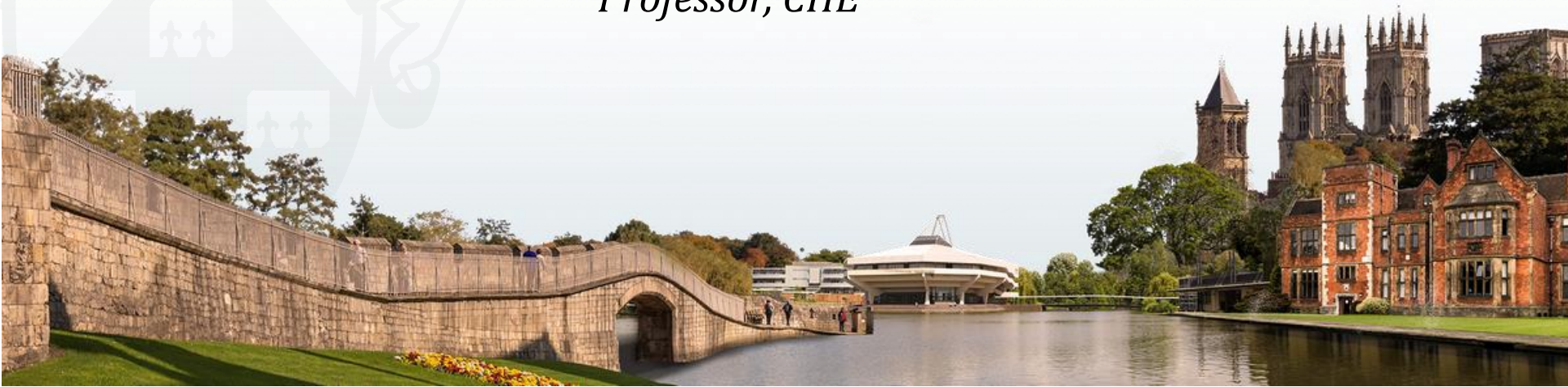
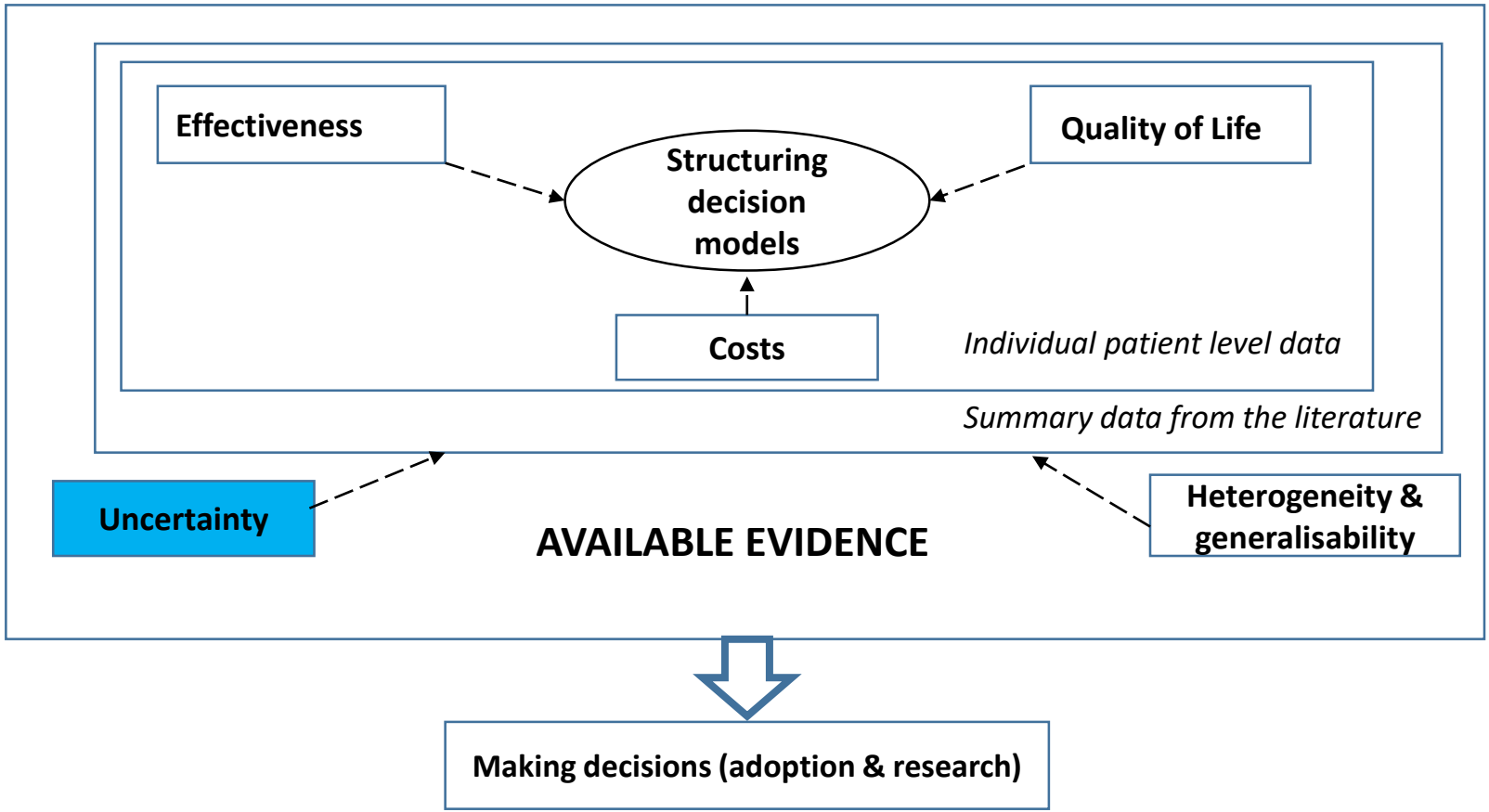
Online Advanced Methods for Cost-Effectiveness Analysis

Presentation 7: Uncertainty, heterogeneity and VOI
7.1: Uncertainty in decision models

Susan Griffin, PhD
Professor, CHE



Course structure – where are we up to?



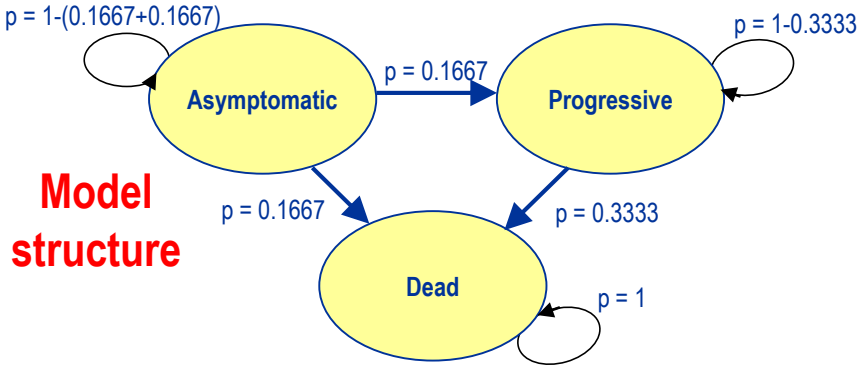
Overview

- Part 7.1
  - Short review of cohort models
  - Definitions of uncertainty, variability, heterogeneity and policy choice
  - Deterministic sensitivity analysis
- Part 7.2
  - Probabilistic sensitivity analysis
- Part 7.3
  - Examining the results of probabilistic models

Objectives

- Understand where and how uncertainty arises in decision models
- Understand the terminology used to talk about uncertainty in economic evaluation
- Be able to differentiate between uncertainty and heterogeneity
- Understand the role and limitations of deterministic sensitivity analysis

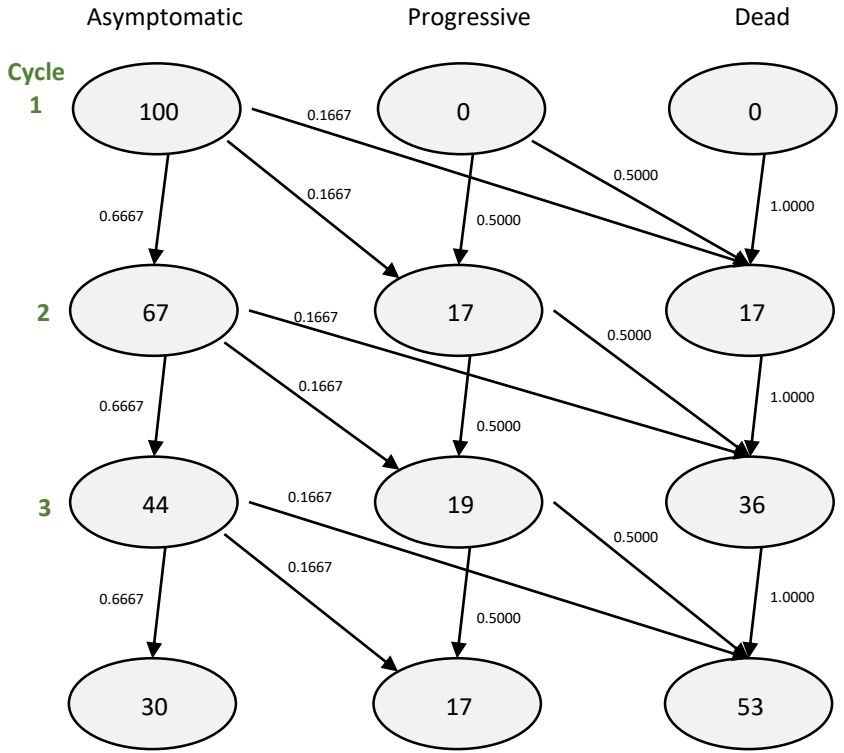
Outline of a simple Markov model



Model structure

Current treatment	Asymptomatic	Progressive	Dead	Cost	QALY
Asymptomatic	0.6667	0.1667	0.1667	£150	0.9
Progressive		0.5000	0.5000	£325	0.78
Dead			1.0000		

Parameter values



Cohort simulation

What is uncertain about cost-effectiveness analysis?

- Decisions should not be based on little or poor quality evidence
- Always a chance that the wrong adoption decision is made, resulting in health benefit and resources forgone
- Different possible values for the parameters
  - Lack of knowledge about the parameter values
  - Different outcomes in different populations
- Structural uncertainty
  - Choice of health states, choice of modelling approach
- Distinguish between
  - Uncertainty, variability, heterogeneity and policy choices

First and second order uncertainty

1st order

- Distribution of outcomes in population

≈ Sample variance

- Standard deviation in a mean value
  - Range of outcomes in sample

- Incorporate in CEA by simulating and recording pathway of individual patients through a model
- Large number of patients required to estimate mean and standard deviation
- Must repeatedly sample large numbers of patients to estimate uncertainty in mean and standard error

2nd order

- Distribution of sample mean outcome

≈ Variance of sample mean

- Standard error of mean
  - Range of population mean values supported by the sample outcomes
- Incorporate in CEA by simulating and recording pathway of cohort through a model
- One cohort provides estimate of mean but no information on standard deviation
- Large number of cohorts entered into models to estimate uncertainty in mean and standard error

1st order uncertainty – screen share example

- Simulate individual patients progress through model
- Random numbers to determine occurrence of chance events
- Markov trace generated for multiple individuals to get mean costs and QALYs

TRANSITION MATRIX ***From***	***To*** Asymptomatic	Progressive	Dead
Asymptomatic	0.6667	0.1667	0.1667
Progressive		0.6666	0.3333
Dead			1.0000

	Asymptomatic	Progressive	Dead
Asymptomatic	1, 2, 3, 4	5	6
Progressive		1, 2, 3, 4	5, 6
Dead			1, 2, 3, 4, 5, 6

Uncertain decisions

- 1st order uncertainty and variation within groups of patients not the focus of CEA
  - Decision must be made for group as a whole
  - Variability cannot be reduced
  - Computationally time consuming when combined with 2nd order uncertainty
- 2nd order uncertainty is the focus of CEA
  - Informs questions about likelihood of making wrong decision, and likelihood of new information changing the optimal decision
- Structural uncertainty
  - Lack of knowledge about most appropriate model structure
  - Different modelling approaches provide different estimates of mean costs and QALYs
    - Contributes to uncertainty in mean outcomes

Heterogeneity – multiple decisions

- ‘Baseline’ characteristics ‘explain’ a proportion of overall variability between patients (e.g. age, sex)
- Can condition decision on these characteristics, and recommend different options in different groups
- To incorporate in CEA, generate mean parameter values per sub-group population
  - Variability within sub-group will remain
  - Need to present results by sub-group (defined by patient characteristics)

Policy choices and value judgements

- The authority taking the decision may set some parameter values
  - For example, the discount rate applied to costs and health outcomes
- The values are relevant for particular decision
  - E.g. NICE specifies 3.5% for costs and health outcomes
  - Sensitivity analysis of 1.5% per annum
- Different decision makers may have different values
  - Heterogeneity in value of parameter between decision makers
  - Choice taken by an individual decision maker is not uncertain

'5.1.2 There is considerable debate about the most **appropriate methods** to use for some aspects of health technology assessment. This **uncertainty relates to choices that are essentially value judgements**; for example, whose preferences to use for valuation of health outcomes.... The reference case specifies the methods considered by the Institute to be the most appropriate for the Appraisal Committee's purpose and consistent with an NHS objective of maximising health gain from limited resources.'

