PrOACT-URL and BRAT frameworks: Rimonabant case study example

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Disclaimers

- Juhaeri Juhaeri is an employee of Sanofi. The views and opinions represented in this presentation are solely those of the presenter and are not endorsed by nor necessarily representative of those of Sanofi.
Objectives

- To understand existing frameworks for a structured BR assessment within current regulatory landscape
- To describe quantitative BR methods to integrate benefits and risks

Using IMI-PROTECT case study as an example
Agenda

- Regulatory landscape
- IMI – PROTECT
- PrOACT-URL/BRAT frameworks
  - Understanding and developing the decision context
  - Understanding and developing an attribute tree
  - Data sources
- Quantitative Methods
  - MCDA and SMAA
- Creating visualizations and data displays
- Remarks
Regulatory landscape

- More systematic approaches to BR assessment are emerging within the regulatory environment
- This shift impacts not only regulators and industry
- Expected to drive research agendas across academia
- Several initiatives in Europe and the US
FDA Structured approach

- Starting in 2009, efforts to develop a more systematic approach
- Review of quantitative methods, 2 concerns:
  - Cannot capture the nuanced assessments
  - Obscuring subjective expert judgment
- Decision – structured qualitative approach
  - Use quantitative analysis to aid rather than replace judgment
  - Flexible to accommodate supporting quantitative analysis
- 5 year plan
  - 2012: road-testing in “live” reviews
  - 2013: further improvement
  - 2014-2017: Implementation

http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm
EMA Perspective

• Need consistency and transparency of the benefit–risk assessment for medicinal products
  - three-year project started in early 2009
• 2 level approach
  - Qualitative approach
  - Quantitative approach:
    - Multi-Criteria Decision Analysis (MCDA) method to derive a numerical value for the benefit–risk balance
    - recommended for more complex situations
• Implementation of MCDA in the assessment
  - practical challenges
  - to be addressed in the last work package of the project

Regulatory landscape

• Must operate within applicable legal, regulatory, and policy framework.

• Structural and **systematic approach** to Benefit Risk Assessment.

• Support of review **throughout the lifecycle** of a drug by capturing the full range of decision from premarket review to post marketing review.

• **Identify critical issues** related to a drug and should focus on discussion and **communication on weighing** of these issues.
Regulatory landscape

• Basic form of Benefit Risk Assessment
  
  Step 1. Define decision context
  Step 2. Identify important relevant information
  Step 3. Identify data
  Step 4. Weigh the information
  Step 5. Draw conclusion based on expert judgement
  Step 6. Communicate decision and its rationale

• How does PrOACT-URL/BRAT fit in these criteria using the PROTECT Rimonabant case study example
The Innovative Medicines Initiative (IMI)

- The largest public-private partnership in Europe to improve the drug development process by supporting a more efficient discovery and development of better and safer medicines for patients
- A joint project between the European Union and the pharmaceutical industry association EFPIA
What is PROTECT?

• Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

• One of the 40 projects under IMI

• Goals
  - to enhance early detection and assessment of adverse drug reactions from different data sources (clinical trials, spontaneous reporting and observational studies)
  - to enable the integration and presentation of data on benefits and risks
Partners

Public

**Regulators:**
- EMA (Co-ordinator)
- DKMA (DK)
- AEMPS (ES)
- MHRA (UK)

**Academic Institutions:**
- University of Munich
- FICF (Barcelona)
- INSERM (Paris)
- Mario Negri Institute (Milan)
- Poznan University of Medical Sciences
- University of Groningen
- University of Utrecht
- Imperial College London
- University of Newcastle

Private

**EFPIA companies:**
- GSK (Deputy Co-ordinator)
- Sanofi
- Roche
- Novartis
- Pfizer
- Amgen
- Genzyme
- Merck Serono
- Bayer
- Astra Zeneca
- Lundbeck
- NovoNordisk
- Takeda
- Eli Lilly

**Others:**
- WHO UMC
- GPRD
- IAPO
- CEIFE

**SMEs:**
- Outcome Europe
- PGRx (LA-SER)
Working Packages

- WP1: project management and administration
- WP2: framework for pharmacoepidemiological studies
- WP3: Signal detection
- WP4: Data collection from consumers
- WP5: Benefit-Risk Integration and Representation - to assess and test quantitative methodologies for the benefit-risk assessment of medicines
- WP6 – Validation studies involving an Extended Audience
- WP7: Training and communication
Classifications of approaches

