UNDERSTANDING THE RISK TOLERANCE OF REGULATORY ASSESSORS IN EUROPE: THE ROLE OF QUANTITATIVE MODELS IN RISK COMMUNICATION

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- *The views expressed here are the personal views of the presenter and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.*

EMA Reflection Paper

European Medicines Agency

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

REFLECTION PAPER ON BENEFIT-RISK ASSESSMENT METHODS IN THE CONTEXT OF THE EVALUATION OF MARKETING AUTHORISATION APPLICATIONS OF MEDICINAL PRODUCTS FOR HUMAN USE

Quantitative Objectives

- To explore further development in methodologies for benefit/risk analysis, including a wide range of quantitative and semi-quantitative tools, e.g. by organising workshops with all stakeholders and specialists of decision-making theory and setting up specific research projects.

Benefit Risk Methodology Project

Work Package	Status
1. Describing the benefit-risk assessment models already being used in the European Union's regulatory network	Completed March 2010
2. Assessing the suitability of the current tools and processes used in benefit-risk assessments	Completed August 2010
3. Field-testing the most appropriate models in five European medicine regulatory agencies	Completed June 2011
4. Refining the most suitable models for use in medicines regulation to create a new benefit-risk tool	Completed February 2012
5. Training European assessors to use the final tool	Started March 2012

Work Package 1

- To understand the process of regulatory approval within national agencies
- Descriptive results of what are benefits and what are risks of medicines from assessors' perspective
- To describe the mental map of medical assessors

List of Benefits

GOOD THINGS

1. everything good
2. improvement in health state
3. effectiveness in the real world
4. efficacy in clinical trials (equivalent to positive effect)
5. clinical relevance
6. improvement of illness
7. "drug works"
8. positive action of a drug
9. unmet medical need
10. positive improvement in health state that is perceived by patient
11. everything that improves health or reduces problem of safety, efficacy in clinical trial
12. safety improvement
13. improvement of convenience/quality of life for patient
14. patient's function and survival
15. value compared to the placebo
16. non-inferior to comparators
17. efficacious
18. an improvement that is meaningful to the patient
19. depends on context
20. more than pharmacological activity
21. pre-defined efficacy for a pre-defined population

1. for vaccines, prevention of disease; for antibiotics, elimination of the microbe; for metabolic disease, maintenance; less adverse effects
2. positive effects
3. changes in the management of a patient re disease progression
4. an improvement to the patient, quality or quantity of life, survival
5. amelioration of symptoms
6. suffering reduced,
7. preventative improvement in health and well-being
8. social benefits,
9. a measurable change in the right direction on a parameter that matters
10. a parameter that everyone agrees about
11. something positive
12. a good medicine, safe, efficacious
13. a decent primary endpoint translated to the patient being better off.

52. inverse of benefit

53. linked to benefits

Uncertainty of good things

1. efficacy for the patient, supported by data, externally validated and clinically relevant
2. potential good effects
3. a statistically significant effect

51. potential or theoretical risks (one interviewee said there is still a lot unknown after clinical trials; a signal may have been obtained from pre-clinical studies)

