Author's response to reviews

Title: Comparative efficiency research: Meta-analysis of cost-effectiveness studies

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Author's response to reviews: see over
Dear Editor,

We would like to thank the reviewers for the constructive suggestions.

All the comments made by the reviewers have been addressed, with corresponding changes made directly to the manuscript where appropriate and detailed responses included below. We have improved the writing style and language. We have restructured the Methods section. Accompanying this letter, please, find attached a version of the manuscript with the changes highlighted by using the track changes mode in MS Word.

All authors listed on the title page have read the new version of the manuscript, and have agreed to the changes and the responses to the reviewers’ comments.

We look forward to hearing from you at your earliest convenience

Yours sincerely,

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Reviewer's report:

   Author’s comments: We have included the reference recommended.
   Line: 255-258.
   Reference: 14

2. I believe that the inclusion of some comment in introduction or discussions about Nixon BMJ. Jun 30, 2001; 322(7302): 1596–1598 paper might improve the paper discussion. This paper from Nixon discusses about the relative merits of commonly used methods and to offer a new descriptive approach that makes interpreting the evidence easier for decision makers who require a clear overview of the findings.

   Author’s comments: We have included the research of Nixon et al in the Introduction and Discussion.
   Line: 90-93 and 407-410
   Reference: 10

3. On page number 6, row 159 there is a missing C, so the right wording should be: \( C(u,1)=u \) and \( C(1,v)=v \)

   Author’s comments: We have included the missing letter.
   Line: 185

4. On the same page there is a mistake in row 141. It should be:

   \[ C(u_2,v_2)-C(u_2,v_1)-C(u_1,v_2)+C(u_1,v_1)\neq 0. \]

   Author’s comments: We have corrected the mistake (from ‘c’ to ‘C’)
   Line: 187

5. As part of the methods chapters, (on page 10 mainly), there is a description about the use of willingness to pay thresholds. This is a “hot topic” among health economists and it would be good to introduce short description about what these thresholds are and about its usefulness in resource allocation processes.

   Author’s comments: We have included some comments related to willingness-to-pay thresholds.
   Line: 121-130

6. As part of the discussion in lines 363 and 364, the authors stated that the measurements for calculating the net monetary benefits to make calculations should be done by using bootstrap in case of have access to individual patient data and with Monte Carlo Simulations when
patient data level are not accessible. This is true, but there should be better to reference that statement with appropriate references and to go explain in a more detailed way.

Author's comments: We have included appropriate references and have explained the rationale of this approach better.
Line: 374-379
Reference: 29-31

REVIEWER 2:
Reviewer's report:
Minor Essential Revisions

1. Abstract / Methods / 1st paragraph/ line 29.
A re-wording of the first line is suggested as the term “meta-analysis” constitutes a broader concept than the one that authors used.

   Author’s comments: We have reworded the first sentence of the Methods in the Abstract.
   Line: 29-30

2. Abstract / Conclusions / 1st paragraph/ line 46.
I don’t think that this conclusion could be drawn from the article in so a taxative way. Maybe a less assertive conclusion would be advisable.

   Author’s comments: We have changed our conclusion in the Abstract and the manuscript.
   Line: 45-46 and 420-426.

3. Abstract / Results / 1st paragraph/ line 44.
Maybe this statement “The TINB test was confirmed when increasing the simple size” seems to be obvious, as if TINB is supposed to follow a normal distribution (assumed by authors; line 259), p-values should decrease as sample size increases.

   Author’s comments: we have deleted this phrase in the Abstract.

4. Background / 2nd paragraph/ line 92.
It is not clear from the text if the term COMER has been used before or it is a new term proposed by the authors for their cost-effectiveness meta-analysis new method.

   Author’s comments: COMER is new term proposed by the authors. We now state that COMER is a new term.
   Line: 93-95.

5. Background / 4th paragraph/ line 112.
Although authors declare that the COMER method is suitable for individual and aggregated data, it seems that they only work on individual data meta-analysis in the remainder of the article. Maybe in the Discussion section a commentary could be inserted on that issue.
Author’s comments: we have included more references to the capacity of COMER for individual and aggregated data.

6. Methods / 1st paragraph/ line 117.
For those not familiar with cost-effectiveness analyses and the ICER, perhaps it should be advisable to insert here an introductory paragraph on the problem that arises when having a ratio with 2 parameters with very different distributions; costs and effects. The ICER is introduced in lines 235-241, but maybe it would be better to explain it earlier.

