Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Pharmacologic and Nonpharmacologic Treatments for Posttraumatic Stress Disorder: An Update of the PTSD-Repository Evidence Base*

Draft review available for public comment from June 8, 2020 through July 6, 2020.

Research Review Citation: O'Neil ME, Cheney TP, Hsu FC, Carlson KF, Hart EL, Holmes RS, Murphy KM, Graham E, Cameron DC, Kahler J, Lewis M, Kaplan J, McDonagh MS. Pharmacologic and Nonpharmacologic Treatments for Posttraumatic Stress Disorder: An Update of the PTSD-Repository Evidence Base. Comparative Effectiveness Review No. 235. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 20(21)-EHC029. Rockville, MD: Agency for Healthcare Research and Quality; November 2020. DOI: 10.23970/AHRQEPCCER235. Posted final reports are located on the Effective Health Care Program search page.

Comments to Research Review

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Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the website approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commenter and Affiliation	Section	Comment	Response
TEP 1	General Comments	Well done report, pretty straightforward. I had several suggestions for improvement.	Noted.
TEP 1	General Comments/Abstract	Abstract: "We included 115 pharmacologic and 264 nonpharmacologic studies" but your "pharm" 115 counts some studies that studied nonpharm also. So really you should report 3 categs (only pharm, only nonpharm, both).	We originally categorized studies as either having one or more pharmacologic arms or none (nonpharmacologic) because there was so much variation in all the other types of interventions that were required/allowed, but the pharmacologic distinction was clearer. Since the Phase 1 work and report, we have worked closely with the National Center for PTSD to obtain updated treatment categories and these are now included in the PTSD-Repository as part of the interactive web-based platform. We have updated the report to make reference to these additional, more granular treatment categories and to refer users to the interactive online database as well.
TEP 1	General Comments	"Loss of PTSD diagnosis" is an odd phrase, is it a standard in the field? If so, keep it. What you mean is that they improved enough to no longer warrant a diagnosis of PTSD. I'm trying to think of a brief phrase that connotes this with using the word "loss" for a positive outcome. Substantial symptom improvement? Not brief enough. Maybe the phrase you use later, PTSD diagnostic change, use it here.	Noted. This phrase is commonly used in the field of PTSD, though so is PTSD diagnostic change. A forthcoming paper is planned to highlight the lack of reporting in this area and we will ensure that both terms are defined and used to aid in searching for these data.

Commenter and Affiliation	Section	Comment	Response
TEP 1	Introduction	"Given the large and varied body of evidence, even some of the most comprehensive systematic reviews on PTSD have excluded some intervention types (e.g., complementary and integrative approaches) due to the prohibitively large number of studies that would have to be reviewed." This doesnt really follow from the previous sentence...which basically said there are 400 RCTs. Perhaps clearer for the next sentence to be "Many systematic reviews also aim to include non-randomized comparative studies, which in theory would number in the 1000s, but to make the review feasible, they sometimes restrict their scope to certain intervention categories (e.g., exclude complementary and integrative medicine approaches)." Or similar rewording to make your point that wholesale exclusions of intervention categories is generally undesirable.	Thank you for this suggestion. We have incorporated a reference to the large body of evidence (including nonrandomized trial evidence) and how this results in limiting the reviews in other areas (e.g., intervention type) for the purpose of feasibility.
TEP 1	Introduction	The purpose and scope paragraph is too long, imho. See if you can break it into 2 or 3 main ideas. Also that first sentence…does it really convey the main point of the paragraph? Seems to me the basic motivation is to re-use as much existing data as possible, precluding the need for re-extraction. So maybe start the paragraph with "Answering important clinical questions about PTSD treatments requires the examination of all available data, yet existing systematic reviews do not make this logistically easy, and they may intentionally exclude important treatments due to resource contraints..."	Thank you for these suggestions. We have edited the section to be broken into 3 distinct pieces and to incorporate the lead sentence you recommend which better highlights the point of the PTSD-Repository and of this update.
TEP 1	Methods	State that the risk of bias assessment was per study overall, not per comparison or per outcome or per timepoint. I suspect this was because there were insufficient resources for this project to provide that granularity.	This addition has been made to the ROB section.

Commenter and Affiliation	Section	Comment	Response
TEP 1	Methods	I noticed you didn't search clinicaltrials.gov. Is it possible that a search could uncover a few as-yet-unpublished studies and authors also put data into the clinicaltrials.gov record? I know it's rare for authors to do that, but it wouldn't take long to search say 2018 or later and comb through the results.	This is a good suggestion and one we will consider if there is future funding for these efforts. In the meantime, we have made sure to do an up-to-date search so that our results reflect studies published through May 22, 2020.
TEP 1	Methods	Last search date Sep 2019. I'm guessing other reviewers will say you should update your search so that the repository is as current as possible. While that would be ideal, I think it takes a back seat to your ROB pilot and also dealing with all other peer review comments.	As noted, we have updated our search to May 22, 2020.
TEP 1	Results	footnote of Fig 2, that's some impressive transparency, good work	Noted.
TEP 1	Results	"The publication dates of the included studies ranged from 1988 to 2020 (Figure 2)." You meant figure 3	Noted. We made this change.
TEP 1	Results	Fig 3, if the last search was Sep 2019, how can there be a 2020 study? I guess the search caught a prepublication copy.	Correct, some were caught in pre-publication, though our search is updated to May 22, 2020 now, regardless.
TEP 1	Results	Fig 4 needs a footnote for what you mean by Mixed (ie multicomponent containing 2 or more of the intervention categories). You also used the word mixed in fig 7 so consider a different word, to avoid confusion	This change has been made.
TEP 1	Results	"Figure 4 shows the distribution of included studies by sample sizes". You mean Fig 5. Recheck all in-text references that use figure numbers.	Noted. We have made this correction.

