PROTECT

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

PATIENTS AND PUBLIC INVOLVEMENT IN BENEFIT-RISK ASSESSMENT AND DECISION-MAKING: METHODS AND APPLICATIONS

IMI-PROTECT Symposium

Benefit-Risk Integration and Representation Workshop

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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."

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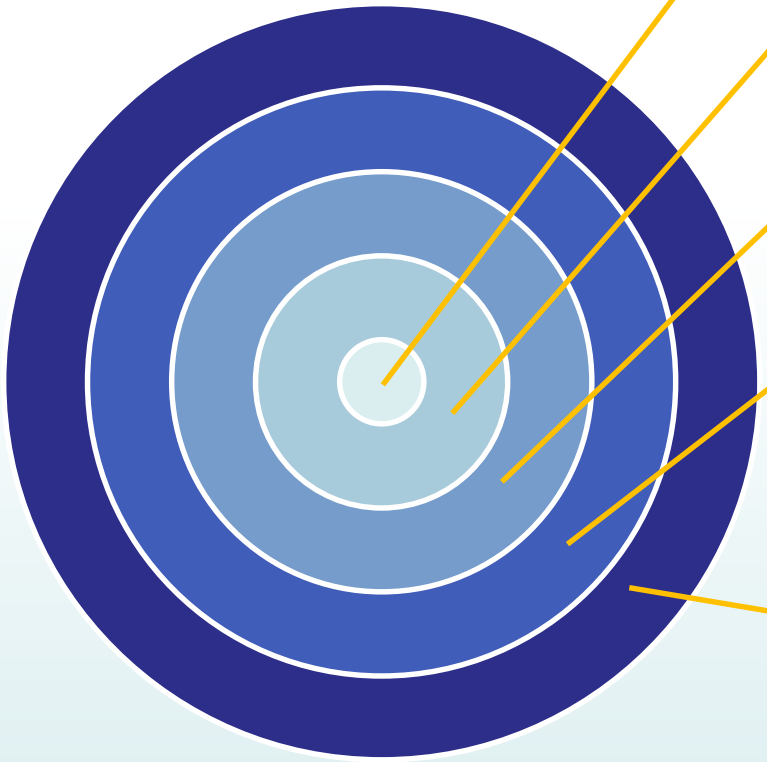
Decision makers



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

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.

