“WHICH CALCULATION METHODS OF CONFIDENCE REGIONS FOR THE COST-EFFECTIVENESS RATIO TO CHOOSE?”

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A working paper will be soon available at the following address :

http://ehess.cnrs-mrs.fr/GREQAM/dt/

INTRODUCTION

Until now, economic analysts most often used sensitivity analysis to examine the implications of uncertainty for their results.

For some years, the development of economic evaluations associated with controlled clinical trials provides patient-level data on ***costs*** and ***effects*** which open up the possibility of statistical analysis of uncertainty.

In cost-effectiveness analysis, the statistic of interest is the incremental cost-effectiveness ratio and we are interested in the building of confidence regions for this ratio, which causes problems when the denominator comes close to zero.

PROGRAMME

- In the paper, we have analysed in details the different calculation methods of confidence region for the ratio and we give advantages and drawbacks of each of them.
  - Particularly, we have demonstrated some theorems in the Fieller's method.
  - We have shown the link between the Fieller's method and the ellipse method which provides a geometrical interpretation to the Fieller's method.

- There, by lack of time, we only present the two conclusions of the paper :

1) <u>A technical conclusion</u> :
Which method provides the best confidence region ?

2) <u>A conclusion concerning the decision-making</u> :
How to use these confidence regions for decision-making ?

- We finish by presenting a detailed Monte-Carlo study that we have performed to complete the theoretical analysis.

BACKGROUND

In cost-effectiveness analysis (CEA), an incremental cost-effectiveness ratio (ICER) which compares a new treatment (T_1) to a standard treatment (T_0) is defined by :

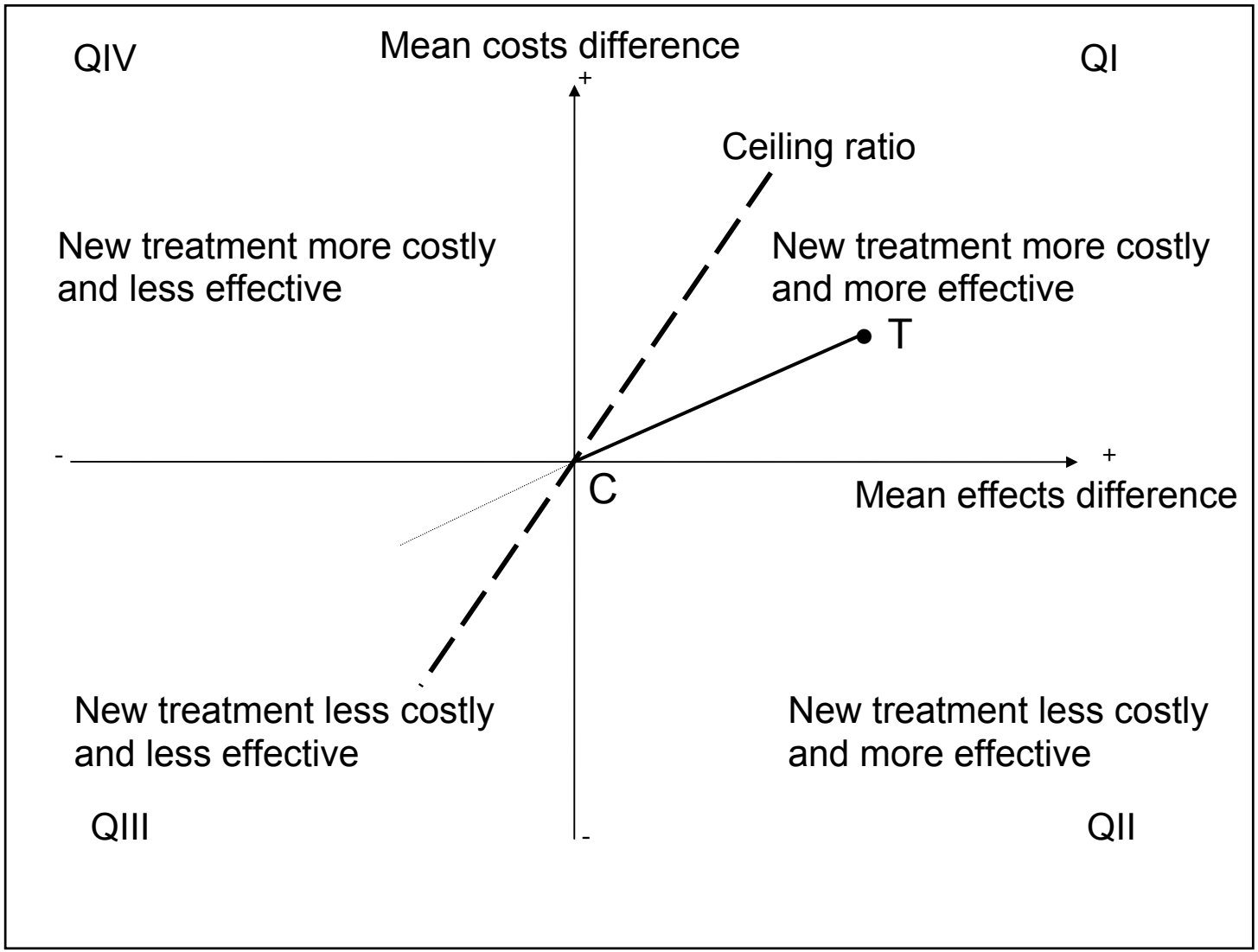
$$R = \frac{\mu_{C1} - \mu_{C0}}{\mu_{E1} - \mu_{E0}} = \frac{\mu_{\Delta C}}{\mu_{\Delta E}}.$$

