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Bayesian Approaches in the Regulation of Medicines: Current and Future Potential

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Imperial College London

BAYES 2018,
Homerton College Cambridge

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ICH-E9 Statistical Principles for Clinical Trials 1998

"Because the predominant approaches to the design and analysis of clinical trials have been based on frequentist statistical methods, the guidance largely refers to the use of frequentist methods (see Glossary) when discussing hypothesis testing and/or confidence intervals. This should not be taken to imply that other approaches are not appropriate: the use of Bayesian (see Glossary) and other approaches may be considered when the reasons for their use are clear and when the resulting conclusions are sufficiently robust."

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ICH-E9 Statistical Principles for Clinical Trials 1998

GLOSSARY

Bayesian Approaches: Approaches to data analysis that provide a posterior probability distribution for some parameter (e.g. treatment effect), derived from the observed data and a prior probability distribution for the parameter. The posterior distribution is then used as the basis for statistical inference.

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2007: AMIHOT II breathes new life into supersaturated oxygen strategy post-PCI

- "AMIHOT II grew out of a post hoc subset analysis from the negative AMIHOT I trial that suggested patients with large infarcts who underwent PCI within the first six hours of symptoms experienced significant improvements following supersaturated oxygen therapy, something not seen in the trial as a whole. For AMIHOT II, Stone et al randomized 301 patients with large anterior infarcts who had undergone early reperfusion to either supersaturated oxygen therapy for 90 minutes following PCI or standard treatment. Findings from these patients were then combined with a similar subset of patients from AMIHOT I using a Bayesian hierarchical model, a strategy that Stone emphasized has the **FDA**'s stamp of approval."

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Vasogen Announces Third Quarter 2007 Results

- "Following our meeting with the Food and Drug Administration (FDA) in May 2007 regarding our ACCLAIM results, the agency strongly recommended that we conduct a confirmatory trial ("ACCLAIM-II") of Celacade in NYHA Class II heart failure patients to support a Pre-market Approval submission for the purpose of achieving regulatory approval in the United States. The FDA also recommended that we use a Bayesian approach in the design of the confirmatory trial. The FDA indicated that they were recommending this approach specifically because it would allow us to borrow power from the ACCLAIM trial and also because it has the potential to substantially reduce the sample size required for a confirmatory study."

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FDA Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials 2010

2.1 What is Bayesian statistics?

"Bayesian statistics is an approach for learning from evidence as it accumulates. In clinical trials, traditional (frequentist) statistical methods may use information from previous studies only at the design stage. Then, at the data analysis stage, the information from these studies is considered as a complement to, but not part of, the formal analysis. In contrast, the Bayesian approach uses Bayes' Theorem to formally combine prior information with current information on a quantity of interest. The Bayesian idea is to consider the prior information and the trial results as part of a continual data stream, in which inferences are being updated each time new data become available."

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FDA Draft Guidance Adaptive Design Clinical Trials for Drugs and Biologics 2010

"Some modeling and simulation strategies lend themselves to a Bayesian approach that might be useful. The Bayesian framework provides a way to posit models (i.e. *priors*) for the study design and the adaptive choices as they might probabilistically occur, and may aid in evaluating the impact of different assumed distributions for the parameters of the model and modeled sources of uncertainty. The Bayesian approach can be a useful planning tool at the study design stage to accommodate a range of plausible scenarios. Using Bayesian predictive probability, which depends upon probabilities of outcomes conditional on what has been observed up to an interim point in the adaptive study, may aid in deciding which adaptation should be selected, while the study design is still able to maintain statistical control of the Type I error rate in the frequentist design."

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The licensing challenge

- The task of regulators (e.g. EMA, FDA) is to make a good and defensible decisions on which medicines should receive a license for which indications, based on the available evidence of risks and benefits
- It is increasingly important to be able to justify and explain these decisions to patients and other stakeholders.
- Can more formal approaches of decision-making, and especially more modern methods of graphical display help regulators do these better?

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Benefit-risk initiatives

- EMA Benefit-Risk methodology project
- PhRMA BRAT Framework and UMBRA Initiative
- ISPOR Risk-Benefit Management Working Group
- Consortium on Benefit-Risk Assessment (COBRA)
- European Federation of Statisticians in Pharmaceutical Industry (EFSPI) Benefit-Risk SIG
- IMI-PROTECT Benefit-Risk Integration and Representation Project

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Public	Private
Imperial College (co-leader)	Merck KGaA (co-leader)
EMA	AMGEN
DKMA	AstraZeneca
AEMPS	Bayer
MHRA	GSK
Mario Negri Institute	Lilly
GPRD	Novartis
LA-SER	Novo Nordisk
IAPO	Pfizer
	Roche
	Sanofi-Aventis
	Takeda

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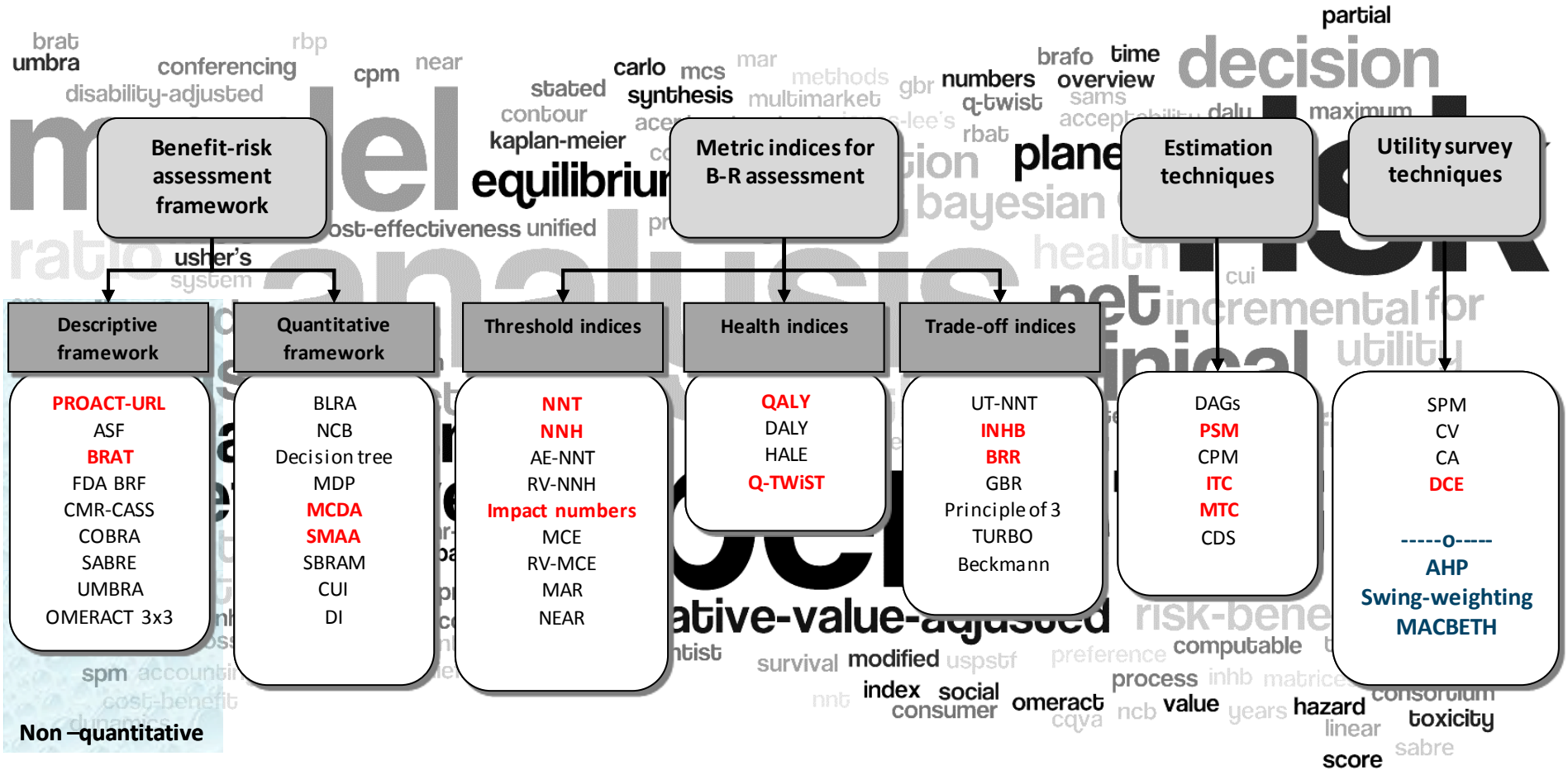
Methodologies available



Mt-Isa *et al*. Balancing benefit and risk of medicines: a systematic review and classification of available methodologies. Pharmacoepidemiology and Drug Safety 2014. DOI: 10.1002/pds.3636.

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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."

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Natalizumab case study

It is an interesting case study because: It is an effective treatment for a serious disease, with a rare but very serious side effect. License suspended in the US but then reintroduced due partly to patient pressure.