Varying degrees of involvement

Consultation

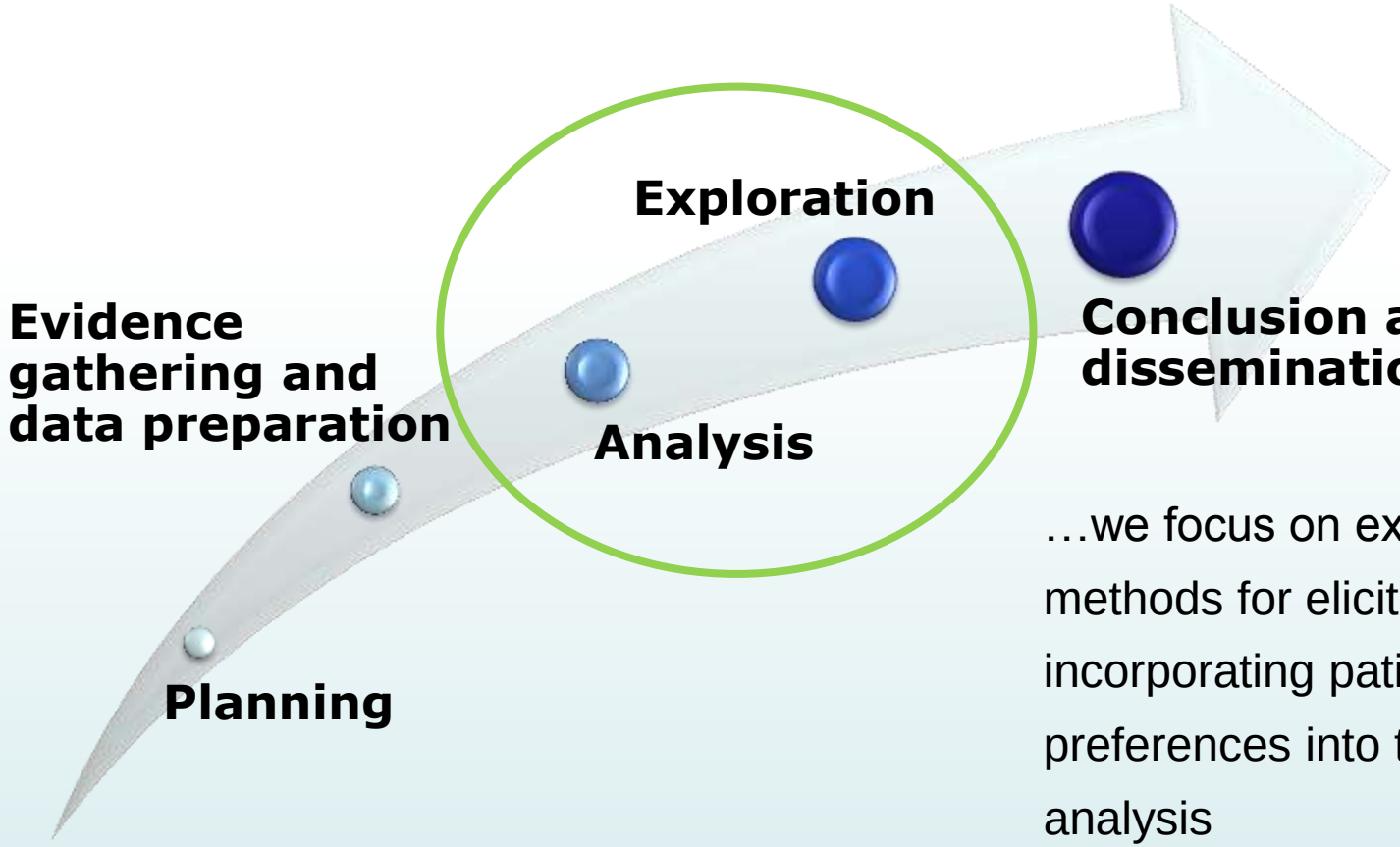
Health professionals elicit the patient and public perspective to inform the decision making process

Collaboration

Health professionals and patients and the public form an active partnership and jointly participate in decision making

At what stage can PPI occur

There is scope for patients and the public to be involved throughout the BR assessment process…



…we focus on explicit methods for eliciting & incorporating patient preferences into the analysis

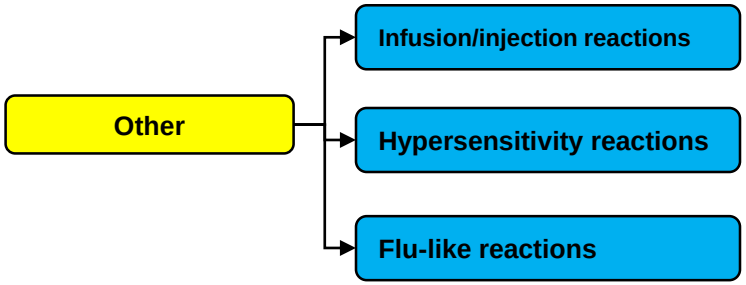
Preference elicitation

- Well-known methods for preference 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)

Simple weighting

Multi Criteria Decision Analysis (MCDA)

