PROTECT

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

A Case Study Using the BRAT Framework for Benefit Risk Assessment

(1) A Generalization of the NNT/NNH concept

Christoph Dierig
Global Integrated Analysis, Bayer Pharma

(2) Application and visualization of Multi-Criteria Decision Analysis (MCDA).

Richard Nixon
Modeling and Simulation, Novartis

Basler Biometric Section, 25 September 2012

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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Outline

- Introduction
  - IMI PROTECT
  - Tysabri Case Study
  - BRAT FRAMEWORK
- Tysabri Case Study
  - Application of the BRAT Framework
- Quantitative Methods for Benefit-Risk Assessment
  - Generalization of the NNT/NNH concept

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 (WP5) is focusing on **Benefit-Risk integration and representation**
  - In wave 1, four case studies were performed (Raptiva, Ketek, Acomplia, Tysabri) to evaluate various **frameworks** and **quantitative methods** for benefit-risk assessment

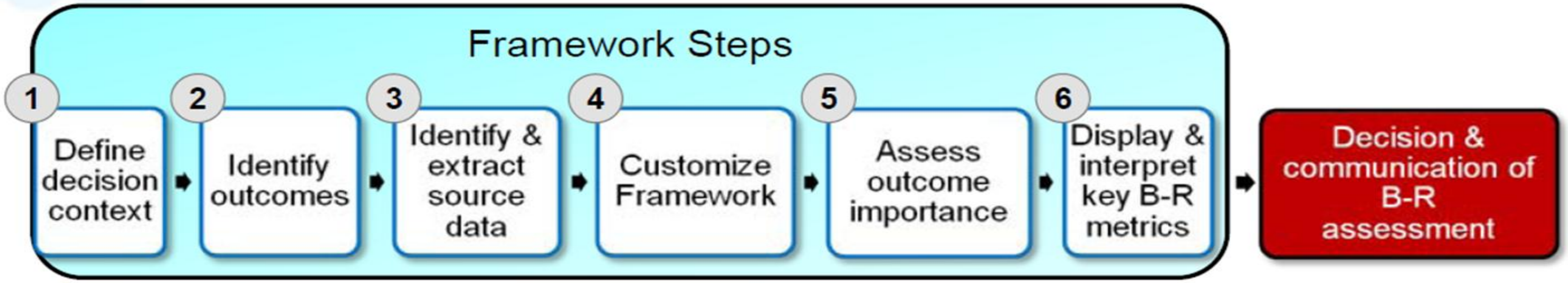
Tysabri Case Study - Background

- Tysabri (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 BRAT *Framework for B/R-Assessment*

Benefit Risk Action Team (BRAT) framework

- Developed by PhRMA (**Ph**armaceutical **R**esearch & **M**anufacturers of **A**merica)
- Structured **6-step approach** for defining the decision context and selecting, organizing, evaluating, and displaying relevant benefit-risk information

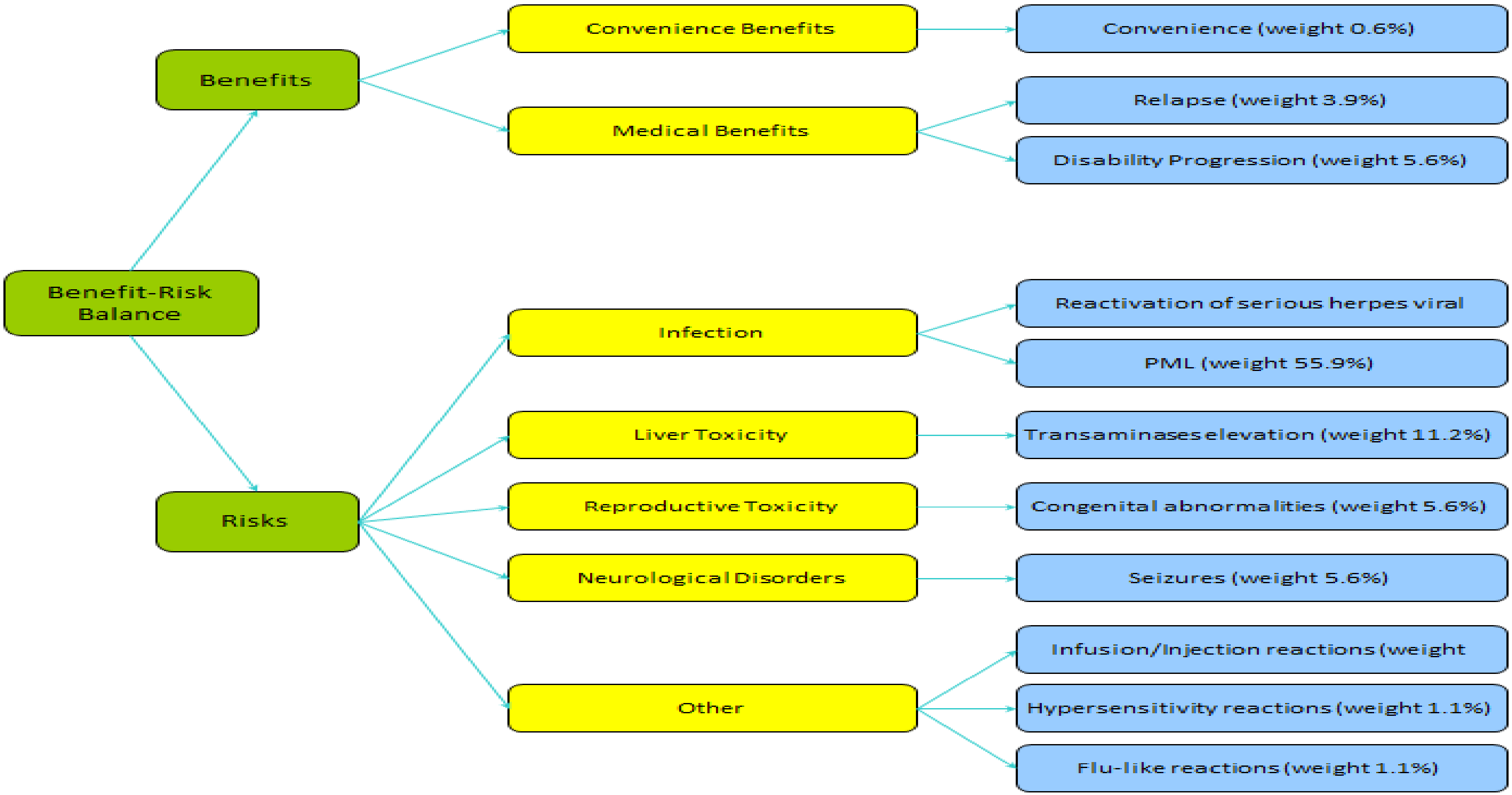


- Process is supported by an EXCEL based tool, however the framework is boarder than the tool

Step 1: Define the Decision Context
Tysabri Case Study

- Decision question:
  - Should Tysabri be given marketing approval at the time of first registration?
  - Should Tysabri be kept on the market given that increased episodes of PML were observed?
- Indication: Relapsing remitting multiple sclerosis
- Drugs to compare: Tysabri vs. (Placebo, Avonex, Copaxone)
- Decision perspective: EMA
- Time frame: 2 years of treatment

Step 2: Identify Benefit and Risk Outcomes – Value Tree Creation



Step 2: Identify Benefit and Risk Outcomes – Value Tree Creation

- For value tree set-up comprehensive discussion is required
  - Display all benefits and risks relevant for BR assessment
  - Strategy for initial set-up
    - Start with a comprehensive draft value tree
    - Reduce to relevant entries
  - Target Product Profile and Risk Management Plan might be appropriate sources
- Value tree needs to be updated whenever new information on risks or benefits is available
- Creation & modification of value tree are well supported by the BRAT tool

Step 3: Identify and Extract Source Data

Preparing the Data Table

Identify

Search strategy

Search query

PubMed.gov
US National Library of Medicine
National Institutes of Health

Drugs@FDA
FDA Approved Drug Products

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Select

Study eligibility criteria

Study worksheet

one row per study

Extract

Extraction guidelines

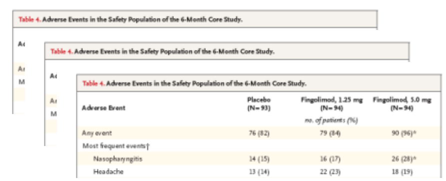


Table 4. Adverse Events in the Safety Population of the 6-Month Core Study.