Drug of interest	Natalizumab
Indication	Relapsing remitting multiple sclerosis
Severe side effect	Progressive Multifocal Leukoencephalopathy (PML)
Regulatory history	2004 Approved in the US 2005 License suspended in the US 2006 Re-introduced because of patient demand in the US and approved in the EU 2009 CHMP reassessed the PML risk and continued approval

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PrOACT-URL Framework

- A generic framework to structure the decision problem
- Divide into 8 steps
- Emphasis on uncertainty via sensitivity analysis

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PrOACT-URL	BRAT	Specifications
Problem	Define decision context	What is the benefit-risk balance of natalizumab following the occurrence of PML cases?
Objective	Identify benefit and risk outcomes	Benefits: Reduction in relapse rate, slowdown in disability progression. Risks: PML, reactivation of serious herpes viral infections, seizures, abortion or congenital abnormalities, transaminases elevation, infusion or injection site reactions, hypersensitivity reactions, flu-like reactions
Alternative	Define the decision context	Interferon beta-1a, glatiramer acetate, placebo. Which option to choose?
Consequence	Extract source data	*Build a data source data table (BRAT) or an effects table (PrOACT-URL)*
	Customise framework	*If required, repeat step 2 following in regards to available data*
Trade-off	Assess outcome importance	*Dealt with in stages 3 (Analysis) and 4 (Exploration)*
Uncertainty	Display & interpret key BR metrics	
Risk tolerance		
Linked decisions		

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Brief on MCDA

- Multi-Criteria Decision Analysis
- Deals with multiple conflicting criteria
- MAUT with requisite criteria
- Requires probabilities (data), utilities (value function elicitation), weights (weight elicitation)
- Governed by PrOACT-URL for structure and transparency
- Deterministic analysis

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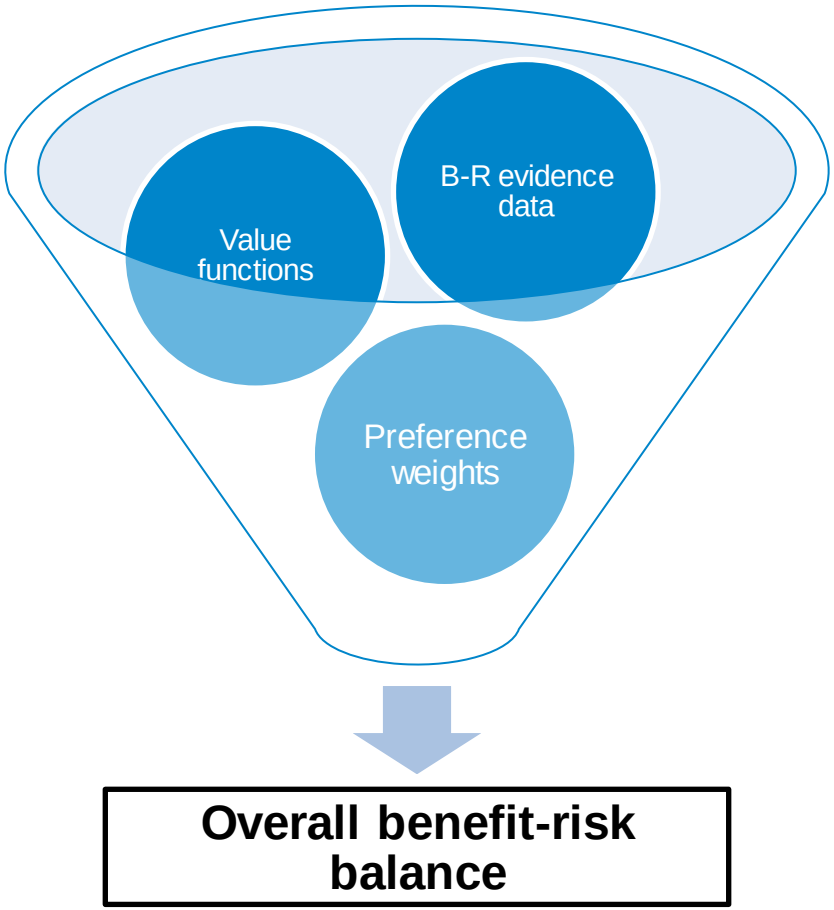
Ingredients of MCDA

MCDA has 3 ingredients:



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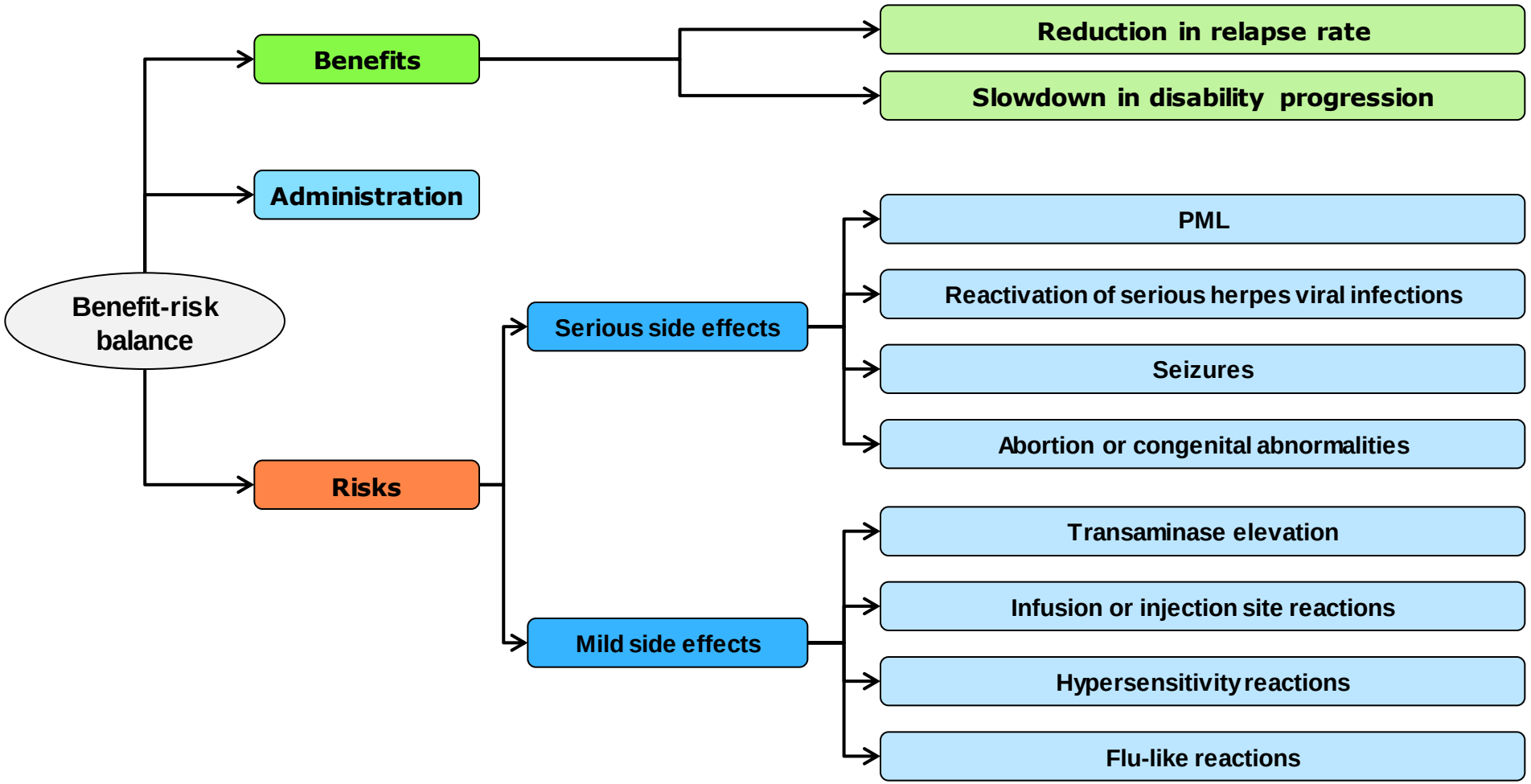
Natalizumab: Value tree



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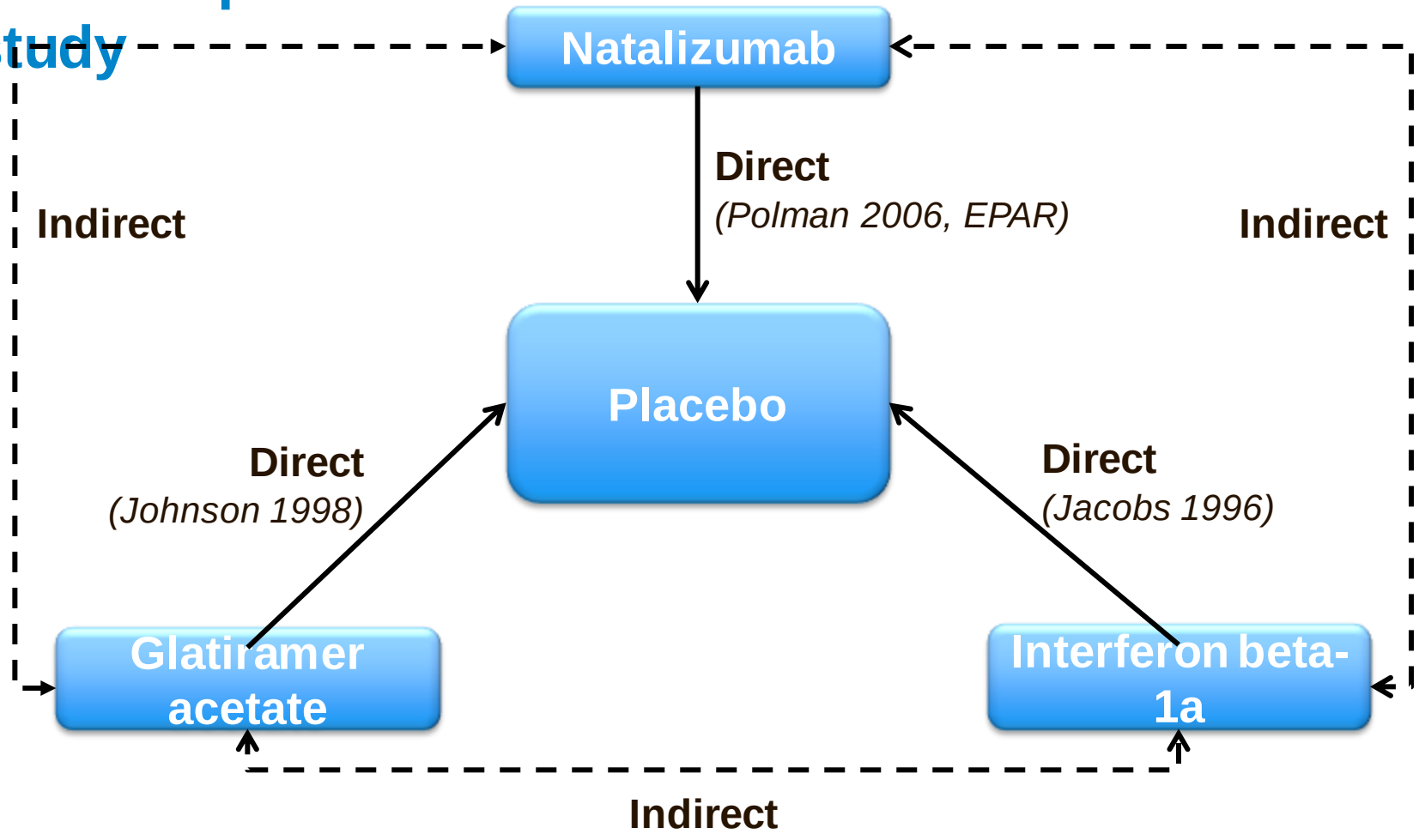
An example of MTC network in the natalizumab case study



