Online Advanced Methods for Cost-Effectiveness Analysis

Presentation 5: Working with Individual Patient Data

5.3: Deriving the quantities of interest

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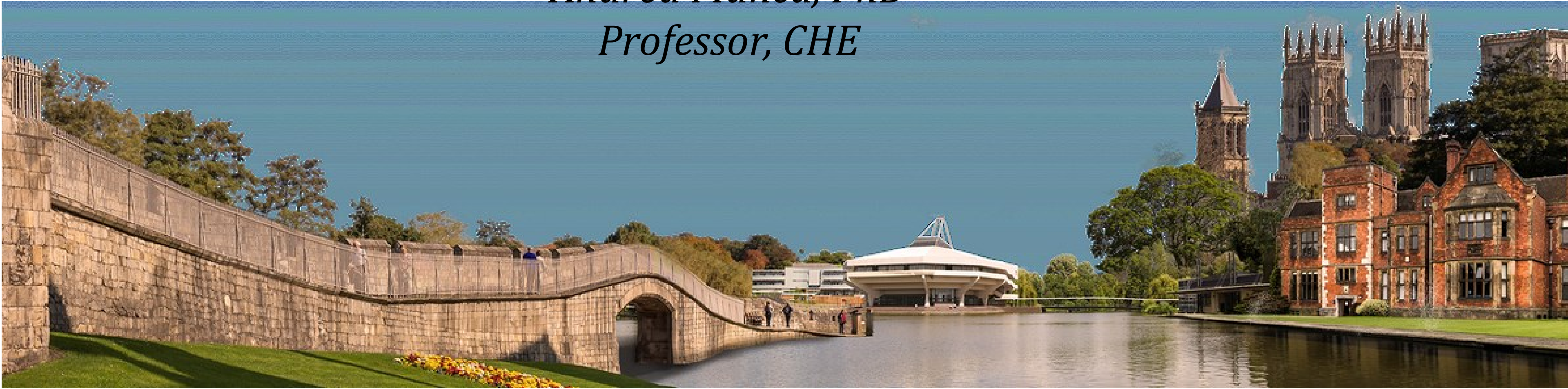


