Overview

- Introduction and motivation
- Case study applying multi-criteria decision analysis (MCDA) in benefit-risk assessment of relapsing-remitting multiple sclerosis (RRMS) treatments
- Lessons learnt
Etiology

- This work was done by Pedro Oliveira on a summer placement from Sheffield University

- The principal objectives were
  - To gain experience in Multi-Criteria Decision Analysis
  - To produce a thesis for Pedro’s degree

- This case study was used as an example to achieve these objectives

What is a Benefit-Risk Assessment?

*Both a quantitative method and a qualitative framework*

- Qualitative framework gives the structure
  - What is the decision that the assessment is supporting?
  - Which drugs, indication, patient population and perspective?
  - Which benefit and risk criteria are relevant to the assessment?
  - Which sources of evidence are relevant?
  - How to trade-off benefits and risks?

- Quantitative method
  - Methods for collecting and synthesizing the objective evidence and subjective judgments
  - Metrics for measuring the benefit-risk (e.g. clinical utility index)
What a Benefit-Risk Assessment is NOT
*It does not make decisions, rather it supports decision makers*

- Benefit-risk assessment does not give you the answer
- Experts make the decision
  - Expert judgment plays the central role
  - Frameworks and models by themselves are insufficient
- Expert knowledge is structured and decomposed in a framework. This helps to:
  - Understand the problem
  - Assess the main drivers of a decision
  - Communicate issues in a transparent, rational and consistent way
  - Appropriately handle uncertainty and perform sensitivity analysis

Motivation for Benefit-Risk methods
- Increasing attention is being given to quantitative benefit-risk assessments
  - EMA Benefit-Risk methodology project
  - PhRMA BRAT Framework
  - IMI PROTECT WP5
  - ISPOR Risk-Benefit Management Working Group
  - EFPSI working group on Benefit-Risk
Motivation for using relapsing remitting multiple sclerosis (RRMS) case study

- RRMS is a serious disease affecting the central nervous system
  - Progressive, chronic, inflammatory disease that can seriously affect quality of life

- The main current first-line treatments
  - Are effective at reducing the progression of the disease and the rate of relapse
  - But also have frequent or serious adverse events associated with them
  - How to judge if the benefits are worth the risks?

<table>
<thead>
<tr>
<th>Lessons Learnt in MCDA</th>
<th>Richard Nixon</th>
<th>May 2011</th>
</tr>
</thead>
</table>

Susan has RRMS and is deciding on the treatment she prefers.

<table>
<thead>
<tr>
<th></th>
<th>Avonex</th>
<th>Movectro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapses per year</td>
<td>0.27</td>
<td>0.14</td>
</tr>
<tr>
<td>Chance of flu-like symptoms in during the next two-years</td>
<td>94%</td>
<td>43%</td>
</tr>
<tr>
<td>Convenience</td>
<td>Weekly IM injection</td>
<td>Monthly oral</td>
</tr>
<tr>
<td>Serious herpes zoster</td>
<td>0%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Hepatic adverse events</td>
<td>0%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

- Are there other adverse events she should also consider?
- Which treatment should she take?
- Or should she consider Copaxone or Tysabri?
Steps in performing a benefit-risk analysis

**PrOACT-URL framework**

- Generic framework for framing and analyzing decisions
- Apply framework to multi-criteria decision analysis (MCDA)
- Some of the steps will be more substantive than others when applied to MCDA

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**Problem**

**Identify the fundamental problem**

- Four first-line therapies for RRMS (in summer 2010)
  - Avonex, Copaxone, Tysabri and Movectro
- These drugs have favourable and unfavourable effects
- Take the patient perspective
- How do we decide among them?
Objectives

*Identify the overall value and the criterion categories*

**Decision**

- Treatment

**Criteria**

- Adverse events
- Efficacy
- Convenience

**Criteria categories**

- Flu-like symptoms
- Injection-site reactions
- Serious herpes zoster
- Hepatic AE
- Annual relapse rate
- EDSS progression

**Outcome measures**

- # patients/1000 after 2 years
- % not progressing after 2 years

**Overall value**

**Benefit-risk**

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**Adverse events of first-line treatments**

*Many adverse events are observed*

<table>
<thead>
<tr>
<th></th>
<th>Avonex</th>
<th>Copaxone</th>
<th>Tysabri</th>
<th>Movelcro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic and hematologic abnormalities</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Common adverse events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection-site reactions</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fatigue</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate post-injection reactions</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipatrophy</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rare malignancies</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Progressive Multifocal Leukoencephalopathy</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Serious herpes zoster</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Adverse events of first-line treatments

Many adverse event types can be reported in different ways

- Flu-like symptoms reported in many ways in different studies
- How to combine these onto a common scale?

