Reviewer's report

Title: Clinical cost-effectiveness analysis: a method for comparing competing interventions in the absence of randomized trials

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Reviewer: Francisco-Jose Vazquez-Polo

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Referee's Report:
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"Clinical cost-effectiveness analysis: a method for comparing competing interventions in the absence of randomized trials"

The paper is not up-to-date with respect to health economics literature. It might make a useful contribution as a case-study or user-guide tutorial for practitioners, but not in its current form. The illustrative examples should be expanded and the simulation improved. The paper deals with an interesting problem that has provoked a large body of health economics literature. Although I found the problem to be interesting, this paper does not present any development of previous contributions to methodological research in this field. Thus, a significant proportion of the paper is devoted to summarizing standard results.

The paper presents as suitable for risk-benefit analysis all the instruments that are already known to be available, and which have been considered in cost-effectiveness analysis. This background has been presented in previous papers, see Lynd and O'Brien (2004), cited in the manuscript, and Shaffer and Watterberg (2006), among others.

A noteworthy absence is any mention of Bayesian methodology in the paper, despite the fact that this approach has been the one most dynamically adopted during the evolution of cost-effectiveness techniques in the last 10-12 years. All the elements presented in this paper regarding the performance of a risk-benefit analysis are well known and, moreover, are set out more clearly in Lynd and O'Brien (2004) and Shaffer and Watterberg (2006). However, this latter paper is not cited. In short, it needs to be made clearer just what the present paper adds to the literature, and more updated references should be made to related research.

Throughout this study, the economic concept of cost-effectiveness analysis and the clinical one of risk-benefit analysis are employed indiscriminately. I suggest the authors change the title of "Clinical cost-effectiveness analysis" to "Clinical risk-Benefit analysis", which I believe to be more appropriate. Although the paper does point out some of the (well known) disadvantages of using the cost-effectiveness acceptability curve (p. 8), the IRBR (pp. 10-11) and the NCB
(p. 12), nothing is said about other problems which, in my opinion, are much more significant:

1) How to quantify the degree of discrepancy between probability-based (to select an alternative that has the highest probability of maximizing expected NB) and expectation-based methods (to select a treatment which maximizes the estimate of the expected NB).

2) Intransitivity in pair-wise comparisons.

Both of these concerns are present in the risk-benefit context, and should be addressed by the authors. Excellent references are Jakubczyk and Kaminski (2010) Health Economics, DOI: 10.1002/hec.1534; and Moreno et al. (2010) European Journal of Operational Research, doi:10.1016/j.ejor.2009.10.012, and references therein.

The idea of estimating clinical costs and benefits using a systematic review is sensible, but the approach adopted here is overly simplistic, and merely contributes known, straightforward results in introductory meta-analysis literature. Similarly, the use of the method of the moments to elicit a beta distribution is a fairly standard technique. It is not made clear how the proposed method would improve on that set out in Lynd and O'Brien (2004).

Data from the nine randomized trials should be given to enable replication of the calculations in Table 1.

Minor points:

1. Bottom of page 8. “(See Box)”. To what “Box” are the authors referring?
2. Page 10. Section “Estimation of uncertainty....” should be in italics. This also applies, on page 11, to “Calculation of the net clinical benefit...”.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests