An Introduction to Decision-Analytic Methods

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Introduction to Economic Evaluation of Health Care Interventions

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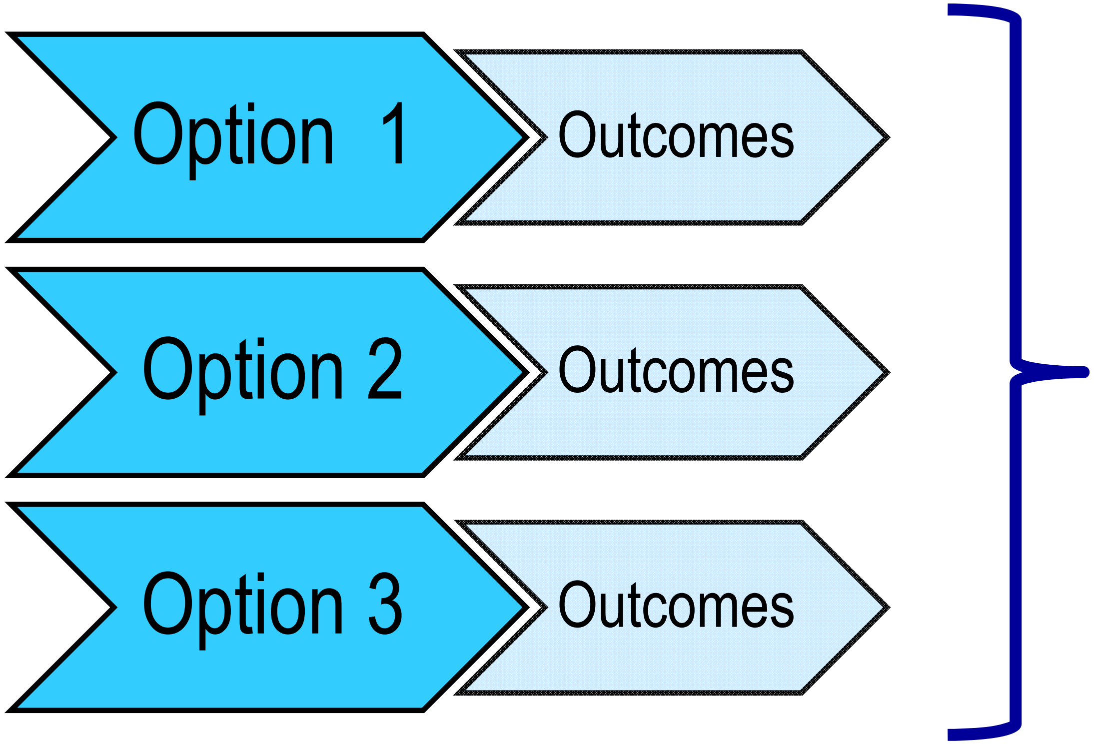
Overview

1. Decision analysis
2. Comparative analysis, incremental cost-effectiveness ratio (ICER)
3. Model development process and model conceptualisation
4. Decision trees
5. Markov models and cohort simulation
6. Parameter uncertainty
7. Probabilistic sensitivity analysis, cost-effectiveness acceptability curve (CEAC)

Decision analysis

Decision analysis is the quantitative method for evaluating a comparison between multiple alternatives under conditions of uncertainty



What should we choose?

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Decision making ≠ Measurement

Measurement

- Testing hypotheses about individual parameters
- Relatively few parameters of interest
- Primary role for trials and systematic review
- Focus on parameter uncertainty

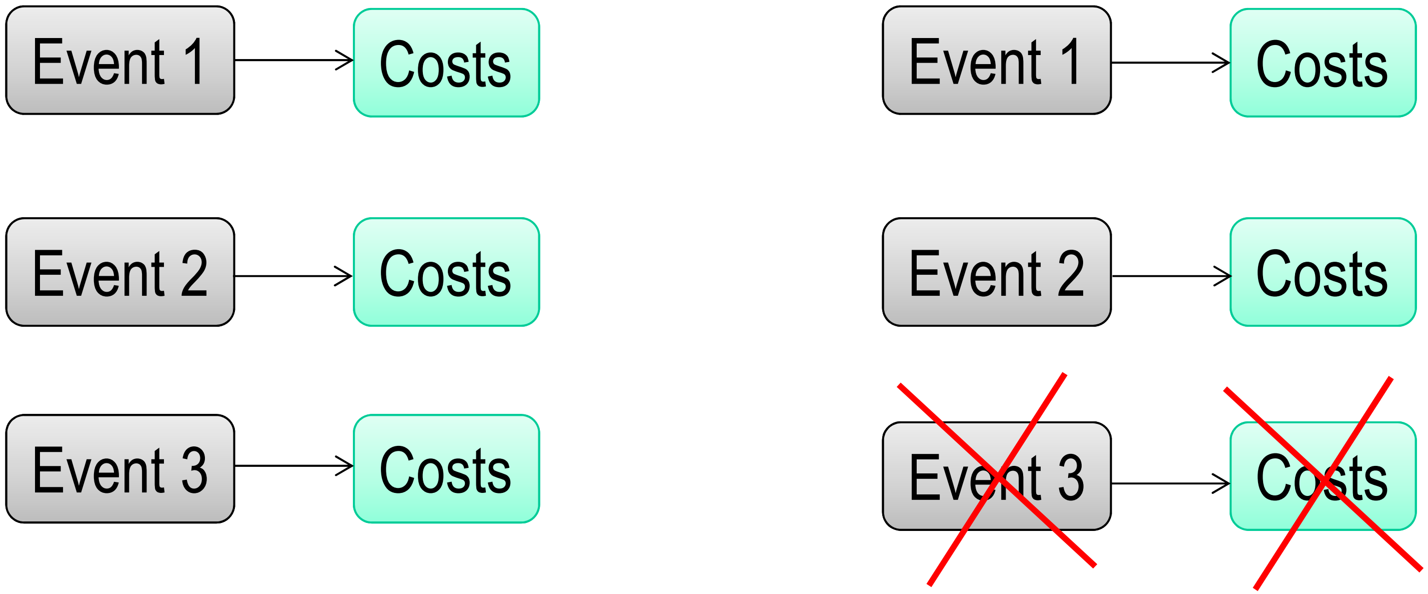
Decision making

- What do we do now based on all sources of current knowledge?
- Decisions cannot be avoided
- A decision is always taken under conditions of uncertainty
- Decision making involves synthesis
- Can be based on implicit or explicit analysis

Decision analysis in health care

A model is a mathematical prediction of events or outcomes (e.g. costs, health)

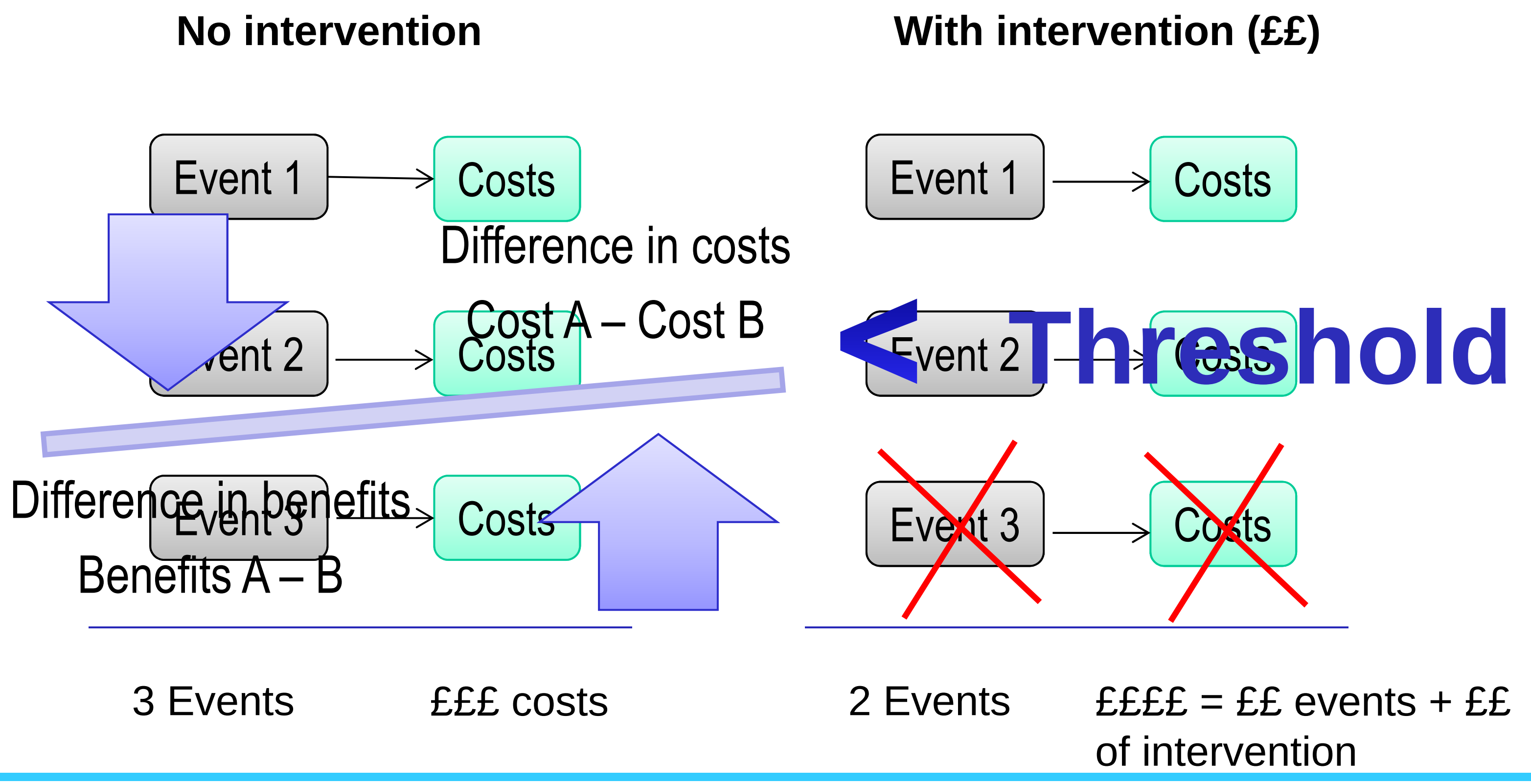
No intervention | **With intervention (££)**



