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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

IMI PROTECT Case Study: Structured Benefit-Risk Applied to Natalizumab

European Statistical Meeting
EFSPI/PSI
Structured Benefit-Risk Assessment

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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."

Acknowledgments

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Decide on a Multiple Sclerosis treatment

Three outcomes are important to you

- For two treatments given over a two-year period the proportion of patients experiencing each of three outcomes is:

	Treatment A	Treatment B
Disability progression	40%	30%
Flu-like reaction	5%	3%
PML*	0%	0.5%

- Which treatment would you choose?
  - How often does each outcome occur?
  - How important is each outcome if it occurs?
- In real life the decision is more complex
  - Which **outcomes** do you choose to make the decision?
  - Which **treatments** do you choose between?
  - How do you assess how **important** each outcome is to you?

 * PML: Progressive multifocal leukoencephalopathy

Fundamental principles of benefit-risk

Built on methods to support decision making

- **Represents a framework, not a recipe**
  - A tool to support decision makers, not an algorithm to replace them.
  - Helps a team develop a common understanding of what is of central importance.
  - Process to structure and analyze information.
  - Visualization tools to communicate benefit-risk.
- **Built on well-established Decision Analysis principles**
  - Promotes traceability, transparency and consistency.
- **Communication tool for internal decision making and sponsor – health authority alignment**
  - Consolidated view of key benefit and risk outcome measures.
- **Provides a structured framework for a drug through its lifecycle**

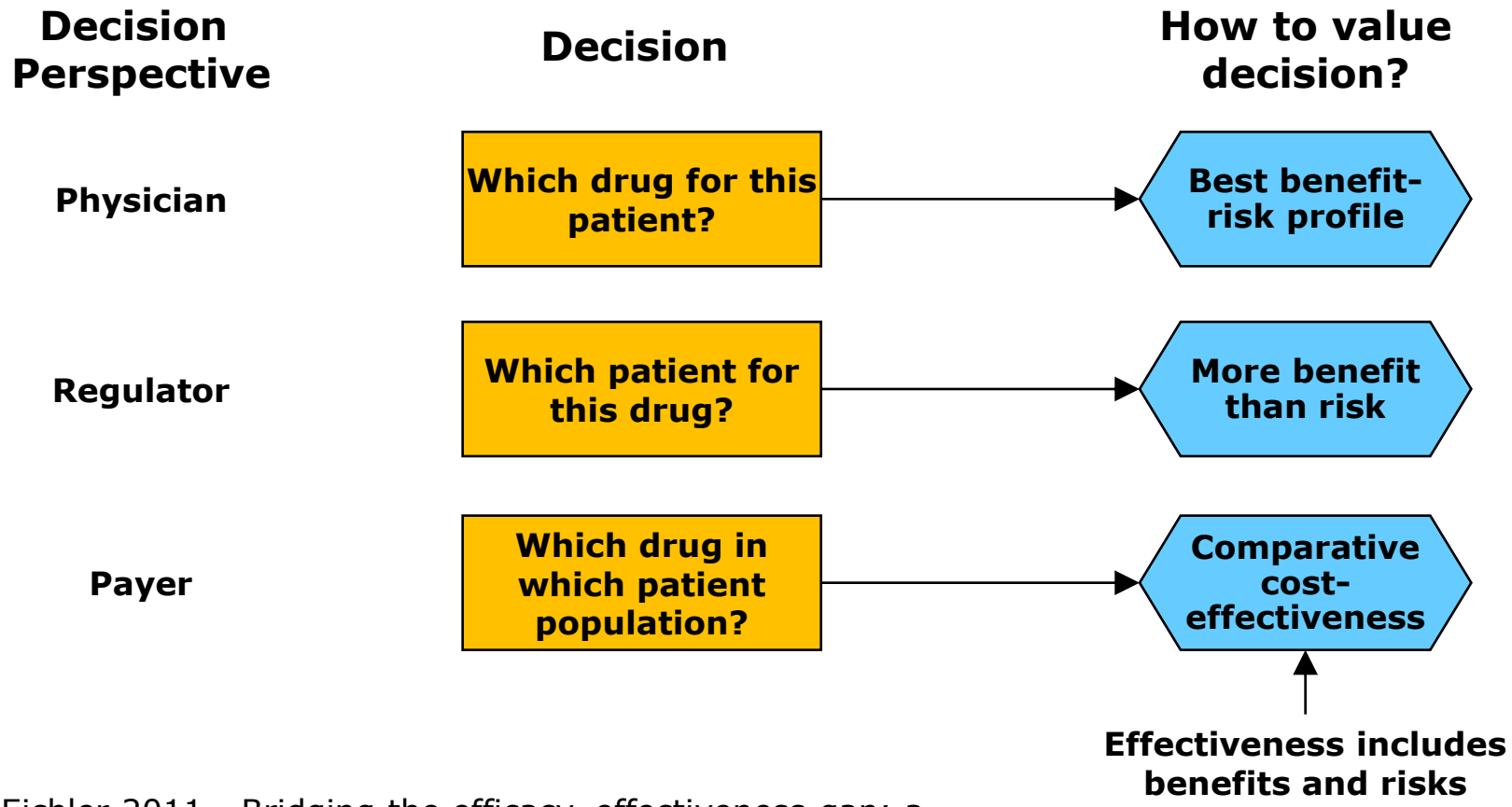
Structured benefit risk assessment - increasingly important role in the regulatory environment

- **Major HAs actively developing benefit risk assessment approaches to increase transparency of decisions**
  - FDA: PDUFA V commitments include use of structured benefit risk assessment in review of NME NDAs and original BLAs as of 2014.
  - EMA: Benefit Risk Methodology project to improve/standardize benefit risk decision making at EMA and in Member State HAs is an EMA priority for 2013.

"The benefit risk assessment represents the most crucial part of assessment report." - *EMA day 80 assessment report guidance:*

- **PSUR**: inclusion of a structured benefit-risk section is now mandatory (EU requirement).
  - "The benefit-risk evaluation should be presented in a **structured manner**...."

Benefit-risk is central to key decisions



Eichler 2011 - Bridging the efficacy–effectiveness gap: a regulator's perspective on addressing variability of drug response

IMI (Innovative Medicines Initiative) PROTECT

- PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium)
  - Collaborative European project coordinated by the EMA
  - Multi-national consortium of 32 partners including academics, regulators, and pharmaceutical companies

- Work program 5 is focusing on **benefit-risk integration and representation**
  - This includes case studies to evaluate various **frameworks** and **quantitative methods** for benefit-risk assessment

Natalizumab – A short history

- Natalizumab was approved in 2004 by the FDA for the treatment of relapsing remitting multiple sclerosis (RRMS).
- In 2005 the drug was suspended because of an associated incidence of progressive multifocal leukoencephalopathy (PML), a rare neurological disorder.
- In 2006 it was re-introduced due to patient demand, but with strict risk minimization measures.
- In 2009, due to occurrence of further PML in monotherapy post marketing, CHMP reassessed the PML risk of Tysabri and confirmed the current approval.

