EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Involvement of patients in benefit and risk evaluations at the EMA

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Benefit-Risk

ben·e·fit

(bĕn’ə-fĭt)*n.* Something that promotes or enhances well-being; an advantage.

risk

(rĭsk)*n.* The possibility of suffering harm or loss; danger.

Consider the situation of sitting outside in the sunlight.

What are the benefits? What are the risks?

Benefit-Risk assessment

Benefit/risk decisions are complex and have considerable consequences on patients' care

Figure 1. The EMA's four-fold model of 'benefits' and 'risks'

Favourable effects	**Uncertainty of favourable effects**
Unfavourable effects	**Uncertainty of unfavourable effects**

Definitions

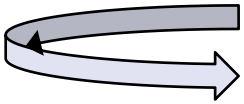
Favourable effects are any beneficial effects for the target population (often referred to as "benefits" or "clinical benefits") that are associated with the product.

Unfavourable effects are any detrimental effects (often referred to as risks, harms, hazards both known and unknown) that can be attributed to the product or that are otherwise of concern for their undesirable effect on patients' health, public health, or the environment.

Uncertainties about both types of effects arise from variation, important sources of bias, methodological flaws or deficiencies (including GCP, compliance, etc.), unsettled issues, and limitations of the data set, e.g., due to sample size, study design, or duration of follow-up.

Situation of rare diseases

- Rarity of disease means less information to support the benefit-risk assessment
- High unmet medical need means more urgency for treatment availability

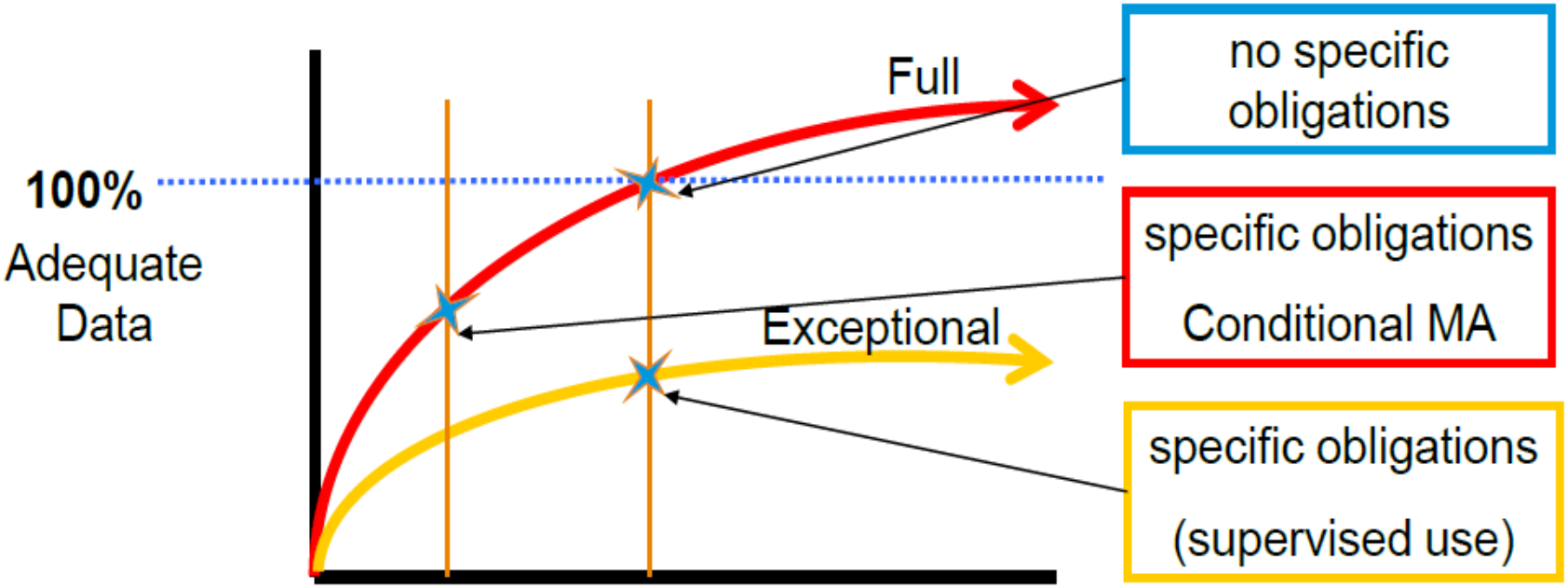


Regulators must cater for

uncertainty in Decision making

'If we didn't take any risks, we wouldn't approve any drugs' (S. Ellenberg)

Regulatory options for approval



Patients' involvement currently in benefit-risk evaluation

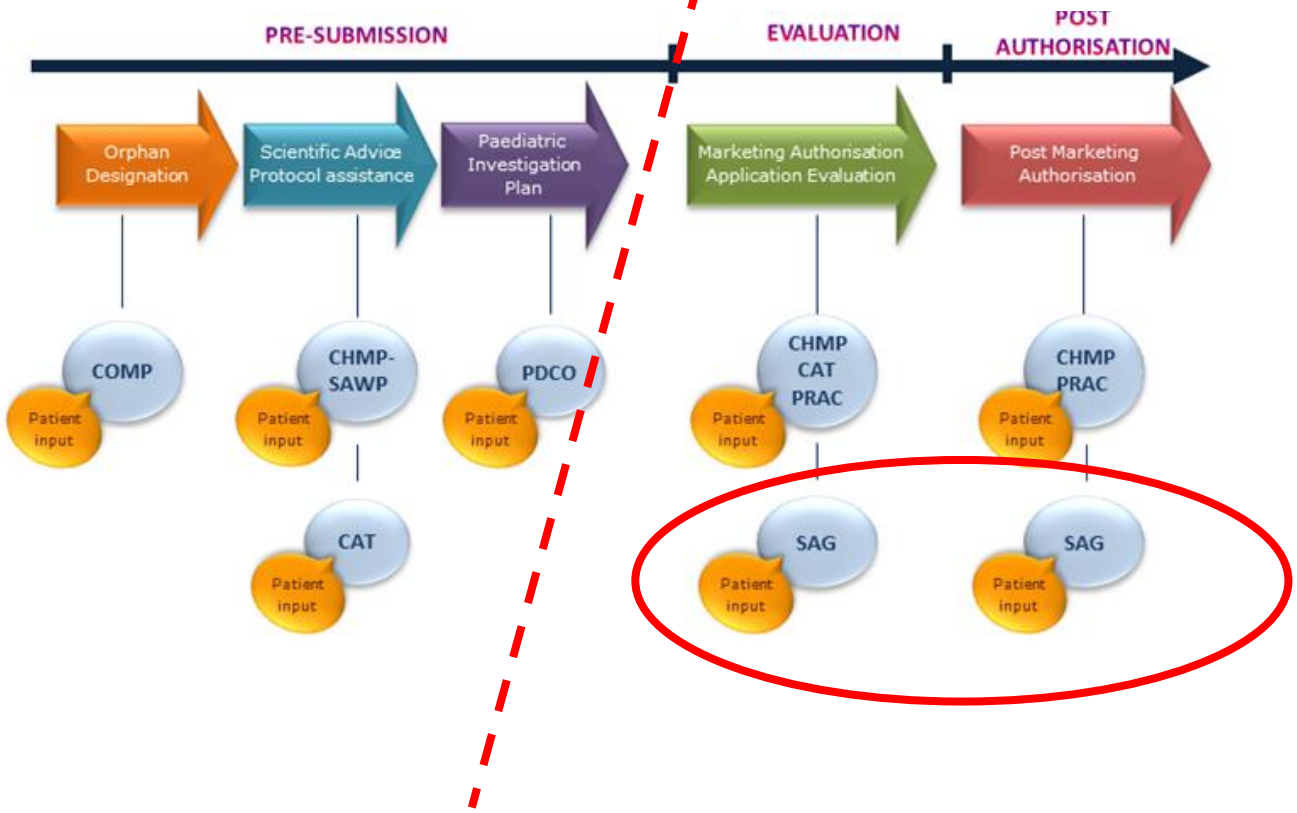
- Members of several of the EMA scientific committees
- Participation in scientific advisory group meetings
- Pilot initiative involving patients in CHMP during oral explanations preceding decision-making
- Additional methodologies currently being tested

Members of several of the EMA scientific committees

Creation of the Pharmacovigilance and Risk Assessment Committee (PRAC);

- Patients and healthcare professional representatives included as full members
  - First time involved within committee discussions on benefits & risks
  - Patient's role is to ensure that their perspectives (based on real-life experience as end users) are delivered throughout the committee's activities and outcomes
  - HCPs' role is to ensure that the potential impact of regulatory decisions in clinical practice are taken into account and to highlight specific areas where additional input from the wider healthcare professionals' community can support the committee's activities

Participation in scientific advisory group meetings



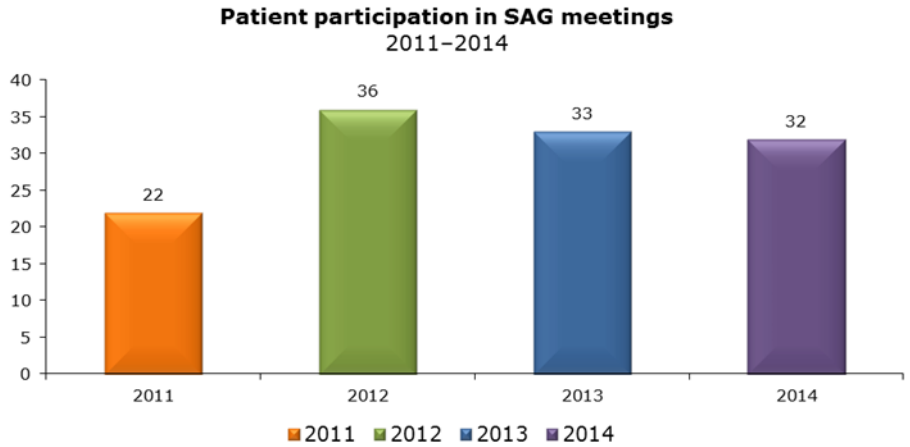
Scientific Advisory / ad hoc expert groups

Scientific Advisory Groups (SAGs) are convened at the request of the CHMP or PRAC to deliver answers to specific questions

Currently there are 8 therapeutic areas for SAGs

Where there is no existing SAG for a therapeutic area – ad hoc expert groups are organised

- Pilot to involve patients began in 2011
- Patients now systematically involved invited to SAG meetings



Examples of patient involvement in benefit/risk discussions

Written consultations, examples…

Humalog / Liprolog - Extension of indication : concerns regarding introduction of a new high strength and how to ensure its safe and correct use

- Consultation with patients & HCPs to obtain input on how best to minimise potential risk of medication errors
  - Input received prompted the PRAC & CHMP to request further changes to the labelling (differentiations of strengths).
  - The MAH subsequently amended the labelling and other measurements in the risk minimisation plan.

Face to face consultations…

Article 31 referral procedure - review of Valproate ; PRAC review of new information on risk of long-term developmental problems in children whose mothers took Valproate

- Patient meeting– included epilepsy, bipolar disorder and migraine patient organisations and organisations representing the patients, families and carers affected by valproate
  - Very constructive exchange of information; patients shared their personal experiences and provided input on how best to raise awareness for all concerned; in turn allowed PRAC to explain the assessment process
  - The need to consult with HCPs was very much emphasised by patients
- PRAC also initiated consultation with relevant HCPs organisations to obtain information on communication, awareness & understanding of risks
  - Valuable input will be taken forward by the PRAC in reaching its recommendation

Framework of interactions with patients/consumers

- Revised framework of EMA interaction with patients and carers
- Adopted in December 2014 by the EMA Management Board
- One of the objectives of the framework is to further enhance participation of patients and consumers in benefit/risk evaluation

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Ongoing pilot to explore feasibility and usefulness of eliciting patients values to inform the benefit-risk decision

Pilots involving patients:

Participation in CHMP oral explanations

Patients (affected by the disease/condition under discussion) will be invited to participate directly within oral explanations at the CHMP;

- Where their involvement can bring added value to the B/R discussion (case-by-case)
  - Likely negative recommendation where there remains an unmet medical need, or restriction of an indication where a significant impact is expected;
  - Likely recommendation to withdraw, suspend or revoke a marketing authorisation, or restrict an indication of an authorised medicine, with expected high impact in patient population
- Initial pilot phase; analysis and outcome report after one year
- Similar developments could be discussed in PRAC..