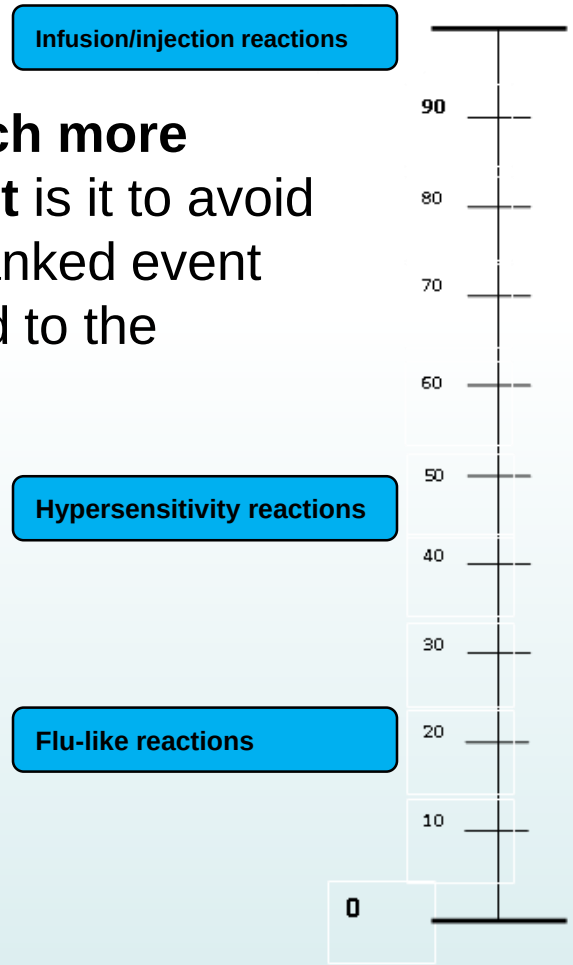
For each outcome category



1. Rank outcomes

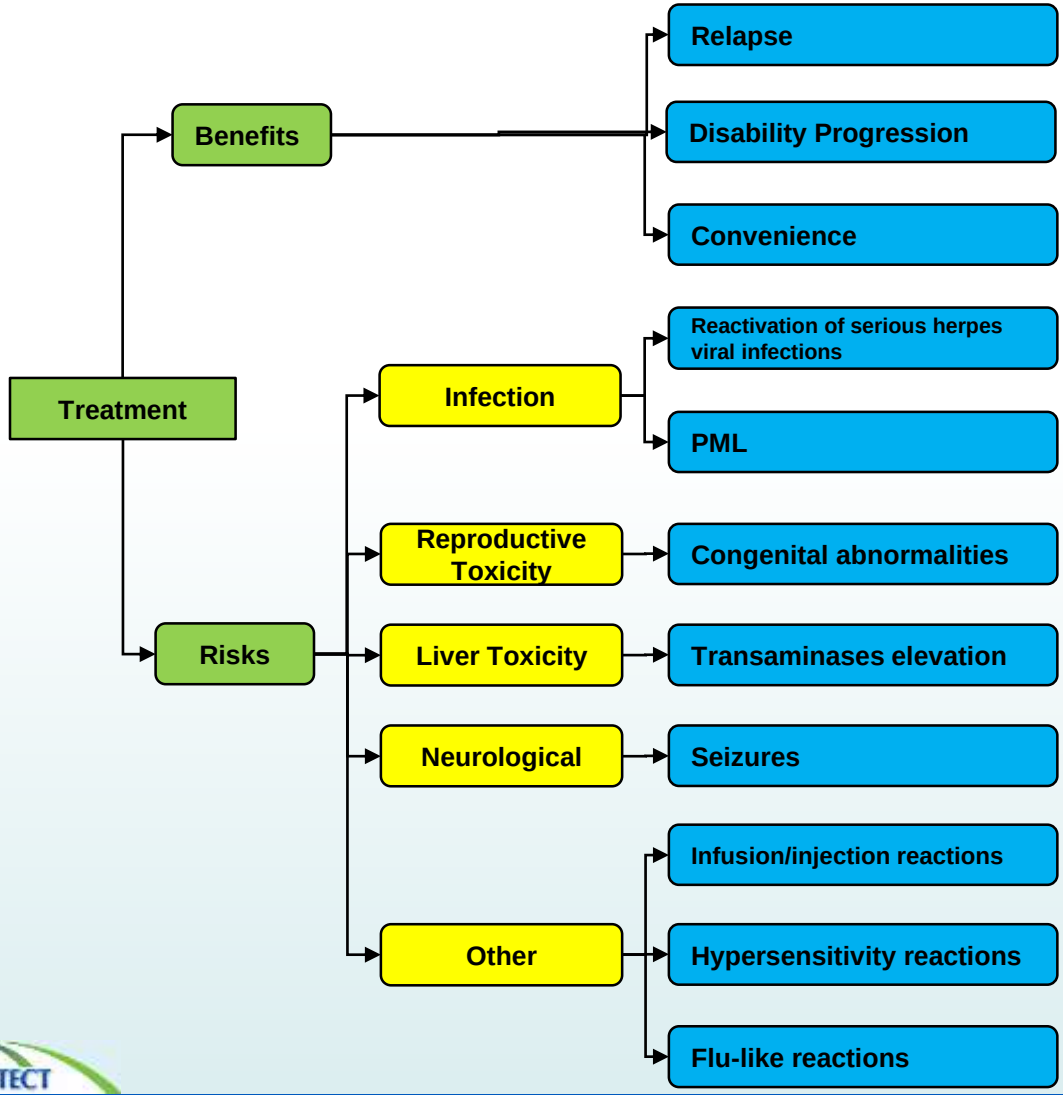
Outcome	Rank
Infusion/injection reactions	1
Hypersensitivity reactions	2
Flu-like reactions	3