The historical context

Built on methods to support decision making

- Structured benefit-risk analysis is a relative new idea in drug development, but is build on well established ideas
  - Daniel Bernoulli (1738) – Expected Utility hypothesis
  - Von Neumann and Morgenstern (1944) - Game theory and Economic Behaviour
  - Keeney and Raiffa (1976) - Multi-attribute value theory

The BRAT* Framework for benefit-risk

Six step process

*Benefit Risk Action Team

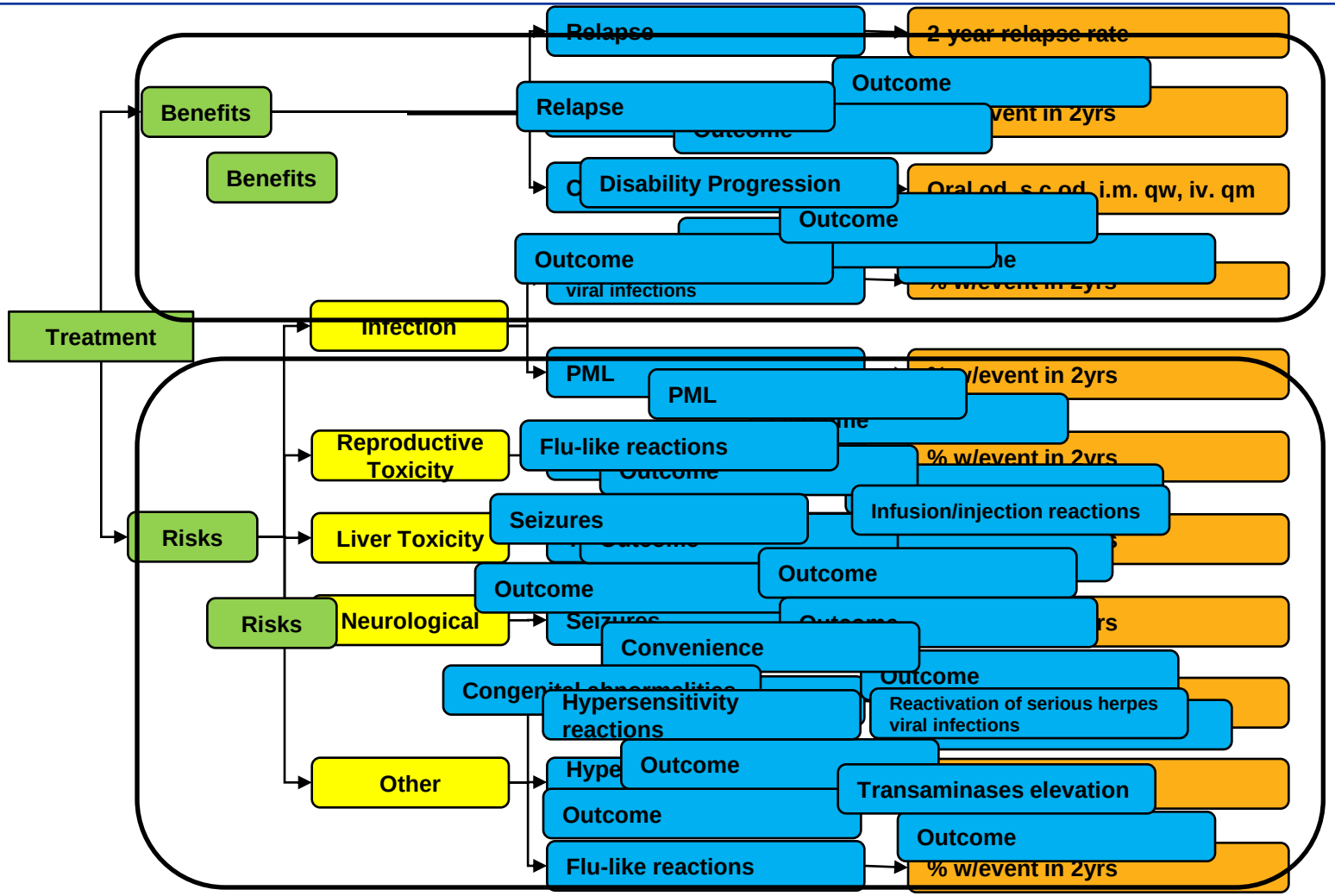
1) Define a decision context

Sets the frame of the structured benefit-risk assessment

Objective	**Should natalizumab be kept on the market given that episodes of PML are observed?**
Indication	**Relapsing remitting multiple sclerosis**
Population	**Adults with relapsing remitting multiple sclerosis**
Drug	**Natalizumab, 300mcg, iv, qm.**
Comparative Treatment Alternative(s)	**Placebo, Interferon beta-1a, 30mcg, im, qw Glatiramer acetate, 20mg, sc, qd**
Time Horizon	**Two years. For PML fives year as it takes longer to manifest.**
Stakeholder perspective	**EMA**

2) Identify key benefits and risks

Organize the key outcomes driving the benefit-risk in a value tree



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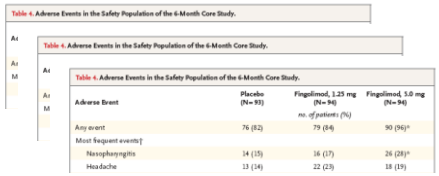
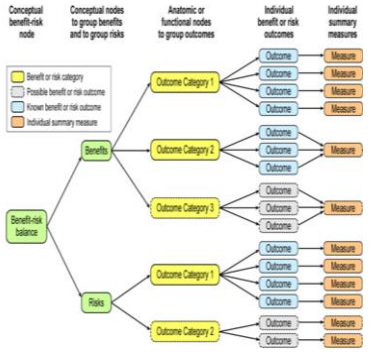
3) Consolidate source data

Pool clinical data from internal and external studies

Identify	Select	Extract	Aggregate
Search strategy Search query	Study eligibility criteria	Extraction guidelines	e.g. meta-analysis, placebo-calibration
PubMed.gov US National Library of Medicine National Institutes of Health Drugs@FDA FDA Approved Drug Products EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH			
Study worksheet		Data source table	Data summary table
one row per study		one row per study/treatment/outcome	one row per outcome

4) Customize and communicate

Re-visit key benefits and risks

- **The benefit-risk process can be iterative.**
- **The key benefits and risks may need to be "tuned".**
  - Changes outcomes in value tree if data are not available.
  - Outcome measures may be refined in response to how data are measured.
- **Guard against bias.**
  - Changing the value tree in response to observed data could bias the benefit-risk balance.

4) Customize and communicate

Effects table of key benefits and risks

		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	540	-260	(-326, -195)
		Disability Progression (weight 5.6%)	110	230	-120	(-, -)
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	0	0	(-, -)
	Other	Infusion/Injection reactions (weight 2.8%)	236	180	56	(6, 114)
		Hypersensitivity reactions (weight 1.1%)	90	40	50	(20, 82)
		Flu-like reactions (weight 1.1%)	399	400	-1	(-114, 114)