This ratio can be interpreted as additional resources required to obtain one unit of health effects using (T_1) rather than (T_0).

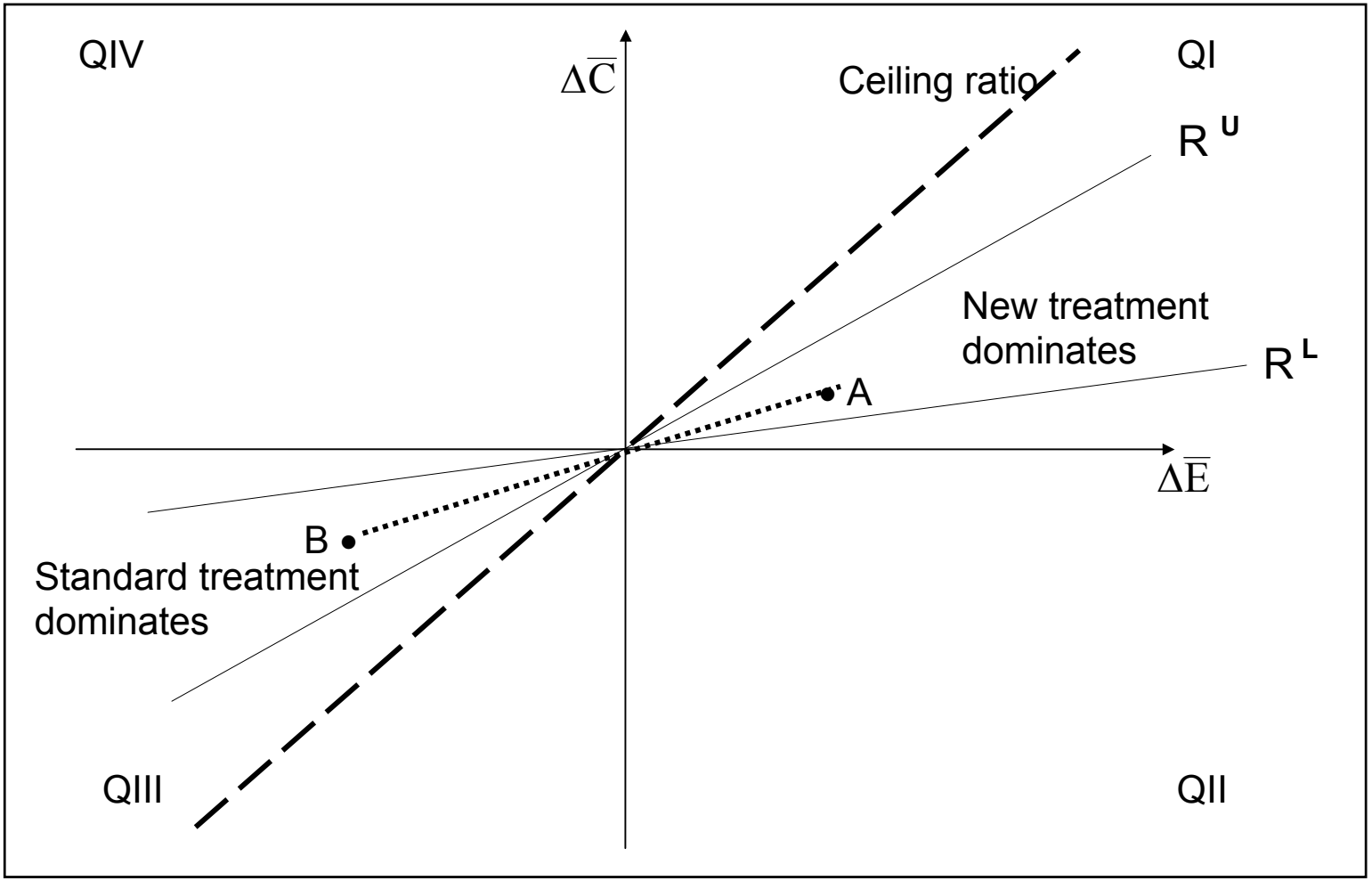
The ICER can be estimated on the basis of data collected form two groups of patients receiving the alternative treatments, in the following way :

