NHS
National Institute for
Health and Clinical Excellence

Presentation 6

Investigating uncertainty

Reasons for uncertainty over results

- Uncertainty over treatment effects
  - confidence intervals around estimates from trials/meta-analysis
  - uncertainty due to queries over internal/external validity of trials?
- Uncertainty over other data inputs
  - baseline risks, costs, utilities,...
  - may be quantitative estimates of sampling error (CIs)
  - but may also need to estimate ranges more informally
- Assumptions and model structure
  - cannot be represented as confidence interval
  - may test impact of changing assumptions in sensitivity analysis

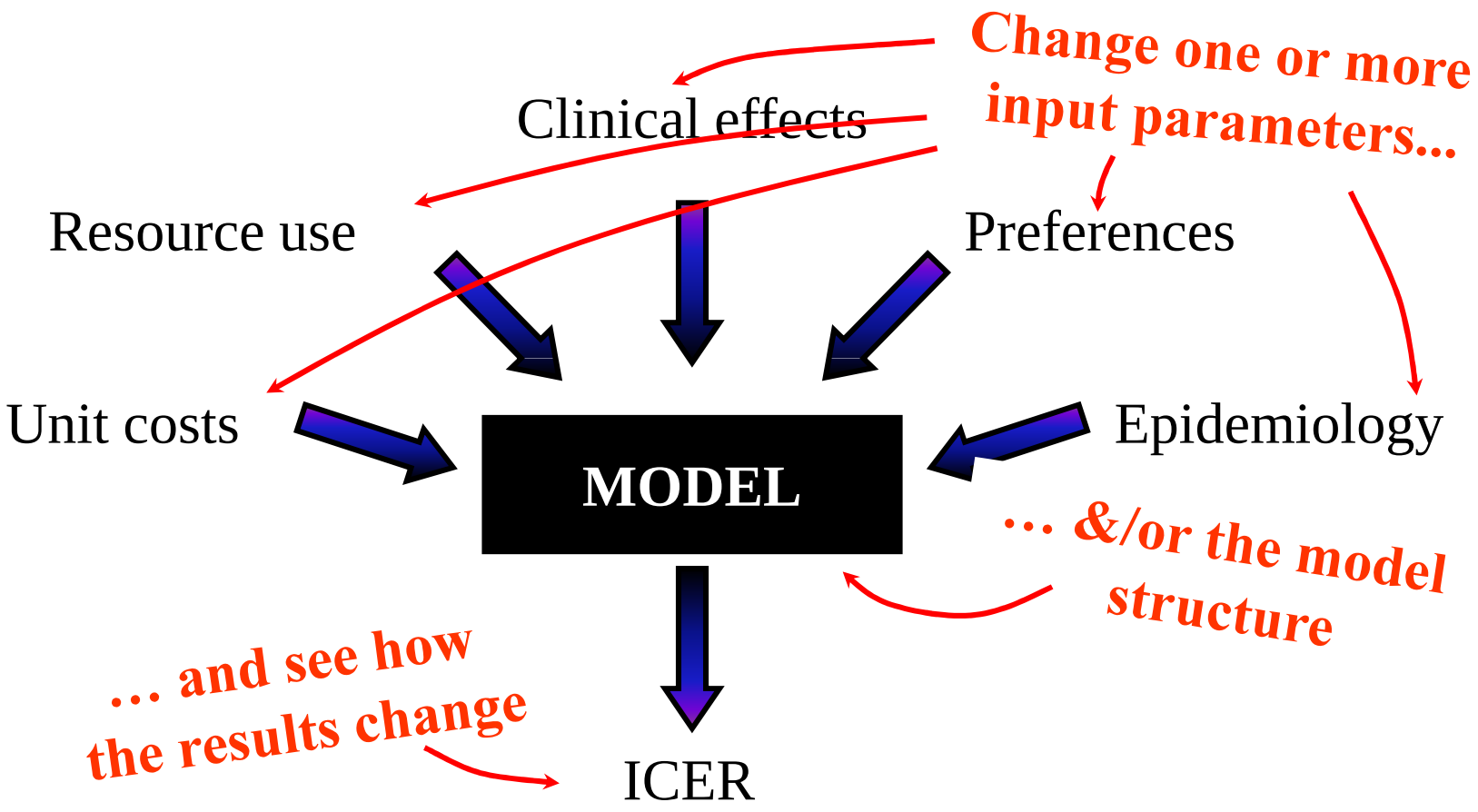
Uncertainty versus variability

- Variability
  - Natural variation among individuals in their response to treatment and the costs they incur
  - Further evidence will not reduce this variation
- Uncertainty
  - Cannot know for certain what the expected (mean) costs and effects of a particular treatment will be when provided for a given population
  - Further evidence can reduce this uncertainty providing more precise estimates of these mean costs and health effects

