Author’s response to reviews

Title: Optimal schedule of Bacillus Calmette-Guerin for non-muscle-invasive bladder cancer: A meta-analysis of comparative studies

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Author’s response to reviews: see over
Dear Dr. Claire,

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript to cater to BMC cancer. We appreciate editor and reviewers very much for their positive and constructive comments and suggestions on our manuscript entitled “Optimal schedule of Bacillus Calmette-Guerin for non-muscle-invasive bladder cancer: A meta-analysis of comparative studies”. (MS: 1484451648545559).

We have studied editor’s and reviewer’s comments carefully. We have made revision which marked in red in a marked-version and refresh this manuscript in cleaned-version. We have tried our best to revise our manuscript according to the comments. Attached please find the revised version, which we would like to submit for your kind consideration.

We would like to express our great appreciation to you and reviewers for comments on our paper. Looking forward to hearing from you.

Thank you and best regards.
Yours sincerely,

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List of Responses

Responses to editorial comments

1. 1. A sentence or two must be included in the abstract to explain how the results were affected when the search was restricted to clinical trials. Text must be included in the main body to comment on the results by study type. In the main body of text, it is important to mention whether there are significant differences between the results obtained from trials and those from other study designs.

   We added two sentence-“Subgroup-analyses stratified by study-design led to very similar overall results and often to a decrease of the between-study heterogeneity. Data from subgroup-analyses confirmed that non-RCT only affected strength rather than direction of the overall results.”-in the abstract and main text.

2. In addition, there are a number of other editorial points that should be addressed, together with some comments that were not addressed adequately from the first round of review. I have listed these below:

Referee 1's comment 2 at first review: Add further discussion of publication bias in high-risk NMIBC subgroup analysis. How does this impact the interpretation of the
results?

Your response: The publication bias has been present at the table 1 and discussion, and the bias can only be solved by including more studies. So the suggestion of promoting more large-volume, well-designed, RCTs with extensive follow-up was post in the end of Conclusions. At the last, we don’t think the significant conclusions can be overturned by the potential bias.

Our concern: The referee asked for discussion to be added to the Discussion section about publication bias in the high-risk NMIBC subgroup, but this does not seem to have been done. Please add this discussion, and mention how bias might impact the interpretation of the results.

We are very sorry for misunderstanding. We have warned the readers to interpret this result with caution in the section of “strengths and limitations of our analysis”.

3. Please add the study flowchart to the main manuscript as one of the main figures, rather than having it in the supplementary section.

Done

4. It has come to our attention that the author list has changed since your initial submission. Before we can proceed, we require email confirmation from ALL authors (including Xiaoshi Li and Bin Hu, who have been removed from the manuscript PDF, and Lihua Li, who has been added) that they are in agreement with the change. Please also ensure that the author list in the online submissions system is the same as that in the manuscript PDF.

As this manuscript revised twice, the author board was refreshed. Signed letter rather than confirm-email was provided to declare no conflict of interest. Some authors were removed because of less contribution compared to others, and they were not considered to have made significant work. New listed authors have done significant work in our manuscript, especially in the twice revisions).

5. Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

Done.

Responses to Reviewers:

Reviewer # 2 (Dr Claire Vale)

1. Are the methods appropriate and well described, and are sufficient details provided
to replicate the work?

The methods are appropriate for a meta-analysis of RCTs. I am still unconvinced by the combining of randomised and non-randomised trials and would still prefer that primary results for this review were based on RCT data alone. This may reduce power but would be more appropriate and easier for the reader to interpret. I had previously suggested that the authors should present a clear rationale for including different study designs in the meta-analysis however this is still missing and would be a vital addition in my opinion. I would advise the authors to read and refer to chapter 13 of the Cochrane handbook of systematic reviews of interventions (http://handbook.cochrane.org/) which addresses the issue of using non RCT designs in systematic reviews.

Firstly, we really appreciate Dr. Claire Vale for his kind suggestions. The sensitivity-analysis had confirmed that the results were not overturned by subgroup-analyses stratified by study-design. If the results were overturned, we will be absolutely confident on pooled results from RCTs if data from RCTs are sufficient. We insisted that observational studies can also provide a valid result, though they can’t catch up with RCTs. So, results from retrospective studies can’t be ignored.

2. Are the data sound and well controlled?
Related to the above. Just to note that in the discussion, the authors state that the RCTs were of low quality - however according to Table 4, the majority of the RCTs included are judged to be Level of Evidence 1b - higher than any of the non-randomised studies.

We are sorry for our ego, and the sentence has been corrected.

3. Are the discussion and conclusions well balanced and adequately supported by the data?
Again - given that many of the results are based on a mixture of RCT and non-RCT data and that some of the outcomes use only non-RCT data, I feel the interpretation needs to be more cautious in places and I think that the authors should not state that they are so confide the stability of their findings - in particular where they are based on mainly non-randomised trials. I would think it more appropriate to allow readers to judge whether they feel this is level 1a evidence.

We are very sorry for that again; some warns have been addressed so as not to mislead readers.

4. Is the writing acceptable?
There are still some major inadequacies in the language used such that in places it is hard to understand the results. Furthermore, the discussion feels quite jumbled and needs to be better structured to allow readers to follow it more clearly. Some sectioning may help with this if the journal style allows.

We performed a general careful review on our revised manuscript again. We hope the revision would satisfy the need of the readers.
Reviewer # 4 (Dr Peter Lee)

My view on this point is that it is not unreasonable to combine data from clinical trials and observational studies as a general principle, provided that results are given separately for the two types of data source. While there may be situations where there is a source of substantial bias in observational studies, where attention should perhaps be restricted to RCTs, in other situations it may be clearly advantageous to include data from observational studies (e.g. large well-conducted observational studies with little bias likely and limited data from RCTs). One should also bear in mind that observational studies may have some advantages, if RCTs are conducted on highly selected populations.

I also feel that, for the current paper, the work was designed at the outset to detect all relevant studies, regardless of type. In this situation, later restriction to results for specific data subsets carries with it the danger of being accused of “cherry-picking”. Given the design, and given that the authors present, in their Forest plots, separate results for the two types of study and a test of heterogeneity by type of study, I would not ask the authors to do as Dr Vale suggests. Rather I would ask them to include in their abstract a sentence or two stating in general terms how the results were affected by restricting attention to clinical trials. Also to include some text in the main body of the paper commenting on the results by type of study.

Done.

At present the only reference to variation by study type is in the Forest plots themselves; there is no mention in the methods of the fact that separate analyses are conducted for the two types.

Done (lines 11-15, page 6).

There is also very little mention of the results in the paper, and no mention of whether there are significant differences between results for RCTs and other study types.

Done.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in red in revised paper. We appreciate for Editors’ and Reviewers’ warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.