Author's response to reviews

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

Authors:

Alejandro Lazo-Langner (alejandro.lazo@alumni.uottawa.ca)  
Marc A Rodger (mroder@ohri.ca)  
Nicholas J Barrowman (nbarrowman@cheo.on.ca)  
Timothy Ramsay (tramsay@ohri.ca)  
Philip S Wells (pwells@ohri.ca)  
Douglas A Coyle (dcoyle@uottawa.ca)

Version: 2 Date: 15 October 2011

Author's response to reviews: see over
Dear Dr. Melissa Norton MD,
Editor-in-Chief
BMC Medical Research Methodology

Please find attached a copy of our revised manuscript entitled “Comparing multiple competing interventions in the absence of randomized trials using clinical risk-benefit analysis” by authors Alejandro Lazo-Langner, Marc A. Rodger, Nicholas J. Barrowman, Tim Ramsay, Philip S. Wells, and Douglas A. Coyle. This title has been modified from the previous one “Clinical cost-effectiveness analysis: a method for comparing competing interventions in the absence of randomized trials” upon advice of the reviewers. We have made extensive revisions and modifications, as detailed below, and we are confident that the manuscript will be acceptable for publication in BMC Medical Research Methodology. As requested, all changes have been highlighted in the body of the manuscript. We have reviewed formatting requirements and we believe that the work now conforms to the journal’s standard.

We state that this is an original work that has not been previously published. However, this manuscript presents work developed as part of a thesis submitted by the first author to the Faculty of Graduate and Postdoctoral Studies of the University of Ottawa, Canada. The aforementioned thesis has been submitted to the Library and Archives Canada for inclusion in their repository under a Theses Non-Exclusive License. Because the license is non-exclusive, the author can pursue any other publishing venture that he/she wishes. The license clearly indicates that authors continue to own the copyright and keep moral rights on the thesis.

In regards to authors’ contributions we state the following: Alejandro Lazo-Langner participated in the conception, design, and development of the method, as well as in data collection, analysis, and drafting of the manuscript. Marc A. Rodger participated in the development of the method, as well as in data collection, analysis, and drafting of the manuscript. Nicholas J. Barrowman participated in the development of the statistical methods and drafting of the manuscript. Tim Ramsay participated in the development of the statistical methods and drafting of the manuscript. Philip S. Wells participated in data collection, analysis, and drafting of the manuscript, and Douglas A. Coyle participated in the conception, design, and development of the method, as well as in analysis, and drafting of the manuscript. Authors declare no conflicts of interest.

Sincerely,

Alejandro Lazo-Langner MD MSc
Response to reviewers:

We thank the reviewers for their many helpful comments. We have made extensive reviews and editing of our manuscript and we are confident that all of the reviewers’ concerns have been addressed. Please find detailed responses below.

Reviewer: J Mar

1. Title (Clinical cost-effectiveness analysis: a method for comparing competing interventions in the absence of randomized trials) needs to be changed. The inclusion of the term cost as an equivalent to risk is misleading. Cost is always measured in monetary units. The approach comes from the cost-effectiveness methods but it is applied to a risk-benefit framework. In my opinion the original terminology by Lynd and O’Brien should be recovered.

R. We have modified the title as suggested.

2. The objective (we elaborate on a method to compare competing interventions through a cost-effectiveness approach using information available in the literature to estimate the costs and benefits of an intervention from a clinical perspective (i.e. the clinical cost-effectiveness analysis, CCEA) and we provide an example to illustrate this method) is not adequately justified. They should specify in the introduction and in the methods the added value of their complementary approach to the previous paper by Lynd and O’Brien.

R. The introduction has been modified and we believe that the value of the proposed approach has been clarified.

3. The example has been used only to draw the pictures. They should include a results section with results of the calculations carried out. At the same time a reader would expect in the discussion comments about the conclusions obtained by applying the method to the example. It is easier to understand the method and its uses when the authors show the calculations and comment a real case.

R. We have redone the whole analysis section applying this approach to the comparison of 5 anticoagulants for the prevention of venous thrombosis in orthopaedic surgery. The results section has also been modified and we believe that it is much more clear now. Additional details on the systematic review and other calculations have been provided in the main manuscript and in the supplementary materials.

4. The discussion is basically a concepts review and lacks of a description of the consequences of using the method in the real world. As an example, the second paragraph of the discussion could be moved to the introduction because does not rely on the results of the paper. My suggestion is to substitute some of the general comments based on concepts by specific comments about the example.

R. We have edited extensively the discussion and included the results of the actual analysis as examples of the potential application of this approach. Sections of the discussion have been moved to the introduction as suggested.