3 Events | £££ costs

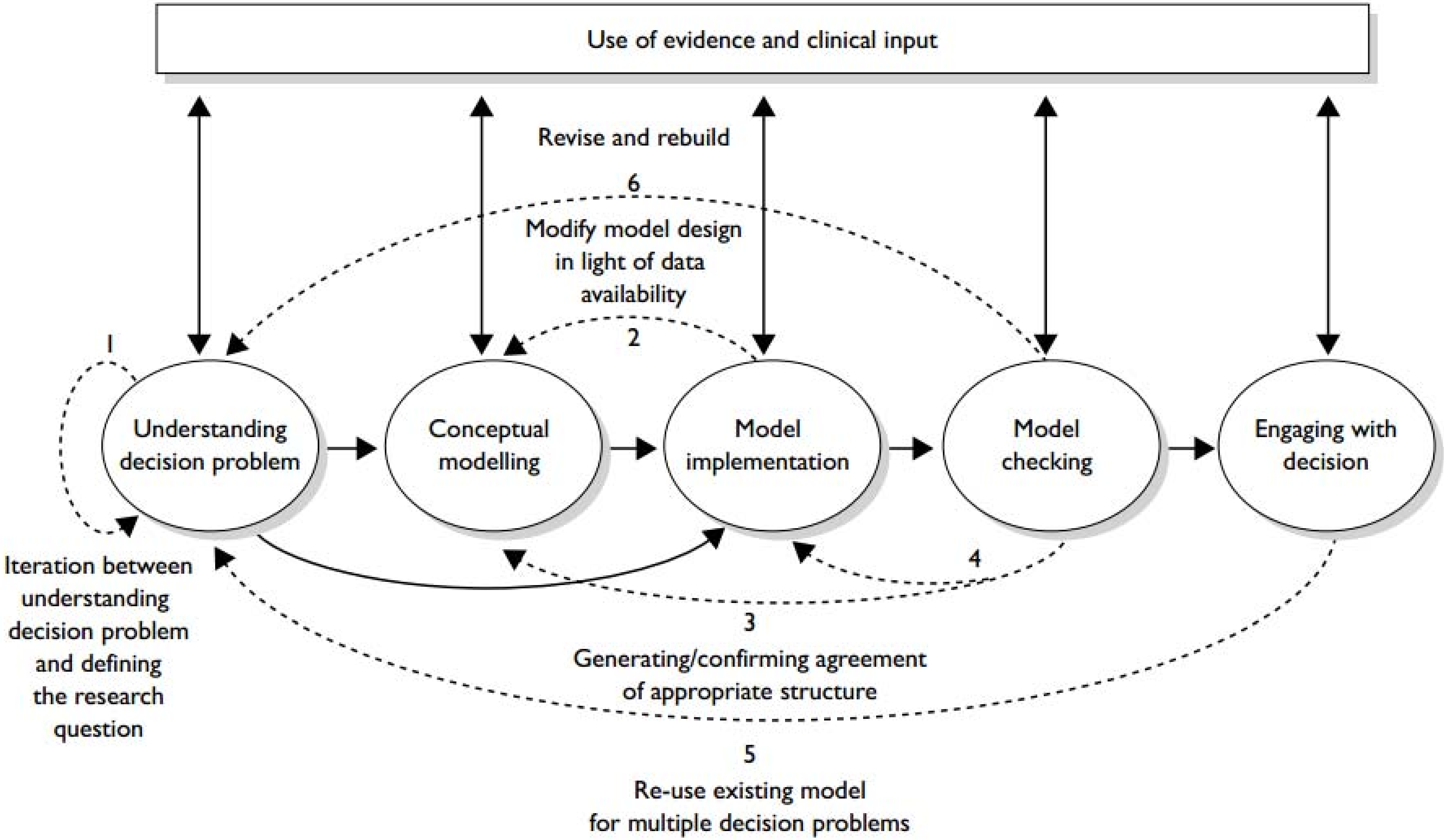
2 Events | ££ costs

How to make decisions in healthcare?



Are the additional costs of the intervention worth the event avoided?

Model development process



Source: Chilcott JB, et al. Avoiding and identifying errors in health technology assessment models. Health Technology Assessment 2009; 14(25):i-135

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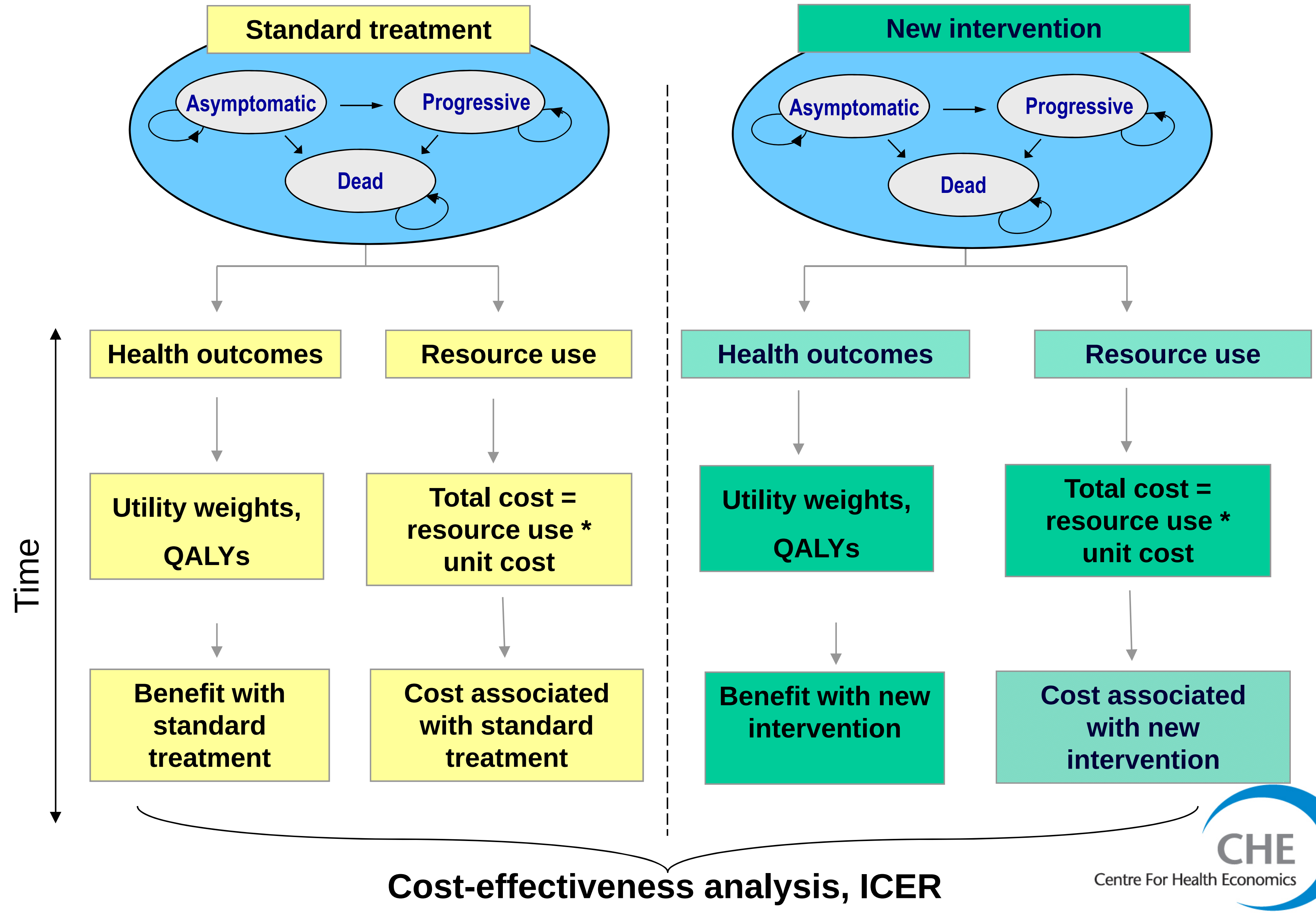
Key model parameters

Type of parameter	Source
Baseline event rates	Observational studies/trials
Relative treatment effects	Trials
Long-term prognosis	Longitudinal observational studies
Resource use	Observational studies/trials
Quality of life weights (utilities)	Cross sectional surveys/trials

Structure of economic evaluation



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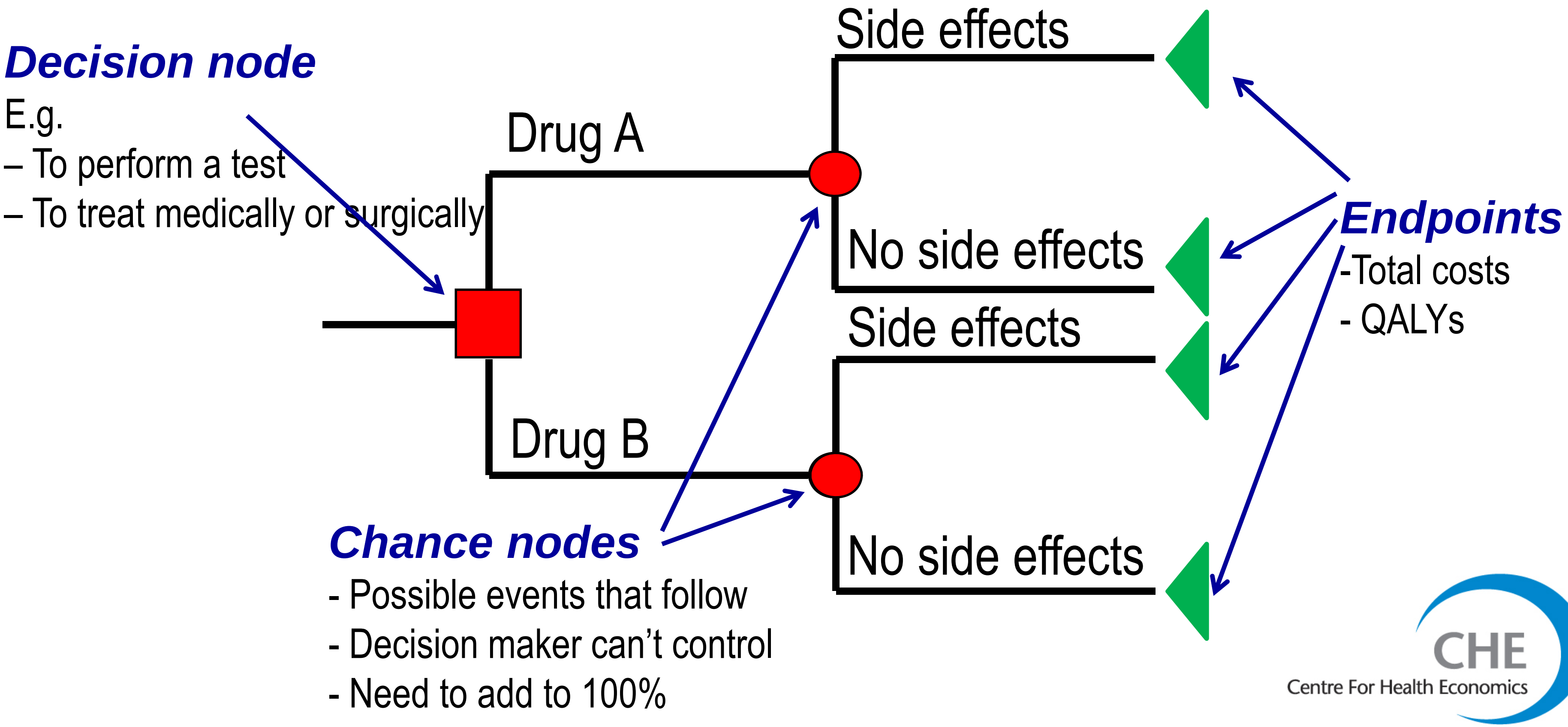
Decision trees

- Intuitive structure
- Typically focussed on a single discrete time period
- Structured around pathways



Example: Cost-effectiveness of ante-natal HIV testing

- Local decision maker wants to assess the cost-effectiveness of testing pregnant women for the HIV virus

- If a woman has HIV and her infection remains undetected during pregnancy, the probability that she will transmit the infection to her child is 26%.
- If a woman's infection is known during pregnancy, however, it is possible to use risk-reduction interventions such as caesarean section, zidovudine antiretroviral therapy and bottle-feeding. These interventions cost £800 more than a normal delivery and reduce the probability of transmission to the child to 7%, but only 95% of infected women accept the interventions.
- Offering the test to women could be achieved at negligible additional cost but each blood test will cost £10
- Tests are 100% accurate (i.e. no false negatives or false positives)
- Prevalence of previously-undetected HIV in the antenatal population is 5%.