$$\hat{R} = \frac{\overline{C_1} - \overline{C_0}}{\overline{E_1} - \overline{E_0}} = \frac{\Delta\overline{C}}{\Delta\overline{E}}.$$

THE DECISION-RULES ON THE COST-EFFECTIVENESS (CE) PLANE



HE PROBLEM OF THE DECISION “MIRROR”



THE COMPUTATION METHODS OF CONFIDENCE REGIONS FOR THE ICER

We can distinguish two kinds of methods :

- methods based on the density function of the ICER :
  - Taylor method,
  - Gaussian parametric bootstrap methods :
    percentile (denoted percentile 0),
    percentile-t (denoted percentile-t0),
    BCA (denoted BCA 0),
  - nonparametric bootstrap methods :
    percentile (denoted percentile 1),
    percentile-t (denoted percentile –t 1),
    BCA (denoted BCA 1),

- methods based on the joint density function of the pair (mean costs difference, mean effects difference) :
  - Fieller's method,
  - ellipse method $\Rightarrow$ provides a *single sector* but is *approximative*
  - "box" method $\Rightarrow$ provides a *single sector* but is *approximative*.

MONTE-CARLO EXPERIMENTS

This study is based on three elements variation around a reference case (for which all methods work well):

- the joint distribution of the cost and effect for each treatment which can be :
  - ➔ a theoretical law: a gaussian law
  - ➔ an empirical law obtained by resampling from real data

- the distance between the $(\Delta\overline{C}, \Delta\overline{E})$ pair and the CE plane origin, determined by their respective coefficients of variation denoted $cv(\Delta\overline{C})$ and $cv(\Delta\overline{E})$:
  - ➔ case 1: far from the origin of the CE plane
  - ➔ case 2: near to the costs-axis
  - ➔ case 3: near to the origin of the CE plane

- the correlation between $(\Delta\overline{C}, \Delta\overline{E})$:

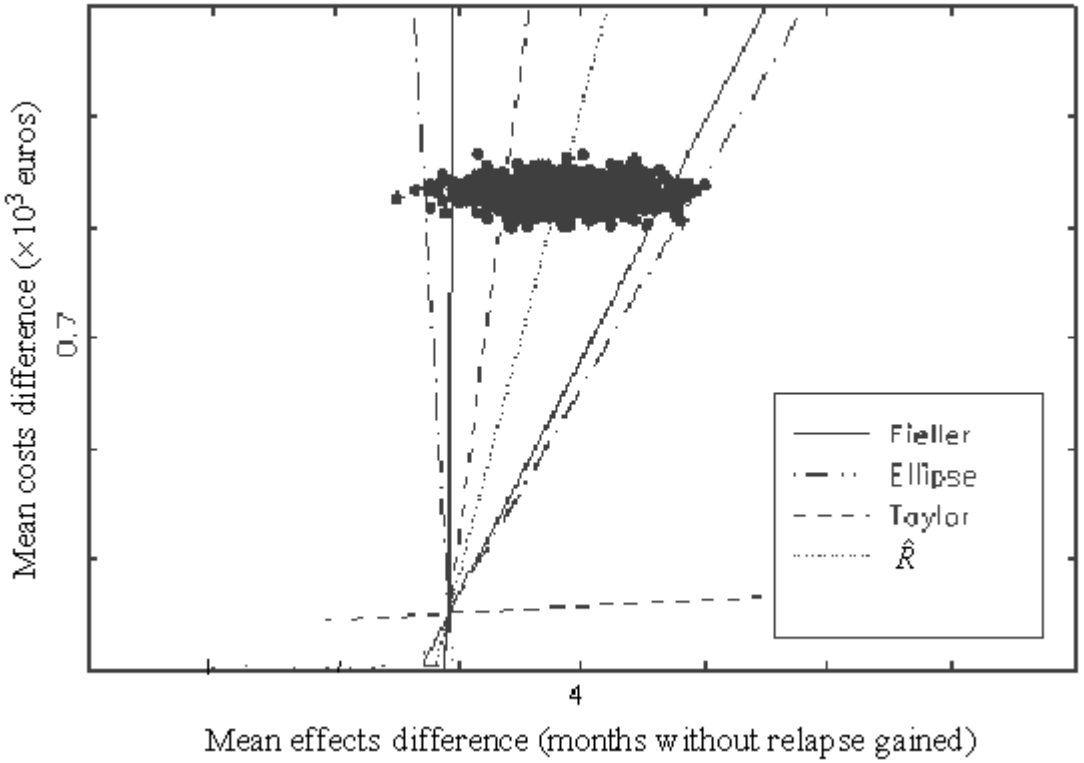
in case of theoretical distribution, the correlation coefficient between costs and effects each treatment belongs to the following set: {-0.9, -0.5, 0, 0.5, 0.9\}.

DESCRIPTIVE STATISTICS OF THE DATA

Group variable	Mean	Standard error	Coefficient of variation	Correlation Coefficient cost & effect	Skewness	Kurtosis
Treatment (n=155)				0.06		
Costs (euros)	17848.38	3364.62	0.19		1.57	7.950
Effects (months of life gained)	33.5	14.46	0.43		-0.03	2.400
Control (n=145)				-0.14		
Costs (euros)	5214.73	2661.94	0.51		6.80	65.900
Effects (months of life gained)	29.7	15.31	0.52		0.51	2.380
Différence				-0.03		
Costs (euros)	12633.65	351.95	0.03		0.19	0.080
Effects (months of life gained)	3.8	1.72	**0.46**		0.01	0.008
ICER (euros / months of life gained)	3348.60					

