PROTECT

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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

A real-life experience into the world of benefit-risk assessment: case studies

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Workstream team

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Validation case studies to test compatibility of recommended B/R methods to real-life decision making constrains

Via case studies chosen to assess real-life conditions of B/R :

- Handling data heterogeneity and scarcity
- Handling the mix of RCT and observational information
- Handling long-term outcomes and different time horizons
- Considering the actual comparators present on the market at the time of decision
- Using primary data for preference elicitations
- Case of re-evaluation over time

Validation case studies to test compatibility of recommended B/R methods to real-life decision making constrains

	Efalizumab	Rimonabant
Handling data heterogeneity and scarcity	X	X
Handling the mix of RCT and observational information	X	X
Handling long-term outcomes and different time horizons	X	
Considering the actual comparators present on the market at the time of decision	X	X
Using primary data for preference elicitations	X	X
Case of re-evaluation over time	X	

Sources of data

	Benefit and risk criteria	Preferences / weights
Efalizumab	• EPAR: literature data, mix of RCTs and post-marketing observational data, • Different time horizons:e.g. PASI75 at 12 and 24 weeks, PML risk over 2 years • Add comparators	Dedicated Expert Panel session mixing regulators, clinical experts and statisticians
Rimonabant	EPAR: literature data, mix of RCTs and post-marketing observational data Model-based adjustment for data heterogeneity	Elicited from obese patients and healthcare providers in UK (workstream 2)

Needs identified by PROTECT for assessment process

Needs Identified	Addressing needs through case studies
Consistency across assessments	• Generic benefit-risk criteria; only benefit outcomes (sub-criteria) disease-specific • Weighting: direct and independent of scoring/ Scoring: generic scales • Test-re test, sensitivity vs. Panel involved
Compatibility with comparative efficacy / safety data	• MTC/modelling to adjust as far as possible time frame of each endpoint • Comparative scoring scales
Flexibility, ability to deal with uncertainty, lack of data, and heterogeneity of outcome measures	• MCDA B/R assessment quantitative framework • Scoring scales not numerical transformations of data ✓ Compatible with any type of data ✓ Allow expressing uncertainty (range of scores) • Uncertainty/heterogeneity of data handled via Bayesian MTC

Needs identified by PROTECT for assessment process – cont'd

Needs Identified	Addressing needs through case studies
Not complex, practical and efficient	• No complex mathematical transformation of outcomes data • Excel-based calculations
Ability to establish a clear audit trail	• By-criterion evidence matrix directly juxtaposes the evidence with the score on that evidence
Inclusion of diverse stakeholders and their different perspectives	• Panel mimicking regulatory board memberships • Diversity of values reflected in variation of weights • Diversity of judgments on evidence reflected in variation of scores
Appropriate visualisations	• Visual representation of: ✓ Positive and negative benefit and risk outcomes (stacked bar) ✓ Overall relative benefit-risk balance ✓ Uncertainty/variability propagated

Efalizumab case

Efalizumab case: WP6 study overview

Development of MCDA Benefit-Risk Framework*

- Leverage WP 5 work
- Benefit-Risk Tree
- By-Criterion Benefit-Risk Evidence Matrix
- Benefit-Risk Calculator and visual outputs

Advanced evidence synthesis

- Analysis for 3 time points : 2004, 2008, 2009
- Consolidation of literature review on efalizumab
- Systematic review on comparators as available on the EU market in 2004, 2008 and 2009
- Bayesian mixed treatment comparison with time dependency to adjust for different time horizons

Collection of semi-quantitative data

Data synthesis into the By-Criterion Benefit-Risk Evidence Matrix

Panel Session: Testing with Stakeholders (clinicians, methodologists, regulators)

