PRE-SYMPOSIUM TRAINING
APPLICATION OF MCDA TO REAL-LIFE DECISIONMAKING

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EMA, London, UK

SESSION CHAIRS

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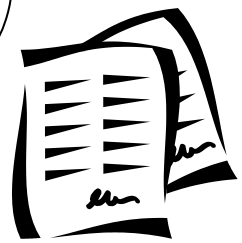
PROGRAM

14:00 - 14:30	OVERVIEW
14:30 - 16:00	HANDS-ON EXERCISE
16:00 -16:30	COFFEE BREAK
16:30 -18:00	RESULTS & DISCUSSION

THE ART OF DECISION MAKING IN HEALTHCARE

WWW

Disease severity
Feasibility
Patient-reported outcomes
System capacity
Safety
Quality of evidence
Unmet needs
Efficacy
Ethics
Individual values
Cost
Population Priorities
Expert opinion
Affordability
Historical context



- Relying on evidence
- Relying on social values*
  - Substantive values (CONTENT - what & why)
  - Procedural values (PROCESS who & how)
- Fair and accountable decisionmaking processes** (A4R)

*Clark and Weale. J Health Org Manag 2012; 26:293; NICE Social Value Judgments 2nd Ed

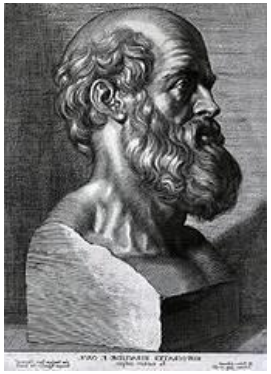
**Daniels and Sabin. Philos Pub Health 1997; 26:305 (4 conditions: Relevance, publicity, revision, leadership).

MCDA - A DEFINITION

Definition:
Multicriteria decision analysis (MCDA) is an application of analytical methods to **explicitly consider** multiple **criteria**

1ST STEP MCDA: OBJECTIVE

DEONTOLOGY



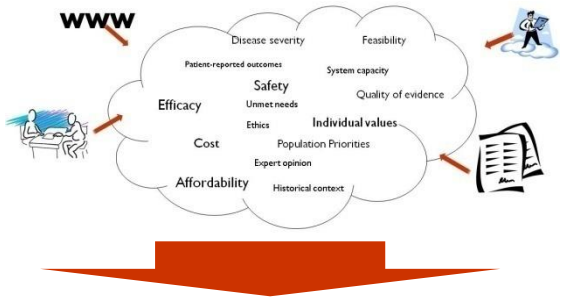
Hippocratic Oath: "I will prescribe for the good of my patients according to my ability and my judgment and never do harm to anyone."

Mission EMA: "…*provide scientific advice on any question relating to the* ***evaluation*** *of the quality, safety and efficacy of medicinal products …"*

Word definition : *Keep safe from harm*

Antonym: *Expose*

METHODOLOGY



CRITERIA SELECTION

DECISION CRITERIA
Quantitative criteria
Efficacy/effectiveness
Safety Etc
Qualitative criteria
Disease severity
etc

What? Identify ***all criteria*** (quantitative and qualitative) that contributes to evaluation of an intervention

Why? Realize ethical and methodological implications of criteria selection

With the goal in mind!

METHODOLOGY

WEIGTHS

DECISION CRITERIA	
Quantitative criteria	Relative Weights
Efficacy/effectiveness	❑ Low ❑ High
Safety Etc	❑ Low ❑ High
Qualitative criteria	
Disease severity	
Etc	

What & Why? Include the diversity of individual perspectives

How? Kepner Tregoe (10 pts scale), Pt allocation, ranking, AHP, Swing Weigths, DCE etc

Who? Committee members

METHODOLOGY

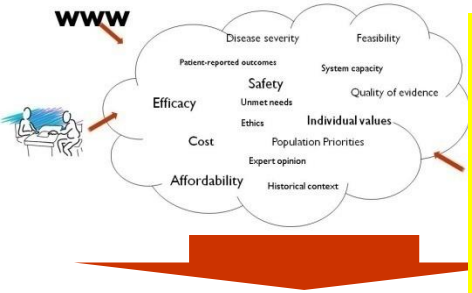
What? Highly synthesized evidence
Why? Avoid data overload

How? Evidence synthesis principles
Who? Analysts and communicators

EVIDENCE

DECISION CRITERIA		HIGHLY SYNTHESIZED EVIDENCE
Quantitative criteria	Relative Weights	
Efficacy/effectiveness	❑ Low ❑ High	
Safety Etc	❑ Low ❑ High	
Qualitative criteria		
Disease severity		**Turner syndrome**: Female specific generic disorder characterized by reduced life expectancy, cardiovascular defects, increased risk of diabetes, absence of puberty, infertility, defects in visuo-spatial organization and non-verbal problem solving, and short stature (details)
Etc		

METHODOLOGY



Scores

Sir Rawlins NICE: Accept that interpretation of data requires judgement

What? Performance of medicine for specific criteria
Why? Explore the quantum leap from evidence to appraisal and decision
How? Scoring scales
Who? Committee members

DECISION CRITERIA		HIGHLY SYNTHESIZED EVIDENCE	APPRAISAL
Quantitative criteria	Relative Weights		Score
Efficacy/effectiveness	❑ Low ❑ High		❑ High ❑ ❑ ❑ Low
Safety Etc	❑ Low ❑ High		
Qualitative criteria			Impact
Disease severity		**Turner syndrome**: Female specific generic disorder characterized by reduced life expectancy, cardiovascular defects, increased risk of diabetes, absence of puberty, infertility, defects in visuo-spatial organization and non-verbal problem solving, and short stature (details	❑ negative ❑ neutral ❑ positive
Etc			

MCDA TOOLS & APPROACHES - EXAMPLES

- **Larry Philips & colleagues - Decision conferencing[1]**
  - Example: benefit/risk of medicines
  - Weight elicitation technique: swing weights
- **Rob Baltussen & colleagues[2]**
  - Focus priority setting
  - Weight elicitation technique: DCE
- **1000 Minds[3]**
  - Software for all types of decisions (not specific to health)
  - Weight elicitation technique : PAPRIKA
- **EVIDEM [4] (not-for-profit collaborative from >30 countries)**
  - Generic multipurpose open-source framework (>10 languages) across healthcare continuum decisionmaking
  - V2.3: several weight elicitation techniques (5 pt scale non hierarchical and hierarchical, point allocation, ranking, AHP,

[1]Philips L et al. Drug Discov Today Technol 2011; 8(1):e3; http://www.lawrencephillips.net/Decision_conferencing.html

[2]Baltussen & Niessen CERA 2006; Baltussen et al. Health Policy 2010, 96:262. Youngkong S et al. Value in Health 2013:15:961.