Objectives

- 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…

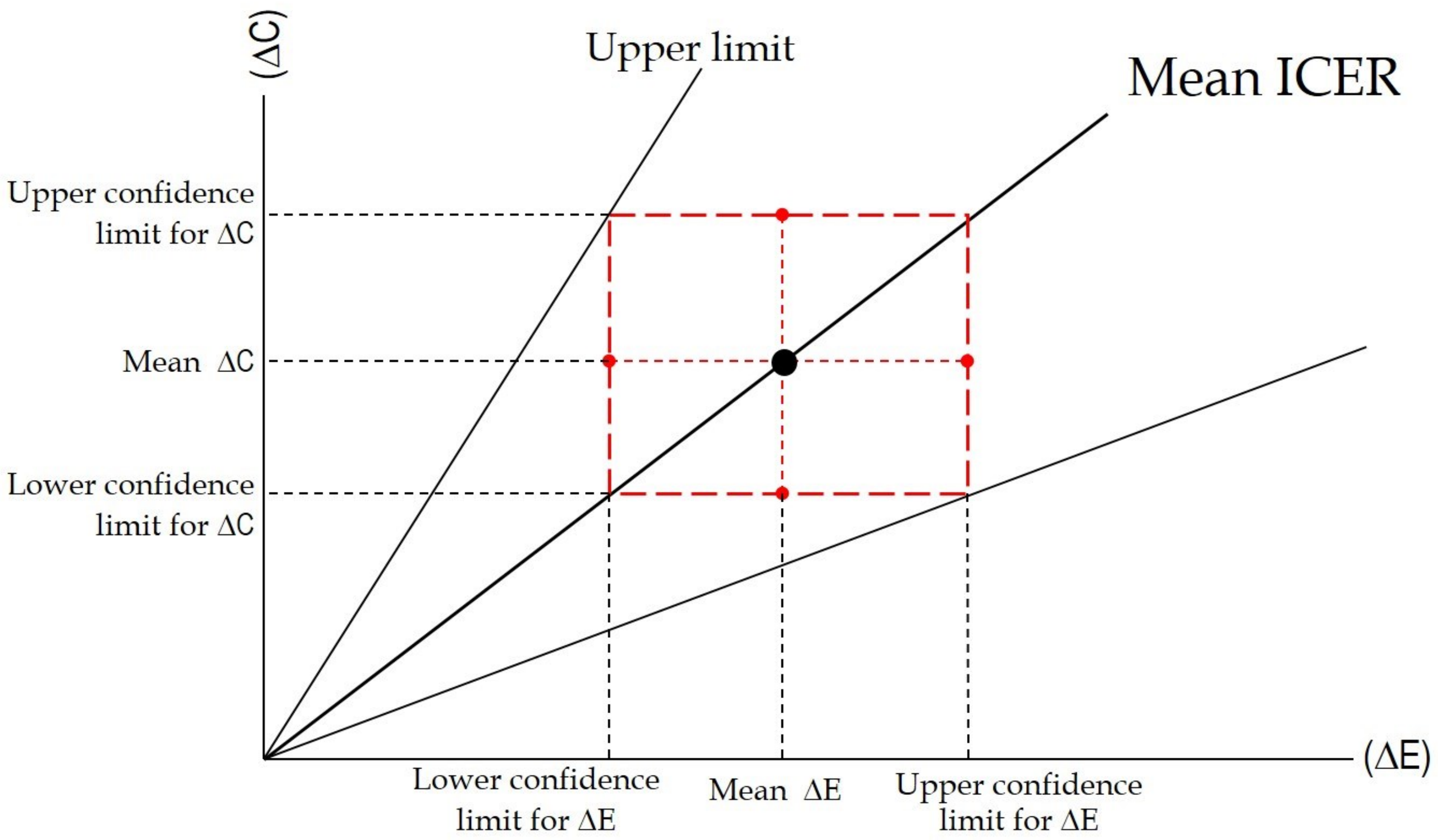
- A and B are two random variables
- We wish to estimate their ratio R=(A/B) together with its 95% CI
- Now, the problem is that
  - If $B \rightarrow 0$ then $R \rightarrow \infty$
  - If $B \rightarrow \infty$ then $R \rightarrow 0$
- Hence the 95% CI could contain infinite values…..an infinite value…doesn't 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)