Commenter and Affiliation	Section	Comment	Response
TEP 1	Results	Nice set of graphs, and maybe could be enhanced by using tableau? Maybe that should be added to your Next Steps. Would need more funding, but PTSD researchers may greatly benefit from an interactive website showing the types of trials that are in your repository, with filters etc. I know OHSU did a well-done tableau-generated visualization of a 2018 low back pain report which was really well done see https://public.tableau.com/profile/connor.jp.smith#!/vizhome/AHRQT01MethodsPilot-PacificNorthwestEPCV2_1/NonpharmacologicalInterventionsforPain and the full report is at https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/nonpharma-chronic-pain-cer-209.pdf	Noted. We agree that this would be a good next step, and in fact, have been coordinating to support this work at the National Center for PTSD. We have referenced this interactive web resource, currently hosted on the Socrata platform and available through the National Center for PTSD and their website, in the final report.
TEP 1	Results	Seems like Table 3 could easily work as a bar graph (two colors, one for pharm and one for nonpharm). We know from the preceding pages that you're not graph-averse.	Table 3 has been left as is for formatting reasons in the report.
TEP 1	Results	Table 6 very graphable to demonstrate the improvement in 2001+	Table 6 has been left as is for formatting reasons in the report

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TEP 1	Results	"Although ROB assessment is meant to take a holistic approach to the final rating, there is a tendency towards a more simplistic summing of the domains, particularly when there is no specific, clear guidance on the approach to determining final ratings". Where is this "tendency"? In other reports but not yours? Or maybe in yours because there's little guidance as to how to holistically evaluate ROB? This section is confusing. There is the issue of how to get an overall ROB rating. And separately there is the issue of how 2 items might interact (eg maybe dont ding for unblinding if it's an objective outcome). Probably there should first be a paragraph about inter-item conditions (though since you are rating each study as a whole and not per-outcome, one wonders how different outcome ratings would be combined), and secondly a paragraph about simplistic summing vs holistic. And in that 2nd paragraph there is a 3rd option, which is more general rule-based integration of items, where you don't just sum the items, but you do use a nonquantitative systematic process for assigning an overall category. For example you say if any of these X items were problematic, we called it high ROB; if none of those items were, but at least 2 of these other items were, then we called it moderate ROB; otherwise we called it low ROB. I'm just saying you can be systematic without simply summing.	We have edited this section for clarity.

Commenter and Affiliation	Section	Comment	Response
TEP 1	Discussion/Conclusion	If you're going to bring in controlled non-randomized studies of interventions, might I suggest that you at least require that the authors used some sort of method to control for confounding (e.g., propensity, instrumental variable) . Obviously this still wouldn't control for unmeasured confounders, but it's a start. I suspect that if you go back to 1980, only like 10% of controlled non-randomized studies actually use these established methods well-known to epidemiologists. So it might be a feasible way to allow a suboptiomal study design by simultaneously requiring the usage of confounding controls.	Noted. We have edited this section to incorporate this suggestion.
TEP 2	General Comments	The report is clinically relevant/meaningful and I found the target population, audience, and key questions to be clear.	Noted.
TEP 2	Introduction	Introduction is clear and relevant.	Noted.
TEP 2	Methods	Inclusion and exclusion criteria are justifiable. There appears to be a discrepancy between the search dates as stated in the methods and elsewhere in the document. Specifically, in the results of the executive summary (page ES-2) the results say that trials were published between 1988 and 2020, yet the search dates in the methods indicate a search date end of September 2019. The specific day in September is also missing.	Noted. We have updated the search dates which now reflect our updated search end date of May 22, 2020.
TEP 2	Results	Results seem comprehensive.	Noted.
TEP 2	Discussion/Conclusion	The implications could be more specific; including some specific examples of how stakeholders may use the information would be helpful.	Agreed. We have updated the discussion to include a paragraph on specific uses by stakeholders.
TEP 3	General Comments	First, I want to congratulate the EPC for working on a fairly unusual task, this is not your typical systematic review. Yet, the did well and the report is helpful and the approach rigorous.	Noted.

Commenter and Affiliation	Section	Comment	Response
TEP 3	Abstract	The abstract says that you have explored these new RoB elements but it leaves the reader hanging without any comment about what this led to. Were these elements feasible to implement, helpful, were they added to the repository, will they undergo additional testing in the future?	We agree and have updated the report to include more information about the ROB process and findings, as well as next steps, since we have now finished with the initial pilot testing phase.
TEP 3	Methods	It is not clear anywhere in the report what was the original risk of bias tool used in the repository. You cite the EPC manual but were these items similar to Cochrane tool 1.0 or 2.0? This remains quite vague to audience not familiar with the EPC methods (but yet very familiar with Cochrane's). I would clarify and link to the source tool and its domains.	This information has been included as appendices and the source tool (and descriptive categories) is included in the evidence tables.
TEP 3	Methods	I argue that the "new" items of RoB map to the Cochrane tools (and EPC tool), of course except for the 5 point scale. I would explicitly map them out because you will be criticized for calling these new items.	We have updated these sections to better describe source materials and describe the "new" system as being a way to make the old template more explicit, replicable, and transparent (i.e., rather than inventing entirely new ROB elements, we are just better describing the criteria to improve reliable implementation).
TEP 3	Discussion/Conclusion	Studies of the type of "a systematic review to guide the structure of a repository" are needed. They make the repository more evidence based and perhaps add credibility and buy in from stakeholders. I suggest the authors cite other similar studies in the discussion to draw the attention to the need for more similar work. They are not common, but here is one that you cancite: PMID: 30768569.	Agreed. We have included this information in a recent publication on the PTSD-Repository and updated the report to reference this information from two closely related fields of TBI and depression.
TEP 4	General Comments	The report describes an important resource for researchers and clinicians; it is a bit difficult to imagine very many consumers interacting with the data in a meaningful way. The key questions are appropriate and clear.	Noted. We have added information regarding ways that other stakeholders might use the report.