NICE Guide to the methods of technology appraisal 2013

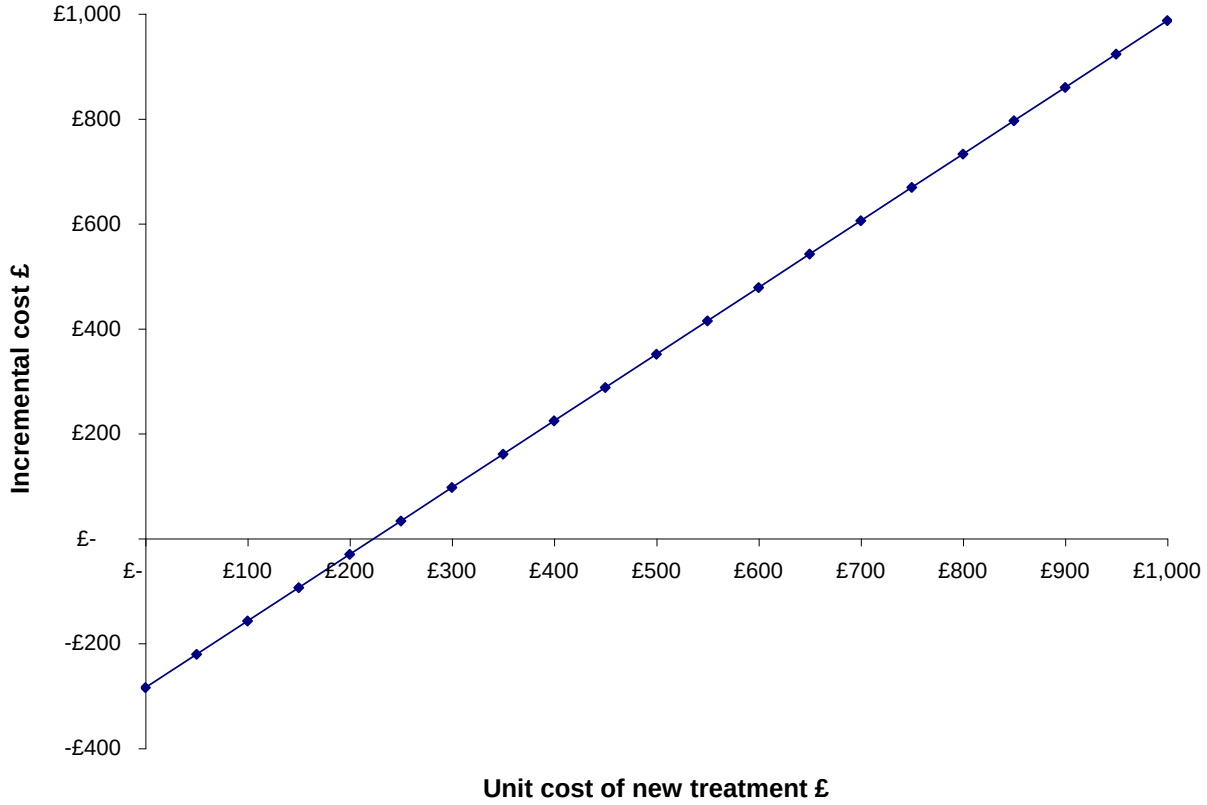
Types of uncertainty - Summary

Need to address	Not main focus of CEA
Parameter uncertainty - 2nd order or epistemic uncertainty - measurement error - e.g. response rate to treatment 0.8 (95% CI: 0.55 to 0.95)	**Variability** - 1st order or stochastic uncertainty - e.g. whether individual patient responds to treatment
Heterogeneity - variability across sub-groups - age, sex, risk factors	**Policy choice** - discount rate - not 'uncertain'
Structural - modelling assumptions	

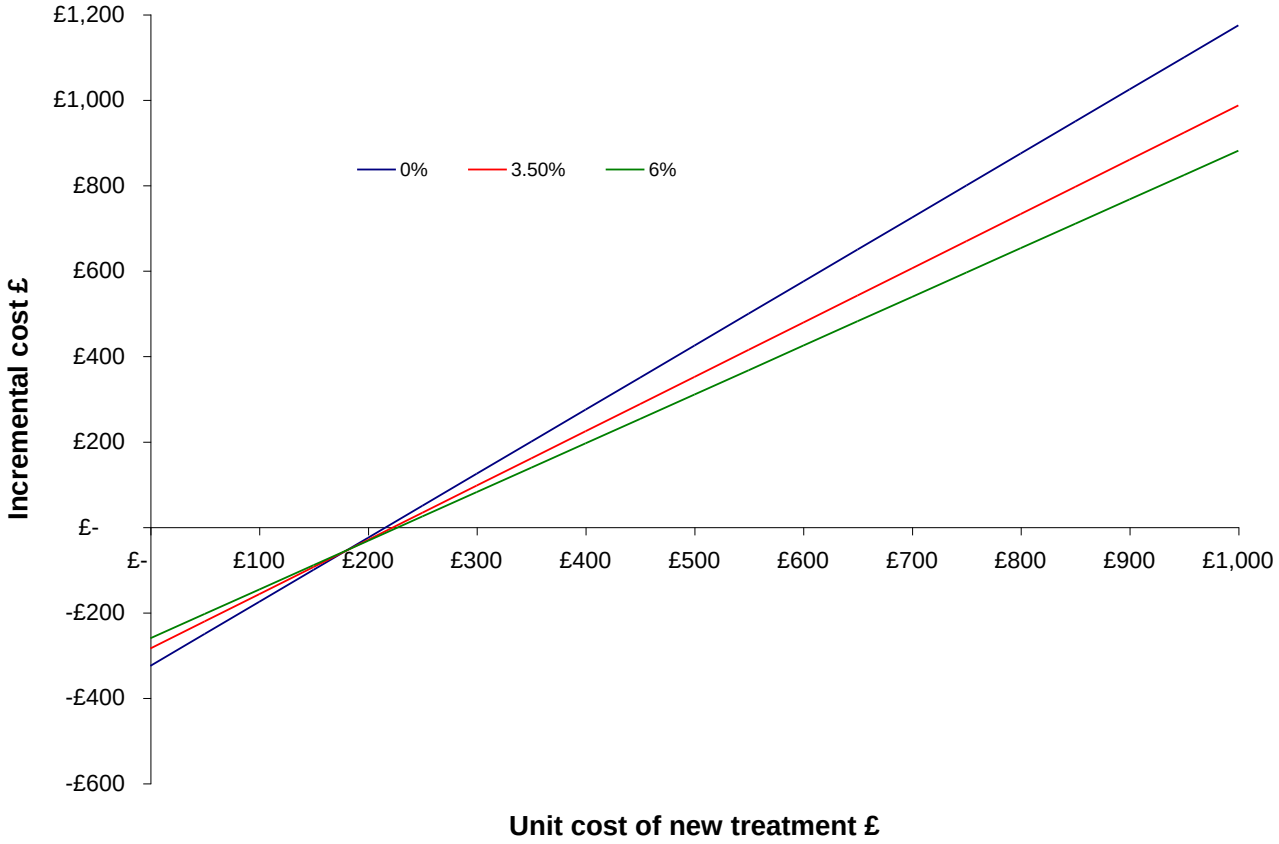
Deterministic methods to address uncertainty

- Sensitivity analysis
  - Reflects sensitivity of the model results to different values of the model inputs
- Deterministic sensitivity analysis - univariate
  - One-way: only vary one parameter
  - Extreme value: examine results under most extreme parameter values
  - Threshold analysis: identify values which would change the decision
  - ‘Scenario analysis’: present results for alternative model structures and assumptions
- Deterministic sensitivity analysis - multivariate
  - Multi-way: vary multiple parameters simultaneously

One-way sensitivity analysis



Two-way sensitivity analysis



Uses and limitations of deterministic sensitivity analysis

- Useful for exploring alternative policy choices
- Useful for identifying which parameters might impact most on model results and hence are worth exploring further
- Useful for identifying the impact of structural uncertainty on model results

- Presenting, summarising and interpreting the results of a large number of deterministic analyses can pose problems
- Can be complicated for more detailed exploration of parameter uncertainty:
  - Not obvious how to select the range of values to generate results for
  - When more than two variables are being explored simultaneously it becomes difficult to present and interpret results

Summary

- You should now be able to distinguish uncertainty, variability and heterogeneity
- You should understand why you might examine uncertainty and heterogeneity within CEA
- You should be familiar with methods for deterministic sensitivity analysis
- For further reading on topics in Part 7.1 please see
  - *Claxton K. Characterising, reporting, and interpreting uncertainty. In: Drummond, Sculpher, Claxton, Stoddart and Torrance eds. Methods for the Economic Evaluation of Health Care Programmes. Oxford, UK. Oxford University Press, 2015.*
- In Part 7.2 we will learn about probabilistic sensitivity analysis

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CHE Centre For Health Economics

Online Advanced Methods for Cost-Effectiveness Analysis

Presentation 7: Uncertainty, heterogeneity and VOI
7.2: Probabilistic sensitivity analysis

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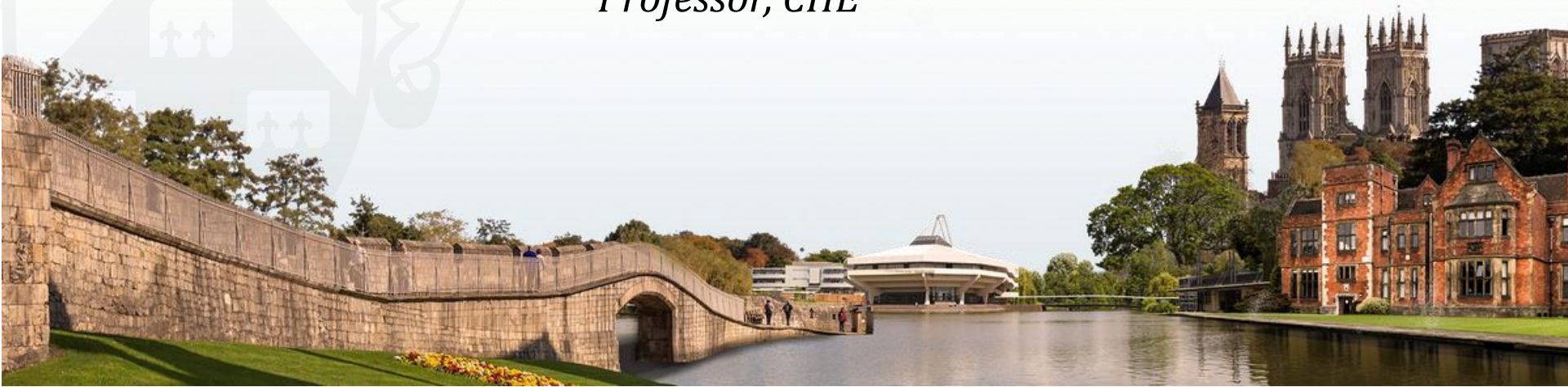
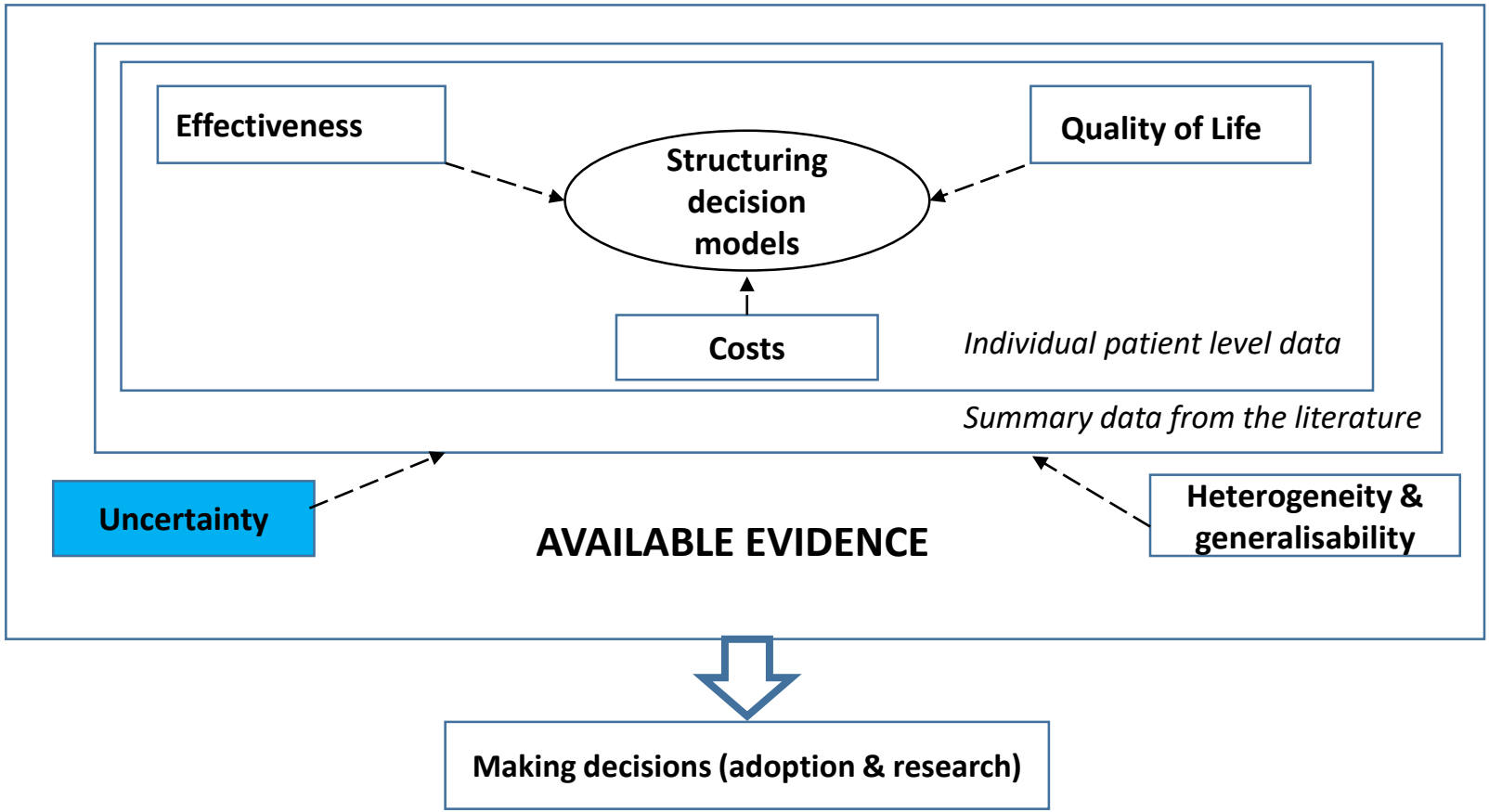
Professor, CHE



Course structure – where are we up to?



