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eloder@bmj.com
Sent: Monday, 4 May 2015 2:36 PM
To: jon.jureidini@health.sa.gov.au
Cc: jo.lenoury@btopenworld.com; nardo.mickey@gmail.com;
david.healy54@googlemail.com; jon.jureidini@health.sa.gov.au; Melissa Raven;
catalin.tufanaru@adelaide.edu.au; elia.abi.jaoude@utoronto.ca
Subject: BMJ - Decision on Manuscript ID BMJ.2014.022376.R2

04-May-2015

Dear Prof. Jureidini

Manuscript ID BMJ.2014.022376.R2 entitled "Restoring Study 329: A randomised, controlled trial of the efficacy and harms of paroxetine and imipramine in the treatment of adolescent major depression" which you submitted to BMJ,

First, I apologise for the delay in getting back to you about this paper. We are learning as we go with RIAT papers and want the paper to be as good as it can be.

The paper has been discussed again at a manuscript meeting and among senior editors. We hope very much that you will be willing to make the changes that we recommend.

Very truly yours,

Elizabeth Loder, MD, MPH
BMJ Editorial Team

Please remember these four important points about sending your revised paper back to us:

1. Deadline: Your revised manuscript should be returned within one month.

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INFORMATION ON REVISING THE CONTENT AND FORMAT OF YOUR ARTICLE

Report from The BMJ’s manuscript committee meeting
Present: Elizabeth Loder (chair); Tim Cole (statistician); Wim Weber; Jose Merino; Tiago Villanueva; Georg Roeggla; Alison Tonks

Decision: Put points.

* Additional detail is needed in the methods section. This should be detailed enough that others could replicate what you have done.

* We recommend that the order of sections should be based on CONSORT, i.e. the RIATAR form.

* We could not find a clear statement about whether paroxetine and imipramine were to be compared with each other or just placebo.

* Page 6, add 20 April 1994. ***[Melissa Raven]*** WHERE? Page 10, OC = observed case. Page 19 and abstract, what is LS MEAN?

* The numbers in Table 3 (and page 21) have far too many decimal places / significant figures (up to 5).

* Table 11 needs to include group denominators. A fresh statistician who reviewed the paper this round cannot tell from reading the paper why you are determined not to test the table for significant differences (top of page 31). He suggests this should be done and if not an explanation included as to why not.

* Page 32 should mention the CRFs before referring to the periscope.

* We did feel this version of the paper is much more readable than the initial version. Thank you for all of your work on that. You make 2 clear points: using the prespecified primary outcomes, there is no significant difference between the 3 groups. We felt that you might be able to pare down the portion of the paper that discusses this. One of our editors noted, for example, that it only takes half a page to nicely summarise this at http://www.ncbi.nlm.nih.gov/pubmed/11437014. ***[Melissa Raven]*** = KELLER ET AL. (2001)

The second point you make is about reporting and coding of AE. I am afraid we continue to find this less convincing, particularly the recoding of some of the AEs, especially given that you may be perceived to have a bias due to involvement in litigation. The sort of analysis you do was not specified in the original study and goes beyond what would have been done at the time of the trial. In fact, you use a classification scheme that was not in use when the study was done. It was also unclear why you do not do any statistical tests on the AEs. This is the least convincing part of the paper and no one felt it was fair. This really detracts from the main point of the paper which was the reanalysis of the efficacy findings, showing that the original claim of superiority rested on post-hoc outcomes. We continue to feel very uneasy about this because of the fact that you did not examine all case report forms. This is beyond your control, but it does reduce our confidence in the findings and is a major limitation. One editor commented that the emphasis on AEs seems like "the tail wagging the dog." ***[Melissa Raven]*** SO DO WE WANT TO DO A SEPARATE PAPER ON THE AEs?

We believe that you need to either present the AEs as they were originally coded and make fewer claims about them, or else ask completely independent investigators to code the AEs, report inter-rater agreement, and so on. It would only make sense to recode AEs, however, if you were also going to apply new methods to the efficacy data.

