

Benefit-Risk of Multiple Sclerosis Treatments: Lessons Learnt in Multi-Criteria Decision Analysis

BBS Spring Conference Comparative Quantitative Assessments: Benefit-Risk & Effectiveness

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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?

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

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

- 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*¹

- 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

1 Hammond JS, Keeney RL, Raiffa H (1999). Smart Choices: a practical guide to making better decisions. Harvard Business Press

Problem

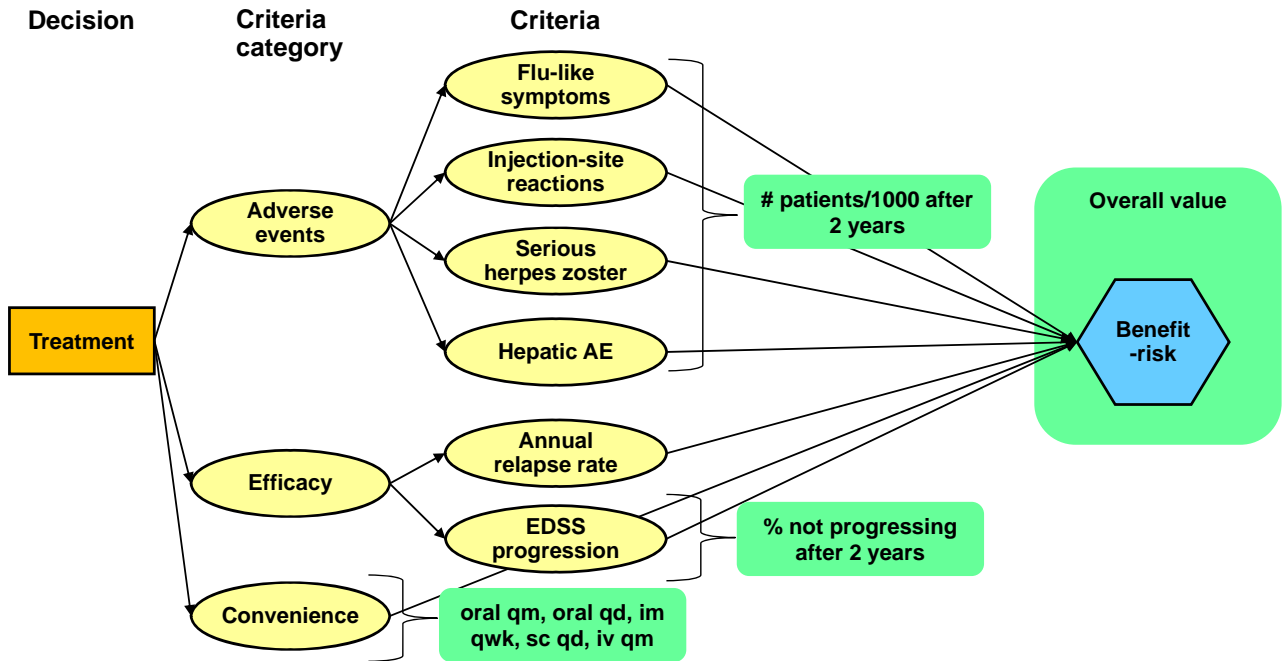
Identify the fundamental problem

- 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?

Treatment

Objectives

Identify the overall value and the criterion categories



Adverse events of first-line treatments

Many adverse events are observed

	Avonex	Copaxone	Tysabri	Movectro
Hepatic and hematologic abnormalities	X	X	X	X
Common adverse events				
Injection-site reactions	X	X	X	
Flu-like symptoms	X	X	X	X
Fatigue	X		X	
Headache	X			
Immediate post-injection reactions		X	X	
Lipatrophy		X		
Serious adverse events				
Rare malignancies	X			
Progressive Multifocal Leukoencephalopathy			X	
Serious herpes zoster				X

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?

Headache	Rhinitis
Chills	Cough
Upper respiratory tract infection	Bronchitis
Nasopharyngitis	Dyspnea
Oropharyngeal pain	Influenza / flu syndrome
Laryngismus	Lower respiratory tract or lung infection
Pyrexia / fever	Flu-like symptoms
Chronic sinusitis	Pneumonia

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?