Objectives

- Understand what probabilistic sensitivity analysis is, and the uncertainty it encompasses
- Understand how to implement probabilistic sensitivity analysis in a decision model
- Understand how to compute cost-effectiveness results after undertaking a probabilistic sensitivity analysis

Beyond deterministic sensitivity analysis

- ‘5.8.11 The use of univariate and best- or worst-case sensitivity analysis is an important way of identifying parameters that may have a substantial impact on the cost-effectiveness results and of explaining the key drivers of the model. However, such analyses become increasingly unhelpful in representing the combined effects of multiple sources of uncertainty as the number of parameters increase. The use **of probabilistic sensitivity analysis** can allow a more **comprehensive characterisation** of the parameter **uncertainty associated with all input parameters**.’

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Probabilistic sensitivity analysis (PSA): Stages

- Assigning distributions to represent uncertainty
  - Estimates of probabilities, quality of life weights and costs are replaced with specified probability distributions
- Propagating uncertainty
  - Randomly select value from each distribution
  - Model evaluated many times (>1,000)
  - Distribution of and average of simulated model results used in decision making
- Reporting results
  - Distribution of outcomes for each strategy
  - Probability that a particular intervention is optimal

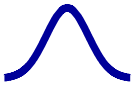
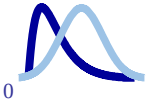
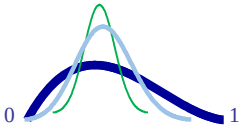
Assigning distributions

- Primary data (individual patient level)
  - Fit regression models and use the resulting variance covariance matrices
  - Empiric distribution from bootstrap samples
- Secondary data (aggregate level)
  - Assign distribution using information reported in the literature
  - This is the usual situation we find ourselves in and is covered in what follows
- No primary or historical evidence
  - Assign distribution using information elicited from experts
  - Elicitation methods available

Choosing a distribution for a parameter

- Match what is known about the model input with the characteristics of the distribution
  - Common distributions include the Normal, Log-normal, Gamma and Beta
- Alternative distributions defined by
  - Logical constraints on the parameter
    - Can it take values less than zero?
  - Type of data
    - Discrete like number of admissions or continuous like weight?
  - Method of parameter estimation or data generation
    - Informed by the output from an ordinary least squares regression analysis

Commonly used distributions

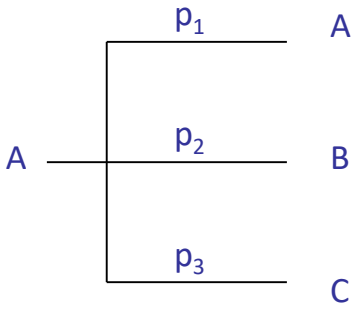
Distribution	Specified with	Characteristics	Drawing values in Excel
Normal 	- Mean, μ - Standard deviation (SD) of mean, σ	- Values unbounded - Continuous; symmetrical - Mean, median, mode at line of symmetry - 95% of values within 2 SD of mean	NORM.INV(RAND(), mean, sd)
LogNormal 	- On log scale - Mean, μ - Standard deviation (SD) of mean, σ	- Any positive value > 0 - Continuous; right (positively) skewed	LOGNORM.INV(RAND(), mean, sd)
Gamma 	- Shape, α - Scale, β	- Any positive value ≥ 0 - Continuous; symmetrical or right skewed - Method of moments: $\mu=\alpha\beta$ and $\sigma^2=\alpha\beta^2$	GAMMA.INV(RAND(), alpha, beta)
Beta 	- α (# of successes) - β (# of failures)	- Any positive value ≥ 0; bounded 0-1 - Flexibly shaped - α+β=n (sample size) - Method of moments: $\mu=\alpha/(\alpha+\beta)$ and $\sigma^2=\alpha\beta/[(\alpha+\beta)^2(\alpha+\beta+1)]$	BETA.INV(RAND(), alpha, beta)

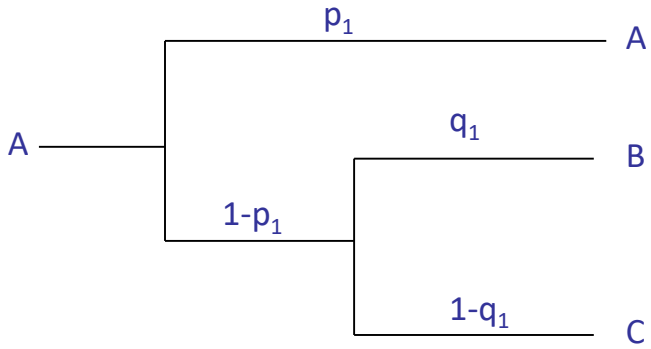
Matching distributions to input characteristics

Parameter	Distribution	Values
Transition probabilities	Beta	Alpha, Beta
Relative treatment effect	Lognormal	Mean, SD
Costs	Gamma	Shape, Scale
Dis-utilities	Gamma	Shape, Scale

Other issues

- Variables enter only once
- Multiple events





Note: $q_1 = p_2 / (1-p_1)$

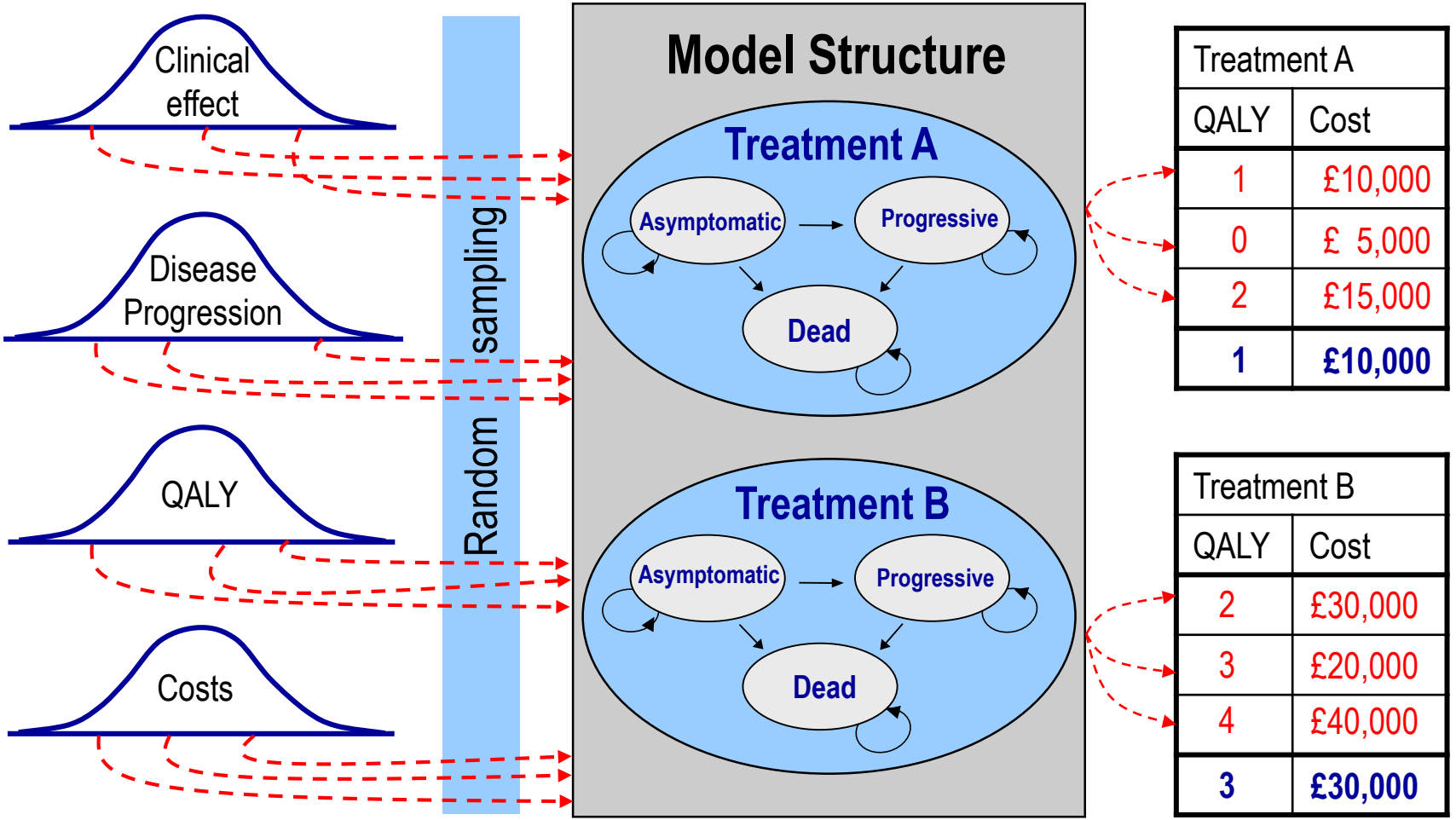
  - Restructure the tree
    (conditioned into dichotomous transitions)
  - Dirichlet distribution

- Characterise correlation between parameters where possible

Propagating uncertainty

- Monte Carlo simulation – 2nd order uncertainty
  - Randomly draw a set of input values (one for each parameter)
  - Put a cohort through the model
  - Determine the expected outcomes – cost, effect, etc
  - Repeat a large number of times (> 1,000)
  - Distribution of expected outcomes
- In non-linear decision models, probabilistic methods provide the best estimates of mean costs and outcomes
  - Mean of the distribution of expected outcomes ≠ outcome with inputs set to mean values

Propagating uncertainty



Treatment A	
QALY	Cost
1	£10,000
0	£ 5,000
2	£15,000
1	**£10,000**

Treatment B	
QALY	Cost
2	£30,000
3	£20,000
4	£40,000
3	**£30,000**

Should the intervention be adopted?

