On the equivalence of the net benefit and the Fieller's methods for statistical inference in cost-effectiveness analysis *

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Abstract

This paper shows that there exists a close relation between the net benefit and Fieller's methods for calculation of confidence intervals and performing hypothesis testing in cost-effectiveness analysis. The prices at which the net benefit confidence interval limits are equal to zero are identical to the Fieller's confidence interval limits for the incremental cost-effectiveness ratio.

Keywords: Confidence intervals; Cost-effectiveness analysis; Fieller's method; Hypothesis testing; Net benefit.

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1 Introduction

In the health economic literature the incremental cost-effectiveness ratio (ICER) has been the main focus of interest for the statistical analysis of random individual patient cost and effectiveness data. Various parametric methods have been proposed, such as the Fieller's, Taylor and confidence box, together with non-parametric bootstrap methods for computing confidence intervals around the ICER [1,2]. An alternative recently suggested approach is based on a reformulation of the ICER into a net benefit measure [3,4]. The information obtained by the net benefit approach is exactly the same as that obtained from analyses based on the ICER and the cost-effectiveness plane. A positive net benefit is equivalent to an ICER below and to the right of the willingness to pay ray in the cost-effectiveness plane.

The purpose of the paper is to investigate the formal relationship between the Fieller's method and the net benefit approach for hypothesis testing and confidence interval estimation in cost-effectiveness studies.

The paper unfolds as follows: Section 2 introduces the notation and basic quantities. Section 3 establishes the relation between the net benefit and the Fieller's method for testing cost-effectiveness. An empirical example is given in section 4, and section 5 concludes.

2 The incremental cost-effectiveness ratio and the net benefit

Assume that two samples of bivariate cost (C) and effect (E) data of a control treatment and a new treatment are available from some general bivariate distribution as

$$\begin{pmatrix} C_{ji} \\ E_{ji} \end{pmatrix} \sim \left(\begin{pmatrix} \mu_{C_j} \\ \mu_{E_j} \end{pmatrix}, \begin{pmatrix} \sigma^2_{C_j} & \sigma_{C_jE_j} \\ \sigma_{E_jC_j} & \sigma^2_{E_j} \end{pmatrix} \right), \; i = 1, ..., n_j, \tag{1}$$

where $j = 0, 1$ index the control and new treatment, respectively. μ_{C_j} and μ_{E_j} denote the expected (mean) values, $\sigma^2_{C_j}$ and $\sigma^2_{E_j}$ denote the variances and $\sigma_{C_jE_j}$ denotes the covariance between the costs and effects for treatment j [5,6].

Denote the average cost difference between the new and control treatment by $\mu_{\Delta C} = \mu_{C_1} - \mu_{C_0}$ and the average effect difference by $\mu_{\Delta E} = \mu_{E_1} - \mu_{E_0}$. If $\mu_{\Delta E} > 0$ and $\mu_{\Delta C} \leq 0$ ($\mu_{\Delta E} < 0$ and $\mu_{\Delta C} \geq 0$) R the new (old) treatment dominates and should be implemented (continued). When $\mu_{\Delta E} > 0$ and $\mu_{\Delta C} > 0$ ($\mu_{\Delta E} < 0$ and $\mu_{\Delta C} < 0$) further analyses are needed. The incremental cost-effectiveness ratio denoted by R is defined as (assuming $\mu_{\Delta E} \neq 0$)

$$R = \frac{\mu_{\Delta C}}{\mu_{\Delta E}}, \tag{2}$$

and represents the additional average cost of producing one more unit of health effects achieved by the new (control) treatment. To decide what treatment to implement information about the willingness to pay p for a gained unit of effectiveness is needed and the new treatment should replace the control according to the following rule

$$\textit{Implement new treatment if:} \begin{cases} R < p, \textit{ given that } \mu_{\Delta E} > 0, \\ R > p, \textit{ given that } \mu_{\Delta E} < 0. \end{cases} \tag{3}$$

As shown by Tambour, Zethraeus and Johannesson [3] and Stinnett and Mullahy [4] the decision rule inequalities can equivalently be expressed as $p\mu_{\Delta E} - \mu_{\Delta C} > 0$. The left hand side of this expression, which is the monetary value of the change in health effects less the change in costs, defines a monetary net benefit measure:

$$NB\,(p) = p\mu_{\Delta E} - \mu_{\Delta C}. \tag{4}$$

The implementation decision rule based on the net benefit is that the new treatment should replace the control treatment if $NB(p) > 0$.