2. Relative importance



Repeat this process all the way up the value tree

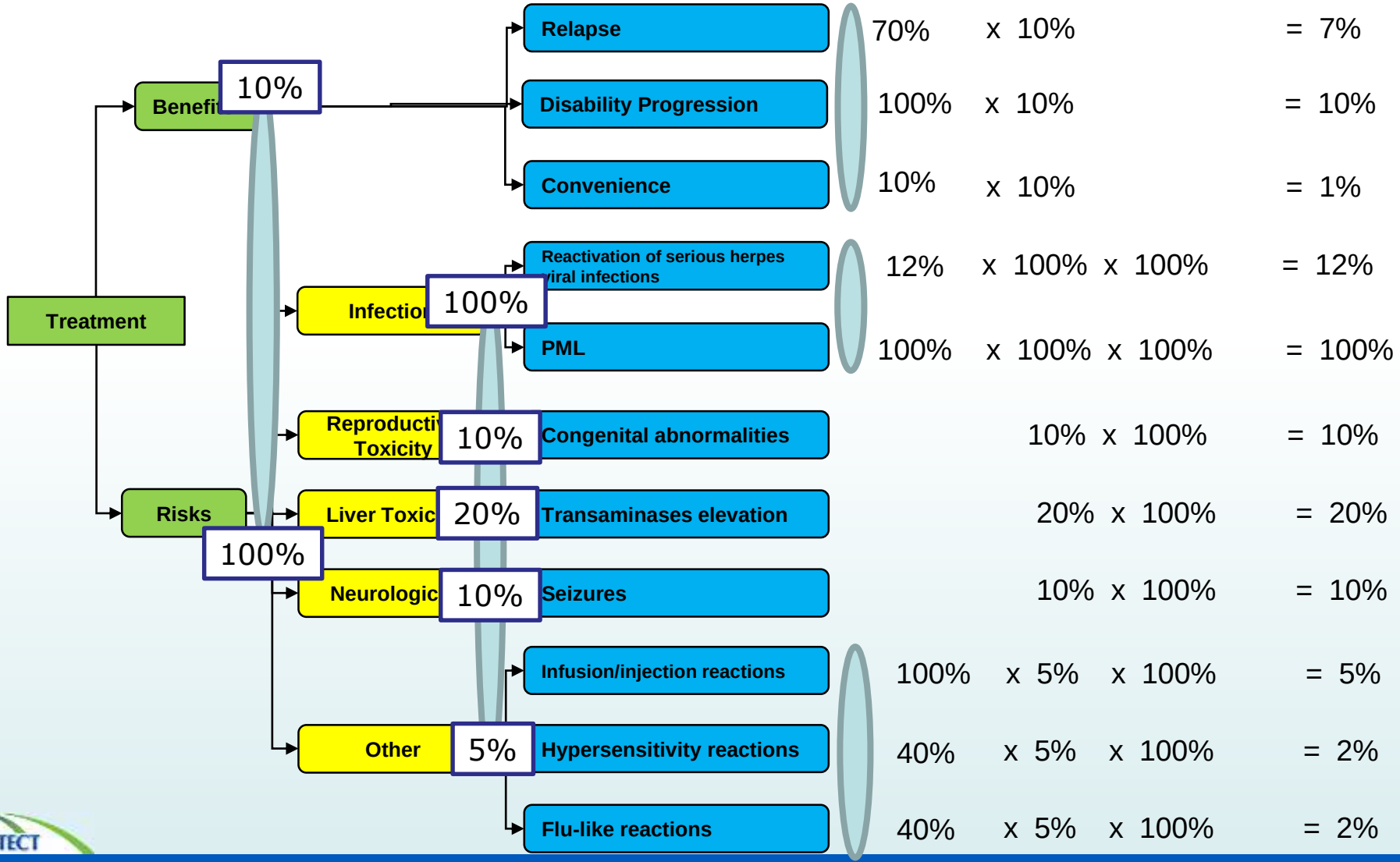
The top ranked outcome in each category is carried up the tree



