Online Advanced Methods for Cost-Effectiveness Analysis

Presentation 5: Working with Individual Patient Data
5.1: Overview and objectives

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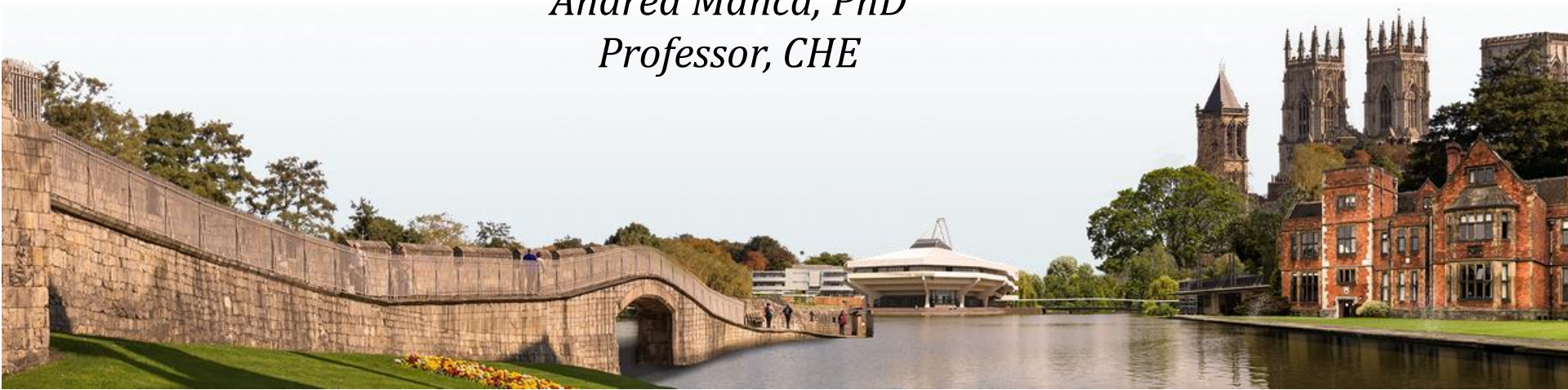
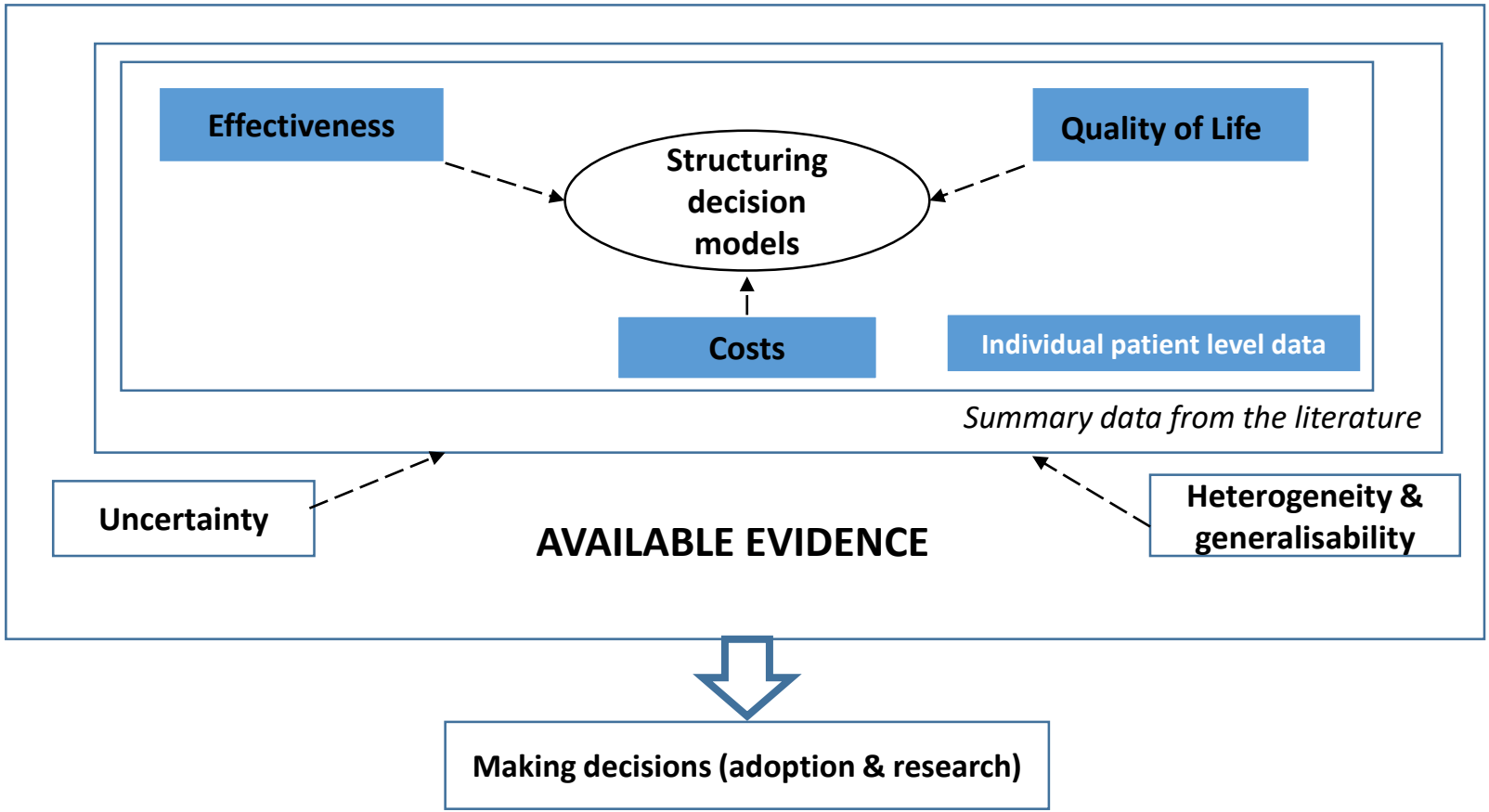


Course structure – where are we up to?



Overview

- Individual patient-level data (IPD) are a key resource to inform HTA decision making
  - Modelling versus IPD: a false dichotomy
  - Policy makers information needs determine type of data and analyses required to inform their decisions

- Some jurisdictions require CEA results obtained from analyses of IPD

Objectives

- Appreciate the importance of using individual patient-level data for CEA
  - Here the focus is on RCT-based CEA

- We will learn how to
  - estimate the key quantities of interest in CEA
  - use these quantities to represent the results of a CEA
  - interpret the graphs typically produced as part of these analyses

- Appreciate the complexities, challenges and (some very simple) approaches in the analysis of IPD for CEA

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Presentation 5: Working with Individual Patient Data

5.2: Know your data and learn how to analyse them

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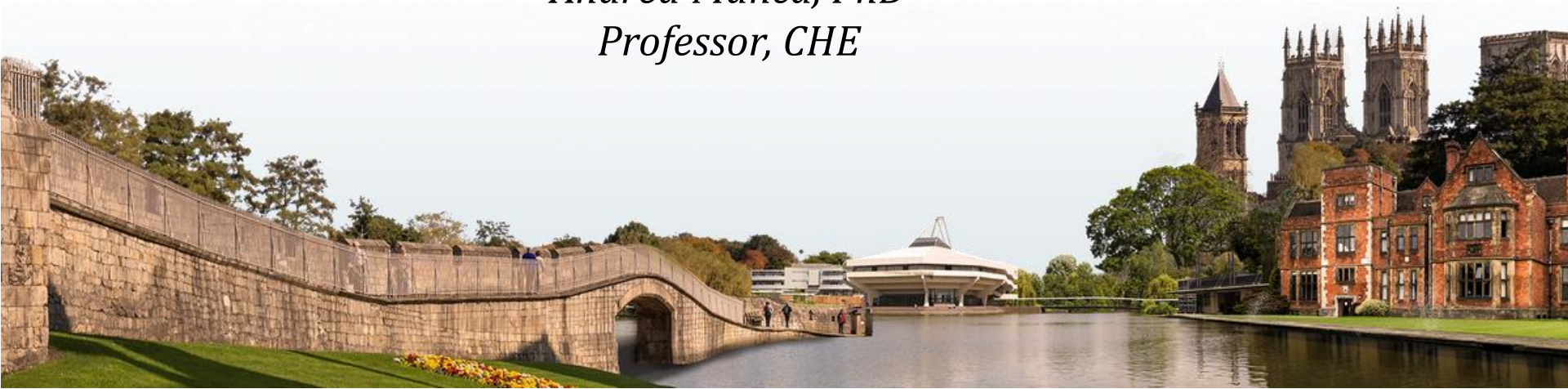


Objectives

- Learn (how) to
  - recognise the idiosyncrasies of the key outcomes in CEA and why we can't just use statistical methods based on the Normal distribution assumption
  - analyse individual patient level costs and QALYs data (in a very simple way)

