Author’s response to reviews

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

Authors:

Sharain Suliman (sharain@sun.ac.za)
Leigh van den Heuvel (lvdh@sun.ac.za)
Alexandra Suryapranata (apsp.suryapranata@gmail.com)
Jonathan Bisson (bissonji@cardiff.ac.uk)
Soraya Seedat (sseedat@sun.ac.za)

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Author’s response to reviews:

Reviewer comments and Author responses:

Reviewer #1: This manuscript reports findings which are not novel, but are important. I think that, in its current state, the purpose of the study and implications of its findings are unclear. The way it is presented is confusing. It could be improved by some clarification and a more focused approach.

Major essential revisions.

1. It would help to be more explicit about the purpose of this study.
   a. What was the question the authors were attempting to answer and did they have a hypothesis?
   b. What were the intended outcome measures of this study?

I seems the outcomes were, what proportion of registered studies go on to be published and how long does this take, but this is unclear (see my later comments).

- Thank you for these points we have clarified them. The reviewer is correct. On pages 4-5 we included the following:

In this paper, we address the following questions:
(i) What proportion of PTSD related intervention trials registered in ClinicalTrials.gov, EudraCT and ICTRP, go on to be published and what are the characteristics of these studies;

(ii) What is the time to publication, and what factors pertinent to registration are associated with time to publication?

We hypothesised that that:

(i) rate 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;

(ii) publication rates of studies with positive (statistically significant) outcomes would be higher than those with null outcomes.

Outcomes were:

(i) proportion of completed intervention trials that go on to be published;

(ii) length of time between study completion and publication;

(iii) factors that contributed to publication.

2. In the methods section, be clearer about the inclusion and exclusion criteria. The authors seem to contradict themselves by saying any PTSD study was concluded, but then saying qualitative studies, reviews, case reports letters to the editor were excluded. Did they have predefined inclusion and exclusion criteria or was this decided post hoc?

- On pages 5-6 we have clarified: Inclusion and exclusion criteria were predefined. We have clarified that any PTSD study with original quantitative data were included. Qualitative studies, reviews, case reports and letters to the editor were thus excluded. We did not expect to find these other study types registered on the trial registries as they do not clearly fall within the purpose of trial registries.

3. In the methods section the authors include study outcome as part of the information they extracted from the trial register. They later say that information extracted from published trial data included whether manuscripts reported results related to studies reported in the registry. This is important information. Whether or not the outcomes reported in the registry entry for a given trial are reported as outcomes in the published article gives an indication of reporting bias. This seems pertinent to this study. I cannot find reference to this in the results
section. I recommend the authors include this (e.g., the proportion of studies where the stated primary outcome was reported as the primary outcome in the subsequent publication) and comment on whether or not they found evidence of reporting bias. Alternatively, the authors could comment on the lack of this data as a limitation.

- Thank you for raising this important point. In the Methods section, on Page 7, we note: Given that all included studies were PTSD related, we evaluated whether PTSD related findings were reported on in the corresponding publication. Some reports/papers reported on other study findings, but omitted to report findings related to PTSD (PTSD might have been a secondary outcome in some of these). If results were reported on in the trial registry, and we found a manuscript/other publication, we did note whether the reported results were the same. We did not check whether all outcomes listed were reported on, however.

In the Results section, on Page 11 we note “With regards to PTSD-related findings, these were reported in 96.8% of interventional trials, versus 80.0% of observational studies (p < 0.001).”

We have added the following to the end of the same paragraph: “Results in 2 (0.6%) publications differed from that reported in the registry. These differences were in the number of participants included in the analysis.”

In the discussion, on pages 17-18, we note: 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. When compared to results reported on the trial databases we found discrepancies in only 2 studies. These pertained to number of participants included in the analysis. This is in contrast to a study that found that statistically significant outcomes had higher odds of being fully reported compared with non-significant outcomes (31). We did not, however, evaluate whether all outcomes were reported on.”

I note that outcomes are reported in Table 2, but the focus of that table seems to be a comparison of interventional and observational studies rather than the outcomes stated in the trial registry compared with the outcomes stated in the corresponding published article.

- Table 2 reports descriptive data relating to publications found presented according to intervention and observational study type. We have changed the heading to make this clearer.