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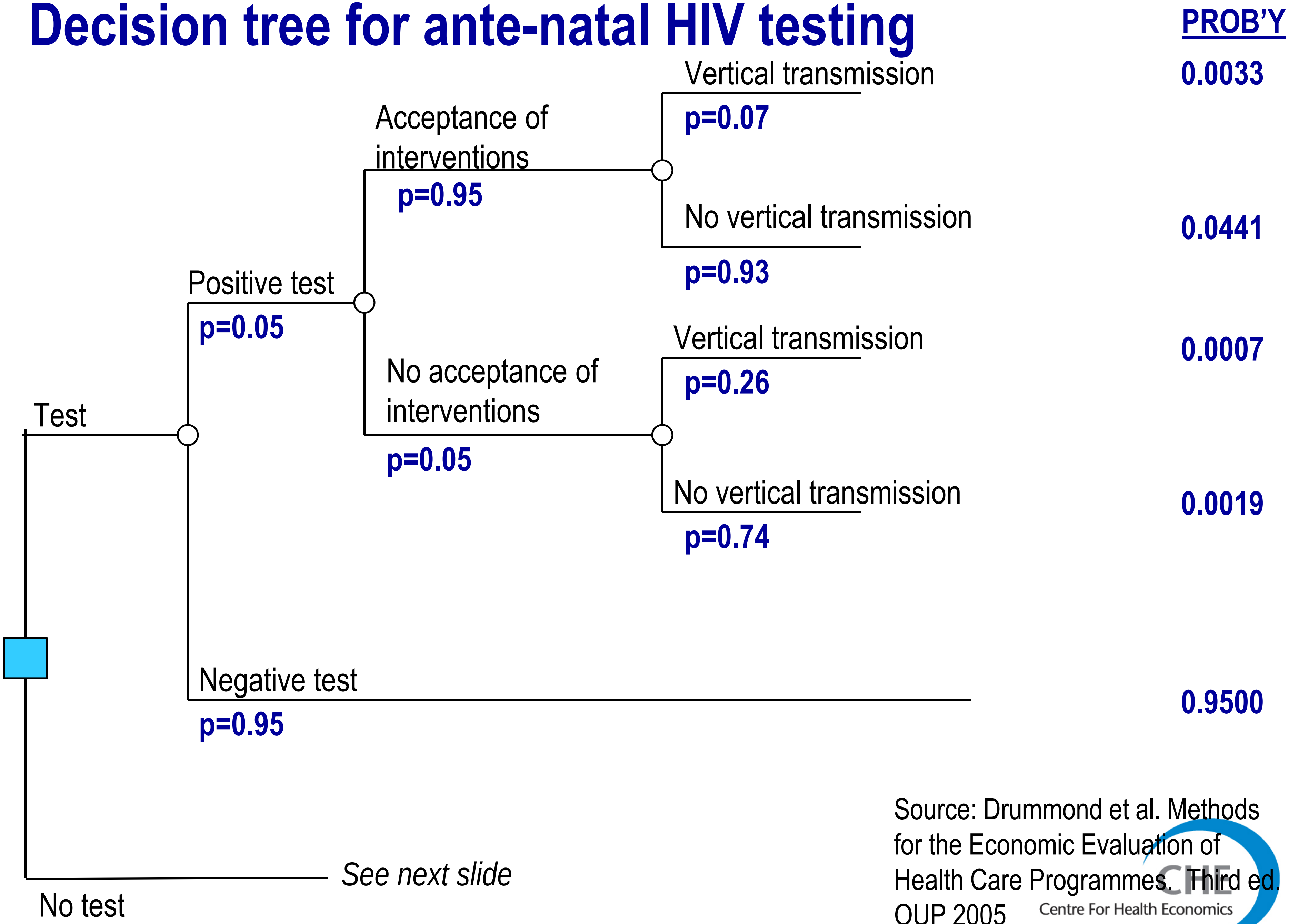
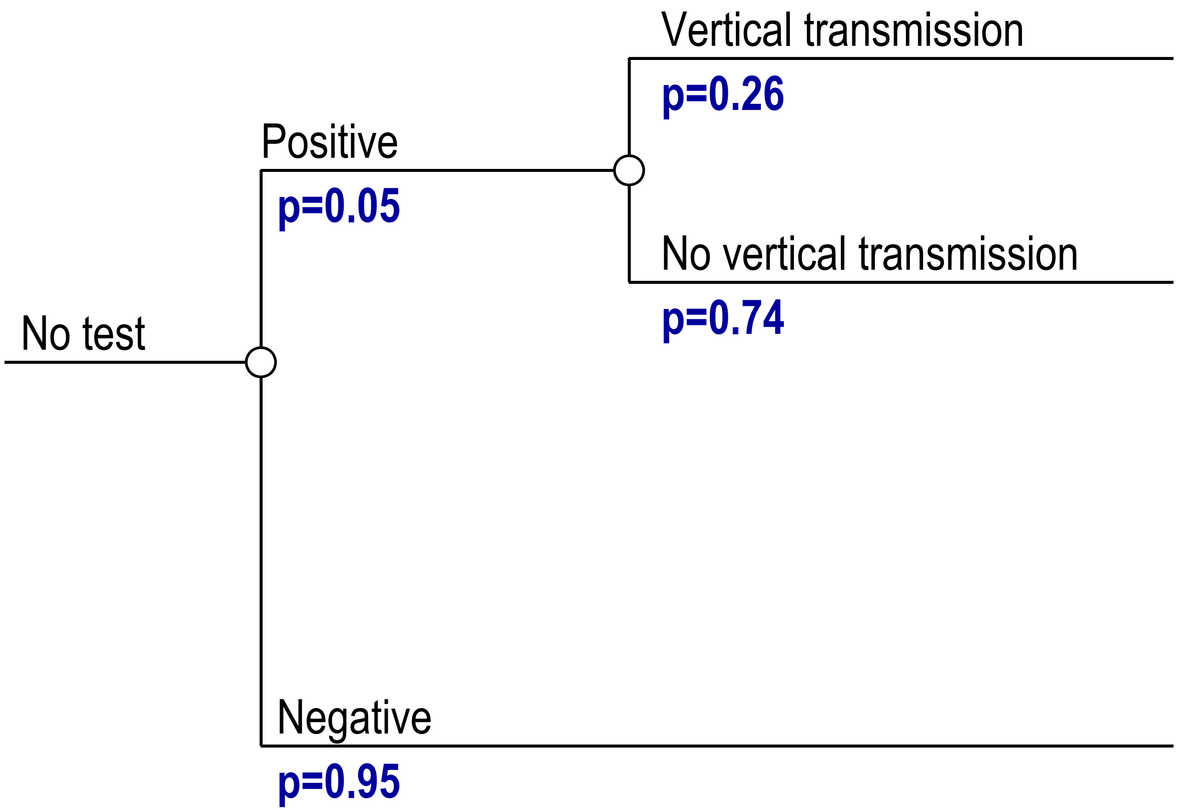
Source: Drummond et al. Methods for the Economic Evaluation of Health Care Programmes. Third ed. OUP 2005

Decision tree for ante-natal HIV testing



Source: Drummond et al. Methods for the Economic Evaluation of Health Care Programmes. Third ed. OUP 2005

Decision tree for ante-natal HIV testing



PROB'Y
0.013
0.037
0.95

Source: Drummond et al. Methods for the Economic Evaluation of Health Care Programmes. Third ed. OUP 2005

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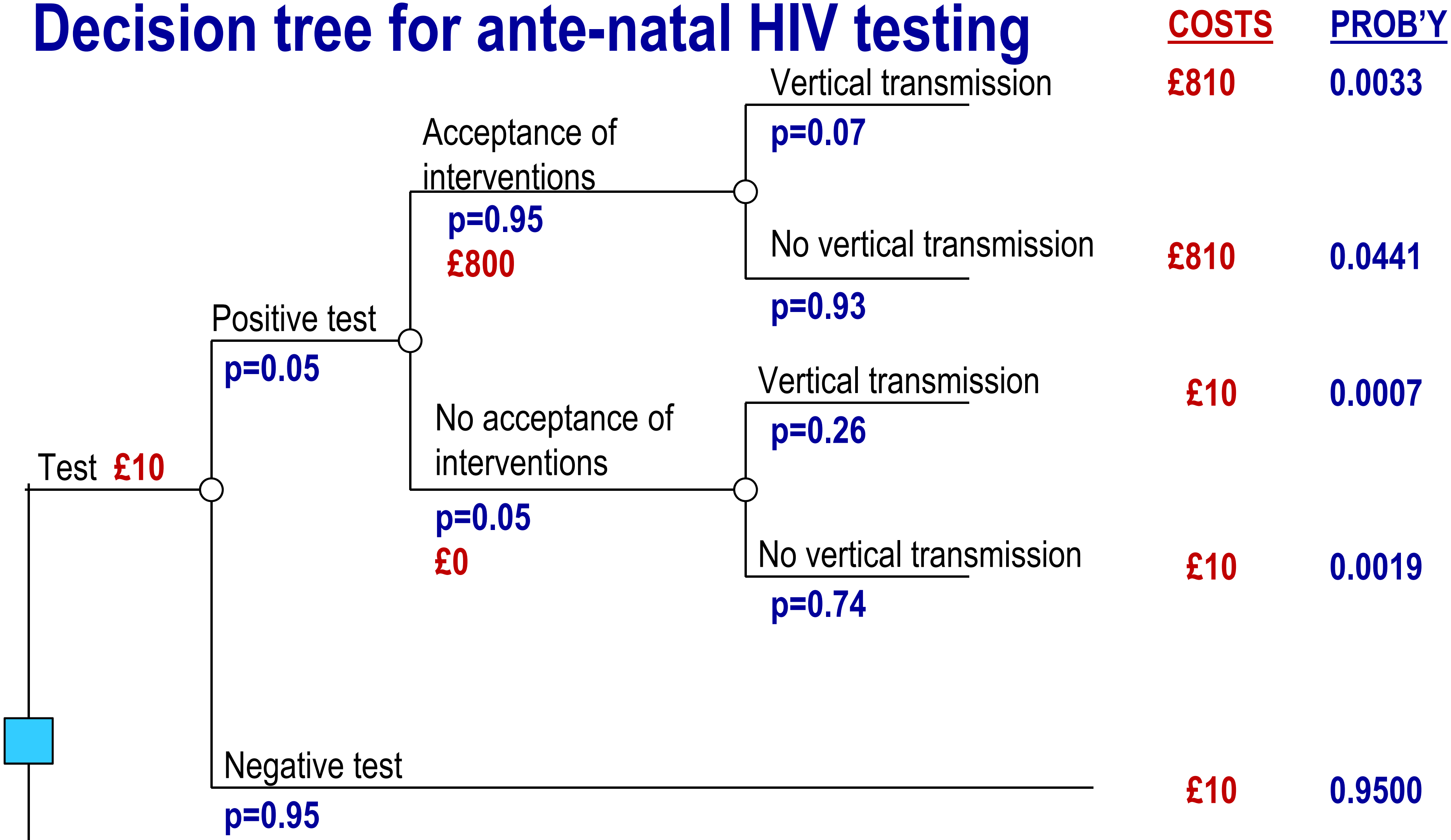
Decision tree for ante-natal HIV testing



Expected cost of testing = (810 x 0.0033) + (810 x 0.0441) + (10 x 0.0007) + (10 x 0.0019)+ (10 x 0.95) = 47.92

