Dear Prof. Jureidini,


First, let me apologize for the delay in sending out this decision letter. I was waiting for an additional review, but was unlucky enough to be traveling when it finally came in. I am sorry that has added to the time this paper spent in re-review.

I believe we are getting close to a version we will all find acceptable. At this point we are offering provisional acceptance provided you satisfactorily address the remaining points raised by reviewers. Along with a number of reviewers and our statistical advisor I continue to think the paper would be stronger if you performed imputation. Performing these analyses would also demonstrate that you are doing your best to be fair and make the best and highest use of the data. There are arguments on both sides, of course, so we will not insist on this, particularly since readers of the prepublication history for the paper will see the back and forth about this matter and will be able to judge the matter for themselves.

On other matters some changes are necessary.

*I agree with Professor Henry that the abstract needs attention and encourage you to adopt the more neutral and balanced wording he suggests in several places, particularly when discussing the balance between efficacy and harms.

*Perhaps I missed it, but I do not see anywhere mention of the short duration of included trials. There was very strong sentiment among the clinically active physicians at the manuscript meeting that the duration of most trials was too short and in some cases the doses of drugs too low to have much effect. You may not agree with this, but can you please acknowledge that possibility? Of course it can be argued that the manufacturers designed the trials and could have studied longer duration treatment or higher doses.

* Please clarify the matter of which protocol you followed and make sure that is available to readers.
* Please also respond to the many other comments of the reviewers. Feel free to group similar comments if that makes sense.

The referees’ comments are available at the end of this letter.

Deadline: Because we are trying to facilitate timely publication of manuscripts submitted to BMJ, your revised manuscript should be submitted by one month from today’s date. If it is not possible for you to submit your revision by this date, we may have to consider your paper as a new submission.

https://mc.manuscriptcentral.com/bmj?URL_MASK=4973daa28e434a01af6cc870020a626c

Yours sincerely

Elisabeth Loder
eloder@bmj.com,
Reviewer: 1

Recommendation:

Comments:

Dear editor,

thank you for the opportunity of reviewing this paper for your journal. First I'm impressed by the number of reviewer and the number of comments. This is an important topic, and this hot paper deserves a careful examination.

I read the new version of the paper and it is better know. It is not messy as was the first draft.

Authors responses are informative (both the general response in their letter and the individual responses).

Concerning the general answers:
Concerning efficacy analyses, I agree that the analysis pre-specified in the protocol is the analysis that must be done.
Concerning AE, I'm satisfied that authors deleted the highly speculative analysis they had initially proposed. One can regret that it was not easier to extract the information from all CRF. I acknowledge that it will be not feasible. This is probably a limitation of the RIAT initiative. I found the boxes that authors have added very interesting in commenting their analysis.

Concerning my suggestions:
Authors have addressed my question in an insightful way. I agree with their response and the paper is better now and could be, from my point of view accepted. It is surely a very important paper.

Please excuse my english.

Kind regards

Florian Naudet
Reviewer: 2

Recommendation:

Comments:

The authors have attempted to address all reviewer and committee queries. There are however some comments to make re their revisions:

1. With reference to utilising more appropriate means of analysis, albeit these were not in the study protocol, as requested by 2 reviewers (Hilde PA van der Aa, comments 1 and 4, Sarah Hetrick comment 9) and the committee (Loder comment 9), I do not think the argument for continuing to use LOCF alone (“It continues to be widely used”) is valid. Although the technique is still seen it is well known to potentially give biased results. In box 1, ‘Missing values’ paragraph: “are frequently preferred” (referring to MI and MM) should be replaced by “are shown to be superior”. However the authors do argue (letter to Loder) that the point of a RIAT is “not to repeat all that was done in a published paper but rather what should have been done according to study protocol”. I do not know RIAT well but it does appear that box 2 point 6 of the original RIAT paper does not preclude the necessity in some cases for analyses additional to the protocol. Additionally the authors argue that “over time and with much back and forth, we ended up deciding that the choice of analytic approach was a potential source of bias (our own bias)”, but I do not think that this a strong argument either since an attempt at multiple imputation would seem standard today (as was requested by 2 reviewers plus the committee). In defence of the authors, the argument that “if more ‘modern’ methods of data imputation could have in any way redeemed this study, one imagines GSK would have done so” does seem reasonable to me. Furthermore, the OC and LOCF results are similar which also suggests that conclusions would not be changed by more appropriate imputation.

Whether this paper should, in addition to documenting the results according to the original protocol, attempt to make best use of the available data according to current methods, is a matter for the research editors to decide.

