, transparent language to describe them is arguably more realistic than finding a one-size-fits-all approach to benefit-risk assessment. PROTECT BR has stopped short of recommending outright any particular framework or methodology, emphasising instead the importance of a structured approach with careful planning and execution. The resulting recommendations provide guidance on the tools available for benefit-risk assessment as the discipline evolves and a more harmonised approach begins to emerge. We suggest that techniques reviewed by this project lend themselves to the inclusion of stakeholders who bring many perspectives and whose input can be included systematically, in qualitative and quantitative ways, to enhance the overall benefit-risk assessment. We strongly encourage the use of structured approaches to provide added clarity around the assessment of favourable and unfavourable effects of medicines.

**Unanswered questions and ongoing research**

The scope of this project was limited in that all case studies refer to pharmaceutical prescription medicines. Vaccines and over-the-counter medicines were not evaluated and may require different techniques. The usefulness of methodologies recommended by PROTECT BR for the benefit-risk evaluation of vaccines is being evaluated within IMI ADVANCE.\(^49\)

One theme whose importance has become apparent during the project is patient and public involvement (PPI) in benefit-risk assessment: It is possible that the benefit-risk balance of a treatment may vary depending on whose perspective is adopted, and there is a strong case for representing all stakeholders in the assessment process. There is work to be done to establish the extent to which PPI in benefit-risk assessment is desirable/feasible and to test specific methods for its application.
References

   [http://www.cioms.ch/publications/g4-benefit-risk.pdf]: CIOMS.


3. Benefit-risk methodology project; Update on work package 5: Effects Table pilot (Phase I). (EMA/74168/2014); 2014. Available from: 


5. Annex 1 – Grant Agreement N° 115004. PROTECT - Description of work; 2013 [cited 2014 8/27]. Available from: 
   [https://eroombayer.de/eRoom/PH-GDC-Pl-SID/IMI-PROTECT/0_10a702].