Introduction: Contextualization of exercise

Step 1: Weighting

Step 2: Scoring

Step 3: On-site calculation and visual presentation of results

Step 4: Structured discussion

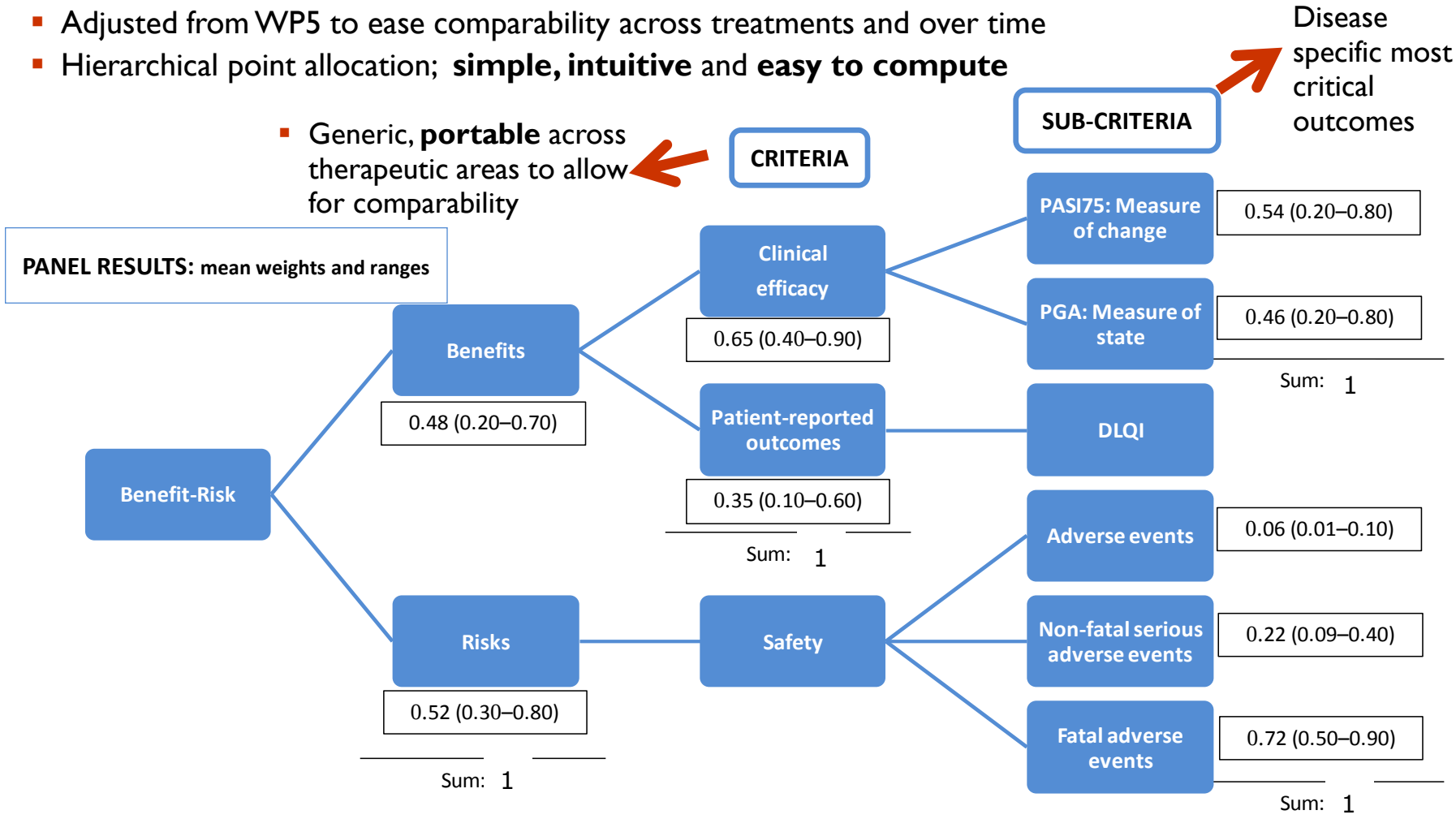
Test-test trial:

Exploration of reproducibility of benefit-risk assessment

*Based on the EVIDEM approach, incorporating ethics, MCDA and HTA principles

Efalizumab case: Weight elicitation technique & results

- Adjusted from WP5 to ease comparability across treatments and over time
- Hierarchical point allocation; **simple, intuitive** and **easy to compute**
  - Generic, **portable** across therapeutic areas to allow for comparability



Efalizumab case: Scores elicitation in evidence matrix

Generic scoring scale Comparative across all types of interventions

Decision criteria	Decision subcriteria	Highly synthesized data	Performance Scores
Benefits **Clinical efficacy**	**PASI75: measure of change** *Percentage of patients achieving at least a 75% reduction of PASI at a given time point when compared to baseline. The PASI is a measure of the average redness, thickness and scaliness of the lesions (each graded on a 0-4 scale), weighted by the area of involvement. PASI range is from 0 to 72.*	**BAYESIAN META-ANALYSES –2008** **% patients achieving PASI75 with efalizumab vs placebo**	5 Much better than comparator 4 3 2 1 0 No difference -1 -2 -3 -4 -5 Much worse than comparator Comments:

Trials/Data	Treatment duration	Odds ratio	*P* value	95% CI	Efalizumab (%)	Placebo (%)
[a]6 RCTs Efalizumab	12 wks					
	24 wks					
	2 yrs					

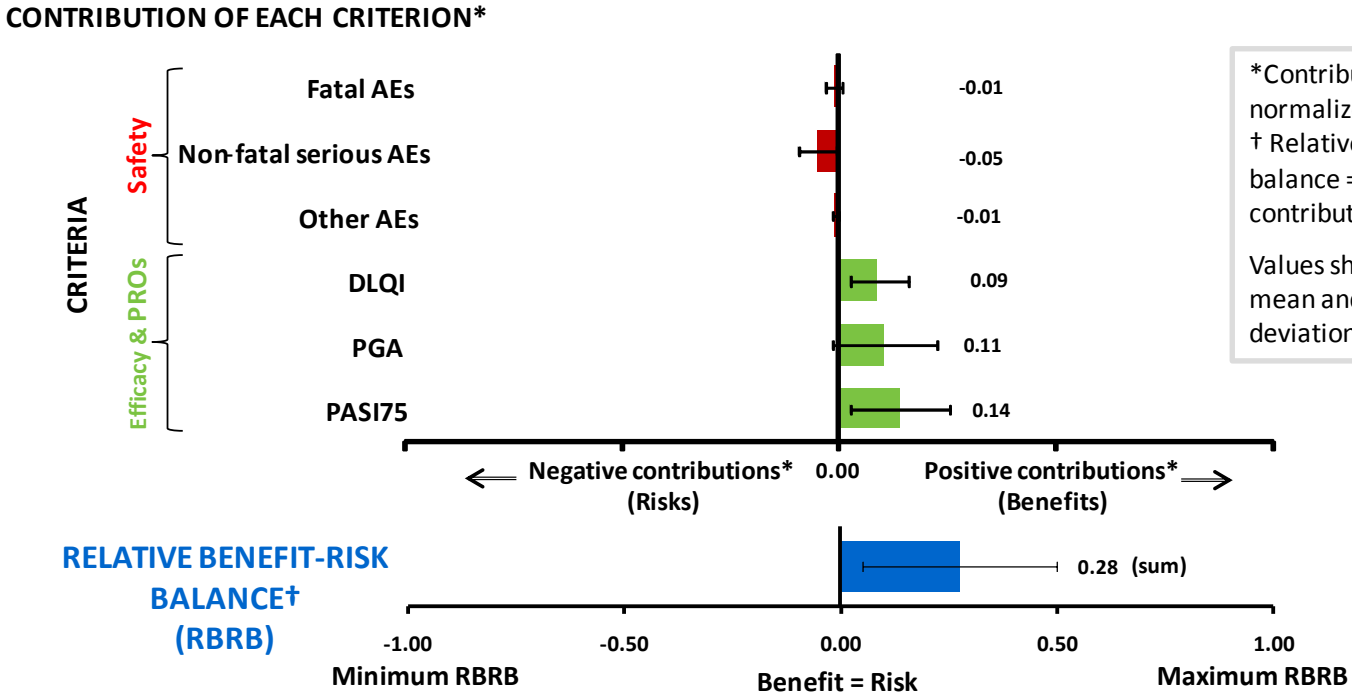
[a]Gordon 2004; Lebwohl 2003; Leonardi 2005a, Leonardi 2005b; Papp 2006; Dubertret 2006 (overall 3016 patients)
[c]etc