[3]Golan O & Hansen P. Isr J Health Policy Res 2012, 1:44; http://www.1000minds.com/

[4]Goetghebeur et al. BMC Health Services 2008, CERA 2010, Medical Decision Making 2012 http://www.evidem.org

MODELED-BASED EVIDENCE SYNTHESIS

- **Bayesian Mixed Treatment Comparison**
  - of each datasets (one for each year) for all criteria (binary and continuous)
  - With study random effect to account for heterogeneity
- **Meta-regression to account for time horizon effects**
- **Extrapolation to common time horizons**
  - With propagated uncertainty quantified and reported
- **Convergence issues and robustness assessed**

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PROTECT - EFALIZUMAB CASE STUDY

Research team WP5
Alain Micaleff, Merck Group, Switzerland
Tornbjorn Calleus (DKMA)
Lawrence Phillips (EMA,LSE)
Diana Hughes (Pfizer)
Kimberley Hockley (Imperial College London)
Nan Wang (Imperial College London)
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Research team WP6
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Mateusz Nikodem, LASER Poland
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Agnieszka Zyla, LASER Poland

PROTECT – SUMMARY OF WP5

- WP5: develop methods for use in benefit-risk (BR) assessment, including both the underpinning modelling and the presentation of the results, with a particular emphasis on graphical methods.
- 34 Contributors from Industry, Academics and Regulatory Agencies
- Working method:
  - Large Reviews of published B-R, and Visual representation Methods
  - Use a Case Study approach with legacy examples as tests for structured Methods and Tools for B-R assessment
  - Case studies: rimonabant (2), efalizumab, natalizumab (2), telithromycine, rosiglitazone, warfarin.

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

PROTECT – SUMMARY OF WP5

- Decision context chosen by the team (for practical reasons of data availability, time and resource limitations)
  - Efalizumab SC 1 mg/kg/week for 12 weeks (Initial Tt)
  - In « high need » patients
  - Compared to placebo only
  - Time frame for outcomes: 12 weeks PASI 75, 3-4 years PML.
  - Regulator's perspective
  - In Feb 2009 at reevaluation of B-R (emerging major risk of PML)

PROTECT – SUMMARY OF WP5

- Objective data from EPAR 2004 and EPAR 2009, supplemented by PSUR10 (last before withdrawal).
- 2 qualitative frameworks and 2 quantitative methods tested:
  - BRAT + BRR
  - PrOACT-URL + MCDA
  - Preferences elicited by the team as a surrogate for Regulator's perspective
- Lessons learnt in Case Study Report

PROTECT – LESSONS LEARNED FROM WP5

Need identified	Addressing need through pragmatic MCDA benefit-risk assessment framework
Consistency across assessments	• Generic benefit-risk criteria; only benefit outcomes (sub-criteria) disease-specific • Weighting: direct and independent of scoring • Scoring: generic scales
Compatibility with comparative efficacy / safety data	• Comparative assessment directly based on comparative data to derive Relative Benefit Risk Balance • Comparative scoring scales (not absolute)
Flexibility, ability to deal with uncertainty, lack of data, and heterogeneity of outcome measures	• Scoring scales not numerical transformations of data (measured scales) but capture judgment on data (constructed scales): ➢ Compatible with any type of data ➢ Allow expressing uncertainty (range of scores)

PROTECT – LESSONS LEARNED FROM WP5

Need identified	Addressing need through pragmatic MCDA benefit-risk assessment framework
Not complex, practical and efficient	• No complex mathematical transformation of outcomes data • Excel-based calculations Generic, comparative scoring and direct weighting represent a practical and intuitive bridge to transition from the current qualitative approach towards a more structured and quantitative approach
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	• 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

PROTECT – WP6

- **Efalizumab case study**

DISEASE SEVERITY & UNMET NEEDS*	Psoriasis is a common chronic inflammatory skin disease associated with joint disease in 25% of patients and impacting patient quality of life. Moderate to severe psoriasis requires systematic treatment. Limitations of these treatments include difficult patient access (phototherapy), long term toxicities treatment (e.g., methotrexate, cyclosporine) and high levels of patient dissatisfaction. The biological agent efalizumab was developed with the hope of addressing these unmet needs.
PRODUCT DESCRIPTION	**Indications**: Efalizumab is indicated in the treatment of adult patients with moderate to severe chronic plaque psoriasis (only indication) **Description/Mechanism of Action** : Raptiva® (efalizumab) is a recombinant, humanized IgG1 monoclonal antibody that targets CD11a, the α-subunit of leukocyte function associated antigen 1 (LFA-1). Mechanism of action may lead to inhibition of leukocyte migration. **Dosage/Administration, instructions for use**: Administered once weekly with subcutaneous injections. The duration of initial therapy is 12 weeks. Therapy may be continued only in patients who responded to treatment (PGA good or better).
COMPARATORS & TIMELINES	2004, only placebo ; Thereafter other biologicals used for other indications were granted approval for psoriasis. 2008 etanercept, adalimumab, infliximab 2009: etanercept, adalimumab, infliximab

CONCEPTUAL BASIS

- **Benefit-risk concept**
  - Benefit: "*a good or helpful result or effect*" = **efficacy & effectiveness** (efficacy in real-life) and also **quality of life**
  - Risk:"*the possibility that something bad or unpleasant will happen*" = **safety** (or adverse events)

- **Improvement / worsening concept (⇒ Relative Benefit Risk Balance)**
  - Improvement vs current situation = more benefit or l
  - Worsening vs current situation = less benefit or m
  - ➔ Concept of **value*** derived from **improvement i benefit-risk balance**

*Full assessment of value involves other aspects (unmet needs, disease severity, etc

Efficacy lower than comparator and safety better than comparator

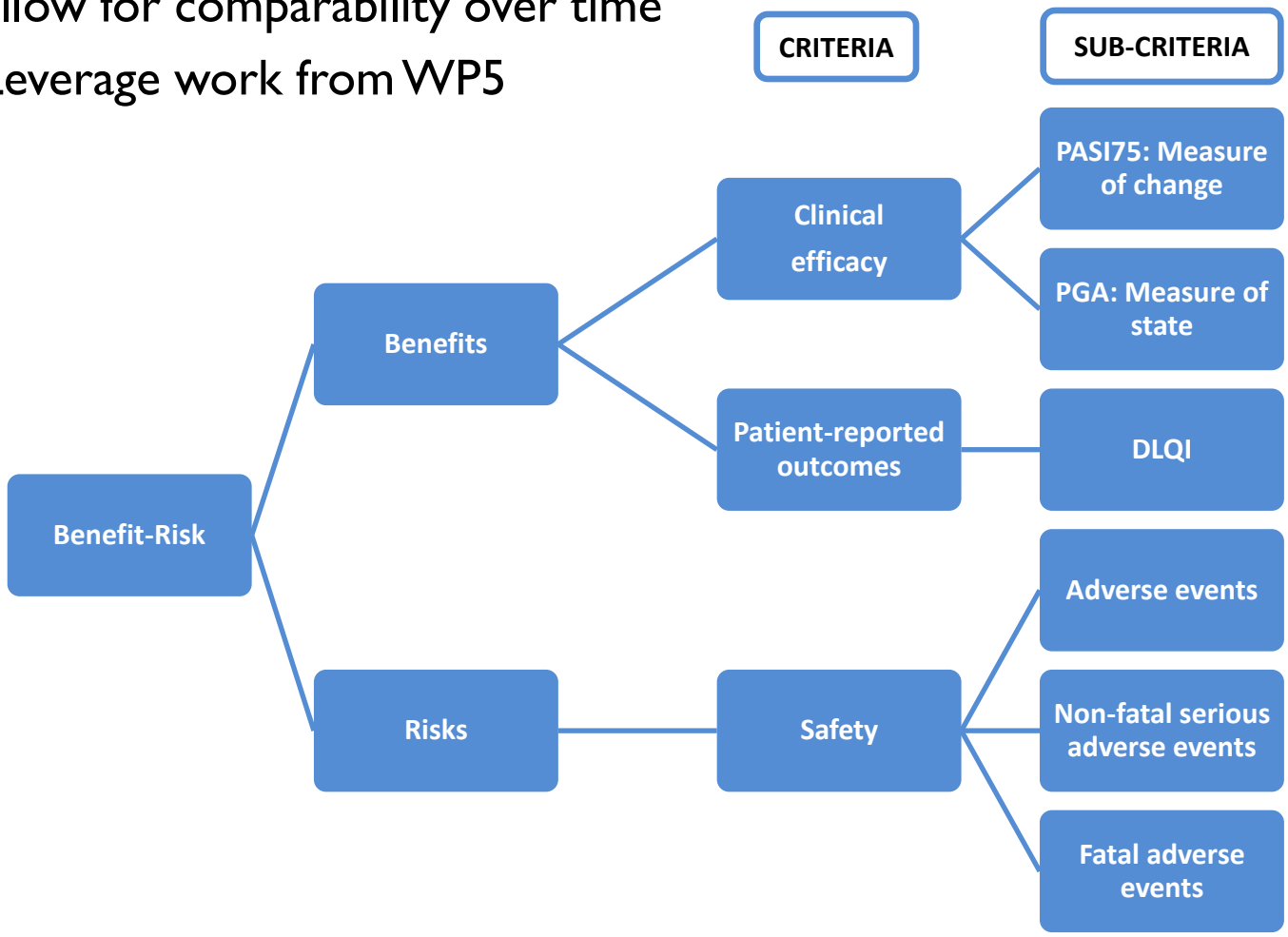
[1] Spielthenner G. Risk-benefit analysis: from a logical point of view. *Bioethical Inquiry* (2012)9:161-170

