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COST-EFFECTIVENESS RATIO FOR COMPARING SOCIAL AND HEALTH POLICIES

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Abstract: The analysis of the incremental cost-effectiveness ratio (ICER) is an important part of the social and health decision-making process, because ICER is used to obtain simultaneous information on the cost and effectiveness of a new intervention when compared to another one. Despite the increasing use of the ICER, studies on its statistical methodology have still not been sufficiently developed. In particular, the calculation of the confidence interval for the ICER is fundamental to take into account the uncertainty due to differences in samples. In this paper, a new parametric technique for the construction of confidence intervals for the ICER is proposed. It is based on the distribution of the ratio of two correlated normal variables. The method discussed has always existed, despite the degenerate cases of the classical parametric method proposed by Fieller, for which the classical region is not an interval. The computation of the confidence intervals proposed in the present paper may also be achieved in a feasible way.

Keywords: incremental cost-effectiveness ratio, distribution of the ratio of two correlated normal r.v., confidence intervals for the ratio.

1. Introduction

The analysis of the incremental cost-effectiveness ratio (ICER) is an important part of the social and health decision-making process, because ICER is used to obtain simultaneous information on the cost and effectiveness of a new intervention when compared to another one.

ICER is used in several social and health studies, including the comparisons of different interventions to avoid social exclusion, anti-social behavior problems [Muntz et al. 2004] and dyslexia.

Despite the increasing use of the ICER, studies on its statistical methodology have still not been sufficiently developed. When comparing two competing interventions, confidence intervals (CI) for ICER provide information on the level of uncertainty in the point estimates. The non-parametric bootstrap method is often used to find the CI

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for ICER, even if it does not consider the shape of distribution of the ratio. Another widely used parametric method was proposed by Fieller [1932; 1954]. The limit of this method is that it does not always produce bounded intervals for ICER, because it is based on a second order equality and the solution may have none, one or two solutions according to the situation in which the discriminant is negative, null or positive.

In this paper, we presented a new parametric technique for the construction of CIs. This method is based on the same parametric assumptions of the Fieller method for constructing CIs and it is based on the exact distribution of the ICER, i.e. the distribution of the ratio of two correlated normal random variables (r.v.).

2. Incremental cost-effectiveness ratio

The ICER is given by

$$R = \frac{\mu_{\Delta C}}{\mu_{\Delta E}} = \frac{\mu_{Cnew} - \mu_{C\,str}}{\mu_{Enew} - \mu_{Estr}} \tag{1}$$

where the numerator is the difference between the cost of the new treatment and the standard one and the denominator is constituted by the difference between the effectiveness of the treatments to be compared.

Often the denominator used to evaluate the effectiveness of a new health intervention as compared to another, is expressed as follows:

$$\mu_{Enew} - \mu_{Estr} = QALY_{new} - QALY_{str} \tag{2}$$

where QALY is the number of years of life that would be added by the new intervention.

In this situation, *R* represents the cost to be paid to increase the life by one year if the new procedure is used instead of the standard one.

Let us consider an experiment in which, in the control group, we observe n_1 participants and in the group where we test the new intervention we consider n_2 participants.

The ICER may be estimated by the ratio

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$$\hat{R} = \frac{\bar{C}_{new} - \bar{C}_{str}}{\bar{E}_{new} - \bar{E}_{str}} = \frac{\hat{\Delta}_{\bar{C}}}{\hat{\Delta}_{\bar{E}}}. \tag{3}$$

We may have the following alternatives:

- $\bar{C}_{new} - \bar{C}_{str} < 0$ *and* $\bar{E}_{new} - \bar{E}_{str} > 0 \rightarrow \hat{R} < 0$.

The new intervention is less expensive and more effective, so it is preferable to the control situation. *R* represents the cost per additional outcome achieved by the treatment.

- $\bar{C}_{new} - \bar{C}_{str} > 0$ *and* $\bar{E}_{new} - \bar{E}_{str} < 0 \rightarrow \hat{R} < 0$.

The intervention proposed is more expensive and less effective than the traditional one, so it must be rejected. The absolute value of *R* reflects the cost per additional outcome achieved by the control approach.

- $\bar{C}_{new} - \bar{C}_{str} > 0$ *and* $\bar{E}_{new} - \bar{E}_{str} > 0 \rightarrow \hat{R} > 0$.

The experimental intervention is more expensive and more effective, so it is worth evaluating the ICER.

- $\bar{C}_{new} - \bar{C}_{str} < 0$ *and* $\bar{E}_{new} - \bar{E}_{str} < 0 \rightarrow \hat{R} > 0$.

The ICER must be examined because the new intervention is less expensive, but also less effective, than the traditional one.