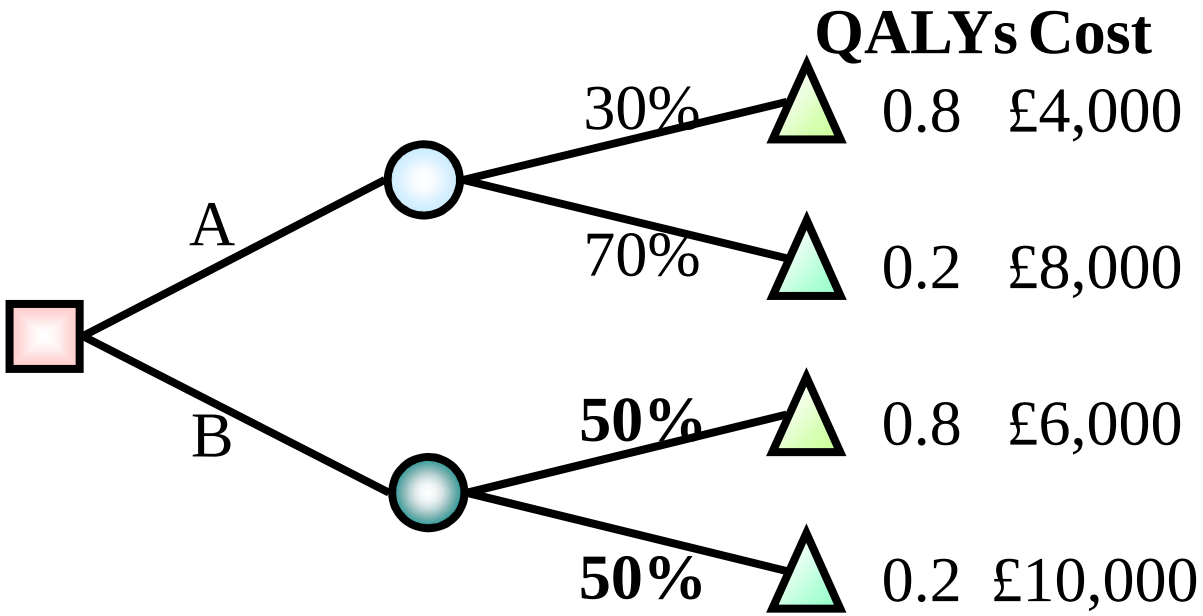
Why uncertainty matters…

- Generally accepted that decisions should be made on the basis of expected (incremental) costs and effects but...
- In non-linear models (e.g. Markov models), the correct calculation of expected costs and effects will require the uncertainty around all the inputs (the parameters) to be expressed
- There is the question whether current evidence is sufficient to inform decision making
- What are the consequences of getting it wrong?
- Need to characterise uncertainty in expected costs and effects – can use “expected value-of-information” techniques

Sensitivity analysis



Example - Decision tree
What if success rate for B is lower?



	A	B	Difference
Expected cost	£6,800	£8,000	£1,200
Expected QALYs	0.38	0.50	0.12
ICER (£ per QALY) =			**£10,000**

Types of sensitivity analysis

- **Deterministic**

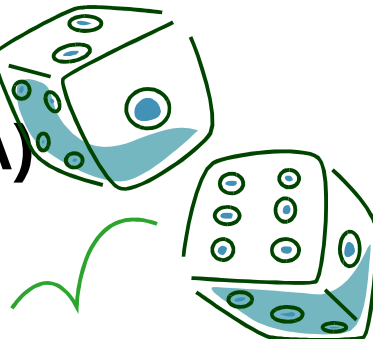
  One way – change one input and observe impact on ICERs

  Two-way – change two inputs and observe impact on ICERs

  ...