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TEP 4	Introduction	This section provides context and establishes the need for the current manuscript and the repository. It is not clear, however, why the repository was expanded to include PTSD/SUD comorbidity as opposed to other potential comorbidities (e.g., depression).	We have added this point in the section identifying possible Next Steps. As noted in Table 1: PICOTS Inclusion and Exclusion criteria, interventions were included if they could be standalone interventions for PTSD. Because many interventions targeting PTSD and comorbid disorders such as depression or insomnia were also applicable to individuals who have PTSD without these comorbidities, many were already included in the PTSD-Repository. Additionally, the TEP provided guidance that data from interventions for PTSD and comorbid SUD would help fill current evidence synthesis gaps in the field of PTSD research.
TEP 4	Methods	Inclusion/exclusion are justifiable. Search methodology and selection of included measures appear to be appropriate.	Noted.
TEP 4	Results	The results section is quite comprehensive. The tables are generally inclusive, but it would be useful to represent the distribution of gender and race/ethnicity (e.g., by % white) in the included studies.	Agreed; however, these data were not able to be compared across the studies due to differences in reporting. We have added the following section to the portion of the report describing lack of reporting to explain why these data are not presented in these tables: "Studies reported race and ethnicity data very inconsistently, making it difficult to abstract into preselected categories and compare in a standard manner across studies. These data are not presented in Table 3 with other lack of reporting data because many studies reported these data, though they were not able to be included in the PTSD-Repository because of different categories and metrics used across the studies."
TEP 4	Discussion/Conclusion	The conclusion nicely summarizes the process and the challenges that were encountered.	Noted.

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TEP 5	General Comments	In general I found this to be a very clear and well done report. The relevance of conducting such a review and updating it with broader criteria is important and useful. The key questions were clear and the reporting of findings was for the most part easy to abstract.	Noted.
TEP 5	Introduction	The background section reports on epi for PTSD, but not for SUD or other comorbidities. Since the scope of this update was broadened to examine sud and other outcomes, I think some more epi directed towards scope of the problem should be added.	We have augmented the introduction with information on comorbid SUD/PTSD.
TEP 5	Introduction	On p. 12 line 52, are these dates correct?	The dates have been updated to reflect the update search conducted on May 22nd, 2020.
TEP 5	Methods	Overall the methods were comprehensive and described in a clear and standard fashion.	Noted.
TEP 5	Methods	A few things: I wondered about the terminology, which probably came from the original repository review, but the use of the term pharmacologic versus non-pharmacologic seems to privilege the minority of treatment type. I don't have a great answer for what overarching category you would use instead...because psychosocial or behavioral doesn't cover something like TMS...Sorry no solution, just a thought.	We agree that this is a complicated issue. As described above, we originally categorized studies as either having one or more pharmacologic arms or none (nonpharmacologic) because there was so much variation in all the other types of interventions that were required/allowed, but the pharmacologic distinction was clearer. Since the Phase 1 work and report, we have worked closely with the National Center for PTSD to obtain updated treatment categories and these are now included in the PTSD-Repository as part of the interactive web-based platform. We have updated the report to make reference to these additional, more granular treatment categories and to refer users to the interactive online database as well.

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TEP 5	Methods	Also, in terms of treatment types, I wasn't sure, but there are no descriptions of SUD treatments...the outcomes and comparators are all pretty PTSD focused. For example, I think the COPE treatment study was included, but isn't listed...included perhaps at PE?	For this phase of development, as recommended by the TEP and NCPTSD, treatments were categorized according to the 2017 Department of Veterans Affairs/Department of Defense clinical practice guideline, and are therefore limited to the categories listed in this document. However, these categories are being further developed and grouped by NCPTSD and are included in more detail as part of the web dissemination of the PTSD-Repository (https://www.ptsd.va.gov/ptsdrepository/index.asp).
TEP 5	Results	Overall, I thought the Tables and Figures presented were clear, highlighted main findings, following the standard PICOT model.	Noted.
TEP 5	Discussion/Conclusion	No comments, well done. Clear and user friendly--a very cohesive summary that will make it usable and easy to abstract from.	Noted.
TEP 5	Clarity and Usability	There was a high degree of repetition which may have been intentional (i.e., shorter summaries for public policy purposes, etc) but reading through the whole document, it felt like I was reading many of of the same sections over and over. Again, perhaps this was by design?	Noted. Yes, this was by design and in accordance with AHRQ guidelines to ensure that different sections of the report are appropriate for various users.
TEP 6	General Comments	yes	Noted.
TEP 6	General Comments	I've attached a copy of the report that includes a few comments related to readability and clarification. My main comments are related to the RoB task. I do not have expertise in PTSD research and so I cannot comment on the approach and success in retrieving the body of relevant peer review literature.	Noted.

Commenter and Affiliation	Section	Comment	Response
TEP 6	General Comments	I appreciate that much of the RoB assessment was conducted earlier and therefore the authors would want to limit their tasks and continue to add to this work rather than start from scratch with a new tool. To support the decision to continue to use of the same tool, I think that it is important that the authors think about and discuss the tool in greater detail in Appendix F (or main text), including each of the domains and how they were measured, including referencing both EPC, Cochrane, and any other useful methods guidance. I think this is important, in and of itself, because the intent is for other researchers to use the database, including the prepopulated RoB assessment. The database authors are also considering adding new items to the tool and this approach would help the users understand how they fit into the (new) whole.	This information has been added to the relevant sections of the appendixes document.
TEP 6	General Comments	The authors may want to consider specifically discussing the relationship between the tool that was used in the database and the new Cochrane RoB tool for RCTs. https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials. The authors could map one to the other and describe how domains have been similarly/dissimilarly addressed in the two tools. For reference, below are the domains included in the two tools. Because the domain naming convention is different, you will need to determine the extent to which the criteria within each domain are also different. Reviewing this tool may also be insightful for thinking about your proposed exploration of new RoB questions and how they would add to the existing instrument.	Noted. We expanded the discussion of these points in the main report as well as in Appendices F and G.