Reviewer: M Shoukri

The authors claim that the chief aim of this paper is “to develop a method for comparing multiple competing interventions in the absence of randomized trials
sing a conjoint assessment of benefits and risks”. I noted that the same statement was made in the Results paragraph. The conclusions are misleading as well. I think the authors need to re-write the objectives, the result and the conclusions

**R. We have extensively edited the objectives, results and conclusions (vide supra).**

Discretionary Revisions

1- Background
This is a nicely written introduction, but the authors make some ambiguous statement such as “highly desirable”, in line 7 from the bottom of page 5. It is not clear what they really mean by highly desirable. In the last line of same page, the wording “size effects” should be effect size, as is commonly used and as the authors wrote in a subsequent section.

**R. The suggested changes have been made.**

2- In the Methods section, terms such as “efficacy”, “risk”, and “beneficial” should be defined or introduced to the reader from the beginning of this section, within the proper context. These terms were later explained in page 8.

**R. This has been corrected.**

3- In page 8, it is not clear what “natural units” mean.

**R. This has been corrected.**

4- In lin7, page 9, I suggest adding the term “due to all causes” after the (e.g. Mortality

**R. This has been corrected.**

1- Line 8 from the bottom of page 9, does not make sense.

**R. This has been corrected.**

2- It is not clear what they mean by sufficient studies.

**R. This has been corrected.**

3- Page 10. There is an unexpected jump into the estimation of the parameters of the Beta distributions, without giving justification to the real need for this distribution. Is there other distributions defined over [0, 1] that may be used. I am very concerned about this part because the authors did not provide a convincing introduction to the logic behind this simulation.

**R. We have modified the description and rationale behind the use of beta distributions to parameterize the simulations. This is a commonly used approach in the economics field, and although certainly is a matter of debate, it is still extensively used.**

4- Top of page 11. What does it mean “the slope of a line through the origin….plane”.

**R. A line drawn through the origin of the quadrants in a risk-benefit plane. This has been included in the description of figure 1 showing a hypothetical risk-benefit plane.**

5- The systematic review section is poorly written. No inclusion or exclusions criteria for the studies were given. No graphics were given, and the result of the heterogeneity testing was not reported. It is also (see page 13) confusing to see a statement like” using a fixed or random effects model as appropriate”.

**R. We have added a number of methodological aspects to the description of the systematic review. We also added additional supplementary materials. We agree with the statement that the review did not adhere to current reporting standards but the main objective of this**
manuscript is not to serve as a systematic review. Finally, regarding the use of fixed or random effects model, appendix 1 details the rationale for using one or the other.

6- In the clinical cost-effectiveness analysis section, page 13: It is still not clear why the need to simulate from the beta. It is not clear what the information on costs and benefits are, and how they were used to estimate the parameters of the beta distribution.

**R. We have rewritten this section and believe that it is much more clear now.**

7- The discussion is too long and is very repetitive. In line 5 from the top of page 15, what do they mean by head-to-head randomized trials?

**R. we have modified the discussion and added new items incorporating the results of the study. Additionally, the term head-to-head has been eliminated and changed for “multiple intervention arms” (i.e. randomized trials including 3 or more intervention arms)**

Reviewer: S Jankovic

The authors should add some important details to their illustrative example: first, they should state the time horizon used for clinical cost effectiveness analysis (CCEA) of anticoagulants in prophylaxis of thromboembolic events after hip replacement (is it only during 5 weeks of prophylaxis or 3 months, or longer); second, they should add a sentence in the same section stating “that results of this CCEA could be different if complete adverse effects spectrum of the compared drugs was taken into account as clinical cost.”. Besides, I am not sure what is compulsory structure of an article for this journal, but it looks to me logic to change subtitle “An illustrative example” to “Results”.

**R. Thank you for the useful suggestions. All have been incorporated in the revised version of the manuscript.**

Reviewer FJ Vazquez-Polo

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.

R. Thank you for the suggestions. We have expanded and modified the introduction incorporating new references.

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.

R. We thank the reviewer for these suggestions. We have included in the discussion the aforementioned issues. However, the manuscript does not intend to exhaust all the many potential problems of cost-effectiveness analysis. Furthermore, some of the concerns raised might not be entirely applicable in their current form to the risk-benefit analysis since the latter deals with a clinical problem. These very interesting propositions will be explored in future studies.

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.

R. This has been modified (vide supra).

Minor points:

1. Bottom of page 8. “(See Box)”. To what “Box” are the authors referring?

R. This has been corrected.
2. Page 10. Section “Estimation of uncertainty....” should be in italics. This also applies, on page 11, to “Calculation of the net clinical benefit...”.

*R. This has been corrected.*