

Response to reviewers comments

Thank you very much for the opportunity to further revise our manuscript. The comments both from the editors and reviewers were very helpful in greatly improving our paper. We have responded to the editorial comments directly on the manuscript file as track-change comments. Please find the response to reviewer comments below.

** Comments from the external peer reviewers**

Reviewer: 1

Recommendation:

Comments:

The authors have satisfactorily responded to my comments and suggestions.

Response

Thank you very much. We are glad that the revisions were satisfactory.

Additional Questions:

Please enter your name: Laurent Azoulay

Job Title: Associate Professor

Institution: McGill University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 2

Recommendation:

Comments:

I have read the responses of the authors to reviewers and editorial questions which overall appear appropriate but have been unable to access the corrected file.

Thank you very much. We are glad that our responses were satisfactory.

Additional Questions:

Please enter your name: Jane maher

Job Title: Consultant

Institution: EN herts hospital and Macmillan cancer support

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 3

Recommendation:

Comments:

This article covers an important topic, but it essentially presents results of a systematic review and meta-analysis, without the required reporting rigour. This seems to go against what the authors are arguing for, i.e. clear and full reporting. I understand that including a detailed description of the methods may not fit with the usual Analysis article format. I can also see that the aim, as the authors state, is not to provide “accurate data on increased risk of toxicities”. However, if the authors present analysis and results of this risk, i.e. the section on “By how much is the risk of toxicities higher...”, then they are running the risk of providing readers with results that, in their words, may not be accurate. I’m not sure how best to take this forward, because I do sympathise with the argument. However, if these analyses are presented, then the methods really should be reported as they would be in any research study, following reporting guidelines for systematic reviews and meta-analyses. At the moment this is not the case.

Response

Thank you for the thoughtful comments.

Indeed, we were in a tricky position to whether report all methods fully making it a systematic review. But we were convinced that an Analysis type article would be more emphatic and useful because we thought that “the risk of toxicities in these trails were 1.5 times higher” versus “they were 1.8 times higher” wasn’t our main purpose as we acknowledged in our paper that pooling these varieties of trials in different conditions were mixing apples and oranges. Our main purpose was to show the absurdity of using statements such as “the treatment was safe” in a trail where some patients died of toxicities. So, while the results have been systematically derived and are accurate to the best of our knowledge, we do appreciate the suggestion of the reviewer (and the editors), and have deleted the paragraphs on relative risks analyses.

As far as the results that are presented go, it is difficult to interpret these. Some of the differences between control and experimental arms may have occurred by chance, and trials would not have been powered to find a difference in AEs between arms – therefore the authors cannot infer that the experimental arms increase toxicities. In fact the confidence intervals for incidence overlap between control and experimental arms, and the same point estimate for FAEs is the same.

Although we have already deleted these paragraphs, we just want to clarify that while its true

that the trials are very rarely, if ever, powered to detect differences in toxicities between the arms. However, meta-analyses of RCTs to detect the increased risk of toxicities have been an established study design. For example:

<https://www.bmj.com/content/360/bmj.k793>

<https://jamanetwork.com/journals/jama/fullarticle/645368>

Minor points:

I thought that it would have been useful to also include an analysis of those studies that did not downplay toxicities as defined by the authors – this would provide a helpful comparison of the risk of toxicities overall.

We have now deleted the risk analyses even for these studies.

Page 5 – studies with no data – why? Was this because there were no severe AEs in these studies? Was this for both arms?

No. If there were no AEs, we would record them as zero. No data meant not reported. That's the absurdity which we want to highlight—to report a drug as tolerable and not provide data on severe or serious or fatal adverse events. Some prior studies have also previously reported such pervasive under-reporting of harms in clinical trials of cancer drugs. For example:

<https://www.ncbi.nlm.nih.gov/pubmed/?term=27301048>

It is not clear how the risk ratios were calculated – particularly 0.89 for the FAEs, when the rate in both control and experimental arms was stated as 1.6%.

We have now deleted the risk analyses, but these were calculated using random-effects meta-analyses.

Additional Questions:

Please enter your name: Katie Harron

Job Title: Senior lecturer

Institution: UCL

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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