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<th>Frameworks</th>
<th>Description</th>
<th>Features</th>
<th>Rationale for use</th>
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<tr>
<td>PrOACT-URL\textsuperscript{7,8}</td>
<td>Problem, Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risk, and Linked decisions</td>
<td>A structured, qualitative approach, based on decision theory, of issues to consider in assessing the benefit-risk balance of a drug and its comparator(s).</td>
<td>All models used either PrOACT-URL or BRAT, or both, to guide the modelling process. They are similar in contributing transparency and structure to the benefit-risk balance. For the Warfarin team, BRAT helped to identify relevant clinical effects and to visualise magnitudes. The Rimonabant team found PrOACT-URL to be more comprehensive, and for the Rosiglitazone team, it encouraged a focus on value trade-offs.</td>
</tr>
<tr>
<td>BRAT\textsuperscript{9,10}</td>
<td>Benefit Risk Action Team</td>
<td>A structured, qualitative approach to assessing benefit-risk, based on MCDA, similar to PrOACT-URL, and supported by a set of guidelines and a tool.</td>
<td></td>
</tr>
<tr>
<td>MCDA\textsuperscript{11-13}</td>
<td>Multi Criteria Decision Analysis</td>
<td>A quantitative methodology for integrating multiple benefit and risk criteria for a drug and its comparator(s), to provide for each option an index of the benefit-risk balance.</td>
<td>All teams chose MCDA in both waves (SMAA for warfarin) because of its comprehensiveness, accommodation of any effect metrics and value judgements, and support for trade-off weighting, all requirements for a fully quantitative model.</td>
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<tr>
<td>SMAA\textsuperscript{14-16}</td>
<td>Stochastic Multi-criteria Acceptability Analysis</td>
<td>An extension of MCDA that formally incorporates uncertainty by replacing point estimates of a drug’s effects with probability distributions.</td>
<td>The Telithromycin, Rimonabant (wave 2) and Warfarin teams chose SMAA so they could explicitly model uncertainty and explore the effects of different weighting systems.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metrics</th>
<th>Description</th>
<th>Features</th>
<th>Rationale for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNT/NNH\textsuperscript{17,18}</td>
<td>Number Needed to Treat/Number Needed To Harm</td>
<td>The reciprocal of the difference in proportions of patients experiencing a given effect between the treatment and control group.</td>
<td>Only rimonabant (wave 1) explored NNT/NNH and Impact Numbers because they are simple ways to communicate a single effect. They are not recommended as general tools for benefit-risk assessment because they do not consider the clinical relevance of the effects nor are trade-offs between effects considered.</td>
</tr>
<tr>
<td>IN\textsuperscript{19-22}</td>
<td>Impact Numbers</td>
<td>An extension of NNT that takes account of the population being represented and other aspects of context.</td>
<td></td>
</tr>
<tr>
<td>Description</td>
<td>Features</td>
<td>Rationale for use</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Benefit Risk Ratio</td>
<td>The ratio of the magnitude of the most beneficial favourable effect to the magnitude of the most unfavourable effect.</td>
<td>Efalizumab, Telithromycin and Rimonabant (wave 1) chose BRR for its simplicity and ability to trade-off the two effects.</td>
<td></td>
</tr>
<tr>
<td>Quality Adjusted Life Years</td>
<td>A health-outcome index describing a patient’s level of health on several generic criteria and how an intervention might improve the states of health over time.</td>
<td>None of the teams applied QALYs or the Q-TWIST approach because their focus on specific health outcomes does not take into account the many favourable and unfavourable effects that make up the benefit-risk balance for the drugs modelled in PROTECT.</td>
<td></td>
</tr>
<tr>
<td>Quality-adjusted Time Without Symptoms and Toxicity</td>
<td>A combination of QALYs from three states of a patient undergoing cancer therapy.</td>
<td>As INHB is defined at present only for cancer treatments, it was not applicable to any of the drugs considered in PROTECT.</td>
<td></td>
</tr>
<tr>
<td>Incremental Net Health Benefit</td>
<td>An extension of QALYs that looks at the difference between benefits of two treatment options minus the difference between risks.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Estimation techniques**

| Probabilistic Simulation Method          | Uncertainty about each of the effects is represented by a probability distribution; Monte Carlo analysis shows the benefit-risk balance distribution for each drug and for the drug-comparator difference. | All wave 2 case studies chose this technique to see its impact on the benefit-risk balance, to explore scenarios about the effects that could not be seen in the deterministic models and to accommodate uncertainties of lower-quality data. |

**Indirect Treatment Comparison/Mixed Treatment Comparison**

| Compares two treatment effects where direct evidence is unavailable. Uses the link of each treatment to the placebo for calculating the variance of the difference in effects. | Natalizumab and Rimonabant chose ITC/MTC in wave 2 either to deal with the heterogeneity of the data sources or to enable comparison with other active treatments. |

**Utility survey technique**

| Discrete Choice Experiment | Effect weights are derived from a person’s preferences between pairs of combinations of health levels across favourable and unfavourable effects. Requires thinking about trade-offs between the effects. | Only Rimonabant used DCE, and this was to elicit preferences from patients. |

Table 1. The 13 methodologies, their features and an explanation of how they were used in the case studies.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efalizumab</td>
<td>Moderate to severe plaque psoriasis</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>Mild to moderate community-acquired pneumonia (CAP), acute exacerbation of</td>
</tr>
<tr>
<td></td>
<td>chronic bronchitis (AECB), and acute sinusitis (ABS) in patients of 18 years</td>
</tr>
<tr>
<td></td>
<td>and older, as well as tonsillitis/pharyngitis caused by Streptococcus pyogenes</td>
</tr>
<tr>
<td></td>
<td>in adults and adolescents, as an alternative when beta-lactam antibiotics are</td>
</tr>
<tr>
<td></td>
<td>not appropriate</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Relapsing remitting multiple sclerosis</td>
</tr>
<tr>
<td>Rimonabant</td>
<td>Weight loss in obese or overweight patients with co-morbidities</td>
</tr>
<tr>
<td>Rosiglitazone + metformin</td>
<td>Type II diabetes</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Ischemic stroke in patients with atrial fibrillation</td>
</tr>
</tbody>
</table>