Author’s comments: We have included an introductory paragraph about ICER.
Line: 113-139

7. Methods / 2nd paragraph/ line 126.
Should it the words “joint distribution” be added to this line, for a better comprehension?

Author’s comments: We have included the words “joint distribution”.
Line: 172

8. Methods / line 139.
A “C” is lacking: C(u,1)=u and C(1,v)=v

Author’s comments: We have included the missing letter.
Line: 185

9. Methods / line 141.
Shouldn’t it be needed a capital “C” in the third one?
C(u2,v2)-C(u2,v1)-C(u1,v2)+C(u1,v1)>-0.

Author’s comments: We have corrected the mistake (from ‘c’ to ‘C’)
Line: 187

10. Methods / lines 164-166.
The data from the allergic rhinitis study are apparently used for creating the hypothetical population and applying the whole COMER process to them, not only for estimating which is the most appropriate copula. Maybe I am wrong but I have understood it this way. So I suggest that perhaps, a better approach to the paragraph could be to move the first line (“Because it is crucial to know the most appropriate copula for this study”) to line 169, after the “…COMER.” sentence. So the logic could be: “as we need to create a hypothetical population where to prove/develop our COMER method proposal, we use data from this study. we will also...”

Author’s comments: We have changed the phrase to reflect this idea.
Line: 208-212

I suggest that authors gave more details about how the process of the creation of cohorts was made: how many cohorts were created (500-15= 485 cohorts?); how the cohorts were assigned to each study (Randomized?). It’s not clear how if sample sizes ranged from 15 to 500 individuals, there could be studies with sample sizes with as few as 3 individuals each. That’s why I think that lines 214-217 would deserve a more detailed explanation.
Author’s comments: We have included more details on the process of the generation of cohorts
Line: 259-263

12. Methods / Creation of cohorts/ line 128.
Perhaps it would be useful at this point to insert a paragraph where authors explain why they are going to consider those different scenarios. Readers could not be so familiar with the cost-effectiveness plane so as to readily understand what those three scenarios mean

Author’s comments: We have included an extended explanation about the type of results.
Line: 113-130

Wouldn’t it be the term “effectiveness” better than “effectivities”?

Author’s comments: we have changed the word “effectivities” to “effectiveness”.
Line 133.

Authors assume that “TINB follows a normal distribution” but maybe authors should justify this assumption.

Author’s comments: We now include an explanation of why we assumed that a TINB follows a normal distribution. Mainly, this is due to the fact that the INB follows a normal distribution and as the TINB is a sum of normal distributions, we made this assumption.
Line 155-159
Reference: 15

15. Results / line 279.
Previous to delivering results based on significance (p-values), perhaps information on the generated cohorts/studies should be advisable; something similar to the “Table 1” of clinical articles. The first 7 columns of Table 2 could serve as a guide. Although there would not be a good idea to submit information on all the studies, at least it would fine to watch at 10-15 of them; just to see how the generation process worked.

Author’s comments: We have included an appendix with an example of the application of copulas in a sample size of 15.
Line: 270-272

16. Results / line 298.
It is not clear from this statement (and more on the rest of the document) if this sample size refers to all the individuals of the study or is a sample size for each cohort of the alternatives being compared.

Author’s comments: The sample size is for each cohort of the alternative compared. We have changed parts of the text where the sample size is referred to.
Line 259-264

17. Discussion / paragraph lines 376-383.
The method that authors present here for generating the patient cohorts for feeding the studies seems to “produce” very homogenous cohorts in parameters other than cost/effects. But this is not the actual scenario when performing meta-analyses in real life: patients differ in basal age, basal severity, come from different health-systems, there are variability among centers, and so on, and those parameters might have an impact on the ICER (inter-studies variability).

Authors talk on homogenization as a potential solution to variability in cost structures or health-systems, but perhaps, the influence of other variables as for example, disease severity, use of resources or the age should be taken into account with a different approach (for example, something similar to meta-regression techniques).

Probably the authors had this fact in mind and it could be a new development line of research for the COMER method; but it would be fine if the authors could also insert this idea as a limitation in this article.

Author’s comments: We now comment, as part of the limitations of the study, references to the homogeneity and heterogeneity of the data generated and their implications for the validation of the method. In addition, we now suggest, as potential future lines of investigation, the expansion of the method with adjustments through covariates that allow homogenization of heterogeneous populations.

Line: 388-397