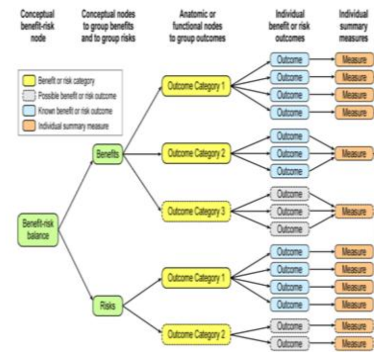
Adverse Event	Placebo (N=93)	Fingolimod, 1.25 mg (N=94)	Fingolimod, 5.0 mg (N=94)
		no. of patients (%)	
Any event	76 (82)	79 (84)	90 (96)*
Most frequent events†			
Nasopharyngitis	14 (15)	16 (17)	26 (28)*
Headache	13 (14)	22 (23)	18 (19)

Data source table

one row per study/treatment/outcome

Aggregate

e.g. meta-analysis, placebo-calibration



Data summary table

one row per outcome

Step 3: Identify and Extract Source Data
Preparing the Data Table

- For the Tysabri case study three relevant clinical trials were identified
  - Tysabri vs. placebo
  - Avonex vs. placebo
  - Copaxone vs. placebo
- Comparisons of active compounds could be established via “placebo calibration”

Note: A full network meta-analysis could have been required in a more complex situation

Step 3: Identify and Extract Source Data
Preparing the Data Table

- By use of filters the BRAT EXCEL tool facilitates consideration of, for example,
  - More than one comparator
  - Several points in time for assessment (here: approval, 2 years post-approval)
  - etc.

Comparator	Timepoint	Filter3	Filter4
Avonex	At time of approval		
Copaxone	After approval		
Placebo			

Step 3: Identify and Extract Source Data
Preparing the Data Table

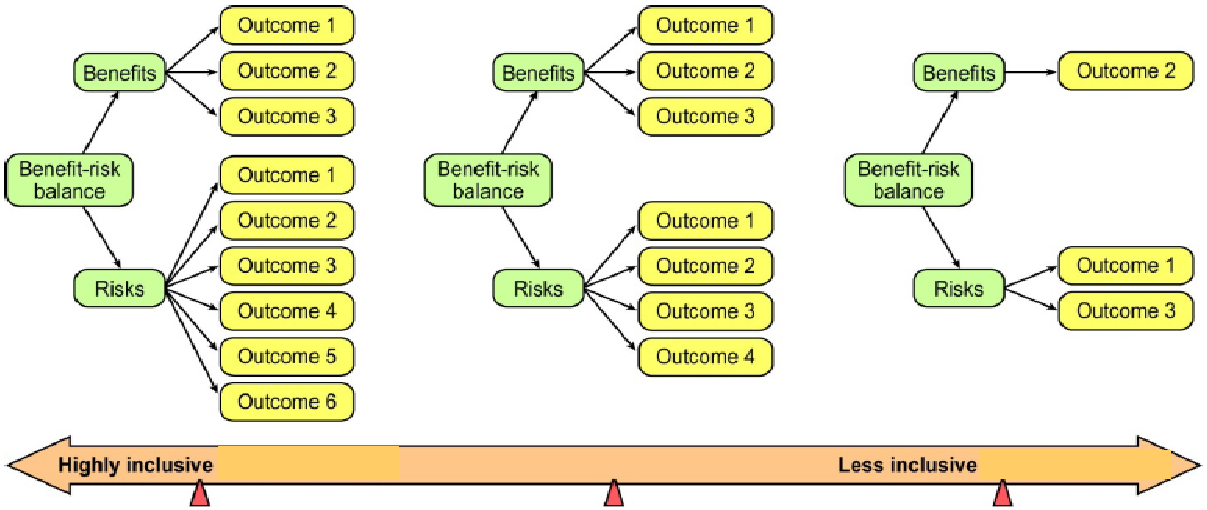
Outcome name	Comparator	Timepoint	Filter3	Filter4	Tysabri rate point estimate	Tysabri rate lower CI	Tysabri rate upper CI
Relapse (weight 3.9%)	Avonex	At time of approval			0,28	0,24	0,31
Relapse (weight 3.9%)	Copaxone	At time of approval			0,28	0,24	0,31
Relapse (weight 3.9%)	Placebo	At time of approval			0,28	0,24	0,31

- Data table provides entry fields for
  - Organizational data (here: outcome, comparator, time point)
  - Data on Tysabri and comparator (active comparator or placebo)
  - Derived measures for risk differences and/or ratios
- Basic error checks are performed by the tool, results are presented in a separate table.
- Non-availability of data is **not** prohibitive for using the tool

Step 4: Customize the Framework

- Update of framework when new information is available
  - Adding/deleting benefits and/or risks
  - Update of quantitative information
- Tuning the value tree

"Tuning" is the ability to temporarily display or not display outcomes depending on the needs of the audience, the decision being made, and the data available



Step 5: Assess Outcome Importance

- Ranking or weighting of individual outcomes according to their importance / severity
  - Forest plot allows different orderings (ranking) of benefit and risk criteria,
    e.g. according to
    - Point estimate
    - Value tree order
- Weighting is not supported by the BRAT EXCEL tool
  - Information on weights can only be added to the labels

Step 6: Display and Interpret Key Benefit-Risk Metrics

- BRAT tool provides a two options for a quantitative overview on benefits and risks focusing on risk differences (or ratios).
  - Key benefit-risk summary table
  - Forest plot

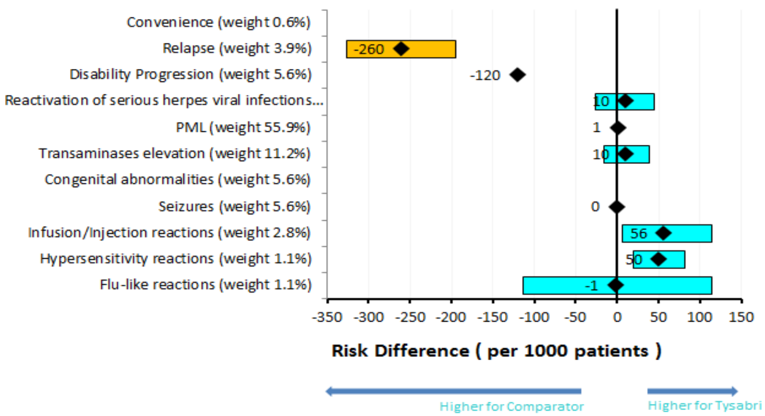
Key Benefit-Risk Summary Table

		Outcome	Tysabri 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%)	1	0	1	(-, -)
	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 Tysabri