The estimators commonly used to estimate R and $NB(p)$ are based on the sample mean of the observed costs and effects in the two samples. The R and the net benefit estimators are given by

$$\widehat{R} = \frac{\widehat{\mu}_{\Delta C}}{\widehat{\mu}_{\Delta E}}, \text{ and } \widehat{NB}\,(p) = p\widehat{\mu}_{\Delta E} - \widehat{\mu}_{\Delta C}, \tag{5}$$

respectively, where the average effect and cost difference estimators are given by the sample mean differences of effects and costs, respectively, as $\widehat{\mu}_{\Delta E} = \overline{E}_1 - \overline{E}_0$ and $\widehat{\mu}_{\Delta C} = \overline{C}_1 - \overline{C}_0$, where $\overline{E}_1$, $\overline{E}_0$, $\overline{C}_1$ and $\overline{C}_0$ are the sample mean effects and costs of the new and control treatments, respectively. Note that we use the notational convention and let $\widehat{R}$ and $\widehat{NB}(p)$ denote the $ICER$ and $NB(p)$ *estimators*. These are separated from the *estimates* obtained in a specific trial denoted by $\widehat{r}$ and $\widehat{nb}(p)$.

3 A relation between the net benefit and the Fieller's method

Following the results of a central limit theorem, for sufficiently large sample sizes, the net benefit estimator will be normally distributed as

$$\widehat{NB}\,(p) \sim N\left(NB(p), \sigma^2_{\widehat{NB}(p)}\right), \tag{6}$$

where the net benefit estimator variance $\sigma^2_{\widehat{NB}(p)}$ can be expressed as

$$\sigma^2_{\widehat{NB}(p)} = p^2 Var\left(\widehat{\mu}_{\Delta E}\right) + Var\left(\widehat{\mu}_{\Delta C}\right) - 2pCov\left(\widehat{\mu}_{\Delta E}, \widehat{\mu}_{\Delta C}\right), \tag{7}$$

with estimate $\widehat{\sigma}^2_{\widehat{NB}(p)}$ obtained by substituting the variance and covariance expressions in (7) by the corresponding sample estimates. Note that the normal distribution result is valid whether or not the individual cost and effect distributions are normal or not. The more skewed and non-normal the individual distributions are larger sample sizes are needed for the normal distribution approximation to be valid.

Based on the normal distribution result a standard $(1-\alpha)$ level confidence interval is obtained as $\widehat{nb}(p) \pm z_{\alpha/2}\widehat{\sigma}_{\widehat{NB}(p)}$, where $z_{\alpha/2}$ is the $\alpha/2$ percentile of the standard normal cumulative distribution function (CDF) determined by $\Phi(z_{\alpha/2}) = \alpha/2$, for $\Phi(\cdot)$ denoting the normal CDF.

This confidence interval can be used to test the hypothesis $H_0 : NB(p) = 0$ that the net benefit is zero and that we are indifferent between which treatment to implement against the alternative hypothesis $H_1 : NB(p) \neq 0$, that either the new $(NB(p) > 0)$ or the old $(NB(p) < 0)$ should be implemented. The lower bound of this two-sided confidence interval can be used to test the null hypothesis $H_0 : NB(p) \leq 0$, that the net benefit is non-positive and that the old control treatment should be continued, against the alternative hypothesis $H_1 : NB(p) > 0$, that the net benefit is positive and that the new treatment should be implemented. If the lower bound of a $(1 - \alpha)$ level double-sided confidence interval is above zero, the null hypothesis is rejected in favor of the alternative hypothesis, at a significance level of $\alpha/2$.