- **Probabilistic sensitivity analysis (PSA)**

  Vary all inputs according to probability distributions reflecting uncertainty & observe net impact on ICERs



Example: two-way sensitivity analysis

PET vs thoracotomy for lung cancer

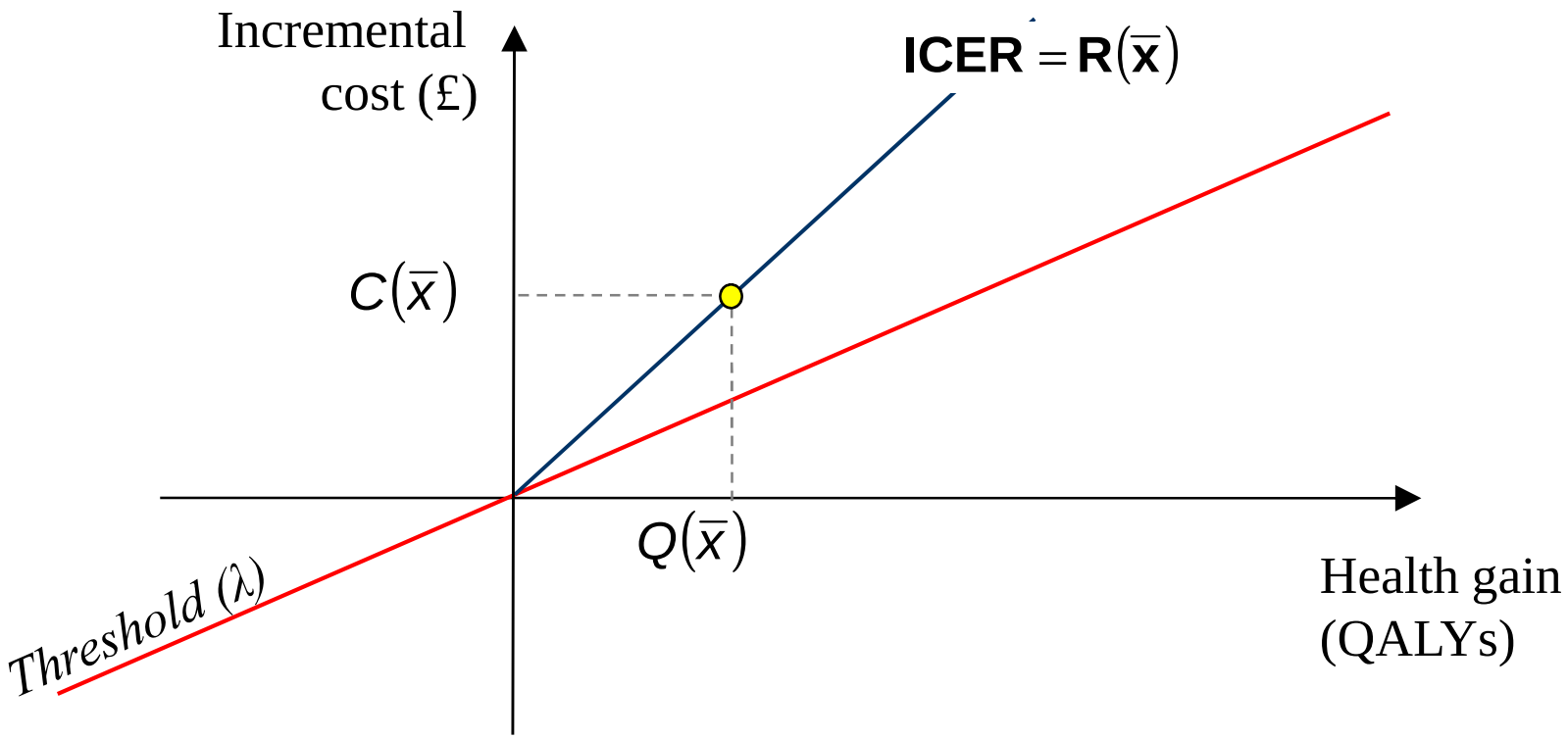
Cost of thoracotomy	Cost of PET scan				
	£600	£800	£968	£1,200	£1,400
£2,000	£14,566	£20,010	£24,583	£30,898	£36,342
£3,000	£8,572	£14,016	£18,588	£24,903	£30,347
£4,000	£2,577	£8,021	£12,594	£18,909	£24,353
£4,900	*	£2,626	**£7,199**	£13,514	£18,958
£6,000	*	*	£605	£6,920	£12,364
£7,000	*	*	*	£925	£6,369
£8,000	*	*	*	*	£375