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TEP 6	General Comments	Whichever approach you decide is best going forward, I think that an important issue is to be able to better document which domain(s) drove a study to be high RoB and why. You state that you are considering a five category RoB score. In my experience, reviewers have primarily focused on high RoB compared to medium/low scores. The usefulness of further gradients is not obvious to me. Alternatively, more information/ability to sort/highlight studies based on specific RoB concerns may be useful, i.e., such as failure to adequately address missing data.	We have described characteristics of the High ROB studies, highlighting which domains were rated as inadequate, in the appendixes document.
TEP 6	General Comments	Lastly, I suggest testing new measures on more than 10 studies. I would select a greater number of studies, including those that do and do not address the new concerns and think about how each affects the total RoB score.	Noted. This will be considered for future work on this project.
TEP 6	General Comments	PTSD Took Categories Selection bias Performance bias Detection bias Attrition Reporting bias Other considerations	Noted in above comment.
TEP 6	Abstract	Line 32 page v: "will be" - Following review of the draft report?	This is correct. The report has been updated to reflect the work that has been finalized since the submission of the initial draft report.
TEP 6	Abstract	Line 36 page v: "1988 to 2020" - 2019 (above) or 2020)	Dates for the updated search have been replaced throughout the report.
TEP 6	Abstract	Line 7 page vi: "loss of PTSD diagnosis" - This is not my field but this phrase is new to me. Consider defining it—including how it differs from remission or other measures of recovery.	Noted. As described above, this phrase is commonly used in the field of PTSD, though so is PTSD diagnostic change. A forthcoming paper is planned to highlight the lack of reporting in this area and we will ensure that both terms are defined and used to aid in searching for these data.

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TEP 6	Evidence Summary	Line 38 page ES-1: "PTSD." - I can't get the #s to add up so I'm missing something. 379 (new total) – 318 (old total) = 61. New includes: 36+22=58	The numbers of included studies have been updated throughout the report.
TEP 6	Introduction	focused on RoB	Noted.
TEP 6	Methods	Focused on RoB	Noted.
Peer Reviewer 1	General Comments	It is great to see this work continue to keep the repository updated. Very nicely done.	Noted.
Peer Reviewer 1	General Comments/Abstract	Minor: 1. Abstract: In the Results, it notes the number of new RCTs identified. Suggest clarifying what time period that refers to (i.e., new since when?). Same comment for the Main Points of the Evidence Summary.	Noted. We have clarified the timeframes for the two PTSD-Repository phases as well as the search, and updated with the dates of the update search conducted on May 22nd, 2020.
Peer Reviewer 1	General Comments/Abstract and Evidence Summary	2. in Abstract and Evidence Summary: in addition to providing the % rated as medium ROB (57%), it would be informative to also report the % rated as low and % rated as high ROB.	This change has been made.
Peer Reviewer 1	General Comments	3. The analytic framework might not be necessary for the repository. It is quite simplified and it doesn't really add anything beyond what is in the KQs or in the eligibility criteria.	Noted. We have chosen to leave it in the report in case it provides a succinct summary for some readers, but will likely not include it in a subsequent publication.
Peer Reviewer 1	General Comments	4. Suggest adding additional limitations about ROB assessments to the Discussion (see comments below).	This change has been made.
Peer Reviewer 1	Introduction/Evidence Summary	page ES-1, line 37-39. "The PTSD-Repository included data from 318...". Suggest clarifying what month and year it went through when there were 318 studies.	This change has been made.
Peer Reviewer 1	Methods	1. Great to see such a comprehensive search that covered so many databases	Noted.
Peer Reviewer 1	Methods	2. Table 1 seems to list fewer eligible Outcomes that what the Introduction lists on page 2 in the abbreviated PICOTS bullets. It seems that Table 1 should have a more comprehensive list of Outcomes for it to reflect the work that was done.	This change has been made.
Peer Reviewer 1	Results	Clearly written. Very informative.	Noted.

Commenter and Affiliation	Section	Comment	Response
Peer Reviewer 1	Results	page 21. "The ROB TEP call discussion...". I'm not sure that the proposed "more nuanced approach" is at all different from our usual approach to assessing ROB. I think we typically do those things, but those details are often not fully written into reports (aiming to keep the information concise). Rather, they are part of internal notes and discussions, and they contribute to final assessments and ratings, but they are often condensed to something very brief. To me, this does not sound like anything different from our usual approach...it just sounds like showing more of the detailed process work of assessing ROB.	Noted. We agree that this is often the case, and have clarified these ROB methods accordingly in the revised report.
Peer Reviewer 1	Results	Minor: 1. In the Figures, Number of Studies is sometimes the x axis and is sometimes the y axis. Consider making it consistently the same axis so that readers don't have to re-orient themselves from figure to figure. It seems that keeping it as the vertical axis (like Figure 3) is easier to follow.	Noted. We have changed the orientation of some figures so that axes are consistent throughout.
Peer Reviewer 1	Results	2. I really like the section that details how reporting has changed over time (post-CONSORT). Although, given the small n from prior to 2001, it could be more informative to split the >=2001 category by decade (into 2001-2010 and 2011 to present) to show whether the improvements are continuing	Noted. We will consider additional exploration of these breakdowns in a planned manuscript describing the updated ROB assessment methods that were explored and pilot tested
Peer Reviewer 1	Discussion/Conclusion	Discussion is good.	Noted.

Commenter and Affiliation	Section	Comment	Response
Peer Reviewer 1	Discussion/Conclusion	Suggest adding more limitations about Risk of bias assessments. Consider adding a limitation of the report to note that risk of bias was assessed by 1 person and checked for accuracy by another person rather than dual independent review (not dual independent ROB assessments). And that risk of bias assessment may not have good reproducibility. ...and that some ROB was done by a different set of authors/reviewers (from the prior evidence report) than the authors/reviewers who wrote this report.	Noted. This information has been added to the discussion.
TEP 7	General Comments	There appears to be an inconsistency with the timeframe of the eligible RCTs publication (June 2018-September 2019 and the statement of studies published from 1988 to 2020.	Noted. Some publications were identified as pre-prints and the published. We have updated the search to end on May 22, 2020, and the dates have been updated accordingly in the report.
TEP 7	General Comments/Abstract	Abstract assumes reader is already familiar with prior creation of data base. Thus wording of "expanded criteria" may be somewhat confusing to original readers unfamiliar with original criteria. Suggest statement of original criteria and noting expansion in this update to also include xyz.	We have expanded the description of the inclusion and exclusion criteria and explained how they have changed from the initial phase of the PTSD-Repository and updated in this next phase of work.
TEP 7	General Comments	The Risk of Bias section wording is inconsistent with the rest of the manuscript. The detail of individual working calls seems out of place and necessary.	Noted. To be transparent about the process of revising the ROB methods, we have retained this information, but have updated the text description of the ROB section for improved clarity.
TEP 7	General Comments	The report would benefit from some additional consideration of the limitations of the original technical brief and the purposeful crafting of this and future annual updates.	This information has been added to the discussion.
TEP 7	Introduction	It may be useful to consider the purpose of the annual update. While the context for the PTSD repository existence is important in and of itself, readers may benefit from considering how the update serves a purpose to continue to evolve the data repository.	This information has been added to the discussion.