Given α we can solve for the prices p at which the bounds of the two-sided confidence interval just equals zero. Thus by rearranging the confidence interval expression $\widehat{nb}\,(p) \pm z_{\alpha/2}\widehat{\sigma}_{\widehat{NB(p)}} = 0$, inserting the definition of the net benefit and its standard deviation and quadrating we obtain the following second order equation in p:

$$\frac{\widehat{\mu}_{\Delta C}^2 + p^2\widehat{\mu}_{\Delta E}^2 - 2p\widehat{\mu}_{\Delta E}^2\widehat{\mu}_{\Delta C}}{p^2\widehat{Var}\,(\widehat{\mu}_{\Delta E}) + \widehat{Var}\,(\widehat{\mu}_{\Delta C}) - 2p\widehat{Cov}\,(\widehat{\mu}_{\Delta E}, \widehat{\mu}_{\Delta C})} = z_{a/2}^2. \tag{8}$$

This expression is completely analogous to the Fieller's expression for the confidence interval limits for the ICER R. As shown by, for example, Briggs and Fenn [1], the Fieller's confidence limits for R are found by solving the second order equation

$$\frac{\widehat{\mu}_{\Delta C}^2 + R^2\widehat{\mu}_{\Delta E}^2 - 2R\widehat{\mu}_{\Delta E}^2\widehat{\mu}_{\Delta C}}{R^2\widehat{Var}\,(\widehat{\mu}_{\Delta E}) + \widehat{Var}\,(\widehat{\mu}_{\Delta C}) - 2R\widehat{Cov}\,(\widehat{\mu}_{\Delta E}, \widehat{\mu}_{\Delta C})} = z_{a/2}^2, \tag{9}$$

which is obtained by substituting R for p in (8) above. Thus solving for R in (9) gives exactly the same roots as solving for p in (8) and the solutions R_1 and R_2 $(R_1 > R_2)$ given by (9) are identical to the solutions p_1 and p_2 obtained by solving (8) and we have that $R_1 = p_1$ and $R_2 = p_2$. The solutions for p are obtained by applying the standard quadratic formula and are given by the two roots p_1 and p_2 as shown earlier by for example [1,7,8]

$$p \in \widehat{R}\frac{1 - z^2_{\alpha/2}\widehat{\rho}\widehat{cv}(\widehat{\mu}_{\Delta C})\widehat{cv}(\widehat{\mu}_{\Delta E})}{1 - z^2_{\alpha/2}\widehat{cv}^2(\widehat{\mu}_{\Delta E})} \pm \widehat{R}z_{\alpha/2}\frac{\sqrt{A-B}}{1 - z^2_{\alpha/2}\widehat{cv}^2(\widehat{\mu}_{\Delta E})},$$

where $A = \widehat{cv}^2(\widehat{\mu}_{\Delta C}) + \widehat{cv}^2(\widehat{\mu}_{\Delta E}) - 2\rho\widehat{cv}(\widehat{\mu}_{\Delta C})\widehat{cv}(\widehat{\mu}_{\Delta E})$ and $B = z^2_{\alpha/2}(1 - \rho^2)\widehat{cv}^2(\widehat{\mu}_{\Delta C})\widehat{cv}^2(\widehat{\mu}_{\Delta E})$, and where the coefficient of variation is defined as $\widehat{cv}(x) = \widehat{\sigma}_x/\overline{x}$. The Fieller's confidence limits and the prices p at which the bounds of the two-sided confidence interval just equals zero are approximate since the two roots may be imaginary in some samples (such cases are rare if $\widehat{cv}(\widehat{\mu}_{\Delta C})$ and $\widehat{cv}(\widehat{\mu}_{\Delta E})$ are less than 0.3 [7,8]).

The result that the net benefit and Fieller's approaches are closely connected might not come as a surprise. Both the net benefit and Fieller's method are based on a normality distribution result which is valid for sufficiently large sample sizes and both approaches are based on a normality result for a linear combination of $\widehat{\mu}_{\Delta C}$ and $\widehat{\mu}_{\Delta E}$. The Fieller's method requires that $\widehat{\mu}_{\Delta C}$ and $\widehat{\mu}_{\Delta E}$ follow a bivariate normal distribution so that the estimator defined by the linear combination $\widehat{F} = (\widehat{\mu}_{\Delta C} - R\widehat{\mu}_{\Delta E})$ is normally distributed as [7,8]

$$\widehat{F} \sim N\left(0, \sigma^2_{\widehat{F}}\right), \tag{10}$$

with variance $\sigma^2_{\widehat{F}}$ is given by

$$\sigma^2_{\widehat{F}} = R^2 Var\left(\widehat{\mu}_{\Delta E}\right) + Var\left(\widehat{\mu}_{\Delta C}\right) - 2RCov\left(\widehat{\mu}_{\Delta E}, \widehat{\mu}_{\Delta C}\right). \tag{11}$$