The expected value and the variance of the numerator of the estimator are

$$E(\hat{\Delta}_{\bar{C}}) = \mu_{Cnew} - \mu_{Cstr} = \mu_{\Delta C} \text{ and } z\ Var(\hat{\Delta}_{\bar{C}}) = \sigma^2_{\hat{\Delta}_{\bar{C}}} = \frac{\sigma^2_{\bar{C}_{new}}}{n_1} + \frac{\sigma^2_{\bar{C}_{str}}}{n_2} \tag{4}$$

The expected value and the variance of the denominator are

$$E(\hat{\Delta}_{\bar{E}}) = \mu_{Enew} - \mu_{Estr} = \mu_{\Delta E} \text{ and } Var(\hat{\Delta}_{\bar{E}}) = \sigma^2_{\hat{\Delta}_{\bar{E}}} = \frac{\sigma^2_{E_{new}}}{n_1} + \frac{\sigma^2_{E_{str}}}{n_2} \tag{5}$$

The covariance, given the independence of the observations in the two groups, is given by

$$Cov(\bar{C}_{new} - \bar{C}_{str}, \bar{E}_{new} - \bar{E}_{str}) = Cov(\bar{C}_{new}, \bar{E}_{new}) + Cov(\bar{C}_{str}, \bar{E}_{str})$$

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The correlation coefficient between the r.v. of the numerator and the one of the denominator is

$$\rho_\Delta = \frac{Cov(\bar{C}_{new} - \bar{C}_{str}, \bar{E}_{new} - \bar{E}_{str})}{\sqrt{Var(\bar{C}_{new} - \bar{C}_{str}) Var(\bar{E}_{new} - \bar{E}_{str})}} = \frac{Cov(\bar{C}_{new}, \bar{E}_{new}) + Cov(\bar{C}_{str}, \bar{E}_{str})}{\sqrt{\sigma^2_{\Delta\bar{C}}\sigma^2_{\Delta\bar{E}}}}. \quad (6)$$

The numerator and the denominator of $\hat{R}$, if the number of observations in each of the two groups is not too small, may be approximated to normal distributions.

The parameters considered above may be estimated through the ML estimators of a bivariate correlated normal (BCN) r.v.

In the above situation, the estimator $\hat{R}$ may be approximated by the ratio of two correlated normal r.v.

3. The confidence intervals for icer based on the exact distribution of the estimator

In order to propose a method for constructing confidence intervals around the ICER, we consider, first of all, the distribution of the ratio of two correlated normal r.v.

3.1. The distribution of the ratio of two correlated normal r.v.

Let us consider a BCN r.v.

$$(Y, X) \sim N(\mu_Y, \mu_X, \sigma^2_Y, \sigma^2_X, \rho).$$

The r.v. $w = \frac{Y}{X}$ has the cumulative density function (CDF) given by [Aroian, Oksoy 1986]

$$F_W(w) = L\left(\frac{a - b\,t_w}{\sqrt{1+t_w^2}}, -b, \frac{t_w}{\sqrt{1+t_w^2}}\right) + L\left(\frac{b\,t_w - a}{\sqrt{1+t_w^2}}, b, \frac{t_w}{\sqrt{1+t_w^2}}\right), \quad (7)$$

$w \in \Re$, where

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$$a = \sqrt{\frac{1}{1-\rho^2}}\left(\frac{\mu_Y}{\sigma_Y} - \rho\frac{\mu_X}{\sigma_X}\right), b = \left(\frac{\mu_X}{\sigma_X}\right),\ t_w = \sqrt{\frac{1}{1-\rho^2}}\left(\frac{\sigma_X}{\sigma_Y}w - \rho\right),$$

and $L(h,k,\rho)$ is the bivariate normal integral according to the indication of [Kotz et al. 2000].

An alternative formula [Oksoy, Aroian 1994] for $F_W(w)$ involving the $V(h,q)$ function of Nicholson [1943] is

$$F_W(w) = \frac{1}{2} + \frac{1}{\pi}\arctan(t_w) + 2V\left\{\frac{b\,t_w - a}{\sqrt{1+t_w^2}}, \frac{b + a\,t_w}{\sqrt{1+t_w^2}}\right\} - 2V(b,a), \tag{8}$$

where

$$V(h,q) = \int_0^h \int_0^y \Phi(x)\Phi(y)dxdy, \quad y = \frac{q}{h}x.$$

Remembering the function of Owen (1956)

$$T(h,\lambda) = \frac{1}{2\pi}\arctan\lambda - V(h,\lambda h),$$

it has been easy to find [Pollastri,Tulli 2012] the following formula

$$F_W(w) = \frac{1}{2} + \frac{1}{\pi}\arctan(t_w) + \frac{1}{\pi}\arctan\left(\frac{b + a\,t_w}{b\,t_w - a}\right) + \\ -2T\left(\frac{b\,t_w - a}{\sqrt{1+t_w^2}}, \frac{b + a\,t_w}{b\,t_w - a}\right) - \frac{1}{\pi}\arctan\left(\frac{a}{b}\right) + 2T\left(b, \frac{a}{b}\right). \tag{9}$$

3.2. Confidence intervals for the ICER

In her PhD thesis [Galeone 2007], Galeone proposed a new approach, called the exact distribution method, to construct the CI for $\frac{\mu_Y}{\mu_X}$, the ratio of two means, based on the inverse CDF of W_n.

