The PROTECT project: benefit-risk integration and representation

Stakeholder perspectives in assessing the benefit-risk balance for medicines

WP5 leaders:
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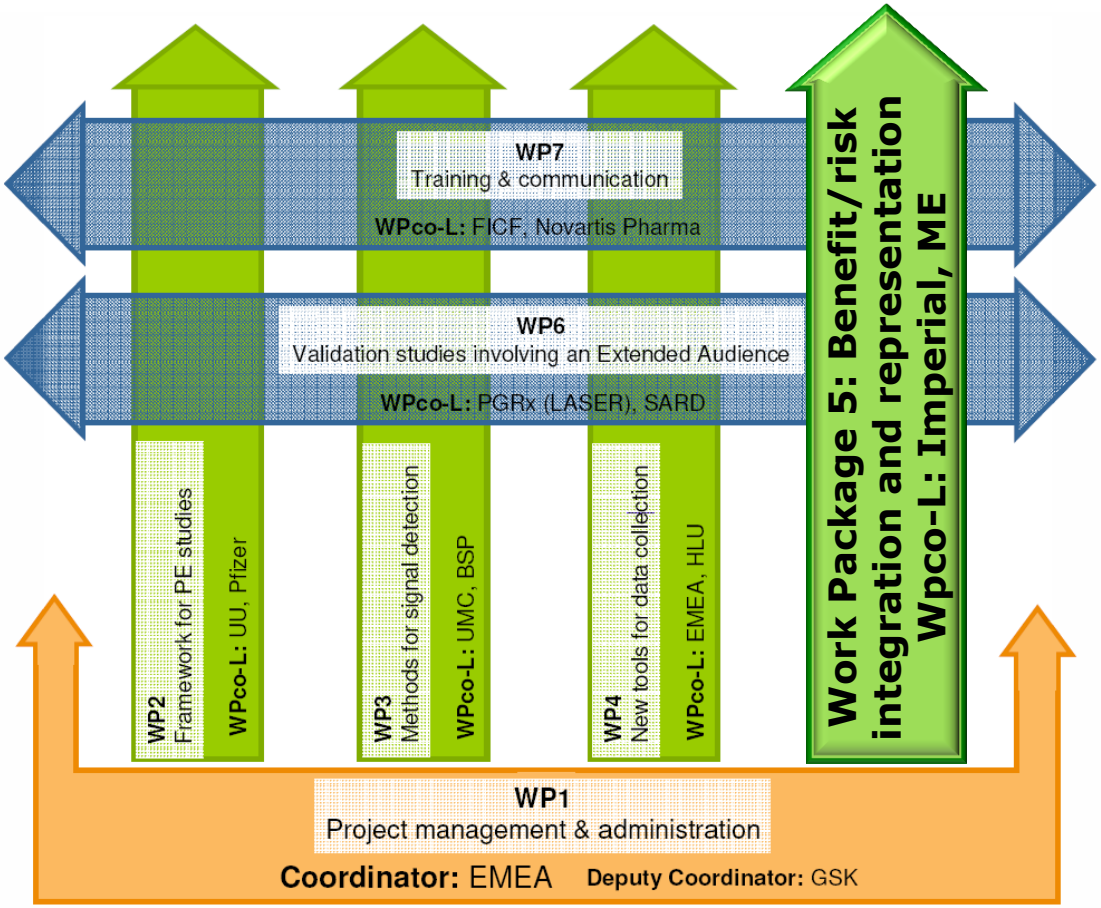
The IMI-PROTECT

- PROTECT[1] (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium)

- "Improving and strengthening the monitoring of the benefit/risk of medicines marketed in the EU" including graphical representation of risk-benefit led by EMA with 31 public and private partners, 2009-2014 (www.imi-protect.eu)

[1] PROTECT is receiving funding from the European Community's Seventh Framework Programme (F7/2007-2013) for the Innovative Medicine Initiative (www.imi.europa.eu)

Work Packages



- One WP concerned with all aspects of the organisation and management of PROTECT
- Four "vertical" WPs targeting the specific objectives and methodological developments
- Two "horizontal" WPs concerned with the communication, validation and integration of the scientific work into an integrated and cohesive European activity