4. On Pages 5 and 6 can the authors refer to PTSD as an outcome. My understanding is that PTSD is a diagnosis. I am assuming the authors didn’t just look at trials where the diagnosis of PTSD was an outcome. Can they better define the different PTSD related outcomes that were included?
We have tried to better define what we mean by PTSD related outcomes.

On page 4 we have clarified that “we included trials where individuals with PTSD were included or where PTSD related outcomes (e.g., severity, symptomatology; dissociation) were assessed for”.

On page 6, with regard to information extracted from databases we clarify that study outcomes included PTSD as “primary or secondary outcomes”; and have included a footnote to define “outcome/s”

On page 6 we also note: “Any report of a trial that had included results for PTSD as a primary or secondary outcome or as a covariate, or had sampled individuals with PTSD was included.”

5. The results section is organised into information about interventional studies and information about observational studies. Tables 1 and 2 provide data separated out into interventional and observational studies with the results of comparative statistical analysis. However, earlier the authors stated that they excluded observational studies from further analysis because there represented only a small proportion of studies found and because registration of these is voluntary. Why have the authors chosen to do a comparative analysis between interventional and observational studies and give this such prominence in the results section given their earlier statement? Was this comparison part of the original aims of the study (if so way?) or were these findings included post hoc because the statistical analysis yielded some statistically significant p values?

- Descriptive results are presented according to study type due to differences in registration requirements (registration of observational studies is voluntary), and we felt that they therefor could not be pooled. Also, as the focus of the paper was on intervention studies, the Statistical analysis section on page 7 we have included: “We present descriptive statistics for all studies split according to interventional and observational trials as our main outcomes of interest are related to interventional trials.”

Minor essential revisions

The results section could be shortened to improve clarity. On page 7, for example, much of the data is already presented in the table 1 and does not need to re-iterated in the results section text unless it is particularly pertinent to the aim of the study. Can the authors consider shortening the results section to remove repetition of results that are already in tables to help the reader focus in on the most important results?
Thank you for the suggestion. We have endeavoured to shorten the results section by removing text of results presented in Table 1.

Note: I am not qualified to comment on whether appropriate statistical analyses were used.

Reviewer #2:

1. Overall, I thought this was an interesting study, but it's not obvious what it adds to what is already known about this issue. For example, what does it add to these studies (Ross is referenced in the discussion, the others are not referenced):

Prayle AP, Hurley MN, Smyth AR. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study. BMJ. 2012;344:d7373


or this review


- We appreciate the reviewer’s concern. Although we agree that the findings are not novel, we do feel that they are an important addition to the literature in that other than confirming (or not), the findings of previous studies, in various conditions/ disciplines, they focus on an area that has not been covered previously- PTSD.

On page 18, we note: “Strengths of this study are that it considered a large number of studies that encompassed a variety of research methodologies and were registered across a number of databases. To our knowledge this is the first to do this in the field of psychiatry and PTSD. Despite our focus on PTSD related trials, our results support the reports of publication bias in other fields”.

We have also incorporated some of the suggested references.
2. The authors should say more about the limitations of their findings. For example, previous studies suggest that the publication rate for registered trials is higher than for other trials (https://jamanetwork.com/journals/jama/fullarticle/2653434), so evidence about a cohort of registered trials would not generalize to all trials. Registered trials might be unlike trials published as abstracts (e.g., https://www.ncbi.nlm.nih.gov/pubmed/30480762, which is referenced but not discussed much) or trials identified through IRBs (e.g., https://www.ncbi.nlm.nih.gov/pubmed/15161896). It is unclear how to interpret the factors associated with journal publication for registered studies, which are systematically different to unregistered studies. For example, FDAAA 2007 applies to trials of FDA regulated products (drugs, biologics, devices), and applicable trials are much more likely than non-applicable trials to be registered. Applicable trials are also more likely to be reported in biomedical journals (which are often members of ICMJE and have registration requirements) compared with non-applicable trials that are more likely to be reported in psychology and allied health journals (which are not ICMJE members and do not have registration requirements). I conducted a study about the registration of published clinical trials in clinical psychology journals (https://psycnet.apa.org/record/2016-28697-001); starting with a cohort of published studies, we learned that most clinical trials in psychology journals weren't registered. Registered trials in clinical psychology are the exception to the rule, and most clinical psych journals don't have registration requirements to my knowledge.

- Thank you for this recommendation. We have incorporated the above into the manuscript limitation section on page 19. Further we feel that the above highlight the similarities and differences in findings between different focus areas, such as between registered trials and registered abstract, making the current manuscript a useful addition.