CRITERIA SELECTION

- ➔ **ENSURE MCDA MODEL MEASURES WHAT YOU WISH TO MEASURE**
- **Ethical foundations: Deontology (Hippocratic oath) and principles of beneficence, non-maleficence and respect of autonomy (principlism)**
- **MCDA principles for defining criteria**
  - Non-redundant *(avoid double counting – use hierarchy to account for double counting)*
  - Mutually independent *(can be assessed independently)*
  - Operationalizable *(scales, data)*
  - Completeness *(all important criteria used for decisionmaking are included - discussion)*
- **Clustering of criteria**
  - Conceptually meaningful
  - *Critical if using hierarchical method*

CRITERIA SELECTION AND DECISION TREE

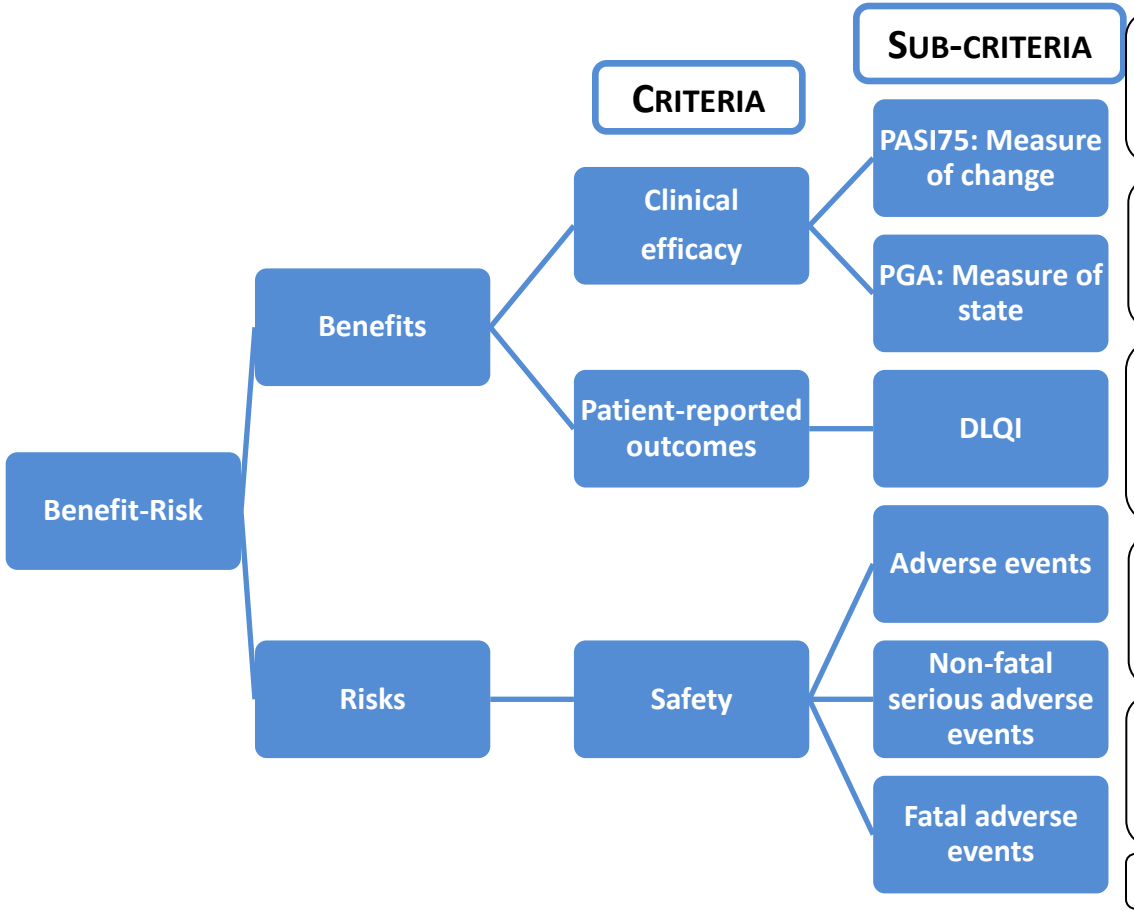
- Generic tree, portable across therapeutic areas (as much as possible) to allow for comparability over time
- Leverage work from WP5



- Efficacy and in some extent PRO data are disease specific

SUB-CRITERIA DEFINITION

- Most critical outcomes – approved, primary, relevant



CRITERIA	SUB-CRITERIA	
Clinical efficacy	PASI75: Measure of change	PASI75:* Percentage of patients achieving at least a 75% reduction of PASI at week 12 compared to baseline. PASI is a measure of average redness, thickness and scaliness of lesions (each graded on a 0-4 scale), weighted by the area of involvement. PASI range from 0 to 72.
	PGA: Measure of state	PGA:* Percentage of patients achieving Physician's Global Assessment clear/almost clear at week12. This is a seven point scale with 7 being clear, 6 almost clear, 5 mild, 4 mild to moderate, 3 moderate, 2 moderately severe and 1 severe psoriasis.
Patient-reported outcomes	DLQI	DLQI: 10-item questionnaire for patient assessments of itch, pain, feelings of embarrassment and self-consciousness, problems with their psoriasis treatment, and interference of their psoriasis with daily activities, relationships, and sexual activity. DLQI scores range from 0 (no impairment) to 30 (maximal impairment).
Safety	Adverse events	Adverse events: any untoward medical occurrence that may present itself during treatment or administration with a pharmaceutical product and which may or may not have a causal relationship with the treatment (ICH)
	Non-fatal serious adverse events	Non-fatal Serious adverse events: events that are life-threatening, or requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability, or is a significant medical event (ICH)
	Fatal adverse events	Reported fatalities

* Clinical efficacy is a composite measure of PASI75 and PGA and potential double counting is handled as it remains within the desired proportion to the other criteria (e.g., PRO, safety).