2. The authors should add confidence intervals to the estimates given in the abstract (addition to response to Loder 9).

Additional Questions:

Please enter your name: Angela Wade
Job Title: Professor of Medical Statistics
Institution: UCL Institute of Child Health
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 declare them here: None
Reviewer: 3
Recommendation:

Comments:

Overview - I think this is getting closer. I still believe the authors could have masked the forms used to adjudicate the relatively small number of assessments that are key to interpreting this study. The manuscript is still long and a bit disjointed in places and could use a tight edit. A few Tables can be removed or combined.

The authors have provided lengthy and quite detailed responses to the questions raised by the reviewers. It's a major task to address every issue both for them and the referees. I will limit my further remarks to those that go to the heart of the issues raised by the re-analysis of Trial 329. My comments are ordered by the different sections of the manuscript. In general I think the manuscript is improved but the authors still offer their own quite strong opinions while arguing that others can make up their own minds. While in theory this is true the reality is that their own interpretation of the data will be what readers take away.

Abstract
I think the abstract will be improved by a bit more editing.
Double-blind should be mentioned under 'Design'.
The authors state: “Clinically significant increases in harms, including suicidal ideation and behaviour and other serious adverse events, were observed in the paroxetine group.” They have chosen to make this prominent in the abstract. They have taken the privilege of featuring a difference in harms between active and control as ‘clinically significant’ without assessing statistical significance. They say that they have discussed the reasons for not applying statistical significance testing to harms but Box 3 is minimal in this regard. The authors make a virtue of not applying statistical analyses to harms and yet want to highlight the differences. For the record, a chi square test with 2 degrees of freedom is significant applied to the psychiatric AE data across the two active and one control group. Assuming the summary estimates of psychiatric AEs are not affected by un-blinded assessment (see below) I think they should present statistical analyses of the main harms.

The authors write: “Paroxetine was neither well tolerated nor effective for major depression in adolescents. Imipramine, given in high doses, was also poorly tolerated and was not shown to be effective” I don’t know what “well” or “poorly tolerated” means in this context. The term often applies to common non-serious symptomatic AEs (eg nausea, dry mouth visual blurring) that interfere with daily activities. Based on what they have presented an alternative would be to say “Neither paroxetine nor imipramine demonstrated efficacy in adolescents, and there was an apparent increase in harms with both drugs.” The key AEs could be quantified here.

“This study has demonstrated that when there is access to primary data, trial conclusions will ordinarily be provisional rather than authoritative.” I think that’s a big call and too difficult to introduce in the abstract. Something like “the re-analysis of trial 329 illustrates the value of making primary trial data available” would be OK.
Introduction
They have to introduce two concepts we could argue which gets mentioned first. My preference would be to mention Trial 329 and the clinical context before introducing RIAT. I accept arguments can be made for both sequences.

Methods
Reordering of the sections of the paper would be helpful. I think the details of randomization and assignment should follow the description of the interventions. In the current version they appear very late in the Methods. The position of Box 1 (challenges to carrying out RIAT) is awkward and breaks up the flow of the manuscript. It should be repositioned in the production phase.
The authors state “Only for six events from the eleven serious adverse event narratives was it not possible to be blind. This was 0.005% of events.” I think we need to know whether the un-blinded assessment of these 6 serious AEs has a possible effect on the results – what do the results look like if they are removed? For instance what does Table 12 (Discussion) look like? In view of their importance and since the unblended SAEs are small in number could those not have been recoded with allocation status masked in some way?

Results
Comments above in relation to the Abstract apply to the Results. In particular how do Tables 5–7 change if the un-blinded adjudications of harms are removed?
The Harms section has too many tables. Table 4 could be in text. Severity ratings in Table 7 could be added to Table 5. The sections on discontinuations and withdrawals are long and perhaps the authors could decide what could be placed in an Appendix.

Discussion
The text in the Discussion section is brief. In part this is because some elements appear in other parts of the paper. A tight edit could identify these and move them – that is a style/editorial decision. Box 3 is useful but the word ‘confounder’ in the title has a technical meaning in epidemiology and its use here is not accurate. Table 12 has been referred to above in regard to un-blinded assessments.

Additional Questions:
Please enter your name: David Henry
Job Title: professor
Institution: University of Toronto
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 declare them here:
Reviewer: 4

Recommendation:

Comments:

I am overall satisfied with the authors' point by point responses to my queries. I read through the other reviewers' concern about modern statistical methods and agree with the RIAT authors' response that the primary purpose of RIAT is to stick to the protocol as best possible. While it is perfectly valid to subject the data to additional analyses, such re-analyses would need to be clearly labeled post-hoc, and can always happen in subsequent papers by different authors given the public availability of the trial data. But unless there is a strong argument that the statistical methods in the original study protocol are not just outdated but simply WRONG, I would agree with the RIAT authors position that the analyses should be conducted according to the original protocol.

Remaining queries for me are:

1. Abstract - Setting. Give exact dates (not just years).

2. Tables 5 & 6. Three columns contain the text "additional AEs found in 93 CRFs". These cannot all be n=93. Please give the respective number of CRFs reviewed for paroxetine, imipramine, and placebo.