List of Harms

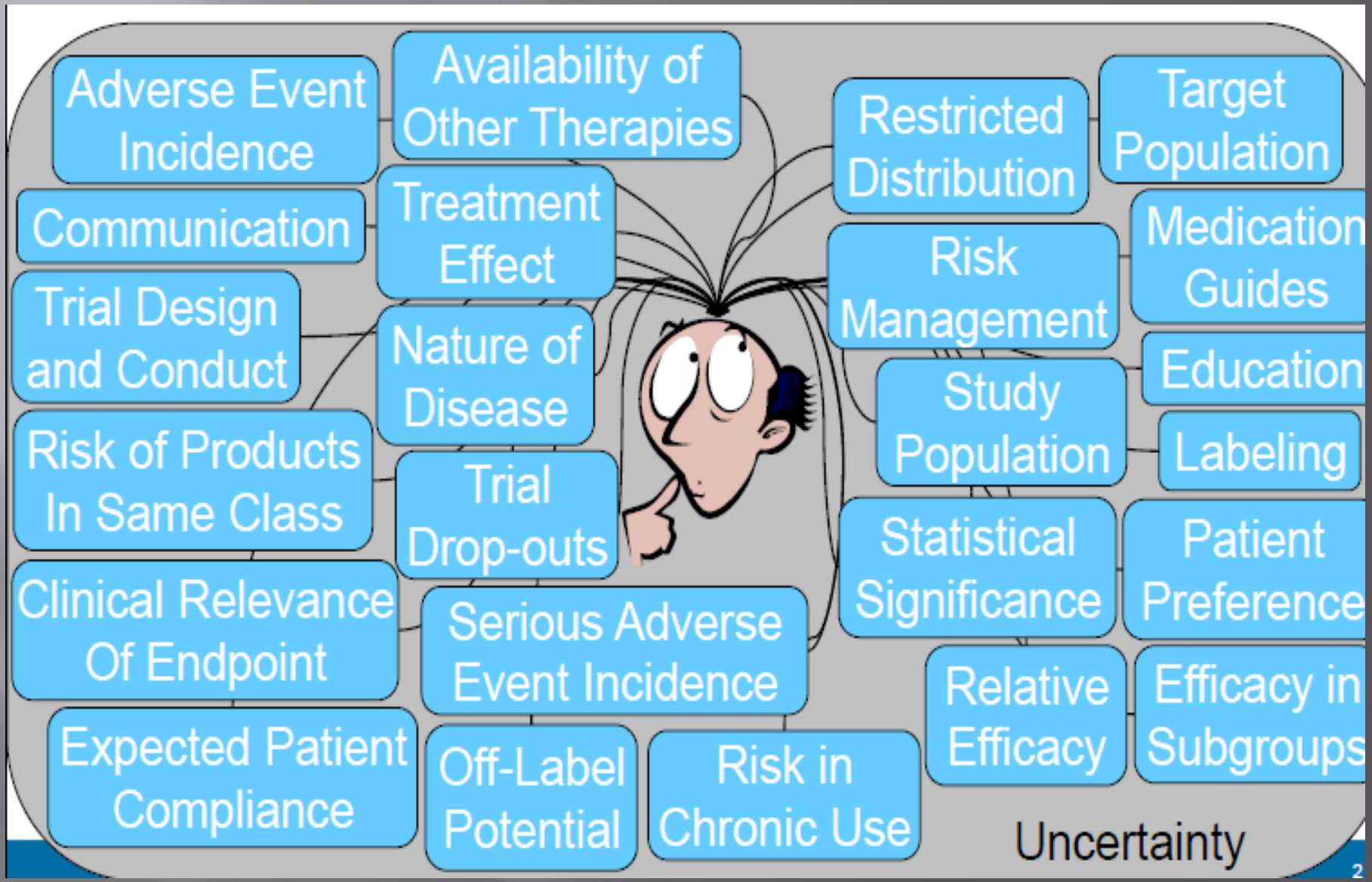
BAD THINGS

1. *all that is negative*
2. *adverse events*
3. *loss of efficacy (e.g. a company's inability to keep quality intact)*
4. *kinetic interactions*
5. *side effects*
6. *serious adverse effects*
7. *reduction in quality*
8. *bad effects.*
9. *danger for the patient*
10. *adverse events*
11. *harm*
12. *long term and short term safety profile*
13. *severity of side effect*
14. *direct harm on patient*
15. *indirect harm through misuse by patient*
16. *harm on non-patients/general public*
17. *how patients tolerate a drug compared to serious side effects like death*
18. *effects observed after a drug is approved*
19. *serious events*
20. *withdrawal*
21. *impact on pregnancies*
22. *22severity of side effects*
23. *for vaccines, reactogenicity (e.g., fever); development of resistance; vaccine failure*
24. *severity of side effects*
25. *what we don't want in this compound*
26. *depends on the disease*
27. *unacceptable damage to the patient.*
28. *inverse of safety*
29. *the inverse of short-term and long-term safety*
30. *harms*
31. *adverse reactions*
32. *severity*
33. *Duration*
34. *quality of life*
35. *negative impact on quality or quantity of life*
36. *detriments to health*
37. *failure to meet endpoints*
38. *tolerability*
39. *side effects*
40. *Mortality*

Uncertainty of bad things

1. *frequency of side effect*
2. *likelihood of negative event*
3. *frequent harmless or infrequent but serious*
4. *chance the benefit won't be realised*
5. *possible negative effects (or probability)*
6. *probability of an adverse event or harm—trivial or serious*
7. *not as expected*
8. *uncertainty surrounding the risks*
9. *a concept of gambling which includes perception*
10. *hurt to patients, variable depending on context*

51. potential or theoretical risks (one interviewee said there is still a lot unknown after clinical trials; a signal may have been obtained from pre-clinical studies)


Adverse Event Incidence
Availability of Other Therapies
Communication
Treatment Effect
Trial Design and Conduct
Nature of Disease
Risk of Products In Same Class
Trial Drop-outs
Clinical Relevance Of Endpoint
Serious Adverse Event Incidence
Expected Patient Compliance
Off-Label Potential
Risk in Chronic Use
Restricted Distribution
Target Population
Risk Management
Medication Guides
Education
Study Population
Labeling
Statistical Significance
Patient Preference
Relative Efficacy
Efficacy in Subgroups
Uncertainty

Magic number seven, plus or minus two


George A Miller

1956: Short-term memory is limited to 7 ± 2 items

Similar items are 'chunked' into memorable items

Chunks are organised in hierarchies

Miller, G. A. (1956). The magical number seven, plus or minus two: some limits on our capacity for processing information. *Psychological Review, 63(2), 81-97.*

Courtesy of L. Phillips, LSE/EMA 2011

Risk Perception

'How people actually perceive risks in any specific situation is an empirical question. Answering this question requires research translating those perceptions into observable interpretable behaviour so we are not left with trying to read people's minds.' Baruch Fischhoff,

Fischhoff. B, Kadvany, J. Risk: A very short introduction, 2011

Technology Crisis

- Nuclear engineering
  - Nuclear weapons fallout
  - Nuclear reactor accidents
  - Toxic waste
- Chemical engineering
  - DDT
  - Food additives
  - Lead paint
- Biological engineering
  - Genetic engineering
  - Medical devices

Traditional Definition of Risk

- Risk is a **measurable**, **objective** function of the probability of an event and the magnitude of that event:

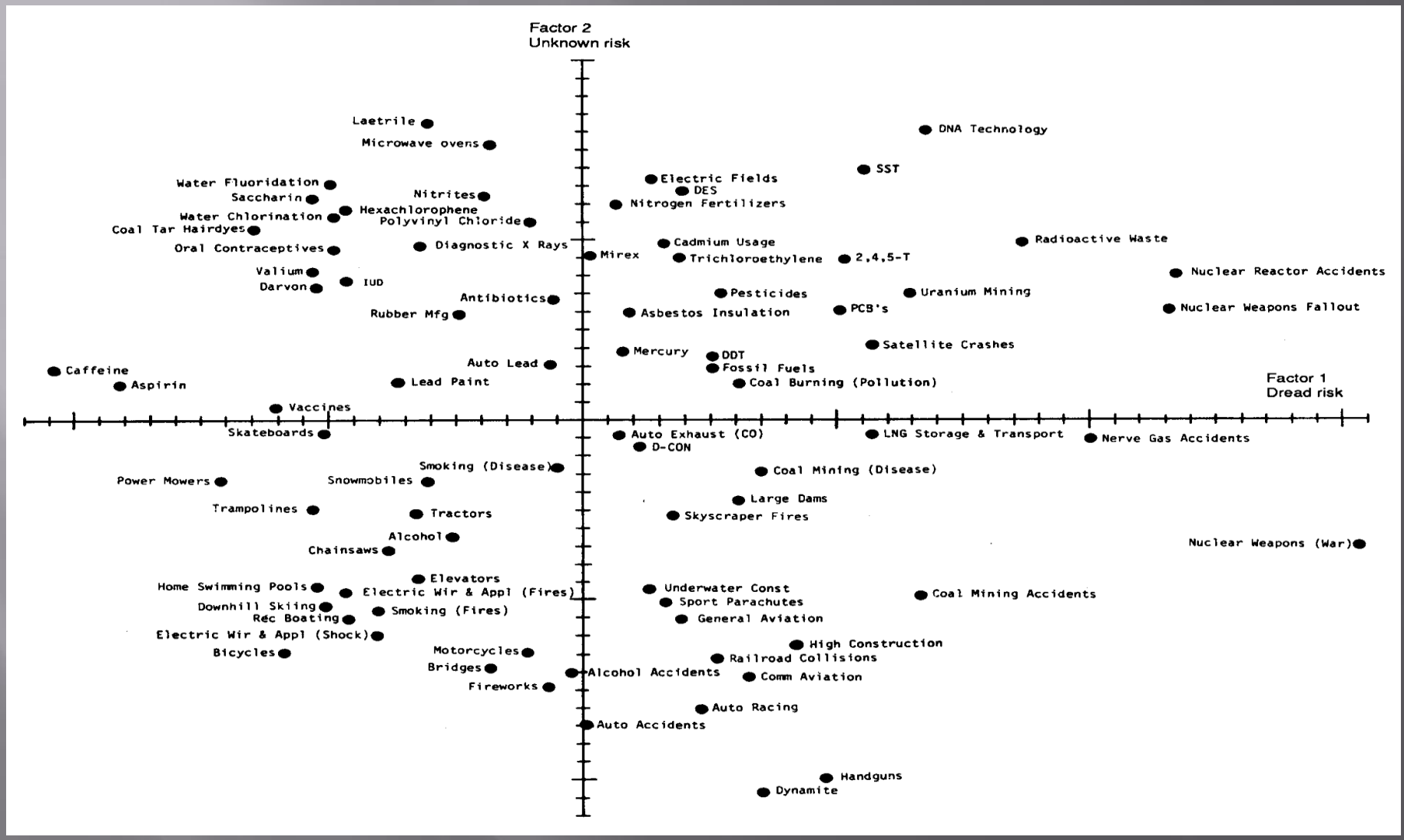
Probability **and** Magnitude

Social Scientists' definition of Risk

- An alternate view of risk proposed by social scientists since the 1970s is that risk is not an objective entity but a social construction[1]
  - People make subjective decisions with regard to how dangerous they perceive hazards
  - There are specific characteristics of a hazard that influence risk acceptability

Fischoff, B., P. Slovic, and S. Lichtenstein, *Which risks are acceptable?* Environment, 1979. 21(May): p. 17-38.

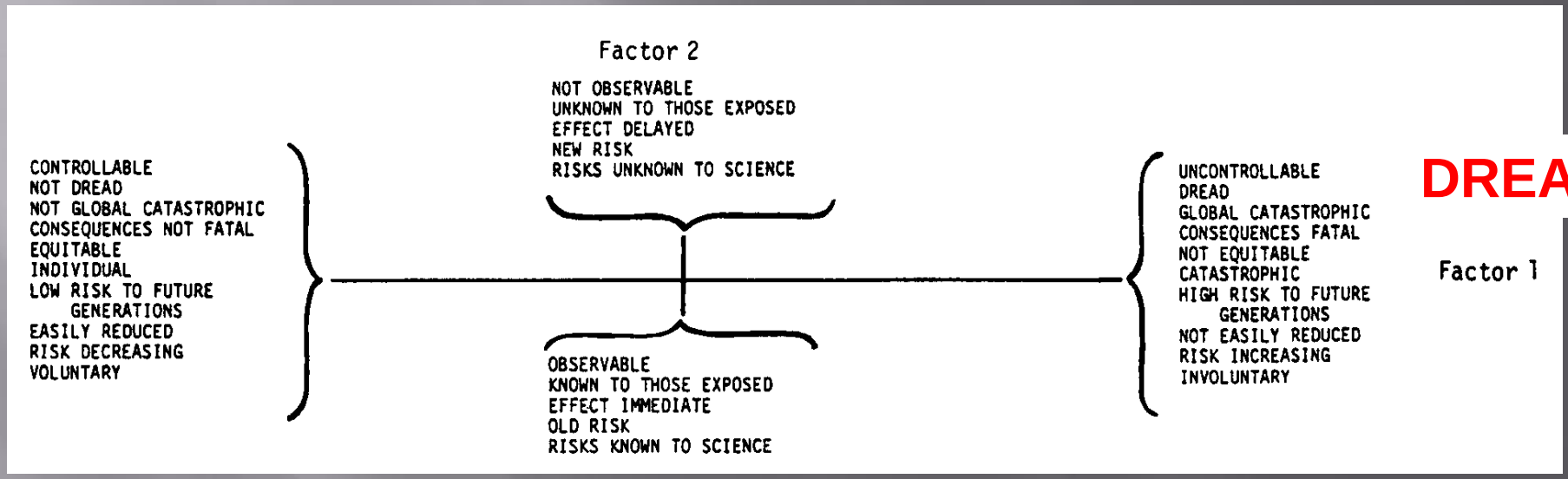
The Psychometric Paradigm



Slovic, P. (1987) Perception of Risk. Science, vol.236, pp280–285.

