Online Advanced Methods for Cost-Effectiveness Analysis

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

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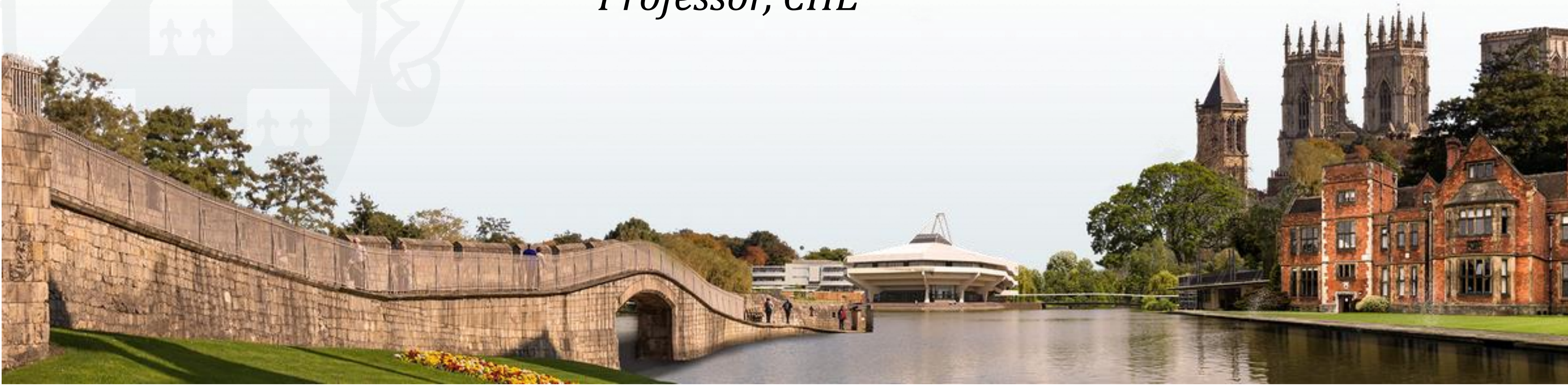
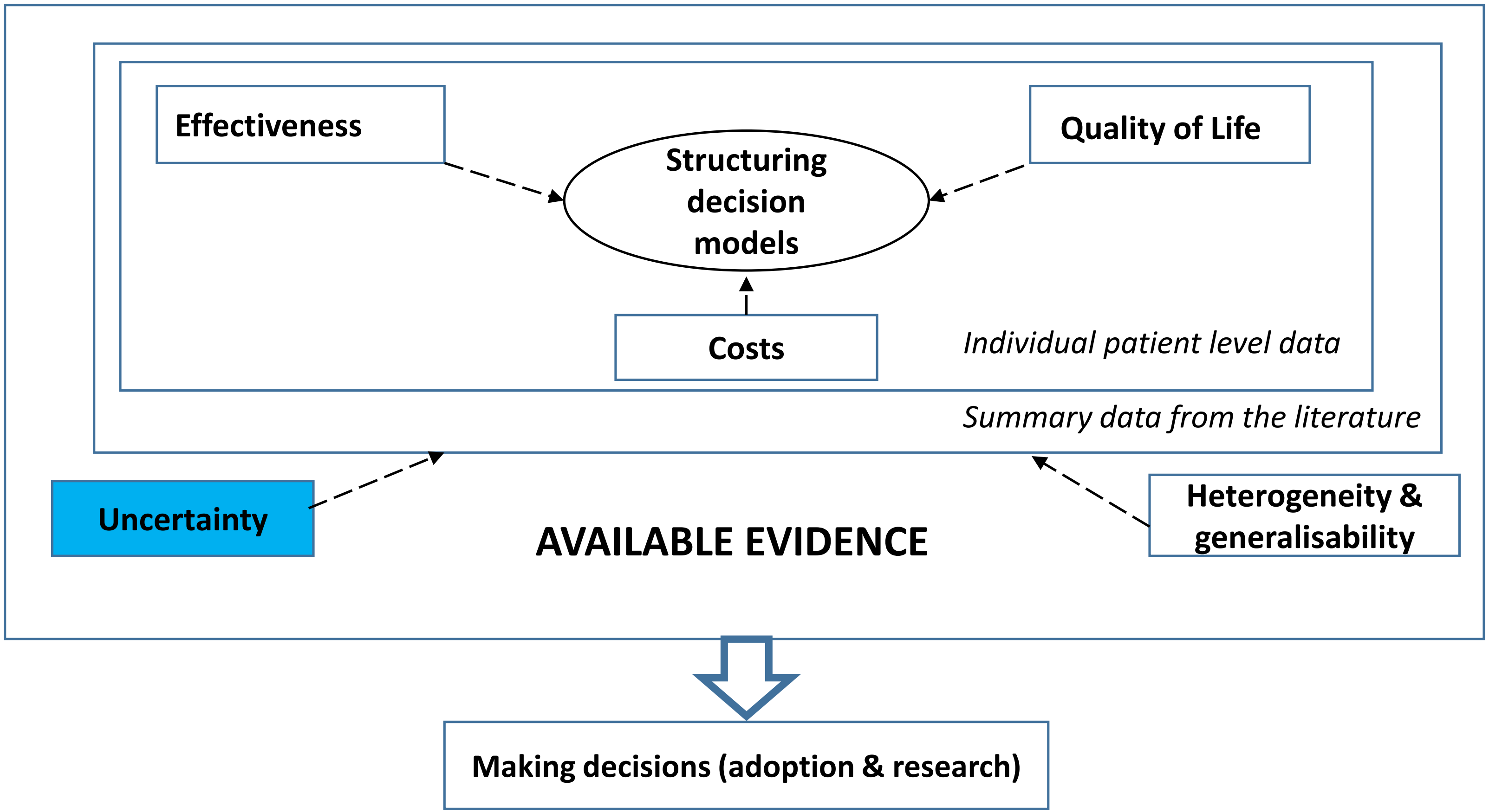