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An example of colour-coded tables of data summary

		Outcome	Natalizumab Risk / 1000 pts	Comparator Risk / 1000 pts	Risk Difference (95% CI)/ 1000 pts	
Benefits	Convenience Benefits	Convenience (weight 0.6%)	-	-	-	(-, -)
	Medical Benefits	Relapse (weight 3.9%)	280	450	-170	(-, -)
		Disability Progression (weight 5.6%)	110	140	-30	(-, -)
Risks	Infection	Reactivation of serious herpes viral infections (weight 6.7%)	80	70	10	(-26, 45)
		PML (weight 55.9%)	2	0	2	(-, -)
	Liver Toxicity	Transaminases elevation (weight 11.2%)	50	40	10	(-16, 38)
	Reproductive Toxicity	Congenital abnormalities (weight 5.6%)	-	-	-	(-, -)
	Neurological Disorders	Seizures (weight 5.6%)	0	11	-11	(-23, 0)
	Other	Infusion/Injection reactions (weight 2.8%)	236	312	-76	(-, -)
		Hypersensitivity reactions (weight 1.1%)	90	40	50	(20, 82)
		Flu-like reactions (weight 1.1%)	399	608	-209	(-320, -98)

Higher for Drug A

Higher for Comparator

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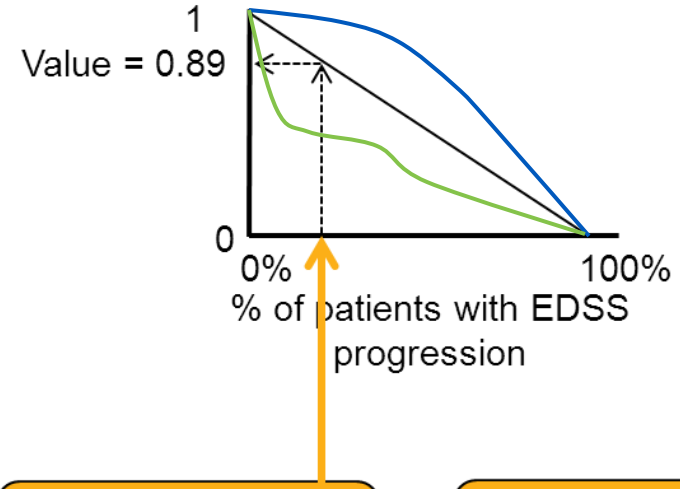
Natalizumab: Weighted utility



Outcome: Disability Progression → **Measure = 11%** → **Value(measure) = 0.89**

Elicited Weight = 5%

BR Contribution = 0.045

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Expected utility for each alternative

Let

w_j = preference weight for criterion j

S_{ij} = utility score for criterion j in alternative i

With constraint $\sum_{j=1}^{k} w_j = 1$ for k number of criteria

Then, the overall expected utility for alternative i is

$$U_i = \sum_{j=1}^{k} w_j S_{ij} = w_1 S_{i1} + w_2 S_{i2} + \cdots + w_k S_{ik}$$

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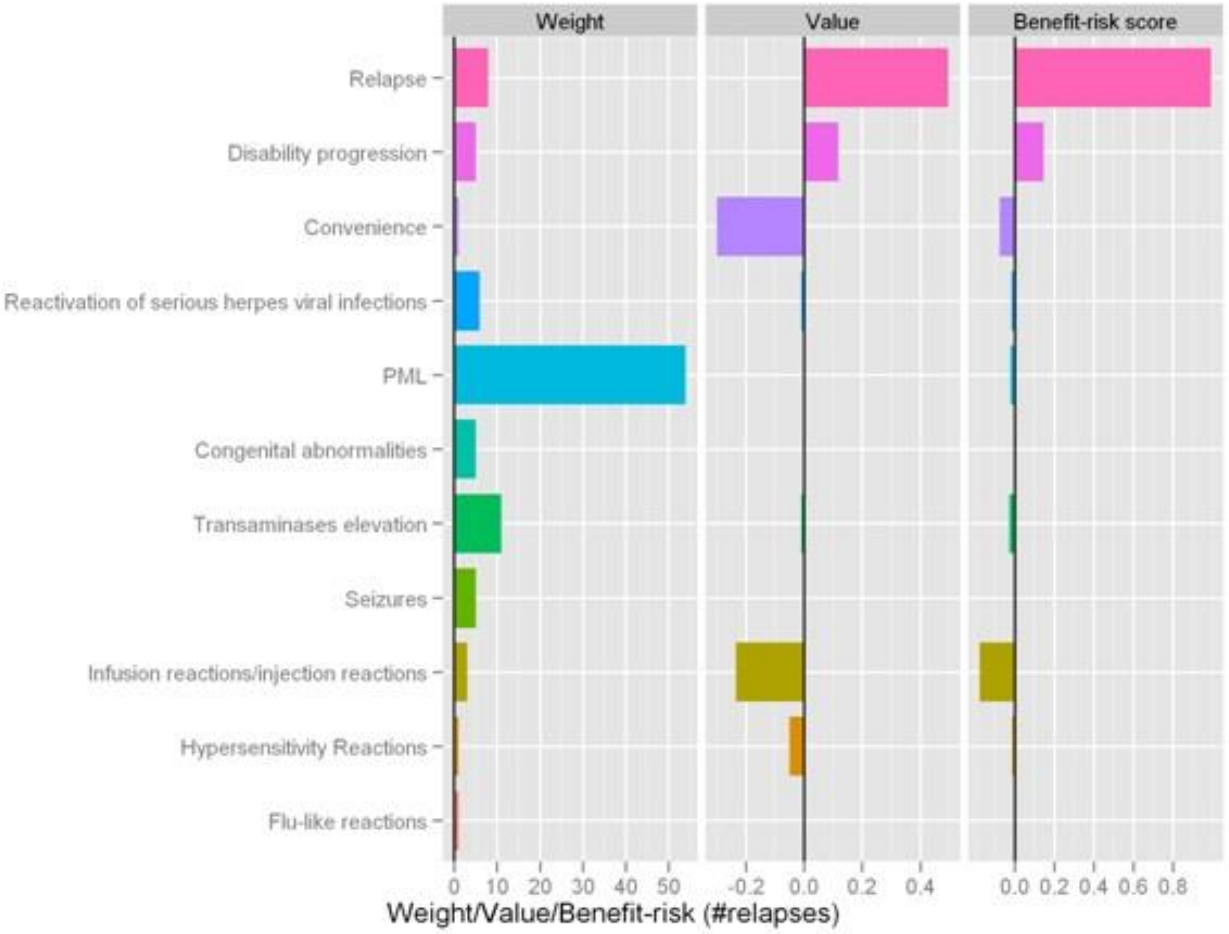
Natalizumab: MCDA weighted utilities analysis

Contribution of each outcome for Natalizumab vs. placebo



- The Benefit-risk is the product of the weight and the value.
- Most of the Benefit-risk contribution is coming from prevention of relapses.
- Infusion site reactions are the worst risk

