BMJ - Decision on
Manuscript ID
BMJ.2017.039945

Body: 20-Feb-2018

Dear Dr. Gyawali

BMJ.2017.039945 entitled "The toxicity profile was acceptable-acceptable to whom?"

Thank you for sending us this paper and giving us the chance to consider your work.

We sent it out for external peer review and discussed it at the Analysis manuscript committee meeting (present: Theo Bloom, Cat Chatfield, Zaki Hassan-Smith, Navjoyt Ladher, Paul Simpson).

Unfortunately we do not consider it suitable for publication in its present form. However if you are able to amend it in the light of our and/or reviewers' comments, we would be happy to consider it again.

The reviewers' comments are at the end of this letter.

The editors' comments are listed below:

1. Editors felt that your paper covered an important topic, with an interesting central point and call for more standardised and precised language when reporting harms from trials.

2. However, we felt that some aspects of the analysis were weak, particularly around defining certain terms (e.g. what is downplaying, what is acceptable risk) and how consensus was reached among the author group. Usually we'd expect such papers to have some standardisation of terms followed by blinded comparisons between different researchers looking at the same papers. We agree with reviewers points that the methods and data should be more transparently described.

3. We felt that some of the language was overly emotive and could be toned down (e.g. preposterous, absurd)

4. The strategies to improve the situation could be developed further. What threshold for harm would be considered acceptable or who has the authority to make the call? How would definining this with patients work in pratice?

5. You allege that triallists and authors knowingly mislead. Are you able to substantiate this?

6. We think that any resubmitted paper is likely to require a substantial amount of revision, with likely legal and statistical review from our end once it is returned. Given the likely extent of revision, and the fact that we are unable to make any promises of publication, you may wish to submit this paper elsewhere.

We hope that you will be willing to revise your manuscript and submit it within 4-6 weeks.When submitting your revised manuscript please provide a point by point response to our comments and those of any reviewers. We also ask that you keep the revised manuscript within the word count of 1800-2000 words.

Please note that resubmitting your manuscript does not guarantee eventual acceptance, and that your resubmission may be sent again for review.

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I hope you will find the comments useful. Please don't hesitate to contact me if you wish to discuss this further.

Please also accept my apologies for the long delay in reaching a decision on this manuscript. I know this falls short of the standard you would expect from The BMJ and am very sorry for any inconvenience and disappointment caused.

Yours sincerely

Navjoyt Ladher
nladher@bmj.com

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Instead of returning a signed licence or competing interest form, we require all authors to insert the following statements into the text version of their manuscript:

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state any competing interests if they exist, or make a no competing interests declaration.

Reviewer(s)' Comments to Author:

Reviewer: 1

Recommendation:

Comments:
This paper makes some important points in relation to the reporting of chemotherapy trials i.e. That the way that toxicity results are presented in high ranking journals does not follow CONSORT guidelines through the use of inappropriate vague terms and through arbitrarily suggesting toxicity is " acceptable" and " manageable " with no patient reported outcome as evidence and as a result , reports may give an inappropriately optimistic view of risk benefit ratio.
The authors point out that this is particularly important given the high cost and relatively small clinical benefit of some new medicines . In order to make this case, They present data on adverse effects reporting together with associated " vague descriptions" from trials reported in 2016. This is an interesting approach to presenting data and I think will stimulate constructive debate.
I have only reviewed a few of the studies reported and I assume there is a brief statistical review for this paper.
I'm not completely convinced by some of the assumptions e.g.adverse effects are "falsely downplayed " if the incidence of adverse effects is more in the control arm than the treatment arm.
The authors , perhaps, fall into the same trap they have identified by using vague terms "downplay " and " falsely downplay " and if these are used They should be clearly defined. Currently the use of inflammatory language reduces the impact of this interesting report and I would suggest a review,restructure and shortening focussing on the key findings .

Additional Questions:
Please enter your name: Elizabeth jane Maher

Job Title: Oncologist and CMO Macmillan Cancer Support

Institution: Mount Vernon cancer centre 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: 2

Recommendation:

Comments:
This paper assessed whether the appropriateness of using favorable toxicity terms in the reporting of cancer drug randomized controlled trials. The authors conclude that a large percentage of such trials (>40%) inappropriately used favorable terms or "downplayed" the harms.

The authors' question has merit from both a scientific and clinical perspective. However, some sections of the paper are 'editorial' in nature and would benefit from a thorough display of all the data. Specific comments are provided below.

1. The paper focuses on trials that downplayed the harms. But what about the trials that did not "downplay" the harms? How good was the reporting of their toxicity information? This information is key to convince readers that there is a difference between trials that "downplay" harms vs those that did not.

2. The authors provide a list of terms that helped them identify trials that "downplayed harms". How was this list derived/constructed? Was it previously validated? As the entire analysis hinges on this list, it is crucial that additional information on its development be presented in detail.

3. Who extracted the data and made the determination of "downplaying harms"? If more than one author, how were discrepancies handled?

4. The title of the section "Was the downplaying of harms true or false?" is a bit odd. The term "downplaying" already offers a judgment on what was reported. In that case, it should not matter if it is true or false? This section also suggests that 23% of trials that "downplayed" the harms were "true"? How do authors reconciliate these apparent divergent ideas?

5. The section on "What was the incidence of toxicities in trials that downplayed harms?" provides overall toxicities reported in the experimental vs control arms. However, these are presented as aggregates, i.e. combining the experimental arms (and control arms) of all trials. As presented, the data are less alarming – for example 50.6% toxicity with experimental drug vs 43.7% toxicity with the control drug. It would be more relevant to provide trial-specific data, as it is likely that some trials have larger differences.

6. Inappropriate reporting of safety information is certainly a valid issue. However, this does not take into account the clinical experience of physicians with a given drug. Physician preference is also influenced by their experience with a given drug, and not solely based on how the safety information was initially reported. The discussion would merit some thoughts on this important point.

7. A major limitation of trials is that they are primarily designed to assess efficacy and not safety. While toxicity information collected during a trial is important, it is important to recognize that often, no firm conclusions can be derived based on the

sample size of these trials. Given this context, at which point can one claim that the experimental drug is safe or unsafe?

Additional Questions:
Please enter your name: Laurent Azoulay

Job Title: Associate Professor

Institution: McGill University

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