Sent: Friday, 2 October 2015 6:35 PM
To: jon.jureidini@adelaide.edu.au<mailto:jon.jureidini@adelaide.edu.au>
Subject: Acta Psychiatrica Scandinavica - Decision on Manuscript ID ACP-2015-5105.R1

02-Oct-2015

Dear Professor Jon Jureidini

I write you in regards to manuscript # ACP-2015-5105.R1 entitled "The Citalopram CIT-MD-18 Pediatric Depression Trial: Deconstruction of Medical Ghostwriting, Data Mischaracterisation and Academic Malfeasance" which you submitted to the Acta Psychiatrica Scandinavica.

First, please let me apologize for having kept you waiting for a reply. However, we have now received the publishers' considerations based on the publishers' legal expert's recommendations. The publishers represented by journal publishing manager Lisbeth Cranfield writes 23 September 2015 about your manuscript to me that she in the "current state cannot recommend that the article is published". Further, she writes "the main issue with this article that needs to be addressed is that Wagner et al is contacted and asked for their side of the story. Their side of the story should be included in the article".

Further, she writes that if I "wish to follow this route" we should further need to involve the legal expert to determine the right questions to be asked".

It seems that the whole matter is getting a bit out of my hands as an academic psychiatrist editing a clinical psychiatric journal. The matter is further complicated by the fact that I am leaving the chair as editor at the turn of the year. That means that the process could be pretty long (we should ask the publishers' legal expert "what questions to ask you". You should then revise the manuscript which should then be sent to the legal advisor, who should respond to me, who should pass the matter on to you, and after your response you should properly start all over again with my succeeding editor.

I therefore suggest that we stop the process at this point. You may benefit from the reviewers' second assessment (found at the bottom of this email) and carry on with a journal somewhat more experienced in this kind of legal matters. Maybe you could ask Professor David Healy about where to submit your paper?

I am not happy about writing this, but I find it the only realistic decision to make to regrettably thank no to publish your paper in the Acta Psychiatrica Scandinavica.

Thank you very for your patience.

Best regards
Professor Povl Munk-Jørgensen
Editor-in-Chief, Acta Psychiatrica Scandinavica

Reviewer(s)' Comments to Author:
Reviewer: 1

Comments to the Author
Thank you for considering all my suggestions.

Reviewer: 2

Comments to the Author
n/a

Reviewer: 4

Comments to the Author
The paper is vastly improved, with some more shocking and important details about the concealing of adverse events, and negative secondary outcomes.
There are just some minor points of presentation:

Abstract: The results section could still be a little clearer. A statement like the following might help: 'the primary outcome was inflated to reach statistical significance by deviating from protocol specified criteria' . I would also be a bit more specific on adverse events and say adverse, 'activation-type' events were not disclosed.

The statement in the Abstract Conclusion that the protocol-specified primary outcome showed no significant effect when analysed according to protocol criteria could also include that there was no clinical difference, if this can be supported (see below).

On P 9, it would be helpful if the authors could specify what a clinically meaningful difference is in terms of CDRS-R scores, provide some justification or reference for this, and show how the citalopram placebo difference fails to reach this level. This is a really important point, and could be mentioned in the Abstract if it can be supported.

P 9-10 where was the treatment by age interaction effect identified? Was it presented in an unpublished study report, or the final report? It would be helpful if the authors should specify how they became aware of this effect (e.g. 'unpublished study documents revealed' or 'the final report presented..'). This also applies to the adverse effects data (i.e. specifying where the reported data that is not in the published paper was obtained from).

P 11. The authors make a very interesting point about the insertion of a post hoc 'response' variable. In the first sentence, please could they change the place of the bracket to clarify that it refers to the post hoc results and not anything contained in the protocol, i.e. place it directly after "post hoc statistically positive results (visit by visit…)…".

This point could be highlighted further in the Discussion and Abstract, and it might stand out more if there was a short paragraph at the beginning of the Results section summarising the important deviations that became apparent, before the detail is provided (e.g. inspection of unpublished study documents revealed that the primary outcome was manipulated to raise it above the conventional level of statistical significance, a post hoc response measure was added and reported in such a way that it appeared to be a primary outcome, protocol specified secondary outcomes which indcated no difference between citalopram and placebo were omitted from the published report and a large and unjustified effect size was reported).