Probability of vertical transmission = 0.0033 + 0.0007 = 0.004

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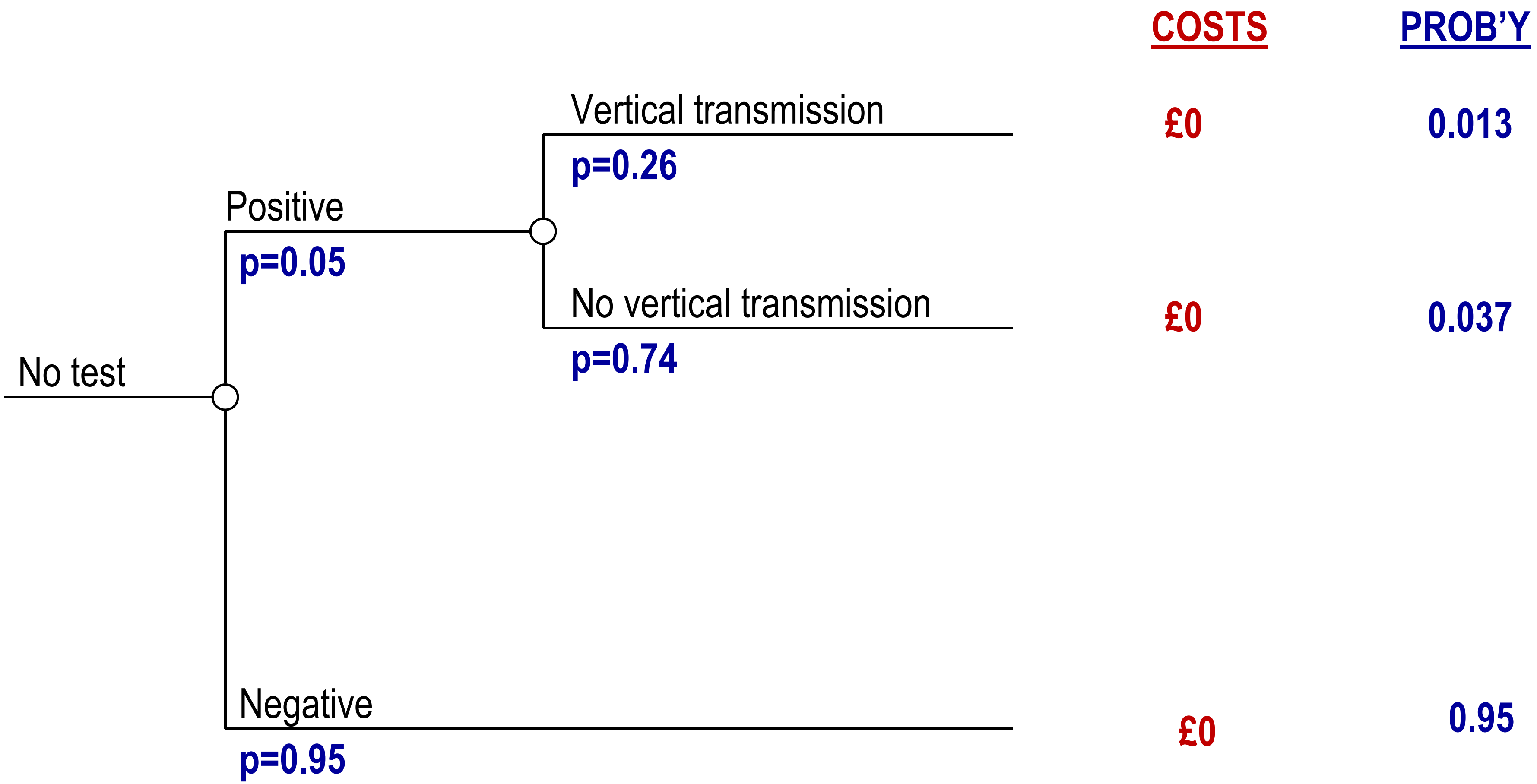
Decision tree for ante-natal HIV testing



Expected cost of no testing = 0

Probability of vertical transmission = 0.013

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Example: Cost-effectiveness of ante-natal HIV testing

Rolling back decision tree:

- Additional cost = 47.92
- Reduced vertical transmission: 0.013 - 0.004 = 0.009
- **Additional cost per HIV-infected birth avoided:**

  £47.92 / 0.009 = £5,324

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Limitations of decision trees

- Models a sequence of events over a particular time period
- Time is not explicitly defined in decision tree
- Time dependency can be difficult to implement for outcomes,
  E.g. adjusting survival duration for health-related quality of life;
  Difficulties with discounting costs and health outcomes
- Decision trees can become excessively ‘bushy’
- Complex to model long-term prognoses and chronic conditions
  E.g. recurrences, remission, mortality risk over time

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Markov models

- Based on a series of 'states' that a patient can occupy at a given point in time, e.g. health states are used to represent the long-term prognosis of patients

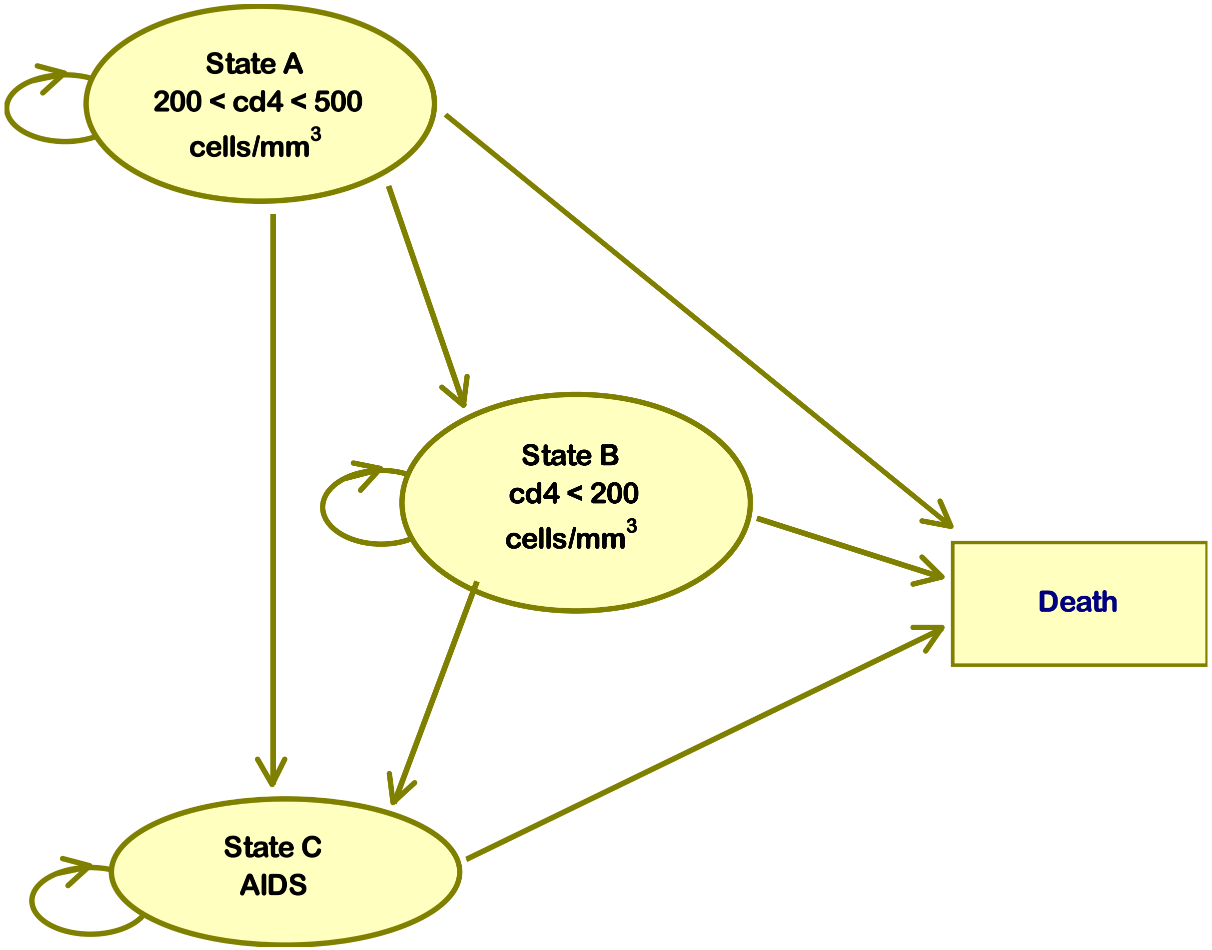
- Time is explicitly modelled with the probability of a patient occupying a given state assessed over a series of discrete time periods called cycles

- Patients move between health states over time. The speed at which patients move between states in the model is determined by a set of transition probabilities

- Each state in the model has a cost and health-related quality of life utility value associated with it

Example: Management of patients with HIV

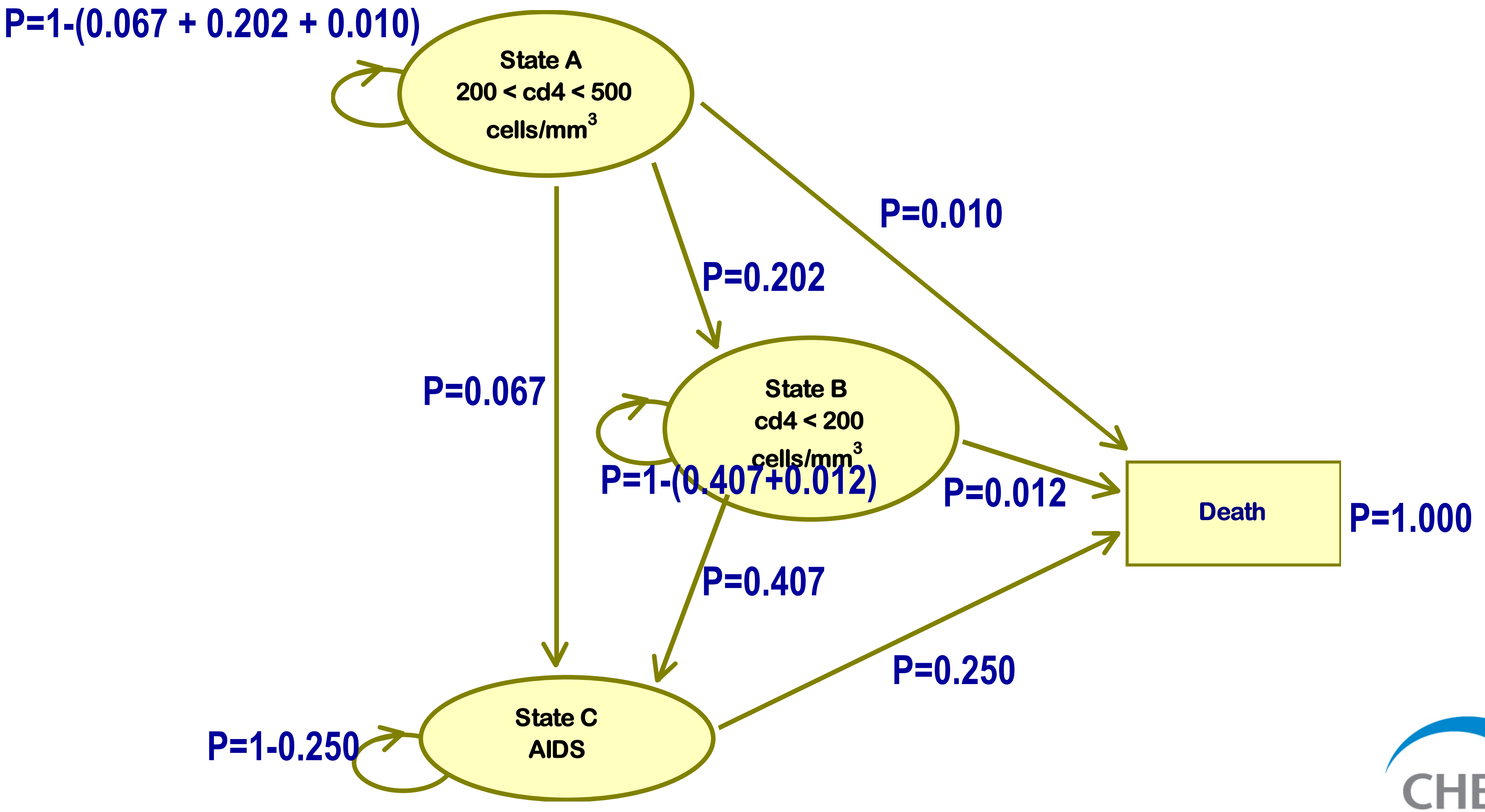
- Decision maker wants to assess the cost-effectiveness of a new drug (lamivudine) in combination with standard therapy vs. standard therapy alone for HIV infection