Given $\mu_{\Delta E} \neq 0$, conditional on the null hypothesis $H_0 : NB(p) = 0$, R is equal to p. This is seen by noting that

$$NB\left(p\right) = p\mu_{\Delta E} - \mu_{\Delta C} = 0 \Leftrightarrow p = \frac{\mu_{\Delta E}}{\mu_{\Delta C}} = R. \tag{12}$$

In other words, the net benefit is equal to zero if $p = R$. Using this result the net benefit estimator can be reformulated as

$$\begin{aligned} \widehat{NB}(p) &= p\widehat{\mu}_{\Delta E} - \widehat{\mu}_{\Delta C} = /given\ that\ H_0\ true \Rightarrow p = R/ \\ &= R\widehat{\mu}_{\Delta E} - \widehat{\mu}_{\Delta C} = -(\widehat{\mu}_{\Delta C} - R\widehat{\mu}_{\Delta E}) = -\widehat{F} \end{aligned} \tag{13}$$

That is, in testing the null $H_0 : NB(p) = 0$, the distribution of the net benefit estimator will thus under the null follow the same distribution as the negative of the Fieller's estimator.

4 Empirical illustration

The following example is based on a study by Obenchain et al. [9] which is a retrospective analysis of antidepressant pharmacotherapy in 1.242 US patients. The health economic question was whether it is good value for money to treat patients with depression with Fluoxetine instead of tricycle antidepressants (TCA). Effectiveness was measured as the proportion of patients being on their initial treatment after 6 months. The resulting ICER estimate $\widehat{r}$ was US$ -16 and, since the new treatment increased the effect, this reflects that Fluoxetine therapy dominated TCA. To illustrate the empirical distribution we use a plot of 1000 bootstrap replications in the cost-effectiveness plane in Figure 1 together with the two parametrically calculated Fieller's confidence limits shown as rays from the origin with the slopes $R_1 = 173$ and $R_2 = -206$. The conclusion based on the Fieller's confidence limits is that for willingness to pay prices above 173 the new intervention should be carried out, that is the willingness to pay for producing another unit of effectiveness is significantly above the cost of producing one more unit of effectiveness.

FIGURE 1 IN HERE

Figure 2 shows the net benefit estimate and the confidence interval for the net benefit estimate for different willingness to pay prices p. p_1 corresponds to the price for which the lower bound of the confidence interval for the net benefit is equal to zero while p_2 corresponds to the price when the upper bound of the confidence interval is equal to zero. The conclusion based on the net benefit approach (given the significance level and disregarding negative prices) is that for willingness to pay prices above 173 the null hypothesis of a non-positive net benefit (and that the old treatment should be continued) can be rejected and the alternative which is to implement the new treatment is accepted.

FIGURE 2 IN HERE

By comparing Figures 1 and 2 we see that $R_1 = p_1$ and that $R_2 = p_2$. Thus R_1 corresponds exactly to the price p_1 at which the lower limit of the confidence interval for the net benefit is just equal to zero while R_2 corresponds to the price p_2 at which the upper limit of the confidence interval for the net benefit is just equal to zero.

5 Discussion and Conclusion

There is a close relation between the Fieller's and net benefit method for testing cost-effectiveness which can be explained by the fact that both methods are based on a normality assumption. It can be shown that the prices at which the net benefit confidence limits are equal to zero are identical to the slope of the rays for the Fieller's confidence limits for the incremental cost-effectiveness ratio.

The two roots, interpreted as prices, generally reflects the situation when the upper and lower bound is equal to zero (see the example above). However, we may also have the situations where the two prices either reflect the case when the lower bound is equal to zero or the situation when the upper bound is equal to zero. The two latter situations should be rare if the difference in health effects are significant.

Adapting a net benefit approach for analysing uncertainty is advantageous since interpretation and statistical problems associated with the ICER approach is avoided [4]. The use of the net benefit approach also facilitates sample size calculations and the use of Bayesian approaches [10,11]. Finally, the net benefit approach allows a formal relation between cost-effectiveness acceptability curves and statistical inference to be established [5].

In conclusion, the use of the net benefit approach for analyzing uncertainty in economic evaluations allows for application of traditional parametric statistical methods for confidence interval estimation and hypothesis testing. Besides that the use of the net benefit approach facilitates uncertainty analysis of individual patient cost and effectiveness data it also gives the Fieller's limits of the confidence interval for the ICER in the cost-effectiveness plane.

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