Context

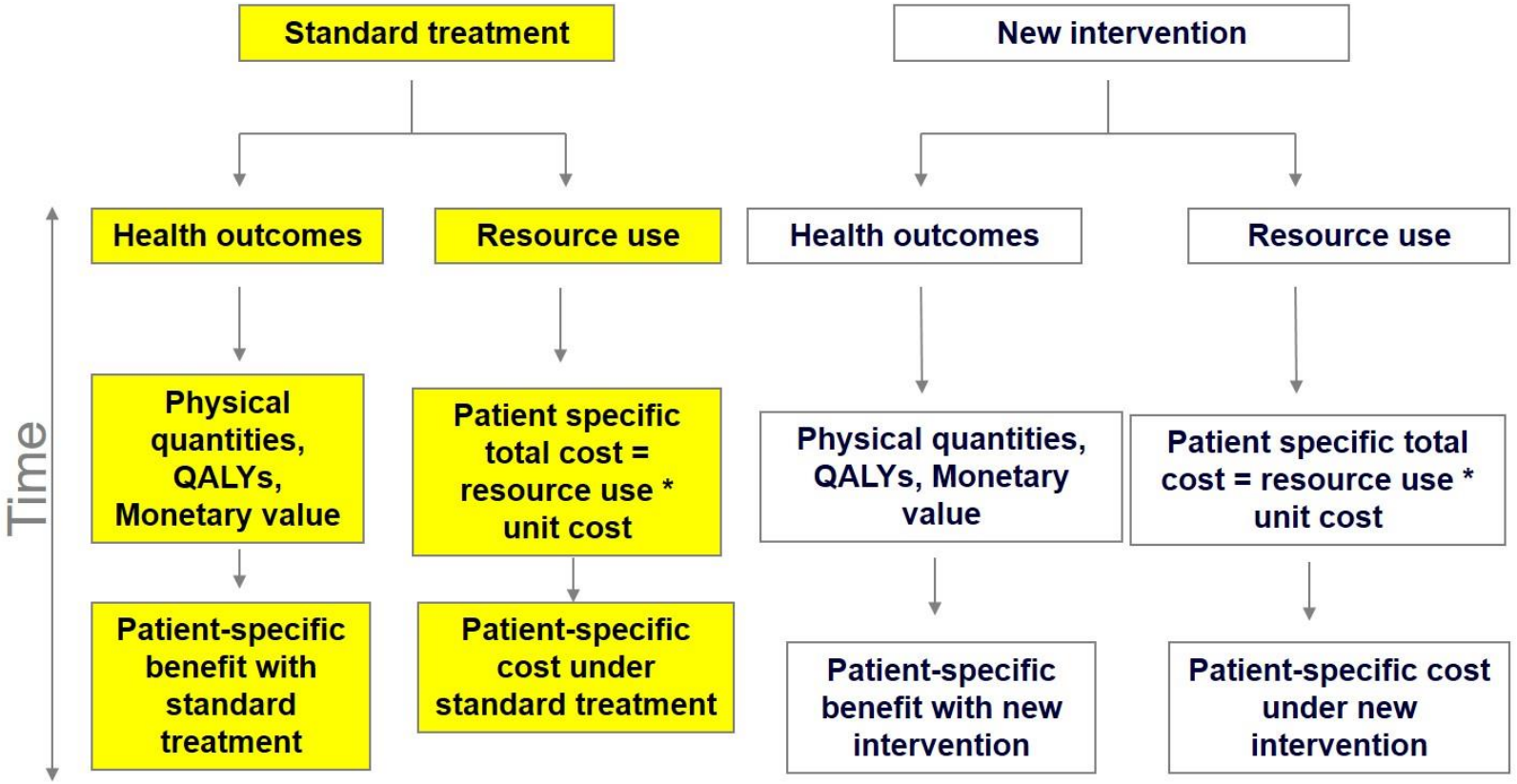
- Increasing need evidence synthesis and decision analysis
  - RCTs continue to be a key a key source of evidence
  - Decisions occasionally made on the basis of evidence from a single RCT

- We have looked at the role of models in HTA decision making in lecture 1.4

- A few jurisdictions continue to prefer economic evidence derived from RCT studies

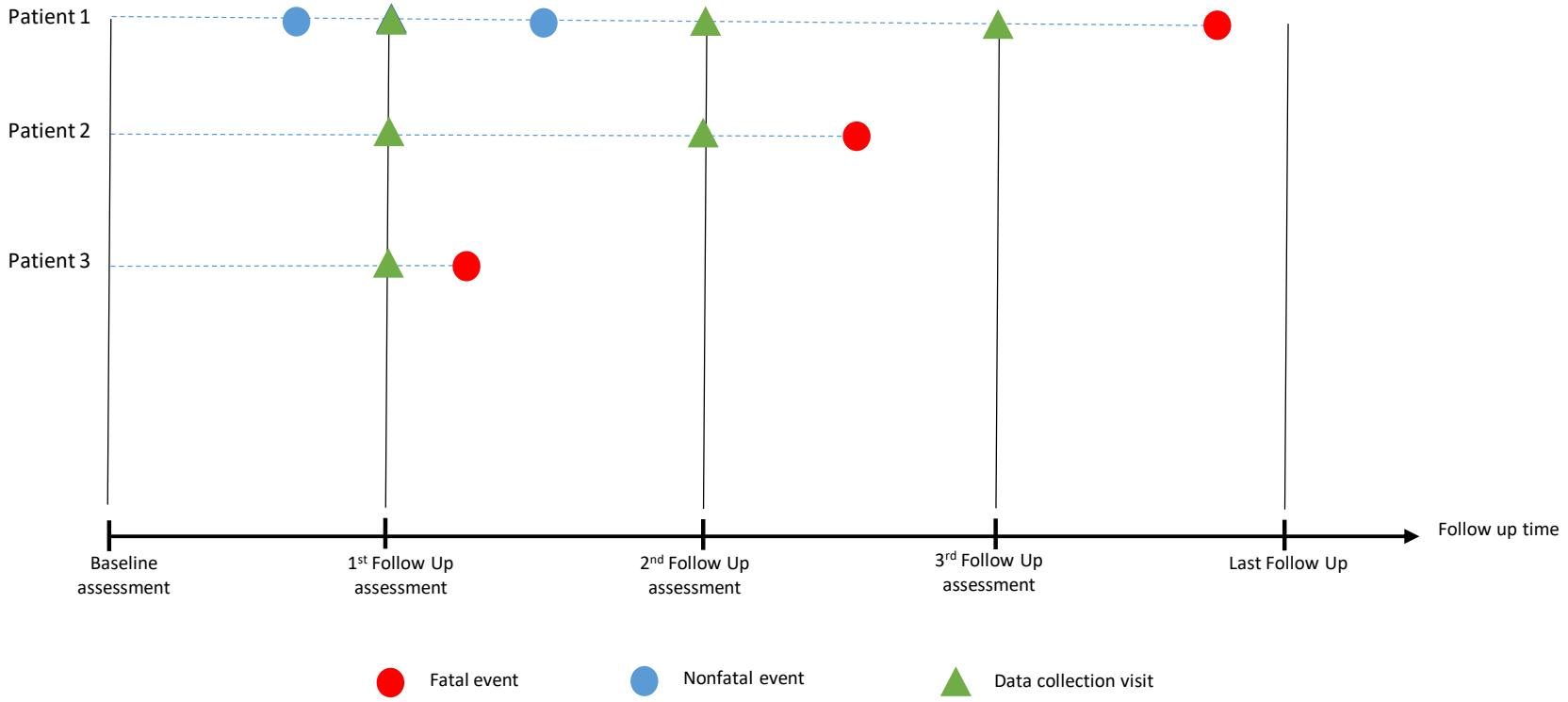
- Important to ensure appropriate analysis of RCT-based economic data, even if such data need to be synthesised with other evidence

Structure of a RCT-based CEA



Patient's history and data accrual

(simple case with no censoring)



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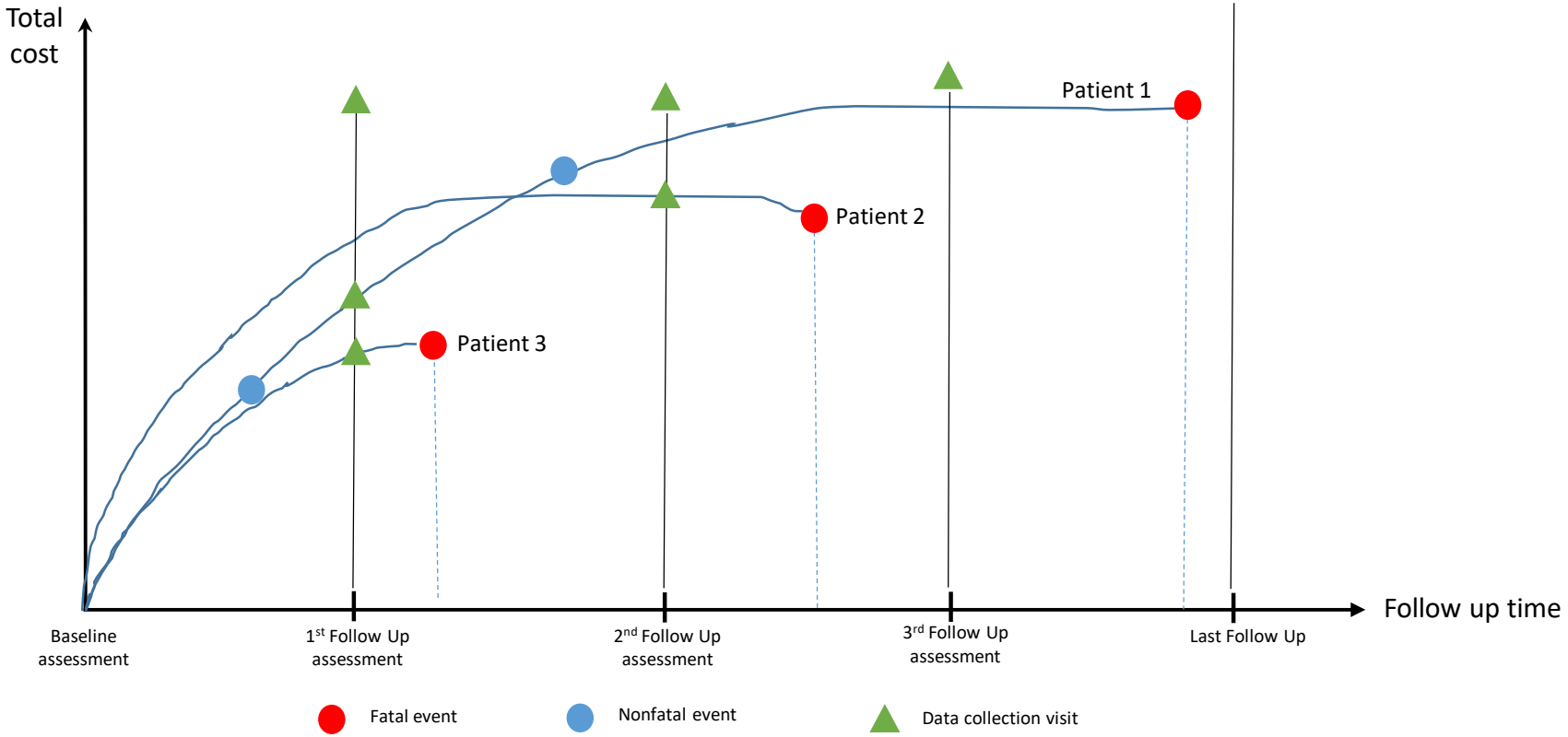