Factors that laypersons use to distinguish hazards

UNKNOWN



DREAD

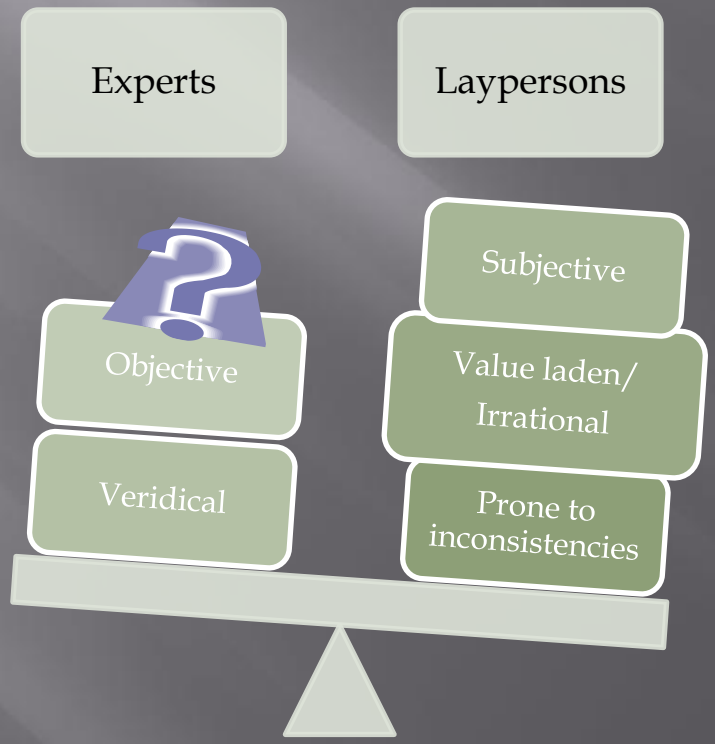
Factor 3 - reflects the number of people exposed to the hazard

Slovic, P. Risk. 1987

Do Experts have a similar 'social' evaluation of risk?

- Very little is known about experts' subjectivity in risk evaluation

Given that experts are not machines one could surmise that if not sufficiently managed, personal values, institutional values may enter any evaluation process



Risk Perception of Nuclear Experts

- Sjoberg (2002) reported four dimensions that explained the risk perception of a group of nuclear experts in Sweden
  - Dread
  - New Risk
  - Tampering with Nature
  - Involuntary Risk

Only other published study assessing risk perception among a group of experts in their field of expertise

Sjoberg, The allegedly simple structure of expert risk perception: An urban legend in risk research, Science, Tech, Human Values. Vol 27, No. 4, 2002

Overall Objectives of the EMA Risk Perception Research

Perception

- Humans perceive a situation as favorable, neutral or unfavorable

Attitude

- This perception impacts their attitude or mental view of the given situation or state

Behavior

- Attitude is then often reflected in the behavior

Hillison and Murray-Webster, Understanding and Managing Risk,. Gower, 2007

Research Questions

- What is the structural relationship between risk perception, risk attitudes and risk behavior among assessors?
- Is the risk attitude among medical assessors consistently risk seeking, risk neutral or risk averse?
- Is there a relationship between risk attitude and the perception of risk?
- Are there dimensions of a medicinal product that predict the risk perception of an assessor?
- Is there a relationship between risk perception of a specific drug and the demographic characteristics of an assessor?

Study Design and Methods

- **Web-based questionnaire launched June - Oct 2010**
- 9 European Countries
- 80 Medical Assessors (CNS, Cardiovascular, Oncology)

Instrument to measure risk perception

- Short versions of real clinical dossiers for 3 pharmaceutical drugs (therapeutic areas of oncology, cardiovascular, central nervous system)

Dimensions used to rate the 3 clinical dossiers

- **Risk Dimension** (How risky is the product?)
- **Benefit Dimension** (How beneficial is the product?)
- **Magnitude Dimension** (How many people are exposed?)
- **Dread Dimension** (How much does patient exposure worry you?)
- **Scientific Knowledge Dimension** (How precise is the scientific knowledge?)
- **New Risk Dimension** (Are the associated hazards new or old and familiar?)
- **Ethics Dimension** (Does this product pose an ethical dilemma?)
- **Risk Acceptability Dimension** (Are the associated hazards acceptable to obtain the benefits?)

Adapted from Savadori L, Stefania S, Elrado N, Reno R, Finucane M, Slovic P. Expert and Public Perception of Risk from Biotechnology. Risk Analysis. 2004; 20(5):1289-99.