Work Package 5 of PROTECT

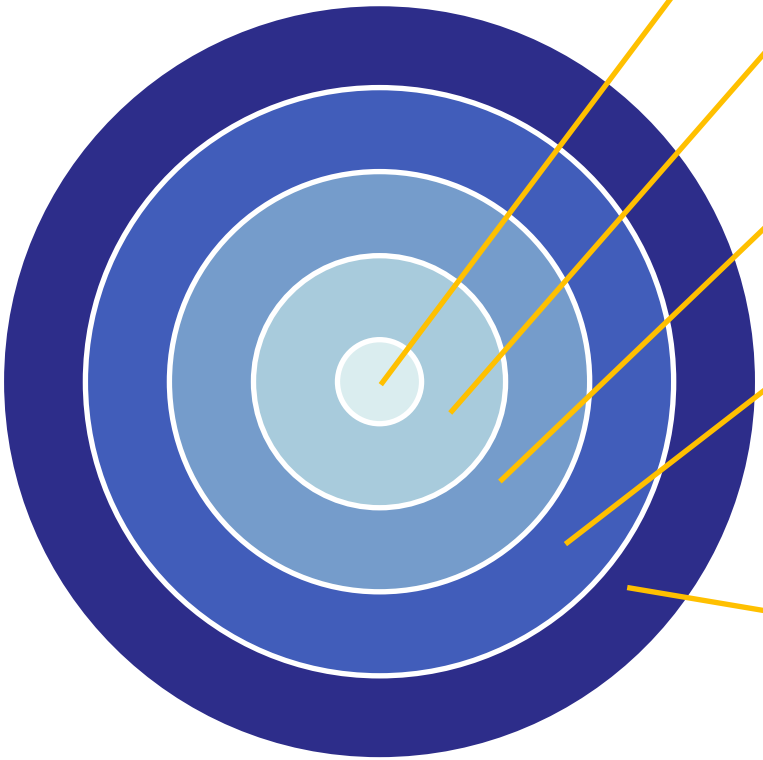
- Benefit-Risk Integration and Representation Charter
  - Scope
    - Submission and post-approval, while recognising the relevance of pre-approval B-R assessment
    - Individual and population-based decision making
    - The perspectives of patients, physicians, regulators and other stakeholders such as societal views needed for HTA
    - Possible interdependencies with other PROTECT Work Packages as well as other relevant external initiatives.
  - Review and selection of methodologies and of visualisation methods
  - Choice and implementation of case studies
  - Visualisation
  - Communication (publications)

Evidence Based Medicine

"EBM is the conscientious explicit, and judicious use of current best evidence in making decisions about the care of individual patients" taking into account "individual patients predicaments, rights and preferences using best evidence from clinically relevant research."

Sackett et al, 1996

Stakeholders as decision makers



Patients

- Make decisions for themselves

Healthcare providers

- Make decisions based on prescribing lists

NICE

- Makes decisions on cost-effectiveness

EMA/MHRA etc.

- Makes decisions on quality, safety, efficacy and benefit-risk balance to individuals and public health

Pharmaceutical companies

- Makes decisions on what to develop for which licenses to apply

Benefit-risk integration

- There are explicit methods of decision-making that have been hypothesised for use within a regulatory context that balance and/or integrate the benefits and risks of treatments
- Many methods combine safety and efficacy data with stakeholder values and preferences
  - Do the benefits outweigh the risks?
- Values and preferences can vary by stakeholder group
  - It is important to take into account the patient perspective

Benefit-risk representation

Recommendations from PROTECT External Advisory Board (EAB)

EAB Rapporteurs: Vicky Hogan, David Haerry

- The optical representation of benefit/risk in WP5 should be tested with one or more patient/consumer and health care professional groups to get their feedback on the usability and interpretability of each representation.
- Recommend to explore the use of groups such as, but not limited to, 1) PCWP, 2) HCPWP, 3) the for Therapeutic Innovation (EUPATI). These groups should be engaged for the purpose of developing and testing the optical representations.
- Recommend that WP5 identify a member either within the team or otherwise to take on the role of engagement of patient/consumer and healthcare professional groups for the purpose of evaluation of optical representations.

Initial presentation Georgy Genov (EMA) at the 7th May PWCP meeting

Work to date…

Six case studies which take publically available data and investigate:

a) Key benefit-risk methodologies to explore the balance of benefit and risk
   - Not intended to replicate or comment on any regulatory decisions

b) Existing and innovative visuals to explore ways in which benefit and risk can be displayed

Stakeholder involvement has been incorporated into the case studies where possible. E.g. Acomplia and Tysabri.

