EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Improving the process of balancing benefits and risks in approving drugs

Decision Analysis Affinity Group
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An agency of the European Union

Consider a new heart attack drug

"There is a risk this drug won't lower your risk and there are risks from taking the drug."

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Risk 1: possibility you are a non-responder

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Risk 1: possibility you are a non-responder

Risk 2: your probability of a heart attack

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Risk 1: possibility you are a non-responder

Risk 2: your probability of a heart attack

Risk 3: possible side effects

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EMA Benefit-Risk Methodology Project

Problem: "assessing 21st century drugs with 19th century methodology"

Aim: adapt or develop tools and processes to conceptualize and make explicit B-R trade-offs, to provide an aid to regulatory decision-making, an aid for training of assessors, and an aid for communicating B-R decisions to stakeholders.

Benefit-Risk Methodology Project

Where will we end up?

quantitative, qualitative, or a bit of both?

Caveats:

- "Drug licensing is too complex an issue, it's not doable"
- "Let them have a go at a quantitative model – they are bound to fail"
- "Expressing B-R in one single figure is deceptive, pretending certainty where there is uncertainty"

Benefit-Risk Methodology Project

Work Packages (2009 – 2011)

1. Describe B-R assessment practice in EU
2. Assess applicability of available tools and processes for regulatory B-R assessment
3. Adapt and field test selected tools and processes to demonstrate usefulness
4. Synthesize information and develop tool(s) and process(es) that can add value to B-R assessment.
5. Develop a training package for assessors

WP1 Results: describe current practise

Methods: structured interviews (55 staff, 6 EU agencies)

Key Findings:

1. No agency uses a structured system or model
2. The benefit-risk balance is assessed intuitively, by a senior assessor, or by a group
3. Consistency is a worry
4. The meanings of "benefit" and "risk" are very fluid, within and across agencies ("What is a risk?" ➔ ca. 50 different responses)

Evidence: 55 interviews in 6 EU Agencies

What is a benefit?

1. Everything good
2. Improvement in health state
3. Real-world effectiveness
4. Clinical relevance
5. Improvement in illness
6. Suffering reduced
7. Positive action of drug
8. Meets unmet medical need
9. Positive improvement in health state as perceived by patient
10. Safety improvement
11. Value compared to placebo
12. Change in managing patient

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37. Statistically significant effect

What is a risk?

1. All that is negative
2. Adverse events
3. Reduction in quality
4. Kinetic interactions
5. Side effects
6. Serious adverse effects
7. Bad effects
8. Danger for the patient
9. Tolerance of a drug compared to serious side effects
10. Harm
11. Severity of side effects11
12. Frequency of side effects

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51. Potential or theoretical risks

Evidence: 55 interviews in 6 EU Agencies

What is a benefit?

Nobody said "Cure"

What is a risk?

Only one person said "Chance the benefit won't be realised"

The new four-fold model of benefit-risk

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

And, there can be multiple favourable effects and unfavourable effects

The Benefit-Risk section of the new Template/Guidance for the CHMP Assessment Report gives guidance for each cell.

Applying the four-fold model

Favourable effects

- Beneficial effects for this condition
- Important endpoints
- What data show beneficial effects?
- Describe in important subgroups
- Relative efficacy in pivotal studies

Uncertainty in knowledge

- Main sources of uncertainty
- Impact of supportive and non-supportive clinical data
- Impact of uncertainties, e.g., range of expected benefits

Unfavourable effects

- Important adverse drug reactions
- Important PK and PD interactions
- Important public health or environmental effects; misuse?
- Relative safety, toxicity

Uncertainty in knowledge

- Data limitations, e.g., due to sample size, study design, duration
- Quality issues, non-clinical safety
- Impact of uncertainties, lack of safety data, unknowns

Source: Guidance Document for the CHMP Assessment Report, 10 September 2009

Results WP2: assess methodologies

Literature research has identified several approaches which may be potentially useful tools for B-R assessment

Selection criteria for progressing to next stage:

- Logical soundness
- Comprehensiveness
- Acceptability of results
- Practicality
- Generativeness

WP3

Results WP2: assess methodologies

Adapt and field test (to be finalised):

- (Markov models, simulation models, decision trees, multi-criteria decision analysis, Bayesian belief networks, system dynamics?)