- 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

Repeat this process all the way up the value tree

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



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 relative attractiveness of outcomes on **pairwise** basis
- **Step 2**: Check consistency of answers (eg cannot have A>B>C>A)
- **Step 3**: Compute initial guess at weights with optimization
- **Step 4**: Refine weights while maintaining consistency

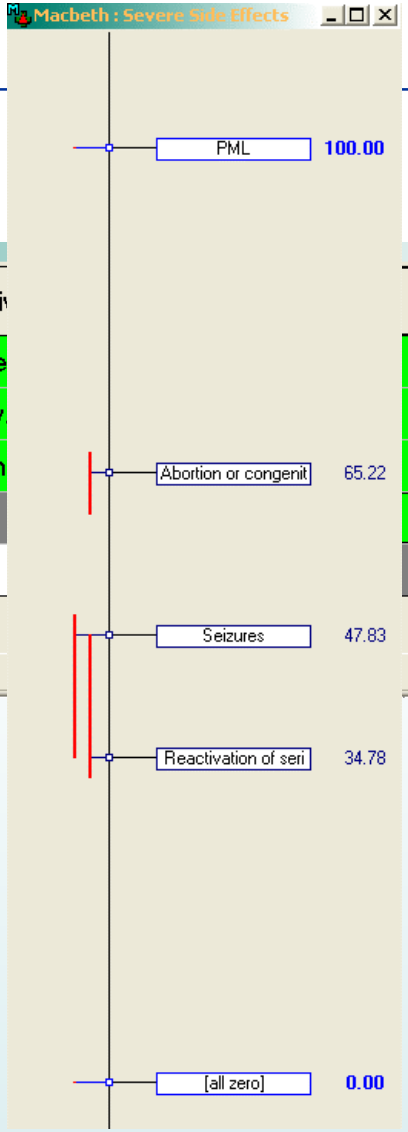
MACBETH

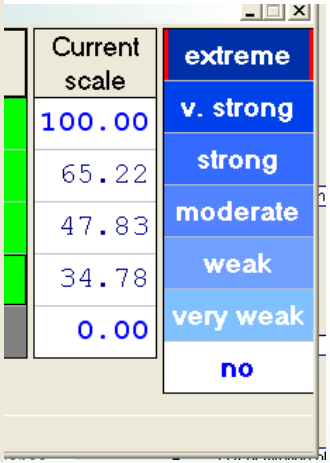
Qualitative assessment

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





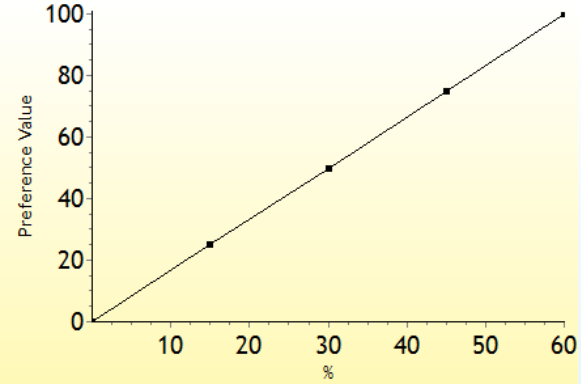
AHP (Analytic Hierarchy Process)