Higher for Comparator

Forest Plot



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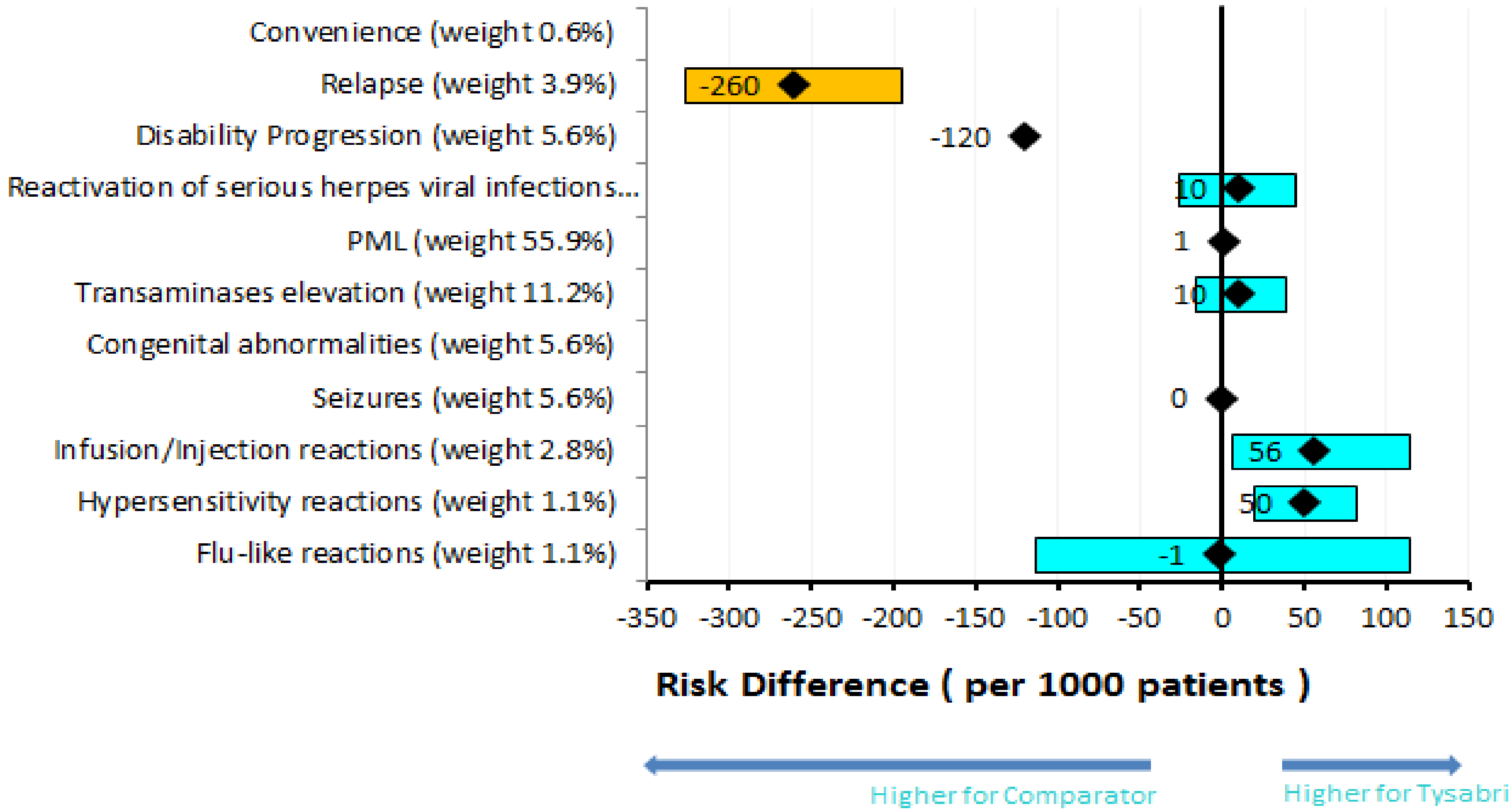
Step 6: Display and Interpret Key Benefit-Risk Metrics

Forest Plot



BRAT Tool From a User's Perspective

Strengths

- Convenient to use
  - Easy creation, modification and tuning of the value tree
  - Update of data table structure depending on filter definitions
  - Basic error check capabilities
  - Various options for customization are available

- Provides tabular and graphical overview on benefits and risks
  - Filters allow quick change of ‚perspective'

- Facilitates structured transparent B-R assessment process

BRAT Tool From a User's Perspective

Limitations

- BRAT tool is designed for the handling of outcomes measured as proportions or rates, but not for categorical or continuous data
- No support of **weighting** and application of **quantitative methods** to aid final interpretation and decision making

Note: These are just limitations of the software tool, not of the framework.

Recommendation

- The BRAT framework process user's guide as well as the software user's guide should always be consulted.

Quantitative Methods for B/R Assessment

- How to properly reduce a **complex multi-dimensional problem** to a “simple” **binary decision?**
  - Regulator: to approve the drug (no/yes)
  - Insurance: to pay for the drug (no/yes)
  - Patient: to take the drug (no/yes)

- In the Tysabri case study two quantitative methods were investigated:
  1. Number Needed to Treat (NNT) – Number Needed to Harm (NNH) approach
  2. Multi-Criteria Decision Analysis (MCDA)

Definition of NNT and NNH

- **Number Needed to Treat** (NNT) is defined as

$$NNT := \frac{1}{(p_C - p_T)}$$

where p_C and p_T denote the proportion of the disease of interest in the control group and the treatment group, respectively

"The (average) number of patients to be treated in order to avoid one case of the disease"

- Similarly, **Number Needed to Harm** (NNH) is defined as

$$NNH := \frac{1}{(q_T - q_C)}$$

Benefit-Risk Assessment based on NNT/NNH

- Benefit outweighs the risk if

$$\frac{NNT}{NNH} < 1 \quad (or\ alternatively: NNT < NNH)$$

- **Limitation:** NNT/NNH approach only works in case of
  - one benefit
  - one risk
  - benefit and risk are of comparable severity

Extension of NNT/NNH concept

– Generalization of NNT/NNH expanding the ideas of Holden (2003) in order to enable
  1. Weighting (here: utility weights)
  2. Multiple risks
  3. Multiple benefits

Simple case:

$$\frac{NNT}{NNH} = \frac{\dfrac{1}{(p_C - p_T)}}{\dfrac{1}{(q_T - q_C)}}$$

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Extension of NNT/NNH concept

– Generalization of NNT/NNH expanding the ideas of Holden (2003) in order to enable
  1. Weighting (here: utility weights)
  2. Multiple risks
  3. Multiple benefits

$$\frac{NNT_w}{NNH_w} := \frac{\dfrac{1}{\sum_{i=1}^{m}\left(p_{C,i} - p_{T,i}\right) * \left(1 - utility\left(AE_i^B\right)\right)}}{\dfrac{1}{\sum_{i=1}^{k}\left(q_{T,i} - q_{C,i}\right) * \left(1 - utility\left(AE_i^R\right)\right)}}$$

Extension of NNT/NNH concept

- Benefit-Risk Assessment: Compare weighted NNT with weighted NNH where benefit outweighs risk if

$$\frac{NNT_w}{NNH_w} < 1 \qquad (1)$$

Notes:

- Holden focused on utility weights, however, other types of weights can be used as well
- Weighted NNH (NNH_w) as well as weighted NNT (NNT_w) can no longer be interpreted as a "number of patients to be treated in order ….".
- Formula from previous slide doesn't look very handy

Can it be simplified?

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Extension of NNT/NNH concept

- Rewriting the formula given in (1) results in

$$\sum_{i=1}^{m+k}\left(\left(p_{C,i}-p_{T,i}\right)*weight\left(AE\left(i\right)\right)\right)>0$$

  - assuming that the treatment has beneficial events with respect to events AE(i) (i=1,…,m), and detrimental effects with respect to events AE(i) (i=m+1,…,k).
  - $p_{C,1}$,…, $p_{C,m+k}$ and $p_{T,1}$,…, $p_{T,m+k}$ denote the proportions of the events AE(i) (i=1,…, m+k) in the control and the treatment group, respectively
  - weights are given, for example, by (1-utility()).