Patient's history and data accrual

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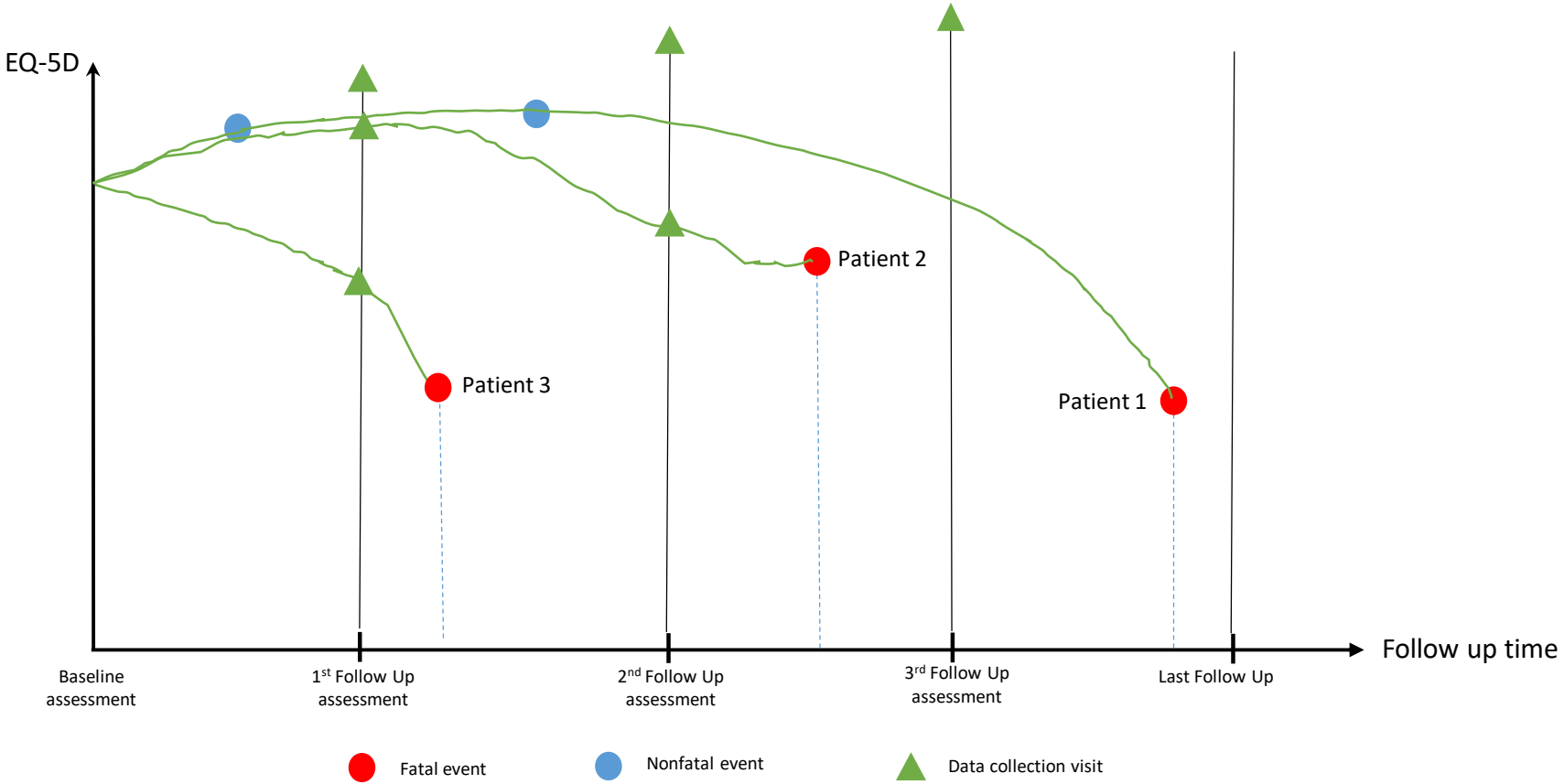


Sample dataset

id	group	Follow up visit	EQ-5D	GP visits	Out-patient visits	In-patient LOS (days)	Medication use (mg)	Dead
1	0	0	0.80	NA	NA	NA	NA	0
1	0	1	0.85	2	1	0	180	0
1	0	2	0.87	3	1	2	180	0
1	0	3	0.54	0	3	20	340	0
1	0	4	-	-	-	-	-	1
2	1	0	0.80	NA	NA	NA	NA	0
2	1	1	0.83	2	1	3	160	0
2	1	2	0.60	4	1	15	180	0
2	1	3	-	-	-	-	-	1
2	0	4	-	-	-	-	-	1

Can you try and add the rows for patient 3?

Data structure

Two independent groups

Control

Patient	(Cost, Effect)
1	C_c^1, E_c^1
2	C_c^2, E_c^2
3	C_c^3, E_c^3
.	
.	
n_c	C_c^n, E_c^n

Intervention

Patient	(Cost, Effect)
1	C_n^1, E_n^1
2	C_n^2, E_n^2
3	C_n^3, E_n^3
.	
.	
n_n	C_n^n, E_n^n

Focus of the analysis

- The interest rests on appropriate quantification
  - mean costs and effects
  - measures of sample uncertainty

- Mean costs are of direct relevance to decision makers for policy making
  - (Mean cost x Number of individuals to be treated) = Total Cost

- Other measures of central tendency are unhelpful
  - Because costs are right skewed the median can be misleading
  - ➔ median < arithmetic mean ➔
    (Median cost x Number of individuals to be treated) < Total Cost
  - Same applies to health outcomes (EQ-5D and QALYs usually left skewed)

Idiosyncrasies of cost data

(issues apply also to QALYs)

- Problems with standard statistical methods of estimation
  - many statistical estimation methods rely on normality
  - problematic to work directly on costs scale
- Reasons why cost data are right skewed
    - large proportion of patients with similar resource use
    - few patients with large resource use
    - presence of zero costs
- Some suggested solutions for statistical inference
  - non parametric tests
  - log transformed cost data and use of back-transformation
  - use non-parametric bootstrap
  - recent return to parametric methods (needed for extrapolation)

Source: Briggs A and Gray A (1999)

Case Study

EVALUATE Trial

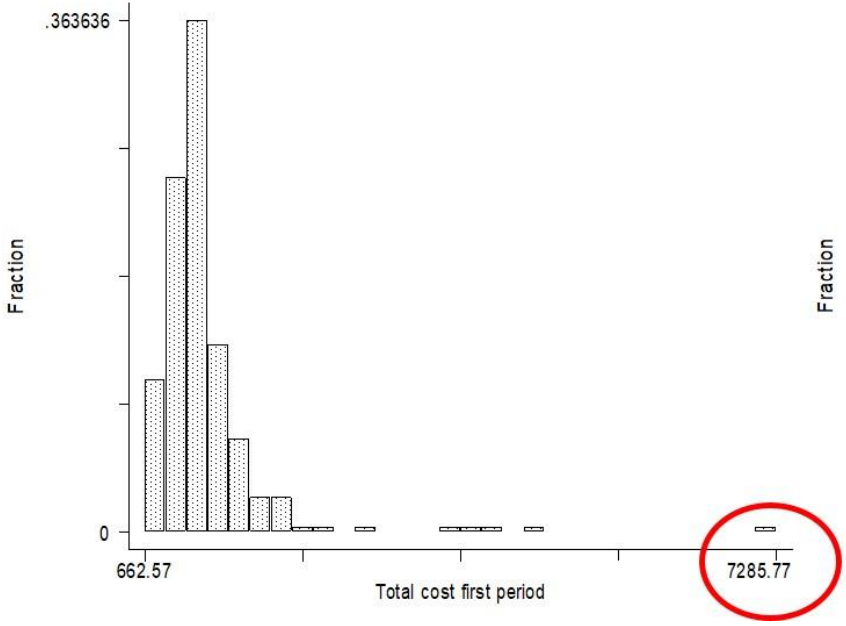
- Multi centre RCT comparing laparoscopic-assisted *versus* standard (abdominal or vaginal) hysterectomy
- Total of 859 patients in 30 centres (25 from England)
- Median follow-up: 12 months
- Follow up: baseline, 6-week, 4 and 12 months
- CEA from UK NHS perspective
- Health outcomes in terms of QALYs

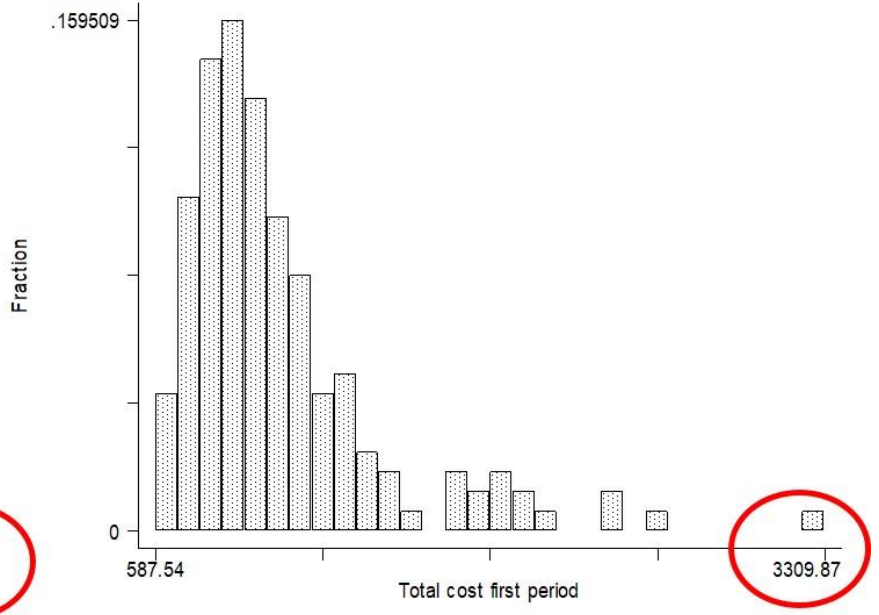
Source: Sculpher MJ, Manca A, *et al.* (2004)

Analysis of cost data

EVALUATE trial

	Abdominal	Laparoscopic
Cost (6 weeks)		
mean (SD)	1,286 (611)	1,561 (1,107)
median	1,167	1,290
range	(662 – 7,286)	(587 – 3,309)