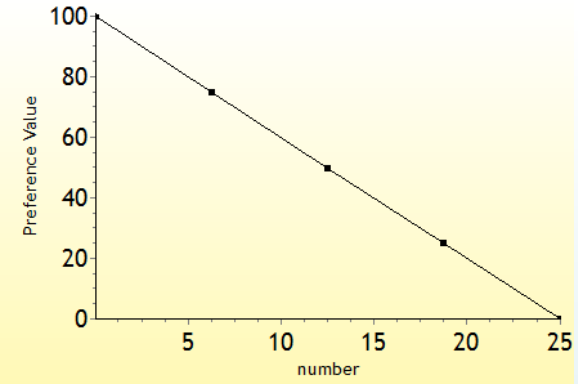
Qualitative assessment

- Based on qualitative pairwise comparisons (similar to MACBETH)
- No consistency check, but rather a score
- Qualitative responses are translated to a quantitative scale (integers from 1 to 9)
- Weight is calculated by finding the dominant eigenvector of the corresponding matrix, or by regression

Weighting individual events has its limits

- Examples so far involved trade-offs between individual events (eg 1 relapse vs 1 disability progression vs 1 case PML)
- This implies that events of a given type are all equal in value i.e. linear (partial) value functions

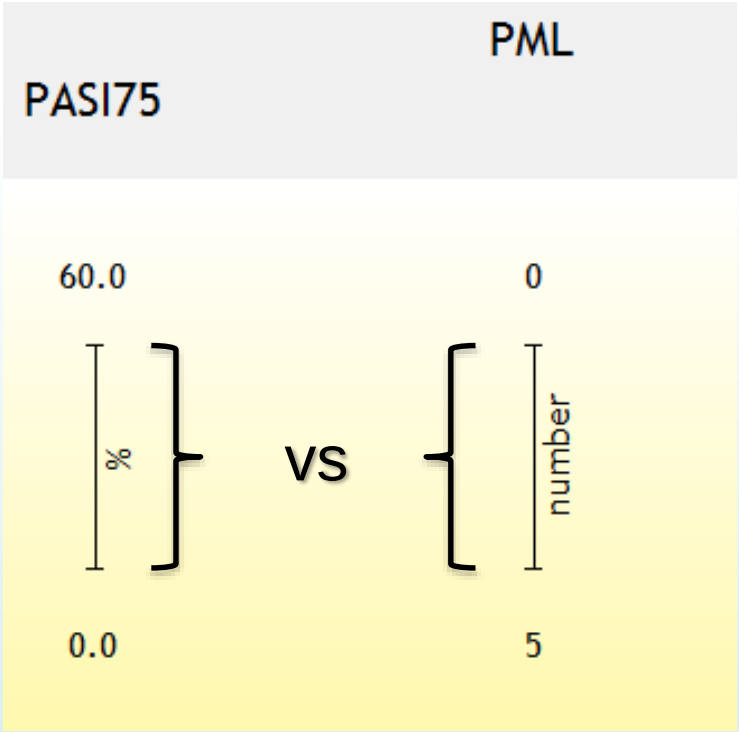




- It can be difficult to trade off events that are very different in importance (eg 1 infusion/injection reaction vs 1 case PML)

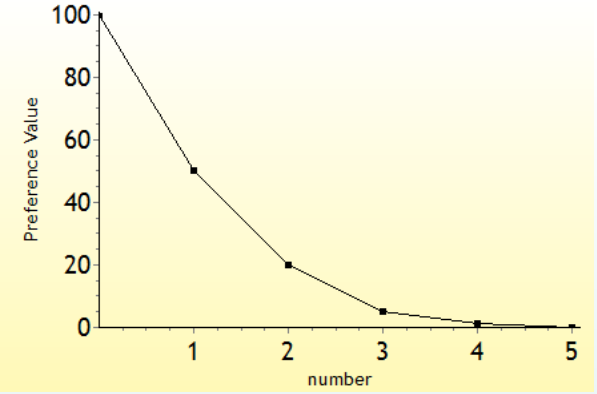
Swing weighting (1)

- Set best and worst possible figure for each outcome
- How much more attractive is it to move from worst to best for outcome A vs moving from worst to best for outcome B?