Benefit-risk assessment framework

- Descriptive framework
  - Non-quantitative
  - PrOACT-URL
  - ASF
  - BRAT
  - FDA BRF
  - CMR-CASS
  - COBRA
  - SABRE
  - UMBRA

- Quantitative framework
  - BLRA
  - NCB
  - Decision tree
  - MDP
  - MCD
  - SMAA
  - SBRAM
  - CUI
  - DI

Metric indices for B-R assessment

- Threshold indices
  - NNT
  - NNH
  - AE-NNT
  - RV-NNH
  - Impact numbers
  - MCE
  - RV-MCE
  - MAR
  - NEAR

- Health indices
  - QALY
  - DALY
  - HALE
  - Q-TWiST

Approaches excluded and not appraised

Estimation techniques

- UT-NNT
- INHB
- BRR
- GBR
- Principle of 3
- TURBO
- Beckmann
- DAGs
- PSM
- CPM
- ITC
- MTC
- CDS

Utility survey techniques

- SPM
- CV
- CA
- DCE

Legend:
- Main categories
- Sub-categories
# Wave 1 Case studies: Methodologies

<table>
<thead>
<tr>
<th></th>
<th>Natalizumab</th>
<th>Rimonabant</th>
<th>Telithromycin</th>
<th>Efalizumab</th>
</tr>
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<tbody>
<tr>
<td>PrOACT-URL</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
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<td>SMAA</td>
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<td>✓</td>
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<td></td>
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<td>NNT &amp; NNH</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impact Number</td>
<td></td>
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<tr>
<td>INHB</td>
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<td>✓</td>
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<tr>
<td>MTC</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCE</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Other:</td>
<td>Decision conferencing</td>
<td>Direct utility elicitation</td>
<td>SBRAM, Swing-weighting</td>
<td>Decision conferencing</td>
</tr>
</tbody>
</table>
# PROTECT WP5: rimonabant case study

<table>
<thead>
<tr>
<th>Person</th>
<th>Expertise</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juhaeri Juhaeri</td>
<td>Epidemiology/Statistics</td>
<td>Sanofi</td>
</tr>
<tr>
<td>Shahrul Mt-Isa</td>
<td>Statistics/Modelling</td>
<td>Imperial College</td>
</tr>
<tr>
<td>Edmond Chan</td>
<td>Statistics/Medicine</td>
<td>Imperial College</td>
</tr>
<tr>
<td>Kimberley Hockley</td>
<td>Statistics/Modelling</td>
<td>Imperial College</td>
</tr>
<tr>
<td>John Pears</td>
<td>Medicine</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Ian Hirsch</td>
<td>Statistics/Modelling</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Johan Bring</td>
<td>Statistics/Modelling</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Georgy Genov</td>
<td>Medicine</td>
<td>EMA</td>
</tr>
<tr>
<td>Billy Amzal</td>
<td>Statistics/Modelling</td>
<td>LA-SER</td>
</tr>
<tr>
<td>Marilyn Metcalf</td>
<td>Decision Analysis</td>
<td>GSK</td>
</tr>
<tr>
<td>George Quartey</td>
<td>Statistics/Modelling</td>
<td>Genentech</td>
</tr>
<tr>
<td>Laurence Titeux</td>
<td>Statistics</td>
<td>Sanofi</td>
</tr>
</tbody>
</table>
Descriptive framework: PrOACT-URL

- An early and established generic framework to structure the decision problem
- Only recently used for medical decision-making
- Divide problem into 8 steps
  - PrOACT
  - URL

Key references:


1. Determine the nature of the problem and its context.
2. Frame the problem.
3. Establish objectives that indicate the overall purposes to be achieved.
4. Identify criteria for (a) favourable effects, and (b) unfavourable effects
5. Identify the options to be evaluated against the criteria.
6. Describe how the alternatives perform for each of the criteria, i.e., the magnitudes of all effects, and their desirability or severity, and the incidence of all effects.
7. Assess the balance between favourable and unfavourable effects. [Weighting]
8. Report the uncertainty associated with the favourable and unfavourable effects.
9. Consider how the balance between favourable and unfavourable effects is affected by uncertainty.