Reflect on score: How currently decided?

Reflect on data - is data available meaningful, sufficient? Quality?

Efalizumab versus placebo 2004 –

Relative benefit risk balance (RBRB) & uncertainty additive linear model



*Contribution of criterion = normalized weight × score
† Relative benefit-risk balance = sum of contributions of all criteria

Values shown represent mean and standard deviations across panelists.

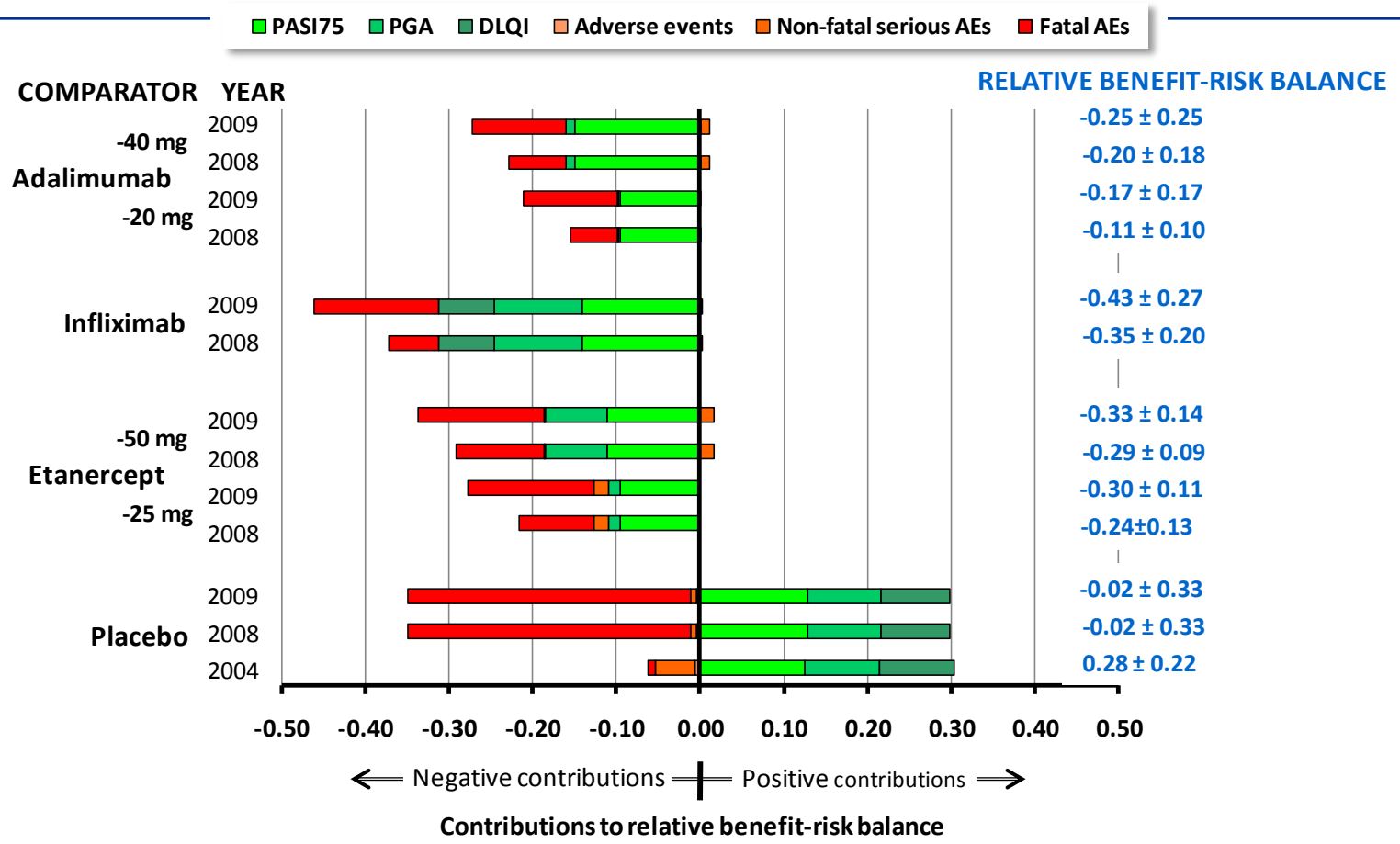
FAVORS COMPARATOR

B/R null

FAVORS EFALIZUMAB

*Total estimate on a range of -1.0 to +1.0

Results over time 2004 – 2009 across comparators



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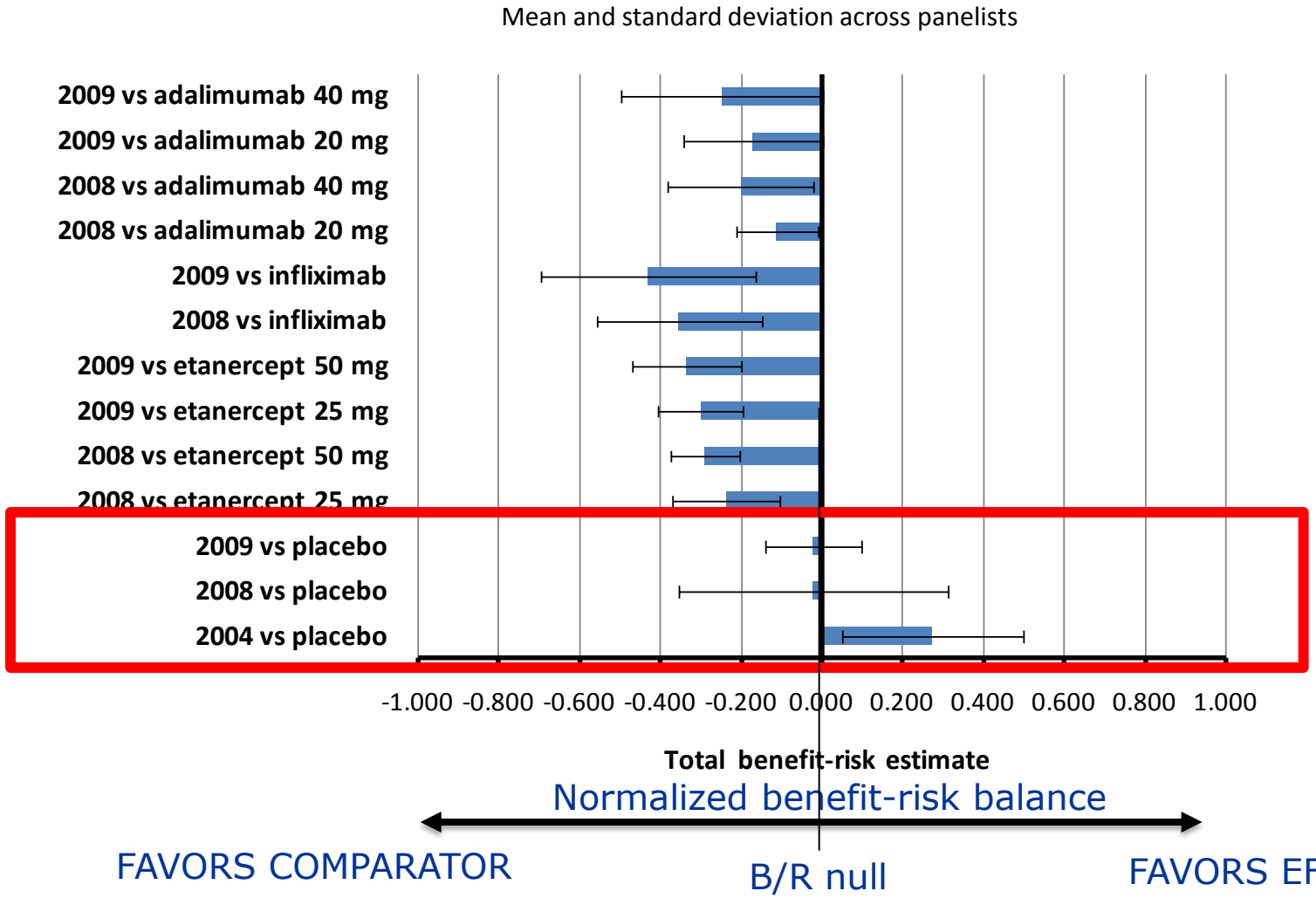
Results over time 2004 – 2009 across comparators