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Extension of NNT/NNH concept - Weighted Net Clinical Benefit

- Rewriting the formula given in (1) results in

$$\sum_{i=1}^{m+k}\left(\left(p_{C,i} - p_{T,i}\right) * weight\left(AE\left(i\right)\right)\right) > 0$$

- The formula above is the **weighted** version of the '**Net Clinical Benefit (NCB)**' concept described by Sutton et al. (2005)
- **Tysabri Case Study**: weighted NCB indicates positive benefit-risk balance at initial approval as well as at CHMP reassessment
- **Limitation** of NCB: Benefit and risk criteria need to be measured as proportions (or rates)

  => Need for methods allowing consideration of categorical and continuous data, too.

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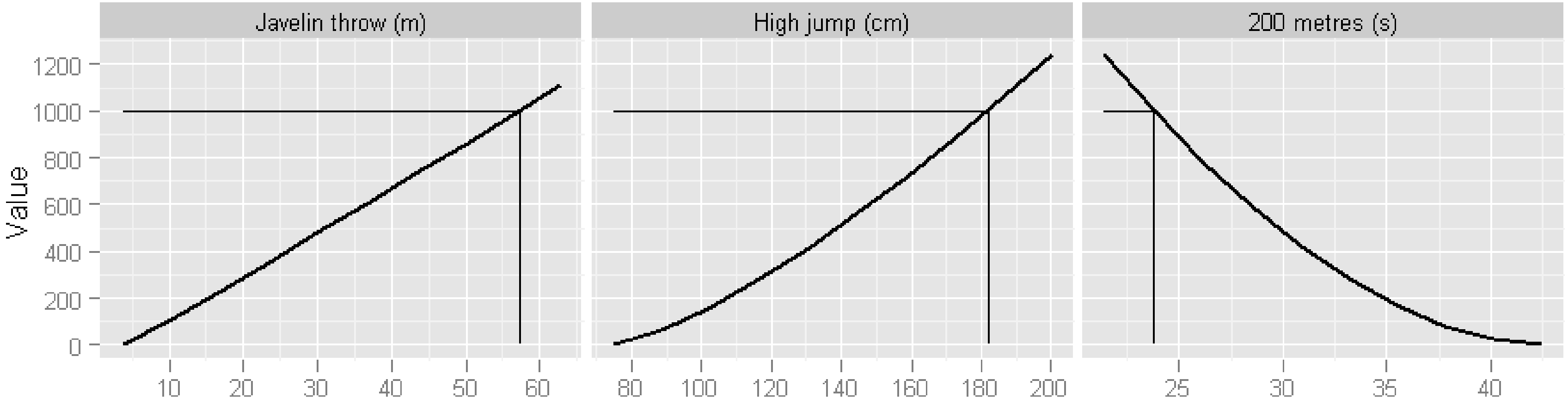
Outline

- Explain the process of Multi-criteria Decision Analysis (MCDA)
  - This is a generalization of the weighted Net Clinical Benefit
  - Allows us to compare different outcomes measured on different scales
- Demonstrate some visualizations of Benefit-Risk
  - BR is fundamentally about bringing clarity to a decision maker by clearly communicating the consequences of different drugs
  - Components of BR
  - Deterministic and probabilistic sensitivity analysis

The historical context

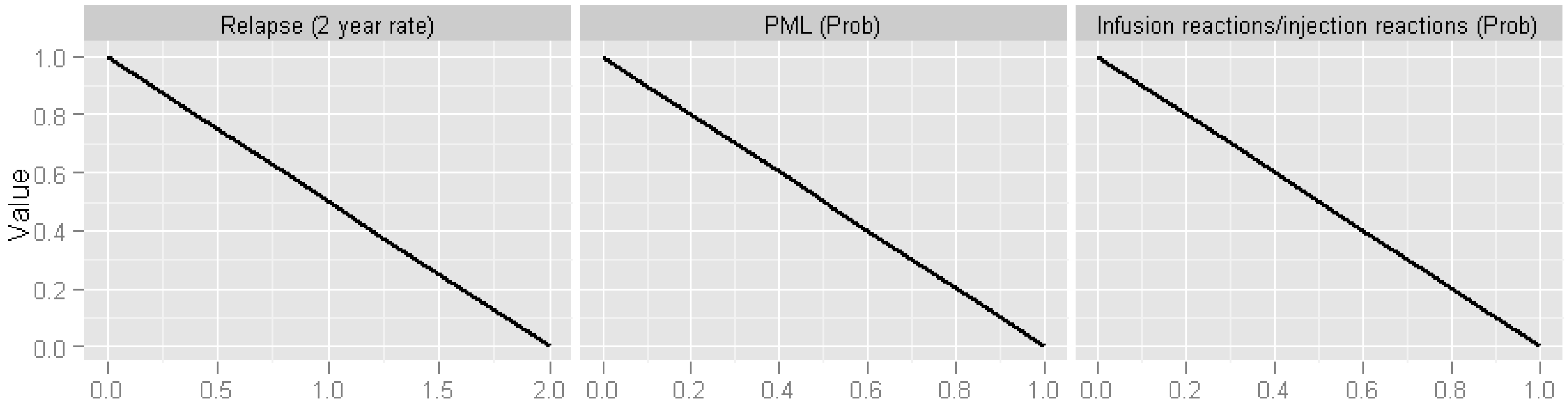
- “If I have seen further it is by standing on the shoulders of giants” – Isaac Newton
- Structured Benefit-risk analysis is a relative new idea in drug development, but is build on well established ideas
  - Daniel Bernoulli (1738) – Expected Utility hypothesis
  - Von Neumann and Morgenstern (1944) - Game theory and Economic Behaviour
  - Keeney and Raiffa (1976) - Multi-attribute value theory