10. Judge the relative importance of the decision maker’s risk attitude for this product.
11. Report how this affected the balance reported in step 9.

12. Consider the consistency of this decision with similar past decisions, and assess whether taking this decision could impact future decisions.
Descriptive framework: BRAT

- To guide selecting, organizing, understanding and summarising the evidence relevant to benefit-risk decisions.
- Aimed at the communication of benefit-risk assessment between pharmaceutical companies and regulators.
- Emphasis on uncertainty via confidence intervals when presenting results.
- B-R criteria should not be integrated.

Key references:


Descriptive framework: BRAT

(1) Define decision context
(2) Identify outcomes
(3) Identify data sources
(4) Customise framework
(5) Assess outcome importance
(6) Display & interpret key B-R metrics

Decision & communication of B-R assessment
# Descriptive framework: BRAT

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>Define decision context</td>
</tr>
<tr>
<td>1.</td>
<td>Define drug, dose, formulation, indication, patient population, comparator(s), time horizon for outcomes, perspective of the decision makers (regulator, sponsor, patient, or physician)</td>
</tr>
<tr>
<td>(2)</td>
<td>Identify outcomes</td>
</tr>
<tr>
<td>2a.</td>
<td>Select all important outcomes and create the initial value tree.</td>
</tr>
<tr>
<td>2b.</td>
<td>Define a preliminary set of outcome measures/endpoints for each.</td>
</tr>
<tr>
<td>2c.</td>
<td>Document rationale for outcomes included/excluded</td>
</tr>
<tr>
<td>(3)</td>
<td>Identify data sources</td>
</tr>
<tr>
<td>3a.</td>
<td>Determine and document all data sources (e.g. clinical trials).</td>
</tr>
<tr>
<td>3b.</td>
<td>Extract all relevant data for the data source table, including detailed references and any annotations, to help the subsequent interpretations create summary measures</td>
</tr>
<tr>
<td>(4)</td>
<td>Customise framework</td>
</tr>
<tr>
<td>4a.</td>
<td>Modify the value tree on the basis of further review of the data and clinical expertise.</td>
</tr>
<tr>
<td>4b.</td>
<td>Refine the outcome measures/endpoints. May include tuning of outcomes not considered relevant to a particular benefit-risk assessment or that vary in relevance by stakeholder group</td>
</tr>
<tr>
<td>(5)</td>
<td>Assess outcome importance</td>
</tr>
<tr>
<td>5.</td>
<td>Apply or assess any ranking or weighting of outcome importance to decision makers or other stakeholders</td>
</tr>
<tr>
<td>(6)</td>
<td>Display &amp; interpret key B-R metrics</td>
</tr>
<tr>
<td>6a.</td>
<td>Summarise source data in tabular and graphical displays to aid review and interpretation.</td>
</tr>
<tr>
<td>6b.</td>
<td>Challenge summary metrics, review source data, and identify and fill any information gaps.</td>
</tr>
<tr>
<td>6c.</td>
<td>Interpret summary information.</td>
</tr>
</tbody>
</table>
## Use of descriptive framework

<table>
<thead>
<tr>
<th>PrOACT-URL</th>
<th>BRAT</th>
<th>Regulatory landscape</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problem</td>
<td>Define decision context</td>
<td>Define decision context</td>
</tr>
<tr>
<td>Objective</td>
<td>Identify benefit and risk outcomes</td>
<td>Identify important relevant information</td>
</tr>
<tr>
<td>Alternative</td>
<td>Define the decision context</td>
<td>Define decision context</td>
</tr>
<tr>
<td>Consequence</td>
<td>Extract source data</td>
<td>Identify data</td>
</tr>
<tr>
<td></td>
<td>Customise framework</td>
<td>Identify important relevant information</td>
</tr>
<tr>
<td>Trade-off</td>
<td>Assess outcome importance</td>
<td>Weigh the information</td>
</tr>
<tr>
<td>Uncertainty</td>
<td>Display &amp; interpret key BR metrics</td>
<td>Weigh the information</td>
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<tr>
<td>Risk tolerance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linked decisions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Rimonabant Case Study: Disclaimers