Acomplia

Active drug	**Rimonabant**
Indication	Weight loss in obese and overweight patients with co-morbidities in adults (>18y)
Regulatory history	Approved June 2006, Voluntary withdrawal in January 2009
Severe side effect	Increased risk with depression
Data source	EPAR Published clinical trials
Comparator	Placebo, Orlistat (Wave 2), Meridia (Wave 2)

Stakeholder involvement

- Benefit-risk assessment method:
  - Discrete choice experiment
- Format: web survey sent to members of Weight Concern
  - Introduction to the study
  - Glossary defining benefits and risks
  - 9 examples of hypothetical scenarios
  - Feedback

Example of a scenario

Two treatments for obesity are described in the table below.
Please imagine that you have an option of receiving one of the treatments, and consider which one you would prefer to receive.

		Treatment A	Treatment B
Benefits (higher is better)	Physician's view on **HDL Cholesterol levels**	Mild improvement	No change
	Number of people who experience a **10% weight loss**	10 out of 1000	450 out of 1000
Risks (lower is better)	Number of people who experience **psychiatric conditions**	100 out of 1000	1 out of 1000
	Number of people who experience **cardiovascular conditions**	1 out of 1000	100 out of 1000
	Number of people who experience **gastrointestinal conditions**	1 out of 1000	None

***6. After considering them, please answer the following question:**

	Treatment A	Treatment B
Which treatment would you prefer to receive?	○	○

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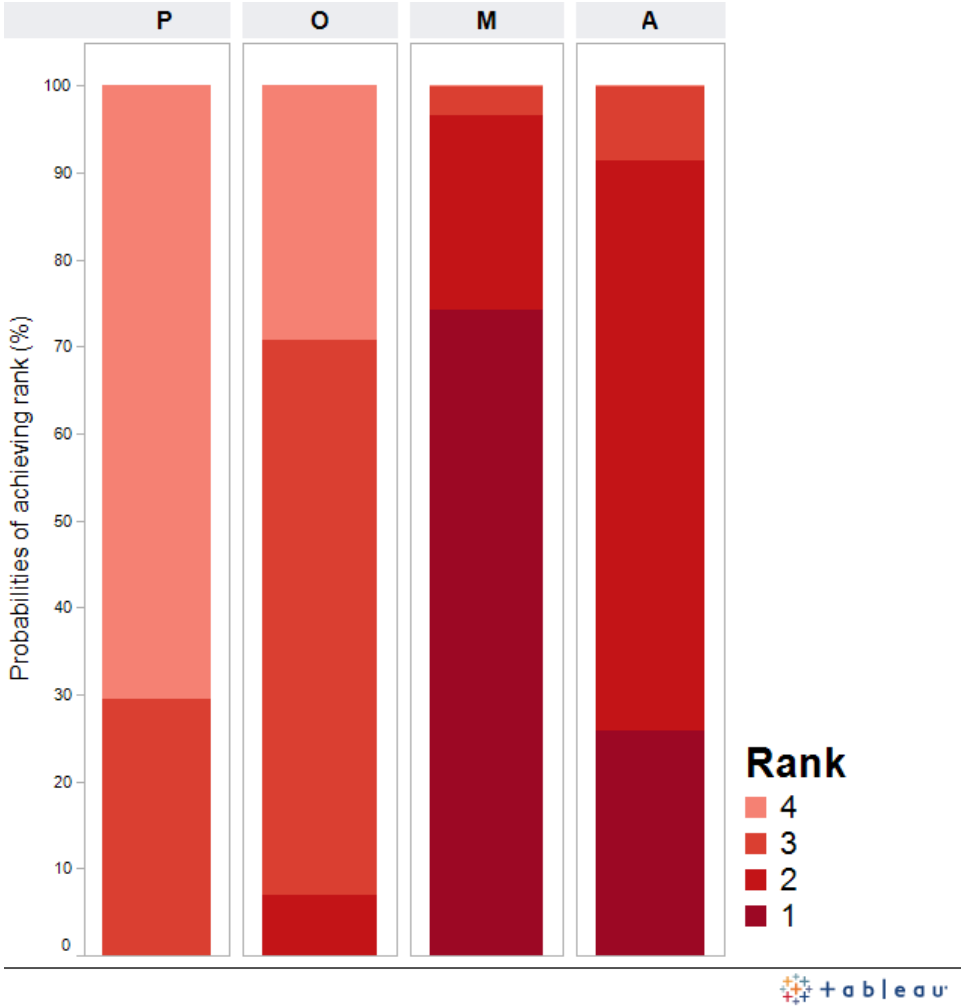
Results