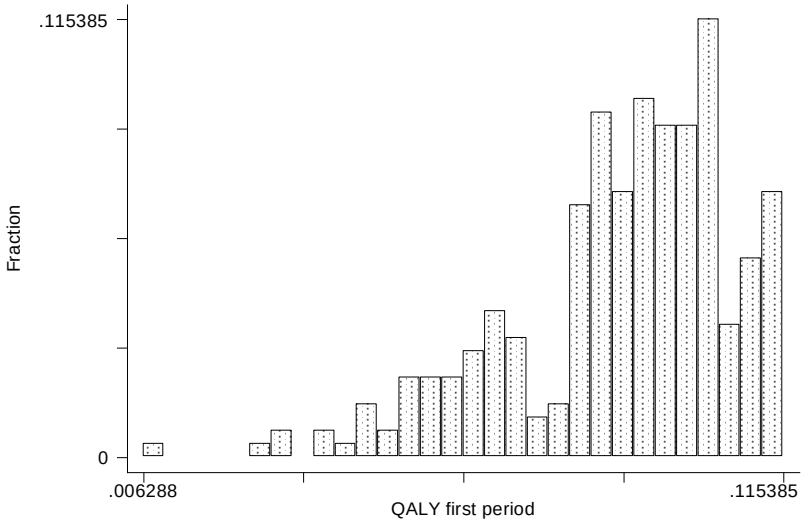


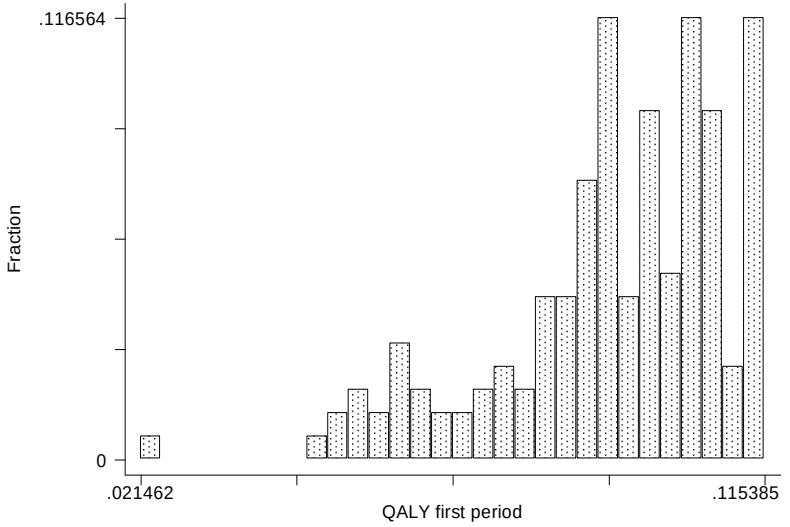


Analysis of effectiveness data

EVALUATE trial

	Abdominal	Laparoscopic
QALYs (6 weeks)		
mean (SD)	0.088 (0.019)	0.090 (0.020)
median	0.09	0.09
range	(0.006 - 0.115)	(0.02 - 0.115)





Quantities of interest

- The analysis of IPD is inherently stochastic; we need to estimate
  - Difference in mean costs: $\overline{\Delta C}$ = ($\overline{C_i}$ - $\overline{C_c}$)
  - Difference in mean QALYs: $\overline{\Delta E}$ = ($\overline{E_i}$ - $\overline{E_c}$)
  - Standard error of the mean costs: $\mathrm{SE}(\overline{\Delta C})$
  - Standard error of the mean costs: $\mathrm{SE}(\overline{\Delta E})$
  - Correlation coefficient between $\overline{\Delta C}$ and $\overline{\Delta E}$

- From which we can derive
  - Mean ICER, mean net benefits
  - 95% confidence intervals for these above quantities

Sampling uncertainty around the ICER

- The ICER is a random variable, just like costs and effects
- Its distribution is unknown, as it is the result of a non-linear combination non-Normal random variables.
- How do we estimate confidence intervals around the ICER?
- Several methods have been proposed

Summary

- Individual patient level data from RCTs can also include costs, quality of life and other outcomes relevant to economic evaluation for HTA

- These data can be analysed using statistical methods that take into consideration the features of these data, to quantify the key parameters that inform HTA decisions

- These parameters are derived from a sample and it is important to quantify both their mean value and sample uncertainty values

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5.3: Deriving the quantities of interest

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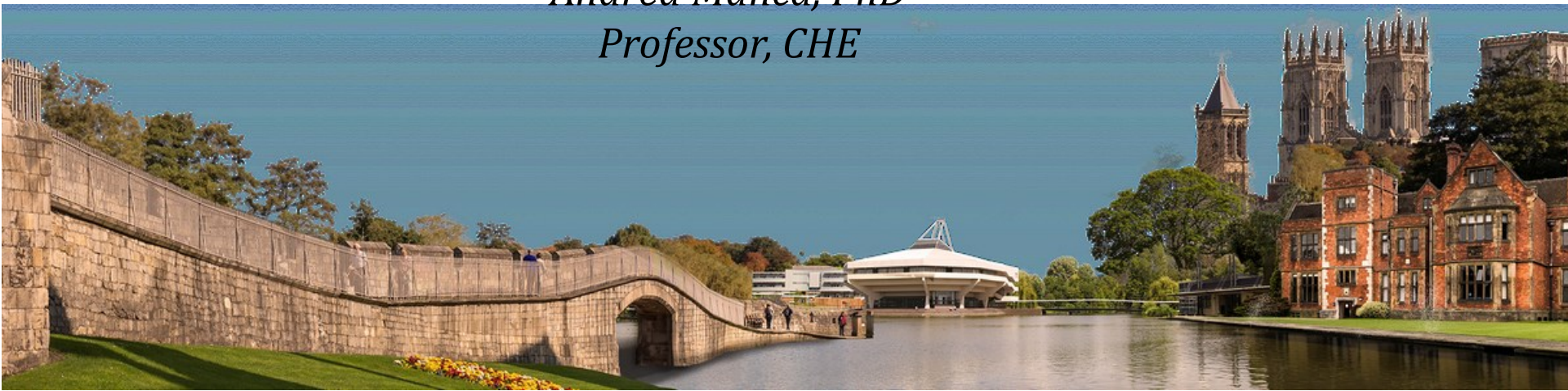


Objectives

- Learn (how) to
  - derive the confidence intervals for $\overline{\Delta C}$ and $\overline{\Delta E}$
  - represent the key information relating to the ICER on the cost-effectiveness plane

The issue is…

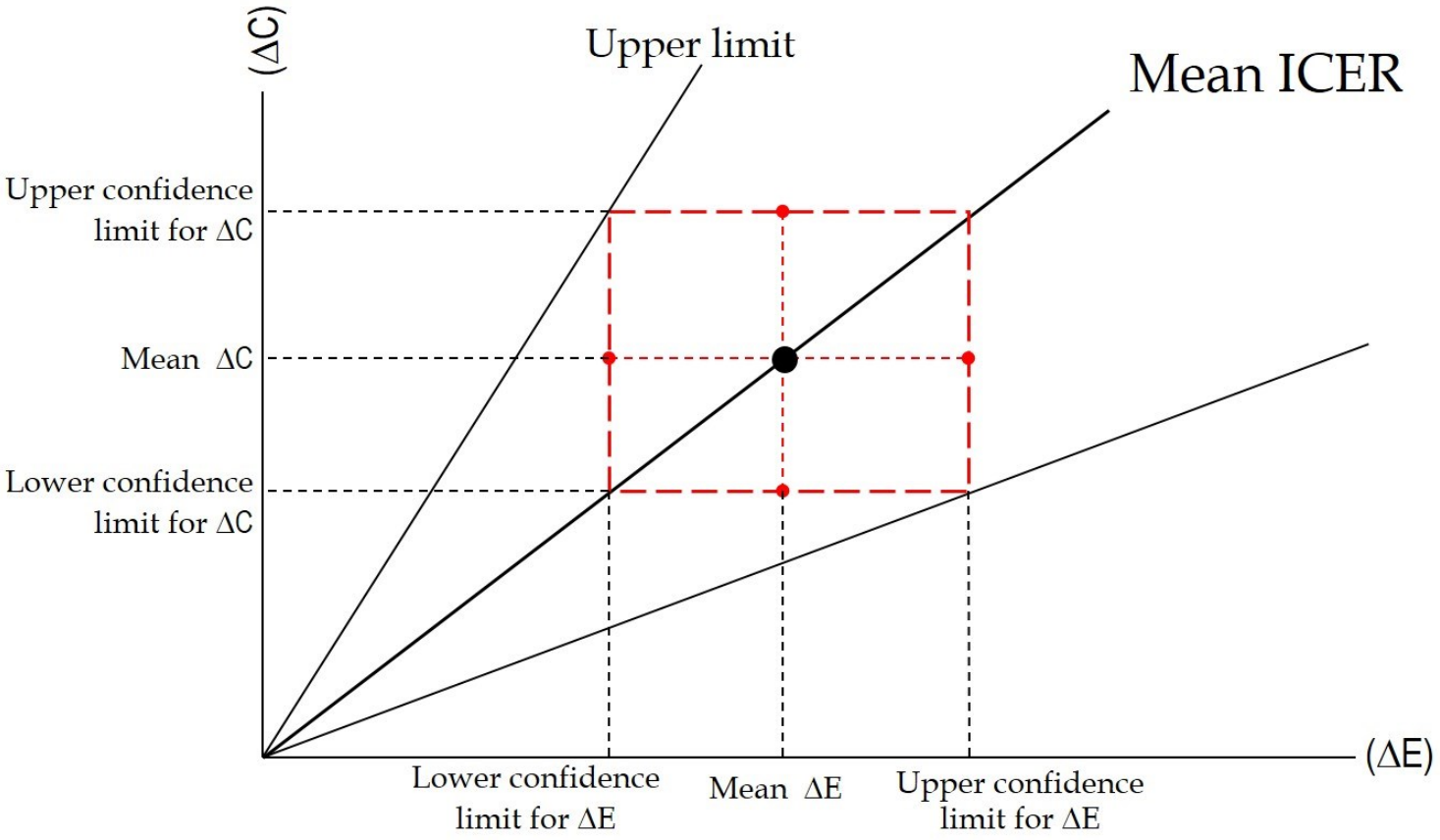
- A and B are two random variables
- We wish to estimate their ratio R=(A/B) together with its 95% CI
- Now, the problem is that
  - If B→0 then R→∞
  - If B→ ∞ then R →0
- Hence the 95% CI could contain infinite values…..an infinite value…doesn't really make much sense here….and it's an artefact of the ratio statistic

Calculating CIs around the ICER

- Suggested approaches include
  - Confidence box ☑
  - Taylor series expansion (or Delta method)
  - Confidence ellipse
  - Angular transformation
  - Fieller's method (parametric method, joint normal)
  - Bootstrap method (non-parametric)