Pilots involving patients:

MCDA eliciting patient preferences

Multi Criteria Decision Analysis (MCDA)

Background here

Webinar

Document

Etc..

Other methodologies for patient preference and values in benefit and risk evaluations

Tested already in 2 patient groups.. Melanoma and myeloma

Two components:

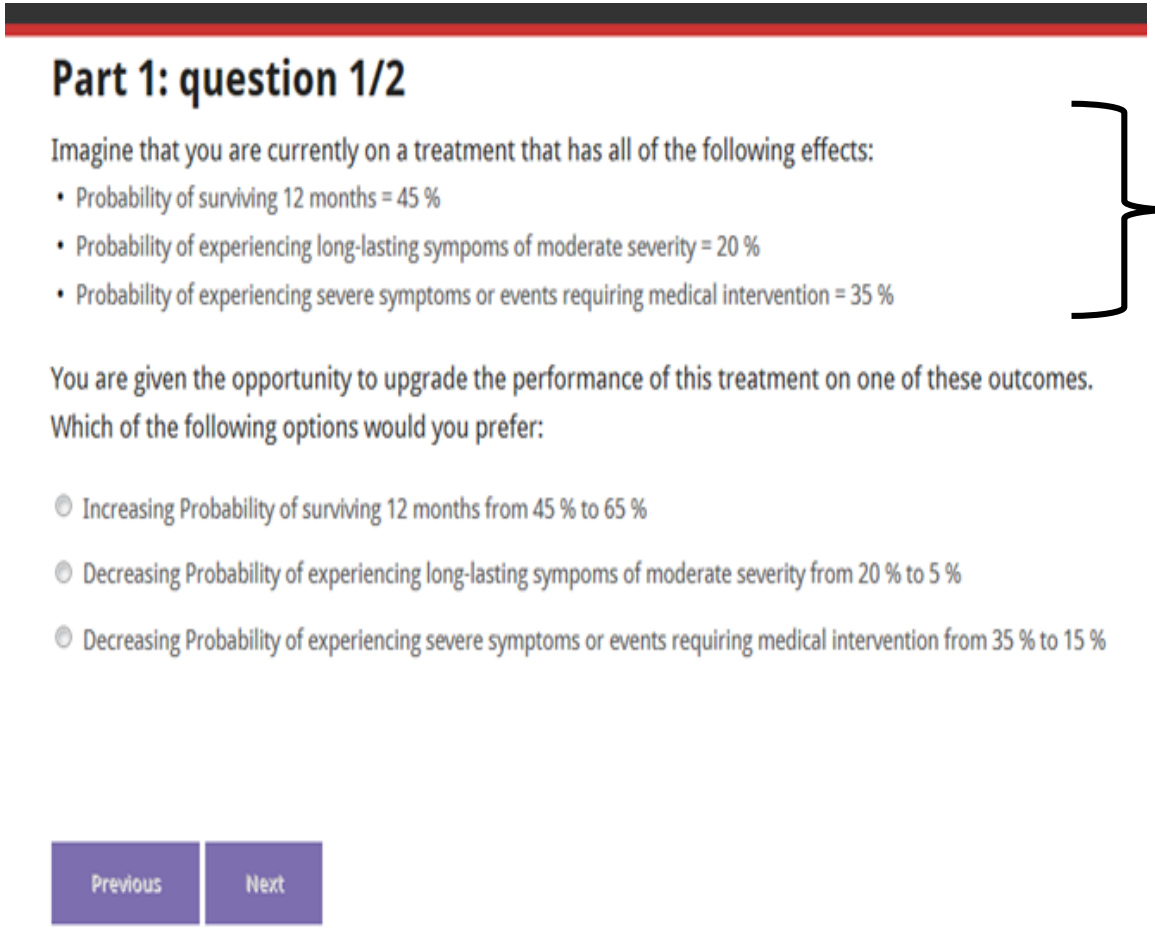
Online questionnaire followed by face to face discussion at workshop