WEIGHT ELICITATION TECHNIQUE

➔ **Capture perspective of evaluators (individual value system)**

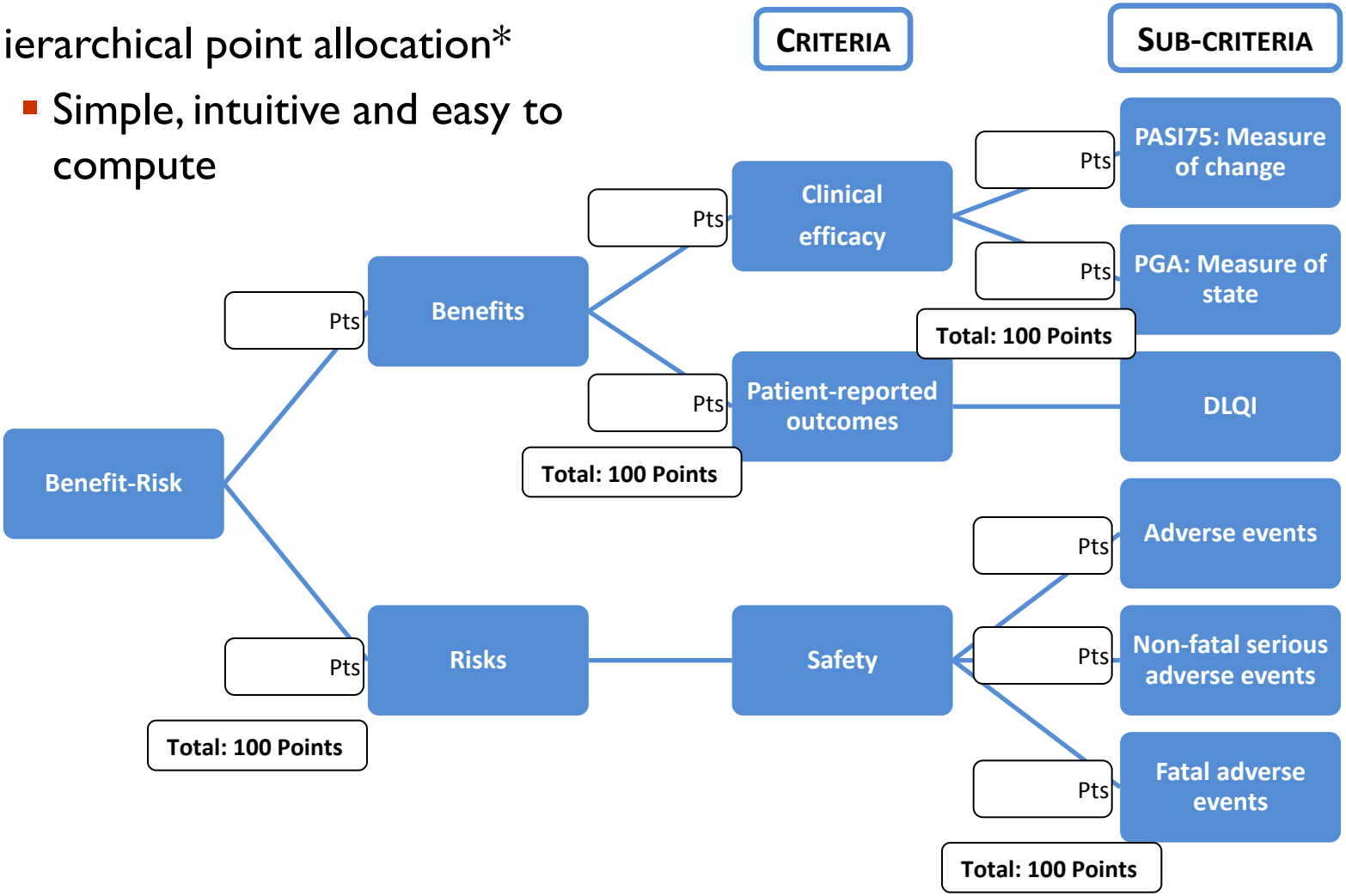
- **Rationale for selecting technique**
  - Number of criteria
  - Ease of use
  - Mathematical complexity
  - Examples: 10 points scale (Kepner Tregoe,) point allocation, ranking, swing weights, AHP, best/worse, DCE

- **Implications of technique selection**
  - Weights vary depending on technique
  - Sensitivity analyses

[1] Dolan J. 2010. The Patient

WEIGHTING METHOD

- Hierarchical point allocation*
  - Simple, intuitive and easy to compute



*Technique to be selected based on preference and capabilities

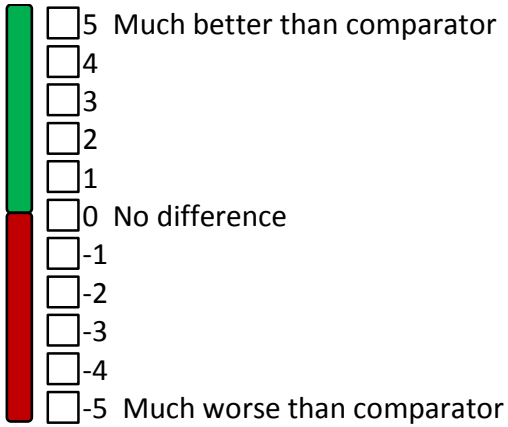
PERFORMANCE SCORING SCALES

➔ **MEASURE THE INTERVENTION PERFORMANCE FOR EACH CRITERION**

- **Rationale for selecting scale**
  - Ease of use
  - Mathematical complexity
  - Measured vs. constructed scale
- **Implications of scale selection**
  - Comparability of interventions
  - Strictly based on numbers (formula type) OR capturing judgment on numbers (reflection support type)

PERFORMANCE SCALES

- **Positive and negative scales**: capture both better and worse outcomes of a new drug vs a given situation (e.g., placebo, standard of care)



- **Generic scales**: captures judgment on data (scale options can be defined further by committee using consensus building exercise)

- **Range of scores allowed**: capture level of uncertainty on the data and its judgment (for **sensitivity analyses**)

EVIDENCE *

- Quantitative: Bayesian meta-analysis for each sub-criterion

Trials/Data	Treatment duration	Odds ratio	*P* value	95% CI	Efalizumab	Placebo
	12 wks					
	24 wks					
	2 yrs					

Data with high uncertainty reported in grey (high coefficient of variation, data mostly based on model assumptions)

- Semi-quantitative: types of adverse events (see appendix 2 for description)

Frequency	Efalizumab	Comparator
Very common AEs (>1/10):		
Very common AEs (>1/10):		
Uncommon SAEs (>1/,1000, <1/100):		
Not known		

*For full evaluation, evidence tables and details on data abstraction and modeling, as well as quality of evidence evaluation, would be made available in appendices for full data transparency; not performed for this exploratory study.

