New perspective on parametric confidence intervals for the cost-effectiveness ratio

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Abstract
The number of economic evaluations of medical treatments or interventions has grown because costs become more important in health decision making. If data on resource use and health benefit are available among patients for competing treatments, confidence intervals (CI) for cost-effectiveness ratios (CER) are useful to compare the two treatments because they provide information on the uncertainty in their point estimates. In literature several parametric methods have been proposed for computing CI for CER. The Fieller method (FM) provides the best performances because it consider the skewness in the distribution of the ratio estimator of CER. Anyway, the FM does not always produce bounded CIs for CER. In particular, this method fails when the incremental effectiveness at denominator is not statistically significant. For this reason, a new parametric technique for the construction of $100(1-\alpha)\%$ CIs is here proposed, and it is based on the exact distribution of the estimated CER. This novel method always exists and produces bounded intervals with satisfactory and very close performances to the FM.

Introduction

The number of economic evaluations of medical treatments or interventions has grown because costs become more important in health decision making (Polsky, Glick et al., 1997). If data on resource use and health benefit are available among patients for competing treatments, confidence intervals (CI) for cost-effectiveness ratios (CER) are useful to compare the two treatments because they provide information on the uncertainty in their point estimates. In literature several parametric methods have been proposed for computing CIs for CER, as the Bonferroni method (BM) and the Fieller method (FM) (Chaudhary and Stearns, 1996). The first method is based on the assumption that numerator and denominator of CER follow separately a Normal distribution, the second one requires that the numerator and denominator of CER are jointly distributed as a Bivariate Normal (BN) random variable (rv). As reported in several other articles, the CIs based on the BM, that presuppose the independence of the two Normal rvs, are too conservative and the corresponding interval widths are always larger as compared to the FM (Laska, Meisner et al., 1997; Polsky, Glick et al., 1997). Moreover, both methods do not always exist (Laska, Meisner et al., 1997; Gardiner, Huebner et al., 2001). In particular the FM does not produce bounded intervals for CER when the incremental effectiveness at denominator is not statistically significant. A new parametric technique for the construction of $100(1-\alpha)\%$ CIs is here proposed and it is based on the exact distribution of the estimated CER.

Material and Methods
In the context of a clinical trial for comparing a new treatment to a standard one, we put $\underline{\mu} = (\mu_C, \mu_E)$, where $\mu_C = \mu_{Cn} - \mu_{Cs}$ is the incremental cost and $\mu_E = \mu_{En} - \mu_{Es}$ is the incremental effectiveness of the new treatment relative to the standard one. The incremental CER is defined as $R = \mu_c / \mu_E$ with $\mu_E \neq 0$. By means of trial data we obtain the maximum

likelihood estimators (MLE) for the means $\underline{\hat{\mu}} = (\hat{\mu}_C, \hat{\mu}_E)$ and covariance matrix $\hat{\Sigma}$. These MLEs are consistent for the true values and by the invariance property of the MLEs the consistent MLE of CER is consequently $\hat{R} = \hat{\mu}_C / \hat{\mu}_E$ (Stuart, Ord et al., 1999). The aim is to construct a $100(1-\alpha)\%$ CIs for CER with the FM and the novel method and to provide comparisons between the two methods.

The Fieller Method

The FM refers to a general approach to obtain CIs for the ratio of means in a BN rv (Fieller, 1954; Chaudhary and Stearns, 1996). The FM assumes that numerator and denominator of the ratio estimator $\hat{R} = \hat{\mu}_C / \hat{\mu}_E$ follow a BN distribution, so that $\hat{\mu}_C - R\hat{\mu}_E$ is normally distributed with expected value equal to zero. By means of the standardization of $\hat{\mu}_C - R\hat{\mu}_E$, Fieller found a pivotal quantity for the unknown parameter *R*. Therefore, the CIs for *R*, if they exist, are derived from the following inequality: $(\hat{\mu}_C - R\hat{\mu}_E)^2 \le z^2_{(1-\alpha/2)} Var(\hat{\mu}_C - R\hat{\mu}_E)$ where $z_{(1-\alpha/2)}$ is the $(1\text{-}\alpha/2)^{th}$ quantile point of a standard Normal rv. The second order inequality may be conveniently expressed as $f(R) = a_n R^2 - 2b_n R + c_n \le 0$ with $a_n = \hat{\mu}_E{}^2 - z^2_{(1-\alpha/2)} \sigma^2_E$, $b_n = \hat{\mu}_C \hat{\mu}_E - z^2_{(1-\alpha/2)} \rho \sigma_C \sigma_E$, $c_n = \hat{\mu}_C - z^2_{(1-\alpha/2)} \sigma^2_C$. The CIs for *R* are bounded only when $a_n > 0$, i.e. the estimated incremental effectiveness $\hat{\mu}_E$ is significantly unequal to zero at level α (Gardiner, Huebner et al., 2001; Galeone, 2007). When this condition is verified the limits of the CI for R are: $\dfrac{b_n \pm \sqrt{b_n^2 - a_n c_n}}{a_n}$.

The Exact Distribution Method (EDM)

On the same parametric assumption of FM, the distribution of $(\hat{\mu}_C, \hat{\mu}_E)$ is a BN rv with means (μ_C, μ_E), variances $(\sigma^2_C / n; \sigma^2_E / n)$ and coefficient of correlation ρ. Therefore, $\hat{R} = \hat{\mu}_c / \hat{\mu}_E$ is the ratio of two correlated Normal rvs jointly distributed as a BN rv and its distribution is a finite non-standard mixture density with dichotomous proportions with a Cauchy component (Marsaglia, 2006; Galeone, 2007). The simultaneous CI for $R = \mu_c / \mu_E$ can be obtained by using the inverse cumulative density function of $\hat{R}$, as follows: $\Pr\left\{ \hat{R}_{\frac{\alpha}{2}} = L < R < \hat{R}_{\left(1-\frac{\alpha}{2}\right)} = U \right\} = (1-\alpha)$ where $\hat{R}_{\frac{\alpha}{2}} = F^{-1}_{\hat{R}}\left(\frac{\alpha}{2}\right)$ is the $(\alpha/2)^{th}$ quantile point and $\hat{R}_{1-\frac{\alpha}{2}} = F^{-1}_{\hat{R}}\left(1-\frac{\alpha}{2}\right)$ is the $(1\text{-}\alpha/2)^{th}$ quantile point of the distribution of $\hat{R}$. This method has not problem in existence of the CIs, since the cumulative density function (CDF) is a monotonic non-decreasing function that can always be inverted.

Simulation study

Monte Carlo experiment was used to assess the performances of the FM and EDM for computing 90% CIs for CER, by differing levels of correlation between numerator and denominator. We started using a simulated population with known means (0.25, 1.20) and variances (9, 16) of costs and effects, respectively, known correlations between costs and effects (0, |0.3|, |0.6|, |0.9|) and a known CER. The sample size varied from 25 to 1,600 with the rule of the doubling technique. Overall, there were 49 combinations of simulation parameters. For each combination of parameters, we simulated 5,000 independent samples for each treatment group from this population. The criterions used to evaluate the performances of the methods were the probability of coverage of the intervals (denoted as $(1-\hat{\alpha})$), the average width of the intervals (denoted as *Amp*) and the symmetric miscoverage of the intervals (denoted as *%ds*).

Results

The performances of the two methods for the construction of 90% CIs for *R* for $\rho = 0.3$ were reported in table 1. For small values of *n* ($n \leq 200$), the CIs constructed with the FM were not always bounded. For this reason the corresponding average widths were denoted as "-", i.e. there was at least one unbounded confidence interval that yielded the average widths not to be expressed as a real number. Consequently, the corresponding coverage probabilities were very low. For elevated values of *n*, the performances of the CIs based on FM and EDM were very close.

Table 1 – Performances of the two methods for the construction of 90% CI with $\rho = 0.3$.

n		FM	EDM
25	$(1-\hat{\alpha})$	0.3941	0.9267
	%ds	0.5619	0.6178
	Amp	-	5.0478
50	$(1-\hat{\alpha})$	0.5947	0.9196
	%ds	0.3476	0.5463
	Amp	-	3.0029
100	$(1-\hat{\alpha})$	0.8192	0.9101
	%ds	0.2367	0.5222
	Amp	-	1.5692
200	$(1-\hat{\alpha})$	0.8639	0.8968
	%ds	0.6352	0.5368
	Amp	-	0.7281
400	$(1-\hat{\alpha})$	0.8974	0.8972
	%ds	0.4815	0.4805
	Amp	0.4338	0.4326
800	$(1-\hat{\alpha})$	0.9018	0.9010
	%ds	0.5173	0.5192
	Amp	0.2905	0.2901
1600	$(1-\hat{\alpha})$	0.9008	0.9006
	%ds	0.4980	0.4976
	Amp	0.2002	0.2001

Extending the simulation results to all other values of ρ considered, the FM always failed for $n \leq 50$, with corresponding non-acceptable coverage probabilities. For ρ equal to -0.6 and -0.9, the FM failed also for *n* equal to 100, but in these cases the coverage probabilities were higher as referred to those for $n<100$. For other values of ρ, i.e. equal to –0.3, 0 and 0.6, the FM failed also for *n* equal to 200. The simulation results highlighted that the FM less frequently produces unbounded confidence intervals for R with increasing values of n. Finally, the performances of the two methods were satisfactory and very close to each other for high values of n.

Conclusions

The EDM for the construction of CIs for CER always exists and produces bounded intervals with satisfactory and very close performances to the FM. Although the calculus of the limits of the confidence intervals by means of the novel method is more complicated, as this involves the calculation of the inverse of a CDF that can be obtained only by a computer support, the EDM always allows to obtain bounded confidence intervals, also when the FM produces unbounded intervals. The implementation of procedures and functions to construct CIs with the EDM is already available in Matlab and will soon be available in SAS package, too. Differently from other parametric methods, these two methods are preferable for the construction of CIs because they consider the skewness in the distribution of the ratio estimator.

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