Commenter and Affiliation	Section	Comment	Response
TEP 7	Methods	Throughout the abstract and manuscript, organization is odd with description of methods appearing in results or discussion. Suggest keeping all approach/method description together.	We agree that this aspect of the organization was challenging because the "results" are essentially methods to establish and update the repository. We have updated the results and methods including providing more information about how these types of systematically reviewed data repositories can provide data for future projects.
TEP 7	Methods	Generally, the authors are clearly intimately familiar with the inclusion/exclusion and the working calls to navigate those criteria. For readers who were not involved in those discussions, it is not always clear what the destinciton is or why thresholds and or criteria were chosen. For example (but not limited to this example), in Table 1, the exclusion for interventions may benefit from additional explanation. The i.e. interventions targeting ptsd and a comorbidity such as depression are included if the intervention can be a treatment for PTSD alone. Could an example be provided of both what would be permissible and what would not be permissible? what treatment might only be a treatment for depression that could not be a treatment for PTSD?	We have updated and expanded the section describing inclusion and exclusion criteria, providing more information on how criteria were applied when determining eligibility of interventions.
TEP 7	Results	The statement that "less than half of the studies reported loss of ptsd diagnosis or clinically meaningful response/remission of symptoms" may be taken out of context to suggest that trials failed to demonstrate benefit of intervention rather than what I believe is intended in this report that studies failed to provide information explicitly on changes in diagnosis or remission of symptoms. Suggest providing an example of what outcomes in those studies were reported and perhaps rewording in the report.	We have rephrased this section to better reflect the intended meaning.

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TEP 7	Discussion/Conclusion	page 35 lines 4-14 appear to be methods and may be better placed in that section.	We have kept that information in the discussion for clarity, though added to the related methods sections with more information on these topics.
TEP 7	Discussion/Conclusion	The discussion does not clearly state the major advance of this update. Rather, it appears largely as a redundant summary of the method rather than a consideration of what the additional data for this annual update will allow for the field. If one were to only read this section and the abstract (as we know many readers do), I am not sure they would be able to answer "why is this important".	This information has been added to the discussion.
TEP 8	General Comments	I found the report to be informative. I imagine it will be quite useful to investigators, clinicians and others who will use the online database.	Noted.
TEP 8	Introduction	Appropriate length and amount of detail.	Noted.
TEP 8	Methods	I found the search strategy to be logical and easy to follow. I learned a few search terms to include in my own searches.	Noted.
TEP 8	Results	I found the figures and tables quite useful. I would have appreciated if in the appendix trials new to the data base were indicated in some way.	Noted. While we did not include this information in this report, we will consider presenting these tables in a subsequent article highlighting the updates to the PTSD-Repository completed in this second phase of development.
TEP 8	Discussion/Conclusion	Well written and thought out. I am not aware of any important literature that was omitted.	Noted.

Commenter and Affiliation	Section	Comment	Response
Peer Reviewer 2	General Comments	Overall, the report provides a nice summary of the process to identify, evaluate and include RCTs in the PTSD Trials Standardized Data Repository. The report will be useful to researchers and organizations seeking to consolidate findings and provide guidance regarding recommended interventions. The repository itself is quite valuable. Please note, this is not a Comparative Effectiveness review although that header appears on the front page of the draft document. Continued inclusion of that will be misleading to users.	Noted. The reference to a comparative effectiveness review has been removed.
Peer Reviewer 2	Introduction	No comments	Noted.
Peer Reviewer 2	Methods	No comments	Noted.
Peer Reviewer 2	Results	We definitely appreciate the use of the CONSORT guidelines to categorize elements in RCTs. Similarly, providing details about all of the data elements identified in Appendix D will be useful for future users of the repository. We would like to see tables in this report regarding percentage of females included in studies along with details about the race and ethnicity of those who received care. The diversity of research populations is a significant concern for our membership so easy access to that content in this report would be useful. The data elements included in the depository are useful and ideally will encourage researchers to more carefully report these in future publications.	Agreed. We have added information to the report regarding the challenges with abstracting these data and where readers can find more information: Studies reported race and ethnicity data very inconsistently, making it difficult to abstract into preselected categories and compare in a standard manner across studies. These data are not presented in Table 3 with other lack of reporting data because many studies reported these data, though they were not able to be included in the PTSD-Repository because of different categories and metrics used across the studies. Details about abstraction methods for race, ethnicity, and other demographic variables is included in the Data Abstraction Guide, included in this report as an Appendix.
Peer Reviewer 2	Discussion/Conclusion	We particularly appreciated the effort to consider how to expand the evaluation of risk of bias. We would like to see future conceptual work consider how to evaluate non RCTs for their implications about treatment effectiveness.	Noted. Expanded testing and refinement of the augmented ROB assessment template is being considered for future funding of this project.

Commenter and Affiliation	Section	Comment	Response
Peer Reviewer 2	Clarity and Usability	We noticed some missing data in the association appendices (Tables F-4 and F-5). Additionally, Page v – review methods- substance use (not used) disorder and Appendix G, first paragraph, last sentence should be rather than (not that).	These corrections have been made.
TEP 9	General Comments	The utility of this type of report is substantial for identifying holes in the existing body of research and crafting new studies, for future systemic reviews and meta-analytic study, for the development of educational tools and for formulating relevant policy. The clinical utility for the average provider is less obvious, but likely critically important. Capturing more of the larger clinically relevant summary points in the abstract or the Evidence Summary section may be helpful to increase the clinical meaningfulness of the document (as this question suggests). This may be a focus for some minor expansions. It is difficult to imagine how the public might leverage this report to inform treatment decisions for themselves or loved ones. (point 5 on page 1). The Appendices are thorough and necessarily onerous to peruse, so will not provide much assistance to many users. Capturing the important take-home points and clinically relevant information in the body of the document and summary tables is clearly essential.	We have updated the abstract objective to read, "To identify and abstract data from posttraumatic stress disorder (PTSD) treatment randomized controlled trials (RCTs) to update the PTSD Trials Standardized Data Repository (PTSD-Repository) with data on PTSD and other mental health outcomes including suicide-related outcomes and substance use."
TEP 9	Introduction	The introduction is very well-written and provides an excellent overview on the need for and purpose of this document. The scope is a bit broad. If the document is intended to accomplish goals 1-7 as laid out in the introduction, it might be worthwhile to return to these goals and provide relevant take home points for each goal in the conclusion of the manuscript.	We have expanded the conclusion accordingly and provide more information on dissemination and uptake of the PTSD-Repository and associated products such as the web-based, interactive PTSD-Repository database and published manuscripts.
TEP 9	Introduction	The Key questions are clear.	Noted.

Commenter and Affiliation	Section	Comment	Response
TEP 9	Introduction	Figure 1 is very helpful. One point of clarification - it is clear that the manuscript expands on previous work to now include SUD. However, the description of study participants in the figure suggests that other comorbidities are not included.	Noted. We have updated the section on inclusion/exclusion criteria with this information.
TEP 9	Methods	Inclusion and exclusion criteria are clear and are justifiable.	Noted.
TEP 9	Methods	The search strategies are clear and thorough.	Noted.
TEP 9	Methods	There are a few terms that are used inconsistently throughout in different combinations (suicide, suicidal ideation, suicidality, self-directed violence).	We have revised the report to include consistent terminology throughout, referencing suicidal ideation/behavior.
TEP 9	Results	I understand that the strength of evidence is not assessed in this project. That said, the addition of some clinically relevant detail in the presentation of results may be helpful in understanding the extent of empirical support or breadth of study in different domains. Several points of clarification might also be considered.	Figure 11 has been added to show number and percent of studies that report depression, suicide, SUD, and QOL/functioning.
TEP 9	Results	Highlight that while SUD is specifically considered in this study, many other studies included PTSD plus comorbid disorders.	Noted. We have updated the section on inclusion/exclusion criteria with this information.
TEP 9	Results	Table 2. The criteria for including which examples in each column is unclear. The table seems fairly exhaustive. Adding the number of studies that included one of those interventions as a treatment arm parenthetically next to each example might provide a simple summary of the breadth of empirical studies associated with each entry.	These interventions are classified in the same subgroup of interventions currently per the 2017 VA/DoD CPG framework (noted in the section below the table). However, additional intervention categories have been developed by the National Center for PTSD and are being applied to the web-based PTSD-Repository. These updated, more granular categories will be applied to future phases of the PTSD-Repository evidence tables for added clarity and granularity, and PTSD-Repository data is able to be sorted by these categories in the web-based tool available online and now listed in the updated report.

Commenter and Affiliation	Section	Comment	Response
TEP 9	Results	The Figure numbers appear to be mislabelled starting with Figure 5?	Noted. The figures have been renumbered.
TEP 9	Results	Figure 7. The categorization of studies by population may require some caveats. Active duty, Veteran and mixed groups might be quite accurate. However, "community" might warrant additional description. Community members can certainly include Veterans and this may not be explicitly described in the study description. Veteran studies most typically heavily recruit VA-engaged Veterans and distinctions between effect sizes across populations might be driven, at least in part, by systemic differences related to VA. The way the table is written (and results described), the categories appear mutually exclusive which, again, may be misleading.	Agreed. We have made a note in this figure to reflect this definition.
TEP 9	Results	Figure 8. Outpatient clinics are a much more variable and heterogeneous category as compared to the other categories. Community mental health is much different than university setting clinic as compared to VA clinic. This caveat might be noted in text.	Noted. We have made this note following the figure.
TEP 9	Results	Figure 9. Consider adding a category of mixed interpersonal trauma and separating from mixed trauma. Mixed trauma implies a wide range of trauma types from MVAs to combat to interpersonal violence (sexual and physical) and natural disaster, etc. The heterogeneity of mixed trauma could be an important area of study (providing the ability to compare outcomes across trauma types, gender differences, etc.) There are a significant number of studies that include only survivors of interpersonal violence (CSA, IPV, adult physical and sexual assault and rape). Identifying this body of research more clearly would also be quite helpful.	Noted. We agree that this is an important area to explore further and will consider these elements for additional exploration and categorization in future phases of this work. We also recently had a paper published in JOTS that describes the challenges of abstracting this particular variable in greater detail. This publication is now cited in the updated report.

Commenter and Affiliation	Section	Comment	Response
TEP 9	Results	Figure 10 (p 30). Assuming that the measures reflected were the primary outcome measure? Many studies use multiple measures. Is that reflected in the Figure?	Thank you for noting this. We agree and have added a longer explanation to this section to ensure that readers understand the data presented.
TEP 9	Results	Table 3. With respect to the population characteristics, an argument could be made for a number of important and clinically relevant variables. Were there any choices that were discarded? Time since trauma (different than chronicity of PTSD) seems important.	Noted. As described in this section, these decisions were made on the recommendations of the TEP and the NCPTSD. Additional variables are being considered for inclusion, and for refinement (e.g., differential abstraction of time since trauma and duration of PTSD symptoms, though few studies report both) in future updates.
TEP 9	Results	Comorbid TBI is an interesting choice, but not necessarily relevant in a number of studies. For example, a study with an adult survivor of CSA might not assess TBI. The same is true for comorbid SUD. If these diagnoses were not the primary aim of a given study, they may not have been reported in the parent paper. However, the data may be there and be published in secondary papers. It seems that suggested population characteristics (in this type of project) should be universally applicable to all trauma populations if the goal is (in part) to help researchers identify gaps, standardize common data elements, etc. Specific areas where information is more sparse and may warrant further research might be described in a different section. This might encourage investigators who may have this data in existing datasets to write it up in secondary analyses. The description of the table is also a little confusing - percentages of unreported data?	Noted. We have expanded the section describing lack of reporting in the studies to provide more clarification about the variables including relevance for only some types of trials.
TEP 9	Results	Information on page 20 seems critical.	Noted.