- “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.”
## Rimonabant

<table>
<thead>
<tr>
<th>Indication</th>
<th>Weight loss in obese and overweight patients with co-morbidities in adults (&gt;18y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory history</td>
<td>Approved June 2006, Voluntary withdrawal in January 2009</td>
</tr>
<tr>
<td>Severe side effect</td>
<td>Increased risk with depression</td>
</tr>
<tr>
<td>Data source</td>
<td>EPAR Published clinical trials</td>
</tr>
<tr>
<td>Methodologies tested</td>
<td>PrOACT-URL, BRAT, MCDA, SMAA, NNT&amp;NNH, Impact numbers, INHB, BRR, PSM + direct utility elicitation via survey</td>
</tr>
</tbody>
</table>
**PrOACT-URL**: Step 1 Problem

**BRAT**: Step 1 Define decision context

- Medicinal product (or device, procedure): rimonabant
- Indication(s) for use: weight loss
- Therapeutic area and disease epidemiology
  - 2/3 US population is overweight or obese
  - 50% European population is overweight, 30% obese
- Unmet medical need, severity of condition, affected population, patients’ and physicians’ concerns, time frame for health outcomes
  - A large number of deaths attributed to obesity
  - Various diseases associated with obesity
  - Cost
  - Diet and exercise had been shown to have a limited long term success, other therapeutic options is needed.
PROACT-URL: Step 2 Objective
BRAT: Step 2 Identify benefit and risk outcomes

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

- Based on a set of criteria
  - Benefit [Favorable effects]
  - Risk [Unfavorable effects]
<table>
<thead>
<tr>
<th>Benefit [15 criteria]</th>
<th>Risk [32 criteria]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight lost at 12 months:</strong></td>
<td><strong>Infection and infestation</strong></td>
</tr>
<tr>
<td>• Percentage of patient reached 10% weight lost</td>
<td>• Upper respiratory tract infection</td>
</tr>
<tr>
<td><strong>Lipid control at 12 months:</strong></td>
<td><strong>Psychiatric disorder</strong></td>
</tr>
<tr>
<td>• Total Cholesterol</td>
<td>• Anxiety</td>
</tr>
<tr>
<td>• HDL Cholesterol</td>
<td>• Insomnia</td>
</tr>
<tr>
<td>• LDL Cholesterol</td>
<td>• Mood alternation with depressive symptoms</td>
</tr>
<tr>
<td>• Ratio HDL Cholesterol/Total Cholesterol</td>
<td>• Depressive disorders</td>
</tr>
<tr>
<td>• Triglyceride</td>
<td>• Irritability</td>
</tr>
<tr>
<td><strong>Waist Circumference at 12 months</strong></td>
<td><strong>Nervous system disorders</strong></td>
</tr>
<tr>
<td><strong>Diabetes control at 12 months</strong></td>
<td><strong>Vascular disorders</strong></td>
</tr>
<tr>
<td>• Fasting glucose</td>
<td><strong>Gastrointestinal disorders</strong></td>
</tr>
<tr>
<td>• Fasting insulin</td>
<td><strong>Skin and Subcutaneous Tissue disorder</strong></td>
</tr>
<tr>
<td>• Insulin resistance</td>
<td><strong>Musculoskeletal and connective tissue disorder</strong></td>
</tr>
<tr>
<td>• HbA1c</td>
<td><strong>General disorder</strong></td>
</tr>
<tr>
<td><strong>Blood pressure control</strong></td>
<td><strong>Injury, Poisoning and Procedural complications</strong></td>
</tr>
<tr>
<td>• Glucose intolerance</td>
<td><strong>Severe Adverse Events</strong></td>
</tr>
<tr>
<td>• Systolic Blood Pressure</td>
<td><strong>Severe Adverse Events</strong></td>
</tr>
<tr>
<td>• Diastolic Blood Pressure</td>
<td><strong>Severe Adverse Events</strong></td>
</tr>
</tbody>
</table>
PROTECT

PrOACT-URL: Step 2 Objective
BRAT: Step 4 Customise framework

• Large number of criteria is clearly unmanageable
• Identify **KEY** benefit and risk
  – Therapy context
  – Primary and secondary endpoints from clinical trials
  – Effects in subpopulations
  – Implications
  – Severity and reversibility of adverse events
  – Potential bias
    ◆ Double counting eg Total and HDL Cholesterol
    ◆ Composite endpoints
### Outcome selection [Wave 2]