Higher for Natalizumab

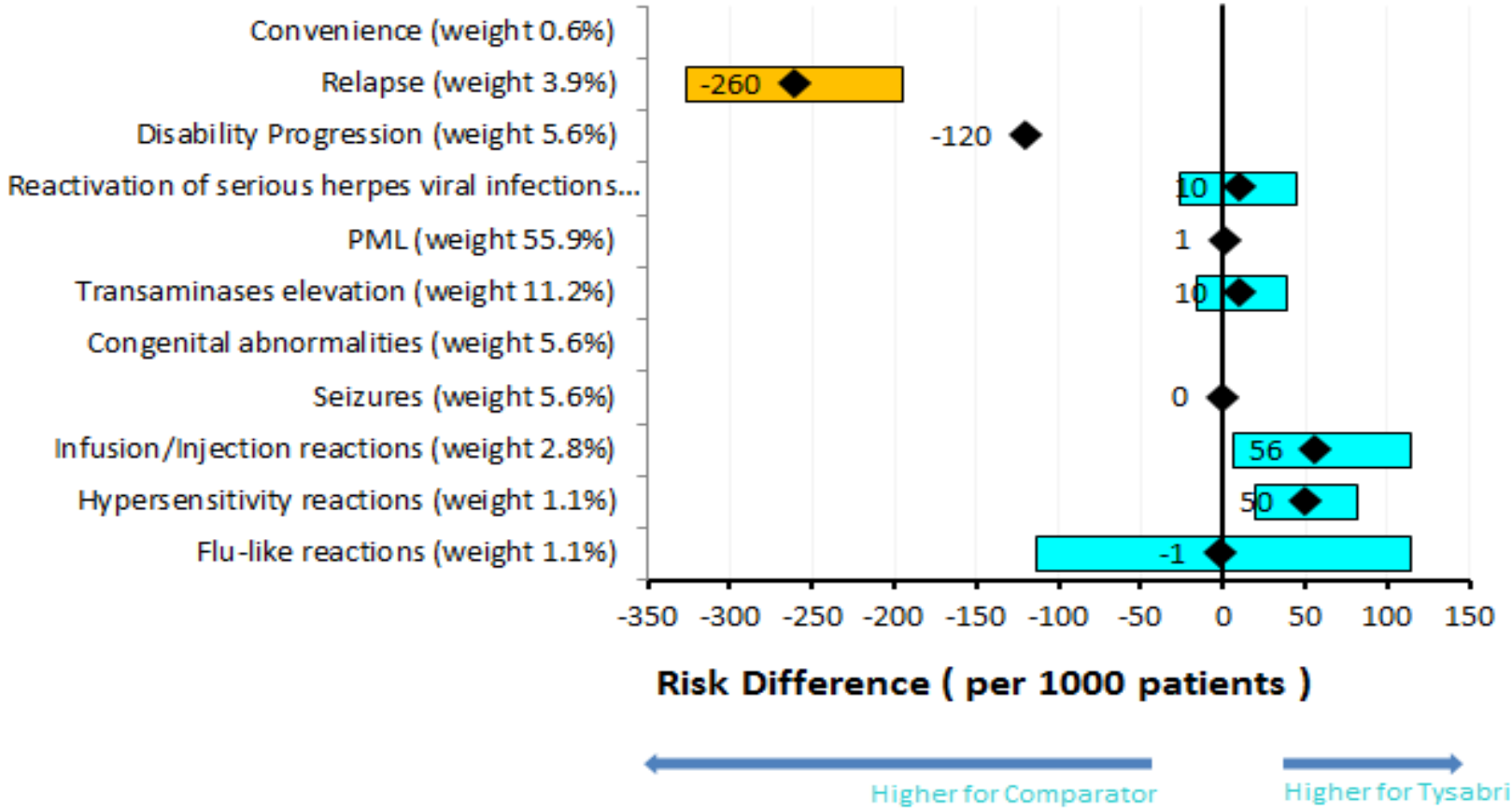
Higher for Comparator

- Summarize in one place all the benefits and risks data that are driving the decision

4) Customize and communicate

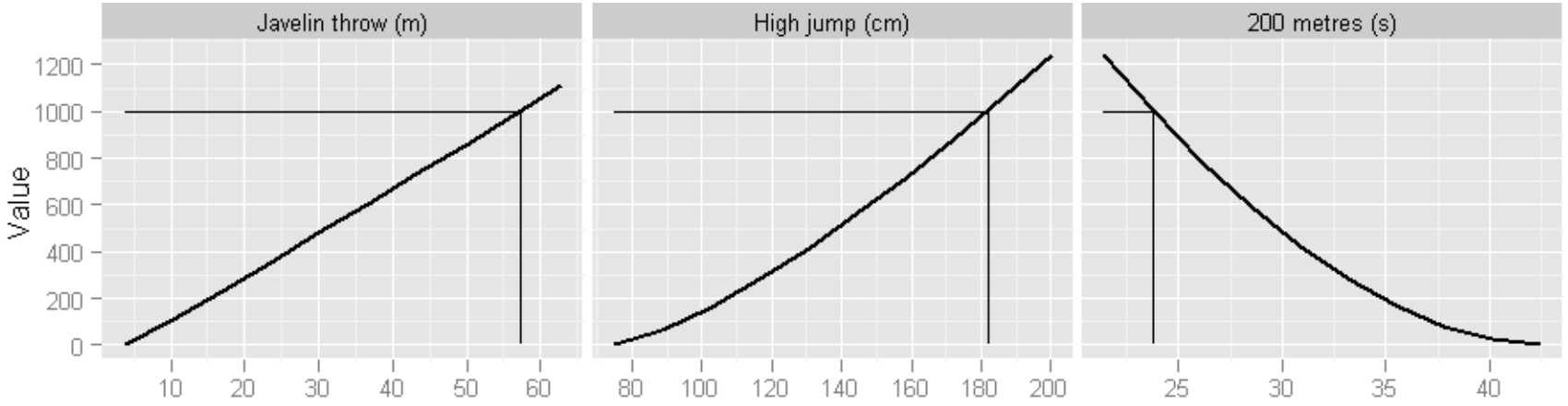
Effects table of key benefits and risks

Forest Plot



5) Assess outcome importance

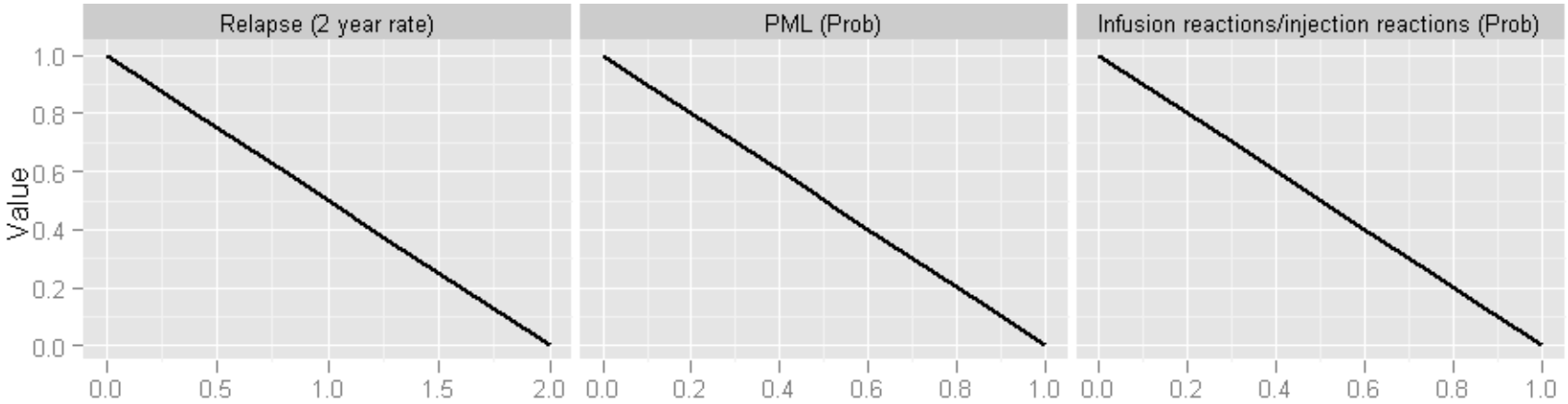
MCDA and the Women's heptathlon



Event	Jessica Ennis	Value	Lilli Schwarzkopf	Value	Tatyana Chernova	Value
Javelin throw (m)	47.49	812	51.73	894	46.29	789
High Jump (cm)	186	1055	183	1016	180	979
200 metres (s)	22.83	1096	24.77	909	23.67	1013
Total		**2963**		**2819**		**2781**