3. The authors states that they followed the April 17, 1994 protocol. However the protocol I see uploaded to Scholar One is dated June 12, 1993. Was this intentional? The protocol that is available on GSK’s website appears to be the one dated from 1996. So unless I have missed it, I don’t see the 1994 protocol. I would suggest that the authors provide the 1994 protocol (which I agree as the final protocol prior to patient enrollment is the appropriate one to use) and ensure that it is available online with the published paper.

4. The authors mention further correspondence with GSK asking them for documentation to support GSK’s claim that the outcomes introduced in the Keller paper which did not appear in the 1993, 1994, or 1996 trial protocols was nonetheless defined prior to breaking the blind. The authors state GSK was not forthcoming with this documentation. I would suggest that BMJ ask the authors whether there are any updates on this correspondence.

5. In their response #21 to the editors, the authors write that the "periscope" model of data access (which GSK required in order for the authors to read CRFs) prevented them from printing off materials and submitting them to a panel of coders in an effort to reduce bias, etc. I think this is a very valuable observation and should be stated in the Discussion of the paper.

6. In response to my query #7 regarding the missing pages of CRFs, the authors write “See Loder, query 25.” But I do not see any answer to my question here. Please clarify as I still think this is an important point.
7. The authors response to my query #11 is helpful, regarding the reasons for how they chose the MedDRA SOC classes. I did not see the authors include this rationale in the paper itself, however, and think it should be included.

8. RIATAR. Section 24 states that the protocol used was the one in CSR Appendix A. But isn’t this the 1996 protocol, not the 1994 one the authors used? Please clarify. Also, in RIATAR section 17a (“Outcomes and estimation”), the authors include numerous sections of the CSR including data tables. This confuses me because based on the Conclusions section of Box 1 (“Challenges in carrying out RIAT”), my impression was that the authors used the electronic IPD they had access to via GSK, and not efficacy data from the CSR. Please clarify. Finally, under this same section of the RIATAR (i.e. 17a), the authors list “Data Source Tables: Safety, pages 113-260”. This confuses me because safety data usually is not included in 17a.

9. Methods. I would revise the sentence in the first paragraph, inserting the BOLDED words, "...the INDIVIDUAL PARTICIPANT LEVEL data access system SAS Solutions OnDemand,[10] on which GSK SUBSEQUENTLY ALSO posted some Study 329 documents (available only to users approved by GSK..." The main point is to clearly convey that the data access system was set up to provide access to electronic IPD and the additional scanned CRFs were posted later, after GSK reversed its decision to deny the RIAT team access to CRFs.

Additional Questions:
Please enter your name: Peter Doshi
Decision: provisional acceptance

Detailed comments from the meeting:

First and foremost, please revise your paper to respond to all of the comments by the reviewers. Their reports are available below.

Please also respond to these additional comments by the committee:

**THE REPORT FROM THE MANUSCRIPT COMMITTEE MEETING, REVIEWERS' REPORTS, AND THE BMJ’S GENERAL REQUIREMENTS FOR RESEARCH PAPERS ARE AVAILABLE AT THE END OF THIS LETTER.**

First, however, please read these four important points about sending your revised paper back to us:

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INFORMATION ON REVISING THE CONTENT AND FORMAT OF YOUR ARTICLE

**Report from The BMJ’s manuscript committee meeting**

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript. Members of the committee were: xxx (chair), yyy (statistician), [and list other eds who took part]

IMPORTANT

When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision.

a. In your response to the reviewers and committee please provide, point by point, your replies to the comments made by the reviewers and the editors, and please explain how you have dealt with them in the paper. It may not be possible to respond in detail to all these points in the paper itself, so please do so in the box provided

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

Title: this should include the study design eg "systematic review and meta-analysis"

Abstract

structured abstract including key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research)

for every clinical trial - and for any other registered study - the study registration number and name of register – in the last line of the structured abstract.
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this should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now

Methods:
for an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found.

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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:

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• 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)

For a systematic review and/or meta-analysis:
point estimates and confidence intervals for the main results
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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strengths and weaknesses of the study
strengths and weaknesses in relation to other studies, discussing important differences in results and what your study adds. Whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses (eg Cochrane reviews)
meaning of the study: possible explanations and implications for clinicians and policymakers and other researchers; how your study could promote better decisions unanswered questions and future research

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was the development and/or selection of outcome measures informed by patients’ priorities and experiences? Please give details (Methods section)
were patients/service users/carers/lay people involved in developing plans for participant recruitment and study conduct? If so, please specify how (Methods section)
have you planned to disseminate the results of the study to participants? If so how will this be done? (Describe in brief footnote)
are patients thanked in the contributorship statement or acknowledgements?
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END