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**

MCDA and multiple sclerosis drugs

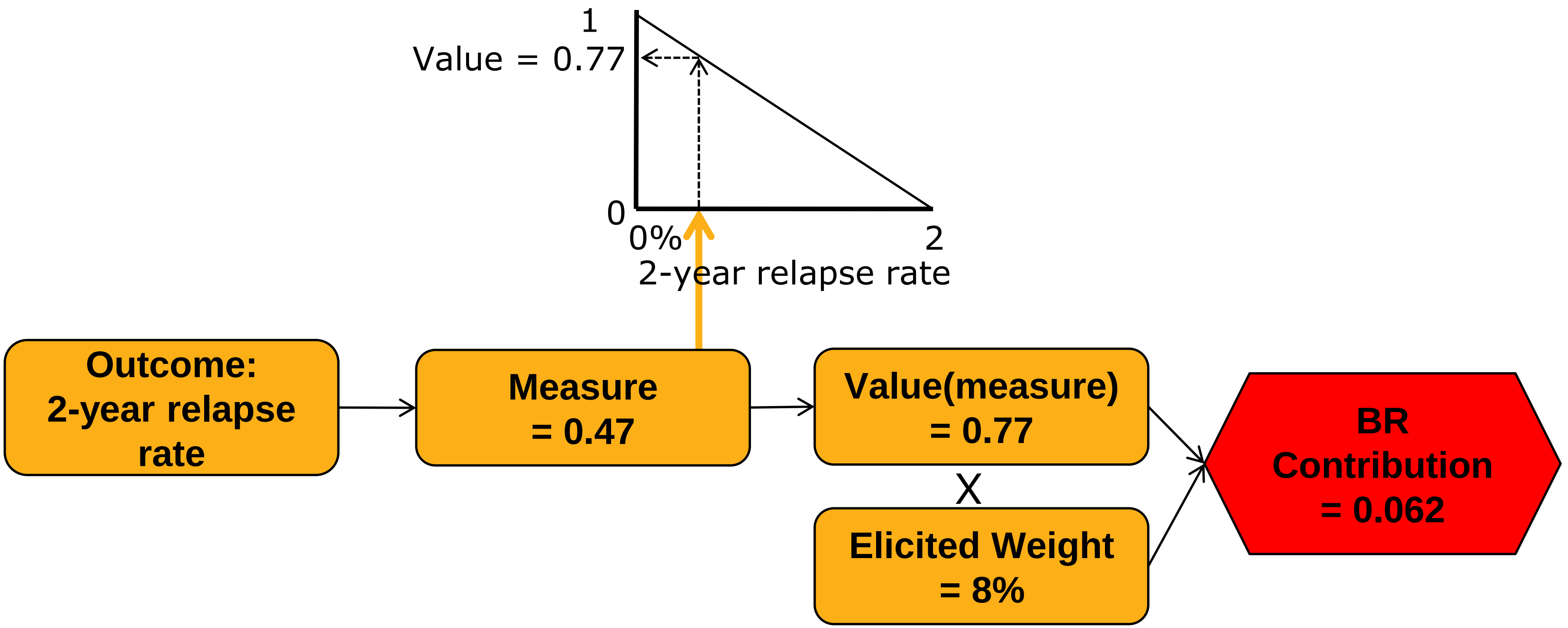


		Placebo			Tysabri		
Outcome	**Weight**	**Measure**	**Value**	**Benefit-risk**	**Measure**	**Value**	**Benefit-risk**
Relapse	8%	1.46	0.27	0.022	0.47	0.766	0.061
PML	54%	0	1	0.54	0.0015	0.998	0.54
Infusion reactions injection reactions	3%	0	1	0.03	0.24	0.764	0.02
Total				**0.59**			**0.62**

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

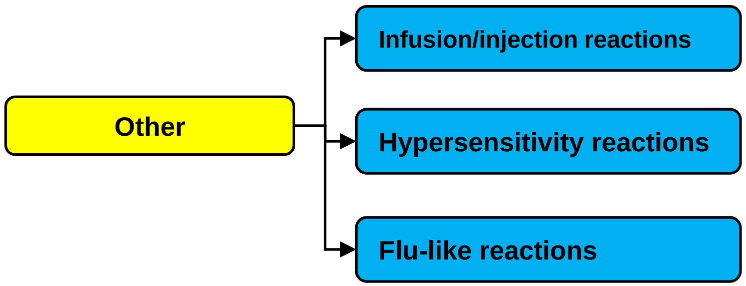
Three common methods for weight elicitation that use linear additive models

- 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

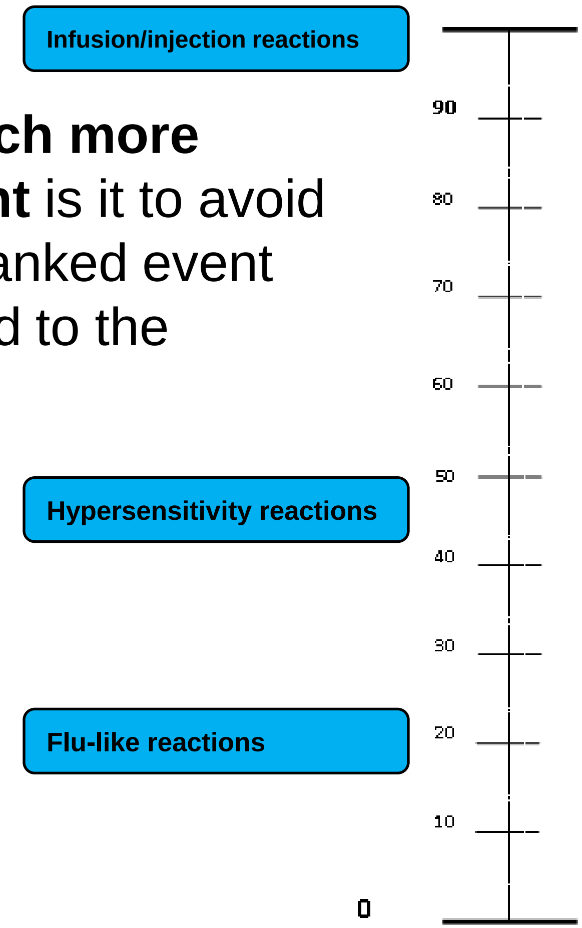


1. Rank outcomes

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

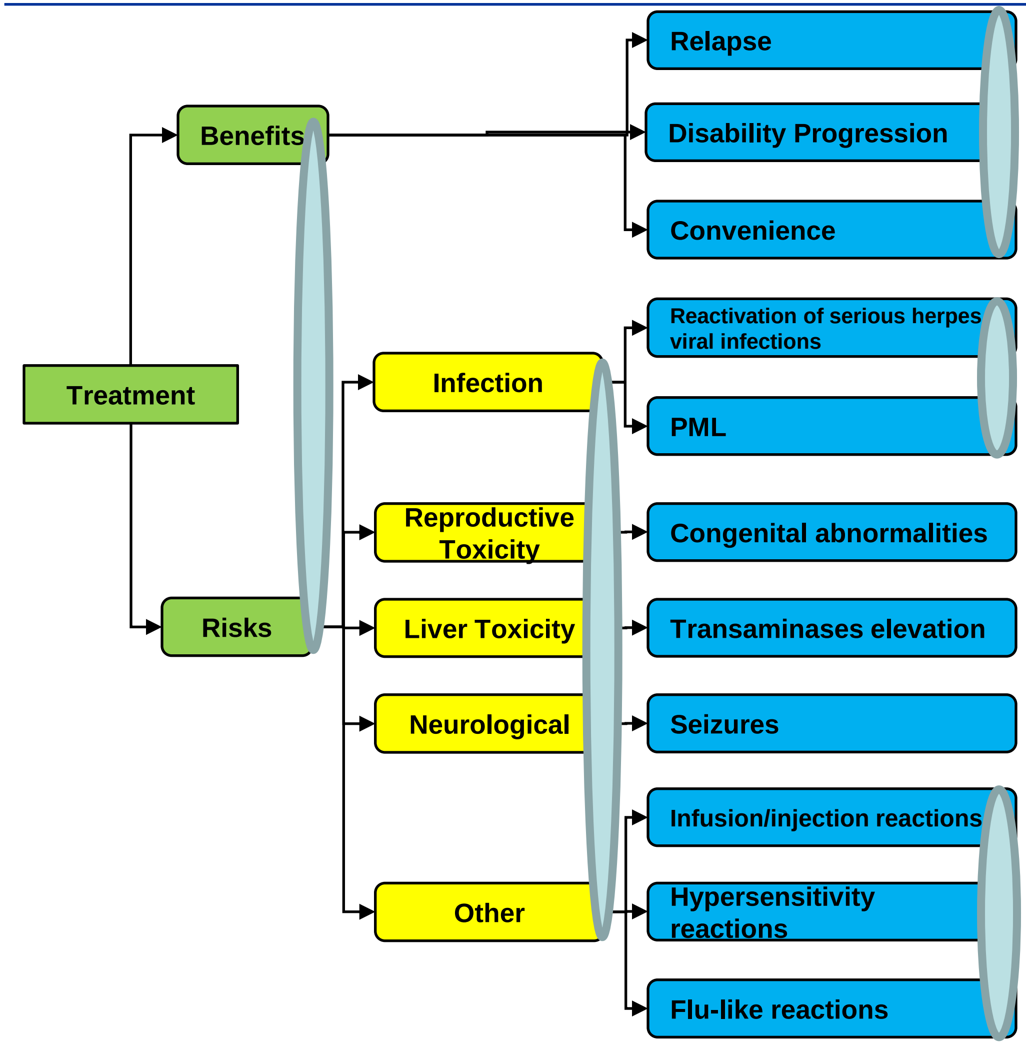
2. Relative importance

How much more important is it to avoid the top-ranked event compared to the others?