- 166 complete responses
  - High level of comprehension
- Results:
  - As the level of benefit increases, a treatment is more likely to be selected
  - As the level of risk increases, a treatment is less likely to be selected
  - Risks ranked by importance:
    1. Psychological adverse events
    2. Cardiovascular adverse events
    3. Gastrointestinal adverse events

Stacked bar chart

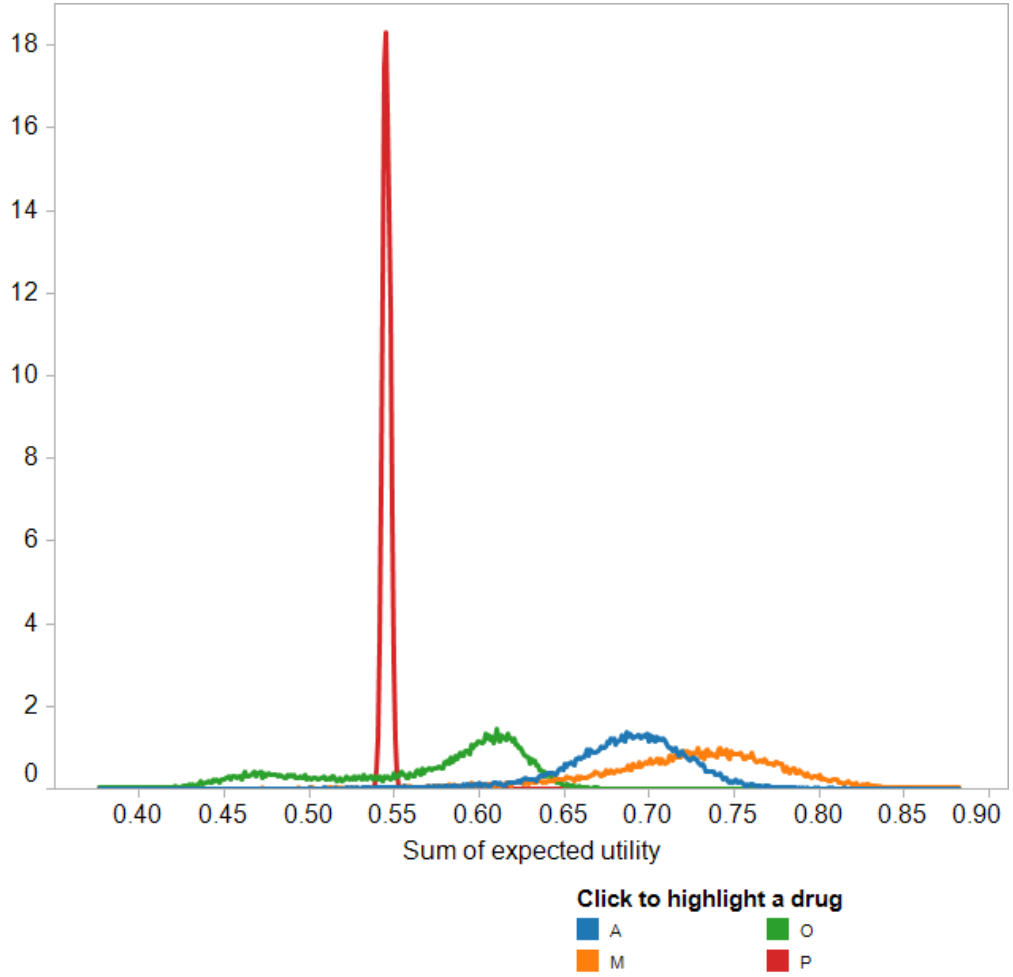
Probabilities achieving rank 1, 2, 3 or 4 (SMAA)



- Non-missing weights model
- Drugs
  - **P**lacebo
  - **O**rlistat
  - **M**eridia
  - **A**complia

Utility distributions

Using a set of decision-maker's weights (SMAA)



- Drugs
  - **P**lacebo
  - **O**rlistat
  - **M**eridia
  - **A**complia
- Online interactive version allows own weights is available

http://public.tableausoftware.com/views/wave2rangeweight/Dashboard2?:embed=y

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Tysabri

Active drug	**Natalizumab**
Indication	Relapsing remitting multiple sclerosis
Regulatory history	• Approved in 2004 • Withdrawn in 2005 • Re-introduced in 2006 due to patient demand (with strict risk minimization measures) • Reassessed in 2009 due to PML risk (current approval was confirmed)
Severe side effect	PML (rare neurological disorder)
Data source	EPAR Published clinical trials
Comparator	Placebo, Avonex, Copaxone