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% weight lost at 1 year</td>
<td>Psychiatric disorder</td>
</tr>
<tr>
<td>HDL cholesterol changes</td>
<td>Cardiovascular disorder</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal disorder</td>
</tr>
</tbody>
</table>
Outcome definition and attribute tree

Benefit-risk balance comparing Acomplia to Placebo, Meridia and Xenical

Benefit
- Achieved 10% weight loss
  - Proportion of patients who achieved at least 10% weight loss at 1 year
- Change in HDL Cholesterol
  - The absolute change in HDL cholesterol in mg/dL

Risk
- Cardiovascular deaths
  - Proportion of patients who died from cardiovascular events
- Psychiatric disorders
  - Proportion of patients who experienced depression
- Gastrointestinal disorders
  - Proportion of patients who experienced diarrhoea or constipation
## BRAT: Step 4 Customise framework

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

**BRAT**: Step 1 Define decision context

- drug vs. placebo and/or active comparator
- dosage
- timing of treatment

<table>
<thead>
<tr>
<th>Wave 1</th>
<th>Wave 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>Sibutramine</td>
</tr>
<tr>
<td></td>
<td>Orlistat</td>
</tr>
</tbody>
</table>
PrOACT-URL: Step 4 Consequence
BRAT: Step 3 Extract source data

- Consequences for each alternative on each criterion (e.g., efficacy and safety effects that are clinically relevant)
- Summarized in an ‘Effects Table’ with alternatives in tables
- Qualitative and quantitative descriptions of the effects in each cell:
  - statistical summaries with confidence intervals,
  - references to source data,
  - graphs and plots
Data source

- Developmental data
  - Pre clinical studies
  - Pivotal studies
- Post-marketing
  - Clinical trials
  - Safety studies
  - Spontaneous reports
  - Registry reports
- Attention on different data source, endpoints and uncertainties
## Consequences

<table>
<thead>
<tr>
<th>Criteria (benefit)</th>
<th>End point</th>
<th>Study</th>
<th>Treatment</th>
<th>N enrolled</th>
<th>N completed at exit</th>
<th>5% Responded Rate(%)</th>
<th>10% Responded Rate(%)</th>
<th>Absolute changes</th>
<th>Changes upper CI</th>
<th>Changes lower CI</th>
<th>Difference to placebo</th>
</tr>
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<td>0.10</td>
<td>0.19</td>
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<td>0.81</td>
<td>6.03</td>
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<td>5.91</td>
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<td>200</td>
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<td>6.03</td>
<td>2.90</td>
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<td>0.86</td>
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## Data source [Wave 2]

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<th>Sibutramine</th>
<th>Orlistat</th>
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<td>Pre marketing RCTs</td>
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<td>7</td>
<td>3 pre marketing RCTs</td>
</tr>
<tr>
<td>Post marketing survey</td>
<td>1</td>
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<td>13 post marketing RCTs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 post marketing survey</td>
</tr>
</tbody>
</table>
Indirect/Mixed Treatment Comparison (ITC/MTC)

- **Mixed Treatments Comparison**
  - Used in evidence synthesis when direct comparison between 2 treatments are not available
MTC [rimonabant example]
### Conversion to absolute values (Median, [Range])

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Placebo</th>
<th>Orlistat</th>
<th>Meridia</th>
<th>Rimonabant</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% Weight lost (proportion)</td>
<td>0.11 [0.10,0.14]</td>
<td>0.24 [0.15,0.34]</td>
<td>0.47 [0.16,0.80]</td>
<td>0.40 [0.22,0.62]</td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dL)</td>
<td>1.02 [0.95,1.10]</td>
<td>1.92 [1.12,2.75]</td>
<td>2.63 [1.19,4.11]</td>
<td>2.12 [0.26,3.93]</td>
</tr>
<tr>
<td>Cardiovascular death (proportion)</td>
<td>0.02 [0.01,0.02]</td>
<td>0.11 [0.00,1.00]</td>
<td>0.04 [0.00,1.00]</td>
<td>0.03 [0.00,0.99]</td>
</tr>
<tr>
<td>Depression (proportion)</td>
<td>0.01 [0.01,0.01]</td>
<td>0.00 [0.00,0.03]</td>
<td>0.02 [0.00,0.11]</td>
<td>0.02 [0.00,0.06]</td>
</tr>
<tr>
<td>Constipation/Diarrhoea (proportion)</td>
<td>0.05 [0.05,0.06]</td>
<td>0.19 [0.06,0.50]</td>
<td>0.09 [0.02,0.35]</td>
<td>0.07 [0.04,0.15]</td>
</tr>
</tbody>
</table>
**PrOACT-URL:** Step 5 Trade-off