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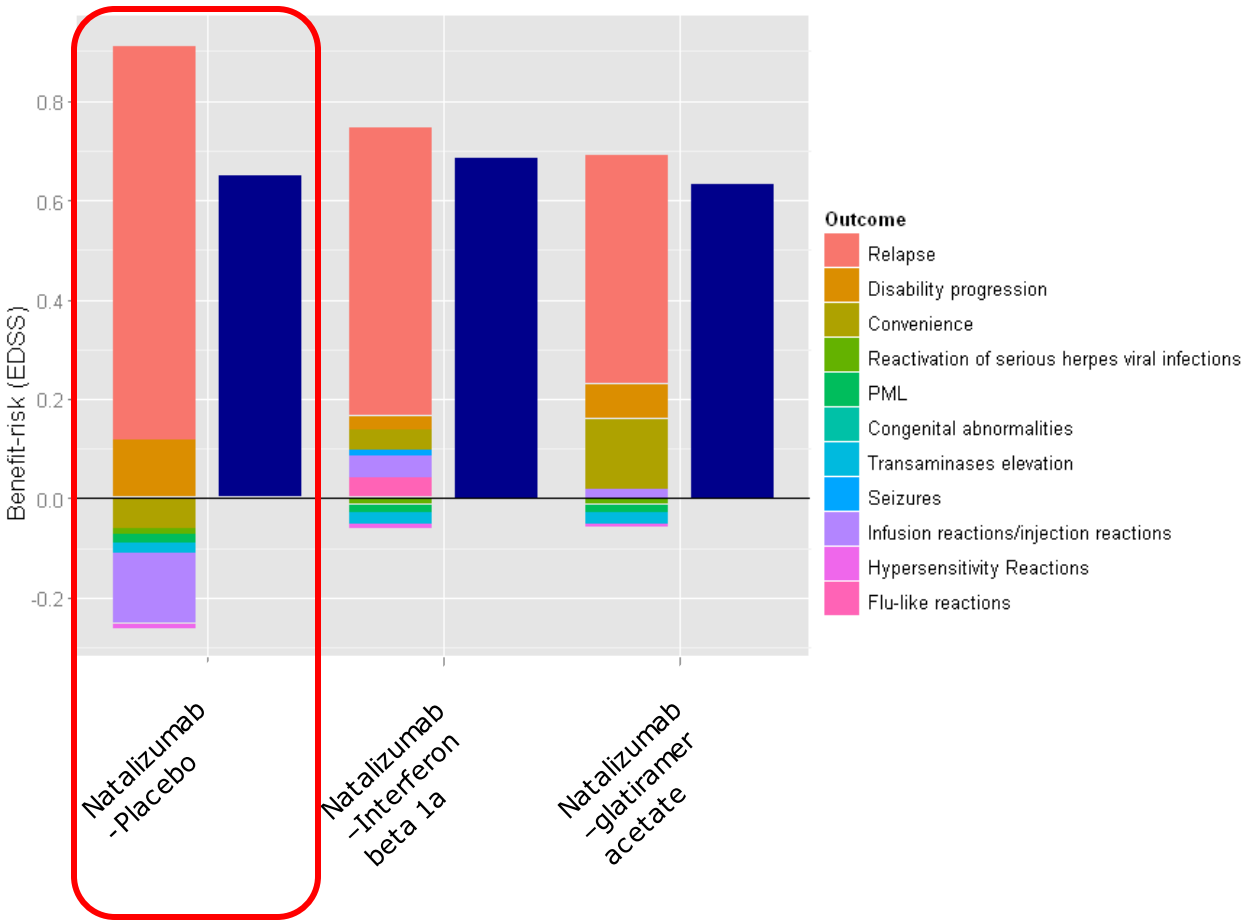
Natalizumab: Criteria contribution

Stacked bar chart for natalizumab vs. all the other treatments.



- Same information shown as a stacked bar chart.
- Positive incremental benefit-risk components above the x-axis and negative ones below.
- Total benefit-risk shown as the dark blue bar.

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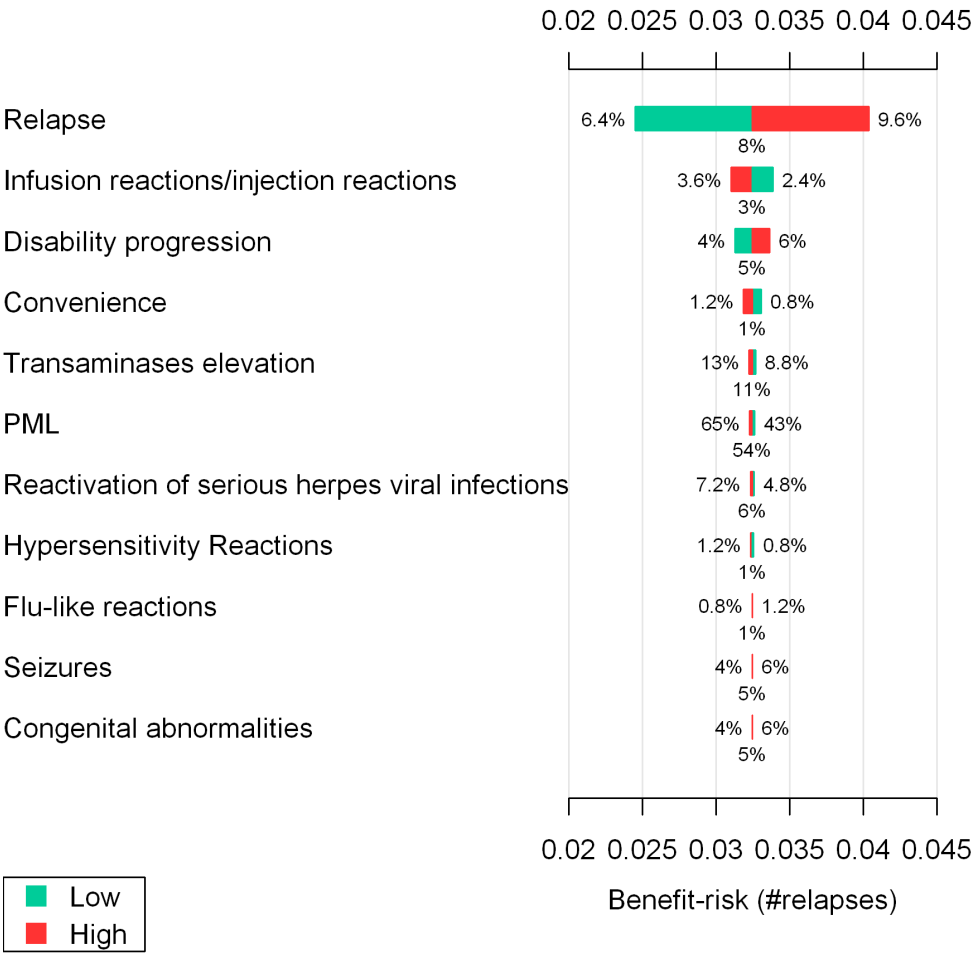
Natalizumab: Uncertainty

Tornado plot for sensitivity to weight: Natalizumab - placebo



- The base case value of the weight for each outcome is shown under each bar.
- The **low values** and **high values** of ±20% change in weight are shown at the ends of the bars.
- The incremental benefit-risk at the base case is the x-axis value at the middle.
- How this changes with each weight is shown by the position of the bar ends.
- From this plot we see that changes in the weight of relapse has the most influence on the benefit-risk score.

tableau SOFTWARE

http://public.tableausoftware.com/views/T_Tornado/T_Tornado

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Decision-making under uncertainty

- Decision-making under uncertainty closely allied with Bayesian statistics for decades, especially in health applications e.g. Raiffa, Schlaiffer, Cornfield, Lindley, Smith AFM, Smith J, Spiegelhalter, Berry, Parmigiani – see Ashby, SiM, 2006 for key references
- Extend uncertainty analysis in a probabilistic model
- Landscape for decisions through entire distributions
- Growing applications but there is still resistance

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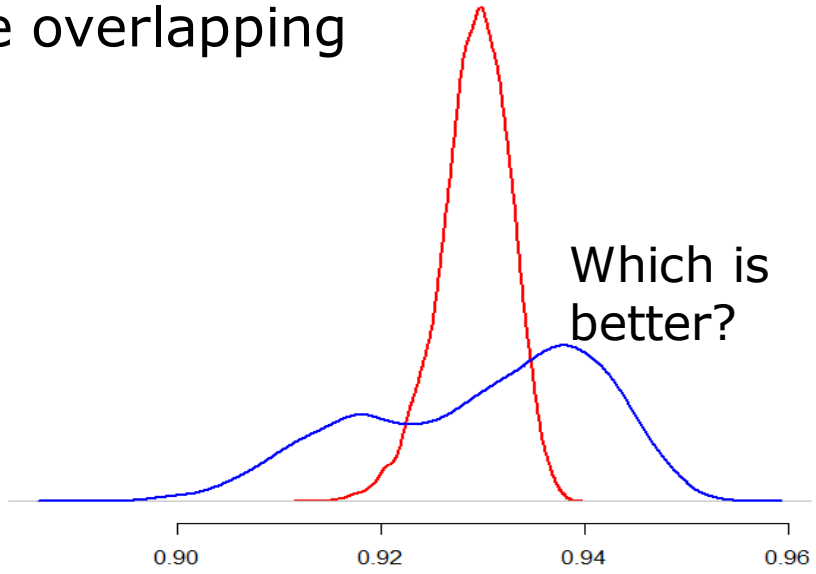
Natalizumab: Probabilistic uncertainty in MCDA

- Extend uncertainty analysis using probabilistic model
  - this allows us to see the distribution of benefit-risk
- Consider how to compare benefit-risk distributions
  - may not be straightforward to choose between treatments when their distributions are overlapping



