Author’s response to reviews

Title: Publication and non-publication of clinical trials in PTSD: an overview

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Author’s response to reviews:

Dear Editor

We would like to thank the reviewers for their detailed comments. Their comments and our responses are listed below.

Best,
Sharain

Reviewer reports:

Reviewer #1: The authors have provided clarification in response to most of my comments. There is still one outstanding point. In my previous review (see point 5.) I asked why, having stated that they excluded observational studies from further analysis because registration of observational studies is voluntary, they performed the comparative statistical analyses between interventional and observational studies presented in tables 1 and 2 (the last two columns). Can the authors clarify their rationale for generating these p values and how they relate to their stated aims of the study?
We did not expect to find so many observational studies, but since we did, we included the comparison for completeness. We have removed the comparative analysis from Tables 1 and 2 and only provide descriptive data. We have also removed any comparative statistics from other areas of the manuscript.

Reviewer #2: Clarify the Methods

The authors have improved this draft, but the Methods still require further clarification.

For example, what does "There was a consensus on…" mean?

- We have changed the sentence to clarify this, on page 5, lines 4-6 of Methods: ‘Researchers agreed on the search terms to use and on study selection and exclusion criteria, as well as on data abstraction (selection of data items extracted from each contributing article) and data extraction.’

The authors say that "Information of interest pertaining to each trial was systematically extracted from the databases by each reviewer" but I assume the 5 authors didn't each extract all of the data. Avoid passive construction throughout the report and describe the search and data extraction process precisely (e.g., was it done by one person, was it checked by a second person, was it done independently and then reconciled?).

- In line 3 of the Methods section on page 5 we say: ‘Two independent researchers (SS1 and LVDH) selected studies through each phase of selection.’

- On page 6, paragraph 2, we clarify: ‘Information of interest pertaining to each trial was systematically extracted from the databases by two researchers (SS1 and LvdH) and reconciled.’

- On page 7: ‘Five investigators then searched for peer reviewed publications or any results disseminated for each individual study registered (LvdH and SS1 conducted the initial search and data extraction, which were verified by AS; IE and SW updated the results which were verified by SS1).’

The authors’ response letter says that the number of participants actually enrolled in each trial was extracted from the journal articles; the manuscript says this was extracted from the databases.
- We apologise for this confusion.

- We looked at numbers planned vs enrolled which was obtained from the registry. On page 6, point #3 we note: ‘Information of interest…. For completed studies…. Included…. numbers planned vs actually enrolled’

- On page 10, Table 1 (titled: Descriptive data for interventional and observational trials listed in registries), we report on number planned vs enrolled in the trial registry: ‘Of the 438 trials included, 171 (31%) enrolled fewer participants than planned, whereas 71 (11%) enrolled more than planned. In 187 (42%) there was no difference between number planned and number enrolled. In the table footnote we write: ‘More/less than planned was based on a difference of 10% or more and obtained from the trial registry’

In many cases "time between end of trial and publication" couldn't have been extracted from the databases (see page 6).

- The reviewer is correct. As with all data, we were only able to collect this data when it was available. ‘If the completion date of a trial was missing (5% of trials) we used the publication date as a proxy when this was available.’

The authors say "If the completion date of a trial was missing we used the publication date as a proxy when this was available"; what are the implications of this assumption for calculating time to publication?

- Thank you for raising this. We have included the number of trials this pertained to on page 7, paragraph 1: ‘5% of trials’.

- We have included the following on page 16 paragraph 1: “Time from the close of a study until publication, was approximately two years and three months……but may, be longer given that when the completion date of a trial was missing we used the publication date as a proxy.”

The search strategy is important because it defines the study cohort. The authors should consult an information scientist about the search terms and documenting the search.

- Thank-you for this suggestion. On page 6, paragraph 1 we note “We obtained independent peer review and approval of the search strategy and documentation by an information specialist who utilizes the PRESS methodology.”
The description of the search in the manuscript doesn't seem consistent with the authors' response letter, which suggests that different fields were searched for different platforms. The failure to identify all ClinicalTrials.gov records on ICTRP should be addressed in the manuscript.

- In the limitations section on pages 18-19, we have included: ‘Although the search strategies were the same across databases/search portals not all the studies were identified in ICTRP. This may be related to differences in search algorithms.’

Other details of the search remain unclear. For example, the authors say they included "Closed and completed trials" but they don't say enough about how trial status was included in the search (which statuses were included and excluded).

- Search terms were not limited based on study status. On page 5, paragraph 3 we have clarified: ‘In each of the registries and search platform, we searched all fields and placed no limits on the searches. Our search terms were broad as we aimed to identify all possible PTSD related studies. Studies were identified via Clinicaltrials.gov (www.clinicaltrials.gov), EudraCT (https://www.clinicaltrialsregister.eu/) and ICTRP (http://apps.who.int/trialsearch/Default.aspx). We extracted data on all studies and manually identified studies that were closed or completed.’

For example, studies with "Unknown" status on ClinicalTrials.gov haven't been updated recently; could trials past their primary completion dates with "Unknown" status be the completed trials that are least likely to have published results? The authors excluded "Terminated" trials, which include trials that might have recruited participants and might be required to report results according to the laws and policies cited; this should be explained.

- No studies had the designation of ‘unknown’

- On page 6, paragraph 1 we have included: ‘terminated trials were excluded as they are less likely to publish results and our main aim was to evaluate the publication of completed studies.’

The authors say they excluded "reviews, case reports and letters to the editor”, but these are publication types and are not relevant to defining a cohort of registered trials.

- We agree, however, in our search some of the registered studies were of these types.
As the other reviewer noted, PTSD isn't an outcome (see lines 37-38 on page 8). To use the framework used on ClinicalTrials.gov, PTSD is a domain and might be associated with multiple outcomes defined using different specific measures, metrics, methods of aggregation, and time points.

- We have ensured that throughout the text we refer to PTSD related outcomes.

As described in my previous comments, numerical differences in the number of participants enrolled in a study might be important or trivial; a study that aims to enroll 200 participants and actually enrolls 198 or 202 participants would be effectively unchanged. If "fewer participants than planned" includes any numerical difference, then these Results aren't necessarily meaningful.

- A difference of 10% or greater was considered significant. We note this in the footnote of Table 1 on page 10.

Many of the results on pages 9 and 10 are unrelated to the stated questions and hypotheses and could be included in a table with descriptives.

- We have included some of the results in the table. For the remainder we feel that it would make the table too clumsy, so have left in the text.

I'm not sure how to characterize results of observational studies as "positive" or "null", and the authors don't describe the criteria used. Do we assume that all observational studies hypothesize that they'll find significant associations among all the variables assessed?

- In response to Reviewer 1’s comment we have removed all data or comparisons pertaining to observational studies, apart from descriptive data in Table 1, from the tables and text.

Trials don't die, so the term "survival" in the report and Table 5 is unclear. Better to define the event.

- We have modified this to ‘Time to publication for interventional trials’
Although these methodologic details might seem minor, this research is not reproducible without these clarifications.

Interpret results cautiously

I think the authors go beyond the data when claiming that "It is encouraging to observe that outcome reporting bias (where rather than reporting on the outcomes as originally stated, only positive outcomes and not negative outcomes for e.g. are reported) was not a notable form of bias here." Data in this report aren't sufficient to comment on changes to outcome definitions and methods of analysis.

- We have removed this.

Added findings about PTSD outcomes might be misleading because readers might infer that studies are at low risk of reporting bias if they report any outcome in a given domain: "With regards to PTSD-related findings, these were reported in 96.8% of interventional trials, versus 80.0% of observational studies (p < 0.001)." With apologies for self-citation, we've shown that investigators define patient-reported outcomes in many ways (https://www.ncbi.nlm.nih.gov/pubmed/28529187) and cherry-pick results for publication (https://www.ncbi.nlm.nih.gov/pubmed/?term=cherry+picking+mayo-wilson). Unless the authors have compared the results in journal articles with the pre-specified outcome definitions and methods of analysis in the protocols/statistical analysis plans, they should interpret their results cautiously. Even if an article includes a PTSD result, the result might be biased if the outcome and the method of analysis are not consistent with the protocol. PTSD is not an "outcome" as outcomes are defined on ClinicalTrials.gov and other registries.

- We have removed all data/statements comparing observational and interventional studies.

Moreover, it's unclear which "Differences between journal/ disseminated information and results reported in trial registry" were assessed. The conclusion that "When compared to results reported on the trial database we found discrepancies in only 2 studies" is likely overstated. Had the authors compared all data sources systematically, I would have expected more discrepancies. It's difficult to interpret the results because I could not reproduce methods and results based on this report. We describe some of the challenges of comparing data sources in this paper https://www.ncbi.nlm.nih.gov/pubmed/29057573. (I've cited my research in these comments because they're relevant to the points I've raised; the authors do NOT need to cite my papers to address my comments.)
- We have removed this, given the above concerns.

Because many of these trials were registered late or retrospectively, causal language in the Abstract like "randomization predicted" and "factors that influenced" is incorrect. It would be better to say that these variables were "associated with" publication and time to publication, which would be consistent with the language on page 11. The authors use causal language again on pages 12 and 13.

- We have been through the manuscript and changed this.

Percentages can be rounded; these data aren't so precise that the information after the decimal is meaningful.

- We have removed the decimals

P-values for the comparisons of interventional and observational studies aren't meaningful (they're obviously different groups of studies), so I'd delete them and report the absolute differences instead.

- We have removed the comparative statistics

I don't see how these findings "highlight the dearth of trials registered in low- and middle-income countries."

- On page 9, paragraph 1 we have included the following: ‘Only 4.2% of studies were registered in low and middle income countries (based on the Word Bank categories).’

Share the materials, data, and code

I'm grateful that the authors have included their data extraction form and dataset for peer review. It is ironic that so many studies about research transparency do not share their data and materials. This study concludes that "more diligent data sharing should be encouraged through prospective trial registration and reporting websites" so I was disappointed by the authors response that "As we may in future want to do a follow-up or use the data to address a different question, we prefer that the data is not made public as yet." I suggest the authors follow best practices, and practice
what they advocate in this paper, by sharing their materials, data, and code. Research about open science should be open.

- We have included the downloaded results, data extraction form and datasets as supplementary material.

Minor changes

I don't know whether this study is "the first with a focus on PTSD" and suggest the authors consider whether claims regarding novelty are needed and whether they can prove these claims are true. It might be more accurate to say that they are not aware of another study with this specific focus.

- We have removed this from the abstract; and on page 17, paragraph 4, we note that ‘To our knowledge, this is the first to do this in the field of psychiatry and PTSD’.

Avoid passive voice: "Conditions set out by the International Committee of Medical Journal Editors need to be adhered to more strictly". How and by whom?

- We have modified this sentence in the abstract: ‘We suggest that authors and journal editors adhere to conditions set out by the International Committee of Medical Journal Editors’

Avoid confusing terms. The paper describes both observational research and interventional research. To avoid confusion, I would not use the terms "study" and "trial" interchangeably; usage in the first paragraph of the discussion is consistent with my understanding of those terms.

- We have been through the manuscript and now use the term ‘trial’ throughout when referring to interventional studies.

Because "sponsor" has a statutory definition and is a field on ClinicalTrials.gov, I would replace the term "sponsor" with "funder" where the authors are referring to funders. I can't tell how the authors derived the data about "sponsors" in Table 1; it would be unexpected for universities and hospitals to fund this many clinical trials, but universities and hospitals would be listed as "sponsors" in ClinicalTrials.gov. As described in my earlier comments, "sponsor" and "funder" are not synonymous. I suspect the authors have conflated these terms and that the revisions in this draft have not resolved a problem with the coding and analysis because of Table 5 and
because the discussion says "Trials with a university involved as a sponsor were likely to be published sooner than those without".

- We used the ICTRP definition of sponsor which does combine the two: “The individual, organization, group or other legal entity which takes responsibility for initiating, managing and/or financing a study.” As this is the only search portal all studies had in common, we feel that this is the best definition to use in this study. This definition is included in the footnote on page 6.

I don't think the distinction between "hospital" and "university" is valid because we can't tell the difference between hospitals and universities from the sponsor's name on ClinicalTrials.gov. Many of the largest university hospitals register studies under a university PRS account that also includes the (relatively small number of) trials done in other parts of those universities. I don't think the limitations now mentioned in the Discussion are sufficient because that this coding is fundamentally flawed.