* PET scanning is cost saving

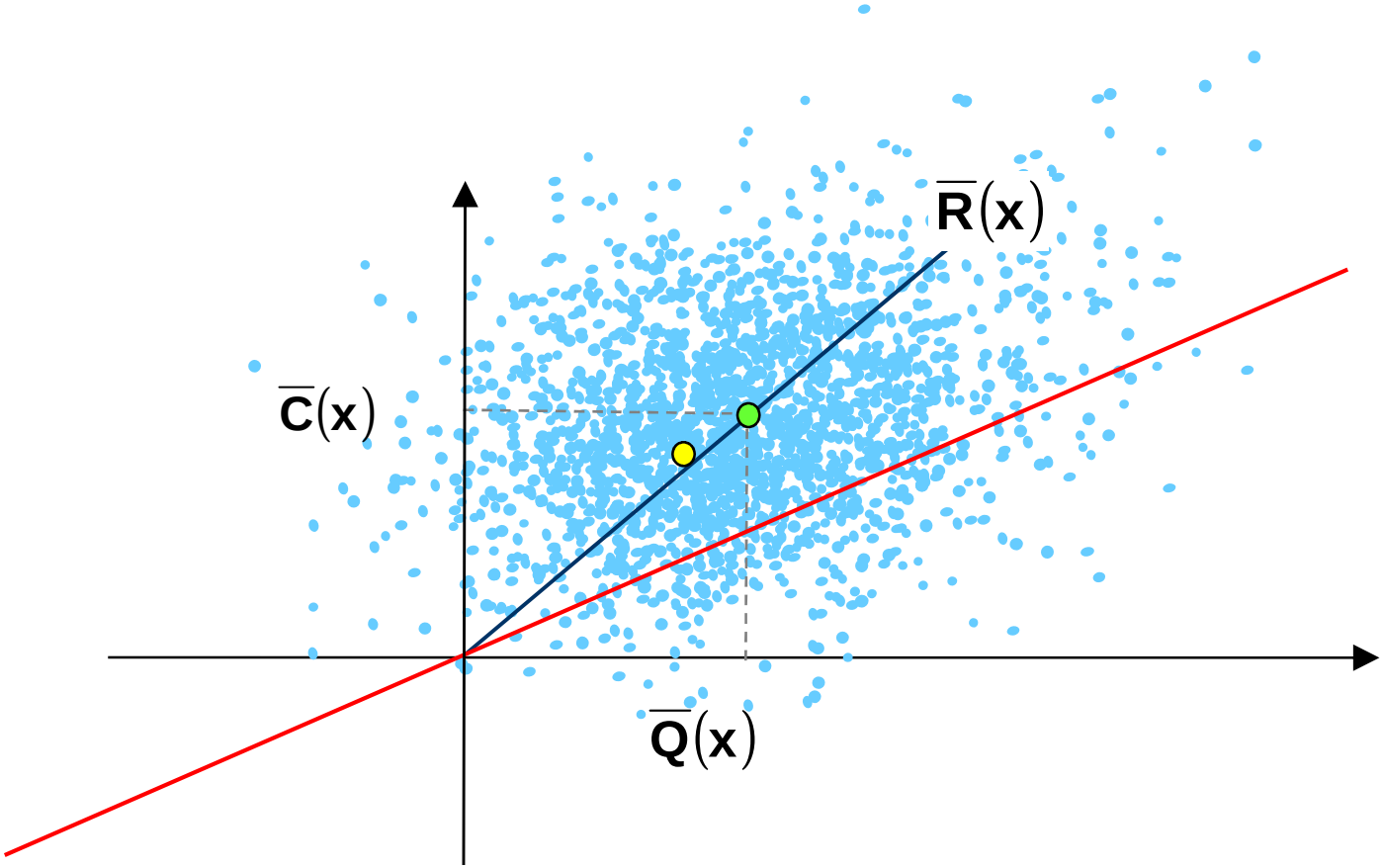
NICE reference case & probabilistic sensitivity analysis

- Refers to three types of uncertainty:
  - structural uncertainty (e.g. assumptions relating to long term extrapolation of costs and benefits),
  - uncertainty related to the sourcing of inputs (e.g. single 'base' RCT versus data from good quality observational data),
  - and uncertainty related to parameter precision.
- **Probabilistic sensitivity analysis** is seen as the **preferred** means for reflecting parameter uncertainty in the results of the analysis.