Stakeholder involvement

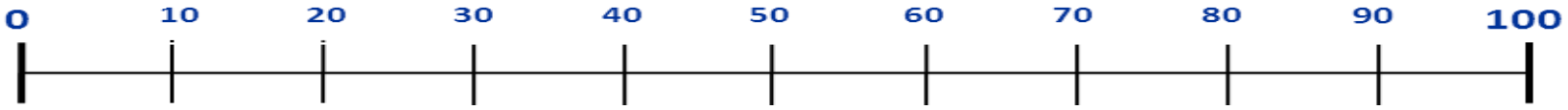
- Benefit-risk assessment methods:
  - Analytic hierarchy method, multi-criteria decision analysis (MCDA), MACBETH
- Format:
  - Online survey, paper questionnaires, focus groups
  - A glossary of terms will be provided

Example of a question (MCDA)

This question is asking about your preferences for the way a drug for multiple sclerosis is administered and how often it is administered.
There are four different ways a dug could be given to you in the table below.
We ask you to assess your relative preferences for each of these methods.

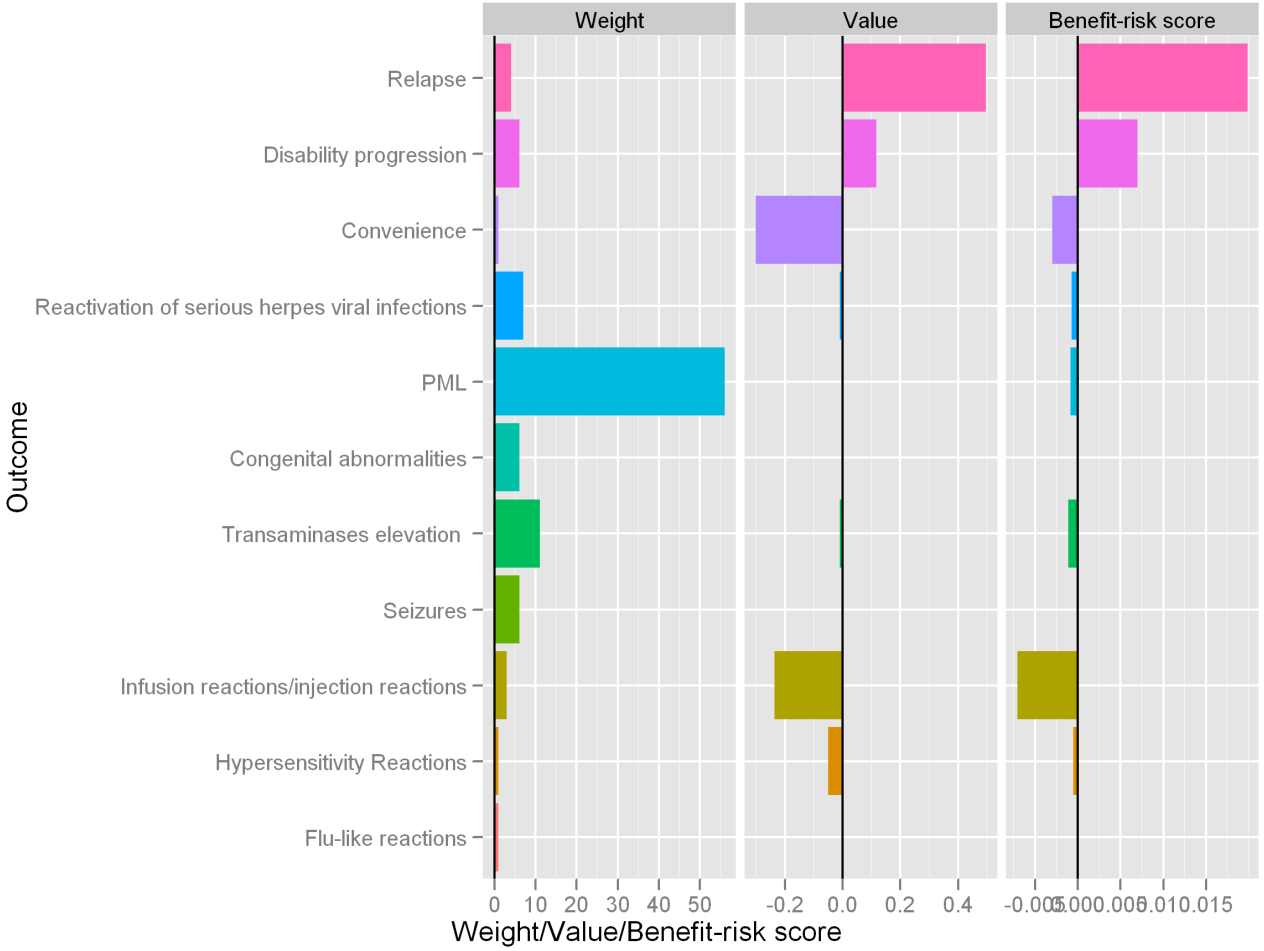
1) Give your most preferred method of administration a value of 100
2) Give your least preferred method of administration a value of 0
3) Gives values between 0 and 100 for the remaining methods of administration