Online questionnaire has two parts:

Part 1: asks you to provide your preferences in a given benefit-risk scenario

Part 2: asks you decide how much you would trade off between one outcome and another

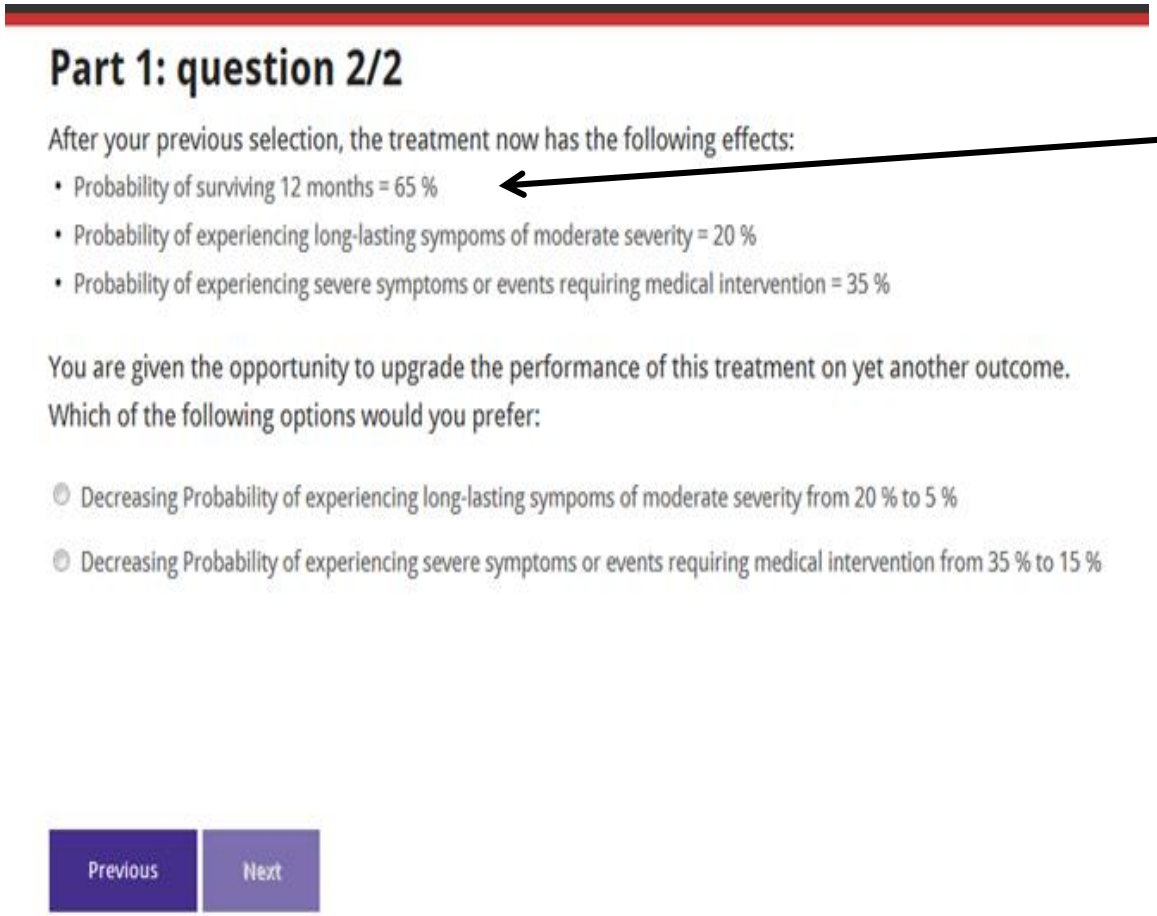
The questionnaire: Part 1- Ranking



Performance outcomes

Which of these would you choose first, second,…?