5) Assess outcome importance

MCDA and multiple sclerosis drugs

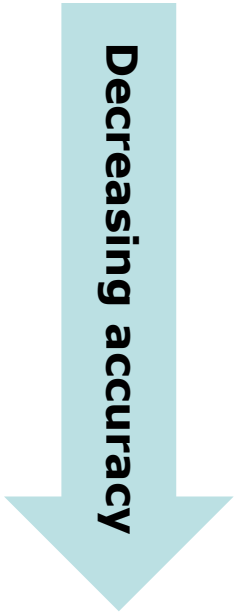


		Placebo			Natalizumab		
Outcome	**Weight**	**Measure**	**Value**	**Benefit-risk**	**Measure**	**Value**	**Benefit-risk**
Relapse	8%	1.46	0.27	0.022	0.47	0.766	0.061
PML	54%	0	1	0.54	0.0015	0.998	0.54
Infusion reactions injection reactions	3%	0	1	0.03	0.24	0.764	0.02
Total				**0.59**			**0.62**

6) Benefit-risk communication

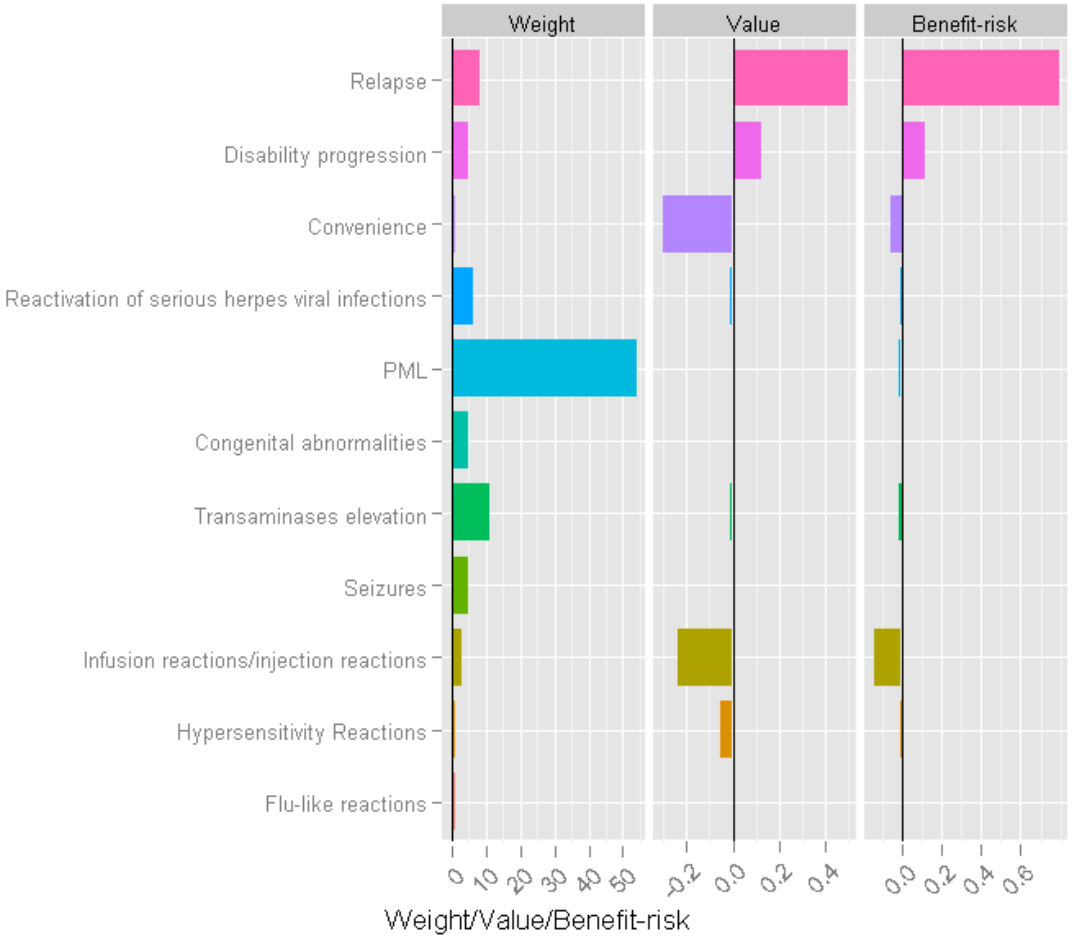
Visualization of benefit-risk. Functional and perceptual tasks

- **Carswell (1992) taxonomy of functional tasks**
  - Point reading (reading one value on a graph)
  - Local comparison (reading and comparing two values on a graph)
  - Global comparison (reading and comparing more than values simultaneously on a graph)
  - Synthesis judgment (extrapolating information beyond what is explicitly shown on a graph)
- **Cleveland and McGill's (1984) perceptual tasks**
  - Position on common aligned scale (e.g. bar charts)
  - Position on common non-aligned scales (e.g. scatter plots)
  - Length (e.g. stacked bar charts)
  - Angle (e.g. pie charts)
  - Area (e.g. circles, blobs)
  - Volume (e.g. cubes)
  - Colour (e.g. coloured circles)
- **Tufte (2001) -** Ink should be reserved for data



Drill down to the values and the weights

Incremental benefit-risk of natalizumab – placebo



- This shows which outcomes are contributing most to the total benefit-risk.
- Even thought the weight given to PML is large, the incidence is small, leading to a small contribution to the benefit-risk.

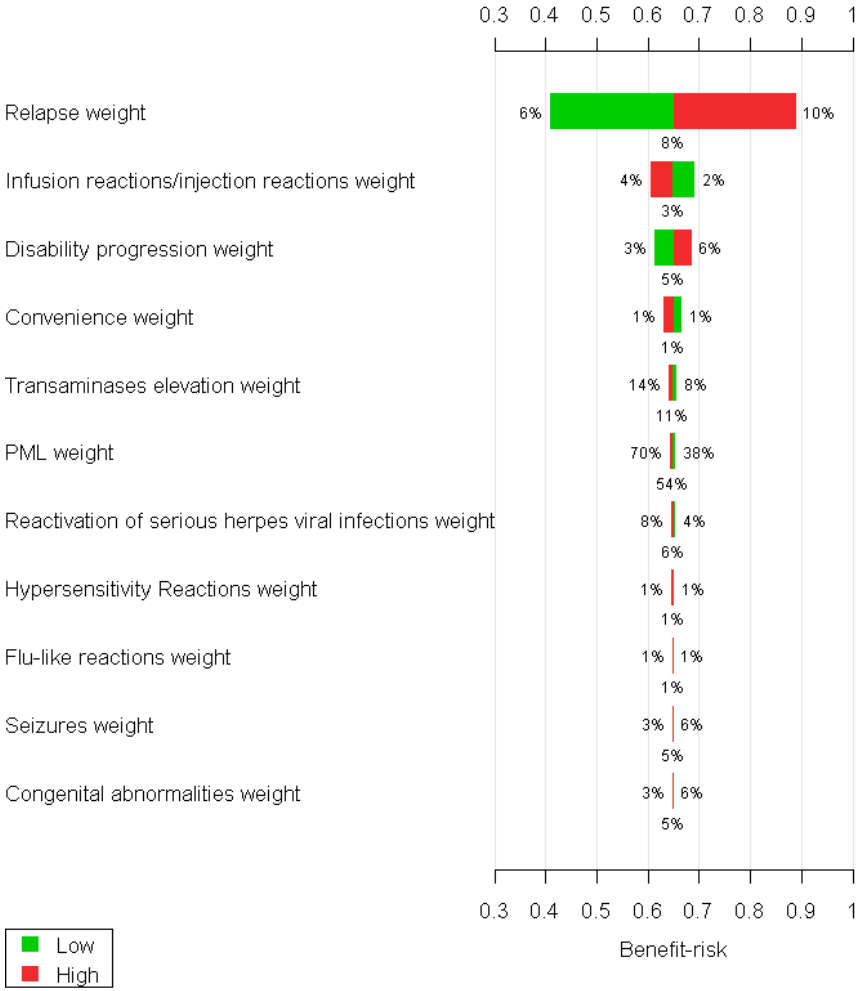
Waterfall plot

Incremental benefit-risk of natalizumab – placebo

- The length of each bar gives the contribution to the overall BR.
- End of the last bar gives the overall benefit-risk.
  - Denominated in the BR of one EDSS progression
- Green = positive BR.
- Red = negative BR.
- The contribution to the overall BR of PML is very small.