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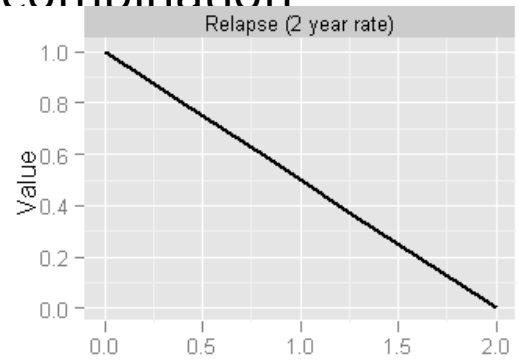
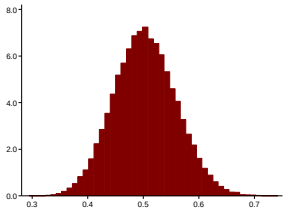
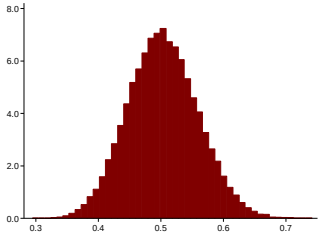
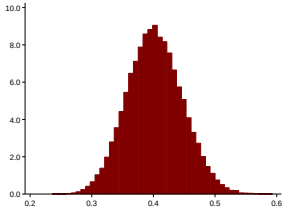
Natalizumab: Probabilistic uncertainty in MCDA

- Bayesian network meta-analysis model for each outcome/treatment combination









Measure:
1.2
(range 0.4 – 1.8)

Partial value:
40%
(range 10% - 80%)

Weight:
7.5%

BR Contribution
3.0%
(range 0.8% - 6.0%)

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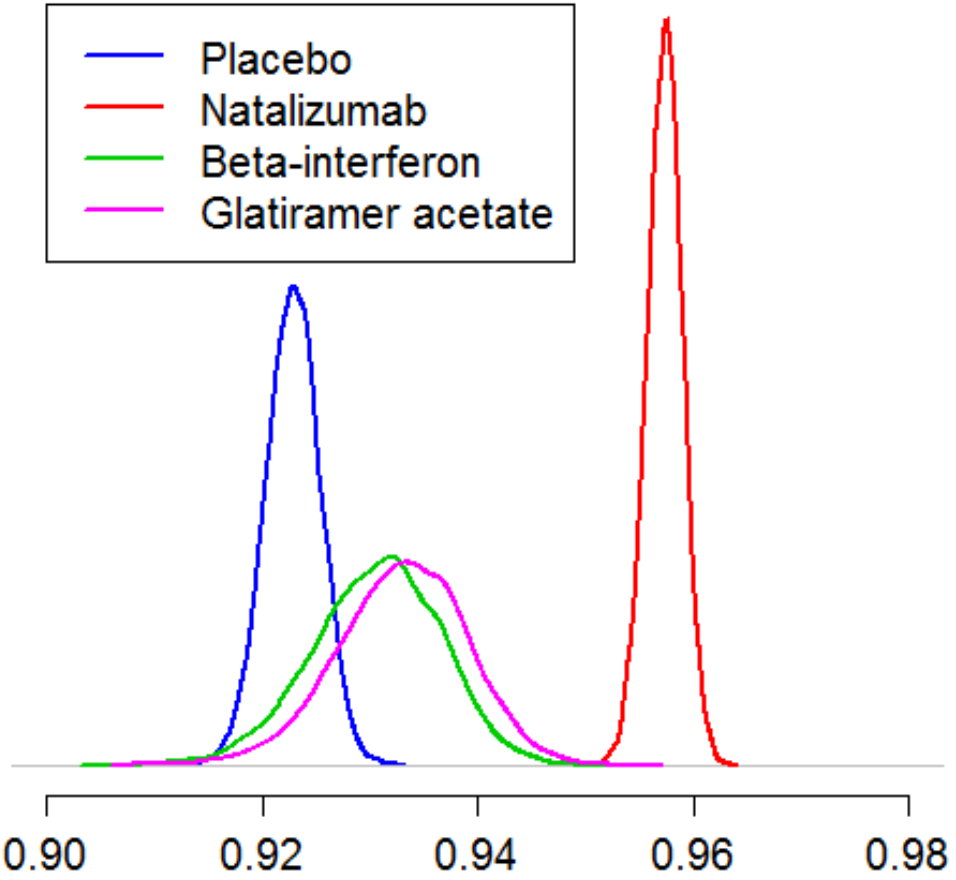
Natalizumab: Probabilistic uncertainty in MCDA

Distribution of overall benefit-risk:

We only allow for clinical parameter uncertainty….

…but the method can in principle be extended to value/weight uncertainty

Provides a sense of the "statistical significance" differences between treatments



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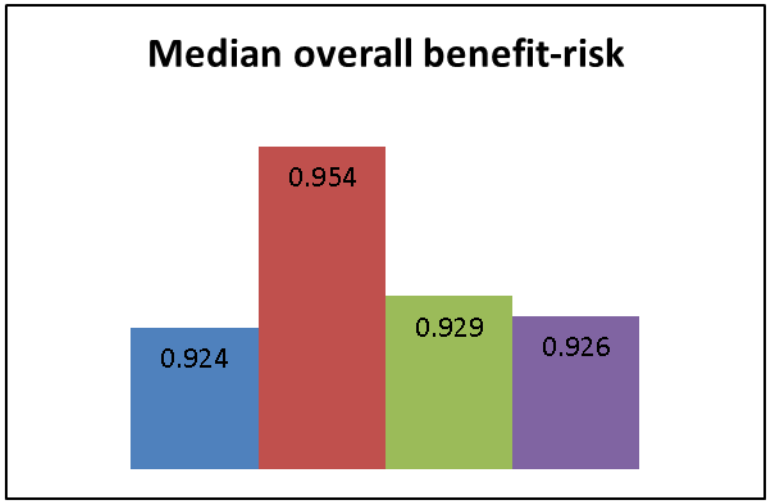
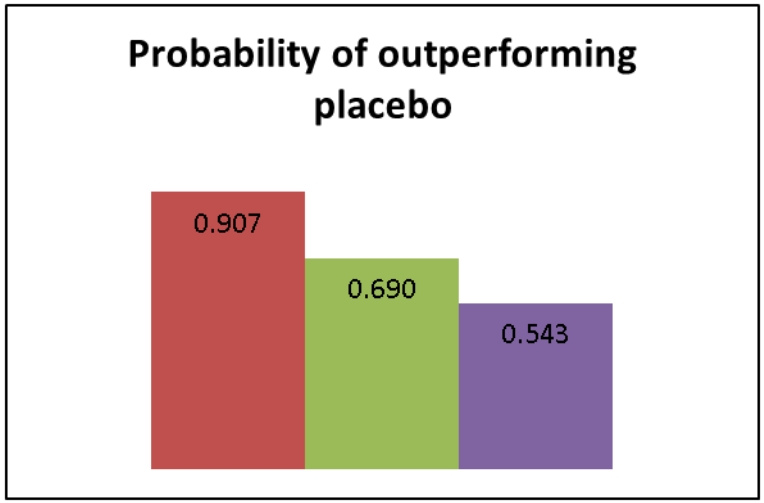
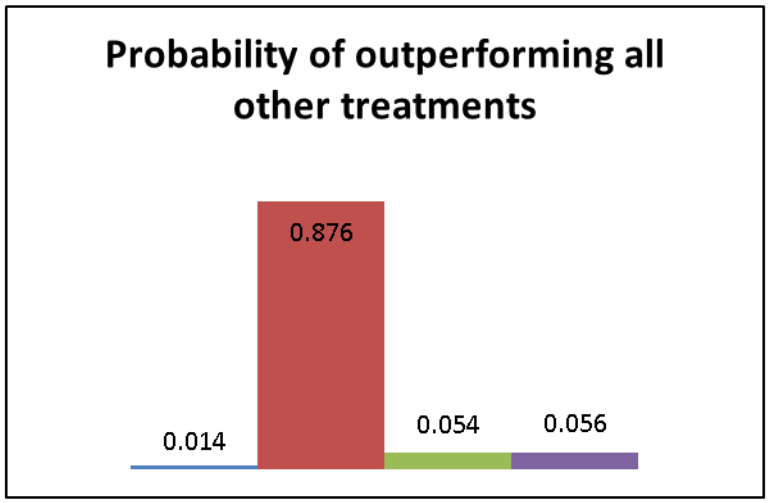
Natalizumab: Probabilistic uncertainty in MCDA







Placebo
Natalizumab
Interferon beta-1a
Glatiramer acetate

Largely consistent rankings
Subtle differences relating to:

- Clinical significance
- Statistical significance
- Ease of communication

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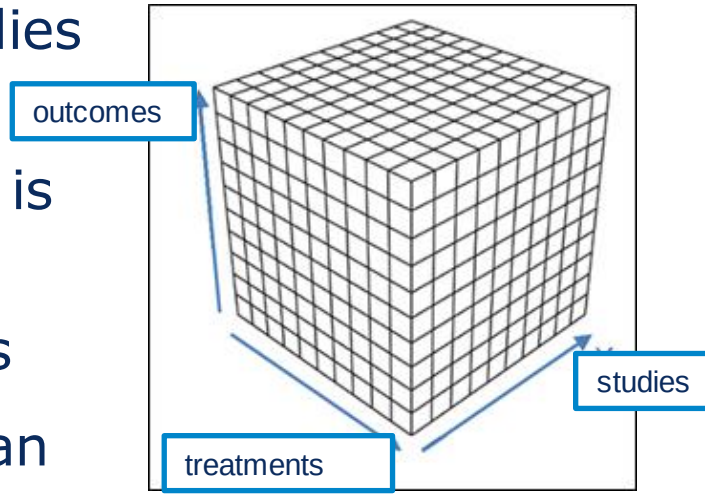
Ongoing PhD – benefit-risk evidence synthesis