Swing weighting (2)

- Allows non-linear (partial) value functions (these can be elicited in the same way as weights)
- Helps to establish common value scale for events that are different in importance



Errors to watch out for:

- **Not communicating swings clearly to participants**
- **Not accounting for swings correctly during benefit-risk assessment**

Discrete Choice Experiments (DCEs)

In A DCE, participants are asked to consider a number of choice scenarios, eg:

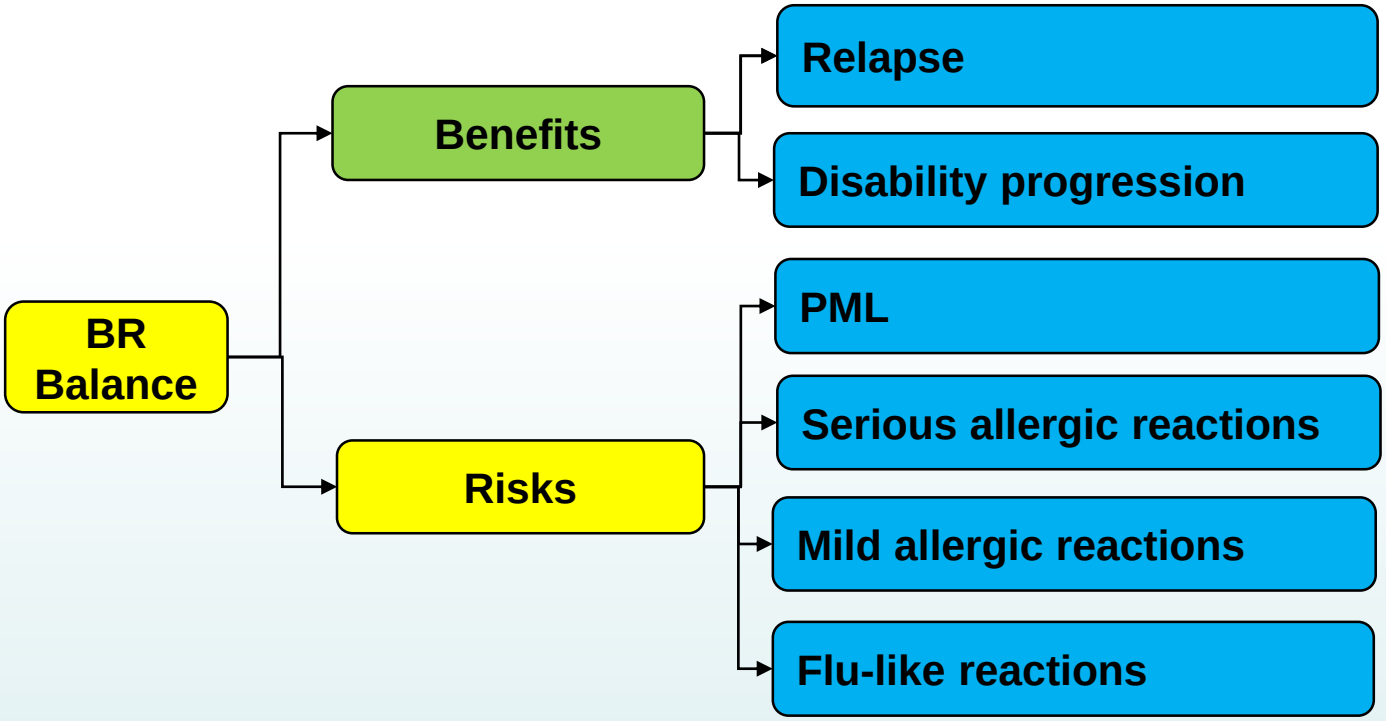
Attributes

Car A	vs	Car B (Levels)
• Manufacturer: Maserati		• Manufacturer: Vauxhall
• Price: £££££		• Price: £££
• Mileage: 0		• Mileage: 10,000
• Fuel efficiency: Poor		• Fuel efficiency: Good