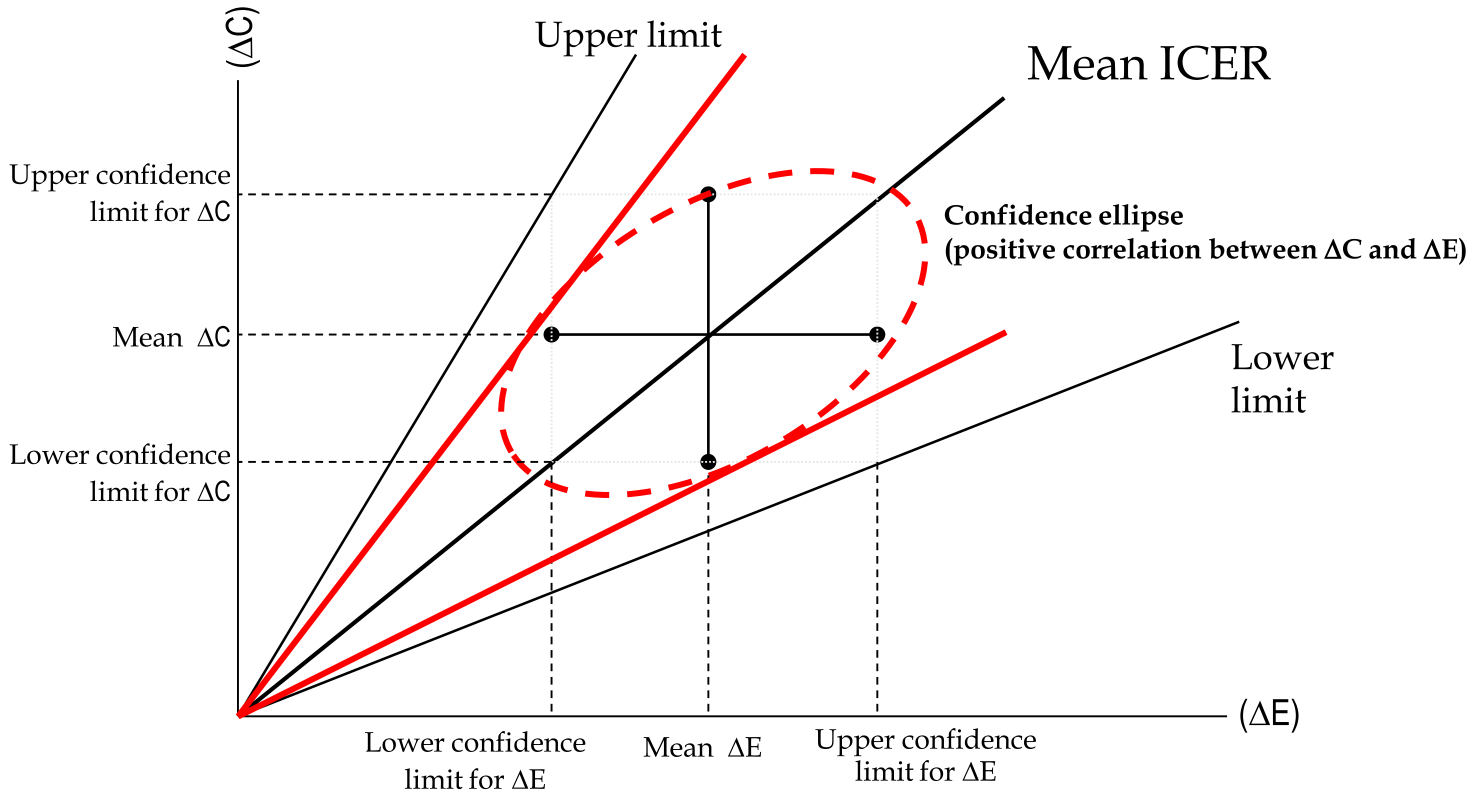
Source: Briggs AH, O'Brien BJ, Blackhouse G (2002)