EVIDENCE SYNTHESIS

➔ **Linking evidence with decision criteria to ensure evidence-based decisionmaking**

- **Evidence synthesis principles***
  - Systematic **review** of the literature
  - **Synthesis** of available data, **meta-analysis**, **modeling**
  - **Assessment of quality** of evidence

- **Adapation to MCDA structure**
  - Data synthesis for each criterion (matrix format rather than report format)
  - Data sufficient and necessary for scoring each criterion

Battista IJTAHC 2006;22:375

MCDA EVIDENCE MATRIX

CRITERIA, EVIDENCE AND SCORING SCALES

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** [a]*Gordon 2004; Lebwohl 2003; Leonardi 2005a, Leonardi 2005b; Papp 2006; Dubertret 2006 (overall 3016 patients)* [c]*etc*	5 Much better than comparator 4 3 2 1 0 No difference -1 -2 -3 -4 -5 Much worse than comparator Comments:

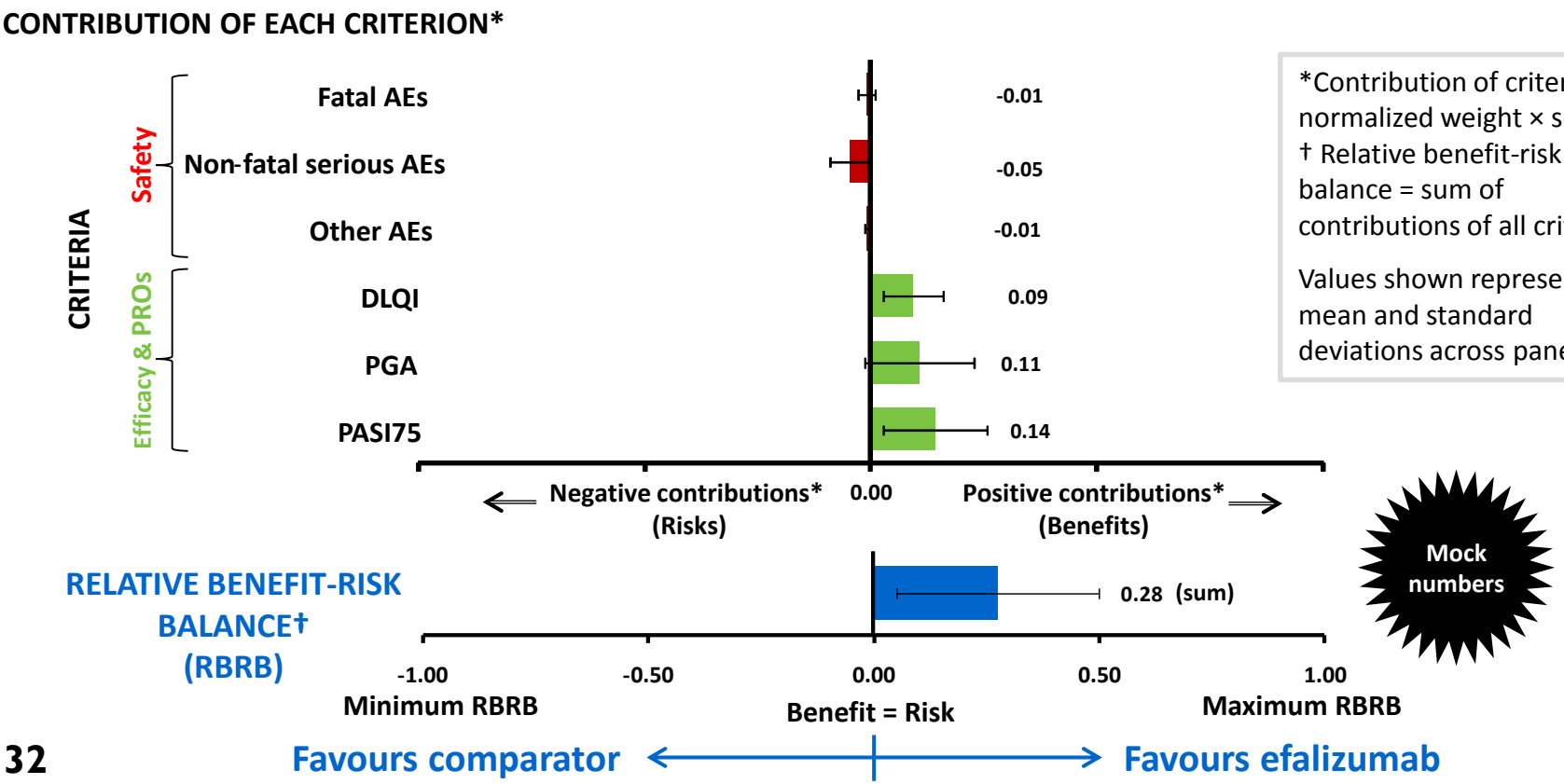
Trials/Data	Treatment duration	Odds ratio	*P* value	95% CI	Efalizumab (%)	Placebo (%)
[a]6 RCTs Efalizumab	12 wks					
	24 wks					
	2 yrs					

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

Reflect on score: How currently decided?

METHODOLOGICAL FOUNDATION BENEFIT-RISK ESTIMATE & UNCERTAINTY

- **Relative Benefit-Risk Balance**: linear additive model (normalized weights x scores) for each subcriterion
- **Graphical representation**: Breakdown of contribution of each sub-criterion (outcome) and its uncertainty (error bars)



EXERCISE

INITIALS:

PARTICIPANTS INFORMATION AND AUTHORIZATION

STEP1 - Weighting criteria:

- Distribute points across criteria and sub-criteria for each domain based on their relative importance. Each domain should total 100 points.

STEP 2 - Scoring medicine – column 4:

- For each sub-criterion, assign a score (or a range of scores) on the scales provided, based on evidence available (highly synthesized data is presented here; for a full scale evaluation full evidence tables would be provided in appendices). You may provide comments.
- Note: performance score ranges will be transformed into a measure of uncertainty