Sensitivity analysis on the weights

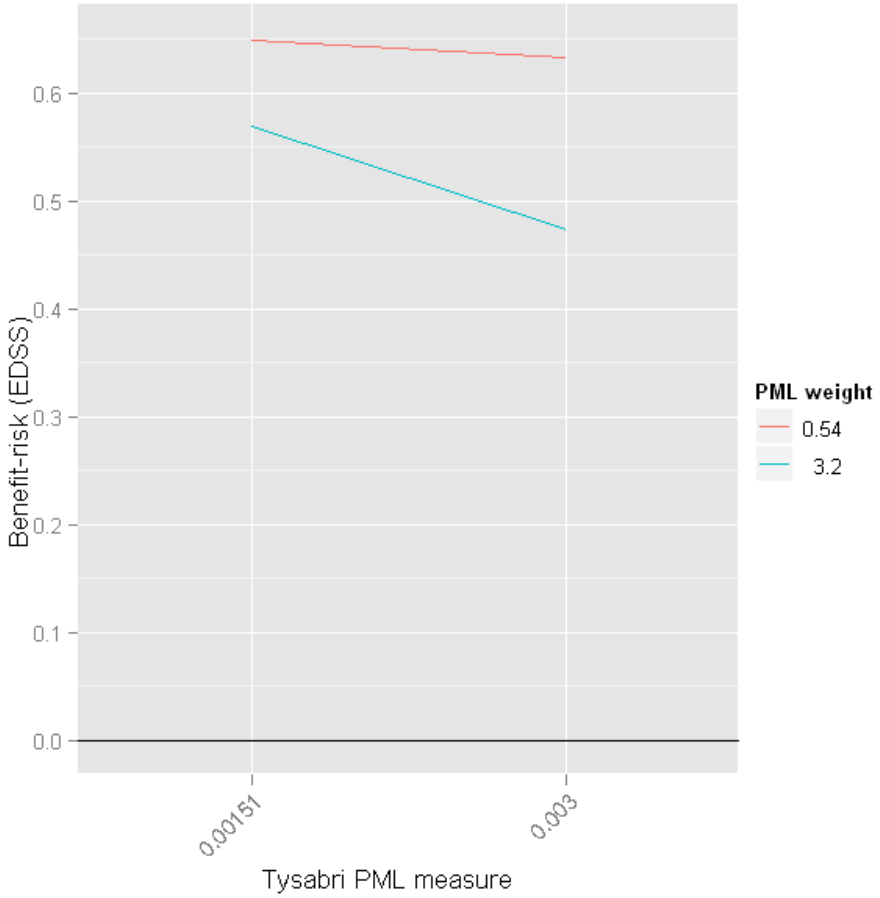
Incremental benefit-risk of natalizumab – placebo



- The weights are shown under each bar.
  - The base case weight is shown in the middle, with a +/- 30% range given at the ends.
- The weights are changed one at a time.
- The most important weight is the one given to relapses.

Two way sensitivity analysis on PML

Incremental benefit-risk of natalizumab – placebo



- Vary the natalizumab PML incidence (x-axis) and PML weight (each line).
- Increase the weight of PML so that it is 6x larger (to the inferred regulator weight).
- Increase the incidence of PML so that it is twice that observed.
- See that the BR is robust to these changes.

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Required natalizumab effect on outcomes to reach a neutral benefit-risk vs. placebo

Outcome	Weight	Current Tysabri Effect	Required Tysabri effect	Required Change (Absolute)	New BR
PML	54%	0.15%	6.36%	6%	0.00
Transaminases elevation	11%	5%	36%	31%	0.00
Relapse	8%	0.47	1.31	0.84	0.00
Reactivation of serious herpes viral infections	6%	0%	56%	56%	0.00
Seizures	5%	1%	68%	67%	0.00
Congenital abnormalities	5%	0%	67%	67%	0.00
Disability progression	5%	11%	78%	67%	0.00
Infusion reactions/injection reactions	3%	24%	100%	76%	0.21
Flu-like reactions	1%	40%	100%	60%	0.55
Hypersensitivity Reactions	1%	0%	100%	100%	0.47
Convenience	1%	iv qm hosp	sc od	NA	0.53

Current vs. future benefit-risk communication

From a narrative to a structured framework

Current benefit-risk communication

- Long text describing benefits and risks.
- Lacking explicit identification of **key** benefit and **key** risk outcomes.
- Limited systematic comparison of active drug vs. comparators for all key benefits and key risks.
- No structured, quantitative summary of all key benefit and key risk outcomes.

In the future, the benefit-risk communication will be transparent and defensible on:

- Which key benefits and key risks were considered and why.
- Which comparators were chosen.
- The magnitude of benefit and risk effects.
- The rationale for the relative importance of outcomes.
- Presentation in a concise graphical/tabular summary.

Conclusions

- The BRAT framework using MCDA is a sufficiently generic and flexible framework for performing a structured benefit-risk in any common context.
- Benefit-risk analysis is conceptually easy but hard to operationalize – in particular:
  - To define consistent criteria across decision options, find data matching these criteria, and elicit value judgments
  - Squash the messy complexity of real life into a simple model
- A structured benefit-risk assessment does not necessarily give you the answer.
  - It is a framework for decomposing and understanding a problem
  - Assesses the main value drivers of a decision
  - Communicates issues in a transparent, rational and consistent way
  - Allows sensitivity analysis

References

IMI PROTECT Benefit- Risk integration and representation Reports http://www.imi-protect.eu/benefitsRep.shtml

Carswell, C. M. (1992). An evaluation of the basic tasks model of graphical perception. *Human Factors*, 34, (5) 535-554.

Cleveland, W. S. and R. Mcgill (1984). Graphical Perception - Theory, Experimentation, and Application to the Development of Graphical Methods. *Journal of the American Statistical Association*, 79, (387) 531-554.