Source: A Briggs, M Sculpher, K Claxton. Decision Modelling for Health Economic Evaluation. OUP 2006

Example: Management of patients with HIV

➢ Baseline transition probabilities per annum (standard therapy)



Source: A Briggs, M Sculpher, K Claxton. Decision Modelling for Health Economic Evaluation. OUP 2006

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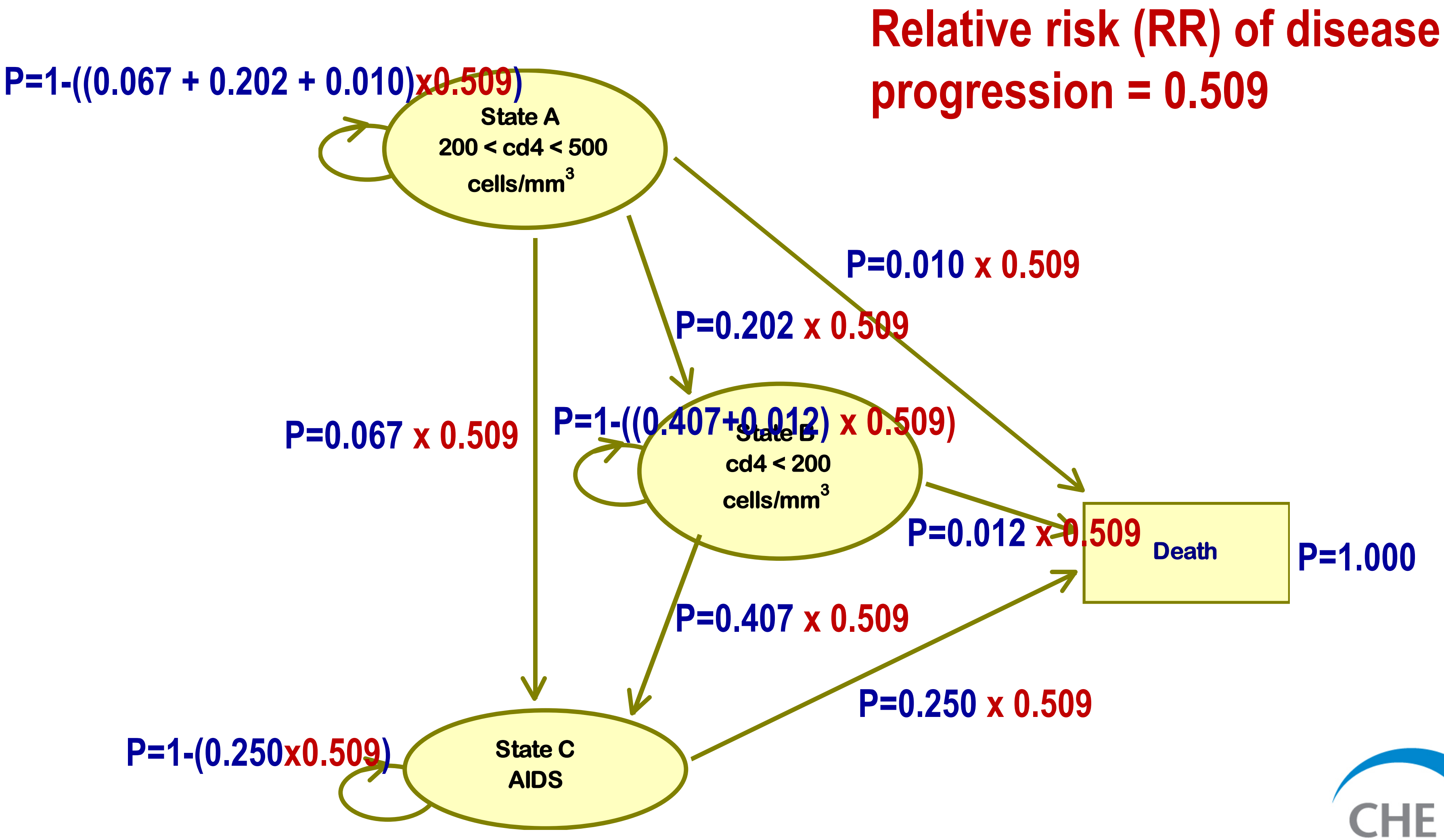
Example: Management of patients with HIV

- Transition probabilities per annum with treatment



Source: A Briggs, M Sculpher, K Claxton. Decision Modelling for Health Economic Evaluation. OUP 2006

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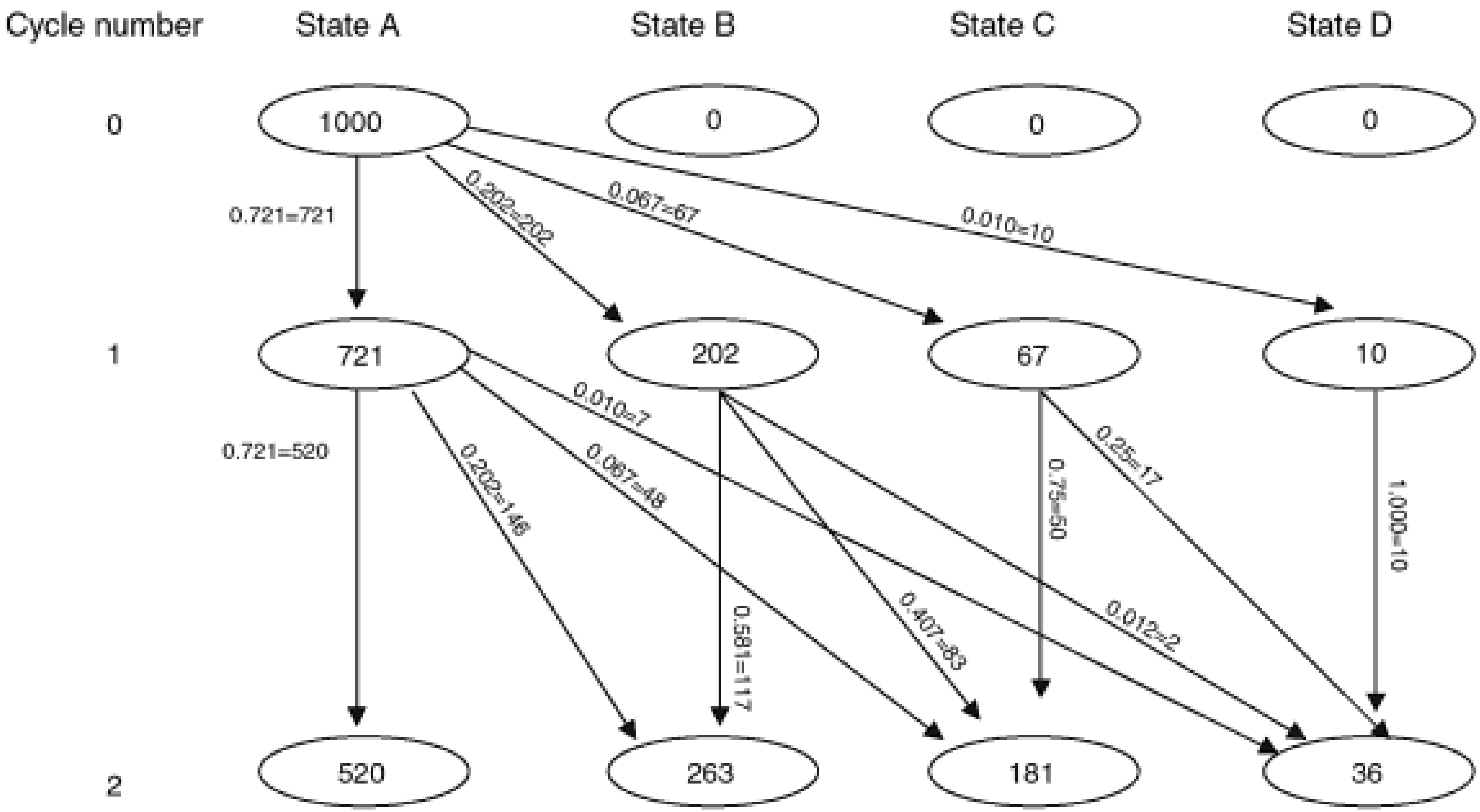
Markov trace – movement of patients between states

One for each alternative treatment option being compared



Source: A Briggs, M Sculpher, K Claxton. Decision Modelling for Health Economic Evaluation. OUP 2006

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Cohort simulation

- Simulate cohort of patients progression through model
- Probabilities determine spread of cohort over states in each cycle
- Size of cohort irrelevant

Cycle	Proportion of cohort in each state				Life years	
(year)	A	B	C	D	Die at start	Die in middle
0	1000					
1	721	202	67	10	0.990	0.995
2	520	263	181	36	0.964	0.977
3	376	258	277	89	0.911	0.937
4	271	226	338	165	0.835*	0.873
5	195	186	364	255	0.745	0.790
6	141	147	361	350	0.650	0.697
7	102	114	341	444	0.556	0.603†
8	73	87	309	531	0.469	0.513
9	53	65	272	610	0.390	0.429
10	38	49	234	679	0.321	0.355

Source: A Briggs, M Sculpher, K Claxton. Decision Modelling for Health Economic Evaluation. OUP 2006

Total costs

Standard therapy

Cycle	State A	State B	State C	State D	Costs Undiscounted	Costs Discounted
0	1000	0	0	0		
1	721	202	67	10	£5,462,269	£5,153,084
2	520	263	181	36	£6,058,692	£5,392,214
3	375	258	277	90	£6,391,940	£5,366,796
4	270	226	338	166	£6,378,070	£5,052,029
5	195	186	363	256	£6,071,973	£4,537,331
6	140	147	361	351	£5,567,917	£3,925,161
7	101	114	340	445	£4,956,362	£3,296,264
8	73	87	308	532	£4,308,646	£2,703,298
9	53	65	271	611	£3,674,533	£2,174,950
10	38	48	234	680	£3,085,021	£1,722,660
11	27	36	197	739	£2,556,689	£1,346,832
12	20	26	164	789	£2,095,933	£1,041,615
13	14	19	135	831	£1,702,487	£798,192
14	10	14	110	865	£1,372,086	£606,875
15	7	10	89	893	£1,098,360	£458,307
16	5	7	72	916	£874,105	£344,088
17	4	5	57	934	£692,086	£257,016
18	3	4	45	948	£545,512	£191,117
19	2	3	36	959	£428,276	£141,551
20	1	2	28	968	£335,051	£104,470
					£63,656	£44,614

State	Cost
A	£5,034
B	£5,330
C	£11,285
D	£0

(721 x 5034) + (202 x 5330) +(67 x 11285)