Outcome	Value Best = 100 Worst = 0
Oral once daily	
Intravenous infusion once monthly (in a hospital)	
Intra muscular injection once weekly	
Subcutaneous injection once daily	



Weighted Scores

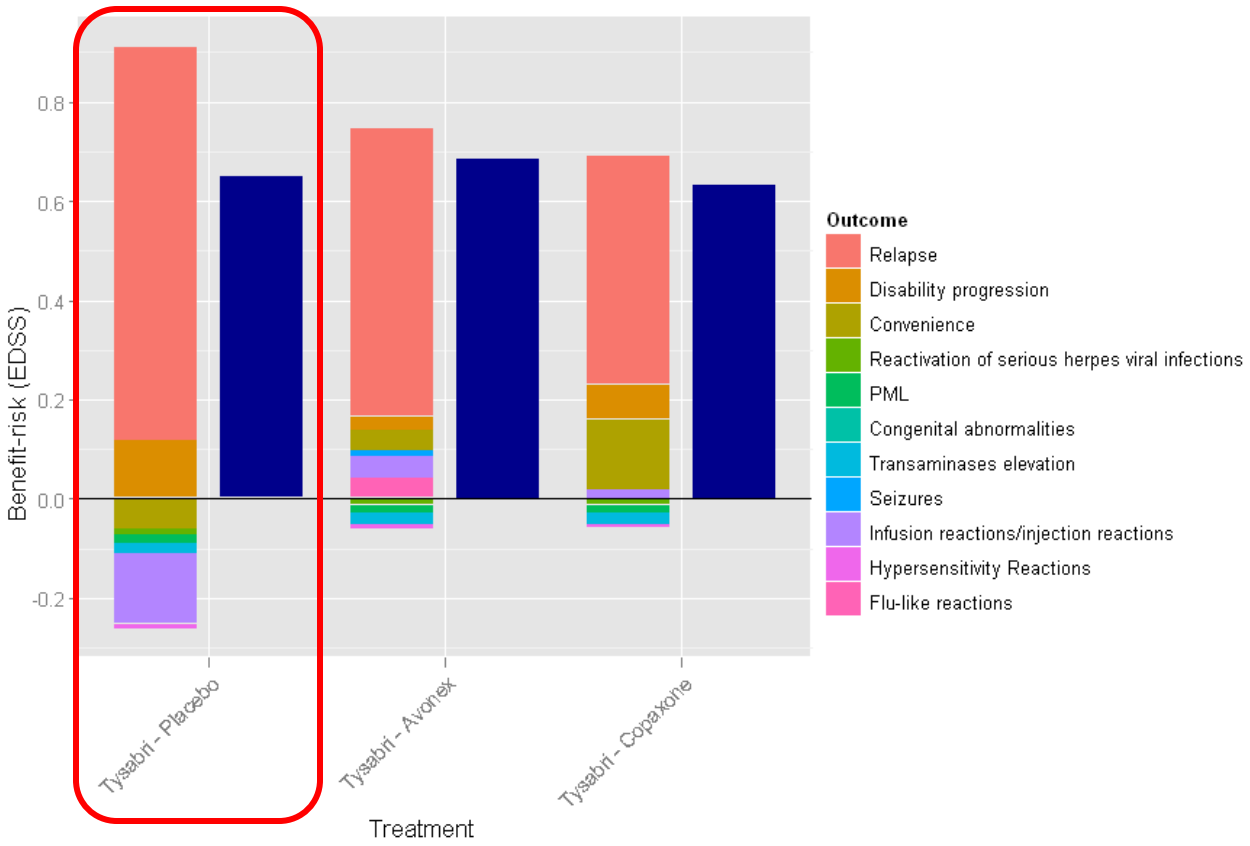
Contribution of each outcome for Tysabri - placebo



