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 where
  - 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

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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)

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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

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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

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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?

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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?

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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, Raïffa H (1999). Smart Choices: a practical guide to making better decisions. Harvard Business Press

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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?

Treatment

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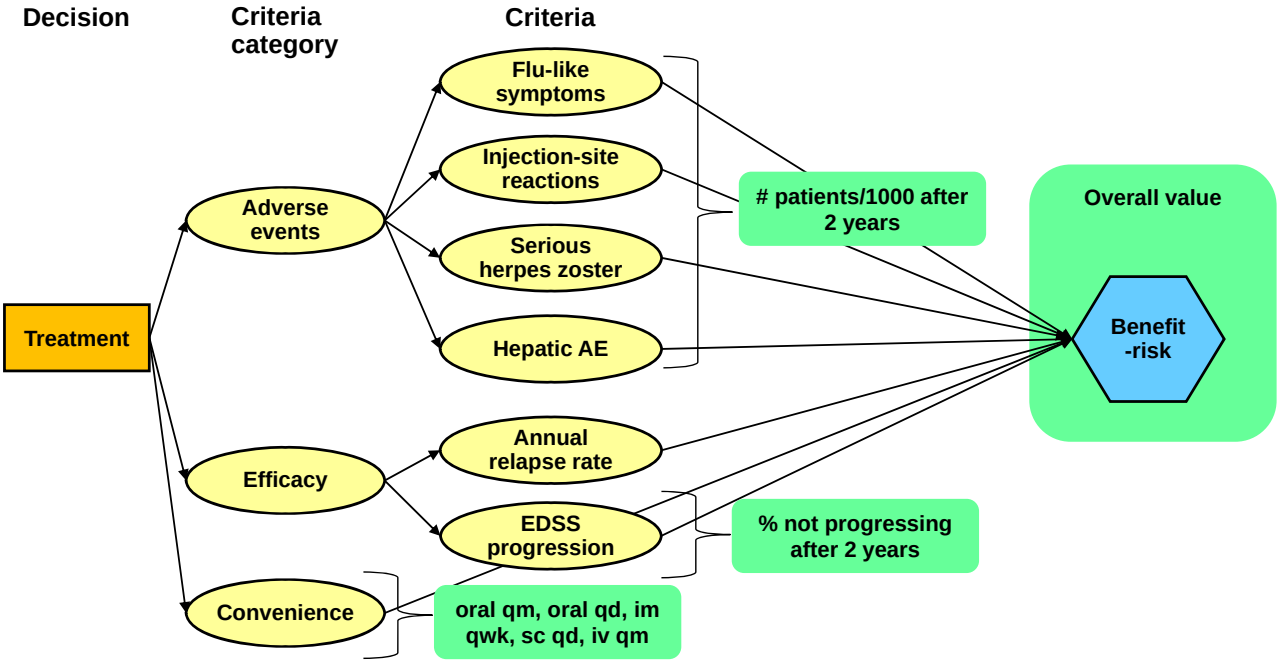
Objectives

Identify the overall value and the criterion categories



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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

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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**

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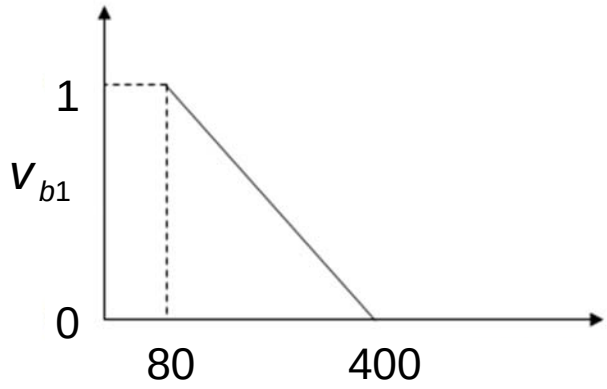
Trade-offs (1)

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

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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.

		Outcomes			
Criterion	**Unit of measurement**	**Worst**	**Best**	**Rank**	**Weight**
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)

