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[mailto:onbehalfof+eloder+bmj.com@manuscriptcentral.com] On Behalf Of
eloder@bmj.com
Sent: Friday, 22 May 2015 6:42 AM
To: Jureidini, Jon (Health)
Cc: pdoshi@bmj.com
Subject: BMJ BMJ.2014.022376.R2

21-May-2015

BMJ.2014.022376.R2 - Restoring Study 329: A randomised, controlled trial of the efficacy and harms of paroxetine and imipramine in the treatment of adolescent major depression

Dear Prof. Jureidini:

Many thanks for your patience with what I know has been an exhausting and tedious process of review and revision. I've had a long discussion with Peter Doshi about how to move forward with this paper. It is our intention at this point to make a decision in-house (without additional outside peer review) if we can agree on a few points. We will send the final version of the paper for review by our legal team, a step we take with many papers.

1. I understand from Peter that you've gone ahead and done the imputation analysis that our statisticians thought was ideal. Thanks very much for that. I realize it took a lot of extra effort to do that. We think this should be included in the body of the paper, noting its post-hoc nature.

2. Similarly, it would work well to present both the ADECS and MedDRA adverse event data in the body of the paper, and acknowledge in the discussion the different interpretations that result from using the two systems. Please also provide more details in the methods section of your paper about the process of determining and coding the adverse events from verbatim term to preferred terms from CSR Appendix D. Who blinded, who coded, who assisted, did anyone double check the coding, how was blinding to drug assignment achieved (given that Appendix D prints the treatment assignment on each page), etc?

Can you also provide references or other information that will convince us that this process of coding is reliable, unbiased and reproducible? Another question that came up is whether individual AE verbatim or preferred terms are ever combined to create a new concept or term. In other words, would separate AEs such as "cough" and "fever" (either as verbatim or preferred terms) ever be combined to create an AE of "pneumonia" or "URI" -- or would pneumonia only be coded if someone said "My doctor diagnosed me with pneumonia"? The example you give about coding the scratch and emotional lability as suicidal ideation made everyone who read it worry quite a bit about the level of subjectivity that might be involved here -- and I hope you are not offended if I say we felt that left everyone open to criticism given that you have acted as expert witnesses in court cases that presumably focused on AEs and harms.

Regarding the non-random audit of case report forms (CRFs), we think the results of this

audit should be presented in an appendix to the paper, not the main body. Your decision to do an audit can be mentioned in the body of the paper and your finding from the audit that not all Verbatim Terms made it from CRF to CSR Appendix D makes sense to mention in the body of the paper as a limitation of the MedDRA dataset you report on. Please let us know if there are any other important findings from this audit that you think should be mentioned in the body of the paper.

For the sake of completeness it would also be good to comment briefly on the objectives outlined in the original protocol section 9.4.3, and why you are not presenting those data in the paper.

Regarding protocol section 9.4.2, this to our reading suggests that results should be presented comprehensively for all preferred terms and body systems. This appears to be your appendix Table iv, but it would help if all of your tables can clearly indicate the population being analyzed (e.g. ITT). Given that reporting on preferred terms and body systems was called for in the original protocol, can you make sure to explicitly reference appendix table iv in the body text (and ensure the methods also mentions this)?

You may want to consult CONSORT Harms for ideas about how to present harms information.

3. There are some narrative paragraphs and boxes scattered throughout the paper -- for example, box 2 and box 3 -- that present interesting information on the backstory of the paper. Still, they don't seem to entirely fit with the idea of a research paper. Could you consolidate these bits into a single "lessons learned" section that will appear in the discussion section of the paper?

If these recommendations are acceptable to you I will look forward to seeing a revised version of the paper.

Very truly yours,

Elizabeth Loder