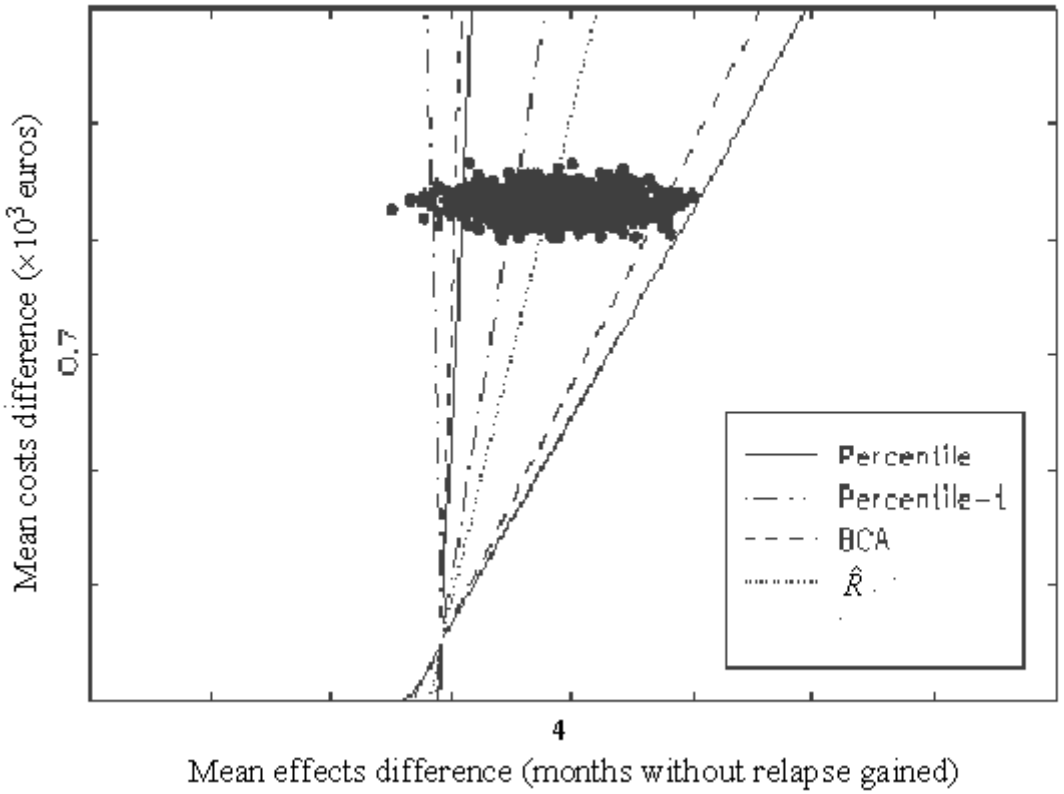
CONFIDENCE REGIONS OF THE DIFFERENT METHODS (1)

(B=1000, R=5,000)



CONFIDENCE REGIONS OF THE DIFFERENT METHODS (2)

(B=1000, R=5,000)



PERFORMANCES OF THE DIFFERENT METHODS

EMPIRICAL LAW

Number of bootstrap samples: B = 1000.

Confidence level of the confidence region: α= 0.05.

Number of simulations: R=10,000 (excepted for the percentile-t method for which R=1000).

Location case 3.

Invalid cases: Ellipse : 18%; other : 8.1%

Method	Coverage		Length	Angle (°)
	Double sector	Single sector		
Fieller	0.948 (0.002)	0.948 (0.002)	infinite	**63.3 (85.4)**
Ellipse	0.985 (0.002)	0.985 (0.002)	infinite	86.5 (89.4)
Taylor	0.924 (0.002)	0.916 (0.002)	562510 (36026008)	148.5 (67.8)
Percentile 0	0.971 (0.002)	0.963 (0.002)	20471 (30259)	113.6 (86.5)
BCA 0	0.930 (0.002)	0.929 (0.002)	infinite	117.8 (85.2)
Percentile 1	0.972 (0.002)	0.964 (0.002)	19879 (29635)	119.1 (84.8)
BCA 1	0.930 (0.002)	0.929 (0.002)	infinite	103.4 (88.6)
Percentile-t 0	0.873 (0.007)	0.864 (0.007)	245664 (1358600)	177.2 (21.9)
Percentile-t 1	0.887 (0.007)	0.878 (0.007)	234051 (917527)	178.6 (15.5)

CONCLUSION

1) Concerning the calculation method problem :

The Fieller's method is the best one because :

- it is based on **the joint density of the pair** (mean costs difference, mean effects difference)
- it is the **best optimised** method.

2) Concerning the decision-making problem :

- So, we must provide the confidence region of the form of **a directed confidence region** and not to give it of the form of a double sector defined by two bounds.

- For that, the Fieller's method "truncated" is, by far, the best method and we can note that the committed error by truncature is quite null with this method.

IF YOU WANT MORE DETAILS

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