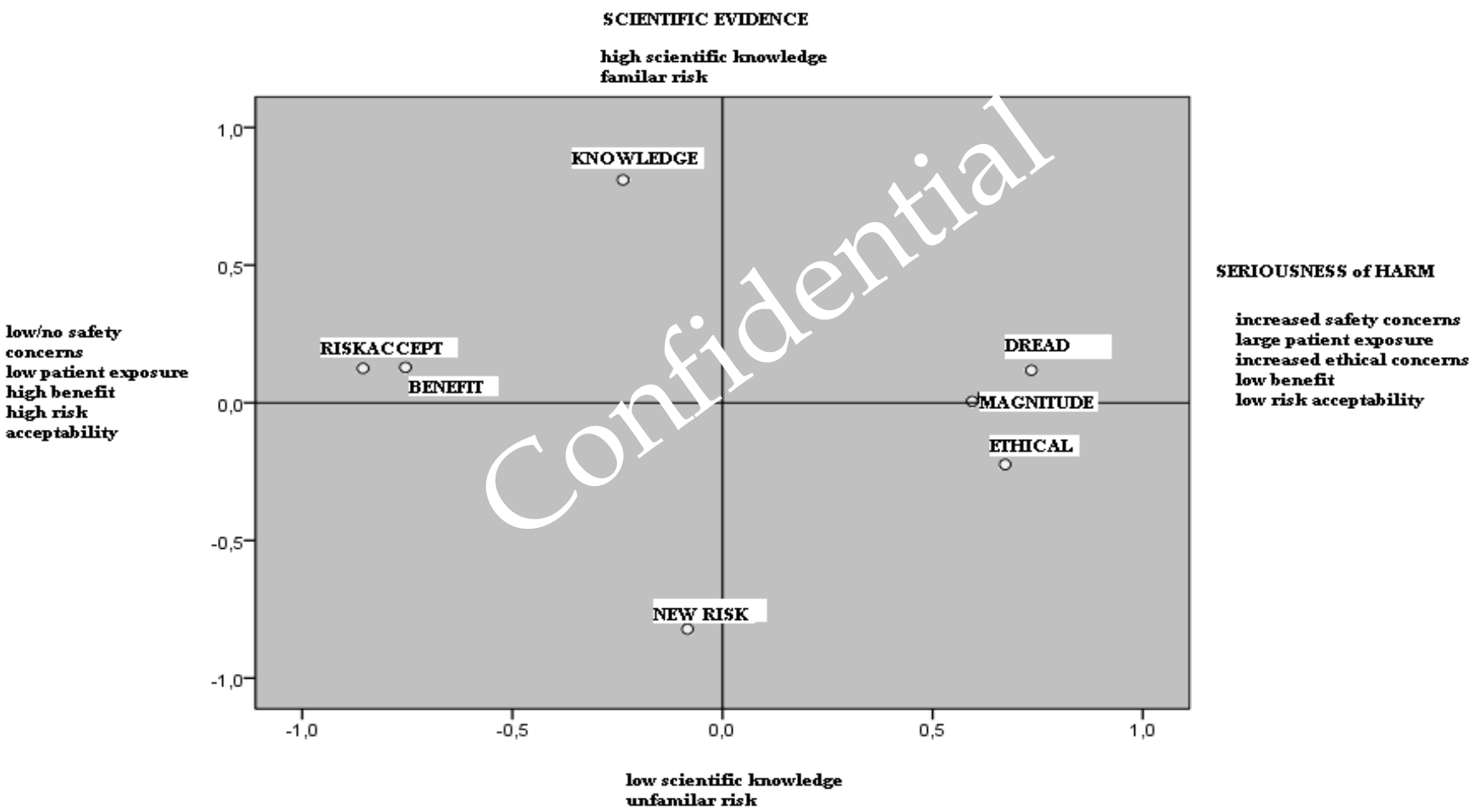
Data Analysis

- 3 clinical dossiers:
- Principal component analysis of the 7 dimensions (excluding risk) to obtain component scores
- Regress the component scores on the values for the risk dimension
- ANCOVA analysis with gender, years of regulatory experience and medicinal product as independent variables, PCA components with risk dimension as the dependent variable

Principal Component Analysis: Correlation of the 7 dimensions

- 2 components emerged from the PCA model and explained 59% of the variability between the assessors:
- Seriousness of Harm (40%)
- Scientific Evidence (19%)