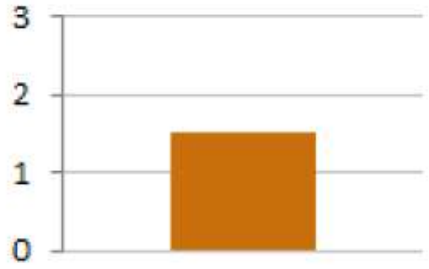
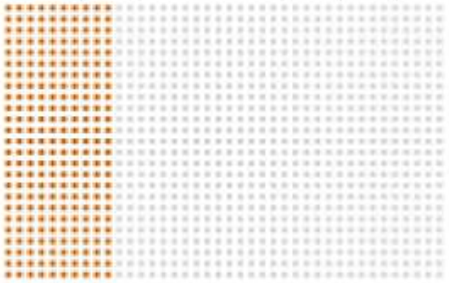
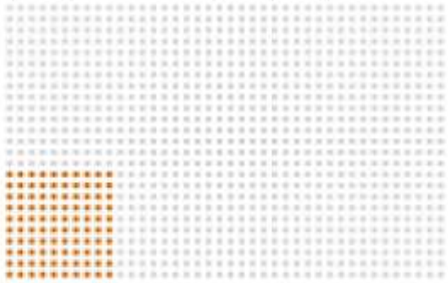
Which car would you choose?

Natalizumab DCE

6 attributes, 2 levels each



Natalizumab DCE: questionnaire (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

Natalizumab DCE: questionnaire (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**

DCE design – technical considerations

- Need to specify utility/value model based on multiple attributes - not restricted to linear additive models (unlike other methods such as MCDA)
- The required number of attributes and levels depends on the model that is chosen and the required level of precision
- Balance with reasonable limit on number of questions

DCE design – burden on participants

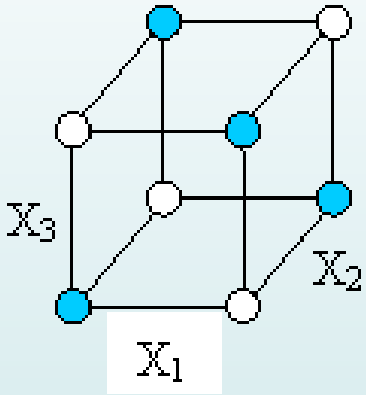
- Cognitive strain becomes an issue in all but smallest DCEs
- Need to limit number of attributes, alternatives, choice sets
- Plus usual need to ensure task & key background info is understood
- Validation questions can be included

DCE design – full / fractional factorial

- **Full factorial**: uses all (!) possible combinations of attribute levels

  # combinations = A^L if all A attributes have L levels

- **Fractional factorial**: uses a subset of the possible combinations of attribute levels
  - Not all fractional factorial designs are equally efficient
  - Efficient designs exhibit various kinds of symmetry:
    - Level balance
    - Orthogonality
    - Minimal overlap
    - Utility balance



Fractional factorial designs: like working out the dimensions of a box given the locations of some of the corners

Comparative overview of elicitation methods

	Swing-weighting	MACBETH	AHP	DCE
Responses	Quantitative	Qualitative	Qualitative or quantitative	Qualitative
How is consistency measured?	Method ensures consistency	Inconsistencies must be resolved	Computes a consistency score	Reflected in uncertainty of estimates
Weight calculation	Direct	Linear optimisation (plus tuning)	Principal eigenvector	Regression
Can be given out as a paper questionnaire?	No	No	Yes	Yes

Conclusions

- Eliciting patient preferences in regulatory assessment can add value and lead to more clinically relevant decisions
  - Political legitimacy, transparency, trust, communicability
- A number of formal methods can be used to elicit patient preferences
  - Each methodology has its own features, strengths and weaknesses
  - The PPI work from PROTECT is still ongoing…

ACKNOWLEDGEMENT

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