Table 2. Drugs forming the basis of the PROTECT Benefit-Risk case studies
Figure 1. The structure and critical path for applying the methods in the case studies. (a) generic template, (b) efalizumab case study.
Figure 2. A tree diagram for the efalizumab example. The same tree was used in the descriptive PrOACT-URL and BRAT frameworks, and with the quantitative MCDA methodology. See Table 3 for an explanation of the abbreviations used.

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Units</th>
<th>Raptiva</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI75</td>
<td>Percentage of patients achieving 75% reduction in baseline PASI(^1) at week 12.</td>
<td>%</td>
<td>29.5</td>
<td>2.7</td>
</tr>
<tr>
<td>PGA</td>
<td>Percentage of patients achieving Physician’s Global Assessment(^2) clear/almost clear at week 12.</td>
<td>%</td>
<td>29.5</td>
<td>5.1</td>
</tr>
<tr>
<td>DLQI</td>
<td>Dermatology Life Quality Index(^3). Mean change from base score.</td>
<td>Change score</td>
<td>5.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Severe infections</td>
<td>Proportion of patients experiencing infections serious enough to require hospitalisation.</td>
<td>%/100 ptyrs</td>
<td>2.83</td>
<td>1.4</td>
</tr>
<tr>
<td>PML</td>
<td>Number of cases of progressive multifocal leukoencephalopathy.</td>
<td>number</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^1\)PASI is a measure of the average redness, thickness and scaliness of the lesions (each graded on a 0-4 scale), weighted by the body region and the area affected. PASI range is from 0 to 72.

\(^2\)PGA is a seven point scale with 7 being clear, 6 almost clear, 5 mild, 4 mild to moderate, 3 moderate, 2 moderately severe and 1 severe psoriasis.

\(^3\)DLQI is a 10-item quality of life index scored by the patient on a four-point scale (0-3).

Table 3. Effects table for the efalizumab example.
For Review Only

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Recommended visualisations:
- Effects table
- Forest plot

Start

Collect data

Classify evidence

Identify favourable and unfavourable effects

Present data on key effects for each alternative

Recommended methods:
- POACT-URL
- BRAT
- ITC/MTC (for indirect evidence)

Aggregate effects data and value judgements explicitly

Is one alternative clearly most preferred?

NO

Semi-quantitative BR assessment

Recommended method:
- MCDA

YES

Judge relative value of benefits and risks

Is one alternative clearly best?

NO

Quantitative BR assessment

YES

Qualitative BR assessment

Recommended method:
- MCDA

Figure 3. Flowchart indicating the difference between quantitative and qualitative benefit-risk assessments, with recommended methods

Table 1. Favourable and unfavourable effects for efalizumab

<table>
<thead>
<tr>
<th>Effect Type</th>
<th>Effect</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favourable Effects</td>
<td>PGA</td>
<td>14.6</td>
</tr>
<tr>
<td>Favourable Effects</td>
<td>PASI75</td>
<td>13.4</td>
</tr>
<tr>
<td>Favourable Effects</td>
<td>DLQI</td>
<td>8.9</td>
</tr>
<tr>
<td>Unfavourable Effects</td>
<td>Serious Infections</td>
<td>-1.8</td>
</tr>
<tr>
<td>Unfavourable Effects</td>
<td>PML</td>
<td>-17.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17.5</td>
</tr>
</tbody>
</table>