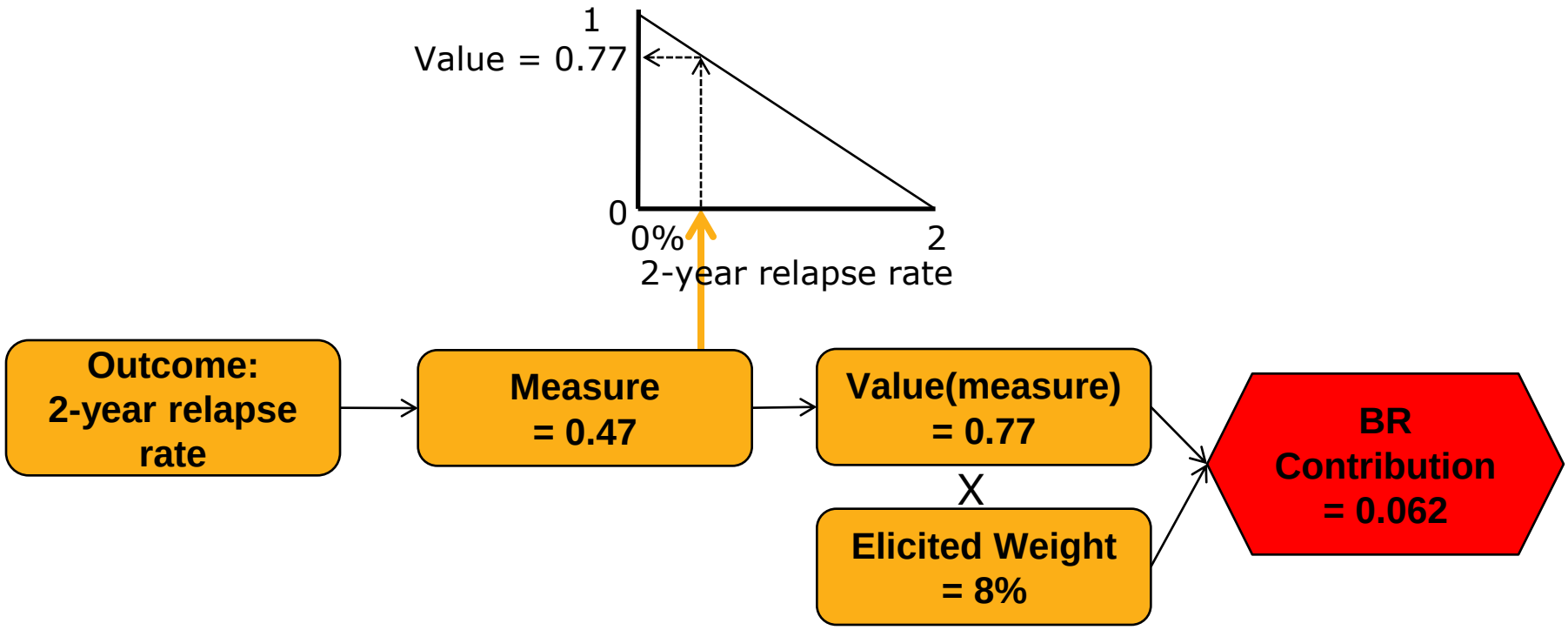
Tufte, E. R. (2001). *The Visual Display of Quantitative Information.*, Second edition ed. Cheshire, CT, Graphics Press.

BACK UP

Step 5: Assess outcome importance

Linear Additive models

- Linear Additive Models with Swing Weights
  - Value functions: Within outcome importance
  - Swing weights: Between outcome importance



Step 5: Assess outcome importance

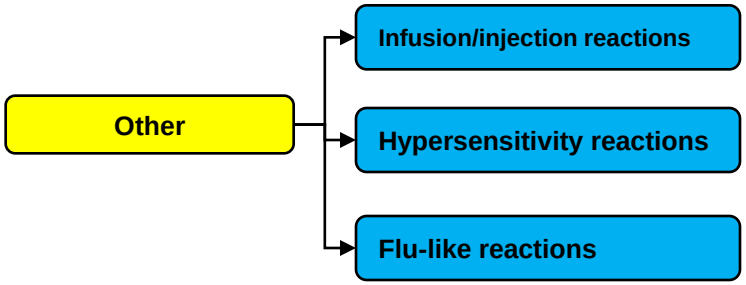
Three common methods for weight elicitation that use linear additive models

- Multi-criteria Decision Analysis (MCDA)
- MACBETH (Measuring Attractiveness by a Categorical Based Evaluation Technique)
- AHP (Analytic Hierarchy Process)

Step 5: Assess outcome importance

MCDA

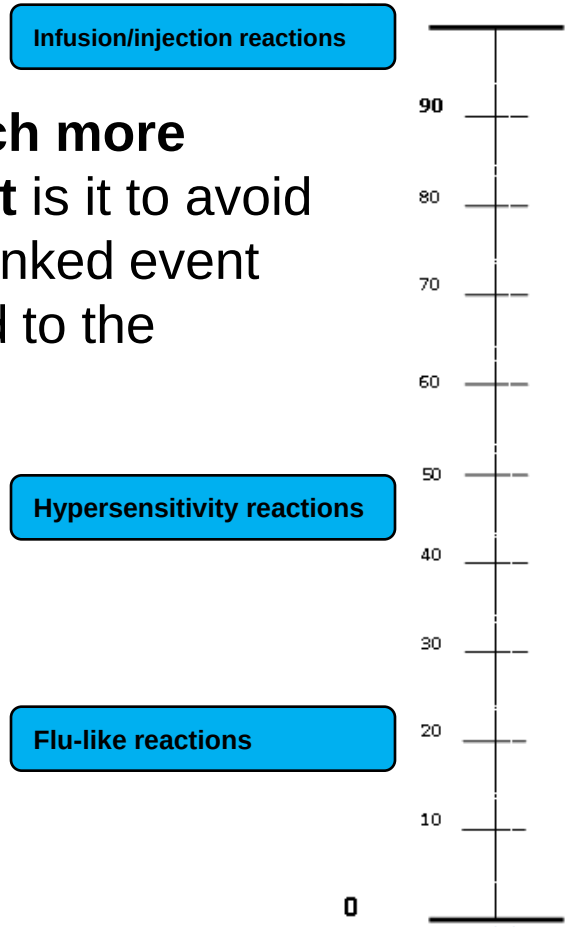
For each outcome category



1. Rank outcomes

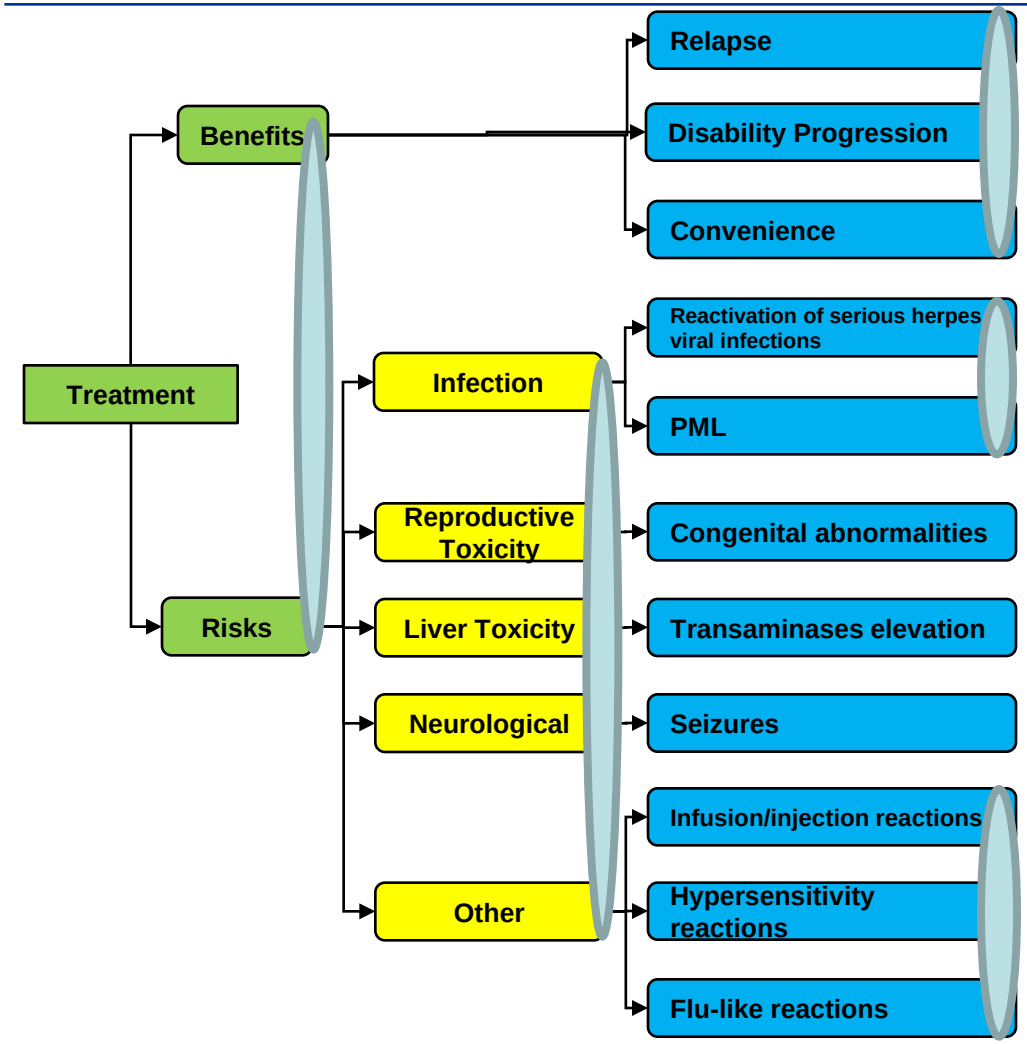
Outcome	Rank
Infusion/injection reactions	1
Hypersensitivity reactions	2
Flu-like reactions	3