Course structure – where are we up to?



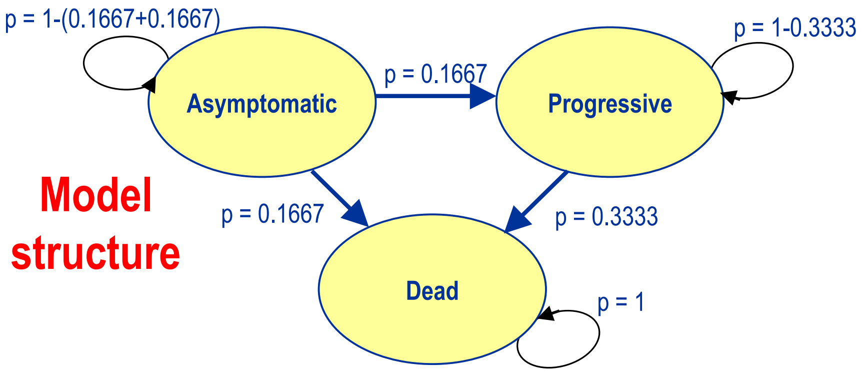
Overview

- 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

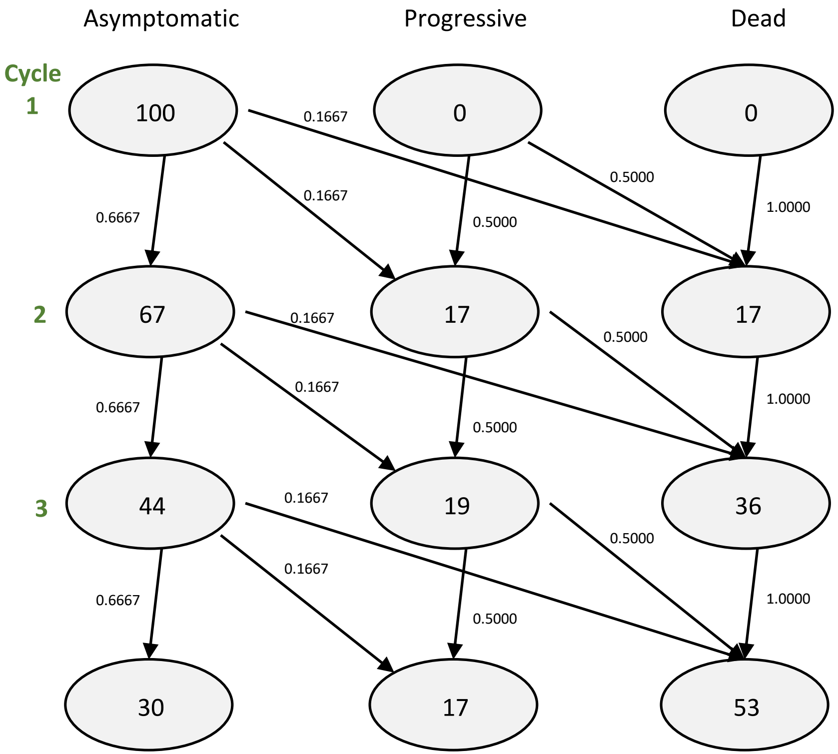
Outline of a simple Markov model



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		***To***	
From	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