Figure 4. Results of a quantitative analysis (using MCDA) for the efalizumab example. The difference display shows the contribution of the weighted difference between drug and placebo for each effect. Right-extending (green) bars favour the drug and left-extending (red) bars favour the placebo, for a 17.5 total difference (out of 100) in favour of efalizumab.
Figure 5. Sensitivity analysis for the efalizumab case study, showing the effect of changing the weight on the PML criterion in MCDA. The vertical red line represents the current weight of 18.5 (out of a total of 100 for all five criteria). The intersections of that line with the slanting red and green lines define the 17.5 difference noted in Figure 4. If the PML weight is increased beyond 32, then the benefit-risk balance favours the placebo.
1- Planning: We recommend using a descriptive framework such as BRAT or PrOACT-URL to structure each benefit-risk assessment. A set of benefits and risks should be chosen that covers the full range of treatment effects, and represented visually using a tree diagram to indicate the hierarchy. A table template (‘effects table’ or ‘source table’) should be prepared, to represent the data that are required to be collected.

2- Evidence Gathering and Data Preparation: Assessors should review all available evidence and select data that are sufficient to and appropriate for the decision problem. The table template must be completed highlighting where data are available or missing for example by colour-coding missing data. The tree diagram and table produced initially may need to be revised in the light of available data.

3- Analysis: The analysis should be appropriate to the complexity of the task. Simple descriptive methods may suffice for everyday benefit-risk assessments, while quantitative decision models can provide additional clarity for more complex problems. When a quantitative benefit-risk assessment approach is used, stakeholders’ value preferences and the benefit-risk magnitudes (by criteria and overall) should be represented by suitable bar graphs (particularly useful is the ‘difference display’), dot plots or line graphs to promote accurate point reading, local and global comparisons, and judging trade-offs among alternatives. Care should be taken to avoid double counting events or effects in any analysis.

4- Exploration: All benefit-risk assessments should include a sensitivity analysis of some kind. Where benefits and risks are finely balanced, quantitative decision models facilitate the execution and communication of sensitivity analyses by clearly setting out the respective impacts of effects uncertainty and preference uncertainty on the results. The visual representations which should be used at this stage are distribution plots, line graphs, forest plots or tornado plots to provide comprehensive overview of the benefit-risk analysis allowing better-informed decisions.

5- Conclusion and dissemination: Adopting a formal structure for a benefit-risk assessment is an effective way to improve the overall transparency and communicability of the process and facilitate robust decision making.
Appendix 1: Descriptions and key references to methodologies and visual types referred to in manuscript

METHODOLOGIES

Descriptive Frameworks

PrOACT-URL\textsuperscript{1,2} is a generic decision-making guide with eight steps: Problems, Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risk attitudes, and Linked decisions.

BRAT (Benefit-Risk Action Team)\textsuperscript{3,4} standardises and supports the decision and communication of a BR assessment between pharmaceutical companies and the regulators through a 6-step process: define decision context, identify outcomes, identify data sources, customise framework, assess outcome importance, and display and interpret key BR metrics.

Quantitative Frameworks

NCB (Net Clinical Benefit)\textsuperscript{5} is a quantitative framework that compares the overall change in the benefits and risks of a drug over a comparator. The framework is divided into three steps; (1) define the decision problem and data sources; (2) establish the functional form of the NCB equation; and (3) estimate the NCB, which is the sum of the change in expected benefits minus the change in expected risks as a result of treatment. Once the functional form of the NCB has been established the benefits and risks must be placed on a common scale, such as health-state related utilities. The expected benefit is calculated by multiplying the benefit, assuming it is realised by the patient, by the probability of its being realised, with a similar calculation for expected risks.

