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Parametric cost-effectiveness inference with skewed data

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ABSTRACT

Comparing treatment effects while taking into account the associated costs is an important goal of cost-effectiveness analyses. Several cost-effectiveness measures have been proposed to quantify these comparisons, including the incremental cost-effectiveness ratio (ICER) and the incremental net benefit (INB). Various approaches have been proposed for constructing confidence intervals for ICER and INB, including parametric methods (e.g. based on the Delta method or on Fieller's method), nonparametric methods (e.g. various bootstrap methods), as well as Bayesian methods. Skewed data are usually the norm in cost-effectiveness analyses, and accurate parametric confidence intervals in this context are lacking. Confidence intervals for both ICER and INB are constructed using the concept of a generalized pivotal quantity, which can be derived for various combinations of normal, lognormal, and other skewed distributions for costs and effectiveness. The proposed methodology is straightforward in terms of computation and implementation even in the presence of covariates, and the resulting confidence intervals compared favorably with existing methods in a simulation study. The approach is illustrated using data from three randomized trials.

1. Introduction

In order to assess the relative performance of a new treatment, subject level data from randomized trials can be used, and comparing the effects of treatments while taking into account their associated costs is clearly important (O'Brien and Briggs, 2002; Willan and Briggs, 2006). Several cost-effectiveness measures have been proposed to quantify these comparisons and one of the widely used measures is the incremental cost-effectiveness ratio (ICER). Given two treatments to be compared, ICER is defined as the ratio between the difference of expected costs and the difference of expected effects. While intuitive as a measure of *cost per gained benefit*, the ICER is difficult to interpret in several situations of practical interest. For example, the ICER will have the same sign if the new treatment is more costly than the standard treatment, but is less effective, or if the

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new treatment is less costly, but is more effective. Furthermore, being a ratio parameter, the construction of confidence intervals for the ICER can be problematic; the issue of infinite confidence intervals arises when there is no (significant) difference between the expected effects. In order to overcome these drawbacks associated with the ICER, a parameter that has been suggested is the incremental net benefit (INB) (Stinnett and Mullahy, 1998). The INB is defined as the difference between the incremental effectiveness and the incremental cost, and it involves the *willingness-to-pay* parameter (denoted by λ).

Although the ICER and the INB have intuitive appeal and the calculation of point estimates is straightforward, the investigation of their statistical properties is challenging. This is particularly the case for the ICER, which is defined as a ratio measure. Within this context, several approaches have been proposed in the literature to construct confidence intervals for ICER and INB. They include parametric methods (e.g. based on the Delta method or on Fieller's method Fieller, 1954), nonparametric methods (e.g. various bootstrap methods Efron and Tibshirani, 1993), as well as Bayesian methods (Thompson and Nixon, 2005). Combinations of these different types of methods, such as the combination of Fieller's method with the bootstrap (Jiang et al., 2000), have also been proposed. Additionally, bootstrap methods based on an angular transformation approach (Cook and Heyse, 2000) and the re-ordering bootstrap percentile method (Wang and Zhao, 2008) have been proposed for ICER.

Several simulation studies have compared some of these alternative methods across various scenarios of interest (Cook and Heyse, 2000; Wang and Zhao, 2008; Polsky et al., 1997; Briggs et al., 1999; Fan and Zhou, 2007; Nixon et al., 2010; Mihaylova et al., 2011). The simulation results suggest that overall, Fieller's method and the parametric bootstrap method perform well (Polsky et al., 1997; Briggs et al., 1999). The limitations of Fieller's method regarding the previously mentioned issue of infinite confidence intervals have been documented (Cook and Heyse, 2000). The most extensive simulation to date (involving 486 scenarios) of the most commonly used methods (Fan and Zhou, 2007) recommends Fieller's method (and also the bootstrap-percentile and the standard bootstrap methods) as consistently providing reasonable coverage across multiple simulation scenarios. The bootstrap Fieller method was compared with Fieller's method and three bootstrap methods in one of the simulation studies (Wang and Zhao, 2008). Based on their limited simulation study, for the case when the cost is lognormally distributed, and the effect is normally distributed, they recommend the bootstrap Fieller method. It is important to note that the other simulation studies previously described have not included the bootstrap Fieller method.

The present work has been motivated by two considerations. First of all, some of the previous parametric approaches (Delta method, Fieller) assume normality or asymptotic normality. However, skewed data is the norm, rather than the exception, in cost-effectiveness studies (Thompson and Nixon, 2005; Briggs and Gray, 1998). For example, the mean and median expenses in US of persons with any health care expenses in 2009 (85% of the population) were \$4855 and \$1301, respectively (Kashihara and Carper, 2009). Even when normality holds, Fieller's method may fail to provide a finite confidence interval. Bootstrapping is usually employed with skewed data. When used alone, it was shown that the nonparametric bootstrap behaves similar to assuming normality (Thompson and Nixon, 2005; O'Hagan and Stevens, 2003), especially for large sample sizes. The statistical properties of the bootstrap used in combination with Fieller's theorem are less clear (as illustrated in one of the examples given later in the paper). In particular, the bootstrap Fieller may provide infinite confidence intervals even when the interval obtained using Fieller's method is finite. An alternative approach, employed here, consists of using a transformation (e.g., logarithm, power) to address the skewness. Secondly, when the data are skewed, having a parametric distribution usually leads to inference problems involving rather complicated parametric functions. For example, if the costs follow a lognormal distribution, then the incremental mean cost involves the difference between two lognormal means, the latter being a function of a linear combination of the mean and variance of the normal distribution of the log-transformed costs. Novel approaches are necessary to obtain accurate inferences in such a scenario, avoiding the drawbacks just mentioned. This is indeed the main goal of our work.

In this paper we use the concept of a generalized pivotal quantity (GPQ) to construct confidence intervals for ICER and INB. A very brief introduction to the GPQ idea is given in Appendix A of the paper. The resulting confidence interval is always finite. Since its introduction (Weerahandi, 1993), the GPQ methodology has been successfully applied by a number of researchers in order to obtain satisfactory confidence intervals for several parametric problems for which traditional approaches are unavailable, or are unsatisfactory. In particular, the GPQ methodology has been applied in the context of ratio parameters (Bebu et al., 2009), where the methodology has been used successfully for a ratio of regression coefficients. The asymptotic accuracy of the GPQ methodology is established in Hannig et al. (2006); however, satisfactory small sample performance has been noted in many scenarios, for example, in Bebu et al. (2009). An added appeal of the GPQ methodology is that if a vector-GPQ is available for a vector parameter, then a GPQ can be constructed for any function of the parameter, by simply obtaining the corresponding function of the vector-GPQ. We will indeed be exploiting this property in this paper. For a detailed discussion of the GPQ methodology, along with numerous applications, we refer to the books by Weerahandi (1995, 2004).

The paper is organized as follows. We start by describing the joint model for Cost and Effectiveness. We investigate in detail two models: (i) the joint distribution of (ln(Cost), Effect) is bivariate normal, and (ii) the joint distribution of (Cost, Effect) is bivariate normal. Power transformations are also briefly considered in the context of the gamma distribution. Note that under (i), marginally, the costs follow a lognormal distribution. Under these setups, the GPQ methodology for inference concerning ICER and INB is presented in the next section for the case when there are no covariates; we have essentially described the derivation of confidence intervals. We assess the performance of the new confidence intervals using a simulation study and illustrate the new methods using data from three previously published randomized trials (Willan and Briggs, 2006; Thompson and Nixon, 2005). In the simulation study, we have also included other competing