Reviewer’s report

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

Version: 1 Date: 26 Mar 2019

Reviewer: Evan Mayo-Wilson

Reviewer's report:

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?

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?).

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.

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

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?

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. 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. 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). 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. 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.

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.

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.

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.

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?

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

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.

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.
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.

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.)

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.

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

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.

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

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.
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.

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?

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.

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".

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.

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

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

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

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 April 18, 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).

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

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