2. Relative importance



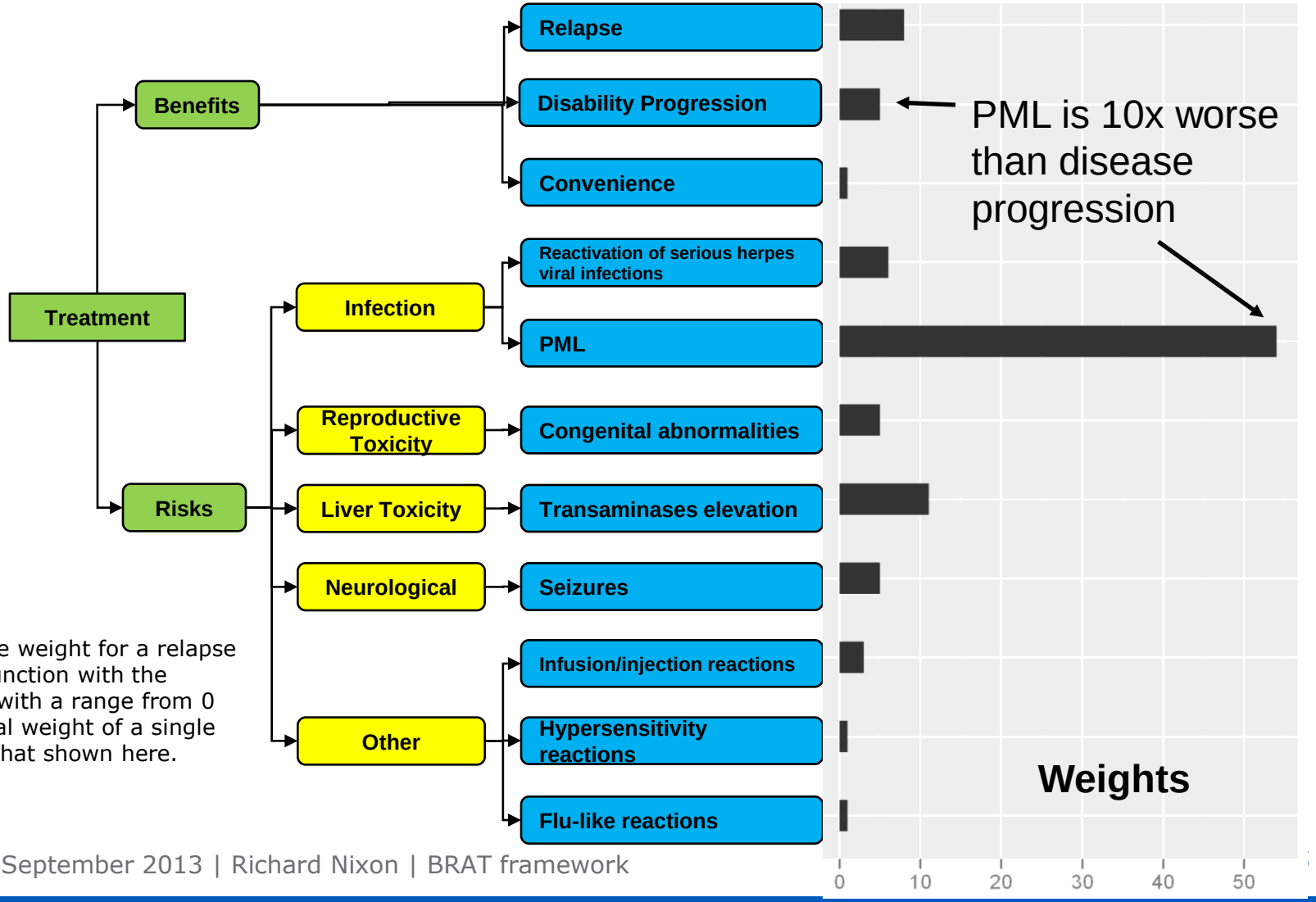
Repeat this process all the way up the value tree

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

Compute the overall weights



Note that as the weight for a relapse is for a value function with the measure scale with a range from 0 to 2, then actual weight of a single relapse is half that shown here.

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Example question to assess between outcome importance

- Imagine a clinical trial of 1000 patients with 1 patient developing PML in the treatment arm.
- How many patients would need to have an EDSS progression prevented for you to be indifferent about the benefit and harm caused by the treatment?

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MACBETH (Measuring Attractiveness by a Categorical Based Evaluation Technique)

Qualitative assessment

- MACBETH is similar to MCDA, except that it provides a different way to get the weights
- **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 optimization
- **Step 4**: Refine weights while maintaining consistency

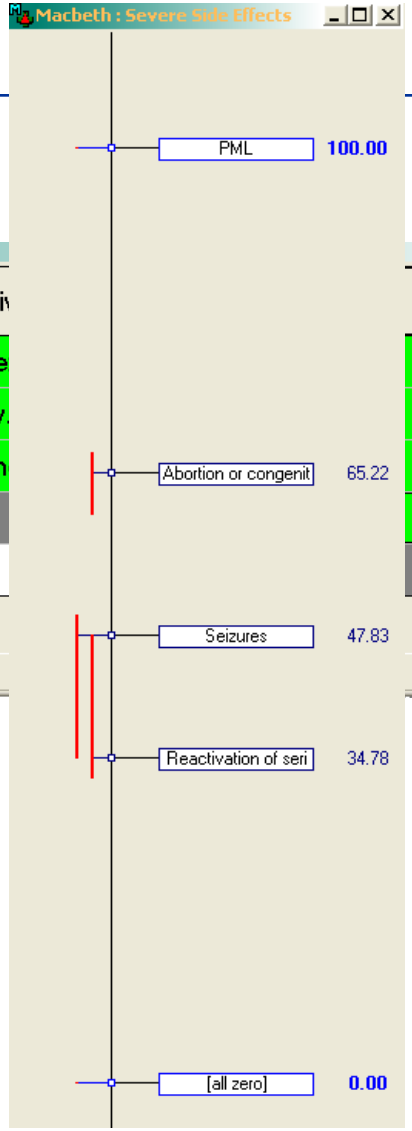
MACBETH

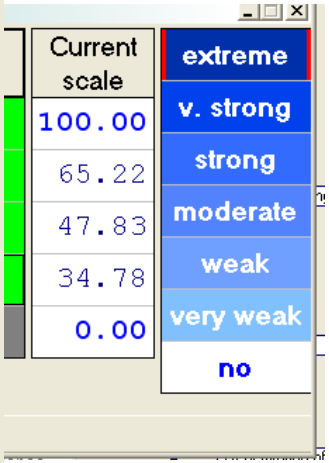
Qualitative assessment

Macbeth : Severe Side Effects

	PML	Abortion or congenit	Seizures	Reacti
PML	no	extreme	extreme	e
Abortion or congenit		no	strong	v.
Seizures			no	m
Reactivation of seri				
[all zero]				