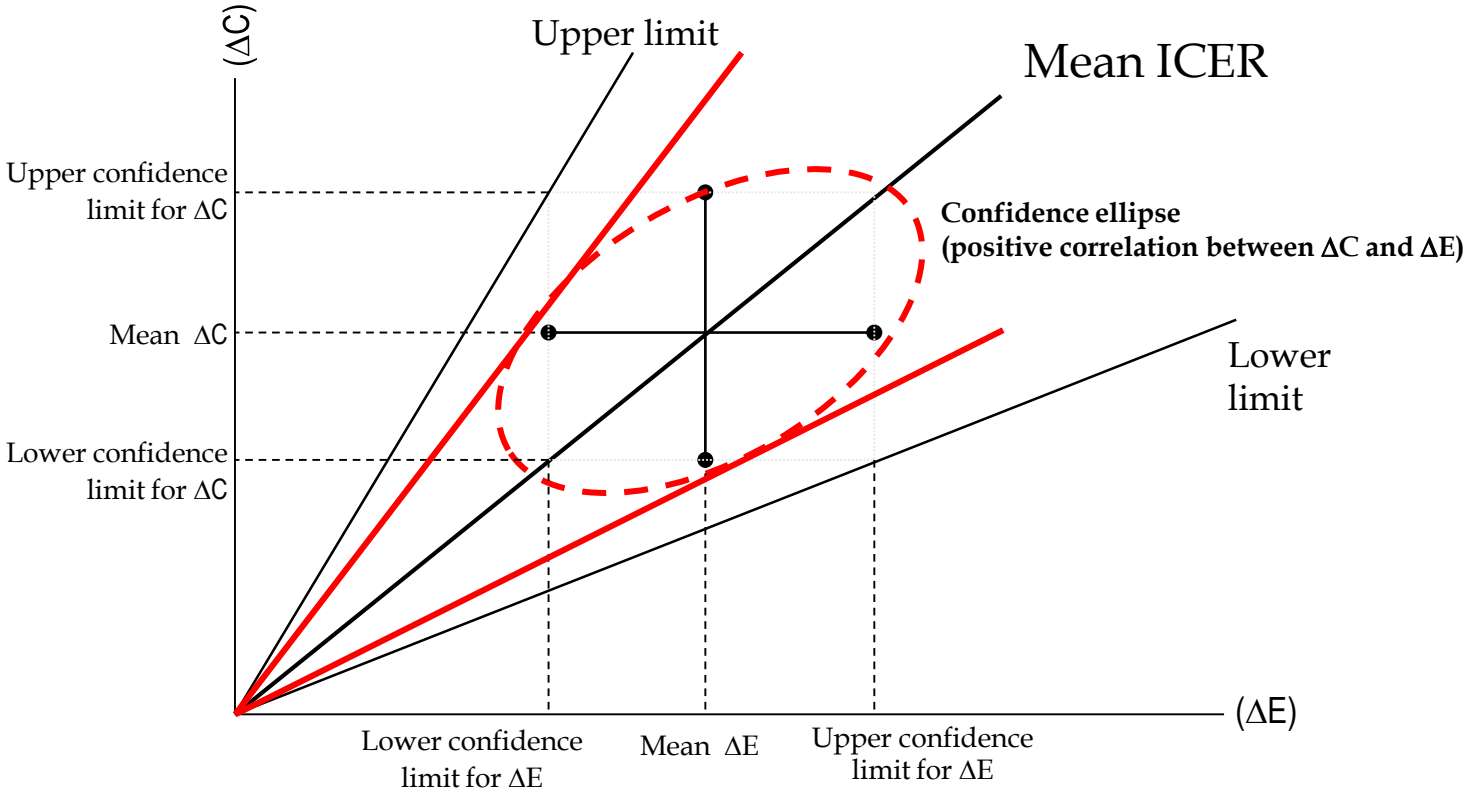
Source: Briggs AH, O'Brien BJ, Blackhouse G (2002)

Confidence box



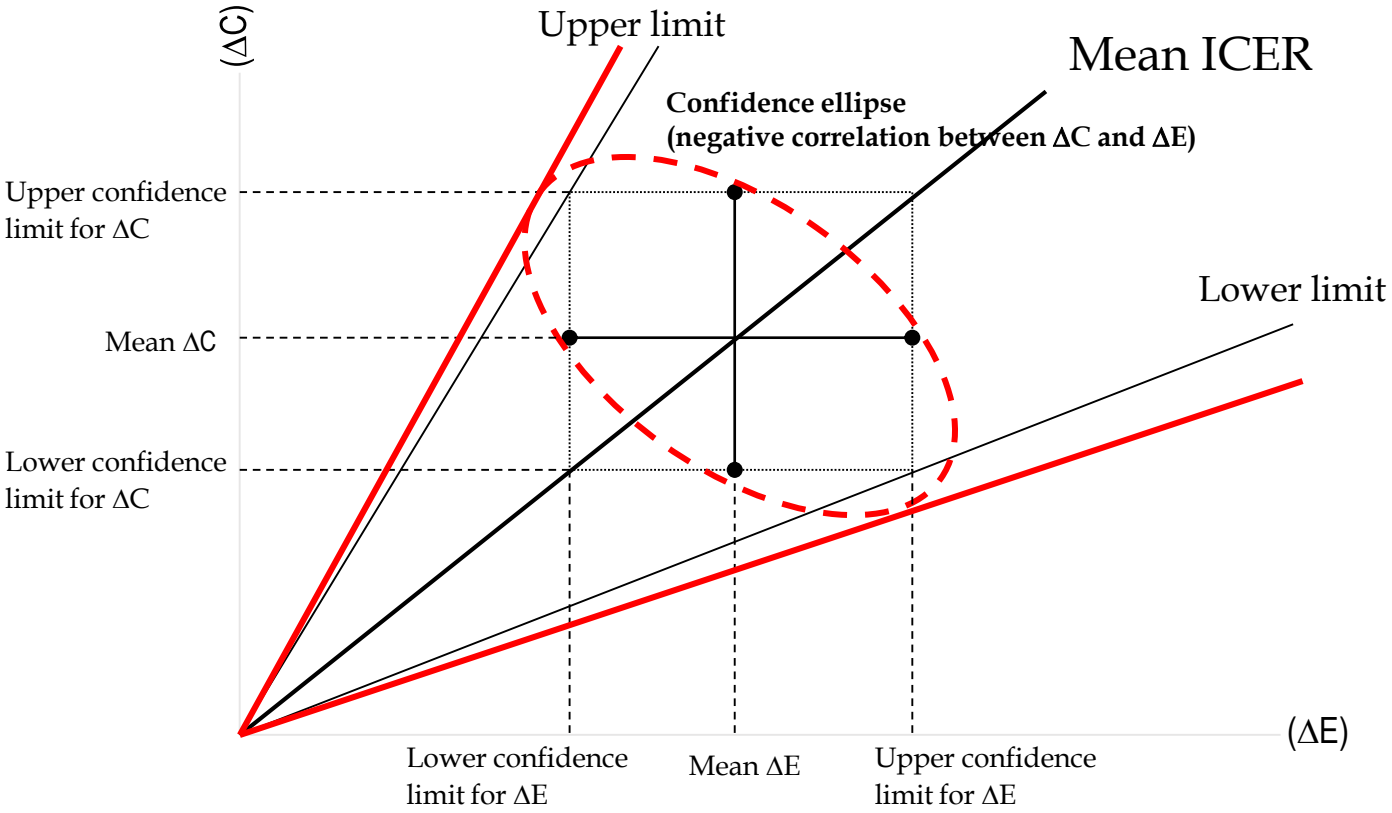
Confidence ellipse

(ΔC and ΔE follow a joint normal distribution, positive correlation)



Confidence ellipse

(ΔC and ΔE follow a joint normal distribution, negative correlation)



Calculating CIs around the ICER

- Suggested approaches include
  - Confidence box
  - Taylor series expansion (or Delta method)
  - Confidence ellipse
  - Angular transformation
  - Fieller's method (parametric method, joint normal) ☑
  - Bootstrap method (non-parametric)

Fieller's method

- Fieller's method was developed (in 1940) to quantify sampling uncertainty around the estimate of a ratio of two random variables that follow a bivariate normal distribution

$$\begin{pmatrix} \Delta C \\ \Delta E \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_{\Delta C} \\ \mu_{\Delta E} \end{pmatrix}, \Sigma \right) \qquad \Sigma = \begin{pmatrix} \sigma^2_{\Delta C} & \sigma_{\Delta C, \Delta E} \\ & \sigma^2_{\Delta E} \end{pmatrix}$$

- See Appendix for details and Exercise in the practical, for application

Calculating CIs around the ICER

- Suggested approaches include
  - Confidence box
  - Taylor series expansion (or Delta method)
  - Confidence ellipse
  - Angular transformation
  - Fieller's method (parametric method, joint normal)
  - Bootstrap method (non-parametric) ☑

Bootstrap method

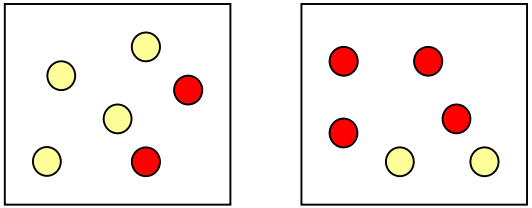
- Fieller's approach may not be robust when differential effects are very close to zero (and cross the y axes)

- Unknown nature of the distribution of the ICER
  - need to be cautious about making parametric assumptions

- The non-parametric bootstrap method allows us to build the CI around the ICER by looking at the empirical estimate of the sampling distribution of the ICER

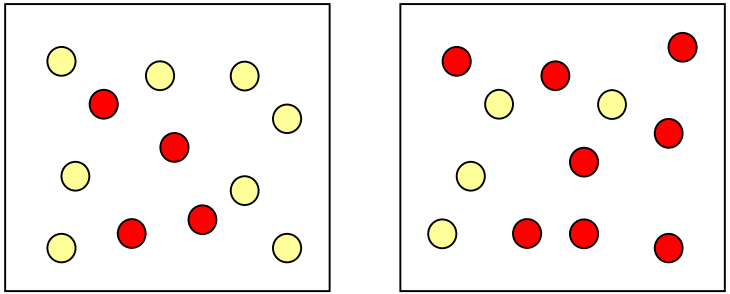
- This is done by re-sampling the original data

How does it work?