Total costs for standard therapy = Sum of costs in cycles/1000

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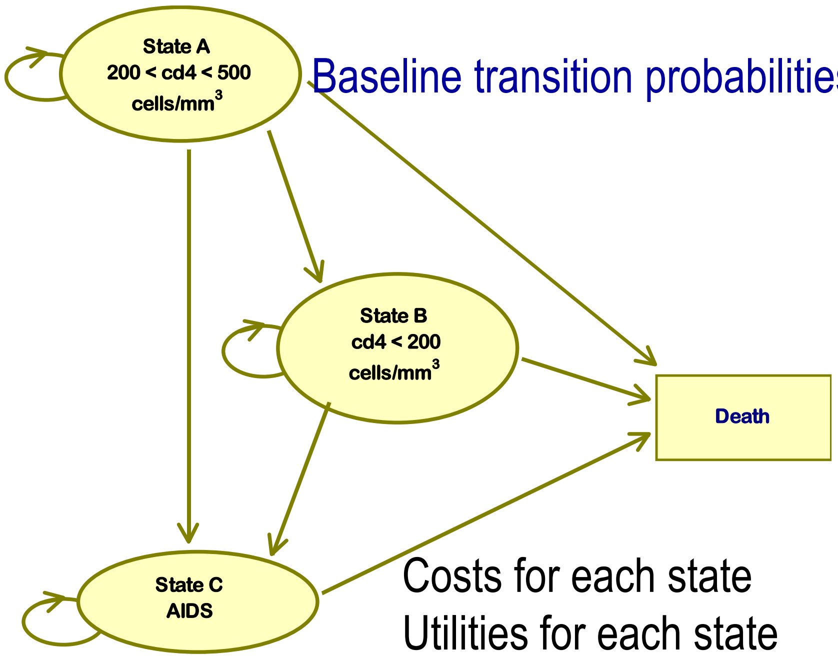
Comparative analysis

Standard therapy

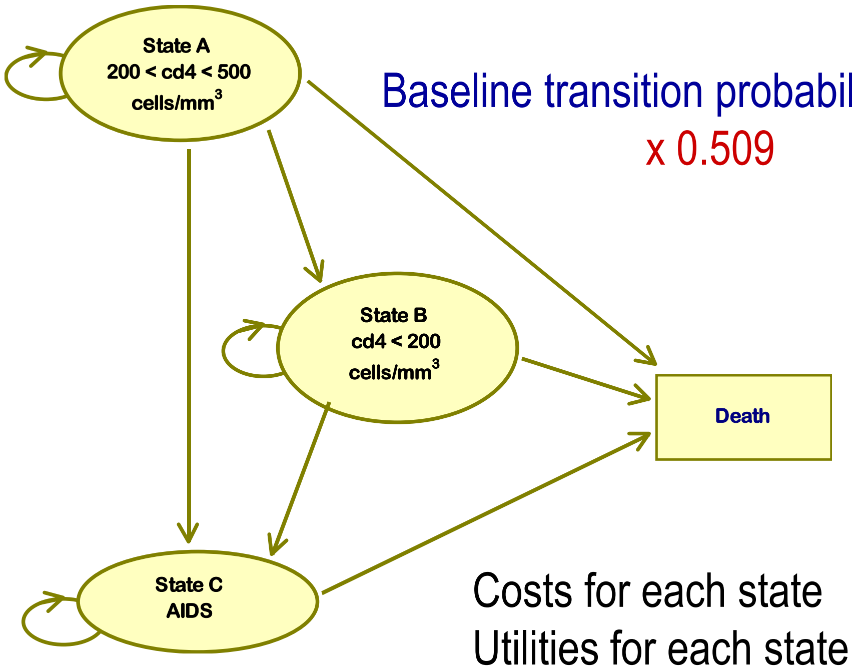


Baseline transition probabilities

Costs for each state
Utilities for each state

Total discounted costs
Total discounted QALYs

New drug therapy



Baseline transition probabilities
x 0.509

Costs for each state
Utilities for each state

Total discounted costs
Total discounted QALYs

$$\text{Incremental cost-effectiveness ratio} = \frac{\text{Costs new therapy} - \text{Costs standard}}{\text{QALYs new therapy} - \text{QALYs standard}}$$

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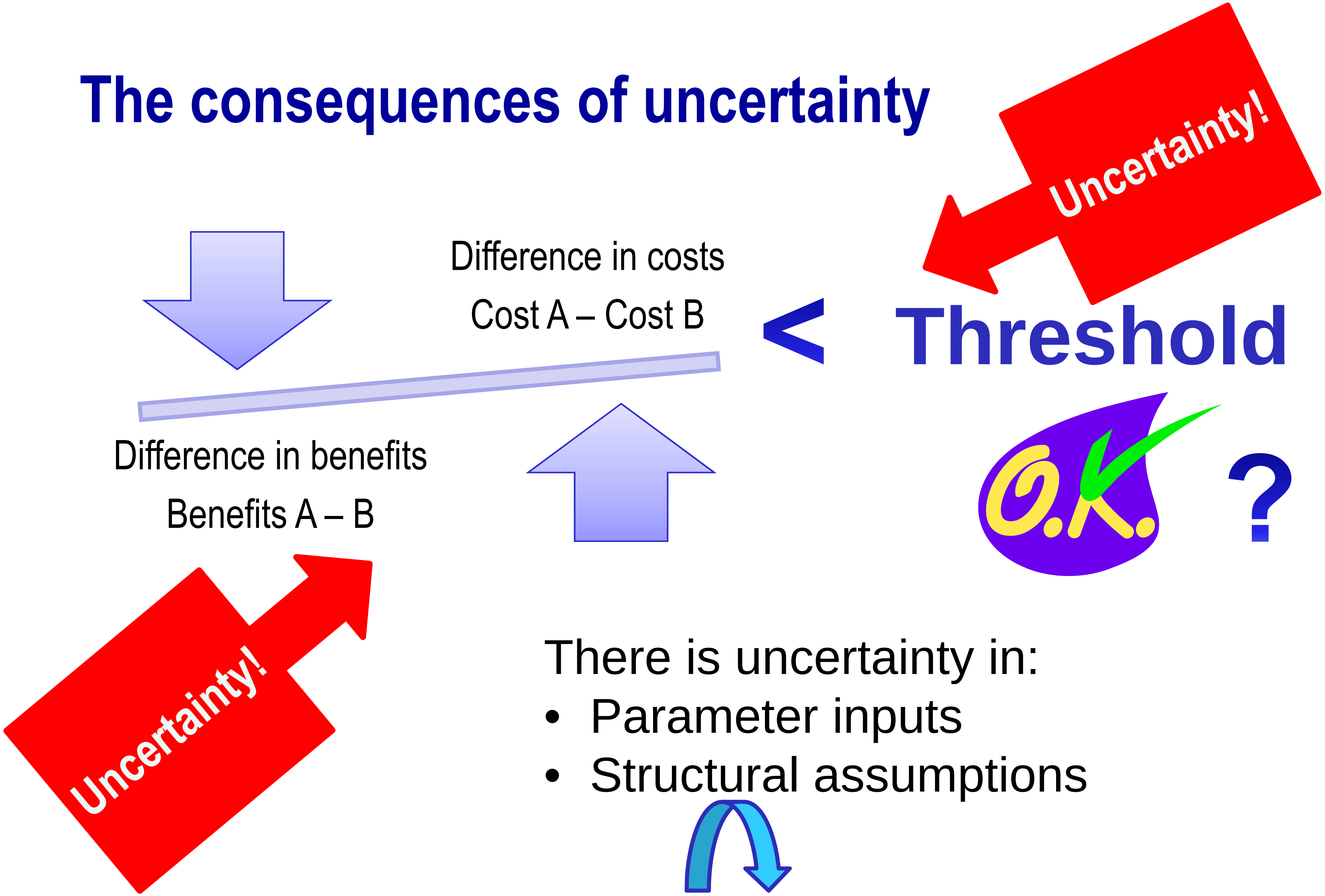
The consequences of uncertainty



There is uncertainty in:

- Parameter inputs
- Structural assumptions

Uncertainty in the costs and benefits

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What is uncertain?

- Different possible values or outcomes for the parameters
- Lack of knowledge about the parameter values
- Different outcomes in different populations
- Structural uncertainty
- Distinguish between
  - Uncertainty, variability, heterogeneity
  - Uncertain values and policy choices

Why uncertainty matters?

- Decisions should not be based on little or poor quality evidence
- There will always be a chance that the wrong adoption decision is made resulting in health benefit and resources forgone

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Addressing parameter uncertainty

- Deterministic sensitivity analysis
  - One-way
  - Multi-way
  - Extreme
  - Threshold
- Probabilistic sensitivity analysis
  - Assigning distributions
  - Monte Carlo simulation

(Probabilistic sensitivity analysis) ‘enables the uncertainty associated with parameters to be simultaneously reflected in the results of the model. In non-linear decision models, probabilistic methods provide the best estimates of mean costs and outcomes’. NICE guidance 2008

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1st order uncertainty: variability between patients

- 1st order uncertainty
  - distribution of outcomes in population
  - ≈ sample variance
  - reflected in standard deviations associated in a mean value
- To incorporate in CEA
  - simulate pathway of individual patients through model, recording 'history' of patients
  - large number of patients required to estimate mean and *standard deviation*
- Not the main focus of CEA
  - Decision must be made for population as a whole
  - Cannot be reduced with further research
- Computationally time consuming when combined with probabilistic sensitivity analysis

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2nd order uncertainty: uncertainty in mean parameter values

- 2nd order uncertainty
  - distribution of sample mean outcomes
  - ≈ variance of sample mean
  - reflected in standard error of mean
- To incorporate in CEA
  - cohorts of patients progress through model
  - large number of cohorts entered into models to estimate mean and standard error
- Focus of CEA
  - parameter uncertainty
  - Informs questions about likelihood of making wrong decision, likelihood of new information causing optimal decision to change

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Heterogeneity

- Heterogeneity
  - 'Baseline' characteristics 'explain' a proportion of overall variability between patients (e.g. age, sex)
  - Generate mean parameter values per sub-group population
  - Variability *within* sub-group will remain
- Model analysis:
  - Need to be able to present results by sub-group (defined by patient characteristics)

Policy choices and structural uncertainty

- Policy choices, value judgements
  - E.g. different possible values for discount rates
  - Values relevant for particular decision
    - NICE specifies 3.5% for costs and health outcomes
    - Sensitivity analysis of 1.5% per annum
- Structural uncertainty
  - Different possible model structures
  - If present results for each structure decision maker can select most appropriate
    - 'Scenario analysis'
  - OR can formally estimate pooled model results, e.g. weighting by likelihood of each model

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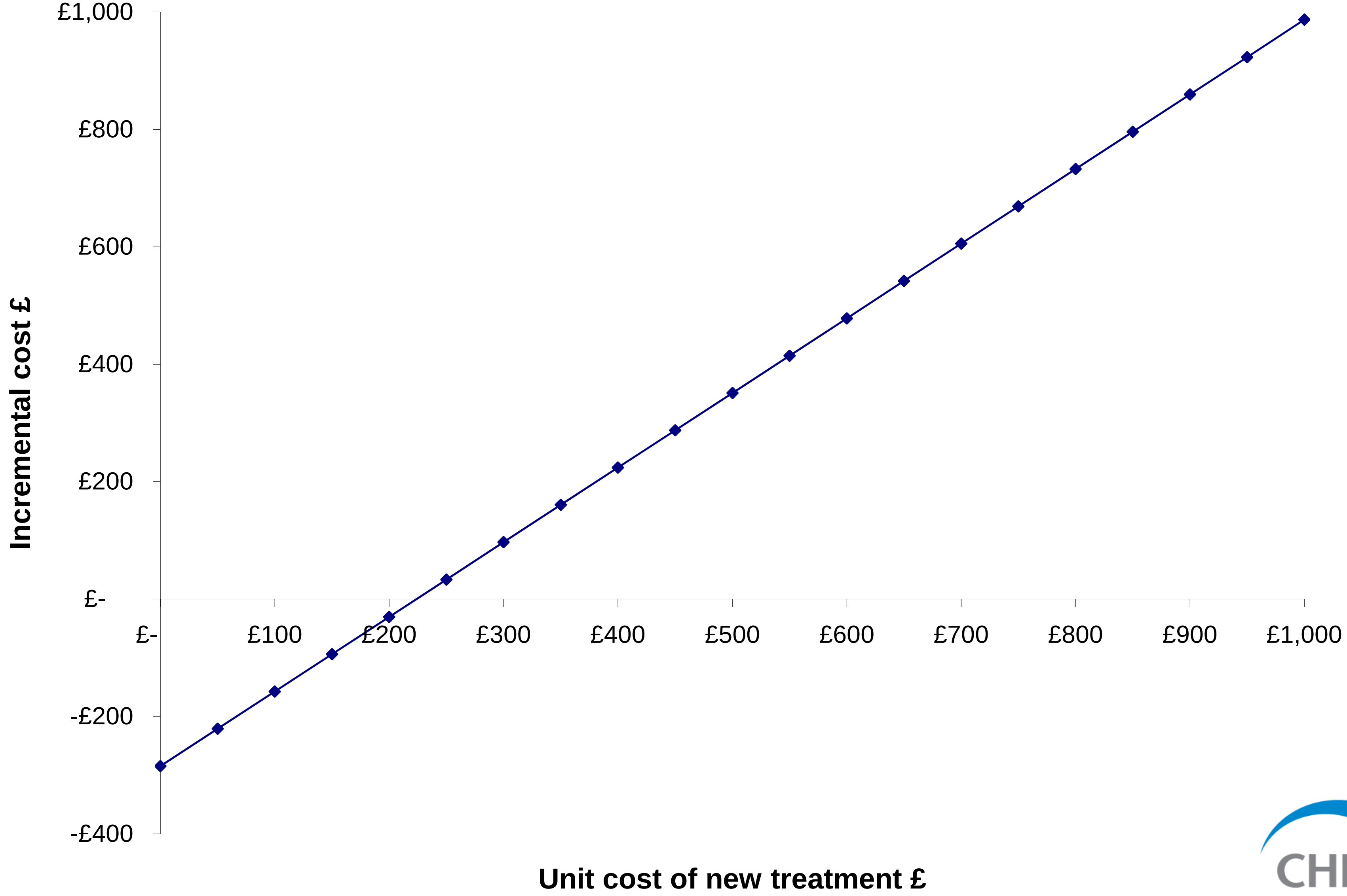
Types of uncertainty - Summary