This approach always guarantees the existence of bounded CIs, since the CDF is a monotonic non-decreasing function that can be

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inverted with computational methods. The (1-α) confidence interval of $\frac{\mu_Y}{\mu_X}$ .obtained by inversing the CDF of *W*, is given by

$$P\left\{W_{\alpha/2} \le \frac{\mu_Y}{\mu_X} \le W_{1-\alpha/2}\right\} = 1-\alpha \tag{10}$$

where $W_{\alpha/2}$ and $W_{1-\alpha/2}$ are the estimators [Galeone, Pollastri 2008] of $\left(\frac{\alpha}{2}\right)^{th}$ and the $\left(1-\frac{\alpha}{2}\right)^{th}$ quantile of the r.v. W.

An alternative approach to obtain the CI for the ratio of the means in a bivariate normal distribution was proposed by Fieller [Fieller 1940; Fieller 1954] known as "Fieller's theorem". Calculation of the CI is relatively simple and this approach has been used as a touchstone by several authors (e.g. see [Kendall, Stuart 1972]), because of its importance in examining the general techniques for constructing CIs using resampling techniques, such as jack-knife or bootstrapping. However, the existence of a bounded (1-α)% CI is not always guaranteed with Fieller's theorem, and the practical interpretation of the results is impossible in these cases. Gardiner at al. [2001] improved that the CI is bounded if, and only if, the estimated mean value at denominator is significantly different from zero at level α.

Returning to the problem of building the CI for the ICER and remembering that, in the above conditions, it is possible to write

$$(\hat{\Delta}_{\bar{C}}, \hat{\Delta}_{\bar{E}}) \rightarrow N(\mu_{\Delta_C}, \mu_{\Delta_E}, \sigma^2_{\Delta_C}, \sigma^2_{\Delta_E}, \rho_\Delta)$$

the estimator of the ICER

$$\hat{R} = \frac{\hat{\Delta}_{\bar{C}}}{\hat{\Delta}_{\bar{E}}} \tag{11}$$

is approximately distributed as a ratio of two correlated normal r.v. The CDF is indicated by

$$F_{\hat{R}}(r).$$

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It is possible to compute the CI as follows:

$$P\left[F_{\hat{R}}^{-1}(\alpha/2) < R < F_{\hat{R}}^{-1}(1-\alpha/2)\right] = 1-\alpha \qquad (12)$$

where

$$F_{\hat{R}}^{-1}(\alpha/2) \;\; and \;\; F_{\hat{R}}^{-1}(1-\alpha/2)$$

are the quantiles of the ratio of two correlated normal r.v.

The procedures and functions for constructing confidence intervals using the exact distribution method may be implemented using, for instance, Matlab [Galeone, Pollastri, 2012] or R code [De Capitani, Pollastri 2012] or Fortran+IMSL.

4. Concluding remarks

The calculation of the CI for the ICER is fundamental to take into account the uncertainty due to differences in samples. The new parametric technique for the construction of the CIs for the ICER here presented is based on the same parametric assumptions of the Fieller method.

Even if the Fieller method is easier from a computational point of view as compared to the new one, when the incremental effectiveness is close to zero the CIs obtained with the Fieller method are not bounded, and for this reason this method is not always relevant. The procedures and functions for constructing CIs with this new parametric method are already available in the Matlab and R code, as indicated before.

Any decision about a new intervention must also be qualitative. The choice between two interventions is very often sensitive, because there are also ethical considerations involved in people's health and solving social problems. The sustainability of the new intervention must be considered very carefully. The new policy must be discussed by the maximum number of experts in the field of intervention in order to arrive at a decision based on collective responsibility, considering also the value of the ICER and of its uncertainty.

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WSPÓŁCZYNNIK EFEKTYWNOŚCI KOSZTÓW DO PORÓWNYWANIA POLITYKI SPOŁECZNEJ I ZDROWOTNEJ

Streszczenie: Analiza inkrementalnego współczynnika efektywności kosztów (*incremental – cost-effectiveness ratio,* ICER) jest ważną częścią społecznych i zdrowotnych procesów decyzyjnych, ponieważ jednocześnie dostarcza informacje o koszcie i skuteczności nowej interwencji medycznej. Szczególne znaczenie dla analizy ma kalkulacja przedziału ufności dla współczynnika ICER. W artykule zostanie zaprezentowana nowa parametryczna metoda budowy przedziałów ufności dla ICER, bazująca na rozkładzie ilorazu skorelowanych zmiennych o rozkładzie normalnym. Zaprezentowana metoda pozwala na oszacowanie współczynnika ICER w każdy warunkach, w przeciwieństwie do klasycznej parametrycznej metody zaproponowanej przez Fiellera.

Słowa kluczowe: inkrementalny współczynnik efektywności kosztów, rozkład ilorazu skorelowanych zmiennych losowych o rozkładzie normalnych, przedział ufności dla współczynnika ICER.