Note: description of adverse events available in appendix for reference

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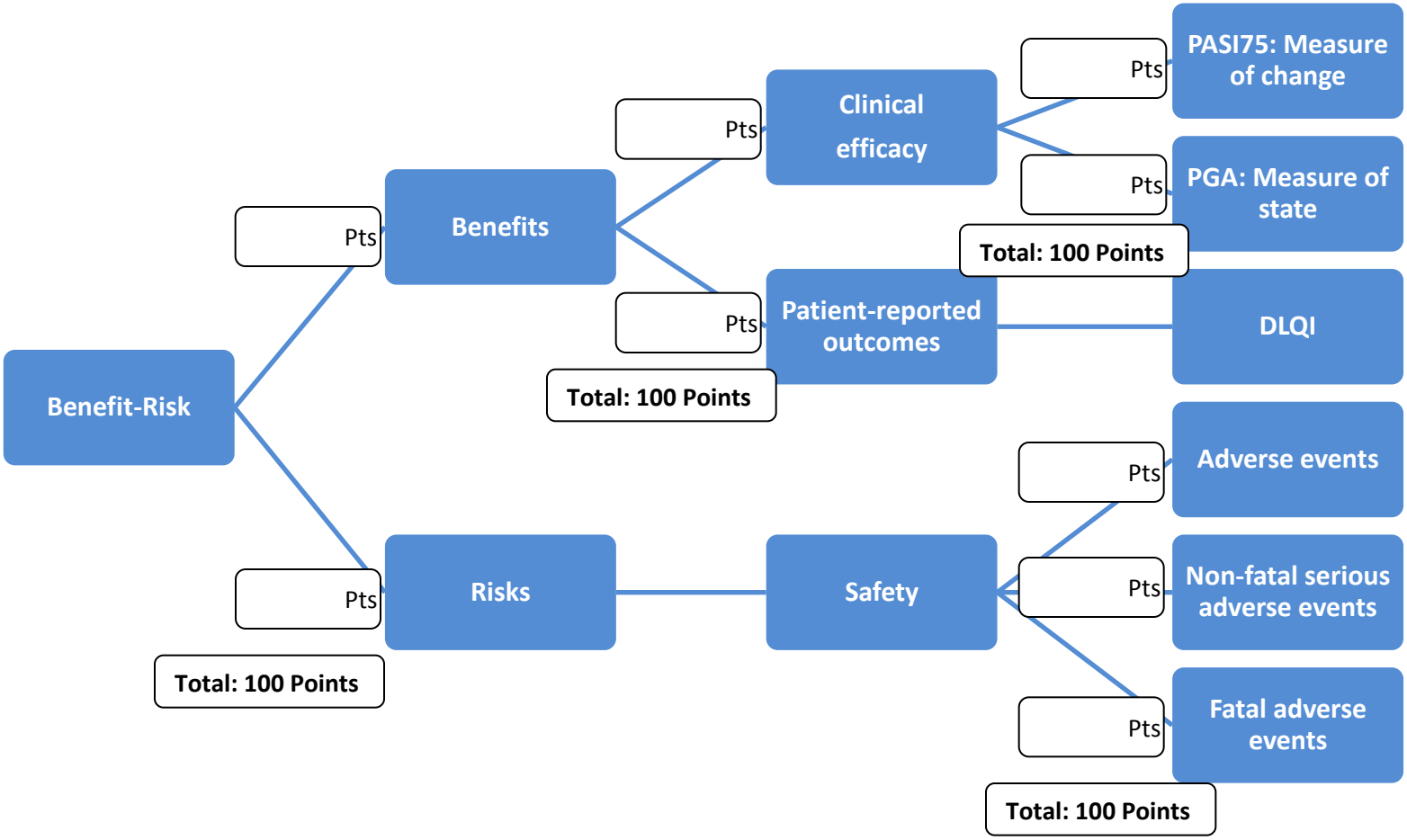
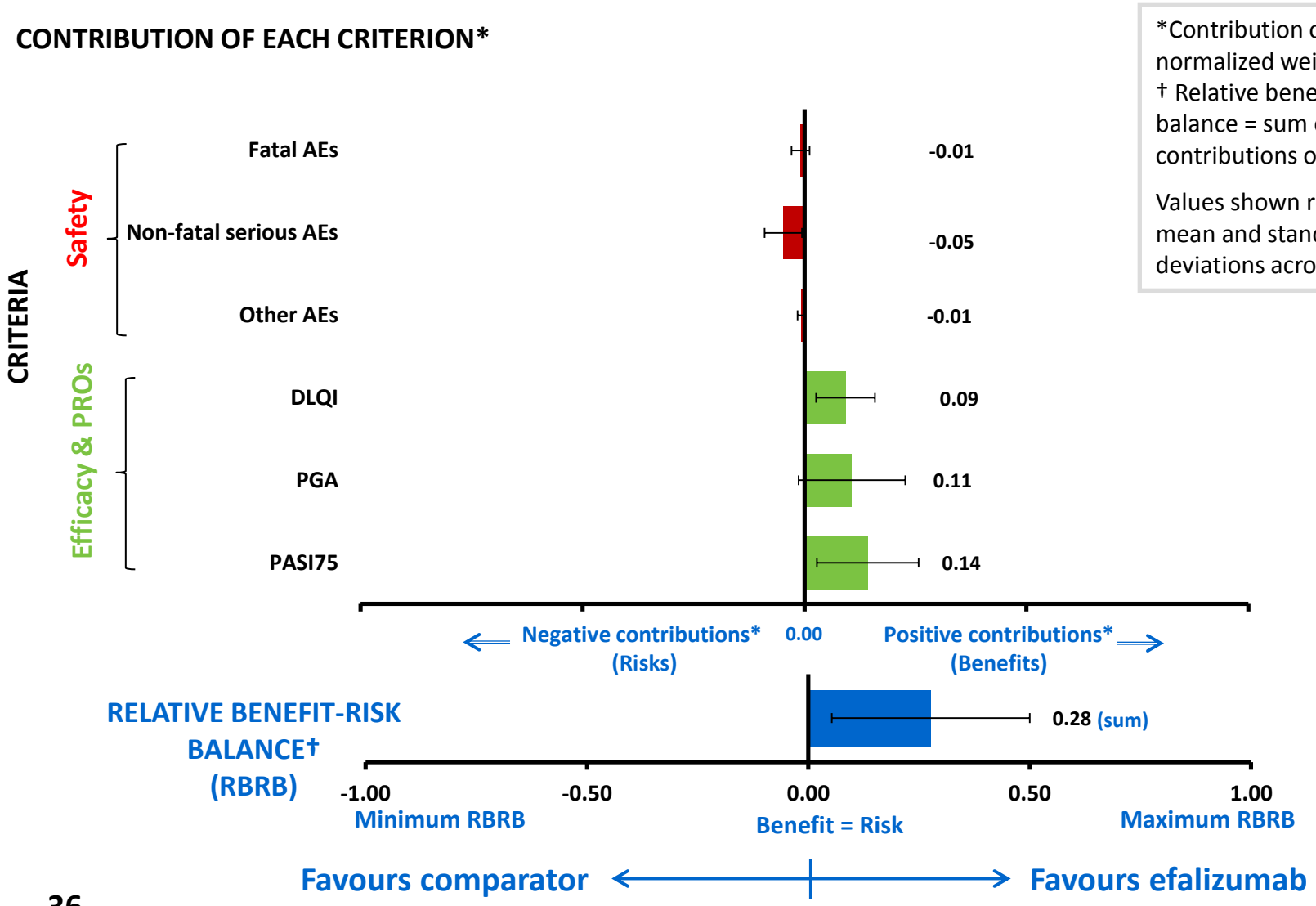
RESULTS – WEIGHTS