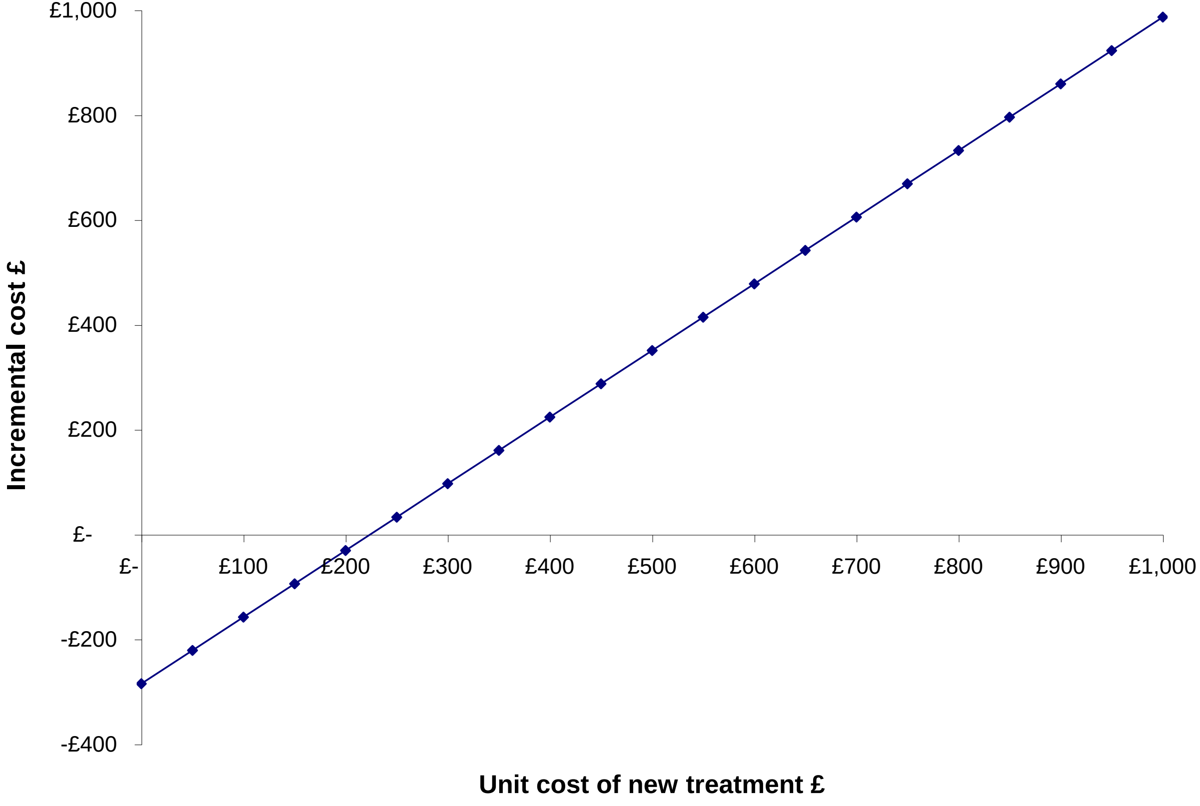
Types of uncertainty - Summary

Need to address	Not main focus of CEA
Parameter uncertainty - 2^{nd} order or epistemic uncertainty - measurement error - e.g. response rate to treatment 0.8 (95% CI: 0.55 to 0.95)	**Variability** - 1^{st} 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	