<table>
<thead>
<tr>
<th>Headache</th>
<th>Rhinitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chills</td>
<td>Cough</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>Dyspnea</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>Influenza / flu syndrome</td>
</tr>
<tr>
<td>Laryngismus</td>
<td>Lower respiratory tract or lung infection</td>
</tr>
<tr>
<td>Pyrexia / fever</td>
<td>Flu-like symptoms</td>
</tr>
<tr>
<td>Chronic sinusitis</td>
<td>Pneumonia</td>
</tr>
</tbody>
</table>

Alternatives

Identify the possible decisions to be evaluated against the criteria

- Generally in MCDA there are multiple decisions to be made
- This leads to many combinations of possible decisions (strategies)
- However, in this situation there is only one decision to make: which treatment should the patient take to treat her RRMS?
  - Avonex: 30mcg, im, qw
  - Copaxone: 20mg, sc, qd
  - Tysabri: 300mcg, iv, qm
  - Movectro: 3.5mg/kg, oral, 8-20 times per year
Consequences

What are the observations relevant to the criteria?

- We considered data only from the pivotal Phase III studies
  - Benefits are calibrated to Movectro patients by using the Movectro placebo benefit and the relative/hazard ratio of the given drug compared to its respective placebo.

<table>
<thead>
<tr>
<th></th>
<th># Patients / 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Avonex</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>938</td>
</tr>
<tr>
<td>Injection-site reactions</td>
<td>125</td>
</tr>
<tr>
<td>Serious herpes zoster</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic adverse events</td>
<td>0</td>
</tr>
<tr>
<td>Benefits</td>
<td></td>
</tr>
<tr>
<td>Relapses</td>
<td>270</td>
</tr>
<tr>
<td>EDSS progression</td>
<td>134</td>
</tr>
<tr>
<td>Convenience</td>
<td>i.m. qw</td>
</tr>
</tbody>
</table>

Trade-offs (1)

Partial value functions for each criterion

- A partial value function maps the range of plausible outcomes for each criteria to the range \([0,1]\)
- Assume a linear partial value function for each adverse event and benefit criteria

![Graph showing a partial value function for a criterion](image)

Number of relapses per 1000 patients at one year
Trade-offs (2)

**Within-category weights are elicited**

- Benefit-risk analysis must contain subjective value judgments
- We used a “bottom-up swing weights” method
  1. Rank-order the criteria by the relative value of bringing each from its worst to its best plausible outcome
  2. Assign the top-ranked criterion a weight of 100, and assign the others weights corresponding to their (subjective) relative values.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Unit of measurement</th>
<th>Worst</th>
<th>Best</th>
<th>Rank</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapses</td>
<td>Number of relapses in 1000 patients in one year</td>
<td>400</td>
<td>80</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td>Disability progression</td>
<td>Number of patients out of 1000 whose EDSS scores increases by at least 1 point at two years</td>
<td>270</td>
<td>100</td>
<td>1</td>
<td>100</td>
</tr>
</tbody>
</table>

Trade-offs (3)

**Between-category weights are elicited**

- Take the top-ranked criterion from each category, and compare these in the same way as the within-category weights

<table>
<thead>
<tr>
<th>Category</th>
<th>Unit of measurement</th>
<th>Worst</th>
<th>Best</th>
<th>Rank</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convenience</td>
<td>Administration route and frequency</td>
<td>Oral, once a month</td>
<td>Subcutaneous injection, daily</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>Disability progression</td>
<td>Number of patients out of 1000 whose EDSS scores increase by at least 1 point at two years</td>
<td>270</td>
<td>100</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Serious herpes zoster</td>
<td>Number of patients out of 1000 with AE in two years</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>90</td>
</tr>
</tbody>
</table>
Trade-offs (4)

Weights measure and accumulate the relative values of the criteria

- Between-category weights
- Within-category weights
- Normalized between-category weights
- Normalized within-category weights
- Cumulative weights

\[
\begin{align*}
W_{b1} &= r_b^* r_{b1}^* \\
\sum w_i &= 1
\end{align*}
\]

Trade-offs (5)