Test-retest

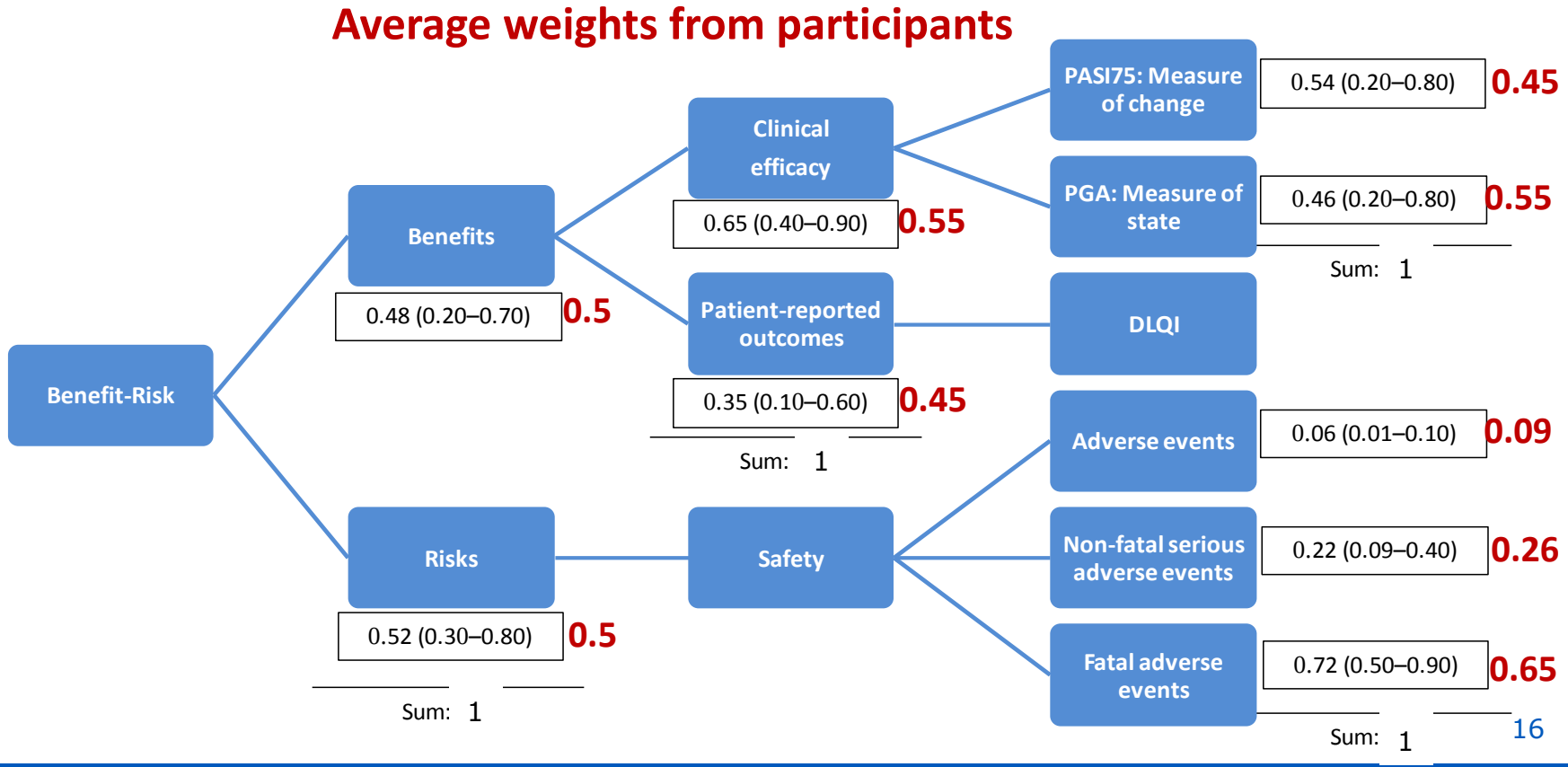
- Intra-rater correlation coefficients ICC* :
  - Weights: ICC =0.988
  - Scores efalizumab vs placebo: ICC =0.919
  - Scores efalizumab vs comparators: ICC =0.800