- For full spectrum of benefits and risks for all comparators, often need multiple studies
- Some outcomes not reported in some studies, or defined differently -> data is sparse/heterogeneous
- Expect correlations between outcomes
- Multivariate meta-analysis methods can deal with these issues
  - Models allow for relationships/correlations
  - Allows drawing of strength between outcomes to help "fill in gaps" in evidence base



Ed Waddingham, Bayesian statistics in benefit-risk assessment using MCDA

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Weight elicitation

Methods

- Assess three common methods for weight elicitation:
  - MCDA swing-weighting (multi-criteria decision analysis)
  - MACBETH (Measuring Attractiveness by a Categorical Based Evaluation Technique)
  - AHP (Analytic Hierarchy Process)
  - DCE (Discrete Choice Experiment)

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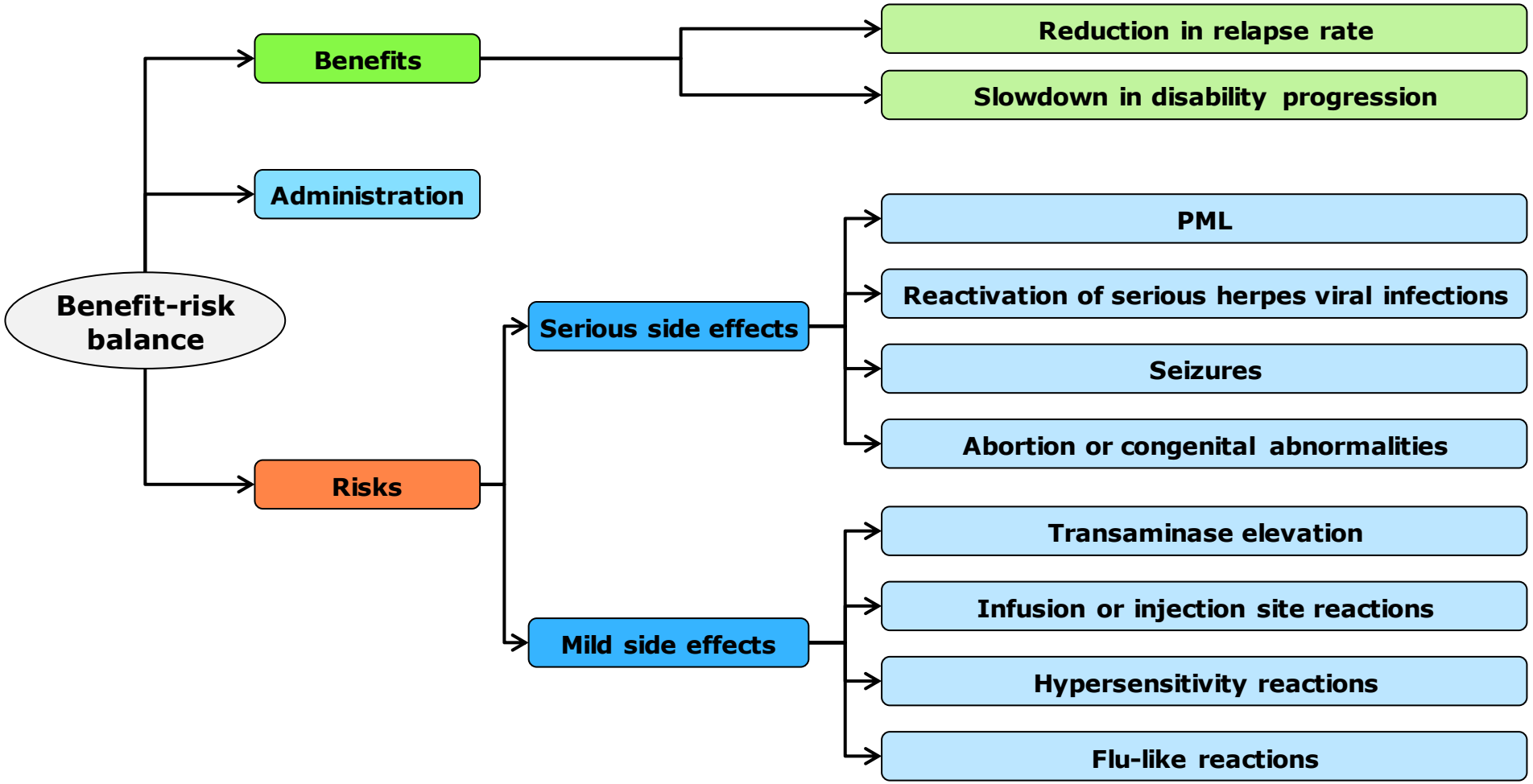
Natalizumab: Value tree



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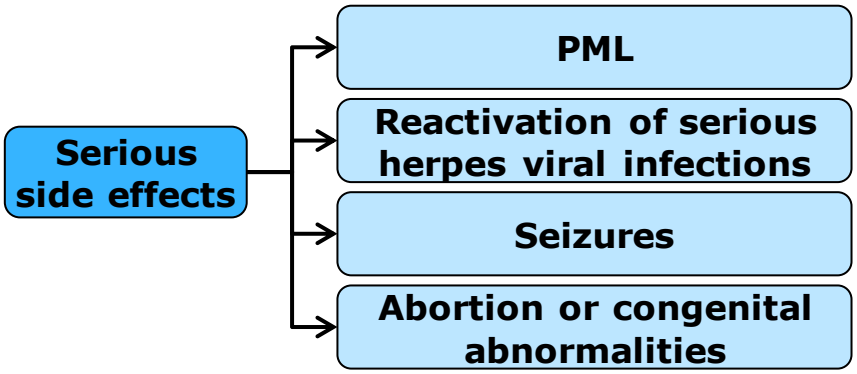
Swing-weighting

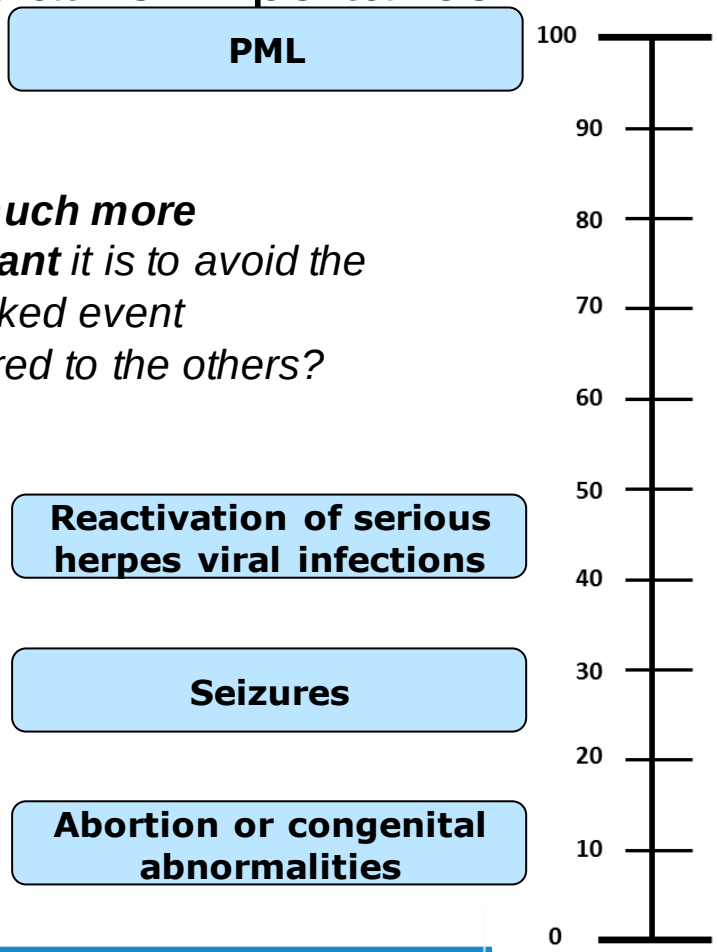
For each outcome category



1. Rank outcomes

Outcome	Rank
PML	1
Reactivation of serious herpes viral infections	2
Seizures	3
Abortion or congenital abnormalities	4