Plot of Rotated Space for Expert Perception of Medicinal Products



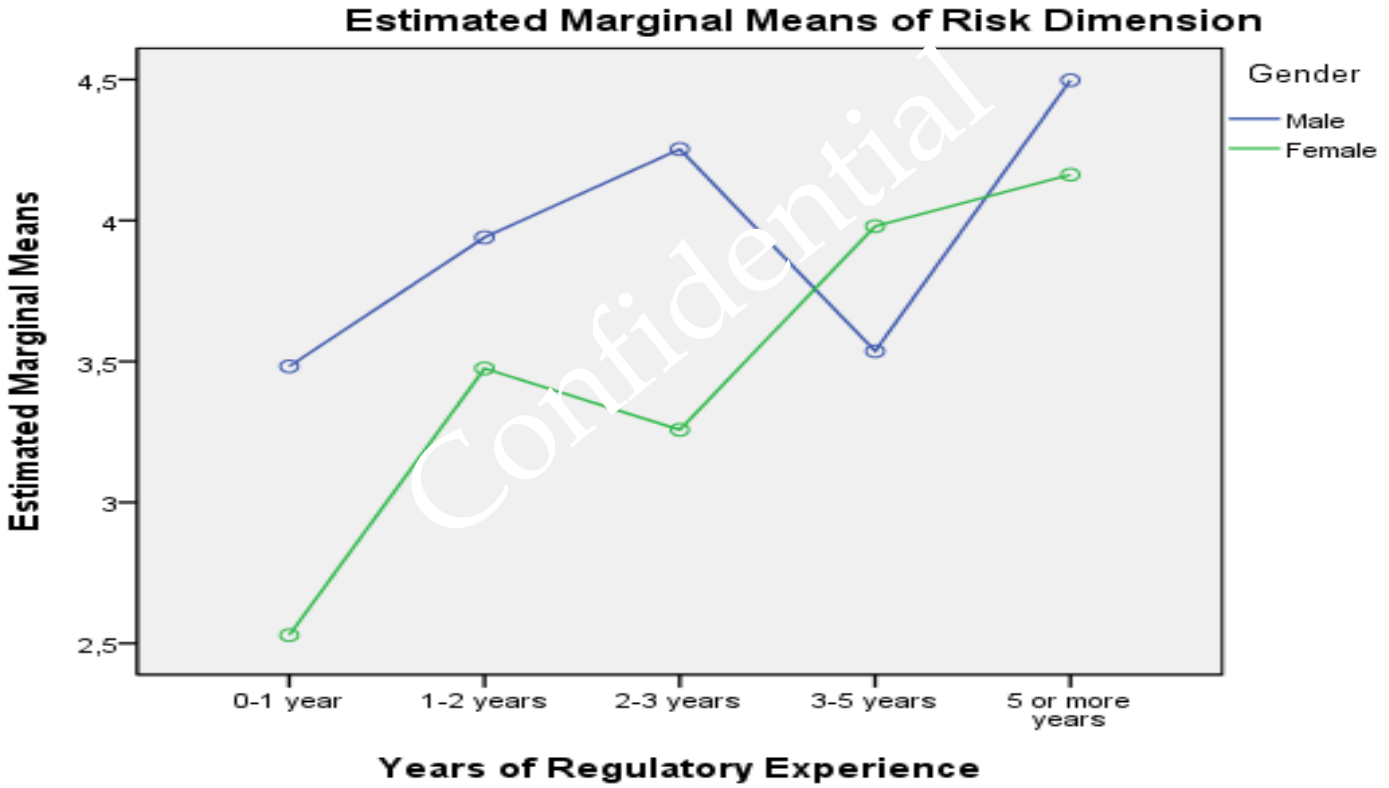
Regression Results

- Seriousness of Harm - only this component was predictive of the scores for the risk dimension
- Scientific Evidence - was not predictive of the scores for the risk dimension

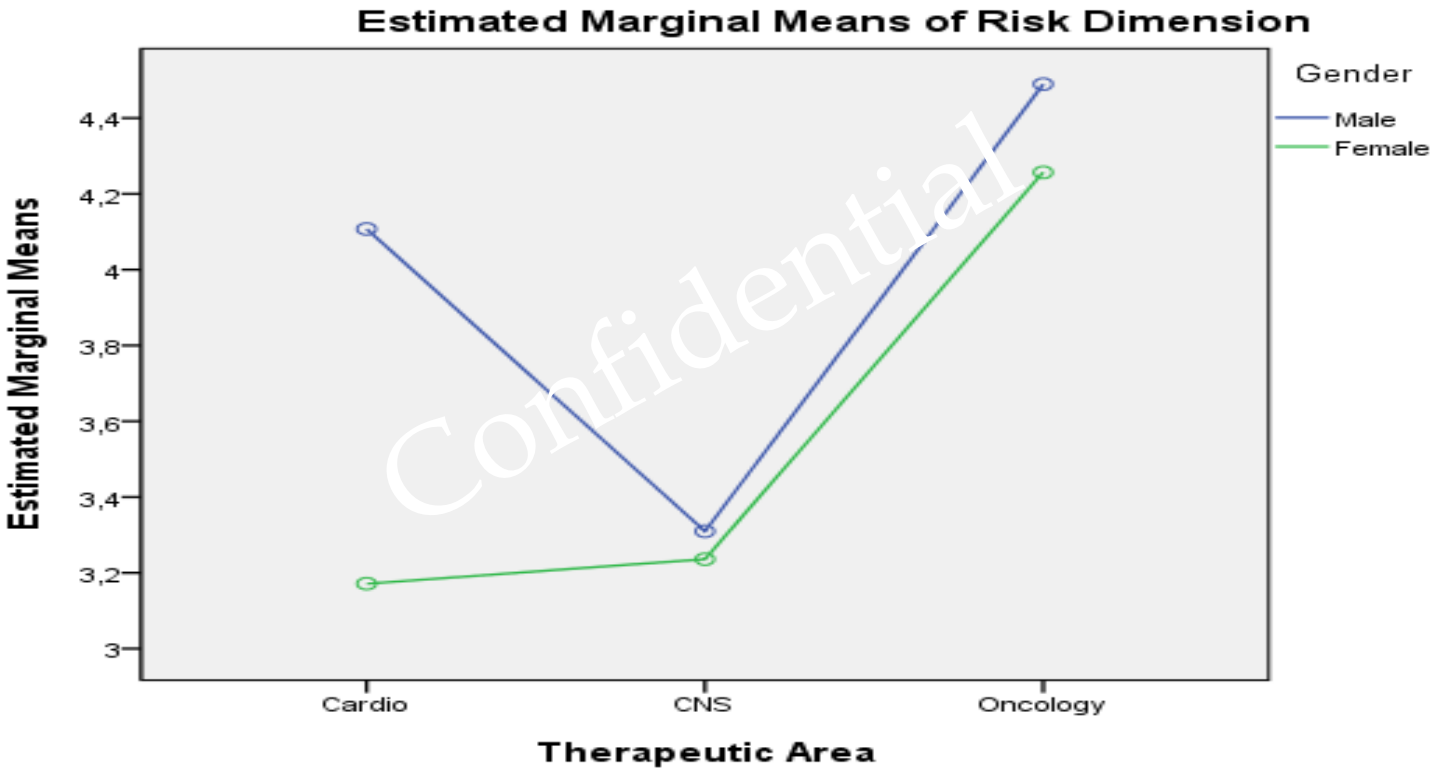
ANCOVA model

- 3 variables were found to predict the risk scores
- Seriousness of Harm, years of regulatory experience, gender by medicine interaction