Commenter and Affiliation	Section	Comment	Response
TEP 9	Discussion/Conclusion	There is not a lot of information on quality of life and functioning outcomes, though mentioned prominently in both the introduction and discussion.	Early phases of the PTSD-Repository development have focused more on study and participant characteristics rather than standardization and synthesis of outcome data. Quality of life and functioning were prioritized for abstraction as part of outcomes, and these comparisons and syntheses are tentatively planned for future updates.
TEP 9	Discussion/Conclusion	The method is succinctly reviewed in the discussion as were methodological challenges.	Noted.
TEP 9	Discussion/Conclusion	Major findings description were sparse and might be more closely linked to project goals as laid out in the introduction.	We have updated and expanded the findings reported in this revised report.
TEP 9	Discussion/Conclusion	The next steps section seems to be more of a review of the methodology and project development. I do not see a clear future research section	Noted. We have expanded this section, in particular, to highlight integration with the web-based PTSD-Repository databases.
Public Comment, Jacob Marzalik	General Comments	These comments were developed by members and staff of the American Psychological Association (APA) who have expertise on the topic, but they are not an official statement of the APA. Thank you for the opportunity to comment on AHRQ's draft comparative effectiveness review Pharmacologic and Nonpharmacologic Treatments for Posttraumatic Stress Disorder: An Update of the PTSD-Repository. We appreciate the inclusion of comorbid PTSD/substance use disorder.	Noted.

Commenter and Affiliation	Section	Comment	Response
Public Comment, Jacob Marzalik	Results	In Table 3, lack of evidence reporting, we recommend including information not reported on demographics such as race and ethnicity in the population characteristics category. This would be helpful information for guideline developers to be able to comment on when developing clinical practice guidelines using this data.	Agreed. We have added information to the report regarding the challenges with abstracting these data and where readers can find more information: Studies reported race and ethnicity data very inconsistently, making it difficult to abstract into preselected categories and compare in a standard manner across studies. These data are not presented in Table 3 with other lack of reporting data because many studies reported these data, though they were not able to be included in the PTSD-Repository because of different categories and metrics used across the studies. Details about abstraction methods for race, ethnicity, and other demographic variables is included in the Data Abstraction Guide, included in this report as an Appendix.
Public Comment, Jacob Marzalik	Results	In Table 2 on p. 11 are the following interventions listed the same or different from each other? • Convulsive therapy • Electric shock therapy • Electroconvulsive therapy (ECT) • Shock therapy	These interventions are classified in the same subgroup of interventions currently per the VA/DoD CPG framework described in Table 2. However, additional intervention categories have been developed by the National Center for PTSD and are being applied to the web-based PTSD-Repository. These updated, more granular categories will be applied to future phases of the PTSD-Repository evidence tables for added clarity and granularity.
Public Comment, Jacob Marzalik	Results	In Table 2 on p. 11, under psychotherapeutic treatments do you mean person-centered therapy (PCT)?	Table 2 replicates the 2017 VA/DoD CPG framework which references Present-Centered Therapy (PCT), an intervention that was initially designed as a time and attention comparison condition in comparative effectiveness research.

Commenter and Affiliation	Section	Comment	Response
Public Comment, Jacob Marzalik	Results	We recommend including information on who provided the services in the randomized controlled trials that are included in the repository (i.e., were services provided by psychologists, military psychologists, counselor, social worker, etc?).	Noted. Because of the many different degree options possible, we currently abstract data into categories of based on whether or not the intervention was administered by a person with a graduate degree. We also list if this information is not reported or unclear.
Public Comment, Jacob Marzalik	Appendix	Will tables F4 and F5 in the appendix have information added to them?	Yes, these tables have been updated in the revised report to include data from all included studies.
TEP 10	General Comments	This is a very helpful report and the update will be very helpful to the traumatic stress field.	Noted.
TEP 10	Introduction	This is clear.	Noted.
TEP 10	Methods	The methods are appropriate and robust.	Noted.
TEP 10	Results	Yes. It would be helpful to know how many papers reported on the different secondary outcomes, especially given the conclusion re suicide-related outcomes.	Figure 11 has been added to show number and percent of studies that report depression, suicide, SUD, and QOL/functioning.
TEP 10	Discussion/Conclusion	I wonder if a call for an increased focus on adverse event/serious adverse event reporting could be considered. This is important and under-reported in non-pharmacological RCTs	Agreed, and we hope that describing these data from the studies will help in the efforts to increase reporting of adverse events for all types of studies.

Commenter and Affiliation	Section	Comment	Response
Peer Reviewer 3	General Comments	This manuscript represents a review of data from PTSD treatment trials in an effort to update the PTSD Trials Standardized Data Repository. The purpose was to identify new RCT and to identify those that address comorbid PTSD and SUD in this update. The authors have identified 36 new RCT and 22 RCT for comorbid SUD. The review identifies risk of bias for these studies. While the scope of this review does not discuss the findings of these RCT, the report updates the studies and variables included in the repository. The report is very well written, and quite thoughtful and detailed. The updating (which includes adding new RCT but also removing those which no longer meets criteria) is important for clinical, research policy and education stakeholders to make decisions about research. The inclusion of RCT that address comorbidity is quite important and has been neglected in past reviews and other materials. This work suggests that most of the PTSD treatment RCT have already been in the repository, so it makes changes that do not profoundly affect the numbers, but updating is an important endeavor. Overall, having a repository is important-but probably most useful for researchers who do exhaustive review of literature in designing studies. Clinicians, educators and policy makes no doubt would find summary material, with clinical conclusions , of more practical help.	Noted.
Peer Reviewer 3	Introduction	The introduction is quite clear and well reasoned. The background is thorough. More information on how the repository is used might be helpful	Noted. This information has been added to the discussion.