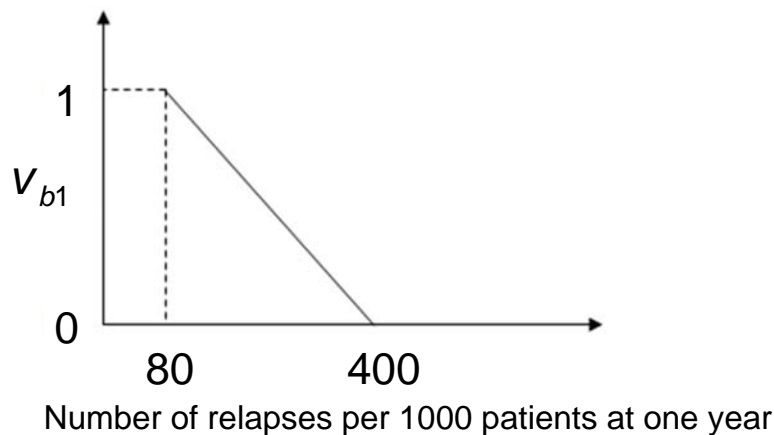
- We considered data only from the pivotal Phase III studies
 - Benefits are calibrated to Movectro patients by using the Movectro placebo benefit and the relative/hazard ratio of the given drug compared to its respective placebo.

	# Patients / 1000			
	Avonex	Copaxone	Tysabri	Movectro
Adverse events				
Flu-like symptoms	938	533	485	433
Injection-site reactions	125	980	252	0
Serious herpes zoster	0	0	0	2
Hepatic adverse events	0	0	55	7
Benefits				
Relapses	270	234	104	140
EDSS progression	134	199	128	154
Convenience	i.m. qw	s.c. qd	i.v. qm	Oral qm

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



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.

Criterion	Unit of measurement	Outcomes		Rank	Weight
		Worst	Best		
Relapses	Number of relapses in 1000 patients in one year	400	80	2	40
Disability progression	Number of of patients out of 1000 whose EDSS scores increases by at least 1 point at two years	270	100	1	100

Trade-offs (3)

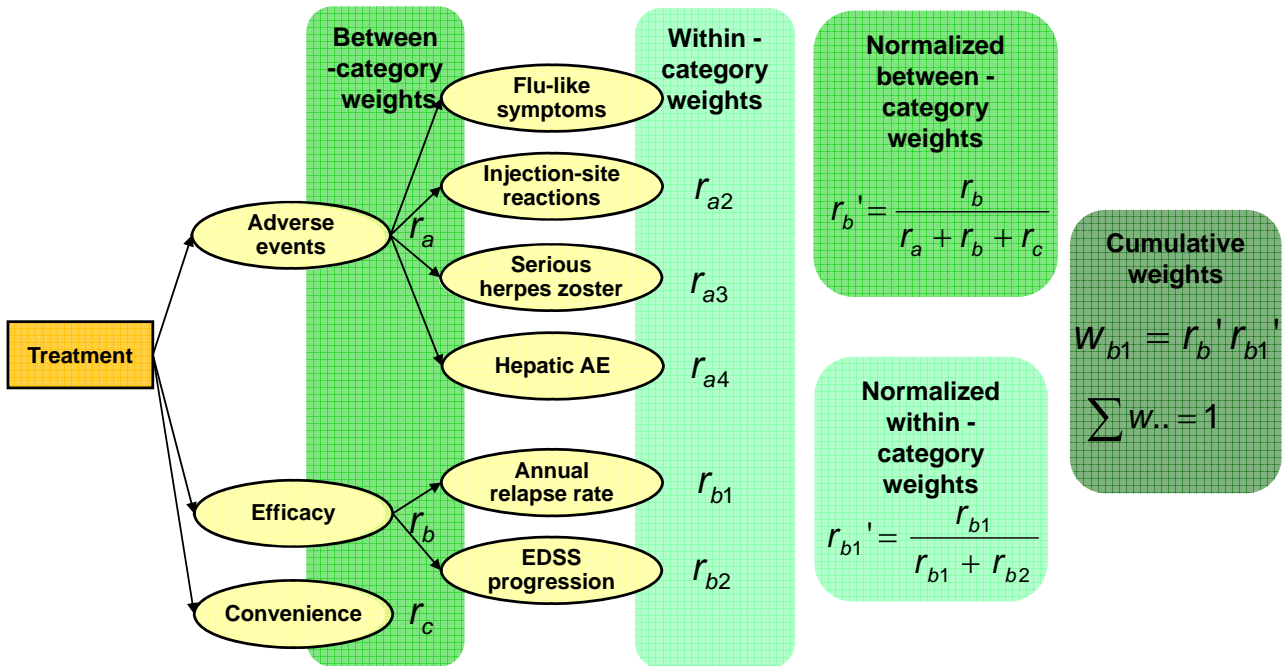
Between-category weights are elicited

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

Category	Unit of measurement	Outcomes		Rank	Weight
		Worst	Best		
Convenience	Administration route and frequency	Oral, once a month	Subcutaneous injection, daily	3	30
Disability progression	Number of patients out of 1000 whose EDSS scores increase by at least 1 point at two years	270	100	1	100
Serious herpes zoster	Number of patients out of 1000 with AE in two years	3	0	2	90