Treatment A	
QALY	Cost
1	£10,000
0	£ 5,000
2	£15,000
1	**£10,000**

Treatment B	
QALY	Cost
2	£30,000
3	£20,000
4	£40,000
3	**£30,000**

$$\text{ICER} = \frac{\text{Additional cost}}{\text{QALYs gained}} = \frac{£20{,}000}{2 \text{ QALYs}} = £10{,}000 \text{ per QALY}$$

Calculate ratio of means, NOT mean ratio

- **Is the ICER less than the cost-effectiveness threshold?**
- **Is the health gained more than the health that would have been produced if the resources had been spent otherwise?**

£10,000 per QALY < £20,000 per QALY → Treatment B is cost-effective

- **Is the net health benefit (NHB) positive?**

NHB= QALYs gained – (additional costs/threshold)

= 2 – (£20,000/£20,000)

= 1 QALY > 0 → Treatment B is cost-effective

Summary

- You should now understand the process of undertaking probabilistic sensitivity analysis
- You should understand how to match distributions to parameter characteristics
- You should understand the process of Monte Carlo simulation

- In Part 7.3 we will learn about presenting and interpreting the results of probabilistic sensitivity analysis

Online Advanced Methods for Cost-Effectiveness Analysis

Presentation 7: Uncertainty, heterogeneity and VOI
7.3: Reporting uncertainty in results

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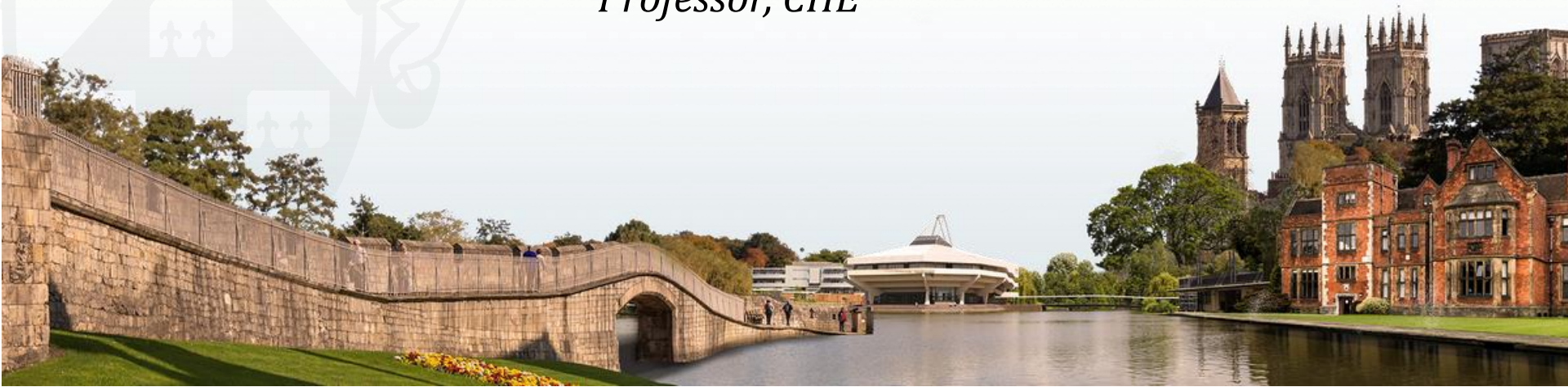

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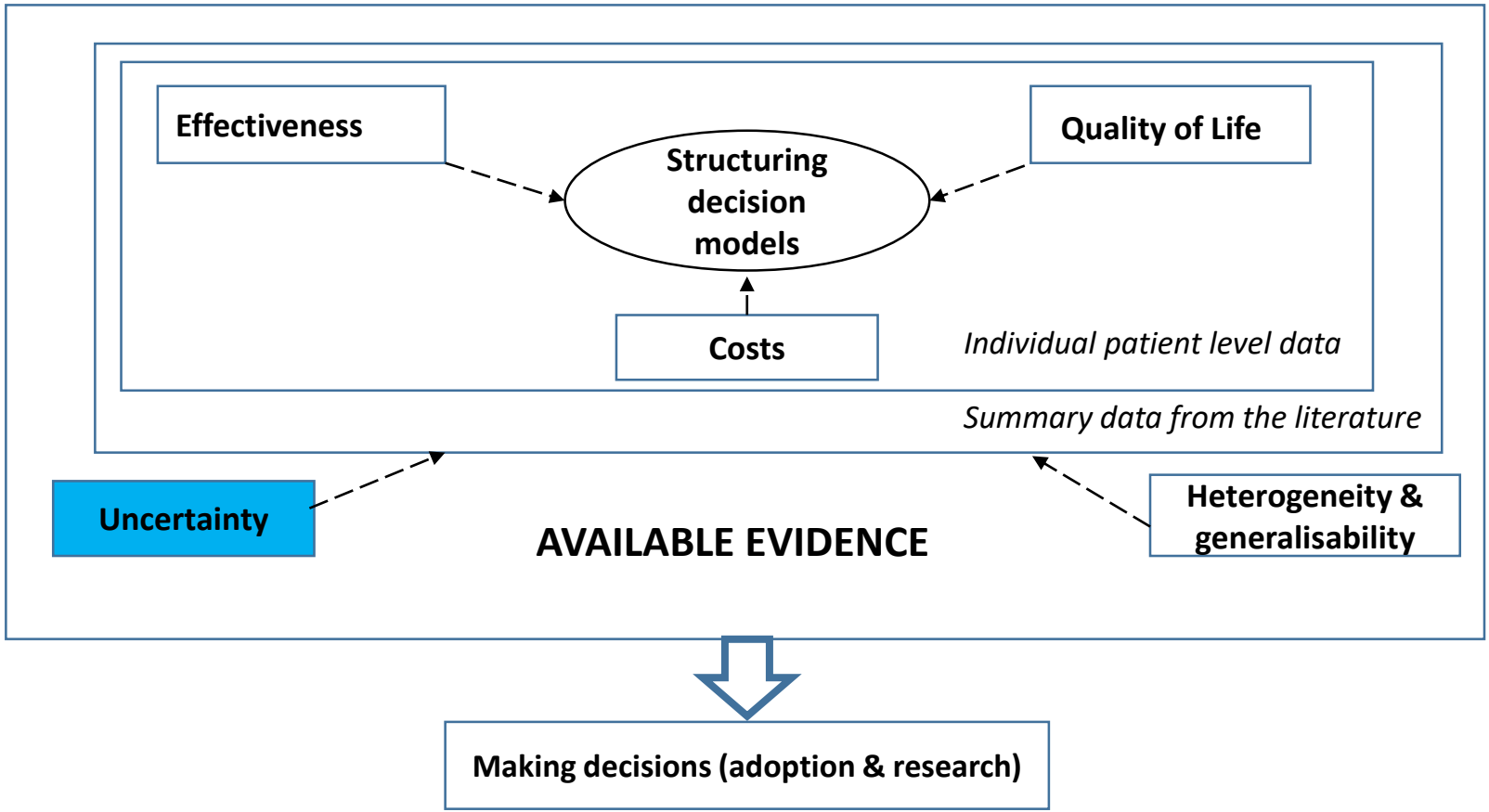


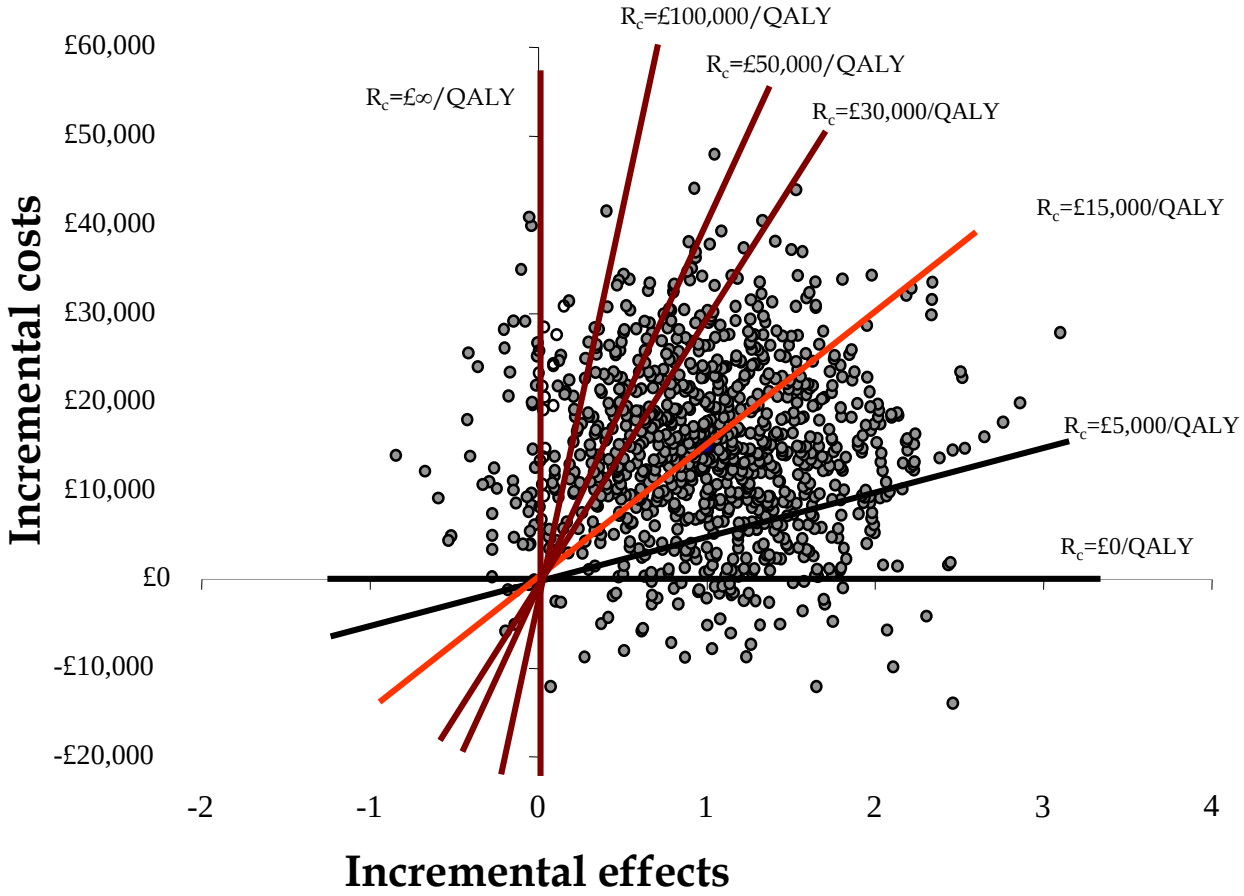
Objectives

- Understand how to interpret the uncertainty captured with probabilistic sensitivity analysis
- Appreciate the limitations of the ICER, and the utility of net benefit statistics
- Understand common methods of display
  - Cost effectiveness planes
  - Cost effectiveness acceptability curves and frontiers

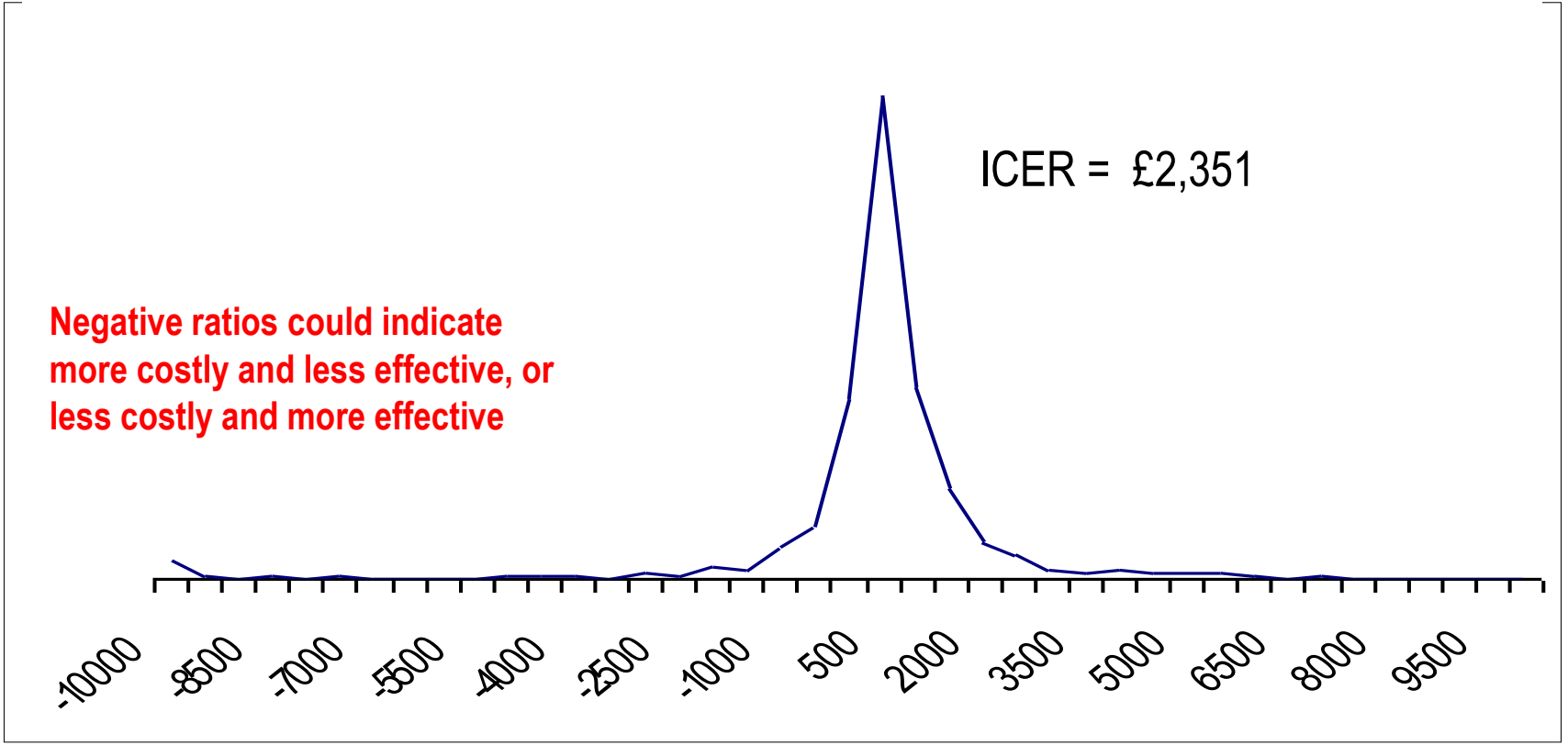
Reporting results

- Distribution of outcomes for each strategy
  - Cost-effectiveness plane informed by output of Monte Carlo simulation
- Confidence intervals for the expected outcome
  - Problems with ICER as ratio statistic
  - Can be used for incremental net benefit
  - Focus on pair-wise comparisons
- Probability that a particular intervention is optimal
  - Cost-effectiveness acceptability curve
  - Cost-effectiveness acceptability frontier

Cost-effectiveness plane



Distribution of ICER



Net Benefit Framework

- Reformulate the traditional decisional rule in terms of
  - Incremental Net Benefit = $(\Delta Q)\lambda - (\Delta C)>0$
  - Net Benefit = Max $(Q_i.\lambda - C_i)$
- Easy to calculate and avoids problems with ICER
  - Negative INB has one interpretation
  - Maximising NB simplifies multiple treatment comparisons
- NB is function of the unknown value λ
  - Not necessarily a weakness of this approach
  - Forced to explicitly consider the value λ

CEACs: Multiple treatment options

- Standard acceptability curve has a complement that represents the comparator alternative
- In the multiple option case, only one treatment can be cost-effective given a particular cost-effectiveness threshold and in any one simulation
- For each option and for each simulation formulate an indicator of whether that option is optimal
- Average across all simulations to find the proportion of times each option is optimal for a given threshold
- Repeat process varying the threshold and plot the results

How uncertain is a decision?