Group A Group B

Representative sample of the population, i.e. our trial sample



Population A Population B

The objective is to analyse the sample data in order to be able to make some sort of statement about the population from which the sample was drawn

Bootstrapping our samples

Group A

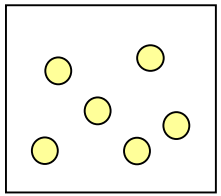
Group B

The experiment is to generate a large number of samples from our original data for group A and B. Each re-sample has the same size of the original. For each re-sample pair we then calculate the proportion of yellow and red circles

Resample Group A

Resample Group B

1



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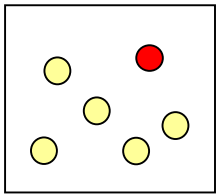

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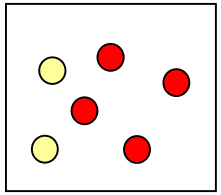

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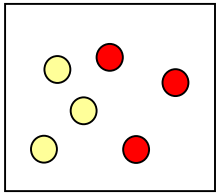

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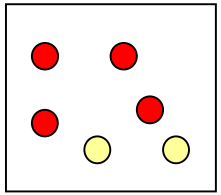

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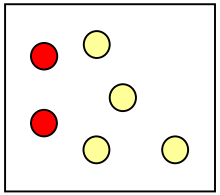

Bootstrap for CIs

Observations from the sample	
1	C_c^1, E_c^1
2	C_c^2, E_c^2
3	C_c^3, E_c^3
..	
n_c	C_c^n, E_c^n
1	C_n^1, E_n^1
2	C_n^2, E_n^2
3	C_n^3, E_n^3
.	
n_n	C_n^n, E_n^n

1. Re-sampling with replacement N groups of equal size to the intervention and calculate the mean
2. Re-sampling with replacement N groups of equal size to the control and calculate the mean
3. Calculate difference between the two mean for each iteration

4. Use these data to calculate the CI for the ICER

Statistic from re-sampling	
1st	$\Delta C_c^1, \Delta E_c^1$
2nd	$\Delta C_c^2, \Delta E_c^2$
3rd	$\Delta C_c^3, \Delta E_c^3$
4th	$\Delta C_c^4, \Delta E_c^4$
.	
.	
.	
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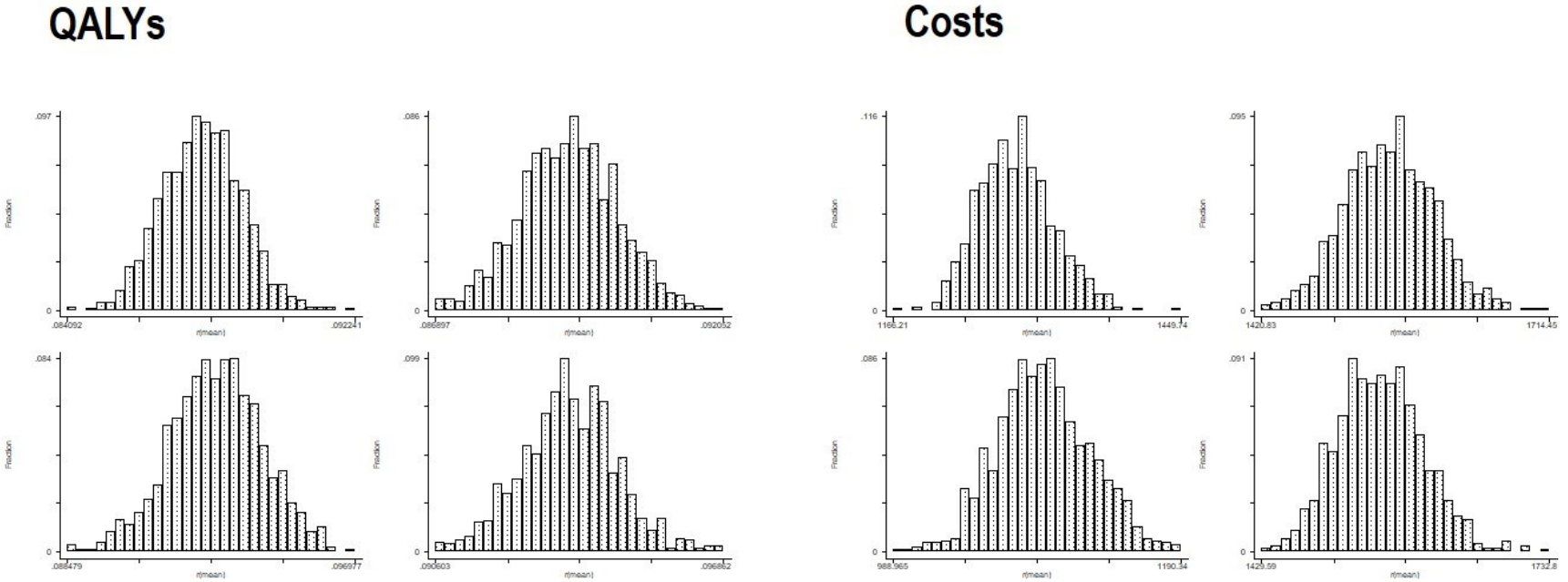
nth	$\Delta C_c^{th}, \Delta E_c^{th}$

EVALUATE: bootstrap results

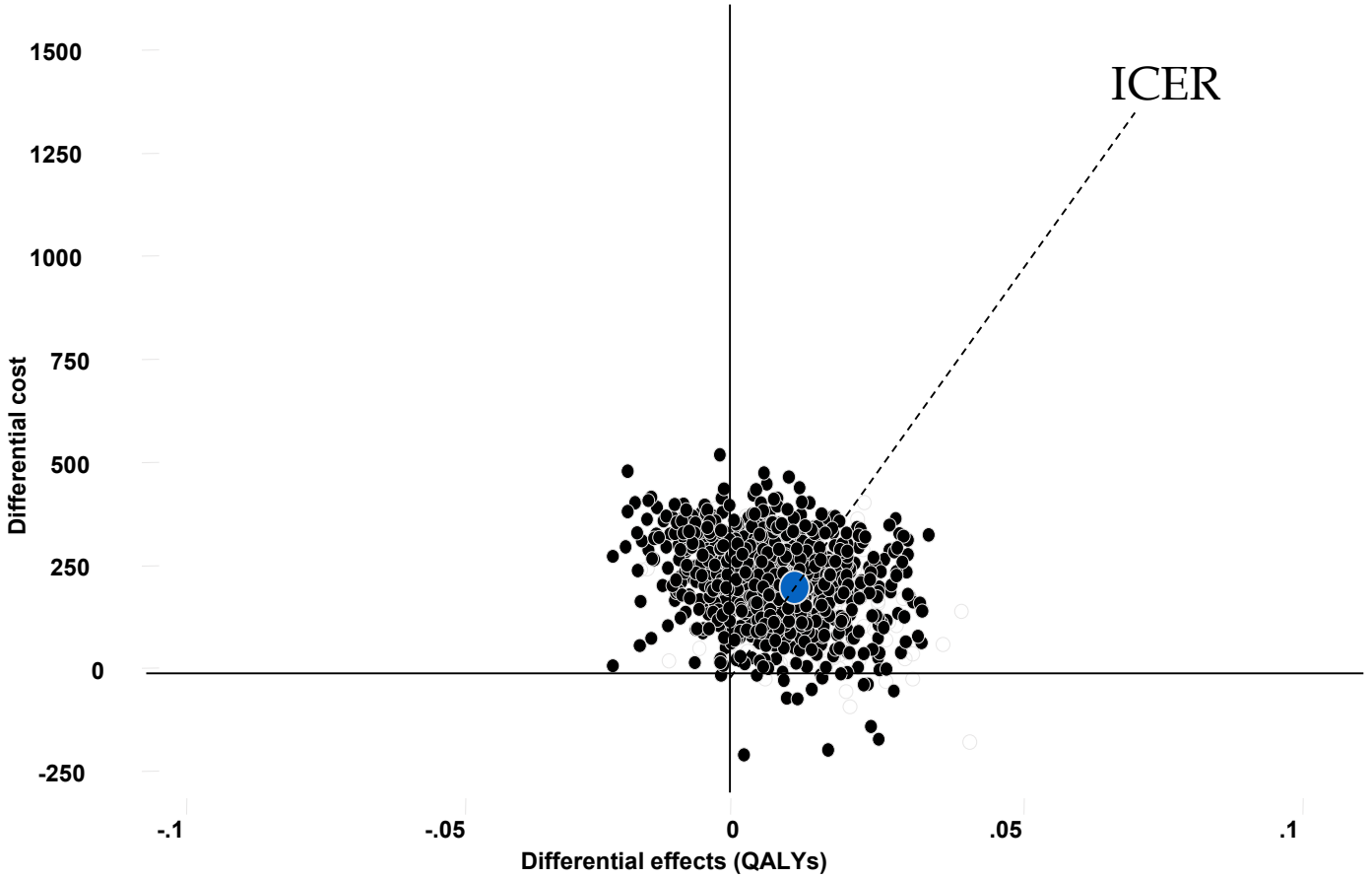
Empirical distribution of the mean costs and effects



Mean is more Normally distributed now

Need to define empirical distribution of ΔC and ΔE

Non-parametric bootstrap on the CE plane



Summary

- Quantifying the sample uncertainty surrounding the ICER can be challenging, because this is a ratio and its distribution is unknown

- Many methods have been proposed, not all of them are robust

- One of the best approaches is to use non-parametric bootstrap of the mean difference in costs and mean difference in effects

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5.4: Representing the results of the analysis

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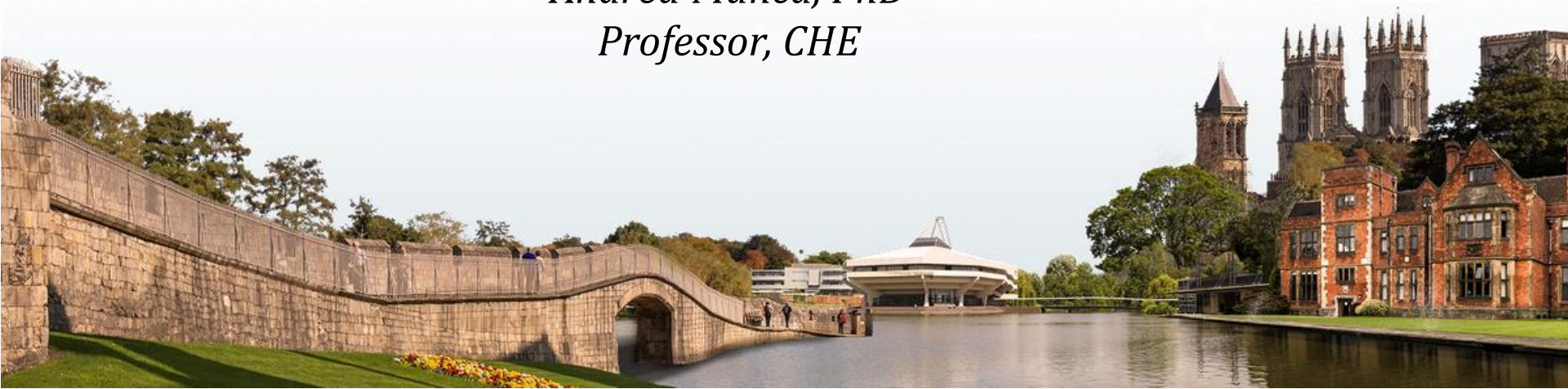


Objectives

- Learn (how) to
  - derive mean and confidence interval for the Net (Monetary) Benefits (NB)
  - represent (and interpret) the Net Benefits results for a range of λ
  - explain the relationship between net monetary benefits and acceptability curve
  - communicate the results to decision makers

Net Benefit Framework

Remember we have seen this before in Lecture 1.4

- One possibility is to reformulate the traditional decisional rule in terms of *Net Benefit* = $(\Delta E)\lambda - (\Delta C)>0$
- Easy to calculate, to represent and it avoids problems with the ICER
- NB is function of the unknown value λ
  - Not necessarily a weakness of this approach
  - Forced to explicitly consider the value λ

The NB is a….
… linear combination of two random variables

- Remember A and B from earlier slide?
- We know that A and B have a mean and a variance
- If A and B are uncorrelated:
  - VAR (A+B)=VAR(A) + VAR(B)
- If A and B are correlated:
  - VAR (A+B)=VAR(A) + VAR(B) – 2 COV(A,B)
- Applying this logic to the net benefit formulas from the previous slide gives…..