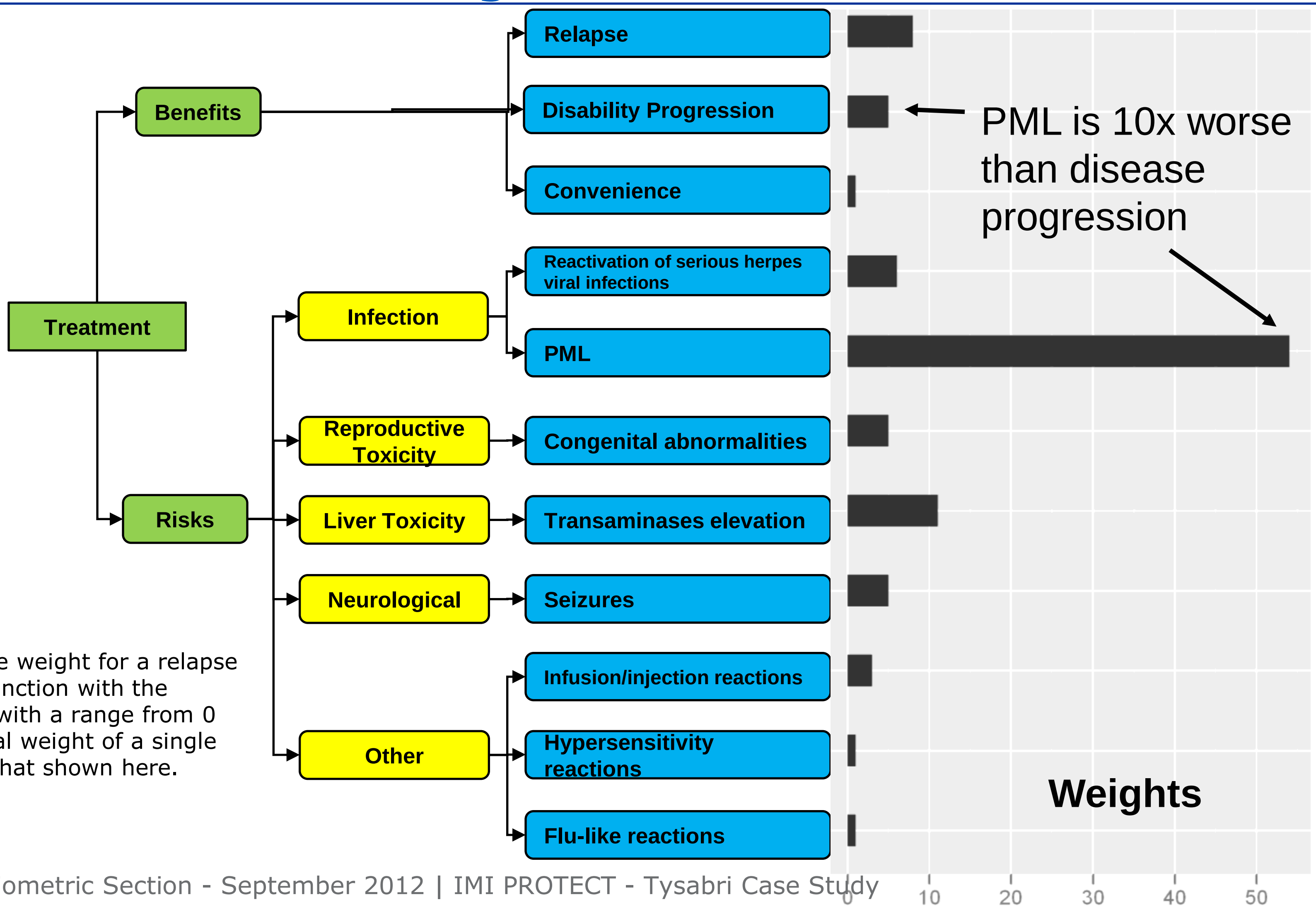
Repeat this process all the way up the value tree

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.

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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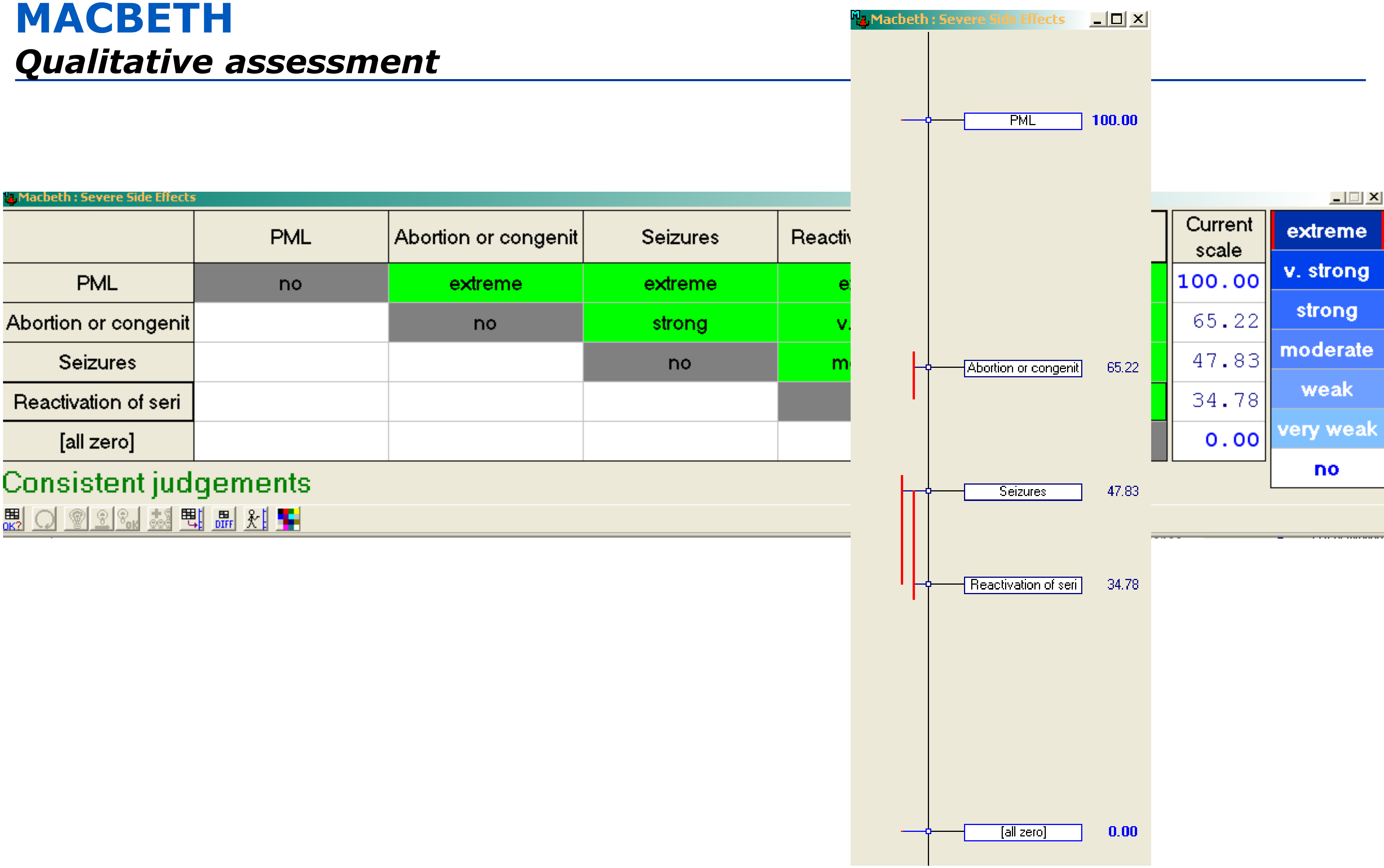
MACBETH (Measuring Attractiveness by a Categorical Based Evaluation Technique)