Consistent judgements





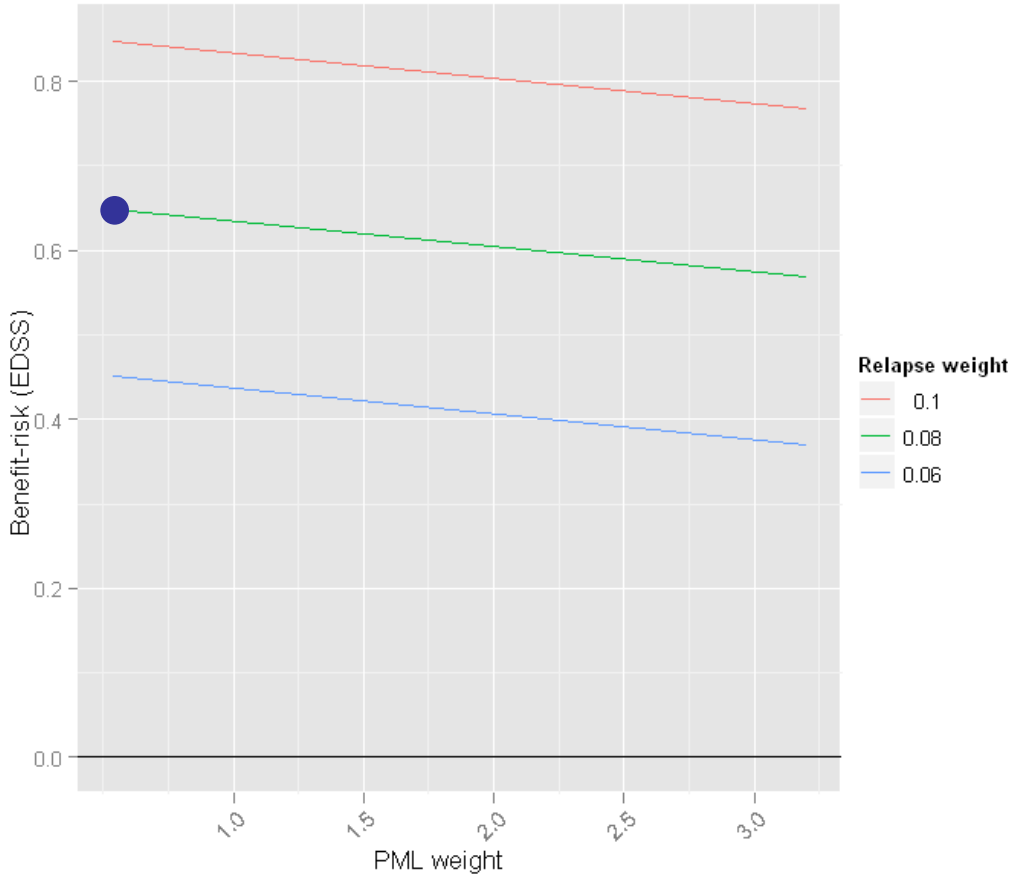
AHP (Analytic Hierarchy Process)

Qualitative assessment

- 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 (<0.2 is okay)

Two way sensitivity analysis on weights

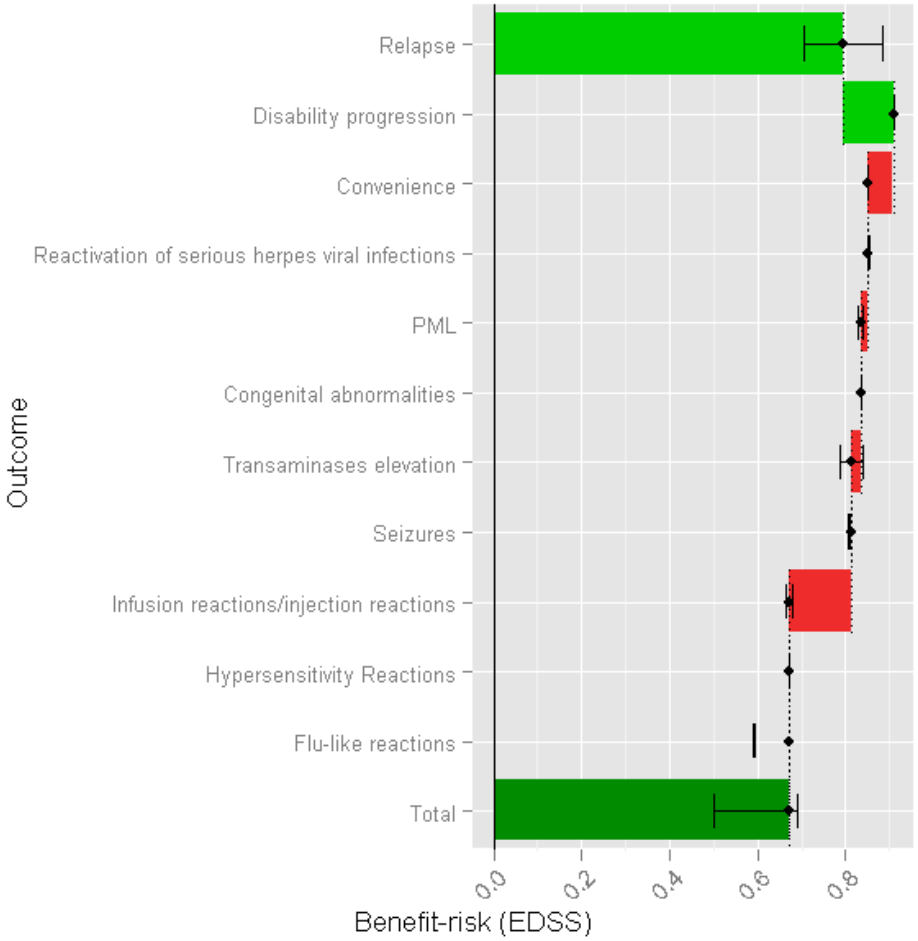
Incremental Benefit-Risk of Tysabri – Placebo



- Vary the PML weight (x-axis) and the relapse weight (each line).
- Green line in the middle is the elicited weight. Change by +/- 30%.
- Again the BR is robust to these changes.

Probabilistic sensitivity analysis of the measures

Incremental Benefit-Risk of Tysabri – Placebo



- 80% CI are included in the waterfall plot.
- The uncertainty in the overall BR is robust to uncertainty in the outcome measures
- The components of the uncertainty can be seen.

Work Package 5 of PROTECT (membership)

Public	Private
EMA	AstraZeneca
DKMA	Bayer
AEMPS	GSK
MHRA	Lundbeck
Imperial College (co-leader)	Merck KGaA (co-leader)
Mario Negri Institute	Novartis
CPRD	Novo Nordisk
IAPO	Pfizer
	Roche
	Sanofi-Aventis
	Takeda Eli Lilly Amgen