- 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 reactions are the worst risk

Criteria contribution

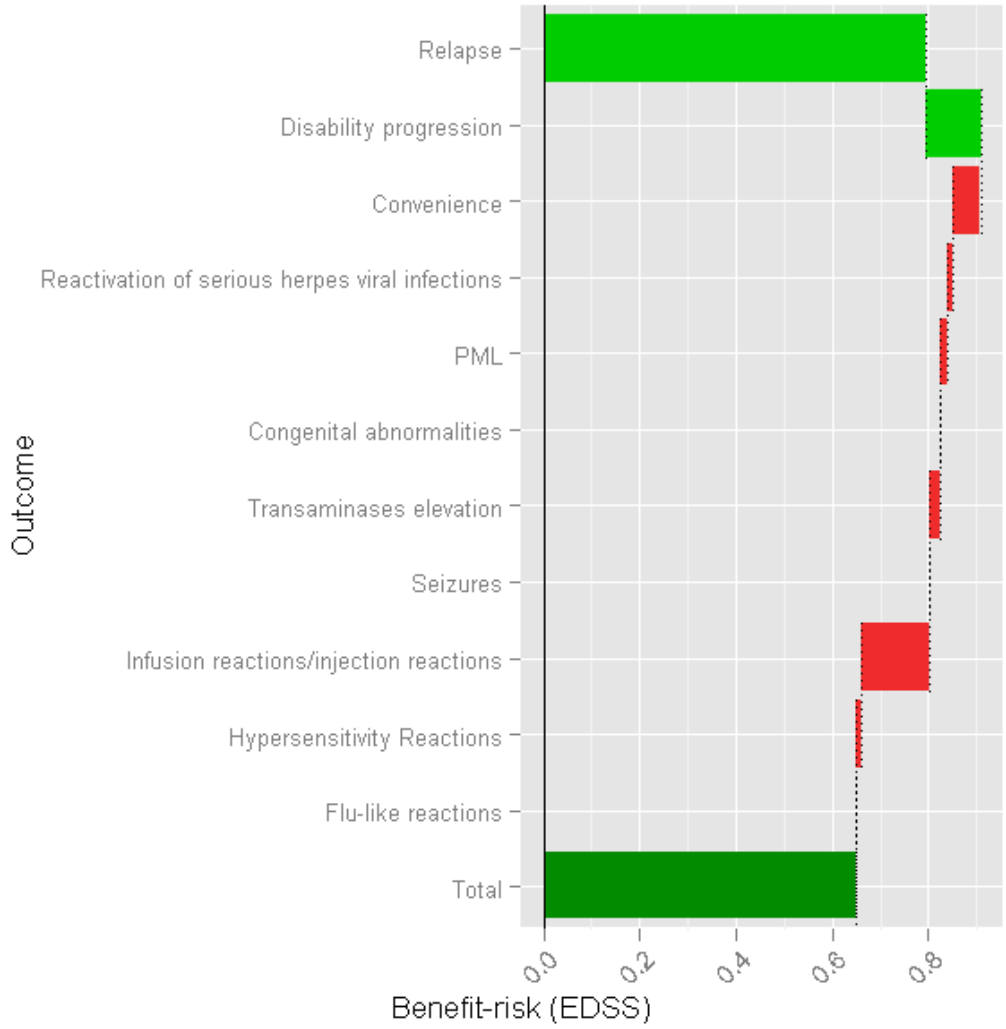
Stacked bar chart for Tysabri vs. all the other treatments.



- 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.