MCDA (Multi-Criteria Decision Analysis)\textsuperscript{6-8} is a process derived from decision theory that quantifies the overall performance of two or more alternatives. Recognising that many decisions are characterised by multiple, often conflicting, objectives, the decision theory had been extended so that the consequences of decisions could be described by their relevant criteria (Keeney-Raiffa approach)\textsuperscript{8}. MCDA and other multi-criteria decision making approaches are realisations of the multi-attribute utility theory (MAUT) which is an extension of unidimensional utility theory that allows multiple criteria to be combined in a logical way. As applied to the benefit-risk balance of a drug and its comparators, performance of the alternatives on the favourable and unfavourable effects are judged for their clinical relevance and all effects are weighted to create a common unit of preference value, or utility. Summing those common units of benefit and risk provides an overall benefit-risk preference value or utility for each alternative, enabling calculation of the difference of the drug against the comparators. It is worth pointing out that MCDA is often used to refer to a collection of other multi-criteria approaches. Many of those are not as comprehensive as the Keeney-Raiffa approach, so have not been evaluated by the group.
SMAA (Stochastic Multi-Criteria Acceptability Analysis)\(^{9-11}\) is a multi-criteria decision method dealing with statistical uncertainty. It combines the distributions of scores \(\xi\) and weights \(w\) for each option across all criteria in \(b = \int f(\xi) \int f(w) \, dw \, d\xi\) which then calculates the probabilities of an option being at certain rank.

SBRAM (Sarac’s Benefit Risk Assessment Method)\(^{12}\) is a multi-criteria method that involves eight successive steps: (1) establishing the decision context; (2) identifying the benefit-risk criteria; (3) weighting the criteria; (4) scoring the criteria; (5) evaluating uncertainty; (6) calculating weighted scores; (7) discussing results; and (8) formulating an overall conclusion. To allow comparison across different benefit-risk categories, criteria are weighted on a scale of 1 (low), 2 (medium), and 3 (high) according to their importance. In order to reduce the impact of subjective judgments, scores are assigned to each criterion on the basis of the data wherever possible. Scoring charts are used to visualize the data under the SBRAM’s scoring technique. Weights and scores are multiplied, and the results are visualized in a tornado-like diagram. Uncertainties are dealt with qualitatively from the scoring charts or quantitatively using bootstrapping.

**Metric indices**

NNT (Number Needed to Treat)\(^{13,14}\) is derived from the probabilities of a favourable effect for the treatment and comparator groups. The difference between the two probabilities, \(p_t\) and \(p_c\), gives the increase in certainty, \(p_t - p_c\). NNT is then calculated as the reciprocal of this difference, \(1/(p_t - p_c)\), and can be interpreted as the number of patients that need to be treated (on average) for one event to be observed as a result of treatment. A parallel but opposite metric, number needed to harm (NNH), is defined similarly but based on the probabilities of unfavourable effects. AE-NNT (Adverse Event Adjusted-NNT)\(^{15}\) penalises NNT for the occurrence of AEs in the same patient. RV-NNH (Relative Value adjusted NNH)\(^{16}\) incorporates stakeholders’ value preferences on the importance of AEs into NNH.

Impact numbers\(^{17-19}\) are a group of metrics that generalise the NNT concept to the population level instead of focusing on only those patients who receive treatment. By considering the baseline event probabilities in the population of interest, estimates of the number of individuals that will be affected by a disease and/or an intervention can be derived. These metrics therefore describe the ‘impact’ of treatments from the public health perspective.

BRR (Benefit Risk Ratio)\(^{20-22}\) is a simple trade-off metric which divides benefits by risks, therefore assumes equal importance of benefits and risks.

QALY (Quality Adjusted Life Years)\(^{23-24}\) is the most used health index, where the time spent in a particular health state is multiplied by the QoL score in that state. The total QALY is simply the sum of all QALYs in all health states. The summary of all individual QALYs in a population is known as the HALE (Health Adjusted Life Expectancy).
Q-TWiST (Quality-adjusted Time Without Symptoms and Toxicity)\textsuperscript{25-26} is in principle a QALY metric, with explicit definitions of the discrete health states in cancer therapy: toxicity, time without symptoms and toxicity, and relapse.

INHB (Incremental Net Health Benefit)\textsuperscript{27-29} calculates the difference in the “incremental” change of benefits to that of risks. INHB uses QALY specifically to characterise benefits and risks, but other metrics can be used, and generalises as INB (Incremental Net Benefit)\textsuperscript{30}.