- Calculate net benefit for λ=£30,000

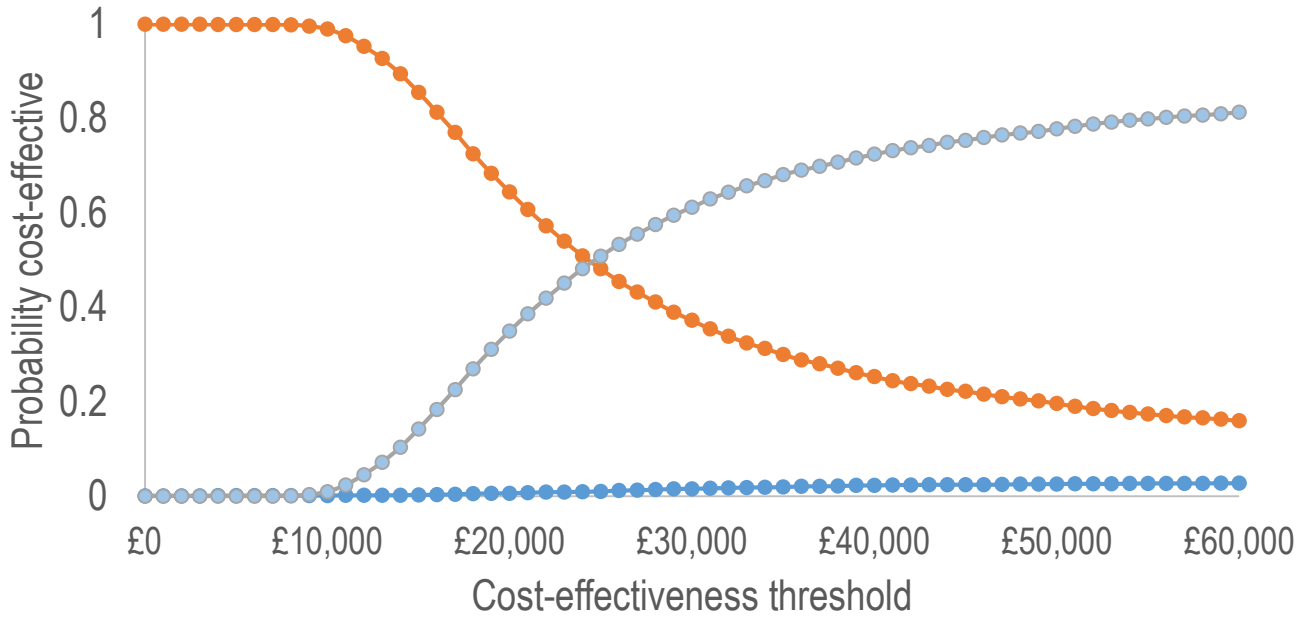
Simulation	Treat X	Treat Y	Treat Z	Optimal choice
Simulation 1	11	12	13	Z
Simulation 2	12	10	9	X
Simulation 3	13	18	15	Y
Simulation 4	14	16	17	Z
Simulation 5	15	14	11	X
Expectation	13	**14**	13	

- Probability X is cost-effective = 40%
- Probability Y is cost-effective = 20%
- Probability Z is cost-effective = 40%

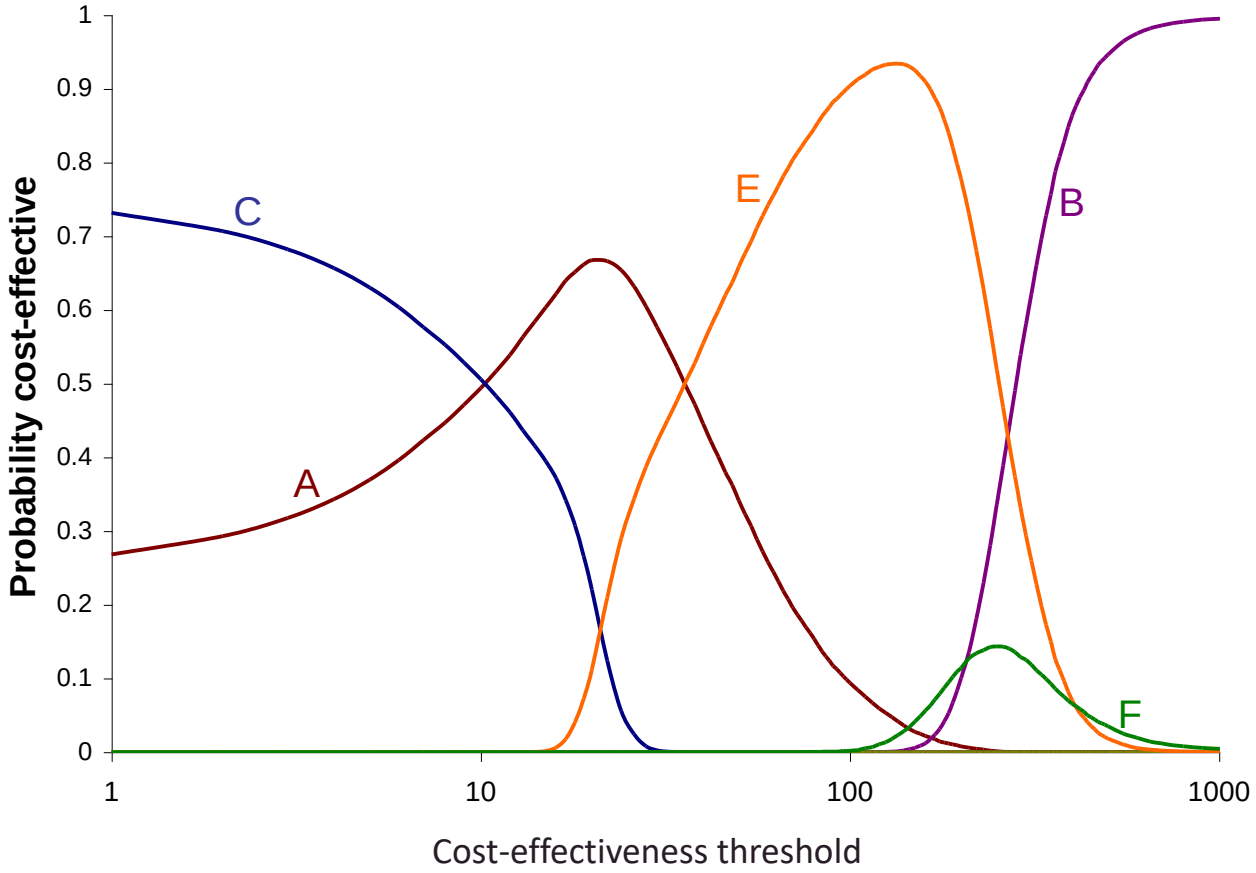
Choose Y and expect 14 QALYs
But we are not always right
Probability of error = 0.8

Cost-effectiveness acceptability curve (CEAC)

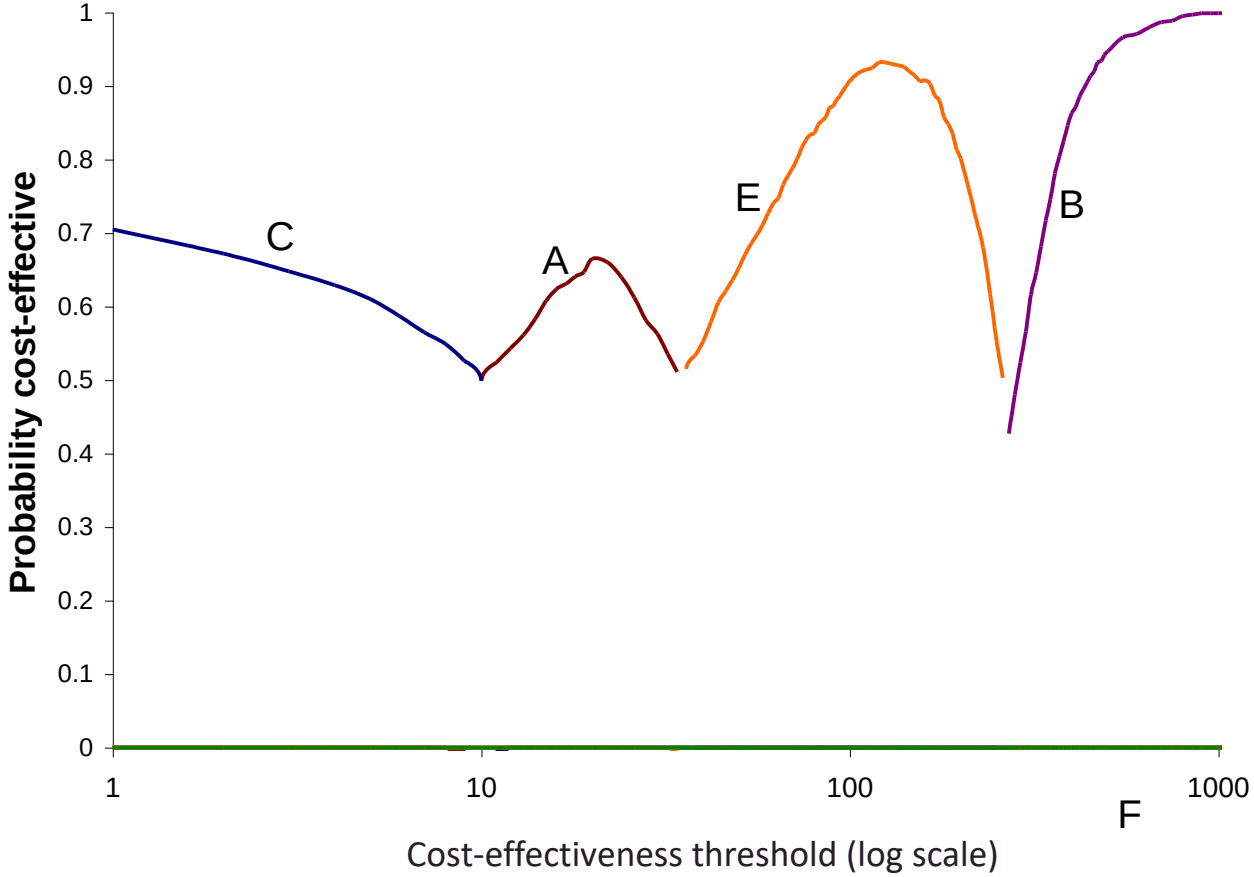
- Illustrates the uncertainty around the estimate of cost-effectiveness
- Shows the probability that one treatment is cost-effective relative to the alternative treatments for a range of threshold values



Multiple CEACs: GERD management example

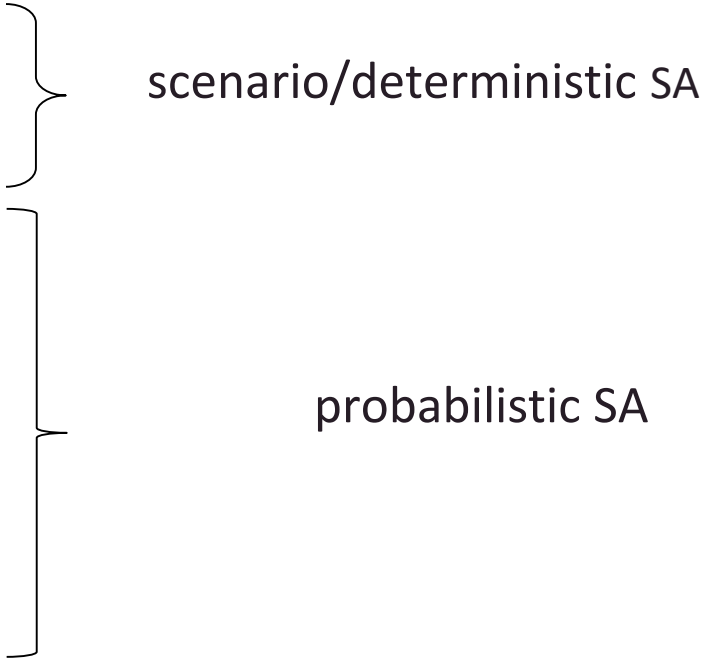


Cost-effectiveness acceptability frontier (CEAF)