RESULTS – 2004

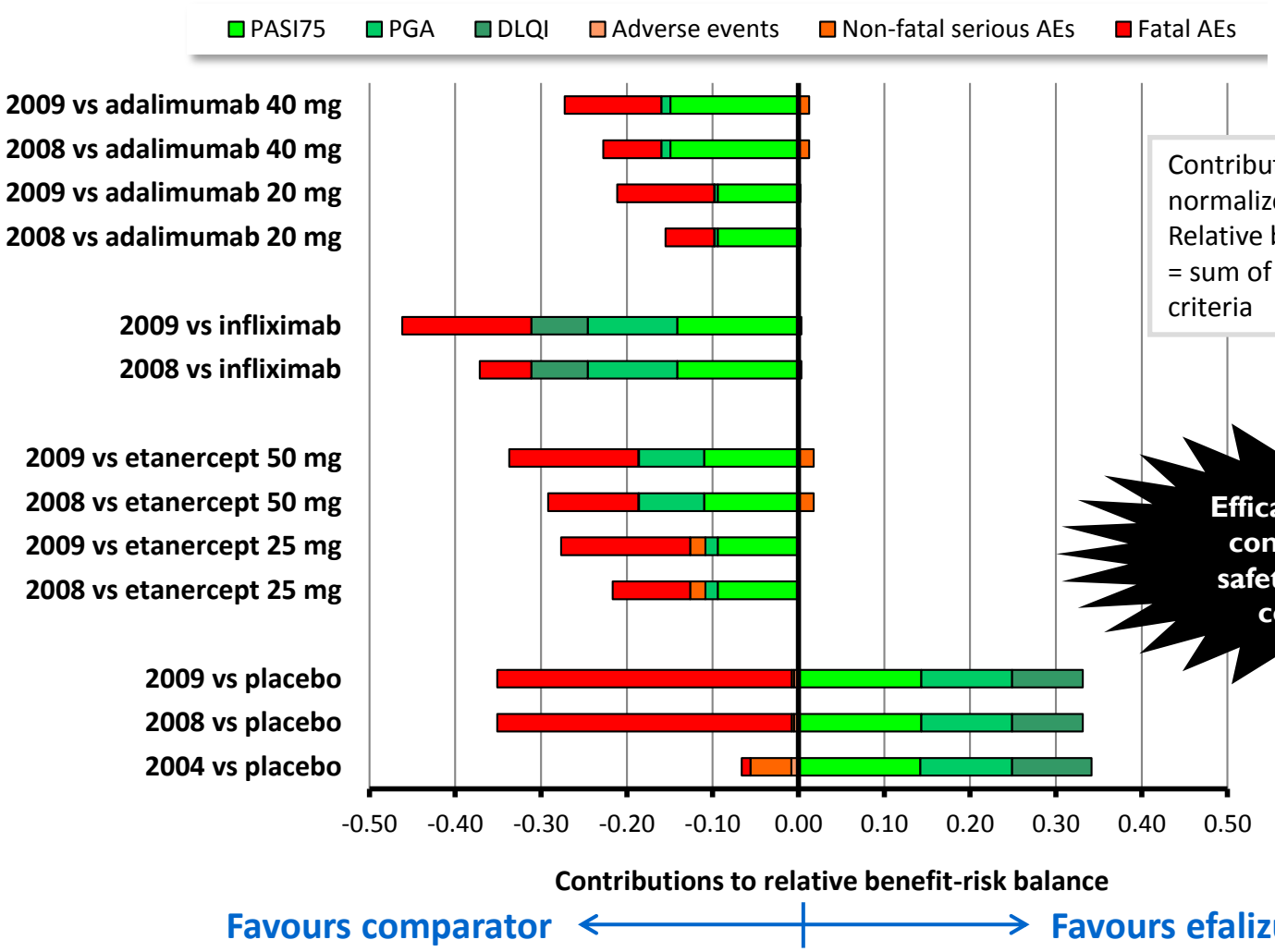


*Contribution of criterion = normalized weight × score
† Relative benefit-risk balance = sum of contributions of all criteria

Values shown represent mean and standard deviations across panelists.

RESULTS OVER TIME 2004 – 2009 ACROSS COMPARATORS

Mock numbers

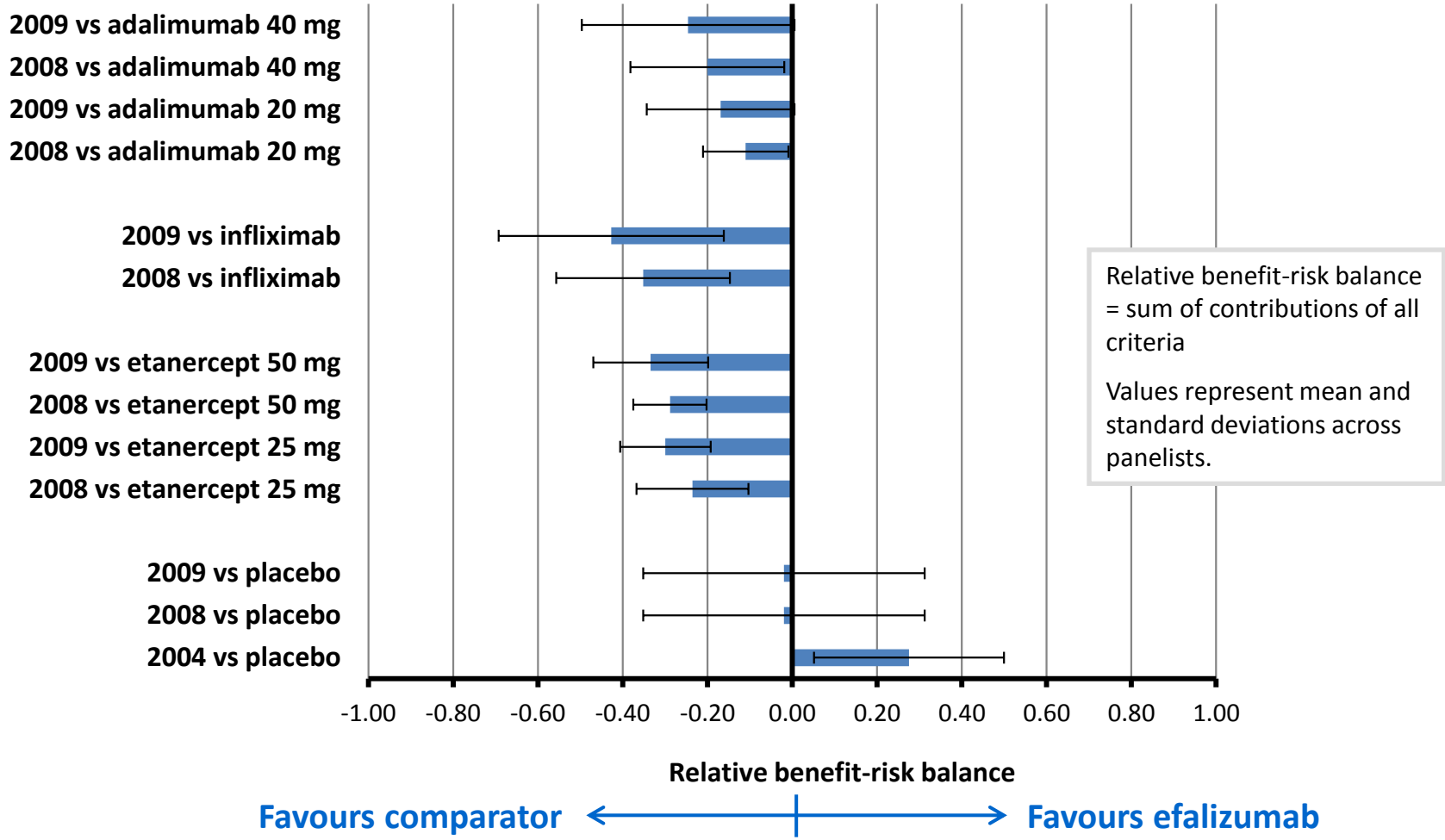


Contribution of criterion = normalized weight × score
Relative benefit-risk balance = sum of contributions of all criteria

Efficacy lower than comparator and safety better than comparator

RESULTS OVER TIME 2004 – 2009 ACROSS COMPARATORS

Mock numbers



STRUCTURED DISCUSSION

- **Was the approach aiding your reflection and evaluation process?**
- **Where you able to express your opinion on the benefit-risk balance of efalizumab?**
- **Do you think there are other criteria beyond efficacy/effectiveness, safety and patient reported outcomes that influence the assessment of the benefit/risk balance?**
  - **Group & individual exercise**
- **What are the challenges and opportunities of such approaches in the regulatory context?**

STRUCTURED DISCUSSION – DECISION AID

WAS THE APPROACH AIDING YOUR REFLECTION AND EVALUATION PROCESS?