\textit{Estimation techniques}

PSM (Probabilistic Simulation Method)\textsuperscript{31,32} is a statistical technique for exploring the impact of uncertainty in data on a model’s results. In applying PSM to benefit-risk assessment, statistical summaries of data in a quantitative model are replaced with probability distributions related to the patient-level data. The overall benefit-risk balance is then calculated a large number of times with different input data drawn from the probability distributions in proportion to their likelihood of being chosen. This generates a probability distribution over the difference between benefits and risks for the drug, and another distribution for the comparator. The same process can then be applied to determine the probability that the benefit-risk balance of the drug is more than that of the comparator. PSM provides a good means to quantify and explore the uncertainty of the benefit-risk balance. PSM can accommodate any type of metric as well as the correlations between favourable and unfavourable effects, if it is known.

ITC (Indirect Treatment Comparison) and MTC (Mixed Treatment Comparison)\textsuperscript{33-35} are meta-analytic methods to synthesise different pieces of evidence into a coherent set of estimates of treatment effects. In the absence of direct comparative evidence between two treatments, ITC can infer their relationship through a common comparator - for example, both treatments may have been directly compared against a placebo. Indirect comparisons are subject to greater statistical uncertainty than direct comparisons, and this effect on uncertainty is captured by ITC. MTC generalises the concept by providing a method to integrate both direct and indirect evidence.

\textit{Utility Survey Techniques}

CA (Conjoint Analysis)\textsuperscript{36,37} breaks down hypothetical scenarios into a set of characteristics and attributes to ease the utility elicitation process, and then mathematically combined them to produce the overall expected utility.

DCE (Discrete Choice Experiment)\textsuperscript{38-40} uses exactly the same principles as CA with a more structured guideline to generating the hypothetical scenarios to be used in the elicitation process.

\textbf{VISUAL TYPES}

<table>
<thead>
<tr>
<th>Visual type</th>
<th>Example</th>
</tr>
</thead>
</table>

http://mc.manuscriptcentral.com/pds
Visual type | Example
---|---
**Bar graph**
**Definition:** Information is presented by rectangular bars for a number of categories. The position (height of bars) along a common scale is judged supported by the length of the bars.
**Applicable Methodologies:** MCDA (also stacked and colour-coded, and the ‘difference display’ where the length of the bars corresponds to the difference in outcomes between alternatives), SMAA

![Bar graph example](image)

**Dot/Forest plot**
**Definition:** Information is presented as a number of symbols, usually representing the mean effect size along common aligned scale. Each symbol sits on a vertical or horizontal line which usually represents the 95% confidence intervals of the mean effect.
**Applicable Methodologies:** BRAT (with summary table), NNT (inc. reversed axis), Impact numbers

![Dot/Forest plot example](image)

**Line graph**
**Definition:** Information is presented by the position of lines along common aligned scales.
**Applicable Methodologies:** MCDA, BRR, QALY

![Line graph example](image)

**Tornado diagram**
**Definition:** Information is presented as length and position of the rectangular bars on non-aligned scales.
**Applicable Methodologies:** SBRAM (also colour-coded)

![Tornado diagram example](image)

**Tree diagram**
**Definition:** Information is presented at the end of “branches” and on the point where they cross.
**Applicable Methodologies:** MCDA, BRAT, PrOACT-URL

![Tree diagram example](image)

The visuals on this table are meant to give a general idea of how each visual representation type may look like and the details are not intended to be legible.
## Appendix 2: Reasons for inclusion/exclusion of methods in the Wave 1 case studies