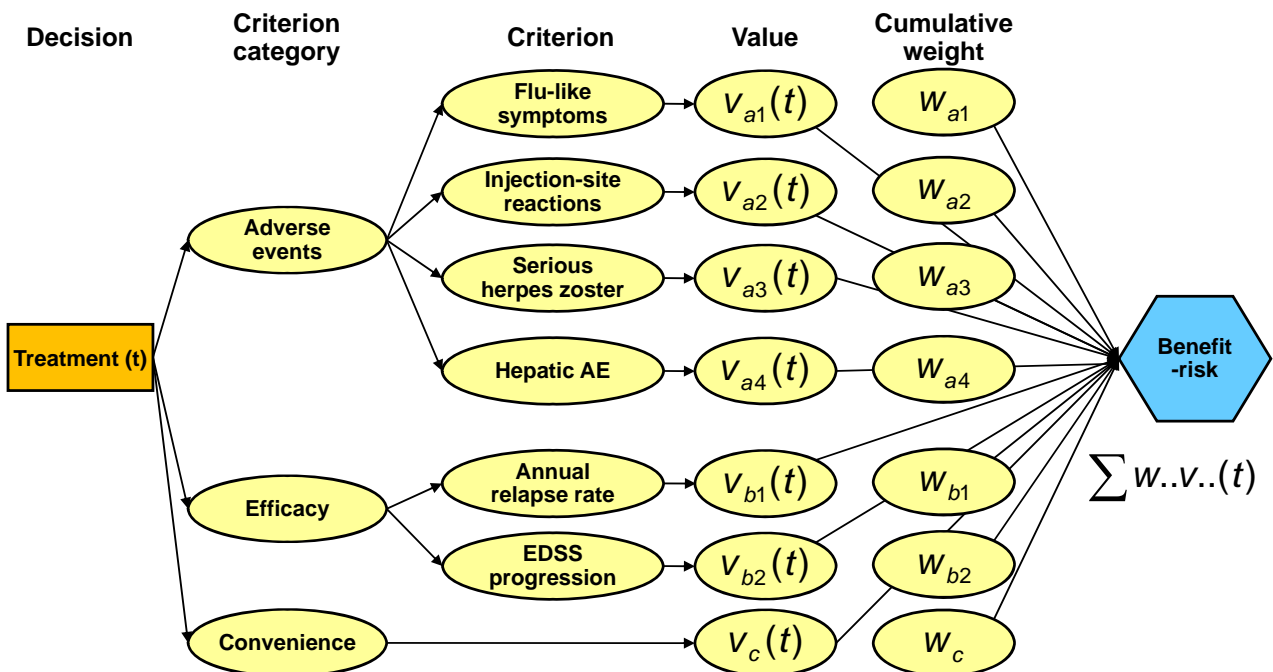
Trade-offs (4)

Weights measure and accumulate the relative values of the criteria



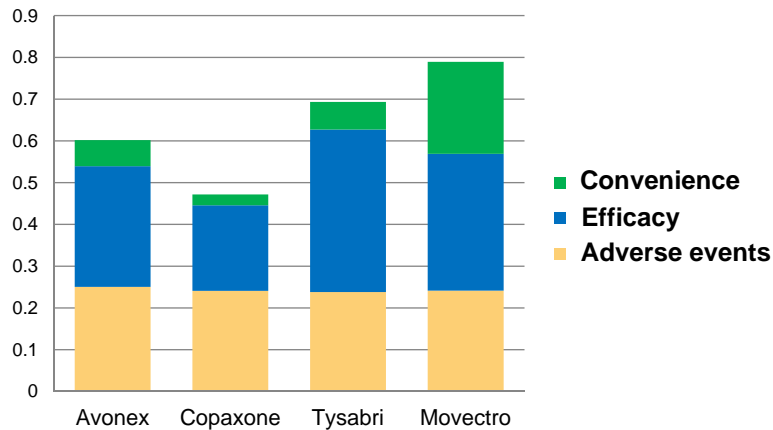
Trade-offs (5)