Most preferred features	Less preferred features

STRUCTURED DISCUSSION - OPINION

WHERE YOU ABLE TO EXPRESS YOUR OPINION ON THE BENEFIT-RISK BALANCE OF EFALIZUMAB?

CRITERIA*	Comments
EFFICAY/EFFECTIVENESS	
SAFETY	
PATIENT REPORTED OUTCOMES	

STRUCTURED DISCUSSION - EXPLORATION OF CRITERIA

DO YOU THINK THERE ARE OTHER CRITERIA BEYOND EFFICACY/EFFECTIVENESS, SAFETY AND PATIENT REPORTED OUTCOMES THAT INFLUENCE THE ASSESSMENT OF THE BENEFIT/RISK BALANCE?

CRITERIA*	Regulatory body perspective
EFFICAY/EFFECTIVENESS	
SAFETY	
PATIENT REPORTED OUTCOMES	
DISEASE SEVERITY	
UNMET NEEDS	
QUALITY OF EVIDENCE	
IMPLEMENTATION & PHARMACOVIGILANCE PLAN	
OTHER CRITERIA	

Note: Additional criteria indicated were identified during 2014 panel session

BEYOND EFFICACY, SAFETY AND PRO CRITERIA

INITIALS:

INSTRUCTIONS:

1. Indicate whether each criterion is currently considered when making a benefit/risk assessment of a medicine; if not applicable in your context, select N/A
2. Indicate whether each criterion, from your perspective, should be considered when making a benefit/risk assessment of a medicine
3. Indicate whether other criterion should be considered

Note: Criteria indicated were identified during 2014 panel session

STRUCTURED DISCUSSION – CHALLENGES AND OPPORTUNITIES

STRENGTH/OPPORTUNITIES*	CHALLENGES
Utility of approach	
• x	
Methodology	
• x	
Data requirements	
• x	
Capacity/training requirements	
• x	

*Institute of Medicine – assessment of approach

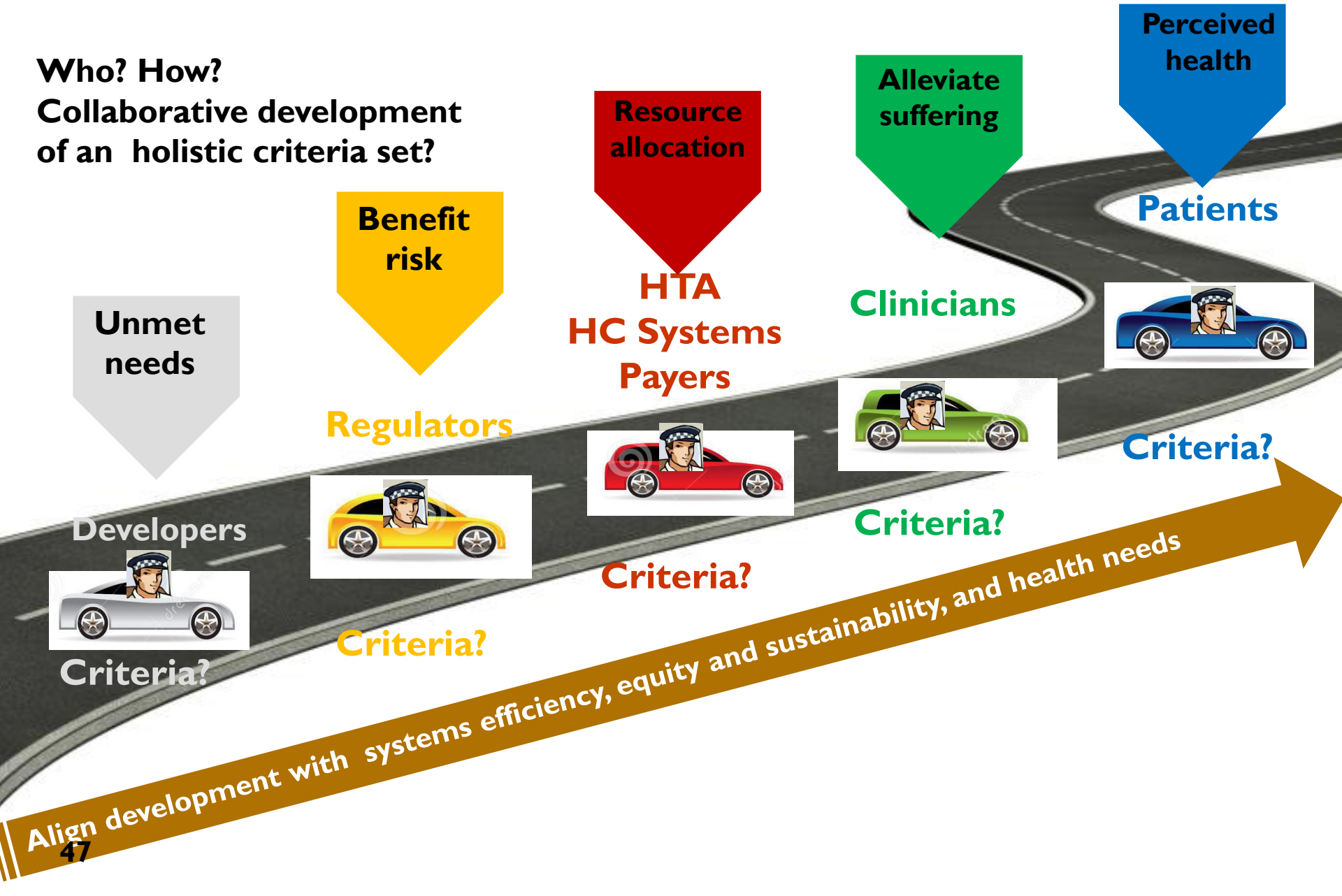
FUTURE – MCDA TO SUPPORT DECSIONMAKING

- Quantification & graphical representation of benefit/risk
- Criteria-based evidence generation and planning
- Multicriteria structuring of evidence
- MCDA methodological development
- MCDA implementation processes
- Web power

FUTURE – WORKING ACROSS THE DECISION CONTINUUM

Ultimate goal of healthcare: develop & promote interventions that optimize health of patients and populations as well as equitable, sustainable and efficient health care systems

A COMMON ROAD MAP ACROSS THE DECISION CONTINUUM?



THANK YOU