<table>
<thead>
<tr>
<th>Method</th>
<th>Efalizumab</th>
<th>Telithromycin</th>
<th>Natalizumab</th>
<th>Rimonabant</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrOACT-URL (Problem,</td>
<td>Used. PrOACT-URL is a qualitative framework which is a convenient initial preparatory stage to application of an MCDA analysis.</td>
<td>Used. The qualitative framework PrOACT-URL forms a base for most of the comprehensive frameworks, and will be used to prepare the case.</td>
<td>Used. MCDA (see below) fits well with this framework.</td>
<td>Used. Two competing but very similar frameworks (PrOACT-URL and BRAT) are tested in this case study to assess the usefulness and ease of use of each.</td>
</tr>
<tr>
<td>Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risk, and Linked decisions framework)</td>
<td>BRAT (Benefit Risk Action Team framework)</td>
<td>Used. BRAT is a framework supported by a set of guidelines and a tool that allows data to be structured for decision making. It allows for a comparison with the PrOACT-URL framework.</td>
<td>Used in order to allow comparison with PrOACT-URL.</td>
<td>Used. Two competing but very similar frameworks (PrOACT-URL and BRAT) are tested in this case study to assess the usefulness and ease of use of each.</td>
</tr>
<tr>
<td>BRAT (Benefit Risk Action Team framework)</td>
<td>Used. MCDA as this is an intricate method capable of integrating multiple benefit-risk criteria. It is one of the more complex methods. MCDA naturally leads to a quantitative benefit-risk balance.</td>
<td>Used. MCDA shares many features with PrOACT-URL, in its stepwise structure to frame the problem. Furthermore MCDA provides decision analytic modelling approach to quantitatively model the benefit</td>
<td>Used. MCDA as this is an intricate method capable of integrating multiple benefit-risk criteria. It is one of the more complex methods.</td>
<td>Used. MCDA is tested within its own framework since it provides a comprehensive approach to assessing benefit-risk balance.</td>
</tr>
<tr>
<td>Method</td>
<td>Used/Not Used</td>
<td>Reason</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>---------------</td>
<td>------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMAA (Stochastic Multi-criteria Acceptability Analysis)</td>
<td>Not used. The first wave of case studies was intended to test relatively simple methods; more complex extensions such as probabilistic simulation are best saved for later case studies.</td>
<td>Used. SMAA is a natural extension for MCDA, which takes into account the uncertainty in data and in criteria weighting.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCB (Net Clinical Benefit)</td>
<td>Not used. This method was not one of those initially recommended for further investigation.</td>
<td>Not used. This is arguably the most complex method so better considered in the second wave of case studies.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBRAM (Sarac's Benefit-Risk Assessment Method)</td>
<td>Not used. This method was not one of those initially recommended for further investigation.</td>
<td>Used. Several features of SBRAM are similar to PrOACT-URL, MCDA and the other framework approaches in its stepwise approach to structure the decision process. At the same time SBRAM has a unique way of evaluating data on each criterion.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNT/NNH (Number Needed to Treat/Number Needed To Harm)</td>
<td>Not used. Similar to BBR, NNT/NNH was initially designed for one benefit and one risk analysis with</td>
<td>Not used. This method was not one of those initially recommended for further investigation.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