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



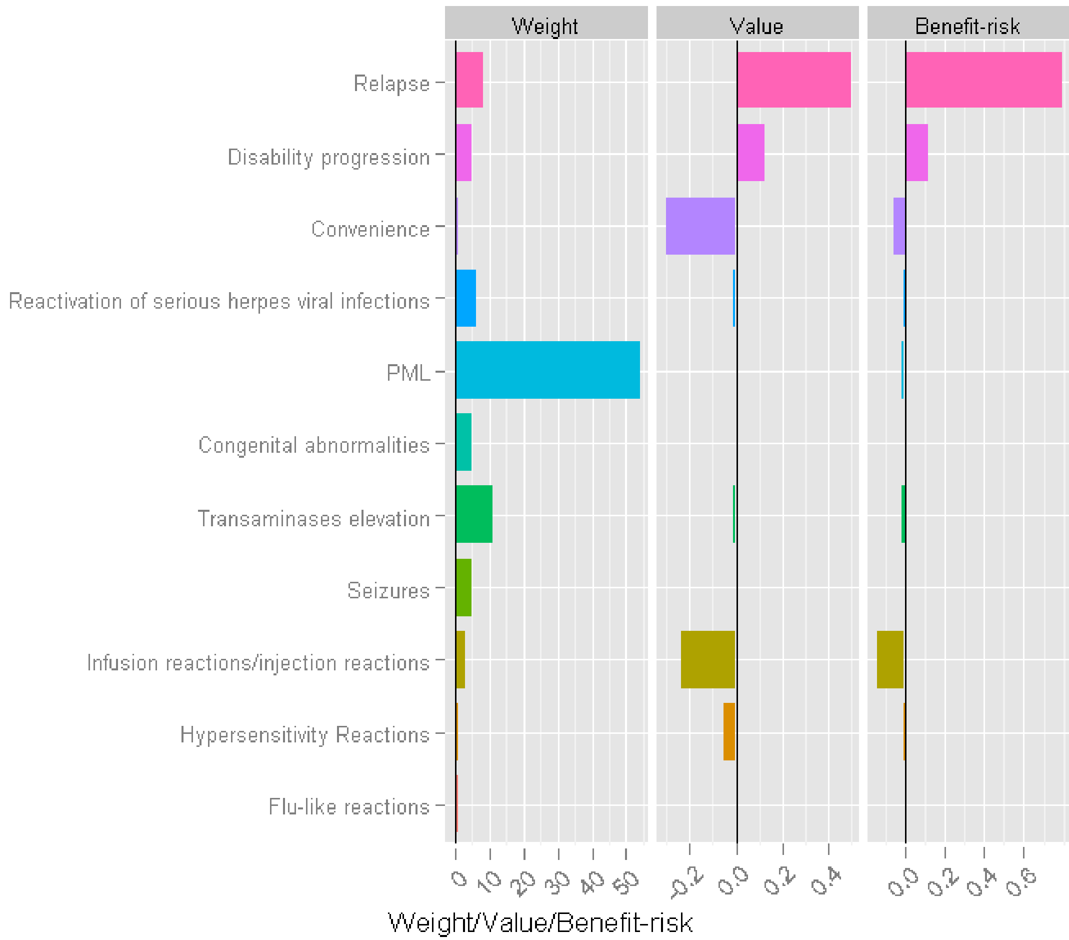
AHP (Analytic Hierarchy Process)

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)

Drill down to the values and the weights

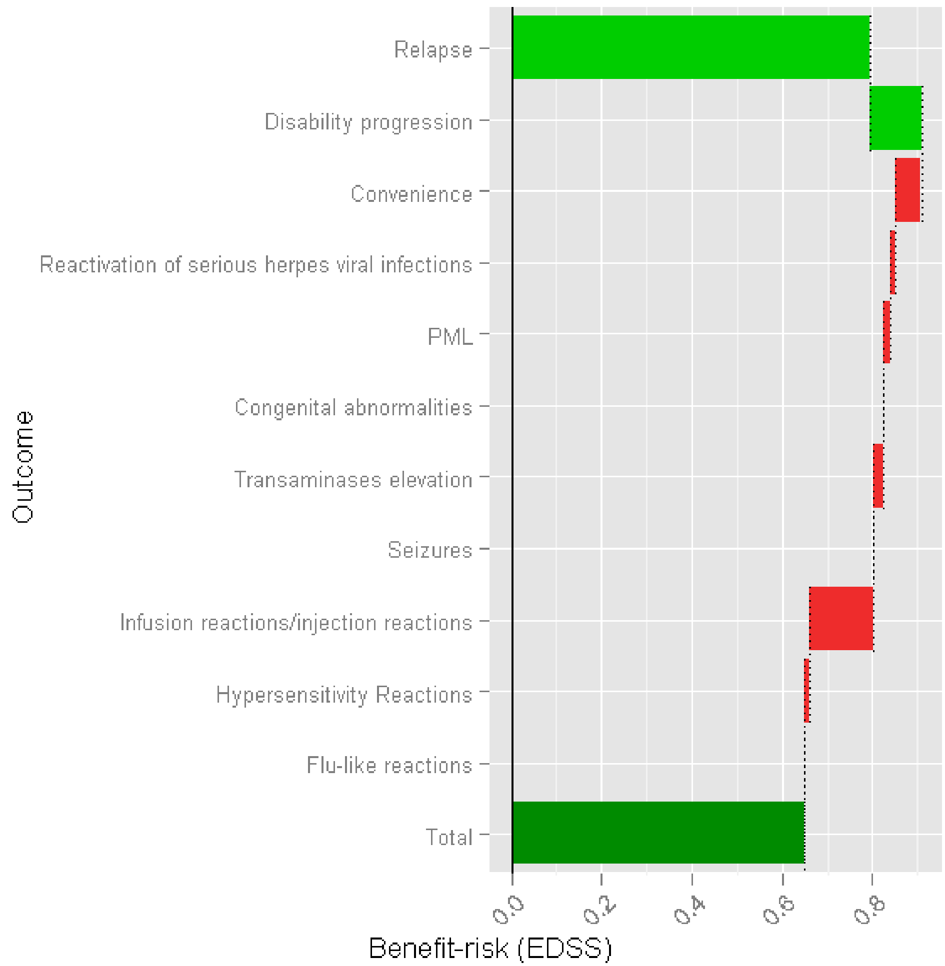
Incremental Benefit-Risk of Tysabri – Placebo



- 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 BR.