3. The authors should clarify the research question. I could not tell from the abstract or from the methods whether the goal was to assess (1) the publication rate for registered trials or (2) the registration rate for published trials. The Results seemed inconsistent with the Objectives and Methods. One could start with a cohort of registered studies and estimate the publication rate, or one could start with cohort of publications and estimate the registration rate.

- Thank you for pointing this out. We have clarified the research questions on page 4:

In this paper, we address the following questions:

(i) What proportion of PTSD related intervention trials registered in ClinicalTrials.gov, EudraCT and ICTRP, go on to be published and what are the characteristics of these studies;

(ii) What is the time to publication, and what factors pertinent to registration are associated with time to publication?
In the abstract we note: “We thus aimed to determine the publication rate of registered trials of posttraumatic stress disorder (PTSD), and the factors associated with publication.”

4a. It is unclear what it means where the authors say "53 (12.1%) were not identified in ICTRP with the search terms used". Search terms should be reported, and search strategies should have been validated and consistent for all databases/portals.

-Search terms were consistent across databases. These are reported in the Methods section on page 5: “There was a consensus on the search terms by the authors and on study selection and exclusion criteria, as well as consensus on data abstraction (selection of data items extracted from each contributing article) and data extraction etc. The search terms included all applicable synonyms for PTSD and were compiled in accordance with the instructions for each database and were tested prior to implementation. The exact search terms used were: “PTSD OR posttraumatic stress disorder OR posttraumatic stress disorder OR post traumatic stress disorder. In each of the databases and search platform, we searched “all fields” and placed no further limits on the searches.”.

b. I couldn't follow the flow chart (Figure 1). Although it is clear that the registers were searched in 2015, it's unclear when or how the authors searched for publications. Reproducible search strategies and exact dates should be reported for all searches.

- The search strategies for the trial registries are outlined on page 5-6 and for the publications that correspond to the included trials on pages 6-7. We hope that this is now clearer.

c. Results, including the number of citations retrieved from each database, should also be reported. If the authors are interested in time to publication and other outcomes with substantial lag, then the authors should have restricted their sample to trials with completion dates long before the search for journal articles. The authors report time to event analyses, but did all trials have enough time to experience the event (i.e., publication)? Because the Methods are incomplete, it's unclear whether the methods were appropriate.

-We have replaced the dates in the Identification box of the flow chart with the number of citations retrieved from each database to make the chart easier to follow.

On page 7 we indicate that there was a minimum of 26 months between study completion (according to the completion date listed in the trial registries) and publication.

We have also include this as a limitation on page 19.
5.a. The Results describe study characteristics like planned enrollment and actual sample size. It is unclear how this information relates to the Objectives described above. For example, the comparison of planned enrollment versus actual enrollment is not mentioned in the Methods. It is unclear whether the source of this information is the trial registration, published report, or both the trial registration and the published report. When the authors say "there was no difference between number planned and number enrolled" do they mean there was no numerical difference (e.g., 200 versus 200) or there was no important difference (e.g., 200 versus 198)? Tests for significance are reported for some variables, but these analyses are not mentioned in the methods and it is unclear which analyses were pre-specified and which analyses were undertaken post hoc.

-We include enrolment information to evaluate whether (i) planned vs actual enrolment information were provided and (ii) numbers in the results section on the registry and associated publication were similar. We have include this in the Methods. Enrolment was obtained from the registry while actual sample size was obtained from the publication.

On page 6 we note that we collected information on: “Differences between journal/ disseminated information and results reported in trial registry”.

On page 11, we have include the following: “Results in two (0.6%) publications differed from that reported in the registry. Differences pertained to the number of participants included in the analysis.”

We have included sub-headings in the Results section in order to clarify where the data is from. From page 8-10 we have “Descriptive results of trials from registry” and on pages 10-11 “Published and disseminated result outcomes”

b. The authors mention a protocol and should report whether they followed a pre-specified protocol and statistical analysis plan. If so, where can it be found? The data extraction form, statistical code, and dataset should be made available during peer review and should be made public upon publication (if not before).