Deterministic result

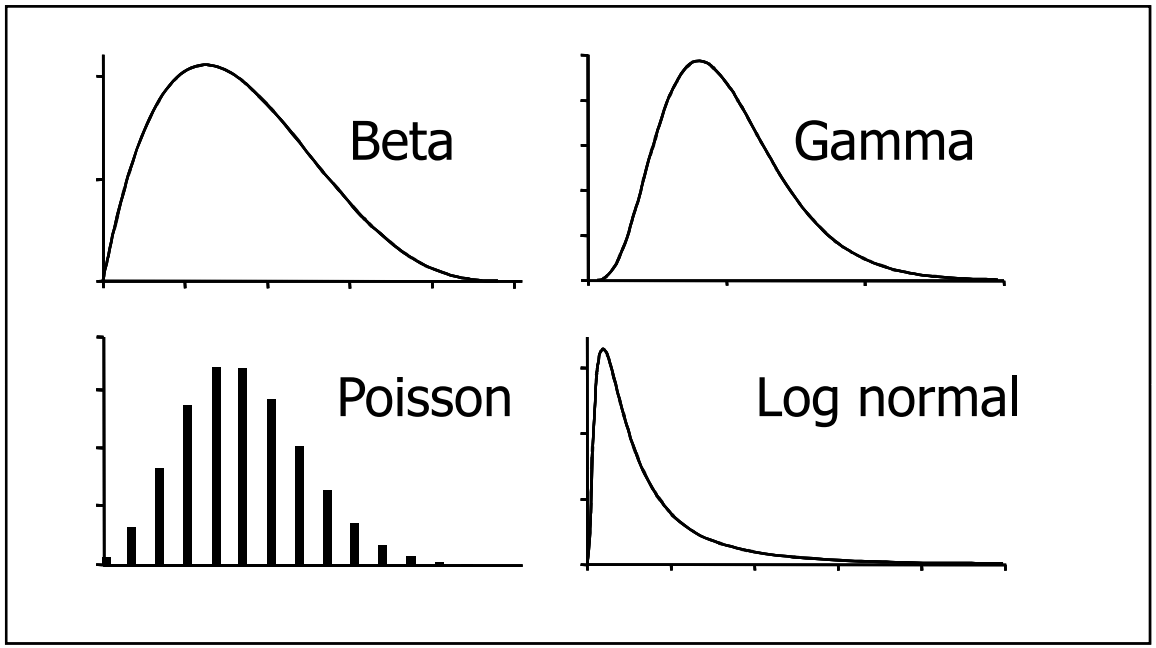


Probabilistic results



While decisions are based on expected costs and outcomes, running a PSA is expected to provide more accurate assessment of these values in non-linear models (e.g. Markov models).