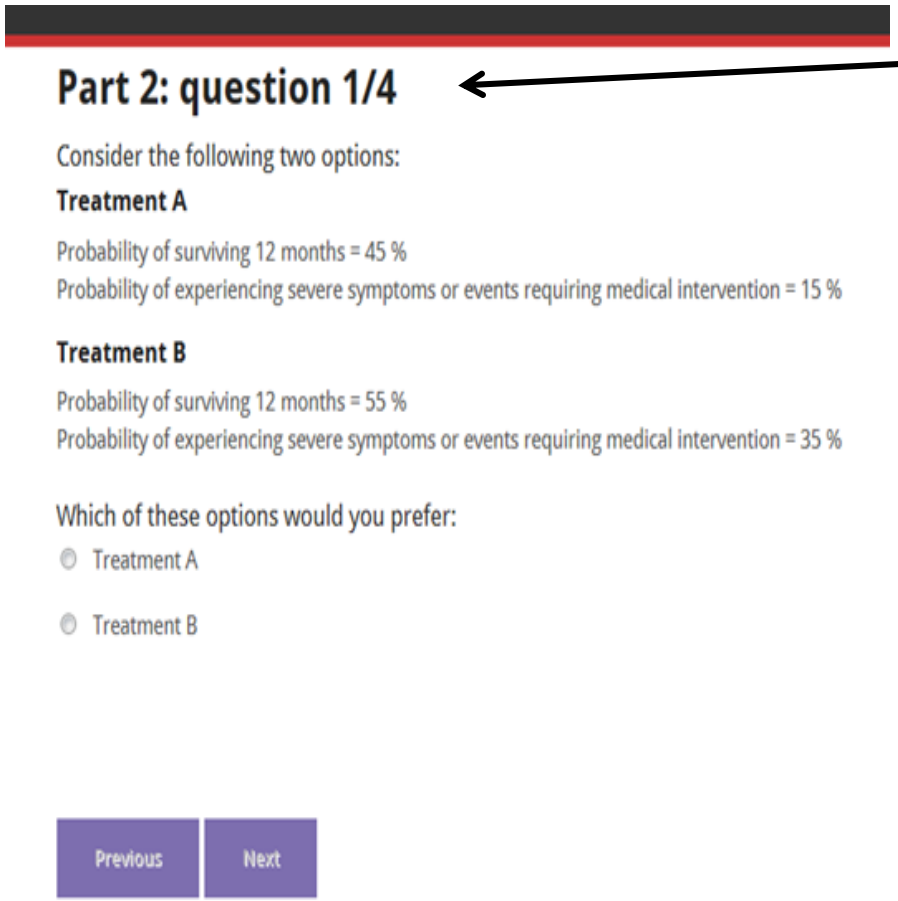
The questionnaire: Part 1- Ranking (Cont..)



This parameter has changed

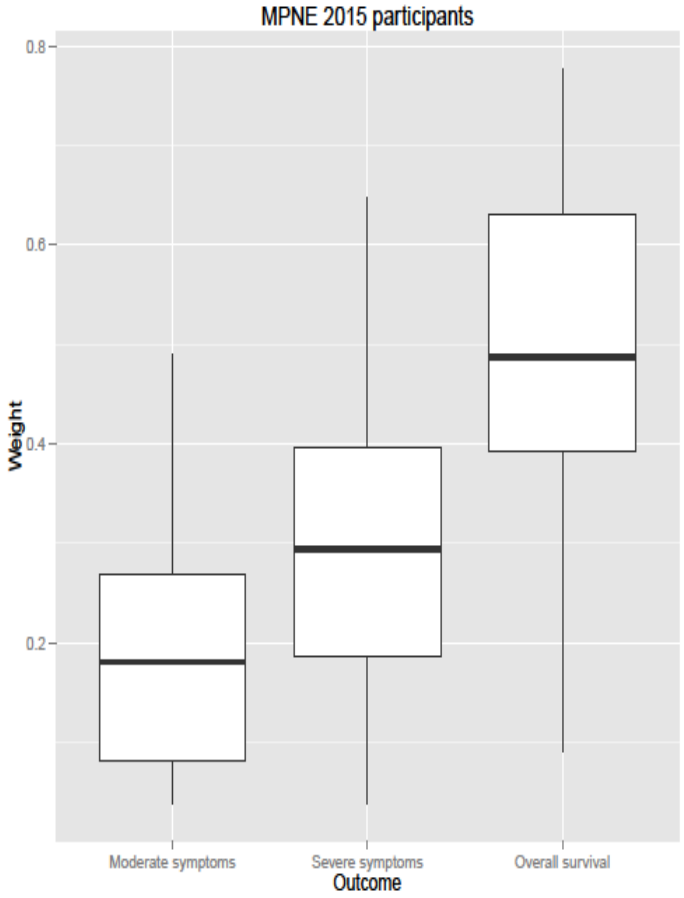
Make your next selection from the remaining 2 options