http://mc.manuscriptcentral.com/pds
<table>
<thead>
<tr>
<th>Method</th>
<th>Used/Not Used</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impact numbers</td>
<td>Not used</td>
<td>It is not meaningful to apply a modified NEPP-approach (Number of Events Prevented in your Population) to very rare events with a close to zero baseline risk in the unexposed.</td>
</tr>
<tr>
<td>BRR (Benefit Risk Ratio)</td>
<td>Used</td>
<td>BRR is conceptually simple and general. The concept of taking the ratio of the magnitude of benefits to risks is tested with the BRAT framework, using the most prominent benefit and the most prominent risk.</td>
</tr>
<tr>
<td>QALY (Quality Adjusted Life Years)</td>
<td>Not used</td>
<td>A benefit-risk analysis can be performed by QALY, only if</td>
</tr>
<tr>
<td>Method</td>
<td>Used/Not Used</td>
<td>Reason</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>QALY data</td>
<td>Collected in the trials or studies or derivable from the available information.</td>
<td>Rimonabant that is not conducted in economic settings.</td>
</tr>
<tr>
<td>Q-TWiST (Quality-adjusted Time</td>
<td>Not used. A benefit-risk analysis can be performed by Q-TWiST, only if Q-TWiST data was</td>
<td>Not used. Q-TWiST is very specific to analysis within cancer domain. It is also not</td>
</tr>
<tr>
<td>Without Symptoms and Toxicity)</td>
<td>collected in the trials or studies or derivable from the available information.</td>
<td>straightforward to define disease states as required by Q-TWiST for obesity.</td>
</tr>
<tr>
<td>INHB (Incremental Net Health</td>
<td>Not used. INHB is based on the QALY metric (see above).</td>
<td>Not used. INHB by definition uses health indices like QALY in its derivation,</td>
</tr>
<tr>
<td>Benefit)</td>
<td></td>
<td>therefore excluded here from testing due to the missing components required.</td>
</tr>
<tr>
<td>PSM (Probabilistic Simulation</td>
<td>Not used. The first wave of case studies was intended to test relatively simple methods; more</td>
<td>Not used. The first wave of case studies was intended to test relatively simple methods;</td>
</tr>
<tr>
<td>Method)</td>
<td></td>
<td>complex extensions such as probabilistic simulation are best saved for later case studies.</td>
</tr>
<tr>
<td>ITC/MTC (Indirect/Mixed Treatment Comparison)</td>
<td>Not used. Direct evidence was available.</td>
<td>Used. Direct evidence comparing all alternative treatments was not available so synthesis using</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ITC/MTC was required. to be evaluated (rimonabant versus placebo), the complexity of having indirect evidence does not apply.

| DCE (Discrete Choice Experiment) | Not used due to limitations on resources; best tested in the second wave of case studies. | Not used due to limitations on resources; best tested in the second wave of case studies. | Not used due to limitations on resources; best tested in the second wave of case studies. | Not used due to limitations on resources; best tested in the second wave of case studies. |
Appendix 3: Aims of the Wave 2 case studies

Natalizumab: to investigate the use of PSM combined with MCDA and to test various visualisations.

Rimonabant: to extend this using ITC to enable comparisons with other active treatments, using DCE to elicit preferences from laypeople and using SMAA to explore the impact of uncertainty.

Rosiglitazone: The aim was to evaluate how a group workshop setting could facilitate a benefit-risk assessment incorporating value judgements elicited within the group.

Warfarin: to investigate benefit-risk assessment of an older medicine.

References to Appendices


30. Lynd LD, Marra CA, Najafzadeh M, Sadatsafavi M. A quantitative evaluation of the regulatory assessment of the benefits and risks of rofecoxib relative to naproxen:


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Alfons Lieftucht is an employee of GlaxoSmithKline UK Ltd. One of the drugs studied is from the company who is manufactured by GlaxoSmithKline.

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Marilyn Metcalf is an employee of GlaxoSmithKline. Data from GSK’s product, rosiglitazone, was used in one of the case studies described in this paper. The data analyzed by IMI were publicly available, and neither Dr. Metcalf nor any other GSK employee, worked on that case study or wrote any of the results.

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8. Manuscript title (first six words are sufficient)

Recommendations for Benefit-Risk Assessment Methodologies and Visual Representations

9. Author’s full name (a separate form must be submitted for each author)

Christine Erikstrup Hallgreen

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   - n/a

2. The sponsor of this project had the right of commenting but the authors retained the right to accept or reject comments or suggestions.
   - n/a

3. The sponsor of this project had the right of final editing and/or approval of the manuscript submitted.
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   - No

5. I, my spouse, or one of my dependent children has significant equity interest (>USD 10,000) in the company that owns the product being studied.
   - No

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I am an employee of Amgen, a participant in the Innovative Medicines Initiative, which is a public-private partnership. The manuscript describes testing benefit-risk methodologies and visualizations using case studies of marketed products.

No Amgen treatments were used in the work associated with this publication.

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Rebecca A Noel is an employee and shareholder of Eli Lilly and Company

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