Sampling Uncertainty in the Net Benefit

- If NB=$\lambda\Delta E-\Delta C$ → let A=$\lambda\Delta E$ and B=ΔC, then
- The variance of the net benefit can be obtained as

$$Var(N\hat{M}B) = \underbrace{\lambda^2 \cdot Var(\Delta\bar{E})}_{\text{Var(A)}} + \underbrace{Var(\Delta\bar{C})}_{\text{Var(B)}} - 2\lambda \underbrace{Cov(\Delta\bar{E},\Delta\bar{C})}_{\text{Cov(A,B)}}$$

or

$$Var(N\hat{H}B) = Var(\Delta\bar{E}) + \frac{Var(\Delta\bar{C})}{\lambda^2} - \frac{2}{\lambda} Cov(\Delta\bar{E},\Delta\bar{C})$$

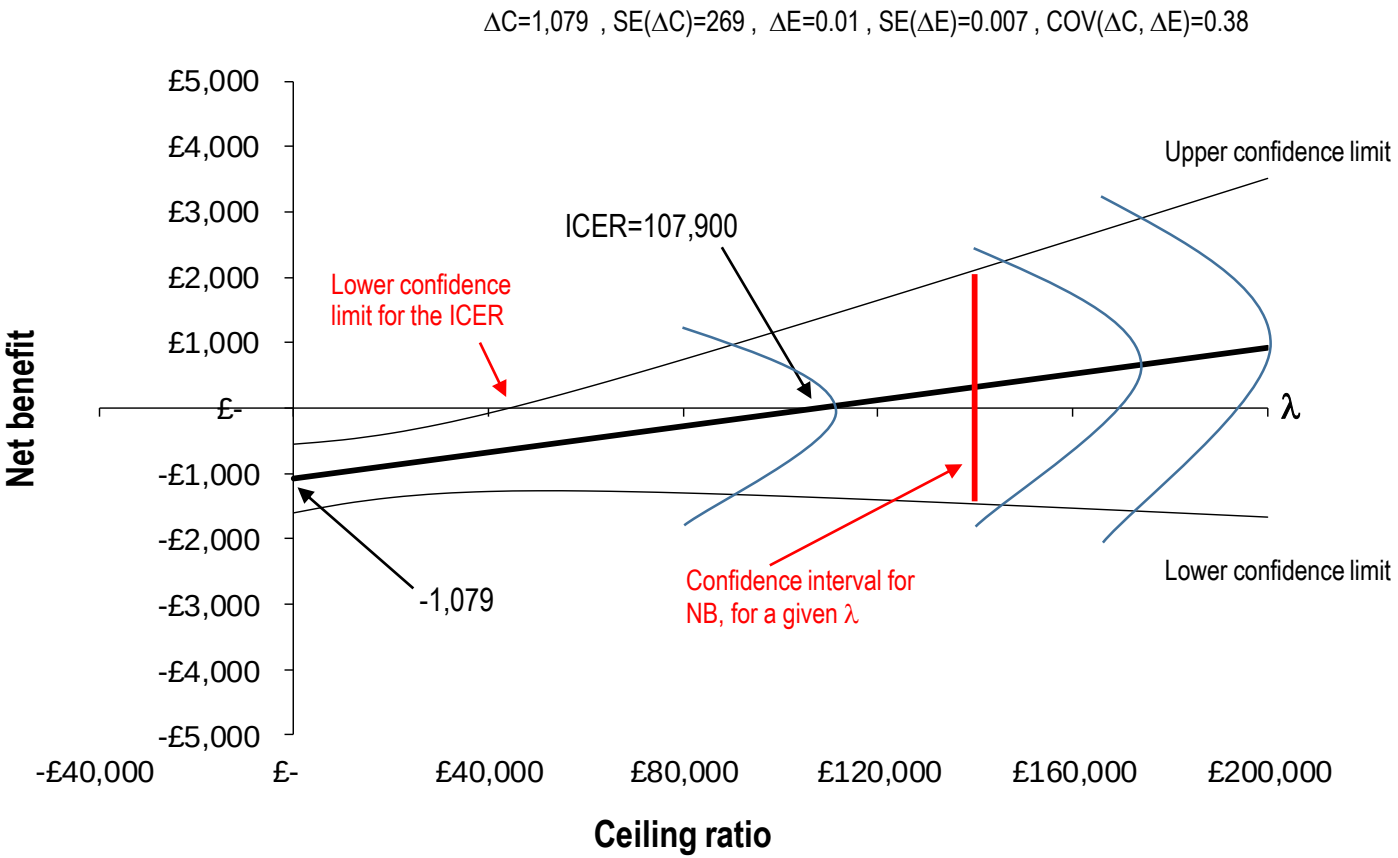
- We can also calculate the 95% (parametric) CI as

$$\left(N\bar{M}B - z_{\alpha/2}\cdot SE(N\bar{M}B), N\bar{M}B + z_{\alpha/2}\cdot SE(N\bar{M}B)\right)$$

or

$$\left(N\bar{H}B - z_{\alpha/2}\cdot SE(N\bar{H}B), N\bar{H}B + z_{\alpha/2}\cdot SE(N\bar{H}B)\right)$$

Net Benefit curve



Net Benefit line: facts

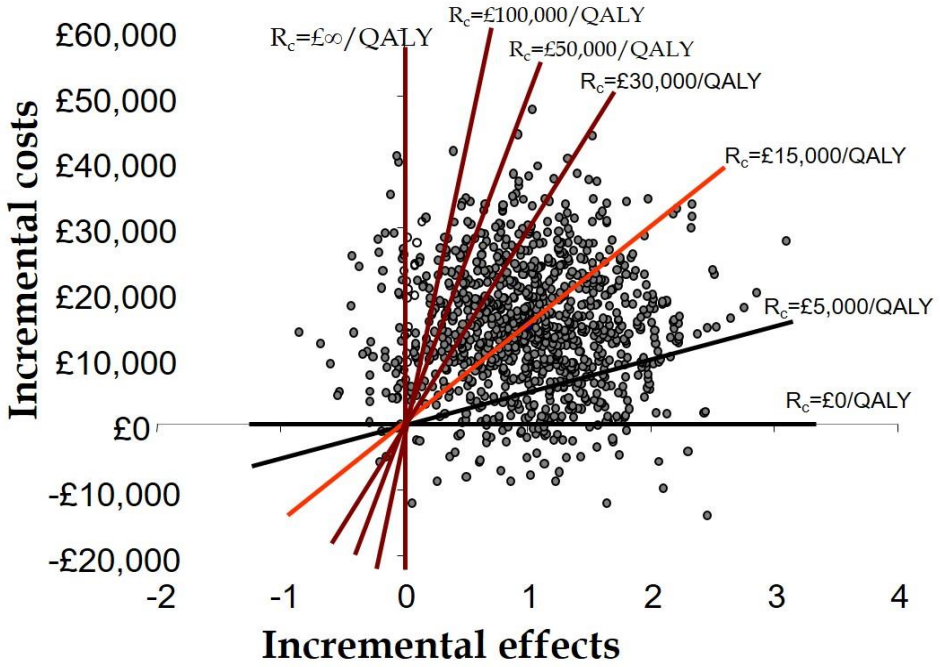
- It is linear with respect to λ
- It crosses the x-axes at the value of λ = ICER
- It crosses the y-axes at *minus* the difference in costs
- Can present CIs plot around the NB line (and ICER !)
  - Can see if upper or lower confidence limit is defined
- It is more informative than a simple ICER with CIs and can immediately give the necessary information for the decision making process

Representing decision uncertainty

- The value of λ is unknown to the analyst so
- An attractive solution to represent decision uncertainty in CEA is the use of the
  - *cost-effectiveness acceptability curve* (*CEAC)*

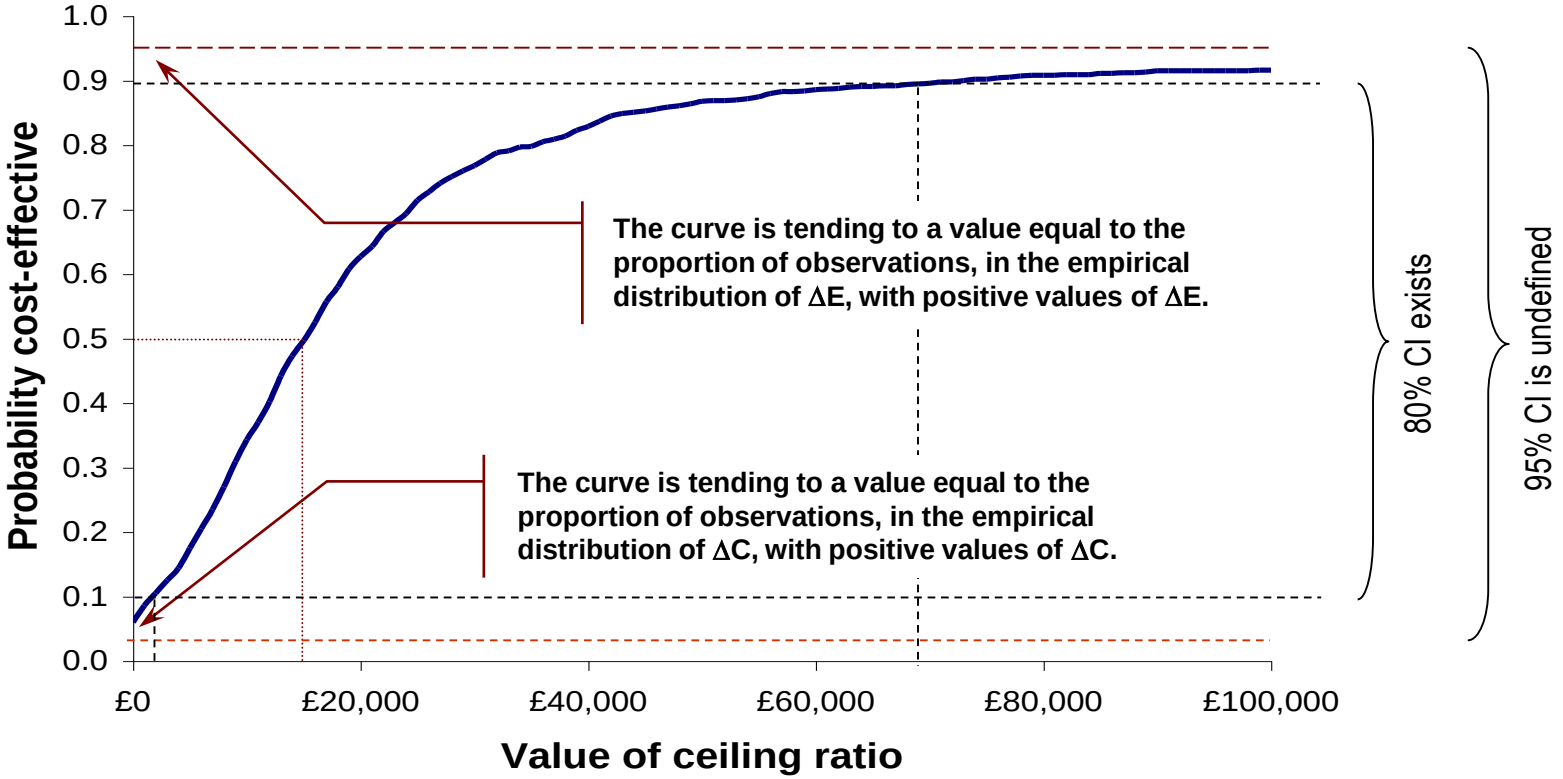
Probability that the new intervention is cost-effective for different values of λ, given the available data