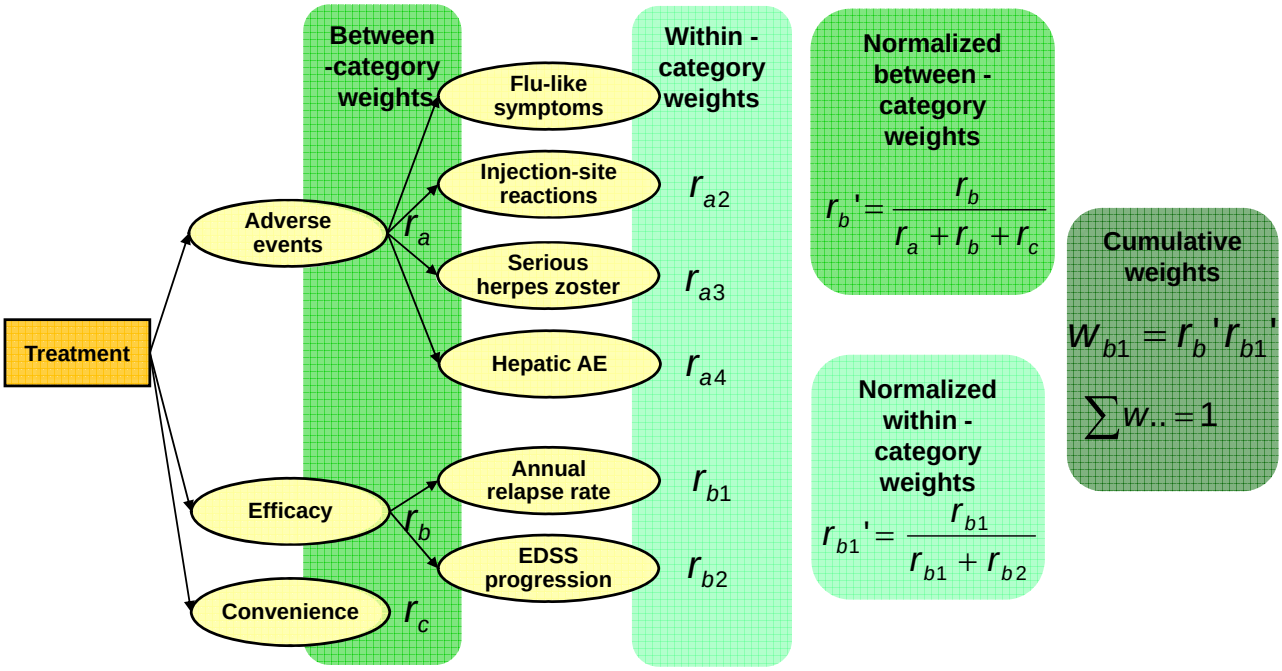
Between-category weights are elicited

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

		Outcomes			
Category	**Unit of measurement**	**Worst**	**Best**	**Rank**	**Weight**
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



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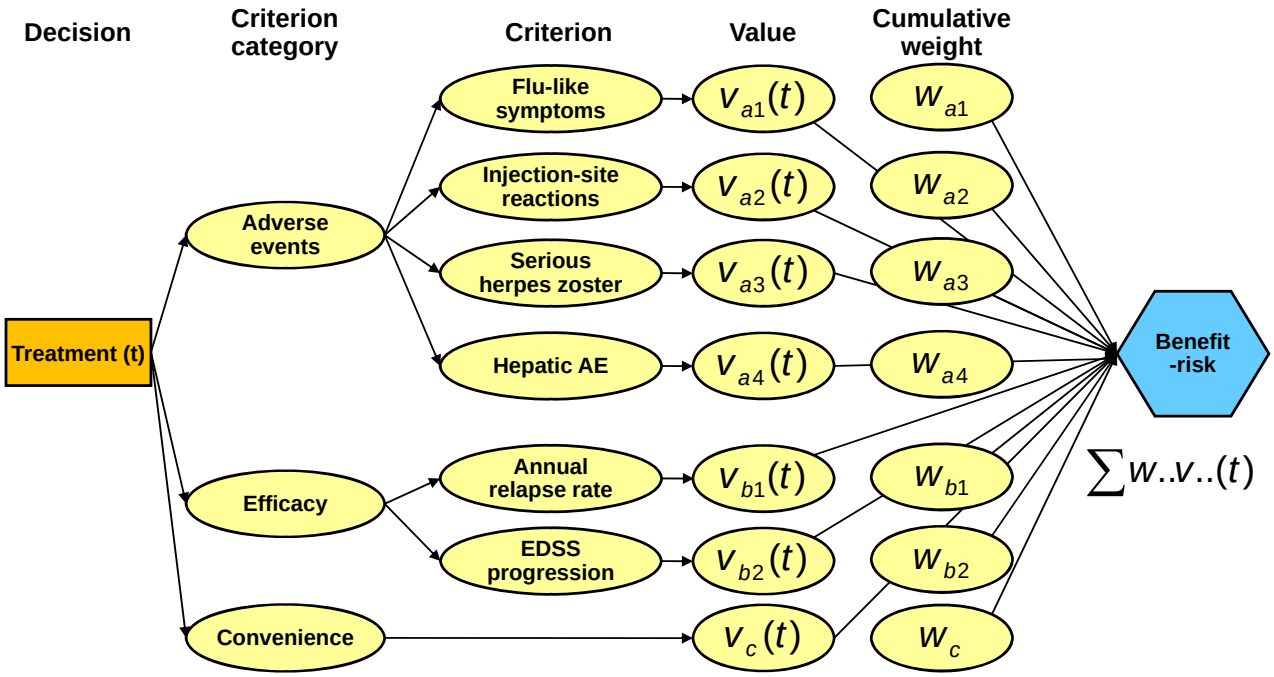
Trade-offs (5)