**BRAT:** Step 5 Assess outcome importance

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Rimonabant</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% weight lost at 1 year</td>
<td>25%</td>
<td>6%</td>
</tr>
<tr>
<td>Changes in waist line at 1 year</td>
<td>-6.2</td>
<td>-1.9</td>
</tr>
<tr>
<td>Incidence of psychiatric disorder</td>
<td>22.2%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Incidence of severe adverse events</td>
<td>1.7%</td>
<td>0.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.8% + (42.9% - 20.7%)/10% x 1% -&gt; 3.02%</td>
</tr>
<tr>
<td>% Reduction in metabolic syndrome</td>
<td>42.9%</td>
<td>20.7%</td>
</tr>
</tbody>
</table>

Assuming we were able to exchange proportion of reduction in metabolic syndrome with adverse events in the following exchange rate:

\[ 10\% \text{ metabolic syndrome} = 1\% \text{ severe adverse events} \]

**PrOACT-URL: Step 5 Trade-off**

- 1% severe adverse events = 5% psychiatric disorder
- 1cm difference in waist line = 2% in proportion patient for reaching 10% weight lost
- 0.20% psychiatric disorder = 1% of patients achieving 10% weight lost at 1 year

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Rimonabant</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% weight lost at 1 year</td>
<td>33.6%</td>
<td>6% 6% + (22.2% - 17.7%)/0.2% -&gt; 28.5%</td>
</tr>
<tr>
<td>Risk of psychiatric disorder</td>
<td>22.2%</td>
<td>17.7%</td>
</tr>
</tbody>
</table>

This trade off model suggesting rimonabant would be a more favourable option.
Multi Criteria Decision Analysis (MCDA)

MCDA has 3 ingredients:

- Value functions
- Preference weights
- B-R evidence data

Overall benefit-risk balance
MCDA

- Select benefits and risks of the drug
- Apply a score to each benefit and risk depending on study results
  - Study results
- Apply a weight to each benefit and risk depending on their importance in the decision
  - Clinical relevance
  - Belief about the results obtained
- Assess the B/R (from 0 to 100) by using both scores and weights
  - Ideal drug would have a B/R = 100
  - Worst drug would have a B/R = 0
- Assess sensitivity of B/R assessment according to weights

Source: Larry Phillips’ presentation

MCDA

- Tree 3: Using results from random effect meta-analysis.
MCDA

- Effect of stakeholder value

Medical/regulatory perspective

Layman perspective

- Risk benefit profile changes on perspective
PrOACT-URL: Step 6 Uncertainty

- Conflicting objectives, health state progression?
- Uncertainty with preference weights
  - Problem regarding safety and trade-offs of risks for benefits in weight lost
  - Uncertainties with perspectives on trade-offs from different stakeholders
- Well conducted randomised controlled studies
  - Different restrictions in study inclusion criteria
  - Uncertainties between patient populations in different catchment area
  - Some uncertainties handled by using meta analysis
- Data (Natural variation in statistic, study design, sources and adequacy of data)
- Adverse events - possibilities of under reporting
- BR balance is influenced by uncertainties and preference weights
The flaw of averages

Sam Savage: *The Flaw of Averages*
Stochastic Multi-criteria Acceptability Analysis

Data sample from distribution on each criterion

Which alternatives is more preferred

Utility score

Weighted sample from a distribution

Weighted average on each alternatives

Weighted utility score

Repeat for n iterations (to account for variations in input)

SMAAA (preference-free)

Acceptability index alternative \( i \) is ranked \( r \)

Preference values for an “average” decision-maker resulting in the preference on the left
PrOACT-URL: Step 7 Risk tolerance

- **Main benefit**
  - weight reduction
  - a selection of licensed alternatives available

- **Key concern**
  - increased incidence of depression and psychiatric disorder
  - could be severe in some cases.