How?

- Back-room models
- One-off approach (e.g. swine flu vaccines)
- Consolidation approach
- Continuing analysis approach

CASE STUDY: DECISIONS ABOUT THE H1N1 FLU VACCINE

Rising concerns, summer 2009

- WHO declares swine flu pandemic
- Drug regulators facing a choice about approving vaccines
  - Wait until more data available on safety and efficacy
  - Decide now to make vaccine available sooner
- Many concerns
  - Seriousness of the pandemic: death rate in Europe
  - Efficacy: will the vaccine work?
  - Safety: how safe will it be?
  - How will vaccines affect critical populations?
  - Extent of unmet medical need (a new disease)

Could a decision conference be helpful?

- An opportunity to test modelling as an adjunct to group discussion
- Group of EMA staff engage in decision conference on 1 September 2009
- Purpose is to test applicability of group modelling: *strictly a research exercise*
- CHMP not involved
- Results not reported to CHMP

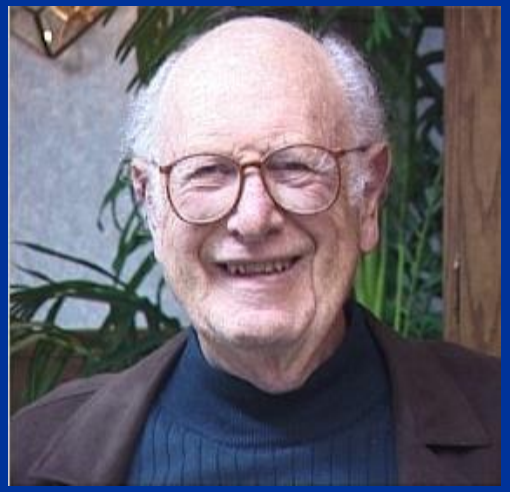
Decision Conferencing

One or more workshops

Attended by key players representing the diversity of perspectives

Facilitated by an impartial specialist in group processes & decision analysis

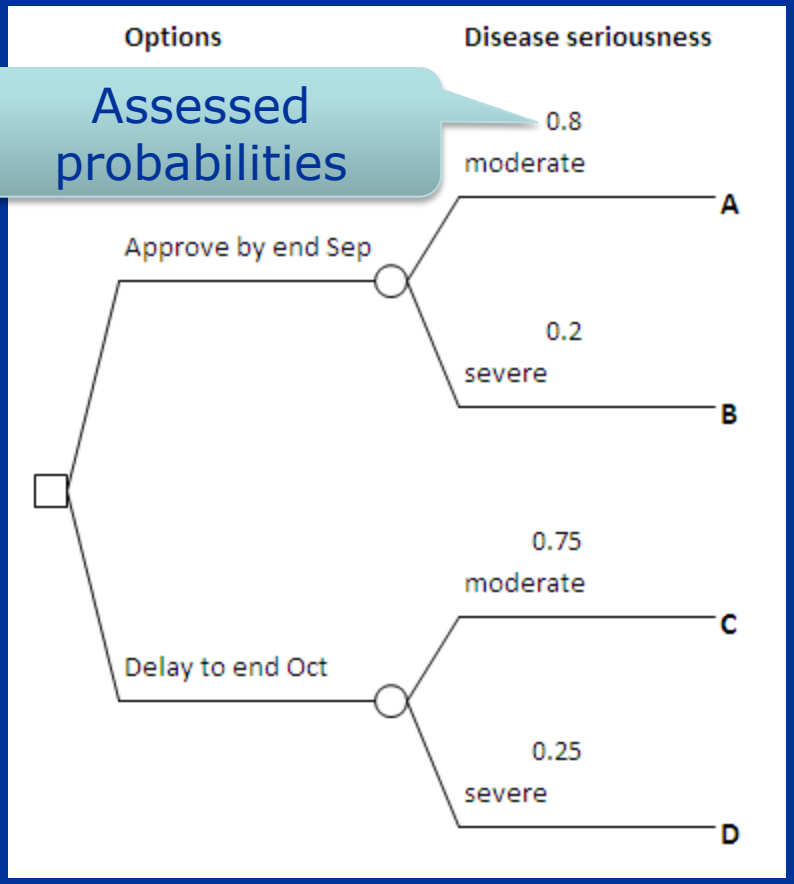
- Using a requisite (just good enough) model created on-the-spot to help provide structure to thinking