Summary

- Heterogeneity
- Structural uncertainty
- Policy choices
- Parameter uncertainty
- Distributions
  - fitted
  - assigned
  - elicited
- Outcomes summarised
  - cost-effectiveness plane
  - CEAC, CEAF



Reading list

- Briggs AH. Handling uncertainty in cost-effectiveness models. *PharmacoEconomics* 2000; 17(5): 479-500.
- Briggs AH, Goeree R, Blackhouse G, O'Brien BJ. Probabilistic analysis of cost-effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. *Medical Decision Making* 2002; 22: 290-308.
- Briggs A, Claxton K, Sculpher MJ. *Decision modelling for health economic evaluation*. Oxford University Press, 2006.
- Claxton K. Characterising, reporting, and interpreting uncertainty. In: Drummond, Sculpher, Claxton, Stoddart and Torrance *eds. Methods for the Economic Evaluation of Health Care Programmes.* Oxford, UK. Oxford University Press, 2015.
- Fenwick E, O'Brien B, Briggs AH. Cost-effectiveness acceptability curves – facts, fallacies and frequently asked questions. *Health Economics* 2004; 13: 405-415.
- van der Bles AM, van der Linden S, Freeman ALJ, et al. Communicating uncertainty about facts, numbers and science. Royal Society Open Science 2019;6: 181870

Online Advanced Methods for Cost-Effectiveness Analysis

Lecture 7: Uncertainty, heterogeneity and VOI
7.4: Introduction to Value of Information (VOI)

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Senior Research Fellow, CHE

Objectives

- Understand why uncertainty matters for making adoption and research decisions
- Introduce the concept of the value of additional evidence
- Estimate the expected value of perfect information (EVPI) and the expected value of perfect parameter information (EVPPI)
- Interpret EVPI and EVPPI for research decisions

How uncertain is a decision?

Realisations that could occur in clinical practice	Net health effects (e.g. QALYs)			Best outcome for each realisation
	Treatment A	Treatment B	Best treatment choice	
Realisation 1	9	12	B	12
Realisation 2	12	10	A	12
Realisation 3	14	17	B	17
Realisation 4	11	10	A	11
Realisation 5	14	16	B	16
Expected (mean)	**12**	**13**		**13.6**

What's the best we can do now?

Choose B and expect 13 QALYs

But we are not always right:

Chance that B is the best = 3/5 = 0.6

Chance that A is the best = 2/5 = 0.4

If we adopt B the probability of error = 0.4

Why uncertainty matters?

- Uncertainty refers to the fact that we cannot know with absolute certainty what the expected (mean) effects of the intervention are
- There will always be a chance that the ‘wrong’ adoption decision is made resulting in a loss of health benefit and resources
- Basing decisions about a health care intervention on expected health effects does not address the question about whether the current evidence is a sufficient basis for guiding decisions in clinical practice. It fails to address the question of whether further research is needed before making a decision that could potentially harm patients due to the consequences of the uncertainty
- The value of uncertainty is the value of future evidence to eliminate that uncertainty

Adoption and research decisions

A number of conceptually distinct but simultaneous decisions to be made:

- Which technology should be adopted into clinical practice given the existing evidence base and the uncertainty surrounding outcomes and resource use?
- Is additional evidence required to support the use of the technology?
  - How uncertain are the expected benefits?
  - Does this uncertainty matter (will it change the adoption decision)?
  - How much does it matter (consequences of getting it wrong)?
- What type of evidence would be most valuable?
- Which research designs would be worthwhile?
- When to approve the technology?
  - Early approval? Can the evidence be provided with approval?

Is further evidence required?

- Information is valuable because it reduces the expected consequences of the uncertainty

  - Better decisions from more information → greater health gains

- Identify the consequences that can result from uncertainty and the likelihood of these consequences occurring

  - VOI aggregates the probability-weighted consequences to yield a net health impact of uncertainty for each alternative intervention

- Compare the value of research to cost of obtaining additional evidence
  - Expected value of research > cost of research → additional evidence is valuable
  - Expected value of research < cost of research → current evidence may be sufficient

Expected value of perfect information (EVPI) per individual

- With current information, must choose: $\max_j E_\theta \, NB(j, \theta)$
  where j are the alternative interventions and
  θ are the uncertain parameters
- If the uncertainty could be resolved (perfect information), the decision maker would choose to maximise the net benefits for each realisation of uncertainty: $\max_j NB(j, \theta)$
- True realisations are unknown, so we must average over all possible values: $E_\theta \max_j NB(j, \theta)$
- Additional value of information, EVPI = NB (perfect) – NB (current)

$$EVPI = E_\theta \max_j NB(j, \theta) - \max_j E_\theta \, NB(j, \theta)$$

Calculating the EVPI – an example

Realisations of uncertainty that could occur in clinical practice	Net health effects (QALYs)			Best outcome for each realisation, max NB(j,θ)
	Treatment A j = 0	Treatment B j = 1	Best treatment choice	
θ_1	9	12	B	12
θ_2	12	10	A	12
θ_3	14	17	B	17
θ_4	11	10	A	11
θ_5	14	16	B	16
E_θ NB(j,θ)	12	13		13.6

What's the best we can do now?

Choose B, expect 13 QALYs, gain 1 QALY

Could we do better?

With perfect information, expect 13.6 QALYs

$$EVPI = E_\theta \max_j NB(j, \theta) - \max_j E_\theta NB(j, \theta)$$

$$= 13.6 - 13 = 0.6 \text{ QALYs per patient}$$

EVPI at a population level

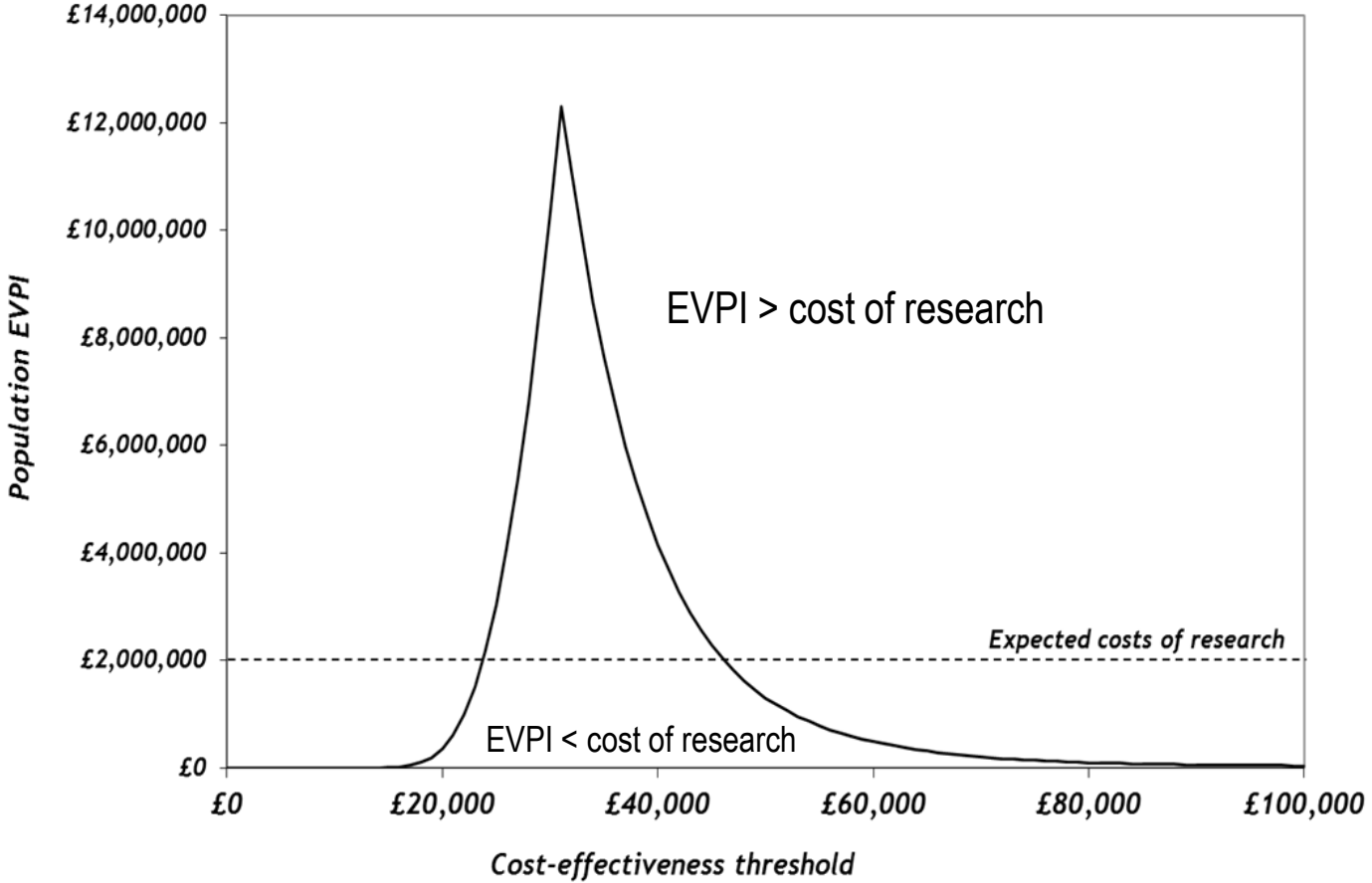
- EVPI at a population level
  - Multiply the 'per patient EVPI' by the number of times this information is used to inform treatment choice (size of the beneficiary population)
  - Depends on size of prevalent and incident population, P_t, I_t
  - Depends on time horizon over which information is valuable, T

$$Population\ EVPI = EVPI. \sum_{t=1}^{T} \frac{I_t}{(1+d)^t}$$

d, discount rate

- Provides an expected upper bound on the value of research
  - Population EVPI > cost of research
  - If EVPI is lower than the expected costs of conducting further research then it is not cost-effective to conduct further research, i.e. EVPI provides a necessary condition for conducting research

EVPI at a population level



Relationship between EVPI, ICER and threshold

- As ICER approaches cost-effectiveness threshold
  - Net benefit of alternatives more similar (INB close to 0)
  - Likelihood of error increases
  - Consequences of error decrease
- For a cost-effective technology (ICER < threshold)
  - Reducing price will reduce EVPI
  - Reducing current uncertainty will reduce EVPI
- EVPI can be used as a first hurdle to identify research which is potentially cost-effective
  - Identify research priorities by comparing the net value of research (EVPI minus costs of research) across technologies

What type of evidence is required?

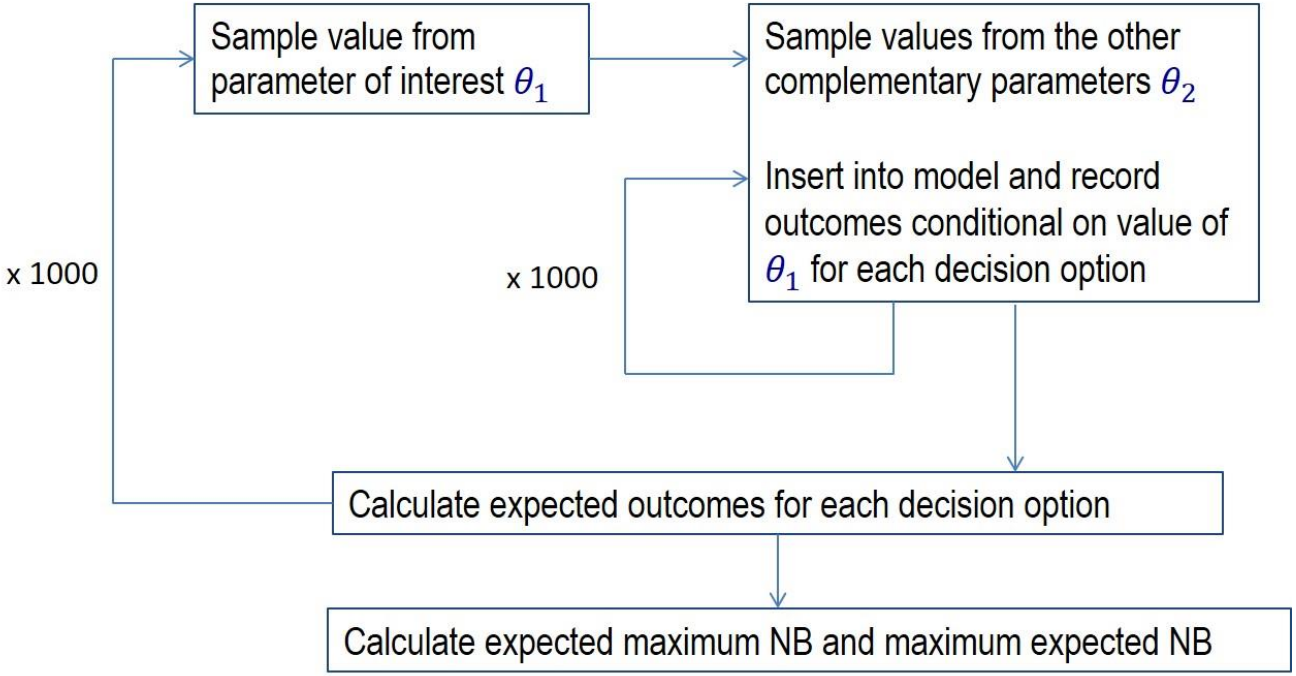
Expected value of perfect information for parameters (EVPPI)