Put it all together



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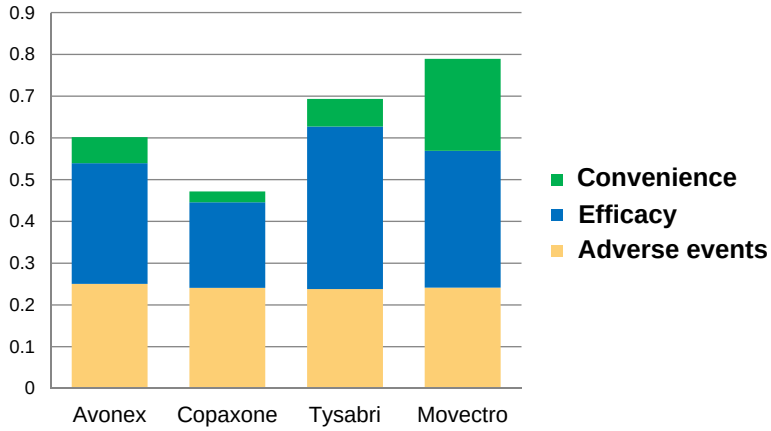
Overall results

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



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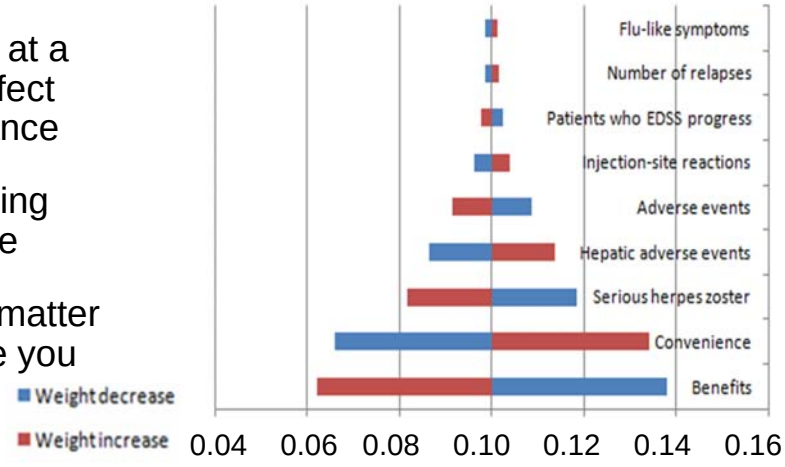
Uncertainty

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



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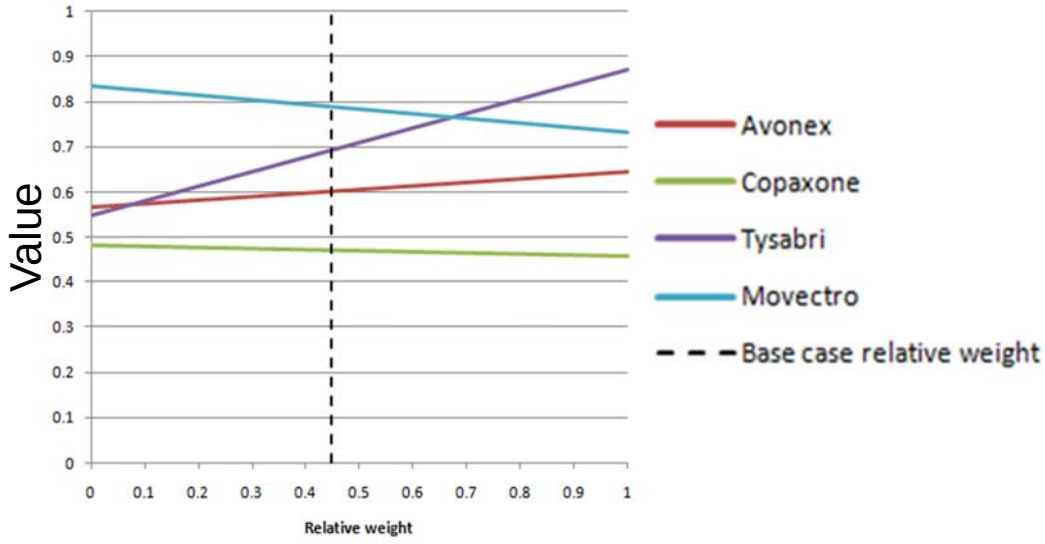
Uncertainty

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



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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

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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 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 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.

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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

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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.

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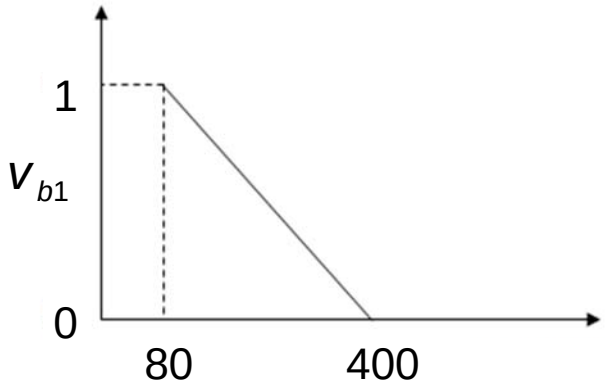

Number of relapses per 1000 patients at one year

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

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