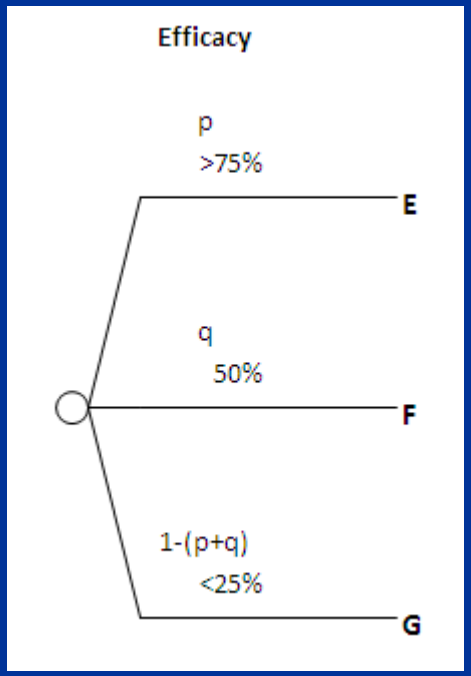


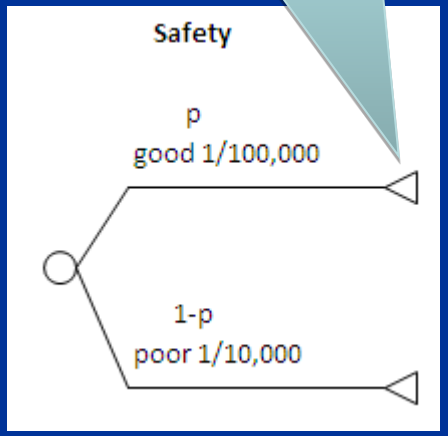
"The spirit of decision analysis is divide and conquer: decompose a complex problem into simpler problems, get one's thinking straight on these simpler problems, paste these analyses together with logical glue, and come out with a program of action for the complex problem"

(Howard Raiffa 1968, p. 271)