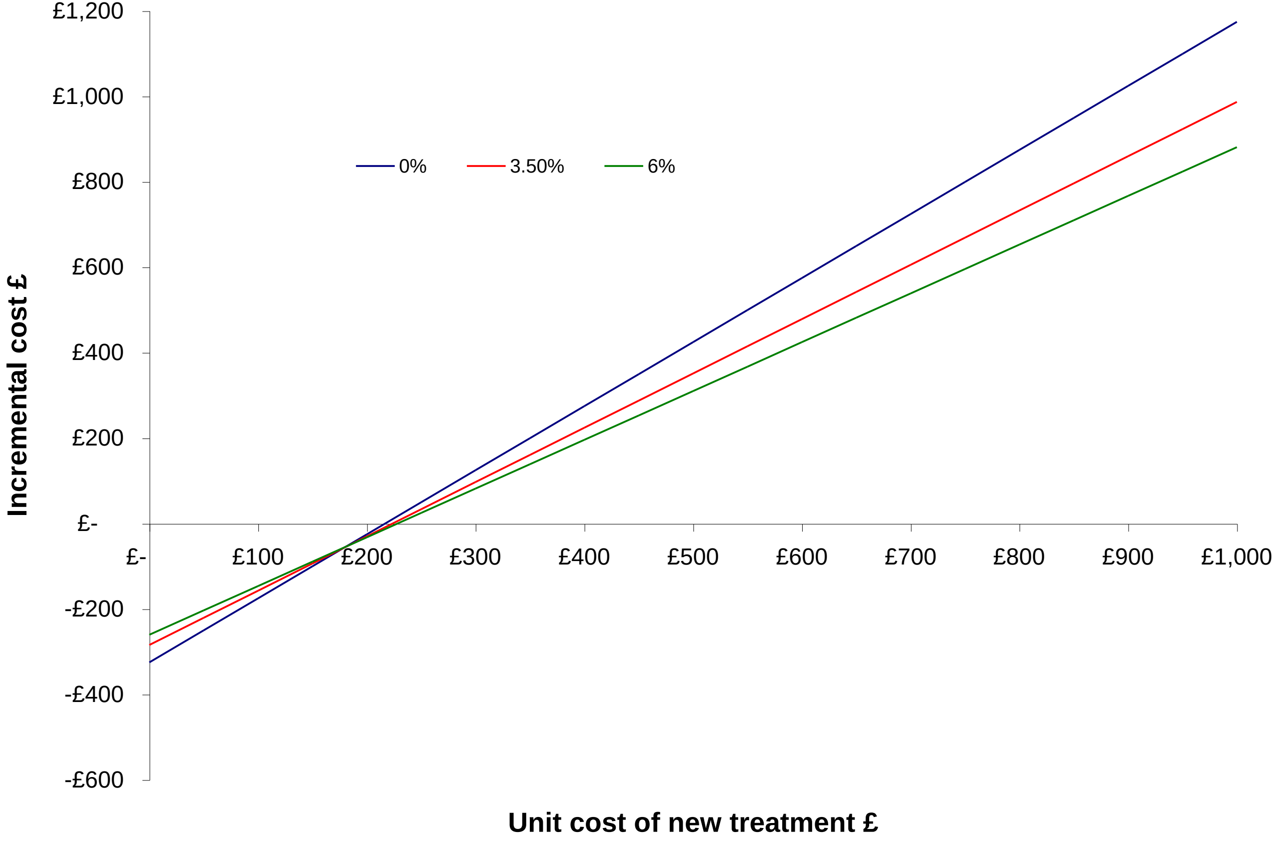
Deterministic methods to address uncertainty

- 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