- While we understand the view taken by the reviewer regarding the approach we used to code the data, we respectfully disagree with the assertion that our coding is fundamentally flawed. Although many universities are linked to hospitals and vice versa, this may not always be the case. In many instances the affiliated university or hospital was added to the registry as a secondary sponsor and thus individuals registering trials have the option of listing all sponsors involved. We cannot account for the studies that have not done as such. We coded the sponsors according to the best available information on the registries. Whether that information is completely accurate and has been entered in a consistent manner is beyond our capacity to know or control.

- In all studies decisions are made as to how to code data, and although there may be limitations in our approach, there is no single correct approach. Our decision was to code the data available without making too many additional inferences. Although we coded the designation of the sponsors ourselves, we did not create the coding approach - we used the ICTRP designation of the primary and secondary sponsors as the base for our coding.

- Combining all hospitals and universities into one category will not necessarily reflect a more accurate representation and is based on an assumption that all universities and hospitals are affiliated, and even if they are affiliated that dual sponsorship is implied for all studies. Just taking our own research environment as an example, although some studies have dual sponsorship, the university and affiliated academic hospitals also conduct many studies independently.
We acknowledge that there are limitations to the approach we used to code the data and have stated as such, but we feel that this approach is the most representative of the actual information abstracted from the registries.

We have also included the following in the discussion: ‘We performed a post-hoc analysis to assess whether the effect of university sponsorship on time to publication was independent of hospital sponsorship by adding hospital sponsorship to the model and university sponsorship remained significantly associated with time to publication, whereas hospital sponsorship was not.’

Publication in a peer reviewed journal is important to disseminate trial results. It is not "the benchmark of a researcher's accomplishments".

On page 3, paragraph 2 we have changed the sentence: ‘Publication in a peer-reviewed journal is an important form of research dissemination.’

The questions (objectives) and hypotheses are better in this revised draft, but the hypotheses don't address the first question.

We have replaced the word ‘rate’ with ‘proportion’ in order to avoid confusion in terms of our questions and hypotheses, and indicated that we did not pre-specify what the individual factors would be: ‘Proportion of and time to publication of PTSD related studies would be similar to other conditions/ disciplines and that individual factors related to study quality and characteristics would influence publication rates and times (we did not have pre-specified hypotheses as to what these individual factors would be).

Some copyediting is needed. Don't end with a preposition, as in: "where PTSD related outcomes (e.g., severity, symptomatology; dissociation) were assessed for".

On page 4, paragraph 3, we have removed the word ‘for’: ‘In order to be as inclusive as possible, we included trials where individuals with PTSD were included or where PTSD related outcomes (e.g., diagnosis, severity, symptomatology) were assessed.’

Please revise the following sentences: "The NIH, concurrently, issued a complementary policy, under which all NIH-funded clinical trials, are expected to submit registration and results
information, whether or not the trials are covered by the FDAAA requirements. This NIH Final Rule (42 CFR Part 11), came into effect on January 18, 2017, with compliance expected by 18 April, 2017 (19)." In the first sentence, the 3rd and 4th commas are unnecessary. In the second, the first comma is unnecessary. Dates in the second sentence are not consistent (first American, second British).

- We have made the suggested modifications on page 4, paragraph 2: ‘This was made publicly available on 16 September 2016. The NIH, concurrently, issued a complementary policy under which all NIH-funded clinical trials are expected to submit registration and results information, whether or not the trials are covered by the FDA Amendments Act requirements. This NIH Final Rule (42 CFR Part 11) came into effect on 18 January 2017, with compliance expected by 18 April 2017 (19)’

In the following sentence, remove the comma and replace "as" with "because": "We selected these three registries/ platforms, as they are the largest."

- We have made the suggested changes on page 5, paragraph 3: ‘We selected these three registries/ platforms because they are the largest.’

The interpretation of Cybulski et al is incorrect; 15% were registered prospectively and 1% were registered both prospectively and completely (that is, all elements of the outcomes defined completely).

- Thank you for pointing this out. On page 16, paragraph 2, we have changed this to correctly reflect the article: ‘Only 15% of RCTs published in clinical psychology journals were registered prospectively and even fewer (1%) were both prospectively and completely registered (30).’