BRAT Step 6: Display and interpret key metrics

Incremental Benefit-Risk of Tysabri – Placebo: Waterfall plot



- 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

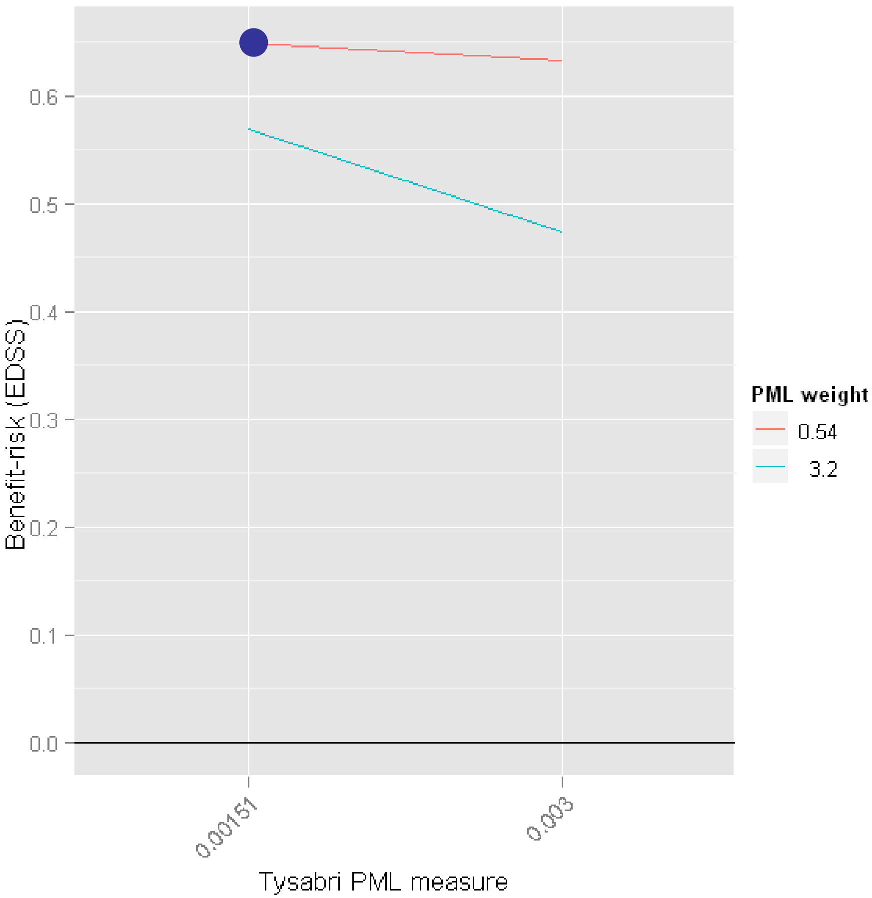
Sensitivity analysis on the weights

Incremental Benefit-Risk of Tysabri – 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

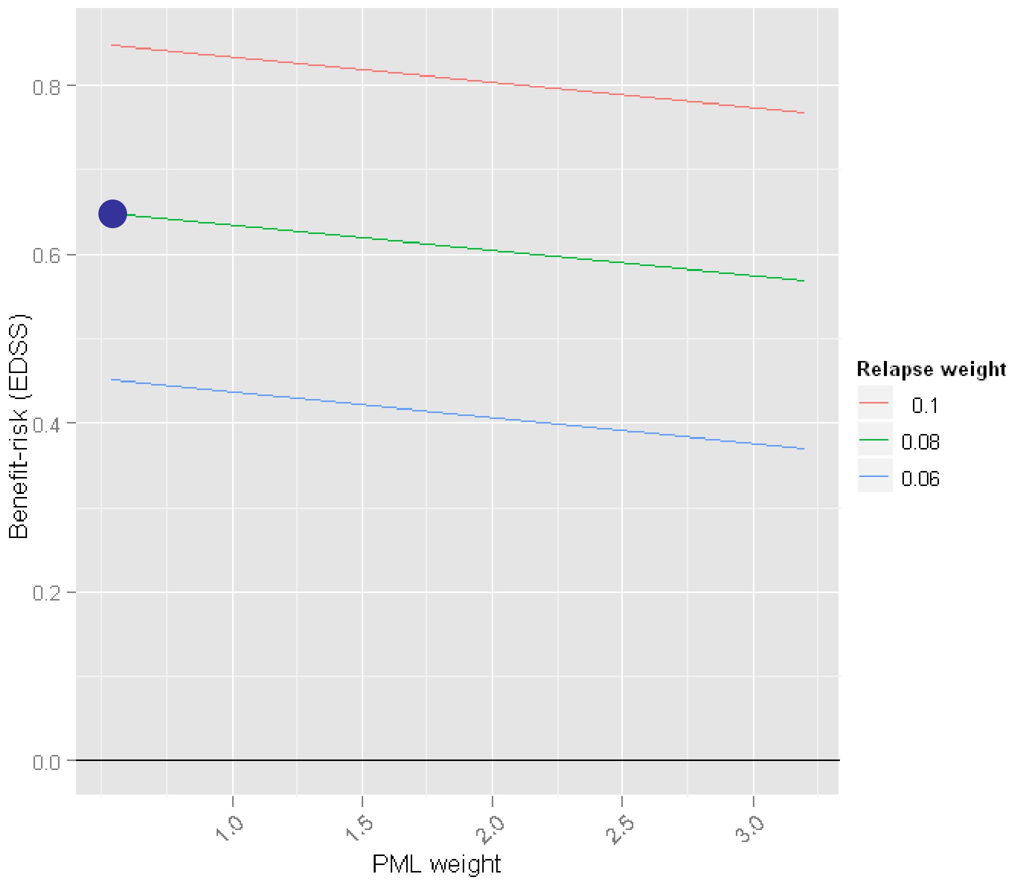
Incremental Benefit-Risk of Tysabri – Placebo



- Vary the Tysabri 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.

Two way sensitivity analysis on weights

Incremental Benefit-Risk of Tysabri – Placebo



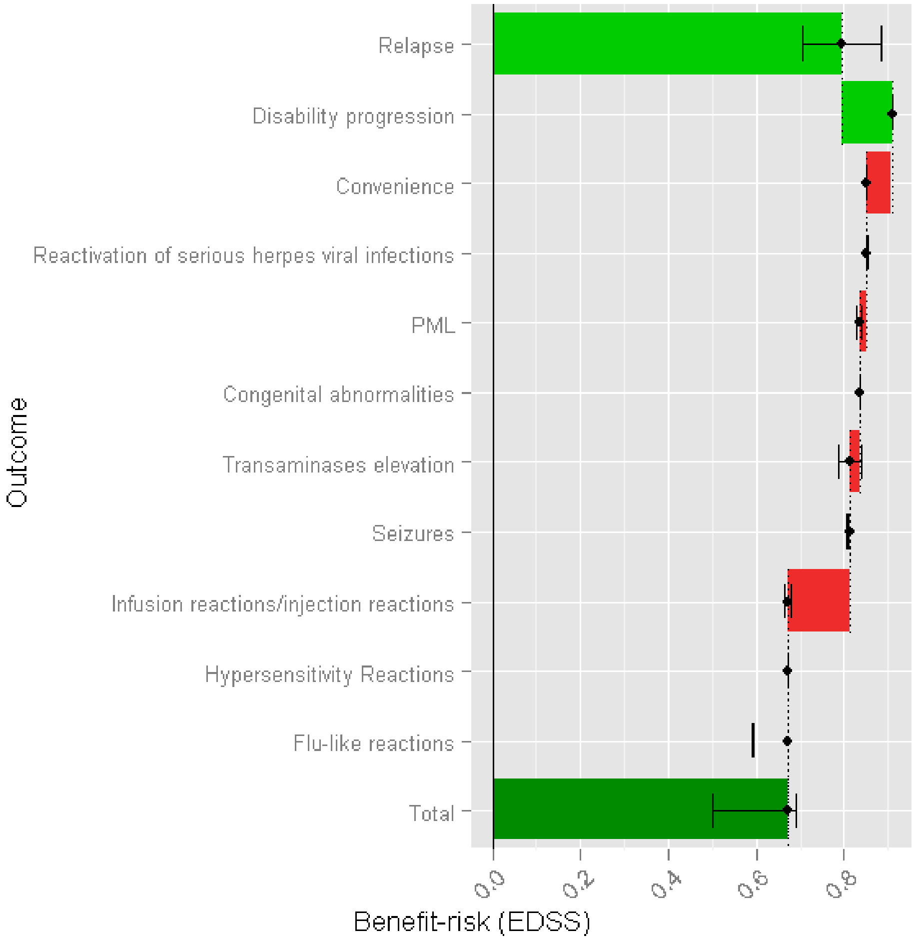
- Vary the PML weight (x-axis) and the relapse weight (each line).
- Green line in the middle is the elicited weight. Change by +/- 30%.
- Again the BR is robust to these changes.

Required Tysabri 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

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.

PROTECT

Take home message

- The BRAT is a framework well suited to benefit-risk analysis
- 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 BR 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 around different perspectives (industry, regulator, patient, payer, prescriber)

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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
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Are there any Questions ?