- Therefore, decision maker might have a lower tolerance of risk related to this medication
  - Lower risk tolerance was reflected in the trade-offs
PrOACT-URL: Step 7 Linked decision

- Consistency of this decision with similar past decisions,
- Assessment whether taking this decision could impact future decisions
- Decision on this drug would certainly influence future application on medications within the same class/indication
**Table 5.** The estimated treatment effect for different outcomes. [95% confidence intervals]

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Outcome</th>
<th>Acomplia</th>
<th>Placebo</th>
<th>Absolute difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight-loss (kg)</strong></td>
<td>-6.3 kg</td>
<td>-1.6 kg</td>
<td>4.7 kg [4.1-5.3]</td>
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</tr>
<tr>
<td><strong>Weight-loss &gt;10%</strong></td>
<td>25.5% [23.8, 27.3]</td>
<td>6.6% [5.5, 7.9]</td>
<td>19% [17, 22] OR=5.1 [3.6, 7.3]</td>
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<tr>
<td><strong>Waist-circumference changes (cm)</strong></td>
<td>-6.2 [-7.2, -5.2]</td>
<td>-1.9 [-2.3, -1.4]</td>
<td>-4.3 [-5.5, -3.0]</td>
<td></td>
</tr>
<tr>
<td><strong>Systolic blood pressure</strong></td>
<td>-1.3 [-2.0, -0.5]</td>
<td>0.5 [-0.6, 1.6]</td>
<td>-1.8 [-2.8, -0.8]</td>
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</table>

<table>
<thead>
<tr>
<th>Risks</th>
<th>Outcome</th>
<th>Acomplia</th>
<th>Placebo</th>
<th>Absolute difference</th>
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<tr>
<td><strong>Psychiatric adverse event</strong></td>
<td>26.2% [24.5, 28.0]</td>
<td>14.1% [12.4, 15.9]</td>
<td>12.1% [10, 15] OR=1.9 [1.5, 2.3]</td>
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<tr>
<td><strong>Neurological adverse event</strong></td>
<td>27.4% [25.7, 29.2]</td>
<td>24.4% [22.3, 26.6]</td>
<td>3.0% [0.5, 5.5] OR=1.7 [1.1, 2.7]</td>
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<tr>
<td><strong>Serious adverse event</strong></td>
<td>5.9% [5.0, 6.9]</td>
<td>4.2% [3.3, 5.3]</td>
<td>1.7% [0.4, 3.0] OR=1.43 [1.03, 1.98]</td>
<td></td>
</tr>
</tbody>
</table>

a) Christensen (2007)

b) Chan-Emond simulations

c) FDA-Briefing-document
BRAT: Step 6 Display & interpret key BR metrics

Figure 4: Forest plot for risk differences between Acomplia (treatment A) and placebo (treatment B). [The number in the box is a point estimate and the width of the box is the confidence interval. Yellow is Benefit, blue is Risk]

- Weight loss - >10%
- Systolic blood pressure - reduction
- Waist circumference - cm reduced
- Psychiatric disorder - percent
- Nervous system disorder - percent
- Severe adverse events - percent

Rate Difference (per 1000 patients)

- Higher for Treatment B
- Higher for Treatment A
Visualisations

- Effects table
- Box plot
- Distribution plot
- Forest/interval plot
- Tornado diagram

Reduction in nausea or vomiting
Reduction in functional disability
Pain-free response
Reduced sensitivity to sound and light
Rapid onset
Headache relief
Sustained response

 transient triptans sensation
CNS AEs
"Chest-related" AEs

- Mean
- Efficacy 95%CI
- Safety 95%CI

Risk difference (per 1,000 patients)
Favors comparator
Favors study drug
Visualisations

• Interactive visualisations
Remarks

• Both PrOACT-URL and BRAT provide transparent framework for benefit risk assessment
• Both framework provide a structural and systematic approach to support benefit risk assessment and can be used throughout the lifecycle of a drug
• Both methods frame the assessment on important issues and allow explicit and transparent weighing between criteria.
• Rationale of assessment must be communicated clearly to stakeholders and visualisation of data and weighs are crucial.
Remarks

- MCDA can be used to integrate data and preference information for quantitative assessment.
- Uncertainty with preference information and data can be handled using SMAA.
- MTC/ITC can be used in data synthesis to estimate relative treatment effect with direct and indirect evidence.
Acknowledgments

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