-We did work from a protocol, albeit brief and not published. Further, we ran the statistics directly from the program interface. We trust that in responding to the review comments and revising/elaborating on the objectives/study methodology, outstanding questions have been addressed. We have included the data-extraction form and dataset for the peer review. 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.
c. There are several technical issues the authors should address:

- In some places, the authors discuss ICTRP as if it were a database. ICTRP is a search portal, which searches ClinicalTrials.gov and EudraCT as well as the other registries mentioned (such as ISRCTN and ANZCTR). All trials registered on ClinicalTrials.gov and EudraCT should also appear when searching ICTRP. Discrepancies between search results suggest there were errors in the search strategies.

- Thank you for pointing this out. We have tried to be clearer in our discussion of the databases and search portal used.

The search strategies, were the same across databases/ search portals and are outlined on page 5. We are unsure why not all the studies were identified in ICTRP but on having another look suspect that it may be related to differences in search algorithms. For instance, ICTRP searches for the term only in the following fields ‘Title, Primary sponsor, Health Condition(s), Intervention(s), Countries of recruitment, Main ID, Secondary ID(s)’ whereas ClinicalTrials.gov searches for the term in additional fields, such as the outcome measures used.

d. Please define "sponsor" and "secondary sponsors". "Sponsor" is a field on ClinicalTrials.gov, and the term is defined by FDAAA 2007 and 42 CFR Part 11. It is not synonymous with "funder", and the authors don't appear to be using the term according its statutory definition.

- Thank you for pointing this out. We have not used the term according to the statutory definition. As such, we have included a definition as a footnote on page 6: “Sponsor refers to an individual or organisation who initiates or funds a clinical investigation.”

e. For the purpose of this manuscript, please clarify the difference between a "trial" and a "clinical trial". The terms are often used interchangeably, and it is unclear what distinction the authors are making. Perhaps the authors mean "study" rather than "trial" when the word is used alone?

- We apologise for the lack of clarity. In order to avoid confusion, we have removed “clinical trial” We do however use “study” and “trial” interchangeably.

f. How did the authors distinguish hospitals from universities in Table 1? Many university hospitals register studies under their institutional accounts (e.g., Johns Hopkins University, Yale University) and I don't know how the authors could make this distinction based on the name of the sponsor.
- This is a good point. We based this on the name of the sponsor as entered in the trial registration database. In some instances university hospitals may be the primary sponsor but the university may, in fact, be listed as the sponsor. We have listed this as a limitation on page 18......that there may be some misclassification of hospital and university sponsors.

g. How did the authors determine whether results were "positive", "negative" or "mixed"? Is "negative" the same as "null"? How did the authors handle non-inferiority and equivalence trials? Are these the results in registries (ClinicalTrials.gov) or the results in journal publications? What did the authors do if the results conflicted (e.g., results in a publication were "positive" and the results on ClinicalTrials.gov were "negative")? There's plenty of evidence that these often disagree, for example: Jones CW, Keil LG, Holland WC, Caughey MC, Platts-Mills TF. Comparison of registered and published outcomes in randomized controlled trials: a systematic review. BMC Med. 2015;13:282

- Whether results were statistically, positive, negative/ null or mixed results were determined from the results in the publication, and in the trial registry. We note this in the methods section, on page 7.

Also on page 7, we have included the following: “Where results differed between publication and registry the publication results were used.”

-We have replaced the word “negative” with “null”.

h. The background and discussion are outdated and should consider the impact of 42 CFR Part 11 and new NIH registration and reporting requirements, which came into effect after searches for this study were conducted. The authors might also wish to note that APA guidelines include registration and reporting requirements for clinical trials published in APA journals (https://www.apastyle.org/jars). The discussion should acknowledge that there have been major developments in this area that make trials from 2015 (and before) unrepresentative of current registration and results reporting practices. [I am a co-author of the APA's JARS guidelines. The authors might choose to cite JARS, or not, at their discretion.] . The following references might be useful:


NOT-OD-16-149. National Institutes of Health. NIH policy on dissemination of NIH-funded clinical trial information.


42 CFR 11. Clinical trials registration and results information submission; Final rule

-Thank you for this suggestion and the provided references.

On page 4, in the Background section, we have included a paragraph outlining the recent developments in the field, citing some of these.

In the Discussion, on page 18, we have included the following: “It is however, important to recognise that there have been major developments in trial reporting regulations and guidelines in recent years (42 CFR Part 11, The Final Rule, APA’s revised JARS guidelines). Thus, trials conducted prior to these may be unrepresentative of current registration and reporting practices.”