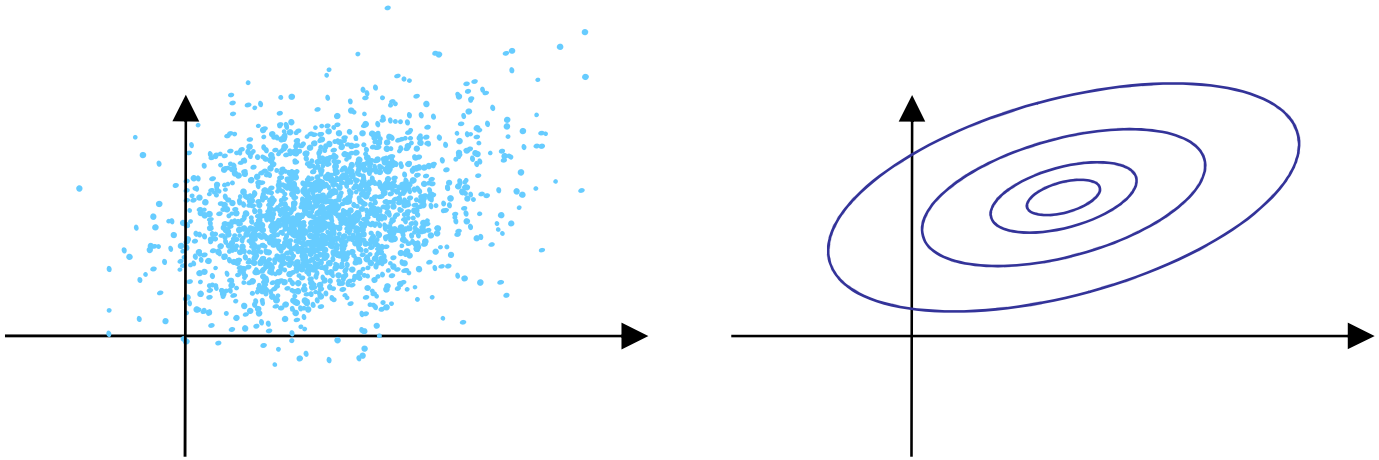
Distributions for a PSA



- Choice of distributions needs to be justified and based on the available evidence on the parameter of interest
- Need to take into account correlations where evidence is available