- EVPPI considers the value of particular elements of the decision problem in order to direct and focus research towards those areas where the elimination of uncertainty has the most value
- The consequences of uncertainty over each of the model parameters can be evaluated: $\theta = \{\theta_1, \theta_2, \ldots.\}$
- Estimate cost of uncertainty that is attributable to:
  - Single parameters or groups of parameters e.g. costs, effectiveness
  - Shows sensitivity of model results to inputs and consequences of error
- For each parameter or group there will be a different potential value of research and appropriate research design

Calculating EVPPI

$$EVPPI_{\theta_1} = E_{\theta_1} \max_j E_{\theta_2|\theta_1} NB(j, \theta_1, \theta_2) - \max_j E_{\theta} NB(j, \theta)$$

θ
- θ_1 = parameter of interest
- θ_2 = other uncertainties (complementary parameters)

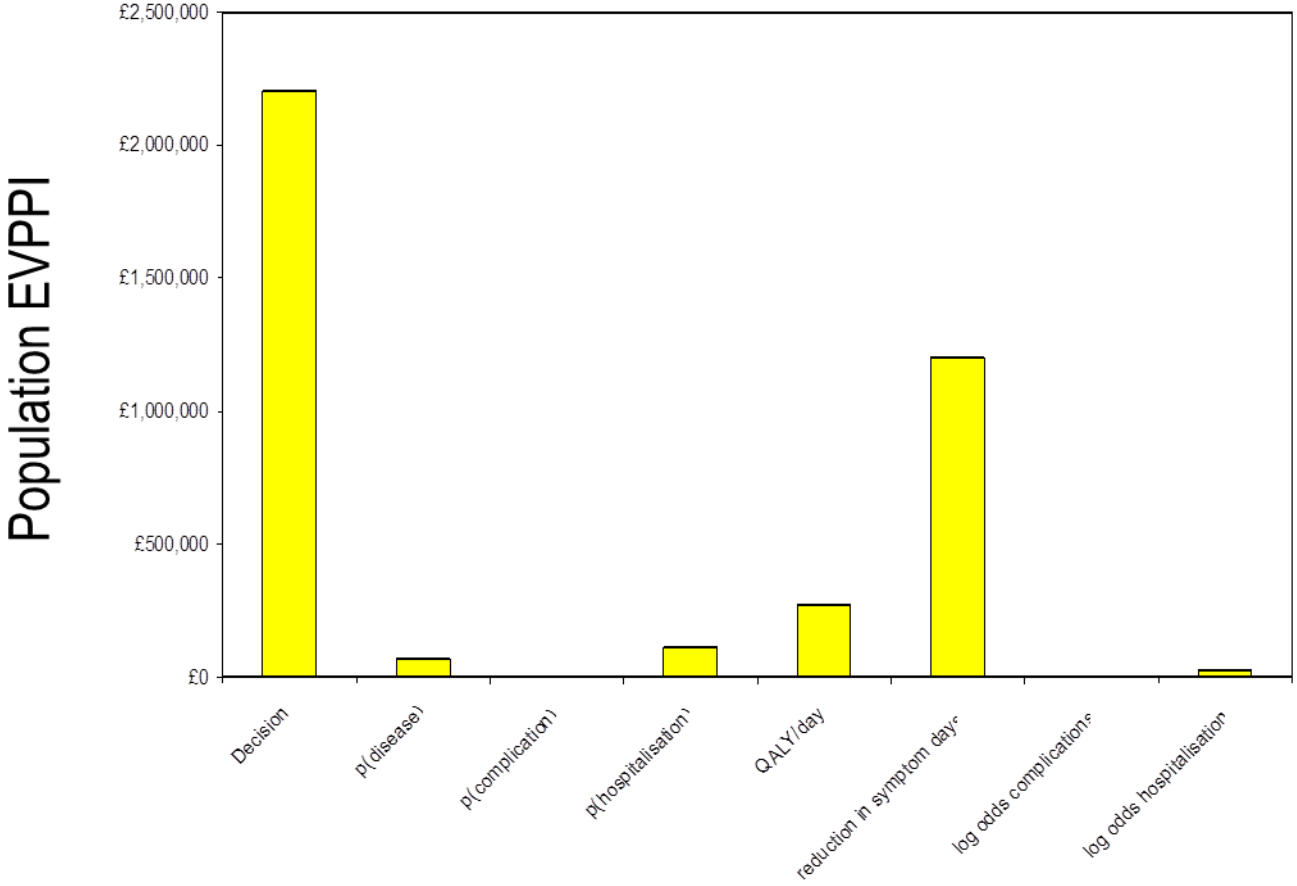


Issues in calculating EVPPI

- Two-level sampling algorithm (unless model is linear)
  - Sample parameter of interest (outer loop)
  - Analyse model probabilistically (inner loop)
- Analysis time
  - How many simulations? Which parameters/groups of parameters to include?
- Sum of EVPPI ≠ EVPI
- Knowing θ1 alters value of θ2
- Can calculate EVPPI as group to embed correlation between parameters
- More flexible regression-based methods available to reduce to single-loop sampling (efficient EVPPI computation)

Ref: ISPOR Task Force report. Value of Information Analytical Methods: Report 2 of the ISPOR Value of Information Analysis Emerging Good Practices Task Force. Rothery et al (2020)

EVPPI at a population level



Summary

- Principles of uncertainty and value of information
  - Why uncertainty matters
  - Scale of the consequences of uncertainty
  - Value of additional evidence

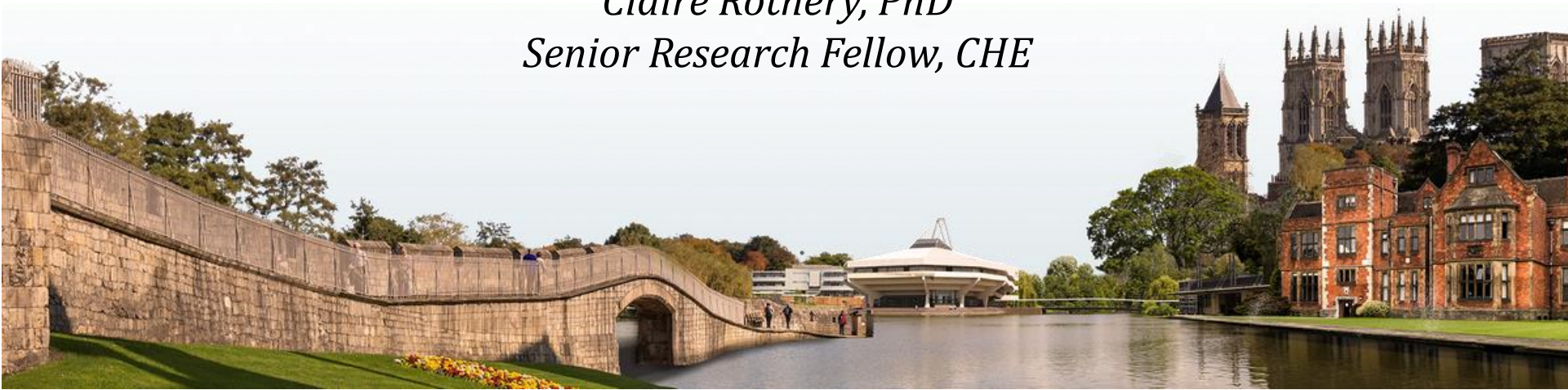
- EVPI and EVPPI
  - Maximum return to research
  - Comparing the EVPI to the opportunity costs of research
  - Comparing EVPI across technologies
  - Comparing EVPPI to focus research design

- In Part 7.5 we will learn about EVSI

Online Advanced Methods for Cost-Effectiveness Analysis

Lecture 7: Uncertainty, heterogeneity and VOI
7.5: Informing research decisions

Claire Rothery, PhD
Senior Research Fellow, CHE



Objectives

- Estimate the expected value of sample information (EVSI) and the expected net benefit of sample information (ENBS)
- Interpret EVSI and ENBS for informing research design
- Implications of VOI for policy decisions
    - coverage with evidence development
    - identifying research priorities
    - link between approval, price and research decisions

Setting research priorities

- EVPI and EVPPI
  - Maximum return to research
  - Comparing the EVPI to the opportunity costs of research
  - Comparing EVPI across technologies
  - Comparing EVPPI to focus research design

- EVSI and ENBS
  - Identify technically efficient research designs
  - Allocations between clinical areas
  - Allocation between research and service provision

What type of research design?
Expected value of sample information (EVSI)

- In practice unlikely to obtain perfect information
  - Additional research will reduce, rather than eliminate uncertainty
- Research design may include sample size, allocation of patients between arms of clinical trial, length of follow-up, endpoints to include
- EVSI provides the value of a decision based on having additional sample information. It predicts possible sample results that would be obtained from a study with a sample size of n
- To establish if the study is an efficient use of resources, the societal value of the study is compared to the costs of gathering the sample information
- Sufficient condition for further research
  - Expected net benefit of sampling (ENBS) = EVSI - cost of research
  - If ENBS > 0 for a particular sample design then further research is worthwhile

Expected value of sample information (EVSI)

Steps required to calculate EVSI as function of study design and sample size:

1. Sample from the prior distributions

   e.g. $\theta \sim \text{Beta}(\alpha = 3.64, \beta = 47.14)$

2. Then sample likelihood to generate possible sample results for size n, $D|\theta$

   e.g. $D \sim \text{Binomial}(\theta, n)$

3. Combine the prior and predicted sample distributions to form predicted posterior results for each sample

   e.g. $X' \sim \text{Beta}((\alpha+n\theta), (\beta+n-n\theta))$

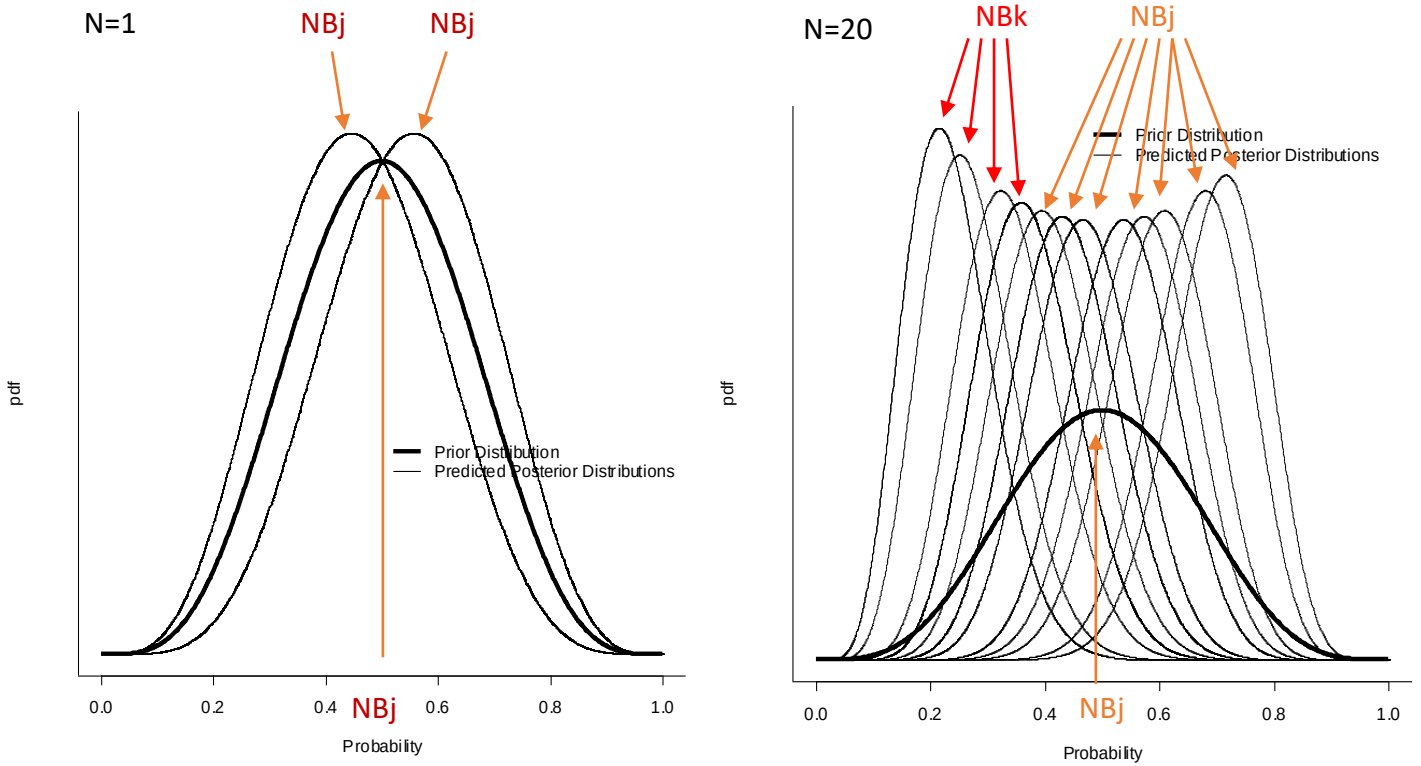
4. Calculate NB for each predicted posterior and choose the treatment with the highest NB