P 11 with the gastro-intestinal adverse effects, the authors say there were 'many more'. How exactly was this presented in the final study report? Were any figures offered, if so it would be useful to present these here, or to state how else this information was presented.

P Discussion: point 3) should specify that the unblinding error compromised the statistical significance of the primary, pre-specified outcome. Point 4) should surely be two points, firstly that an interaction that revealed no effect in children was not reported, and secondly that misleading effect sizes were reported._____

Acta Psych Decision

From: onbehalfof+actapsych+rm.dk@manuscriptcentral.com [onbehalfof+actapsych+rm.dk@manuscriptcentral.com] On Behalf Of actapsych@rm.dk [actapsych@rm.dk]
Sent: Tuesday, 7 July 2015 7:27 PM
To: jon.jureidini@adelaide.edu.au
Subject: Acta Psychiatrica Scandinavica - Decision on Manuscript ID ACP-2015-5105

Dear Professor Jon Jureidini

I have now received the assessments of your manuscript - ID ACP-2015-5105 entitled "The Citalopram CIT-MD-18 Pediatric Depression Trial: Deconstruction of Medical Ghostwriting, Data Misrepresentation and Academic Malfeasance". The comments from the reviewers can be found at the bottom of this e-mail. Based on these I invite you to revise your manuscript according to the reviewers' comments.

One of the reviewers noted this in the comments to me: ” However, it is not very well written or presented, and at present is not in a state to be published in an academic journal. There is almost no attempt to contextualise the data within the relevant literature, and the Results section could be written and presented more clearly and with more detail. The paper gives the impression of something that was written for other purposes, maybe a report.” I in particular ask you to pay attention to these comments.

Moreover, the legal aspects of your paper should be clarified. I therefore ask you to get a comment from your university’s lawyer about the lawfulness of the material, in particular the question about public access to the material used.

Please notice that if we decide to publish your paper in the Acta Psychiatrica Scandinavica, we will publish it in our December issue this year.

To revise your manuscript, log into https://mc.manuscriptcentral.com/actapsych and enter your Author Center where you will find your manuscript title listed under the feature “manuscripts awaiting revision".

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using the track changes mode in MS Word or by using bold or colored text. Once the revised manuscript is prepared, you can upload it and submit it through your Author Center.

When submitting your revised manuscript, you will be able to respond to the comments made by the reviewers in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewers.

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Please forward your revised version within 30 days from the above date, otherwise we will consider the case closed.
Please notice that at this stage of the process we cannot guarantee a publication of your manuscript. A decision to publish your manuscript is also dependent on the result of the reviewers' assessments.

Once again, thank you for submitting your manuscript to the Acta Psychiatrica Scandinavica. I look forward to receiving the revised version of the manuscript.

Best regards
Acta Psychiatrica Scandinavica

Povl Munk-Jørgensen
Editor

Reviewer(s)' Comments to Author:
Reviewer: 1

Comments to the Author
Definitely, this is a very unique and important article deserving rapid publication.
Given the fact that this report comes from the US and that the authors seek for publication in a European/Scandinavian journal, there should be a clear statement about the cultural background of the trial and the report.
This should start with the title (The Citalopram CIT-MD-18 Pediatric Depression Trial in the United States. …..), should continue with the abstract (rephrase objective), and should be made clear also in the first paragraph of the introduction.
Furthermore, it should be indicated by the ®symbol both in the abstract and in the first paragraph that Celexa and Lexapro are US brand names for Citalopram and Escitalopram, respectively, and that Forest stands for Forest Research Institute (describe function of the institute).
From reading the results, it does not become sufficiently clear how the primary outcome measures were substituted by post hoc outcome measures (page 8).
It is a common procedure to regard a difference at p=0.052 as a trend for significance (page 9). This could be admitted in the manuscript to avoid further discussion.
Does the typo in the cited sentence ” Any patient....” on top of page 10 stem from the protocol or from the authors of this manuscript?
Both in the introduction and the discussion a comment on the broader frame of reference of drug trials in children might add to the value of the paper. For instance, there could be a reference to the higher vulnerability of the developing brain and the lower efficacy of most psychotropic medications including the higher risk of adverse events in this young population.
In addition, the concern about a worldwide trend of prescribing more drugs to children could be mentioned (as evidenced also in this journal recently). Similarly, it could be addressed that the US absorbes the vast majority of worldwide drug prescriptions for children.