Commenter and Affiliation	Section	Comment	Response
Peer Reviewer 3	Methods	The inclusion and exclusion criteria are clear and well justified. The search strategies are explicitly stated and conform with good practice. It should be noted that the authors do not mention that PTSD criteria have changed with DSM-5. Many of the studies in the repository most likely use DSM-IV criteria. This could of course affect outcomes.	We have added this point to the discussion.
Peer Reviewer 3	Methods	How were studies that evaluated both behavioral and pharmacologic agents handled?	The executive summary and Table 1 of the main report both include a description of pharmacologic studies, defining them as any studies with at least one pharmacologic arm.
Peer Reviewer 3	Results	The results are adequately detailed, with adequate figures and tables .	Noted.
Peer Reviewer 3	Results	There is a question of whether all RCT have adequately been identified. The authors state that most of the studies have n of 25-99 participants and most were in outpatient settings. This does raise the question of whether large VA funded COOPERATIVE STUDIES were included in this review (did not see them listed).	Yes, these VA Cooperative Studies Program studies were identified and included in the report when results were published in a peer-reviewed journal.
Peer Reviewer 3	Results	The authors mention that they now exclude several studies previously included-but do not give much data on those details. There ARE details on those that were previously excluded but now will be included since there is new evidence that these interventions may improve PTSD.	We have provided additional clarification in this section.
Peer Reviewer 3	Results	The authors mention that they did not include studies which did not treat PTSD alone-yet they included studies such as CBT for insomnia-how these were selected would be important.	We have provided additional details in the section on inclusion/exclusion criteria.
Peer Reviewer 3	Results	The authors do mention several variables that make evaluation across studies difficult (like type of trauma), but do not really mention others (civilian vs. military, gender).	These additional variables have been added to the discussion of these challenges.

Commenter and Affiliation	Section	Comment	Response
Peer Reviewer 3	Results	The issue of missing data -identified in this review-is clinically important.	Noted.
Peer Reviewer 3	Discussion/Conclusion	The implications of this are clearly stated, although as mentioned above while the repository is important-it is probably most useful for researchers while clinicians, educators and policy makers may prefer summary material, with clinical conclusions.	Noted.
Peer Reviewer 3	Discussion/Conclusion	The future research section, is quite clear - although it did not always seem to be derived from the data as presented (e.g sub-threshold PTSD not mentioned previously	Noted. We have clarified that these potential future areas for expansion were developed on the recommendation of the TEP.
Peer Reviewer 3	Clarity and Usability	The manuscript was mostly clear, the section on Risk Bias was the most difficult.It did not always read like a stand alone document.	Noted. We have revised the ROB section, though agree that because this project had 2 major components (ROB and updating), these are somewhat separate foci and could be presented together or separately. For manuscripts, we will likely separate the topics, though for the purposes of this contract, one report is required and therefore they are presented together.
TEP 11	General Comments	Well, at this point I think the report is most meaningful to researchers as there is not yet a distillation of how well the various types of interventions perform or even of how many times a given intervention has been tested in an RCT. I see the current report as a solid initial step that is giving a high level overview of the state of the literature and don't see it as having much clinical utility in and of itself.	Noted. We have expanded the section describing purposes of this type of database. In many cases, it is a step along the way for another process (e.g., a step towards writing a systematic review, answering a media request, writing a background/rationale section for a grant.
TEP 11	Introduction	The introduction does a fine job of laying out the relevant background particular to the specific research questions. However, please see below for concerns about the framing of the Purpose and Scope section.	Noted.

Commenter and Affiliation	Section	Comment	Response
TEP 11	Methods	Yes, I think all of this is fine in so far as they map onto the current report's research questions. Should there be actual meta-analytic work done in the future, there will likely need to be some additional honing of the methods.	Noted, and agree that additional methods and data refinement will be needed for future meta-analytic pursuits based on these data.
TEP 11	Results	Again, in so far as the current research questions go, the amount of detail and how it's presented is fine. But I think it's important to recognize that the current research questions are really quite limited, and in and of themselves, they are not all that useful to the field.	Noted. We have expanded our discussion of how this could be used as an initial step for research projects and other ways these data could be useful for the field, including highlighting the web-based PTSD-Repository datasets developed and recently released online by the National Center for PTSD.
TEP 11	Results	I am not sure it fits the I/E criteria, but you may want to look at the EMDR paper by Perez-Dandieu & Tapia (doi.org/10.1080/02791072.2014.921744), though it may have omitted it because of the tiny N (= 12).	This is an included study and results are abstracted in the evidence tables.
TEP 11	Discussion/Conclusion	Yes, I think so -- the synthesis around risk of bias is especially useful as it signals to researchers in the field that for the literature to become useful over time, we have to step up in X, Y, Z ways to improve the rigor of our trials.	Noted.
TEP 11	Discussion/Conclusion	What would be useful is if there were additional information providing a tally of the number of times specific treatments have been tested and also how many studies exist where at least two active treatments have been compared (and which active treatments have been compared). Such finer-grained information would help researchers and administrators get a sense of where the weight of the evidence (or at least the inquiry) is and where there may be opportunity to follow-up on promising interventions that perhaps haven't been tested as much.	Noted, and we agree that this information would be useful to the field. To this end, the National Center for PTSD has developed a web-based version of the PTSD-Repository, available through their website and able to be searched and manipulated by users. This effort included extensive coding of treatment categories and definitions so that these sorts of questions can now be more easily answered. We have referenced this web resource in the report to alert readers to this additional PTSD-Repository resource.

Commenter and Affiliation	Section	Comment	Response
TEP 11	Clarity and Usability	The two key questions are very bare bones and to answer them, one only needs Table 2, which frankly isn't all that useful as it just lists every type of non-pharmacological and pharmacological intervention that's been tested in an RTC. The report goes into a lot more detail about the quality of the RTCs and so it seems like the questions need to speak to all the descriptive work that was done so that readers know what they are getting into when they undertake delving into these materials.	Noted. The Key Questions are set from early in this project.