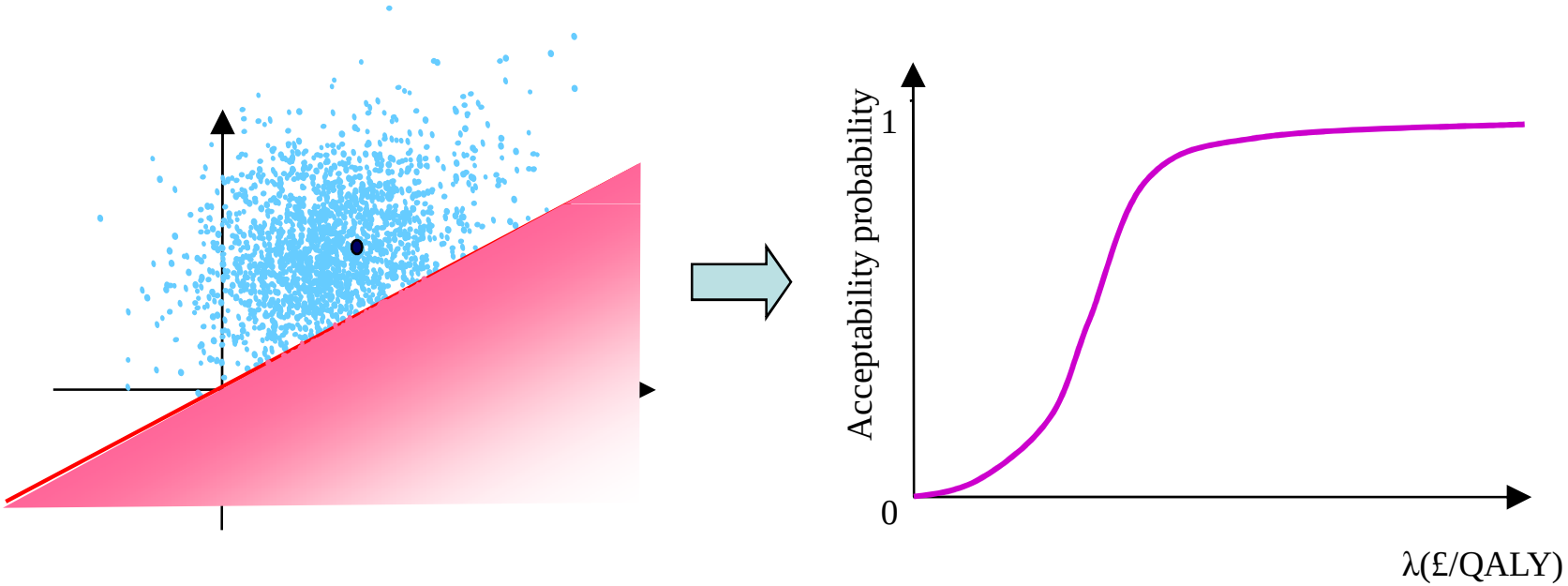
Representing uncertainty

For two alternatives, may use scatter plot or confidence ellipses on CE plane

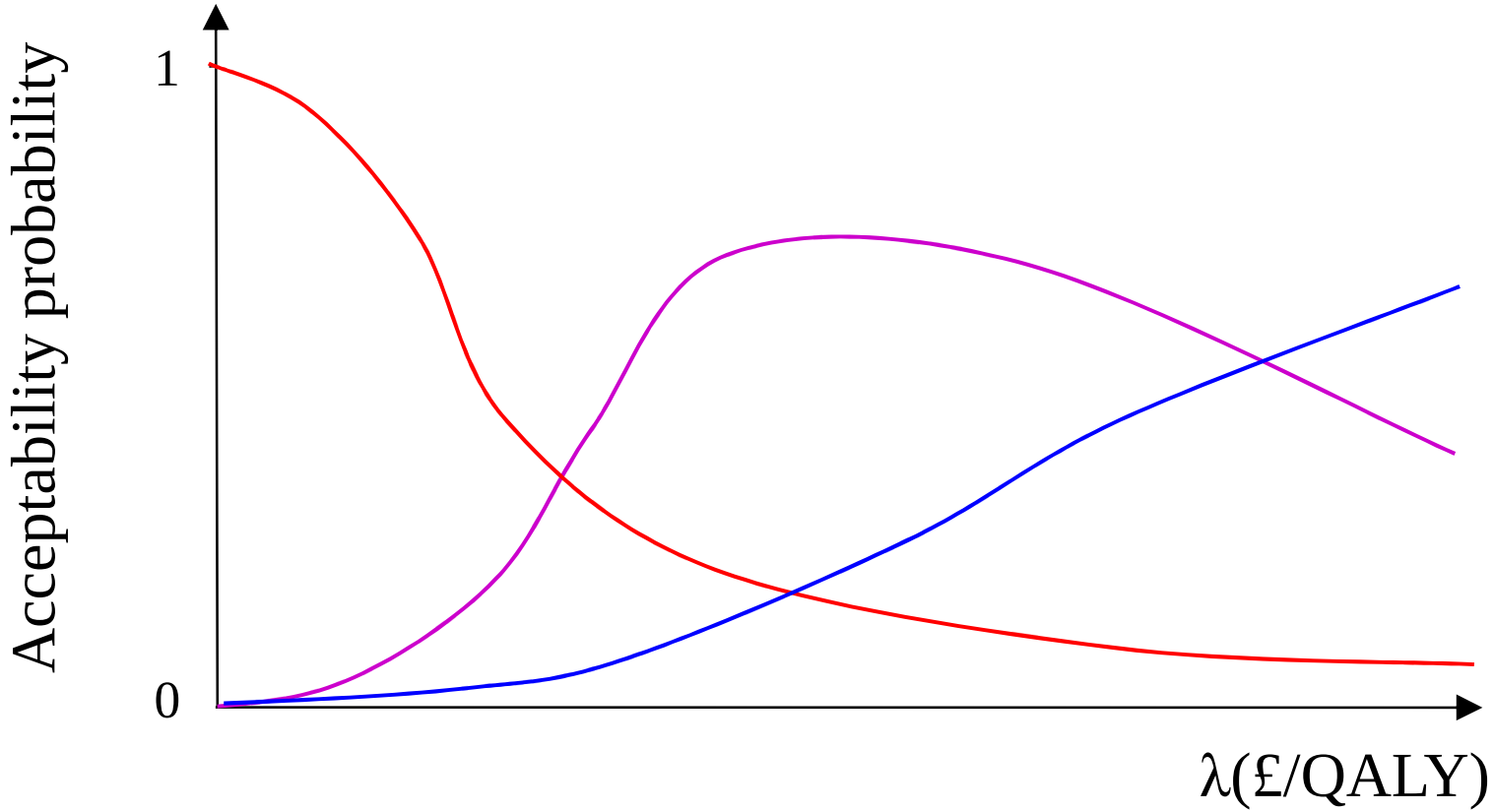


or cost-effectiveness acceptability curves (CEACs), for multiple options.