Reviewer: 2

Comments to the Author
I have read this paper carefully and write to you alone and do not include any reviewer comments.

In essence, we have been informed on multiple occasions over the last decade in particular about inappropriate conduct in undertaking pharmaceutical trials and in their reporting, with particular concerns about psychiatrists being accorded prominent authorship status without being in charge of the data or even aware of the probity of the evidence. I am not aware of any paper that has been published in any journal that details a number of the inappropriate practices so well or in such detail and therefore, if it were to be published, it would be a prominent piece that would attract considerable attention. While the first two authors acknowledge that they have had legal support in giving evidence to the legal challenge mounted by a group of plaintiffs, if the article were to be published it would need to be over-viewed carefully by a lawyer to ensure that the journal was not compromised legally. This may be relatively straightforward if the lawyer were to judge that everything reported here had been considered in court and therefore was 'public' information. However, that may not be so.

Reviewer: 3

Comments to the Author
This manuscript provides extensive primary source documentation of corporate intent to mislead the anticipated professional readership of Am J Psychiat regarding the effectiveness of citalopram in treatment of major depressive episodes in youth. Because of the importance of documentation that no selective reporting by he authors of this submitted manuscript occurred, it is reasonable that they be asked to make such a statement.
Similarly, the corporations and other agents engaged in the planning, funding, and preparation of the citalopram study manuscript, as well as those individuals engaged in the writing or review of such writing of the citalopram manuscript, should be provided opportunity to comment on the actions described in the manuscript submitted to Acta that involve putative distortion of facts and recommendations. However, a professional journal generally has little or no staff or budget to utilize in investigative inquiry. If any court system or regulatory system evidence has been brought regarding the citalopram study and preparation of the original manuscript, some of such may be germane to what might be published in Acta. For several reasons, the judicial/regulatory system is best suited to address many of the actions asserted in this manuscript. That said, there is still a useful societal and professional value of publication of such a manuscript in a respected, widely read journal such as Acta.

Reviewer: 4

Comments to the Author

The paper uses archival documents released during court proceedings to document the process of ghost-writing, and the manipulation of study data by a drug company. The content is interesting but could be improved.
Introduction:
Reference to some more general data on rates of use of antidepressants in children would be useful, along with a description of existing literature on ghost-writing (e.g. David Healy's work) and previous findings of publication bias in antidepressant research, including the meta-analysis by Whittington et al which included unpublished data and found few effects.
Methods:
Note it is 'materials and methods'
Some more description of the process of analysis would be useful, such as comparison between published report and study data revealed in the confidential documents, including the study protocol, scrutiny of e mails and other correspondence relating to authorship and manuscript production.
In the description of the power calculation, is it specified what effect size they were aiming to detect?
Results:

Overall this section could be more clearly presented and more data would be useful.
I would suggest the section is divided into a sub-section on 'authorship' and one on 'results' or 'data', and to incorporate the first paragraph in the second section.
I would not describe the e mail about authorship that is quoted on P 7 as 'banter'. I agree this is a very important quote, but to my mind it simply states the bold fact that the writer and author are not the same under this system of authorship, and might not have been meant light-heartedly.
The statement that there is no evidence the manuscript was circulated to the other authors is potentially libellous, so the authors need to be very sure that they have grounds to make this suggestion, and provide more evidence to back it up. Are they sure they have seen all the correspondence about the trial? Are there e mails suggesting these authors agree to be authors without evidence that they have seen the manuscript?
The data on the results of the study is difficult to follow. The authors seem to be making two substantive points: first that the original, per- protocol primary outcome was not statistically significant (although it was very nearly so, which should be acknowledged), and was inflated by adding the unblended participants; second – an interaction effect was not reported.
It is difficult to judge the situation with the effect size, so I wouldn't make this a big point, but just it is worth mentioning.
I wanted to know if any other outcomes were misreported. Was the response criterion used in the published paper the same as the one in the protocol? Were the other secondary outcomes like the CGI reported accurately in the published paper? Were the reasons for the dropout of the five citalopram subjects reported? Was there any other discrepancy in how adverse events were reported?
On the subject of the Lundbeck trial, why should the company have been expected to know the results if it had not been published? I agree it seems likely, but not certain that they should have known.
Discussion:
This section should relate the findings back to the literature covered in the introduction, and should mention the similar analysis of study 329. It needs to stress why this sort of analysis is important.