Put it all together



Overall results

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

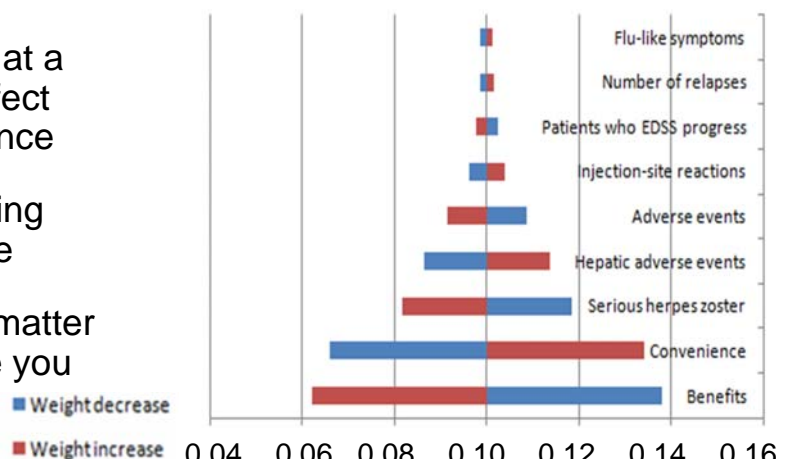


Uncertainty

Deterministic sensitivity analysis

- Deterministic sensitivity analysis of the weights
 - Could also look at the value functions
- Vary each of them one at a time and assess the effect on the benefit-risk balance
- Assess where the “tipping points” of a decision are
- If convenience did not matter so much to you, maybe you would choose Tysabri

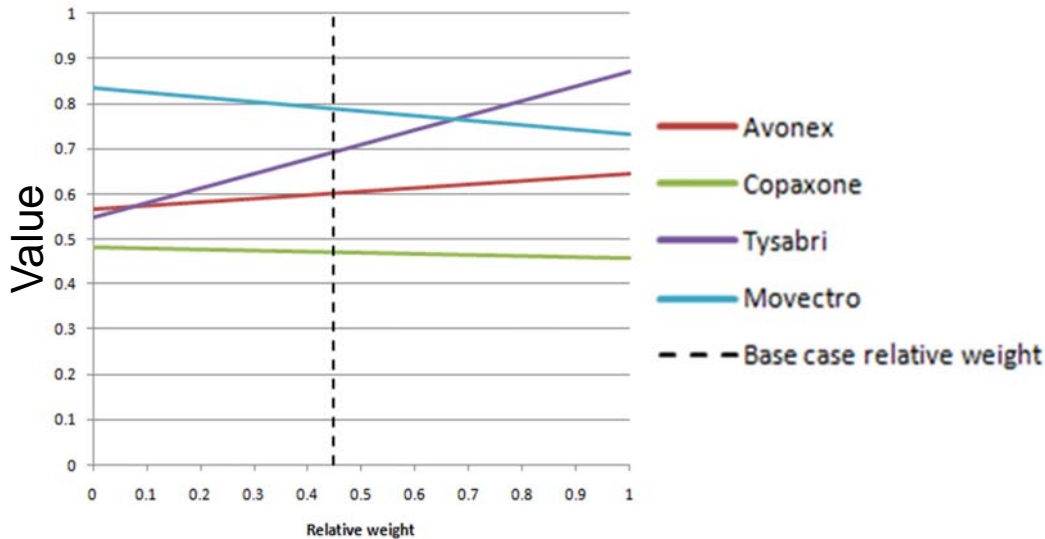
Variation of incremental benefit-risk of Movectro over Tysabri due to a variation of +/- 20% in weights for the average respondent



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



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

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 precedent for future decisions

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 RMMS.
- 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

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Appendix

Assumptions of linear additive value model

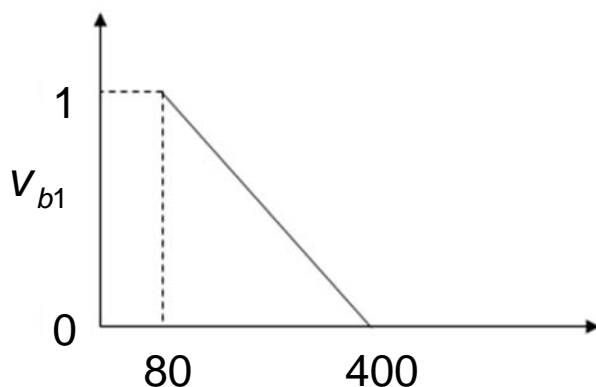
- Partial value functions satisfy interval scale properties
changes in attributes rather than attributes themselves matter
- Preferential independence: elicitation of relative preference between a subset of criteria not affected by levels of attributes achieved in criteria outside the subset
- Note: 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 criteria to the range [0,1]
- Assume a linear partial value function for each adverse event and benefit criteria



Number of relapses per 1000 patients at one year

Convenience criteria	Value
Oral, once a month	1
Oral, daily	0.9
Intramuscular injection, once a week	0.4
Subcutaneous injection, daily	0
Intravenous infusion, every month	0.3