- Stability in judgment observed for weigths
- Stability in judgment affected for scores, especially vs comparators (uncertainty of data, uncertainty in interpretation of data)

* ICC(3,1) defined in Shrout and Fleiss, 1979

Sensitivity Analysis w/r Panel Preliminary results

- A PROTECT Training was organized on 18-Feb-2015 to reproduce the weights and scores elicitation from the participants



Overall learnings

Discussion

- Feedback from participants (Panel and training combined)
  - Helps structuring thinking and evaluation process; structured audit trail useful for decision accountability and consistency
  - Generic scoring scales accommodate heterogeneity of data and allow to express uncertainty; adapted to real life situations
  - Difficult to handle heterogeneity of safety data; need for better visualisation of safety data
  - Breakdown of contribution of each criteria to the RBRB can be used to discuss & validate interpretation of data
  - Modelling methods useful for missing/scarce evidence; presentation of all type of data available (not just the ideal data) is useful
  - Other criteria to consider such as disease severity, unmet needs, risk-mitigation plan
- Difference in implementation can translate in difference in results
  - WP5: BR favorable to Efa vs. pacebo (13% weight PML) VS WP6: BR unfavorable to Efa (38% weigth fatal events)

Take-home messages

- MCDA-based benefit/risk analysis in the real-life decision context can be successful and used as a quantitative support to structure discussions
- Real-life application requires consistency, comparability, ability to deal with heterogeneity, simplicity, audit trail, visualisation and ability to express various perspectives
- Handling of variability and uncertainty and propagating it down to the B/R balance is manageable and supports informed decision making

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Thank you!

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Back -up

Discussion – background slide for difference in efalizumab cases studies

- *WP 5 (swing-weighting methodology: weights assessment-specific and dependent on performance ranges):*
  - *Total normalized weight: Benefits (PASI75, PGA and DLQI): 66% vs Risks: 34% (includes 13% for fatal PML; PML weight in natalizumab case study: 56%)*
  - ➢ *Positive benefit-risk balance vs placebo in 2009 (51 vs 31)*
- *WP 6 (hierarchical point allocation: weights generic [except for efficacy & PRO outcomes] and independent of performance scores):*
  - *Total normalized weight: Benefits (PASI75, PGA and DLQI): 48% vs Risks: 52% (includes 38% for fatal AEs)*
  - ➢ *Slightly negative relative benefit-risk balance vs placebo in 2009 (-0.02, on a scale from -1 to 1) but a lot of uncertainty (sdv 0.332)*
  - ➢ *Clearly negative relative benefit-risk balance vs active comparators (-0.25 to -0.43)*