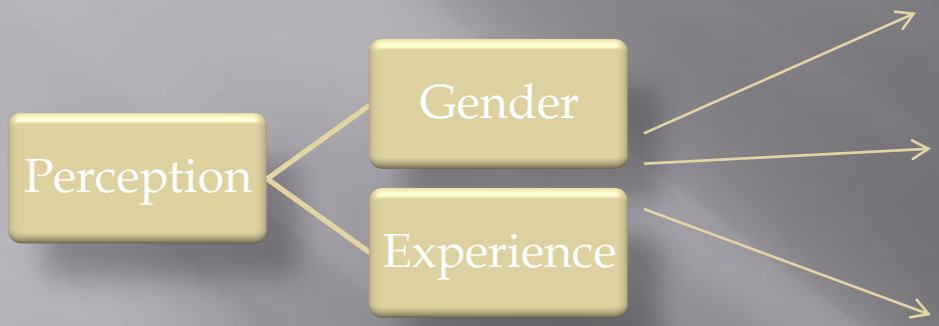
Plot of the Marginal Means for Gender and Regulatory Experience

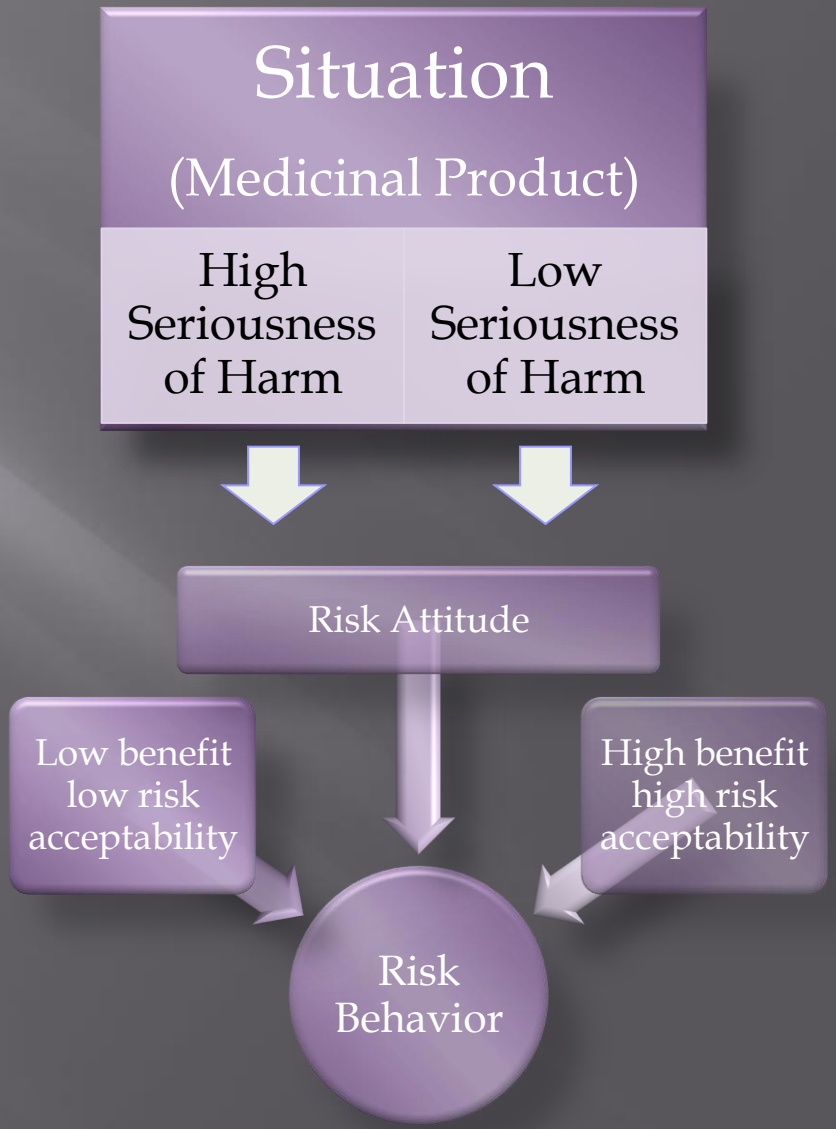


Plot of the Marginal Means for Gender and Therapeutic area



Summary





There are multiple dimensions through which assessors must integrate the data they receive in a clinical dossier, individual, situational and attitudinal that may ultimately impact behavior. These need to be correctly measured and managed.