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	

One-way sensitivity analysis



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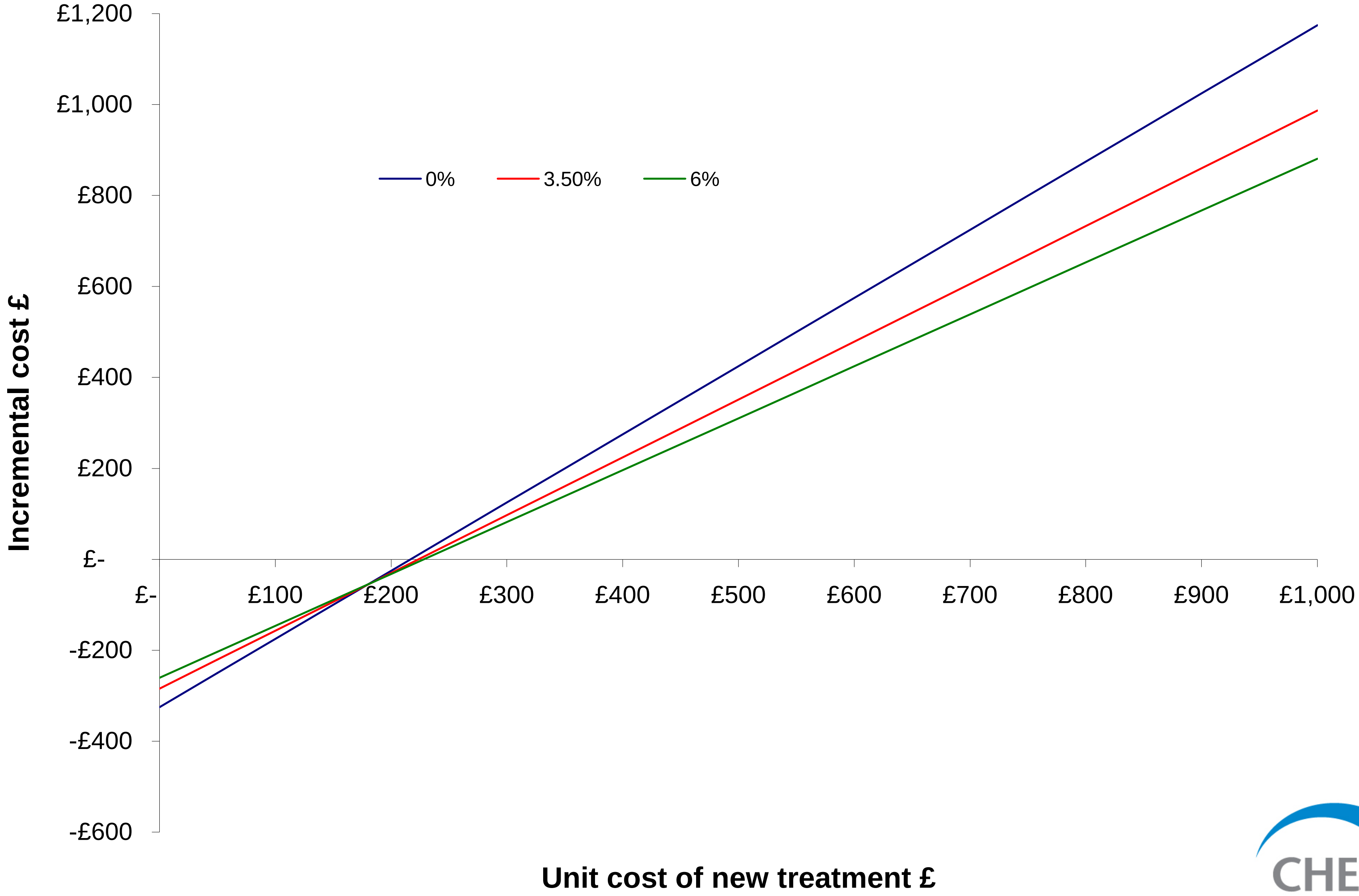
Two-way sensitivity analysis



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Role of deterministic sensitivity analysis

- Useful for exploring alternative policy choices
- Useful for identifying which parameters might have an impact on model results and hence are worth exploring further
- However 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 becomes very difficult to present and interpret results

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Probabilistic sensitivity analysis (PSA): Stages

- Assigning distributions to represent uncertainty
  - Estimates of probabilities, utilities and costs are replaced with specified probability distributions
- Propagating uncertainty
  - Model evaluated many times (>1,000)
  - Randomly select value from each distribution
- Reporting results
  - Distribution of outcomes for each strategy
  - Confidence intervals for the expected outcome
  - Probability that a particular intervention is optimal

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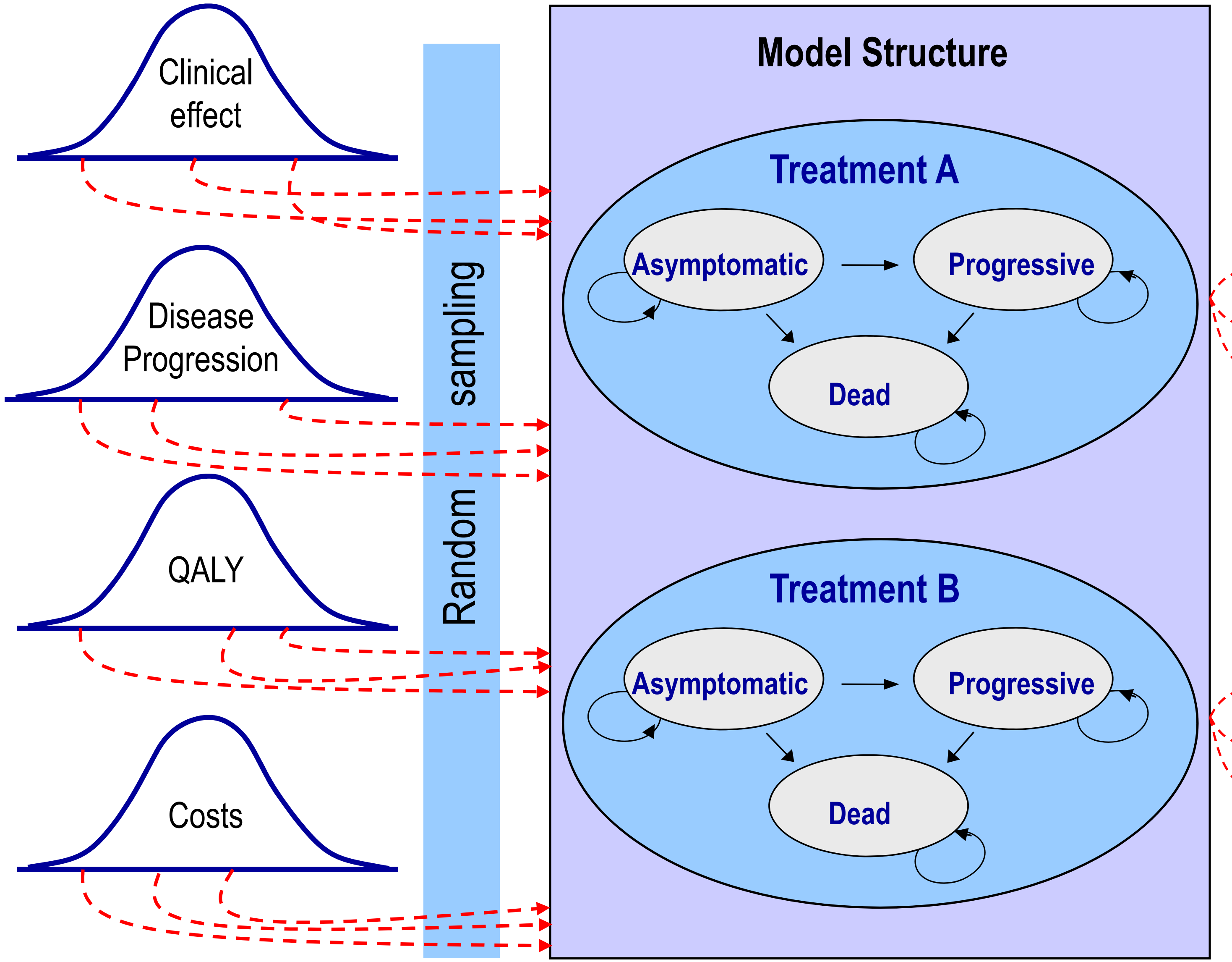
Probabilistic sensitivity analysis: illustration



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**

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

Is the ICER less than the cost-effectiveness threshold?

£10,000 per QALY < £20,000 per QALY

→ Treatment B is cost-effective

Is the net health effect (NHE) positive?