Building the CEAC



Source: Briggs (2001)

Cost-effectiveness acceptability curve



Source: Adapted from Briggs (2001)

EVALUATE trial: Cost results

One year results. Values in table are mean (median) [IQR]

	Laparoscopic (N=573)	Abdominal (N=286)
Theatre cost	787 (646) [523-890]	453 (431) [381-489]
Hospital cost	548 (542) [407-678]	692 (678) [542-813]
Other post.op. cost	21 (0) [0-0]	13 (0) [0-0]
Follow up cost at 6 weeks	193 (46) [0-108]	128 (46) [0-108]
Follow up cost at 4 months	39 (0) [0-46]	88 (0) [0-46]
Follow up cost at 1 year	115 (46) [0-46]	146 (46) [0-46]
Total cost	**1706**	**1520**
Differential cost (95% CI)	***188 (-26 to 375)***	

Source: Sculpher MJ, Manca A, *et al.* (2004)

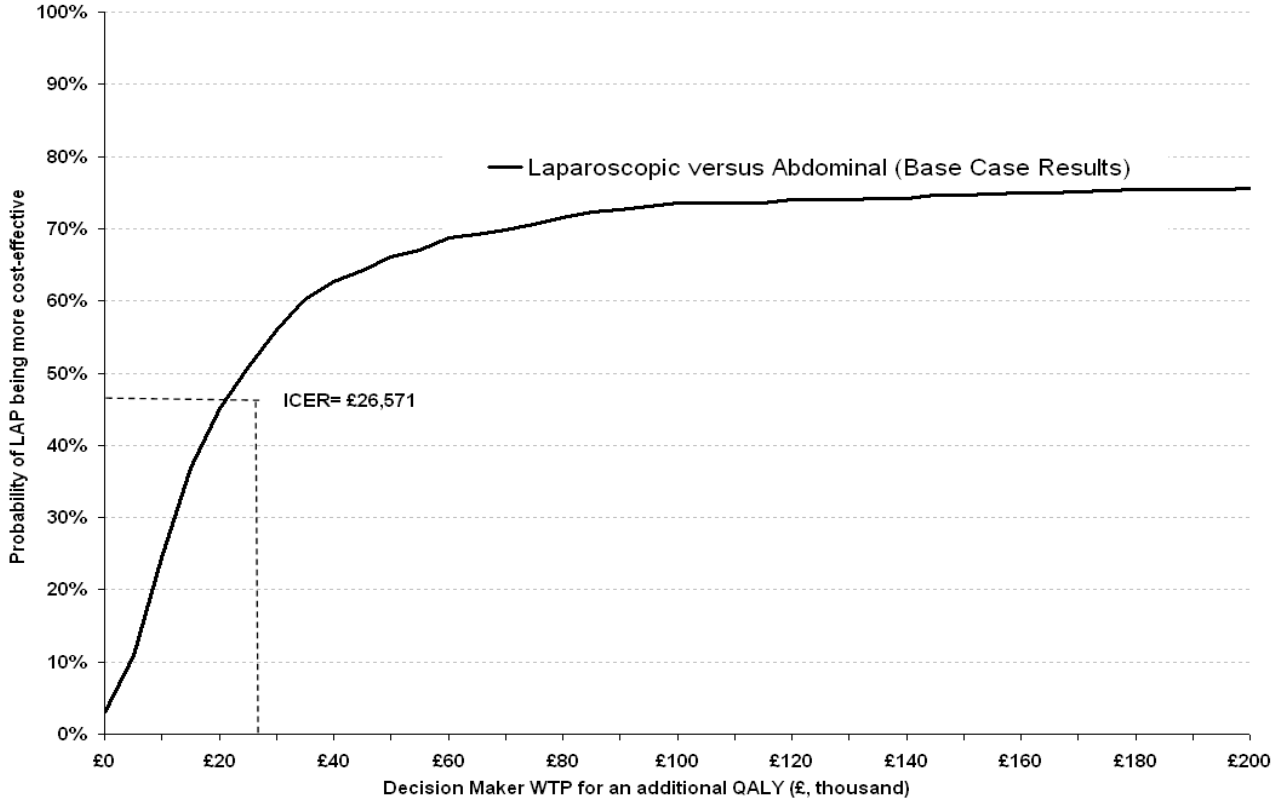
EVALUATE trial: EQ-5D and QALYs results

One year results. Values in table are mean (median) [IQR]

	Laparoscopic (N=573)	Abdominal (N=286)
Baseline	0.716 (0.760) [0.691-0.848]	0.690 (0.725) [0.689-0.812]
6 weeks	0.832 (0.869) [0.760-1]	0.833 (0.889) [0.760-1]
4 months	0.888 (0.959) [0.812-1]	0.866 (0.888) [0.796-1]
1 year	0.897 (0.929) [0.848-1]	0.897 (0.959) [0.822-1]
QALY	**0.870**	**0.862**
Differential QALYs (95% CI)	***0.007 (-0.008 to 0.023)***	

Source: Sculpher MJ, Manca A, *et al.* (2004)

CEACs in the EVALUATE trial



Source: Sculpher MJ, Manca A, *et al.* (2004)

Summary

- An alternative to represent the result of an economic evaluation study is to frame the analysis in terms of net benefits

- There are several analytical advantages when using this numeraire over the ICER

- It is also a lot easier to communicate the results to decision makers using a net benefit framework

Online Advanced Methods for Cost-Effectiveness Analysis

Presentation 5: Working with Individual Patient Data

5.5: Conclusions

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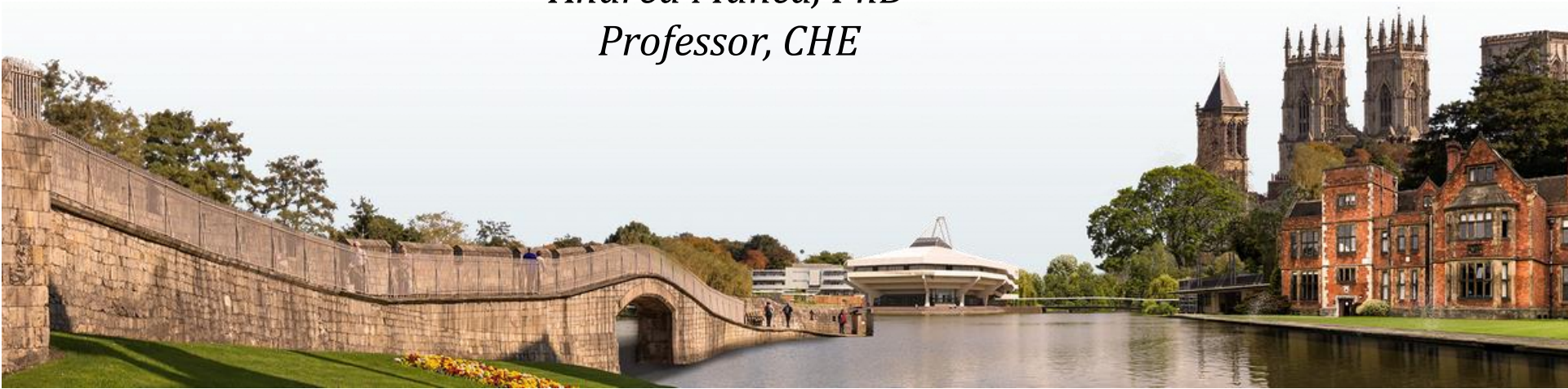

Conclusions

- Costs and effects have their own specific idiosyncrasies and the analysis needs to take into account these features to avoid bias
- The analysis of these data can be complex, but methods exist to handle the challenges these data pose
- The key is to understand how to correctly interpret their outputs and how to spot errors and inaccuracies
- We learned how to analyse individual patient-level RCT data for CEA
  - estimate the key quantities of interest in CEA
  - use these quantities to represent the results of a CEA
  - interpret the graphs typically produced as part of these analyses

Further readings

- Drummond, M.F., Sculpher, M.J., Claxton, K., Stoddart, G.L. and Torrance, G.W., 2015. *Methods for the economic evaluation of health care programmes*. Oxford university press. [Chapter 8]
- Briggs AH (2001) Handling uncertainty in economic evaluation and presenting the results. Economic evaluation in health care. Merging theory with practice. MF Drummond and A McGuire. Oxford, Oxford University Press.
- Briggs AH, Gray AM (1999) Handling Uncertainty When Performing Economic Evaluation of Healthcare Interventions. *Health Technology Assessment*; 3(2). (www.hta.nhsweb.nhs.uk/htapubs.htm)
- Briggs AH, O'Brien BJ, Blackhouse G (2002) Thinking outside the box: Recent Advances in the Analysis and Presentation of Uncertainty in Cost-Effectiveness Studies. *Annual Review of Public Health*; 23: 377-401.
- Sculpher MJ, Manca A, *et al.* Cost effectiveness analysis of laparoscopic hysterectomy compared with standard hysterectomy: results from a randomised trial, *British Medical Journal* 2004; 328: 134-139.
- Gabrio, A., Baio, G. and Manca, A., 2019. Bayesian Statistical Economic Evaluation Methods for Health Technology Assessment. In *Oxford Research Encyclopaedia of Economics and Finance*.