5. Since the actual results of each sample are not known in advance, average the maximum expected NB over the distribution of possible sample results: $E_\theta E_{D|\theta} \max_j E_{\theta|D} NB(j, \theta)$

   EVSI = NB with sample information – NB with current information

   $$EVSI = E_\theta E_{D|\theta} \max_j E_{\theta|D} NB(j, \theta) - \max_j E_\theta NB(j, \theta)$$

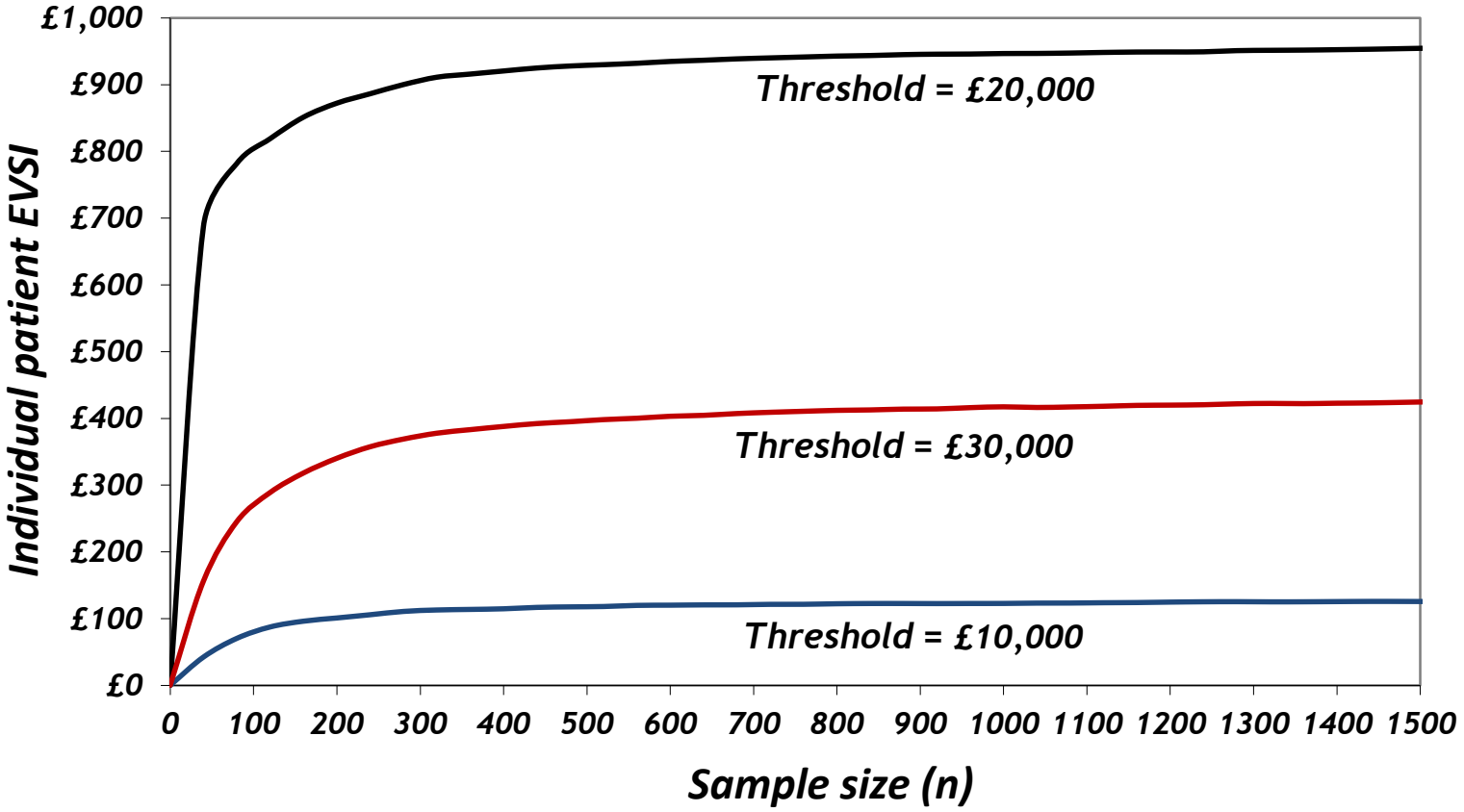
Expected value of sample information (EVSI)



Source: Karl Claxton, Centre for Health Economics, York

Ref: Ades AE, Lu G, Claxton K. Expected Value of Sample Information Calculations in Medical Decision Modeling. *Medical Decision Making* 2004; 24(2): 207-227

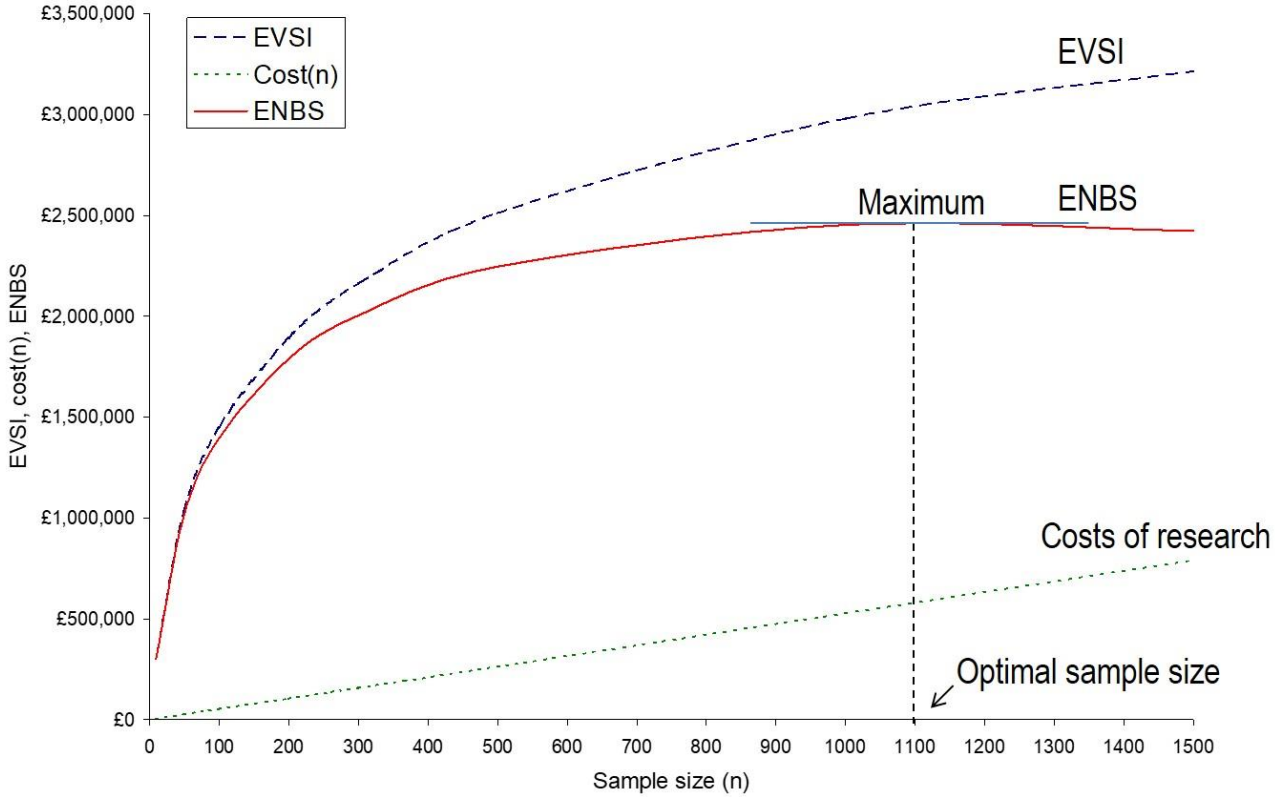
EVSI for different sample sizes



Is research an efficient use of resources?

- ENBS = Population EVSI - cost of research
- Cost of research as function of study design and sample size
  - Costs of running study and opportunity costs to patients
  - Patients enrolled in study no longer part of population to benefit from additional information (acute condition)
- Use ENBS to prioritise research and in place of traditional power calculations
  - ENBS > 0 for a particular sample design then further research is worthwhile
  - Choose between alternative research designs, e.g. appropriate length of follow-up, sample size, where the **ENBS reaches a maximum**

Expected net benefit of sample information (ENBS)



Feasibility of research

- Likelihood of research
  - Research itself may be uncertain prospect (fail to complete)
- Type of research design
  - Observational versus experimental
- If treatment is adopted and available outside research
  - Randomisation may be viewed as unethical
  - Patients may be unwilling to randomise (or drop out)
  - Manufacturer lacks incentive to fund research
- Time to research versus time horizon for decision
  - Value of research only realised from time research reports

Opportunity costs of adoption

- Decision to adopt/reject a technology based on expected net benefit
  - No impact of adoption decisions on research
- Sunk costs with implementation of technology, i.e. a cost that has already been incurred and cannot be recovered
  - Delay adoption until research reports?
  - Opportunity costs of delay
- Adoption reduces further research
  - Incentives/ethics, e.g. may be considered unethical to enrol patients into research if the technology is available for widespread use
  - Unable to enforce conditional permissions/coverage with evidence

When to approve the technology?

Approve: Could impact the prospects of acquiring further evidence

Reject: Could restrict patient access to promising new technologies

Additional policies overcome the problems associated with making coverage decisions under uncertainty:

Only in research (OIR): 'No' decision until further evidence establishes value

Approve with research (AWR): 'Yes' decision until further research is completed and guidance is established

What assessments are needed?

- Expected cost-effectiveness
- Irrecoverable costs
  - Costs committed by approval that cannot be recovered
    - Capital costs of long lived equipment (training and learning)
    - Initial losses (negative NB) offset by later gains
    - Significance depends on whether initiation of treatment can be delayed
- Value of additional evidence
- The need for evidence, type of evidence, design of research
- Uncertainty that cannot be resolved by research but only over time
- Are the benefits of early approval greater than the opportunity costs?

Framework for health technologies

Claxton K, *et al*. (2012) Informing a decision framework for when NICE should recommend the use of health technologies only in the context of an appropriately designed programme of evidence development. *Health Technology Assessment*; vol. 16

Summary

- Policy analysis based on value of information analysis can be used to consider the value of
  i. research compared to its expected costs;
  ii. being able to conduct research while a technology is approved;
  iii. the trade-off between the expected benefits to current patients from early access and the benefits to future patients from more research
- Understanding the relationship between the time taken for research to report and the value of the evidence can help inform
  i. investments which might make research findings available quickly;
  ii. the trade-off implicit in the choice of alternative research designs;
  iii. those areas where research must be reported quickly to be of value

Reading list for lecture 7 (parts 7.1 – 7.3)

- Briggs AH. Handling uncertainty in cost-effectiveness models. *PharmacoEconomics* 2000; 17(5): 479-500.
- Briggs AH, Goeree R, Blackhouse G, O'Brien BJ. Probabilistic analysis of cost-effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. *Medical Decision Making* 2002; 22: 290-308.
- Briggs A, Claxton K, Sculpher MJ. *Decision modelling for health economic evaluation*. Oxford University Press, 2006.
- Claxton K. Characterising, reporting, and interpreting uncertainty. In: Drummond, Sculpher, Claxton, Stoddart and Torrance *eds. Methods for the Economic Evaluation of Health Care Programmes.* Oxford, UK. Oxford University Press, 2015.
- Fenwick E, O'Brien B, Briggs AH. Cost-effectiveness acceptability curves – facts, fallacies and frequently asked questions. *Health Economics* 2004; 13: 405-415.
- van der Bles AM, van der Linden S, Freeman ALJ, et al. Communicating uncertainty about facts, numbers and science. Royal Society Open Science 2019;6: 181870

Reading list for lecture 7 (parts 7.4 – 7.5)

- Fenwick E, Stotten L, Knies S, et al. Value of information analysis for research decisions: an introduction report 1 of the ISPOR Value of Information Analysis Task Force. Value in Health. 2020;23(2):139–150.
- Rothery C, Strong M, Koffiberg H, et al. Value of information analytical methods emerging good practices: report 2 of the ISPOR VOI Task Force. Value in Health. 2020;23(3):277–286.
- Claxton K and Sculpher MJ. Using value of information analysis to prioritise Health research: some lessons from recent UK experience. *PharmacoEconomics* 2006, 24:1055-1068.
- Claxton K, Palmer S, Longworth L, et al. Informing a decision framework for when NICE should recommend the use of health technologies only in the context of an appropriately designed programme of evidence development. Health Technology Assessment 2012;16.
- Claxton K, Griffin S, Koffijberg H and McKenna C. How to estimate the health benefits of additional research and changing clinical practice. *BMJ* 2015; 351.