* We do not think the abstract makes sufficiently clear for readers who may not be familiar with the RIAT initiative that this is a reanalysis of a trial published years ago. Perhaps the objectives could start by saying: "This is a reanalysis of data from GSK's Study 209 (originally published in xxx) done as part of the RIAT initiative. The objective

was to see if reanalysis led to similar..." You might also mention in the abstract that registration in a trial registry was not required at the time the study was done. ***[Melissa Raven]*** I THINK WE SHOULD ASK FOR PERMISSION TO HAVE A SLIGHTLY LONGER ABSTRACT – OR JUST RESUBMIT IT WITH A LONGER ABSTRACT

* Can you discuss in the methods whether a change in the HAM-D of 4 points is clinically significant? ***[Melissa Raven]*** APPARENTLY SEVERAL GUIDELINES (INCLUDING NICE) SPECIFY A THREE-POINT DIFFERENCE AS CLINICALLY SIGNIFICANT [HAVEN'T FOUND SPECIFIC SOURCES YET]

* Was there a pattern to the missing data: “At least 1000 pages were missing from the Case Report Forms reviewed with no discernible pattern to missing information” ***[Melissa Raven]*** ??? WE'VE SAID THERE'S NO PATTERN!

* It may be helpful to have an additional box listing where the authors deviated from the original plan/protocol or where their findings differ. While the information is provided throughout the paper, we thought it would help readers to see a summary. [Melissa Raven] SOUNDS GOOD TO ME

* We also feel uneasy about the recategorisation of the lack of efficacy dropouts based on factors such as Adverse Events and HAM-D scores. These decisions seem very subjective and again, there may be a perception of potential bias given your involvement in litigation related to this matter.

* We were puzzled by the statement that “This analysis contrasts with both Keller et al.'s published findings and the outcomes reported in the CSR.” My understanding is that the CSR was the source of the information. ***[Melissa Raven]*** SHE SEEMS TO BE SERIOUSLY MISSING THE POINT THAT MICKEY, JO, AND DAVID REANALYSED THE DATA

* We think questions about this paper should be channeled through the BMJ's traditional rapid response feature, and ask that you remove the following from the paper: "We invite readers to contact us for clarification of any ambiguities through a public Q&A forum at www.xxx.com [TBA], where we will respond to any queries about our data or analysis, with further follow-up as required." ***[Melissa Raven]*** I THINK DELETING THIS IS ACCEPTABLE. WE CAN USE OTHER PUBLICATIONS TO INVITE COMMENTS

* Although we have told you that we will not require you to present results using imputation, we continue to think that would be useful. One of our editors, who had not previously seen this paper, asks "What is the purpose of the RIAT initiative? Is it (a) a way to beat the original authors over the head for misrepresenting the data?
Or (b) is it an opportunity to see if reanalysis teases out findings that might have been missed the first time round? This is pertinent when considering whether or not to use imputation, and whether or not to statistically analyse the adverse events. Clearly if (a) above, one should stick with the original protocol, but if (b), one should go beyond the protocol." You would be on firmer ground in reclassifying the AEs using a new approach if you were open to doing the same with the efficacy data.

* Finally, we remain concerned about the tone of the paper. It should be neutral. In several places you stray into editorial comments about the difficulties of doing the analysis and so forth. Those things detract from the presentation of the research itself.

[Melissa Raven] I THINK MINIMISING COMMENTS ABOUT THE DIFFICULTIES IS ACCEPTABLE. WE CAN SAY THIS IN OTHER PUBLICATIONS

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d. Please include these items in the revised manuscript to comply with BMJ style:

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this should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now

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summary statistics to clarify your message. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

For a clinical trial:

- Absolute event rates among experimental and control groups
- RRR (relative risk reduction)
- NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000)

For a cohort study:

- Absolute event rates over time (eg 10 years) among exposed and non-exposed groups
- RRR (relative risk reduction)

For a case control study:

- OR (odds ratio) for strength of association between exposure and outcome

For a study of a diagnostic test:

- Sensitivity and specificity
- PPV and NPV (positive and negative predictive values)

one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used for articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system Discussion please write the discussion section of your paper in a structured way, to minimise the risk of careful explanation giving way to polemic.Please follow this structure:
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