2. Relative importance



PROTECT

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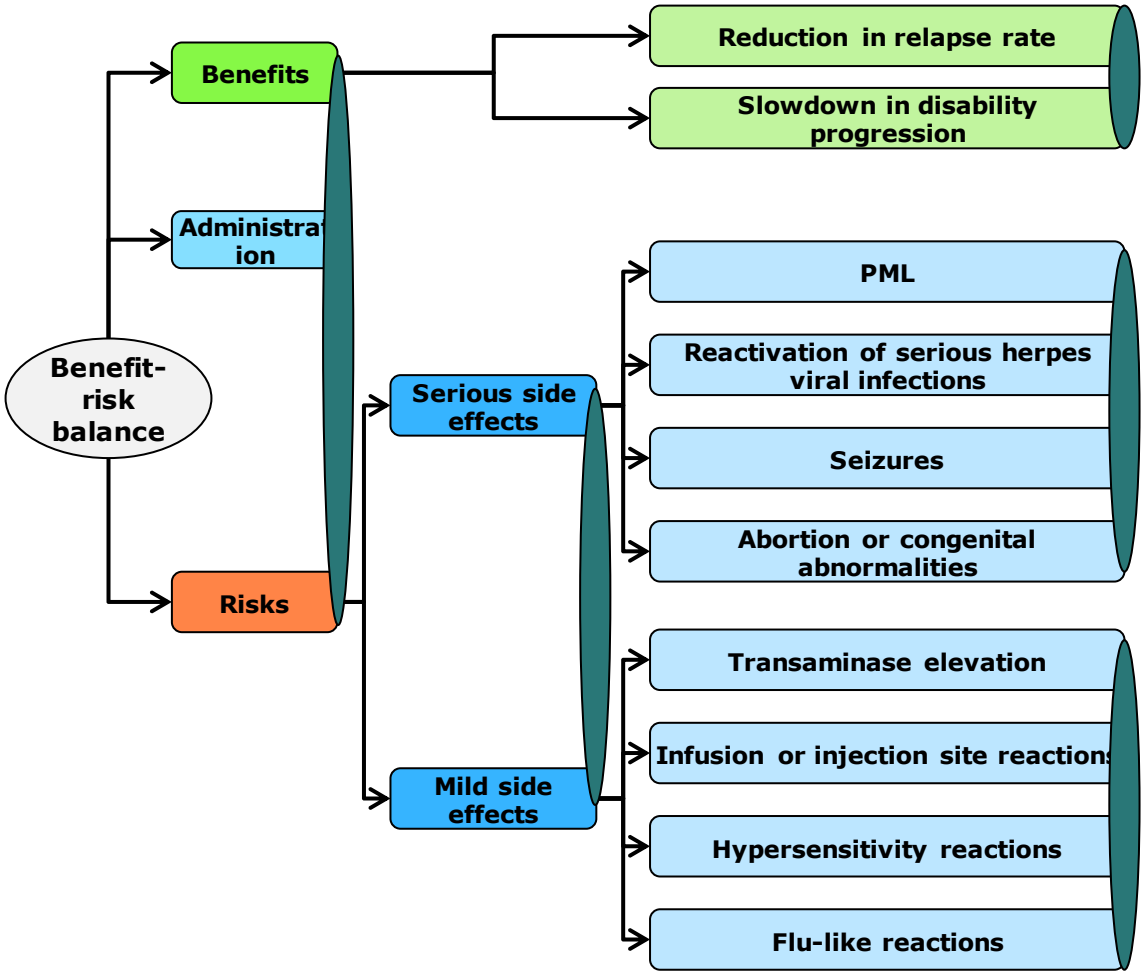
Swing-weighting

The top ranked outcome in each category is carried up the tree



- Move bottom-up through the tree and compare the **top-ranked** outcomes from each category
- Finally, the top-ranked benefit is compared to the top-ranked risk
- The individual weights for each outcome can then be calculated

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MACBETH

- **Step 1:** Qualitatively assess how much more attractive it is to move from worst to best for outcome i vs. moving from worst to best for outcome j and keeping everything else at the worst measure (Do this for each pair of criteria)
- **Step 2:** Check consistency of answers
- **Step 3:** Compute initial guess at weights with optimisation
- **Step 4:** Refine weights while maintaining consistency

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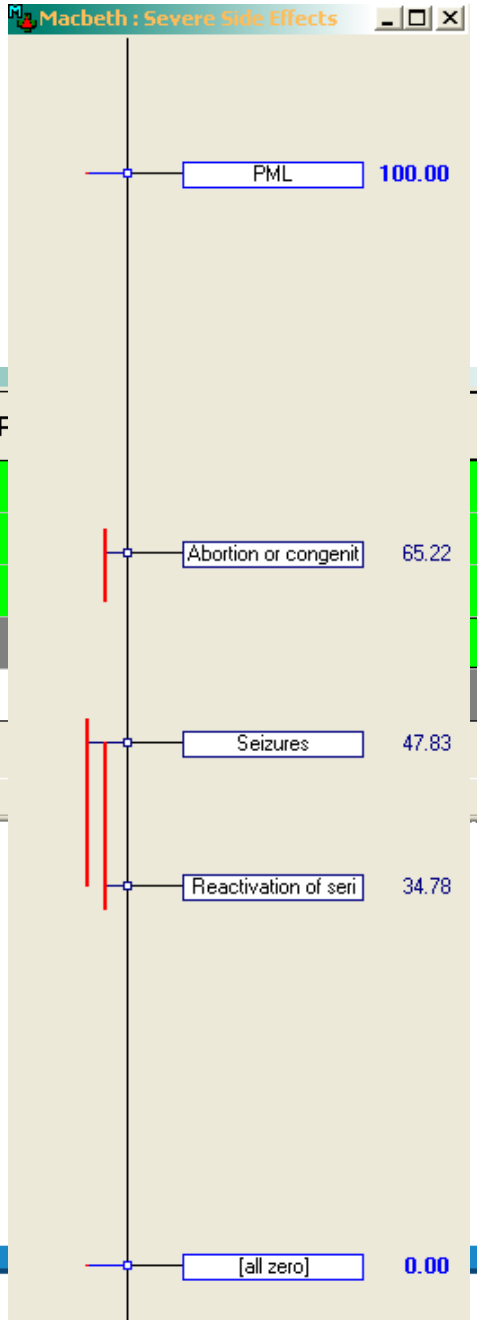
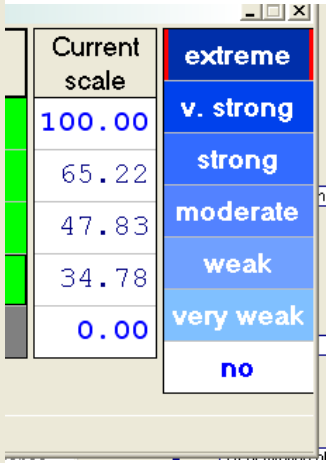
MACBETH

Macbeth : Severe Side Effects

	PML	Abortion or congenit	Seizures	F
PML	no	extreme	extreme	
Abortion or congenit		no	strong	
Seizures			no	
Reactivation of seri				
[all zero]				

Consistent judgements





Fine tuning…

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Analytic Hierarchy Process (AHP)

- Weights are elicited by making pairwise comparisons between criteria
- "How much more important is outcome i vs. outcome j?"
- Must provide number from 1 to 9 on relative scale
- Weight is calculated by finding the dominant eigenvector of the corresponding matrix
- Value functions are computed in a similar manner (do not necessarily come from linear function)
- No consistency check, but rather a score <0.1

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AHI

	PML (A)	Reactivation of serious herpes viral infections (B)	Seizures (C)	Abortion or Congenital abnormalities (D)
PML (A)				
Reactivation of serious herpes viral infections (B)				
Seizures (C)				
Abortion or Congenital abnormalities (D)				

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	Swing-weighting	MACBETH	AHP
Responses	Quantitative	Qualitative	Quantitative
Consistency	N/A	Inconsistencies must be resolved	Computes a consistency score
Weight calculation	Direct	Linear optimisation (plus tuning)	Principal eigenvector

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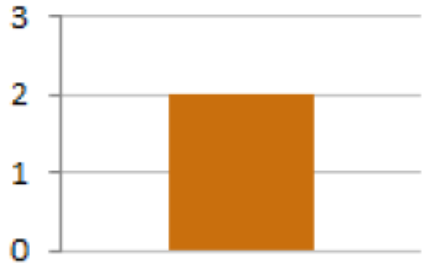
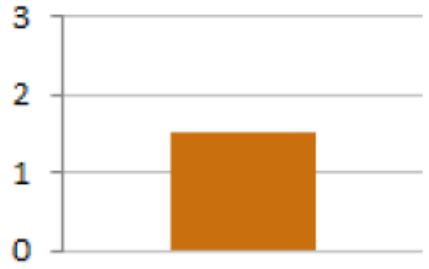
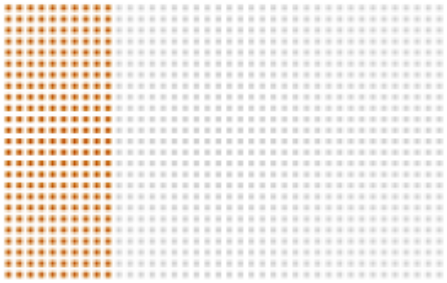
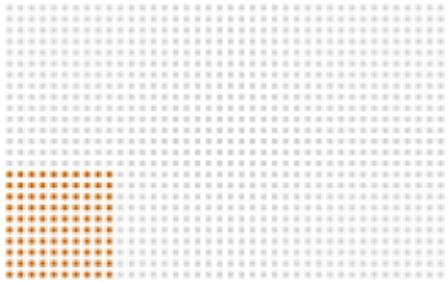
Natalizumab: Discrete choice experiment(1)

Outcome *(measured over 2 years)*	Treatment A	Treatment B
Number of relapses per patient	2 relapses 	 1 to 2 relapses
Disability progression	250 patients out of 1000 	 100 patients out of 1000
PML	3 patients out of 1000	0 patients out of 1000

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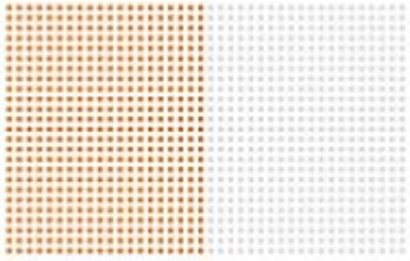
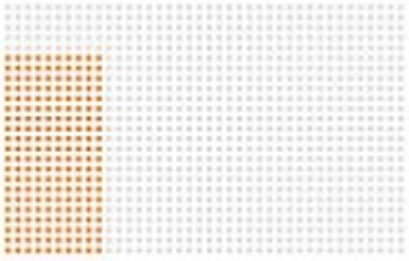
Natalizumab: Discrete choice experiment(2)

Mild allergic reactions	0 patients out of 1000			500 patients out of 1000
Serious allergic reactions	0 patients out of 1000			0 patients out of 1000
Depression	200 patients out of 1000			100 patients out of 1000
Which would you prefer? *(Please tick one)*	☐ **Treatment A**		☐ **Treatment B**	

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Preference elicitation – questions remain

- Several methods available – **which** one(s) to use?
- **Whose** preferences – patients? Clinicians/experts?
- **What** to do about multiple viewpoints?
  - Build consensus in group setting?
  - Aggregate individual responses?
- **How much** heterogeneity is there?
  - …within a single elicitation study?
  - …between studies?