Part 2 - Trade-off ratios

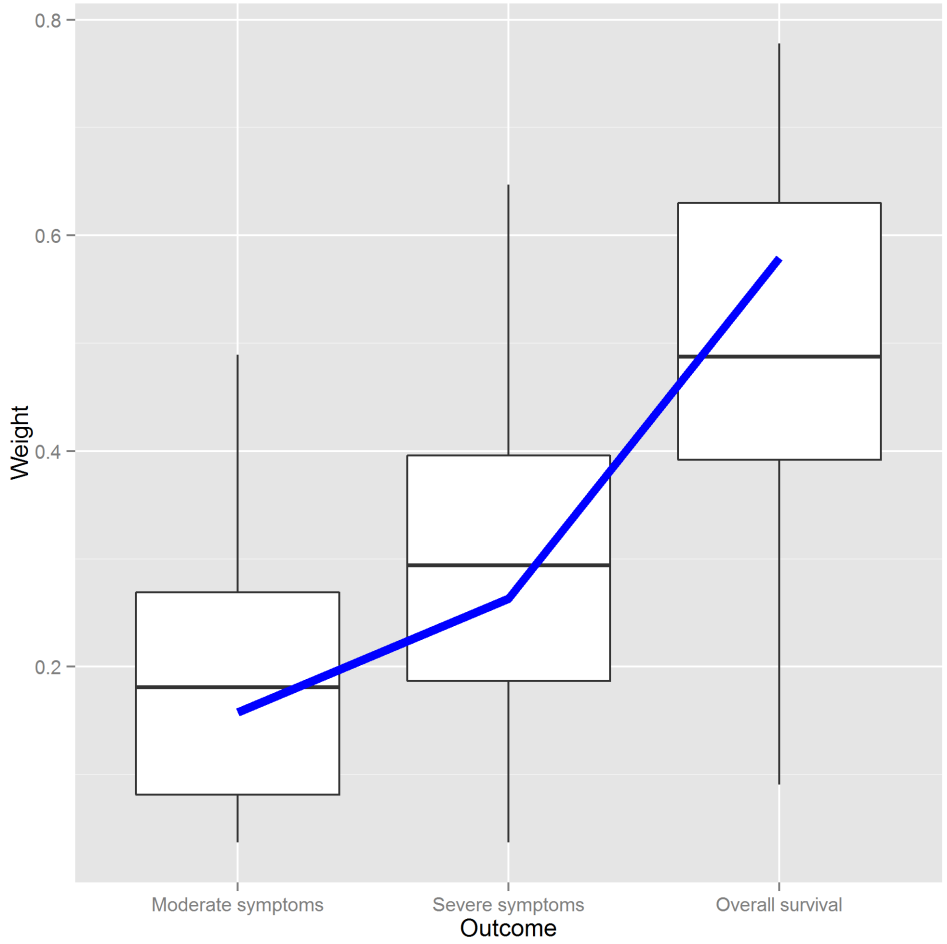


There are 4 questions to answer here

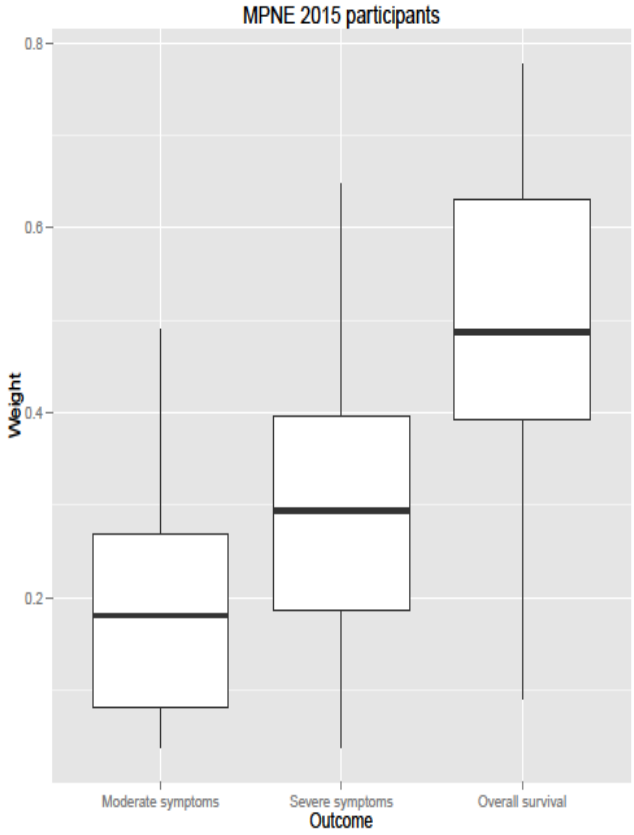
Results of all questionnaires combined (n=22)

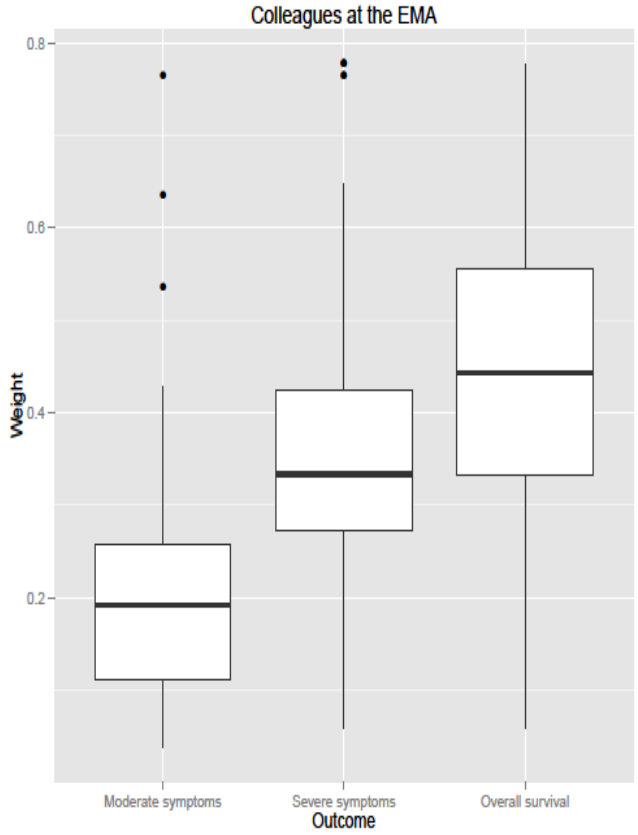


Results of decision conferencing



How does this compare which the survey conducted at the EMA (n=73)?





What will be done with the preferences collected?

The collected responses will be analysed by the researchers conducting the study

The results will be shared with conference organisers and participants (all data collected remains anonymous)

Outcomes will be shared with the Committee for Human Medicinal Products (CHMP) to consider the use of this methodology during their assessment of specific medicines

Summary

- Identify situations where patient input could be beneficial
- All participants treated as any other EMA experts and declare any potential conflicts of interest and sign a confidentiality agreement
- Receive personalised support

Summary

In some situations a single patient may be sufficient

Other times more opinions are needed

There is a need to find the right time for qualitative or quantitative patient input but both are necessary and one should not replace the other