Confidence box



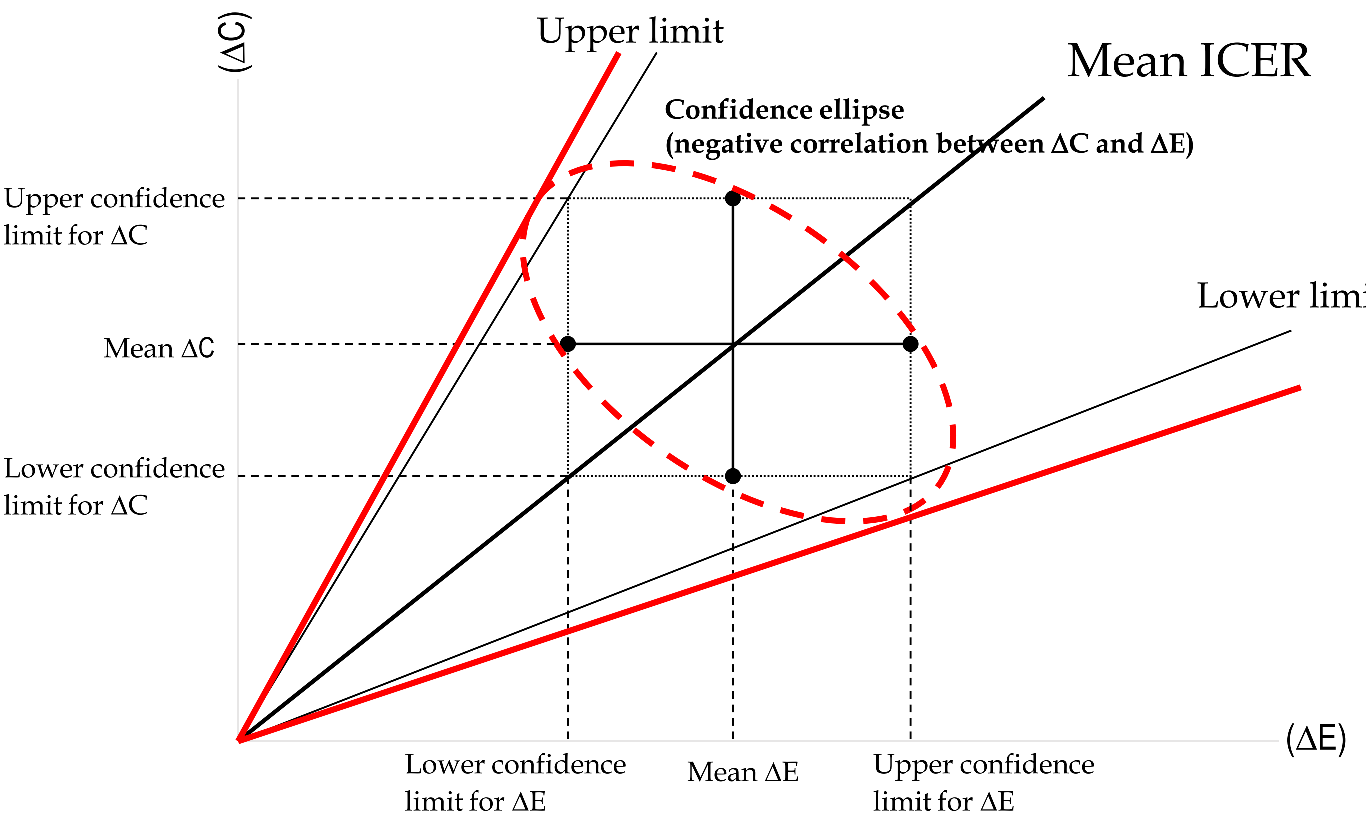
Confidence ellipse

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



Confidence ellipse

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



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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

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Bootstrap method

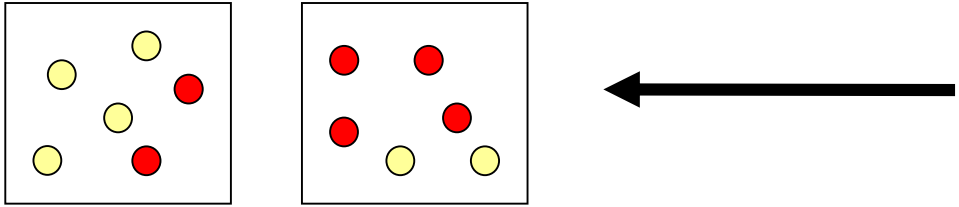
- Fieller’s approach may not be robust when differential effects are very close to zero (and cross the y axes)

- 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

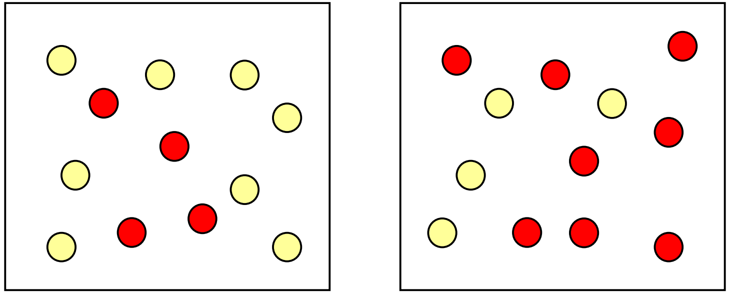
- This is done by re-sampling the original data

How does it work?