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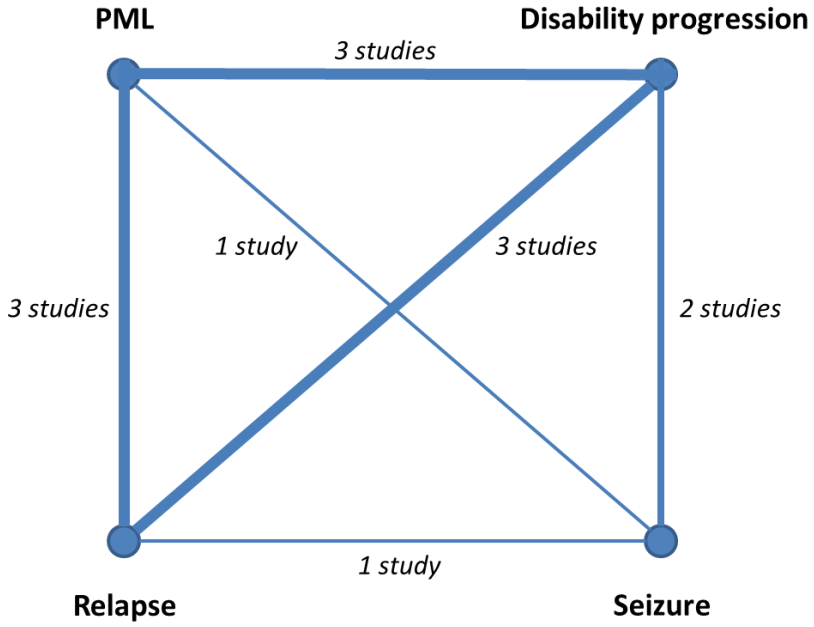
Meta-analysis of previously elicited preferences

- Ongoing PhD work (Ed Waddingham)
- Extract preference ratios from source studies and combine using model analogous to network meta-analysis
- Examine heterogeneity
- Aggregate results

(if appropriate)



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Remarks

- This is still work in progress…
- Eliciting patient preferences in regulatory assessment can add value and lead to more clinically relevant decisions
  - Political legitimacy, transparency, trust, communicability
- Many different formal methods of benefit-risk assessment can be used to elicit patient preferences
  - Each methodology has its own unique features, strengths and weaknesses: further exploration needed
- A focus on the process(es): feasibility and validity?
- IMI PREFER now building on this work

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Patient and public involvement

Patient and public:

Clinical trial participants, patients and potential patients, disabled people, parents and guardians, people who use health and/or social care services, carers, members of the public, and the organisations who represent the interests of these consumers.

Involvement:

An active partnership between stakeholders in the research process, rather than the use of people as ‘subjects’ of research. Public involvement in research is often defined as doing research ‘with’ or ‘by’ the public, rather than ‘to’, ‘about’ or ‘for’ them.

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Varying stages, varying degrees

- **Varying stages:** Where can PPI be applied to benefit-risk decision-making methodologies?
  - All the way through, or specific stages
  - E.g. (a) the selection, inclusion and exclusion of relevant outcome measures, or (b) the ranking and weighting of outcome measures
- **Varying degrees:** How much of an active role patients and the public should take in the decision-making process?
  - Consultation: health professionals elicit the patient and public perspective to inform the decision-making stage or entire decision-making process
  - Collaboration: health professionals and patients and the public form an active partnership and jointly participate in the decision-making stage or entire decision-making process

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Recommendation Roadmap

Planning

- critical issues
- think & discuss purpose and context
- documentation
- foundations for future analyses and updates

Evidence gathering and data preparation

- relevant evidence
- data collection
- data aggregation
- missing/incomplete data

Analysis

- Evaluate data
- Quantify benefits and risks
- Weigh or integrate

Exploration

- robustness
- sensitivity
- assumptions and uncertainties
- other consequences
- impact or added value to the RMPs

Conclusion and dissemination

- communicate results/consensus
- any influence on future actions
- transparent audit trail
- ensures "big picture" is not lost

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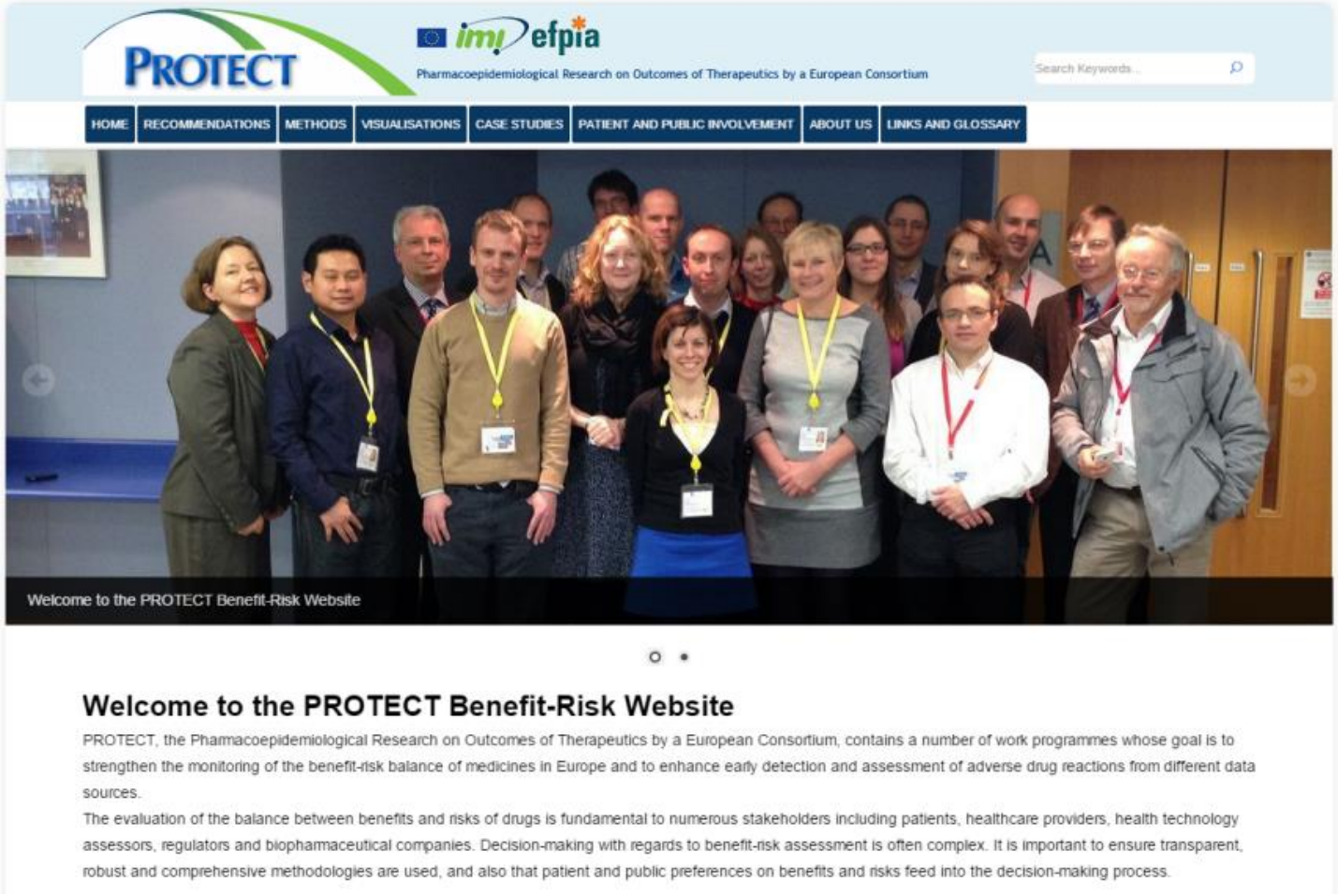
Dissemination and recommendations arising from PROTECT



http://PROTECTBenefitRisk.eu/

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EMA Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (PROTECT): Results and their impact on regulatory practice 2016

6.10.3. Future use

- "This work has "cleaned" this field and is a cornerstone for future research. There will be a "before" and an "after" PROTECT, even if it is difficult to state at this stage what will be the practical applications in regulatory practices. PROTECT has shown that they can be used in practice. It is noteworthy that in the survey these two outputs were found to have a high level of readiness for implementation and were reported to have a high impact. There is however a sharp difference between regulators and other participants. This difference may reflect some of the respondents' *willingness* for these outputs to have an impact."

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ICH-E9 Statistical Principles for Clinical Trials 1998; *my suggested update 2018.....*

GLOSSARY

Bayesian Approaches: Approaches to data analysis that provide a posterior probability distribution for some parameter (e.g. treatment effect), derived from the observed data and a prior probability distribution for the parameter. The posterior distribution is then used as the basis for statistical inference *and decision-making, in combination with appropriate measures of utility*.