NHE= QALYs gained – (additional costs/threshold)

= 2 – (£20,000/£20,000)

= 1 QALY > 0

→ Treatment B is cost-effective

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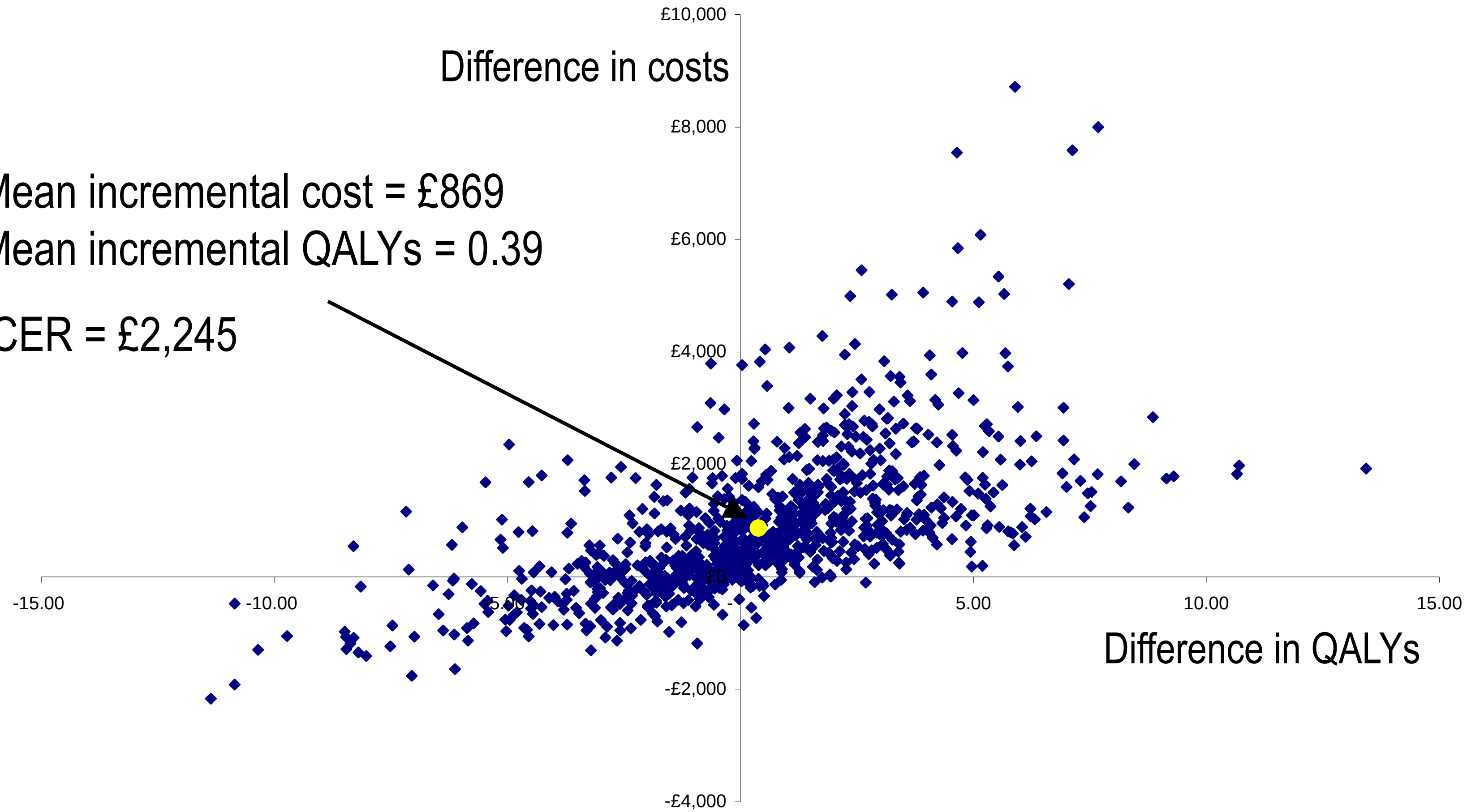
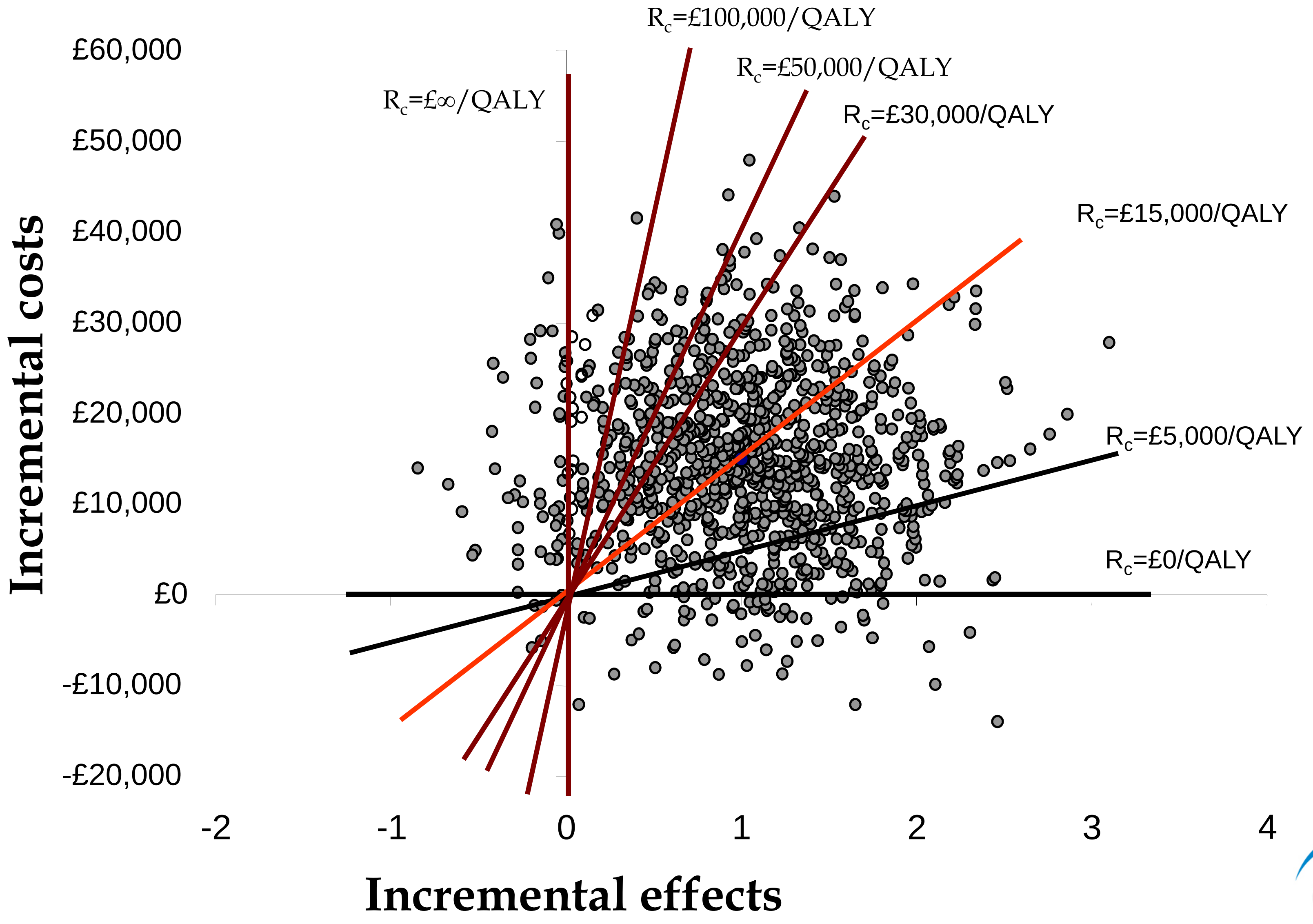
Cost-effectiveness place

Mean incremental cost = £869
Mean incremental QALYs = 0.39

ICER = £2,245



Building the cost-effectiveness acceptability curve



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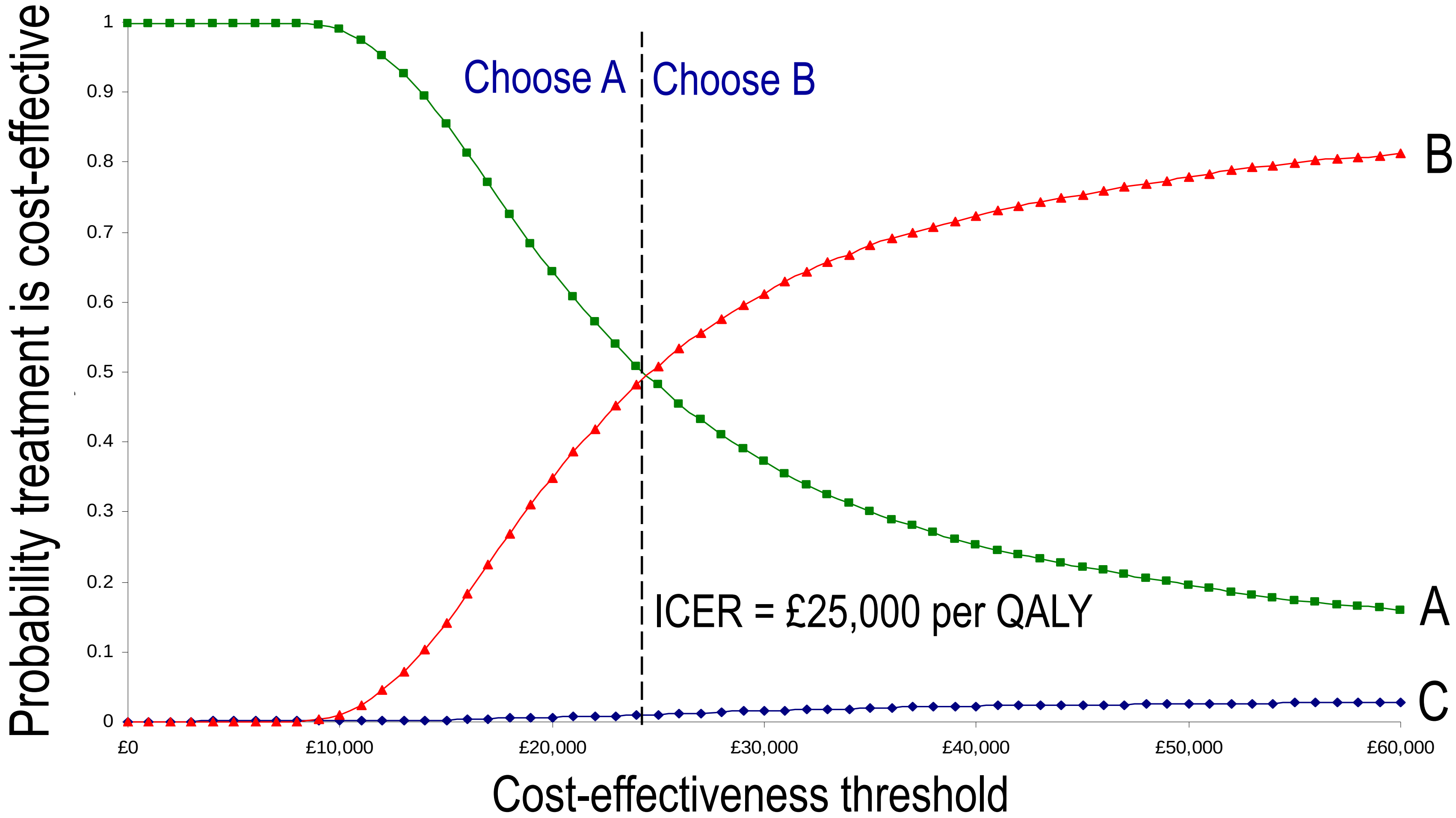
Cost-effectiveness acceptability curve (CEAC)

- 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



Structural uncertainty and scenario analysis

- Scenario analysis can be used to evaluate the impact of using alternative structural assumptions in model

- Bayesian model averaging is a method for accounting for structural uncertainty in the model outputs by evaluating a weighted combination of alternate model structures with weights assigned to the different potential model structures based on the relative likelihood of each

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In summary

- Decisions are unavoidable
- A good decision model:
  - Synthesises all relevant evidence
  - Extrapolates costs and outcomes over the appropriate time horizon
  - Incorporates uncertainty in the parameter inputs
  - Explores uncertainty in its structural assumptions
  - Indicates if and where more research is needed

Key reading references

- Briggs A, Sculpher M. An introduction to Markov modelling for economic evaluation. *Pharmacoeconomics* (1998) 13: 397-409.

- Briggs, A., Claxton K., Sculpher, M.J. (2006). Decision modelling for health economic evaluation. Oxford University Press

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- Siebert U, Alagoz O, Bayoumi A, Jahn B, Owens D, Cohen D, Kuntz K. “State-transition modelling: A report of the ISPOR-SMDM Modelling Good Research Practices Task Force-3 ”, *Med Decis Making* (2012) 32:690-700.

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