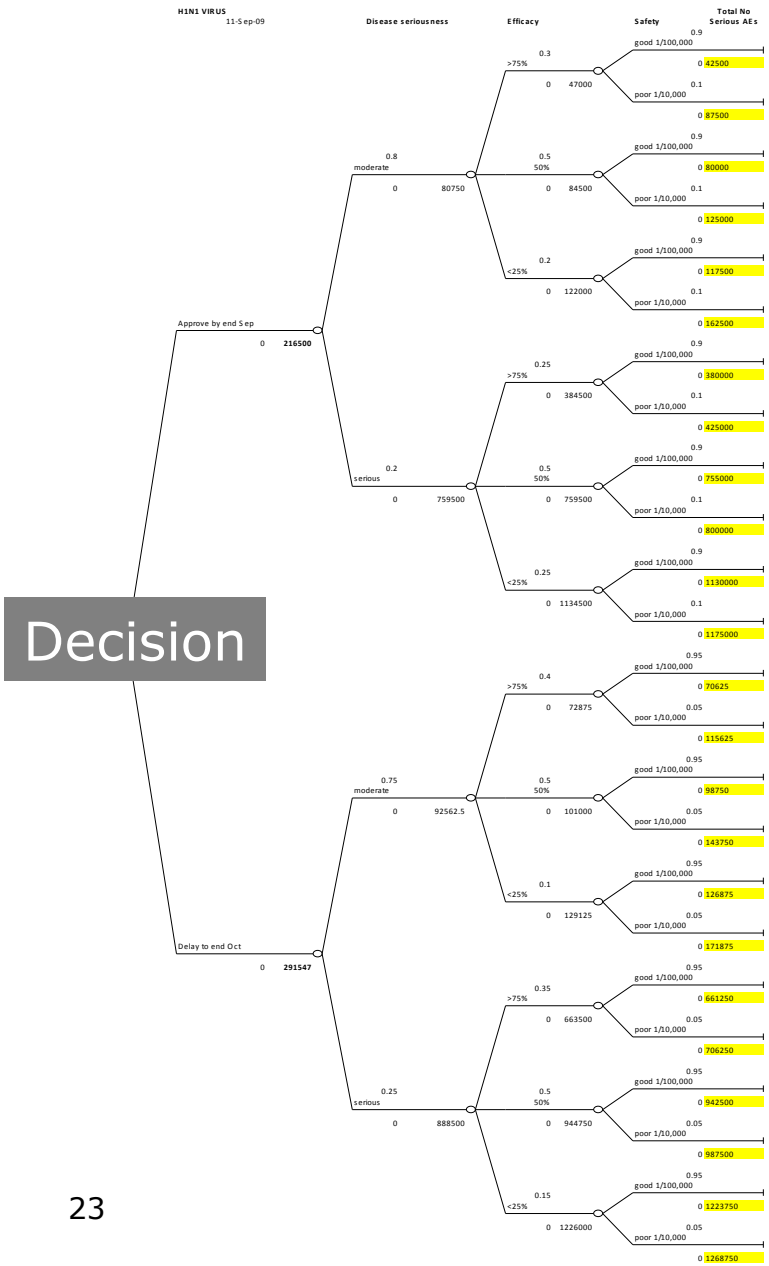
Decision tree model





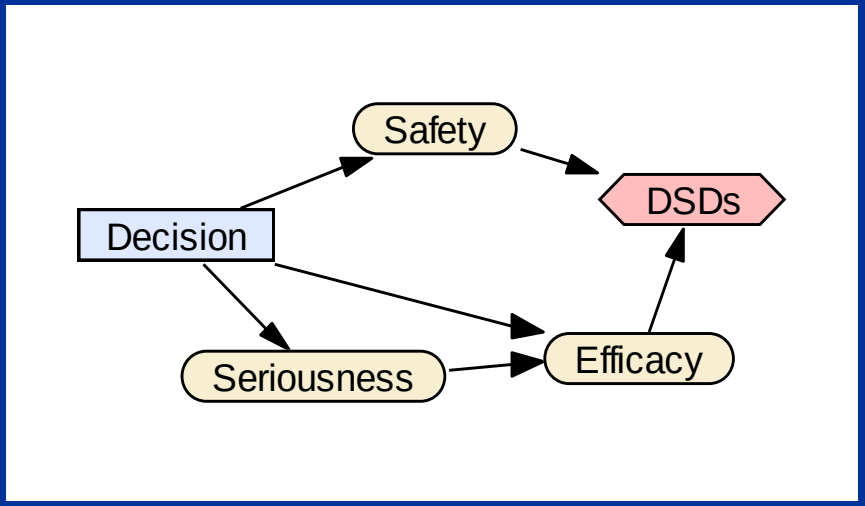


24 scenarios



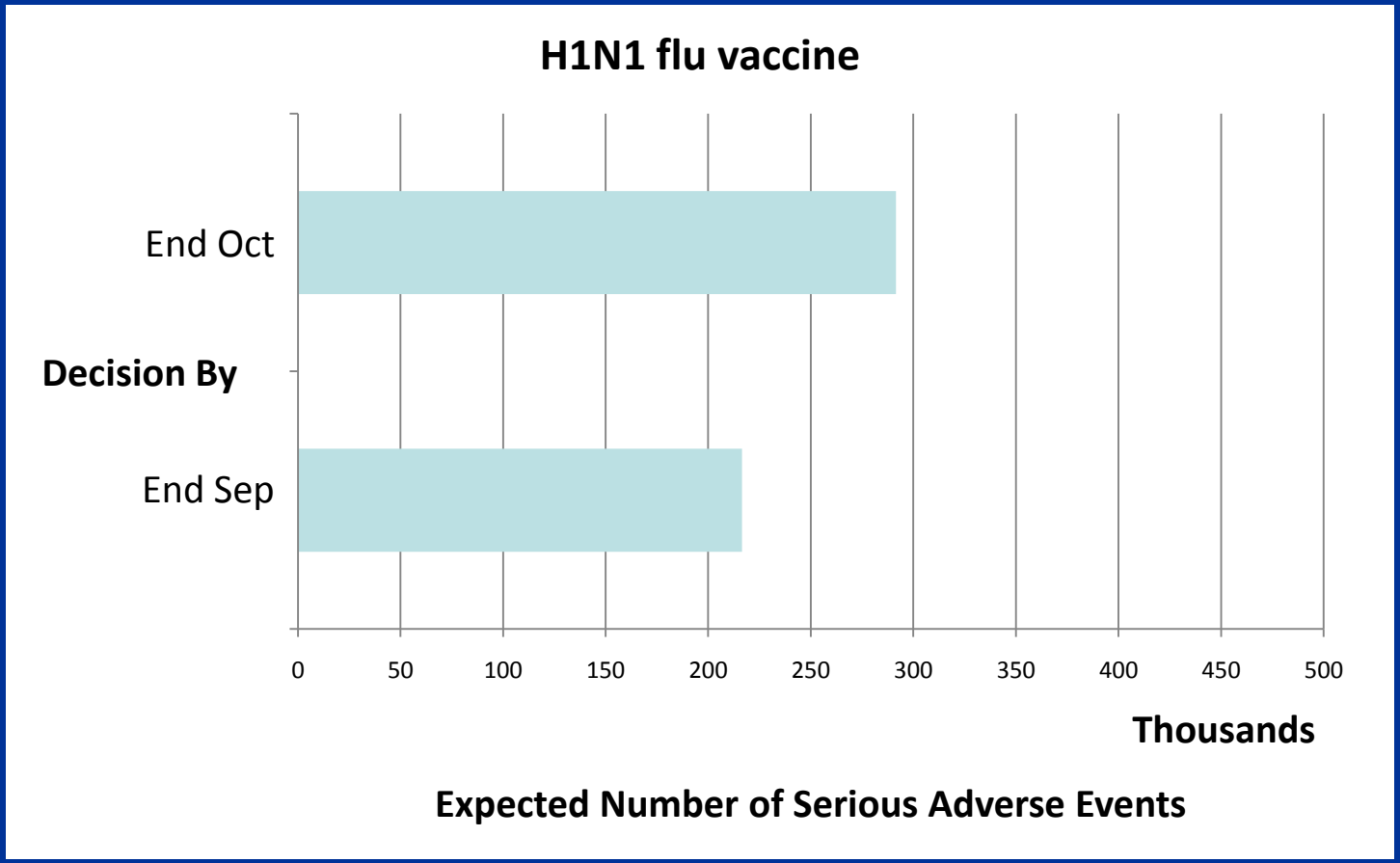
Relevance/Influence Diagram

- More compact display
- Shows how knowledge about one event can be relevant to uncertainty about another event