Waterfall plot

Tysabri - placebo

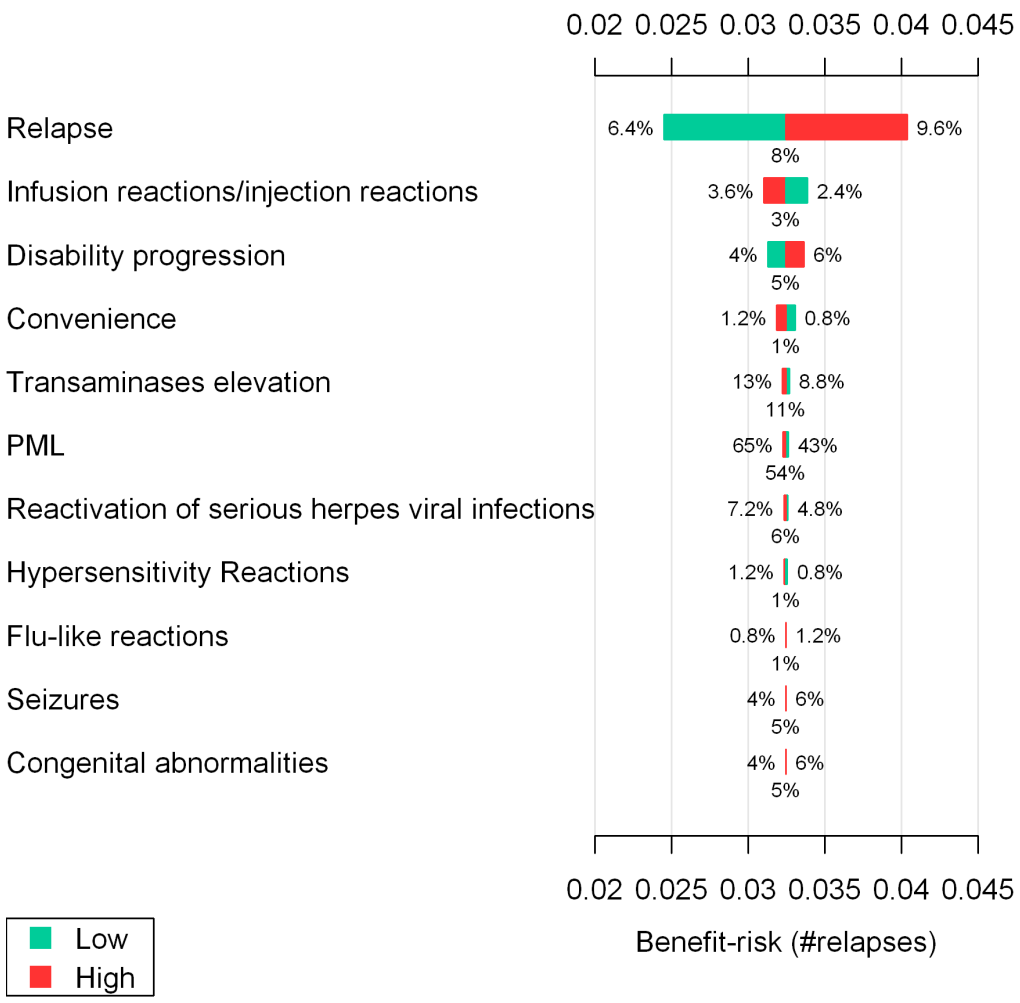


- Like a horizontal bar chart, except that the end of the previous bar determines the start of the next bar
- End of the last bar gives the overall benefit-risk.
- Green = positive BR
- Red = negative BR

http://public.tableausoftware.com/views/T_Waterfall/WaterfallRisk

Tysabri: One-way sensitivity analysis

Tornado diagram for sensitivity to weights. Tysabri - 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.

Challenges of stakeholder involvement

- Requirements of funder/ethics committee/institution or organisation
- Time required for ethical approval and establishing links with patient organisations
- Complex issues surrounding reimbursement
- Lack of methodological guidelines for stakeholder involvement within a benefit-risk context. Examples:
  - Selecting participants: methods of recruitment, number of people
  - How:
    - Method: E-mail, website, through the post, telephone, in-person
    - Format: Questionnaires, focus groups, interviews

But, patient values and preferences are a key and required aspect for taking this work forwards and ensuring its relevance

Going forwards: Ways of collaborating

Your input can help provide;

- Increased understanding of values and preferences within benefit-risk decision-making for medications
- Increased understanding of the kinds of visual representation that may prove most useful

How can this collaboration be achieved?

- Online surveys
  - Presenting a series of hypothetical scenarios (either presented numerically or visually/graphically), where respondents are asked to decide between two treatments for a specific indication, each with a different benefit-risk profile
  - Option to provide comments but answering the questions themselves involves clicking a tickbox
  - Usually ~10 questions (15 minutes), maximum 2 occasions
- Focus groups
  - Exploring the feasibility of selected benefit-risk decision-making methods and their application with patient stakeholders
  - E.g. selection of benefit and risk outcomes, description of tasks, presentation of benefits and risks, interpretation of visualisations, time demands
  - 1 day workshops
- Further discussion/interaction at future working party meetings

Disclaimer

"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."