Group A Group B

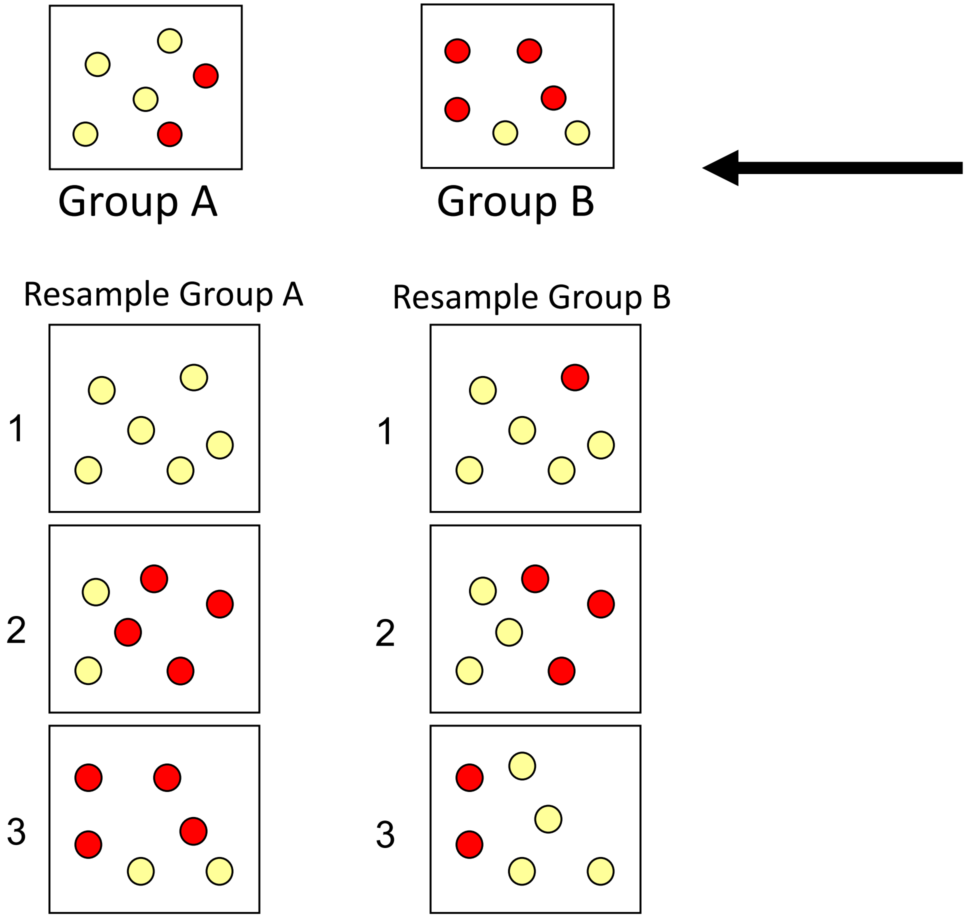
Representative sample of the population, i.e. our trial sample



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



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

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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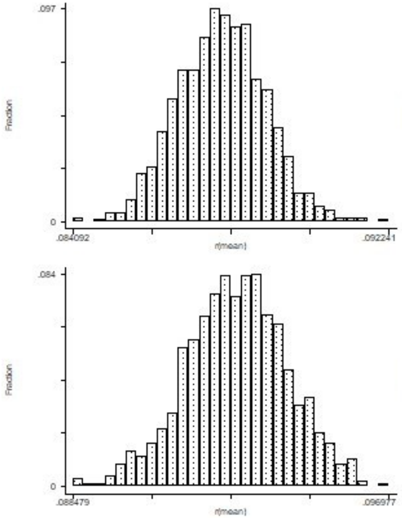
nth	$\Delta C_c^{th}, \Delta E_c^{th}$