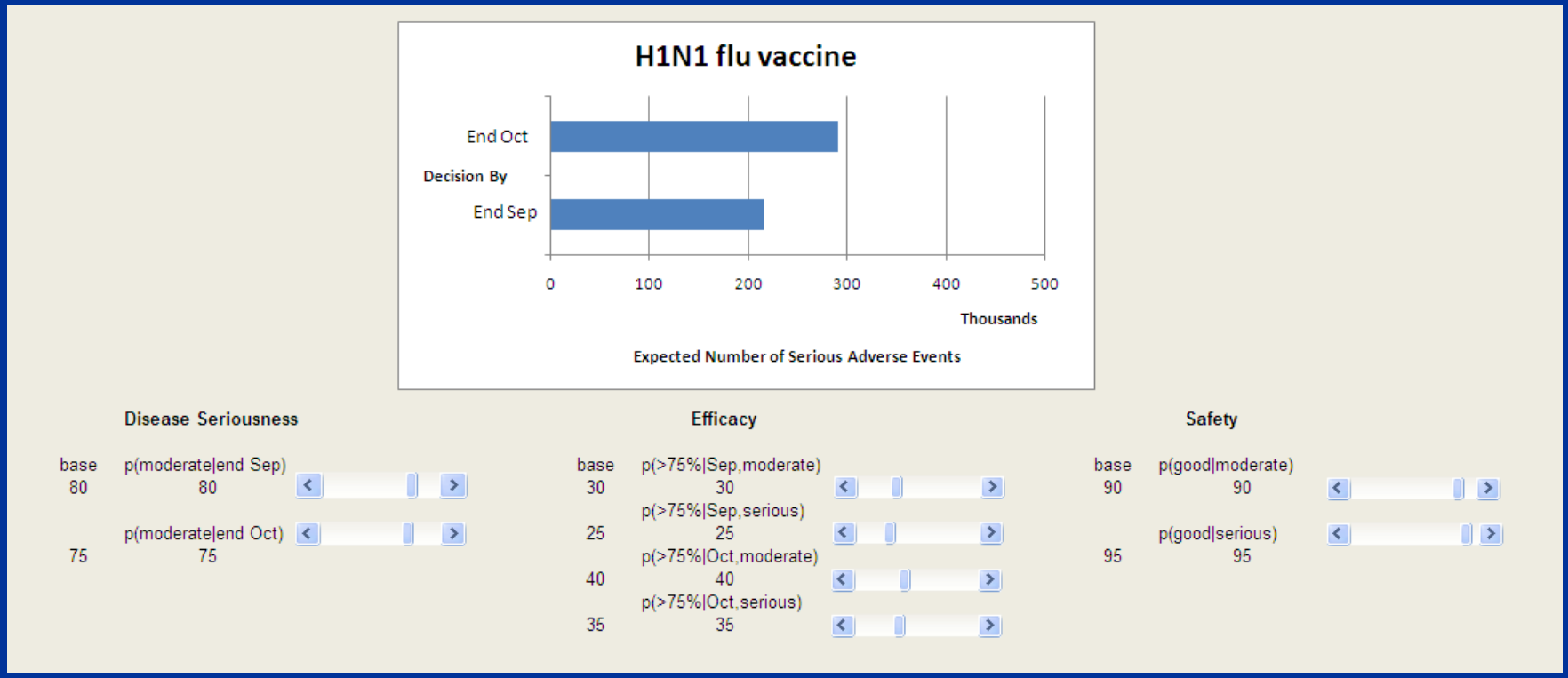


DSDs: Numbers of Deaths and Serious Disabilities

'Folding back' the decision tree



Decision 'dashboard'



This enables decision makers to try out different assumptions, helping them to form their own preferences.

What did we learn?

- The process generated alignment of participants
- It revealed characteristics of the decision problem that were not obvious at the start
  - Differences in opinion about safety and efficacy probabilities did not change the decision
  - Only if the probability of the disease being moderate rather than severe was more than 0.84, which nobody believed in September 2009, would it be better to delay the decision
- The model made explicit the reasoning behind the decision
- The model and the process helped participants to form their own preferences (people decide, not models!)

Conclusions

- This case shows how modelling can deepen insights in problematical situations
- Working with groups of key players allows an exchange of views
- Modelling enables the group to challenge assumptions and develop new perspectives
- The process generates shared understanding, develops a sense of common purpose, and gains commitment to the way forward
- The results are auditable, transparent and communicable.

BUT FIRST

WE NEED TO AGREE ABOUT WHAT WE MEAN BY "BENEFIT" AND "RISK"!

EUROPEAN MEDICINES AGENCY

THANK YOU!