Put it all together

Decision | Criterion category | Criterion | Value $v_i(t)$ | Cumulative weight $W_i$
---|---|---|---|---
Treatment ($t$) | Adverse events | Flu-like symptoms | $v_{a1}(t)$ | $W_{a1}$
 | | Injection-site reactions | $v_{a2}(t)$ | $W_{a2}$
 | | Serious herpes zoster | $v_{a3}(t)$ | $W_{a3}$
 | | Hepatic AE | $v_{a4}(t)$ | $W_{a4}$
 | Efficacy | Annual relapse rate | $v_{b1}(t)$ | $W_{b1}$
 | | EDSS progression | $v_{b2}(t)$ | $W_{b2}$
 | Convenience | | $v_c(t)$ | $W_c$

\[
\sum w_i v_i(t)
\]
Overall results

- Although Tysabri has the highest benefit-risk from efficacy, the convenience of Movectro gives it the highest overall benefit-risk.
Uncertainty

**Deterministic sensitivity analysis**

- The between-category efficacy weight would have to change from 0.45 (basecase) to 0.68 for Tysabri to be preferred treatment

![Graph showing value versus relative weight for different treatments](image1.png)

Uncertainty

**Stochastic sensitivity analysis**

- Could also perform a stochastic sensitivity analysis of the
  - Clinical effects of the different treatments
  - Judgments of the different treatments

- Stochastic sensitivity analysis could be performed, e.g. by using Monte Carlo simulation with sampling from distributions of various parameters
  - For clinical effects this comes from the evidence synthesis
  - For judgments distributions could be based on eliciting distributions for the weights, and/or combining weights from different people

- Results would include
  - Distribution of benefit-risk score for each treatment
  - Probabilities that each treatment has the highest score
Risk tolerance and linked decisions

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**Risk in this context mean uncertainty**

- **Risk tolerance**
  - Uncertainty analysis indicates how robust the benefit-risk assessments are
  - Are there factors that could affect the decision makers attitude and accept more uncertainty? E.g. Orphan drug or high unmet need

- **Linked decisions**
  - Consistency with other decisions
  - How this decision could set a president for future decisions

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Lessons learned

**Improvements and developments**

- Perform a more rigorous evidence synthesis, for example using mixed-treatment-comparisons, possible with case-mix adjustment.
- Choice of adverse events should have included progressive multifocal leukoencephalopathy (PML) for Tysabri.
- Use Patient Reported Outcomes, for example discrete choice experiments included in a clinical study, to assess patient values directly from patients.
- Include a probabilistic sensitivity analysis on clinical parameters.
- Use an underlying disease progression model to incorporate long-term effects of RMMMS.
- Use MCDA to identify patient segments who would most benefit from a treatment.
- Use MCDA in development decisions. E.g. Go/no-go or indication selection.
Take home messages

- MCDA is a framework well suited to benefit-risk analysis
- MCDA analysis does not give you the answer
  - It is a framework for decomposing and understanding a problem
  - Assesses the main value drivers of a decision
  - Communicate issues in a transparent, rational and consistent way
- Benefit-risk analysis is conceptually easy but hard to operationalize
  - Define consistent criteria across decision options, find data matching these criteria, and elicit value judgments

Acknowledgements

- Didier Renard
- Francois Mercier
- Gordon Graham
- Gordon Francis
- Fabrice Bancken
- William Collins
- Marisa Bacchi
- Daniela Piani Meier
- Ana de Vera
References

- **MCDA**

- **Working groups**

Appendix

- | Lessons Learnt in MCDA | Richard Nixon | May 2011 |
- | Lessons Learnt in MCDA | Richard Nixon | May 2011 |
Assumptions of linear additive value model

- Partial value functions satisfy interval scale properties; changes in attributes rather than attributes themselves matter.
- Preferential independence: elicitation of relative preference between a subset of criteria not affected by levels of attributes achieved in criteria outside the subset.
- Note: Linearity of partial value functions is not a feature of the linear additive model.

Trade-offs (1)

Partial value functions for each criterion

- A partial value function maps the range of plausible outcomes for each criterion to the range \([0,1]\).
- Assume a linear partial value function for each adverse event and benefit criteria.

<table>
<thead>
<tr>
<th>Convenience criteria</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral, once a month</td>
<td>1</td>
</tr>
<tr>
<td>Oral, daily</td>
<td>0.9</td>
</tr>
<tr>
<td>Intramuscular injection, once a week</td>
<td>0.4</td>
</tr>
<tr>
<td>Subcutaneous injection, daily</td>
<td>0</td>
</tr>
<tr>
<td>Intravenous infusion, every month</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Number of relapses per 1000 patients at one year