Dear Sir,

London Sept. 19. 1772

In the Affair of so much Importance to you, wherein you ask my Advice, I cannot for want of sufficient Premises, advise you what to determine, but if you please I will tell you how. When these difficult Cases occur, they are difficult chiefly because while we have them under Consideration all the Reasons pro and con are not present to the Mind at the same time; but sometimes one Set present themselves, and at other times another, the first being out of sight. hence the various Purposes of Inclinations that alternately prevail, and the Uncertainty that perplexes us. To get over this, my Way is, to divide half a Sheet of Paper by a Line into two Columns, writing over the one pro, and over the other Con. Then during three or four Days Consideration I put down under the different Heads short Hints of the different Motives that at different Times occur to me for or against the Measure. When I have thus got them all together in one View, I endeavour to estimate their respective Weights; and where I find two, one on each side, that seem equal, I strike them both out: If I find a Reason pro equal to some two Reasons con, I strike out the three. If I judge some two Reasons con equal to some three Reasons pro, I strike out the five; and thus proceeding I find at length where the Balance lies; and if after a Day or two of farther Consideration nothing new that is of Importance occurs on either side, I come to a Determination accordingly. And tho' the Weight of Reasons cannot be taken with the Precision of Algebraic Quantities, yet when each is thus considered separately and comparatively, and the whole lies before me, I think I can judge better, and am less likely to make a rash Step; and in fact I have found great Advantage from this kind of Equation, in what may be called Moral or Prudential Algebra. Wishing sincerely that you may determine for the best, I am ever, my dear Friend, Yours most affectionately.

B Franklin

Dr Priestly

Title and Quantitative Approach	Parameters for Assessment
Quantitative Framework for Risk and Benefit Assessment (QFRBA)	Risk focuses on adverse events or outcomes. Benefit focuses on risk differences (relative risk reduction, absolute risk reduction)
Benefit-less-risk analysis(BLRA)	Intensity scores are used to compare severity and frequency of adverse drug events (ADEs) and assigned for each patient. Data on observed benefit from the treatment are required. Proportionality constants determines how much penalty the ADEs offset benefit measures
Quality -adjusted Time Without Symptoms and Toxicity (Q-TWIST)	Benefit measured as drug-attributed gain in quality- adjusted life-years (QALYS); Risk measured as drug-attributed loss of QALY; Compare gain versus loss of QALY
Number needed to treat (NNT) and number needed to harm NNH)	Benefit is number of persons treated (NNT) to avoid one person developing disease of interest (absolute risk reduction, relative risk reduction); Risk is number of persons treated when one person experiences ADE (NNH); Ratio of NNT and NNH
Relative value adjusted number need to treat (RV-NNT)	Expand NNT to include relative utility values (RV) based on patient preferences
Minimum clinical efficacy (MCE)	Benefit is efficacy difference between new treatment and conventional treatment or placebo; Risk is probability of AEs in patients receiving new treatment vs. conventional treatment or placebo;
Incremental Net Benefit (INHB)	Risk is a decrease in QALY; Benefit is improvement in QALY; INHB as relative gain or loss of QALYs due to treatment vs. usual care or placebo
Risk-benefit plane (RBP) and risk-benefit acceptability threshold (RBAT)	Risk is a relative probability of risk of AEs between treatment and control groups; Benefit measured as relative probability response between treatment and control groups
Probablistic simulation methods (PSM) and Monte Carlo simulation (MCS)	Average difference in the probability of risk and benefit for the new therapy relative to conventional therapy; Incremental risk-benefit ratio (IRBR)
Multicriteria decision analysis (MCDA)	Benefit is endpoints from clinical trials; Risk measured as ADE, and other safety criteria; Decision tree is developed to preferences to all key benefits and risks
Risk-benefit Contour (RBC)	Probability of potential benefit of treatment such as an increased survival rate; Probability of potential risk due to severe ADE or drug toxicity
Stated preference method (SPM) or maximum acceptable risk (MAR)	Patient surveys needed to provide data on the value of benefit vs. negative impact of risk

Guo et al. Value in Health ,2010 Vol 13 No. 5.

Fit for Purpose ?

- Noted the strengths and weaknesses in each model for the purposes of pharmaceutical regulatory assessment
- INHB, RBP, PSM, MCDA, SPM, and RBC seem to be flexible and easier to adopt for certain clinical situations than others
- Despite research activities both at FDA and EMA with attention on INHB , MCDA , SPC (expert reviewer comments) not sufficient research has been conducted or consensus reached on the most appropriate model (s) for BR assessment

Guo et al. Value in Health ,2010 Vol 13 No. 5.

Recommendations to Increase Transparency

- Four –fold model implemented in the EMA Assessment Report Template Guidance

Favourable Effects	Uncertainty of Favourable Effects
Unfavourable Effects	Uncertainty of Unfavourable Effects

- PROACT-URL Framework (Hammond et al., 1999; Hunink et al., 2001)

The PrOACT—URL process: Steps 1-5

PrOBLEM

1. Determine the nature of the problem and its context. Frame the problem.

OBJECTIVES

2. Establish objectives that indicate the overall purposes to be achieved and identify criteria of favourable and unfavourable effects.

ALTERNATIVES

3. Identify the options to be evaluated against the criteria.

CONSEQUENCES

4. Describe how the alternatives perform for each of the criteria, i.e., the magnitudes of all effects, and their desirability or severity, and the incidence of all effects. Create an Effects Table. For quantitative modelling: convert data to 0-100 value scales.

TRADE-OFFS

5. Assess the balance among favourable and unfavourable effects and determine the overall benefit-risk balance. For quantitative modelling: first assess swing weights.

EMA BR Methodology Project Work Package 2, 2010

The PrOACT—URL process: Steps 6-8

UNCERTAINTY

6. Assess the uncertainty associated with the favourable and unfavourable effects. Consider how uncertainty affects the benefit-risk balance. For quantitative modelling: conduct sensitivity analyses and scenario analyses to see their effects on the B-R balance.

RISK TOLERANCE

7. Judge the relative importance of the decision maker's risk attitude for this product in its context and indicate how this affects the balance reported in step 5.

LINKED DECISIONS

8. Consider the consistency of this decision with similar past decisions, and assess whether taking this decision could impact future decisions.

EMA BR Methodology Project Work Package 2, 2010

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