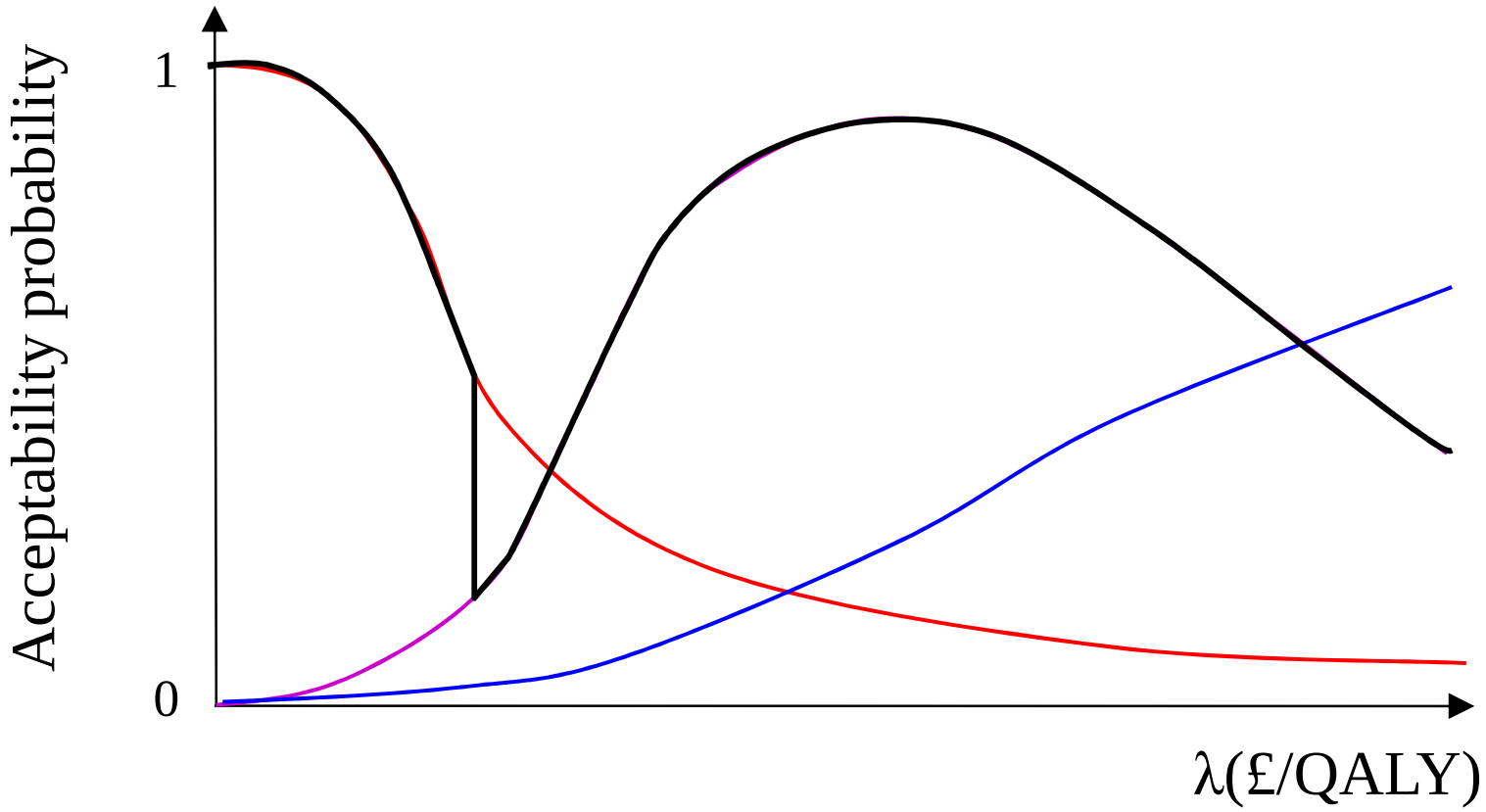
Derivation of CEACs



Multiway CEACs



... and CEAFs



If CEACs are presented, these should include a representation and explanation of the cost-effectiveness acceptability frontier.

The need for multiple types of sensitivity analysis

- PSA is not the only sensitivity analysis that should used
- Model structure and choice of data are also subject to uncertainty, which should be identified and formally examined using sensitivity analysis.
- This can be done by re-running analysis using alternative model assumptions or source of data (e.g. excluding a study from a meta-analysis) where there's doubt.
- Simple deterministic analysis can also help to validate models - does it behave as expected?
- Can also help to develop the advisory body's understanding of and confidence in the model.

PSA issues

- When isn't PSA needed / ‘feasible’?
- How many parameters should be included in the PSA to make the results meaningful?
- How to estimate correlations?
- Interpreting CEACs and CEAFs…

Dealing with structural uncertainty

- Options
  - Model averaging
    - Explicitly assigning probabilities to different scenarios
    - How to choose the weights?
  - Parameterising structural uncertainty
    - Structural uncertainty as a missing uncertain parameter in model
    - Include this parameter in model and assign a distribution
    - Eliciting distributions? Who and what methods?