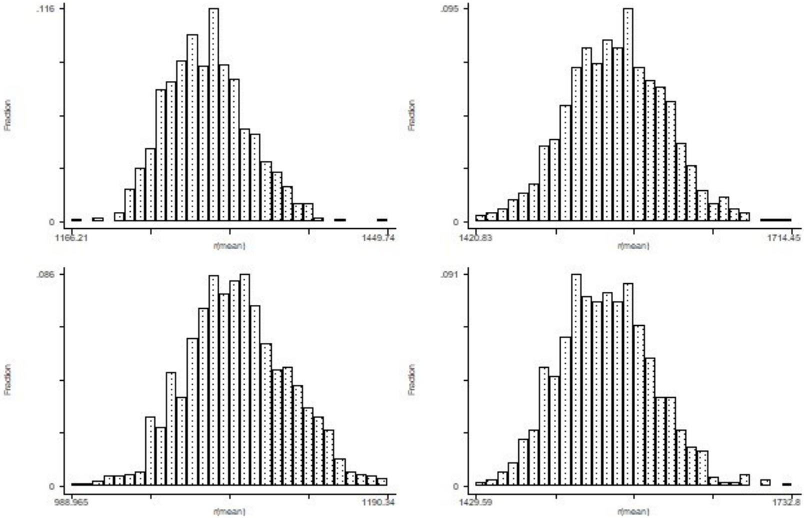
EVALUATE: bootstrap results

Empirical distribution of the mean costs and effects

QALYs



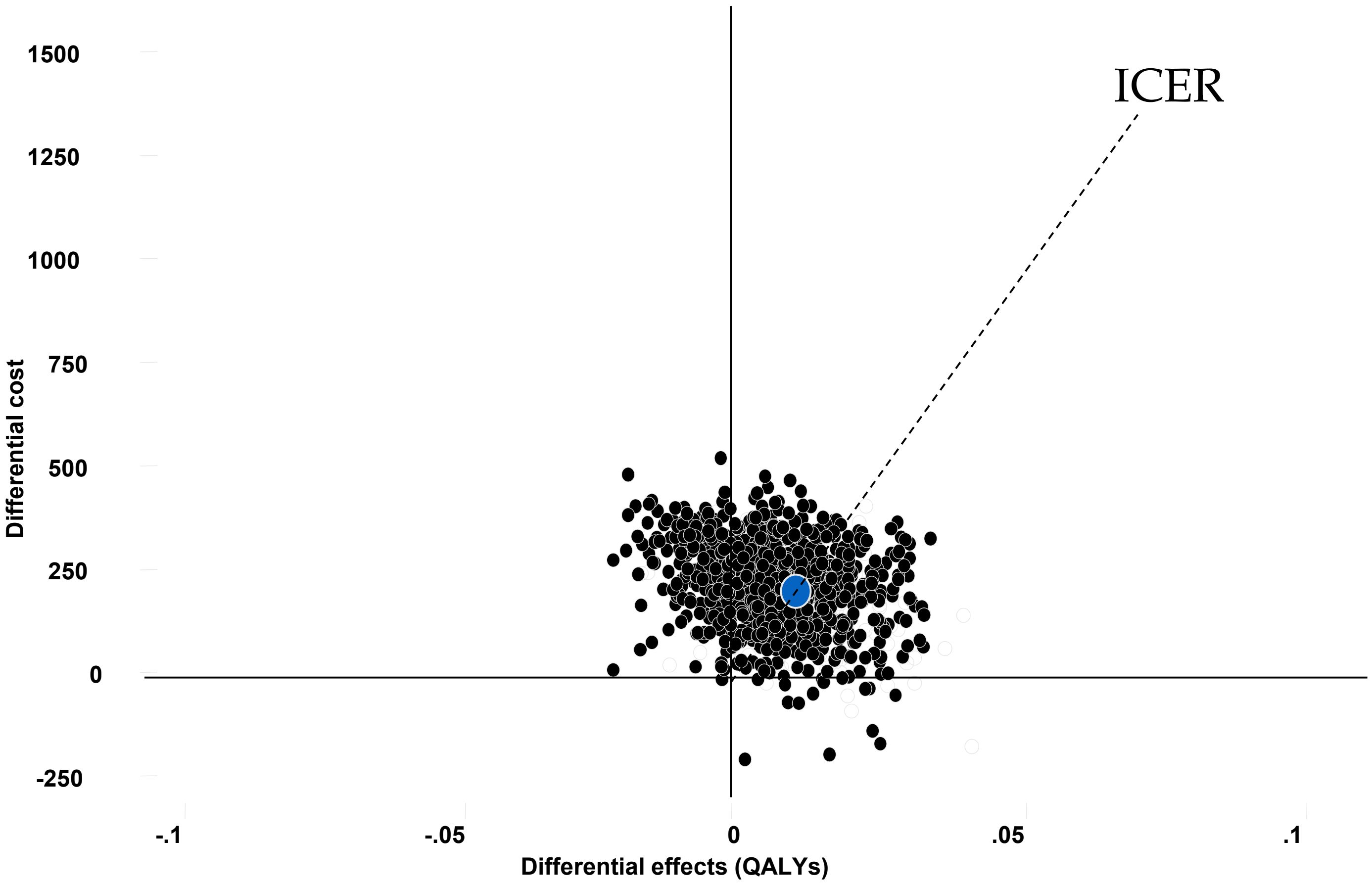
Costs



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