Technical Brief Disposition of Comments Report

Research Review Title: *Pharmacologic and Nonpharmacologic Treatments for Posttraumatic Stress Disorder: Groundwork for a Publicly Available Repository of Randomized Controlled Trial Data*

Draft review available for public comment from December 21, 2018 to January 18, 2018.

Research Review Citation: O'Neil M, McDonagh M, Hsu F, Cheney T, Carlson K, Holmes R, Ramirez S, Hart E, Murphy K, Graham E, Chou R. Pharmacologic and Nonpharmacologic Treatments for Posttraumatic Stress Disorder: Groundwork for a Publicly Available Repository of Randomized Controlled Trial Data. Technical Brief No. 32. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 19-EHC018-EF. Rockville, MD: Agency for Healthcare Research and Quality; May 2019. Posted final reports are located on the Effective Health Care Program search page. DOI: https://doi.org/10.23970/AHRQEPCTB32.

Comments to Research Review

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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.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Background	1. Abstract Background: last sentence. Suggest changing “studies” to “trials” or “RCTs” given how this was scoped.	Thank you, we have edited this to "trials".
Peer Reviewer #1	Background	2. Abstract Findings: “exemplar studies” shows up for the first time here in the abstract and it’s yet not clear what that is intended to mean or how/why those were chosen as exemplars.	Thank you. We have edited this section to remove references to the initial "exemplar" studies from the NCPTSD since this initial process was part of project development and is not relevant to the final report.
TEP Reviewer #3	Background	Exec Summary-1, can suggest minor wording change to emphasize why “selecting a treatment for a given patient can be fraught with uncertainty ”…..People with PTSD CAN PRESENT WITH A DIVERSE AND UNEVEN COLLECTION OF have symptoms such as intrusive thoughts, nightmares, flashbacks, avoidance of trauma-related stimuli, negative beliefs about oneself and/or others, and hypervigilance. Untreated, these symptoms can last for years and reduce quality of life and functioning. While there are treatments that have been found to improve symptoms, there is not one single treatment known to be most effective, and selecting a treatment for a given patient can be fraught with uncertainty.	Thank you for this suggestion. We have added this statement to the section.
TEP Reviewer #3	Background	Exec summary-1 Would be good to provide estimated timeline for completion of data abstraction for public review	We have indicated that data abstraction will be completed by the end of 2018.
Peer Reviewer #4	Background	The background was well-written and provided an appropriate rationale for the importance of the topic. Please see the attached document for specific comments.	We appreciate this comment, thank you.
Peer Reviewer #4	Background	p.10 ln 16-17: in stating "specific era", it's not clear if this refers to the next sentence or something else. It would be clearer to delete the "specific era" phrase, include data on rates in Vietnam era veterans and then have the current sentence about the RAND survey.	Thank you for this recommendation. We agree that this statement should be clarified and have made edits to reflect this comment.
Peer Reviewer #4	Background	p. 11 line 55: Presumably the population also should include DSM-IIIR PTSD	Thank you. We have updated this line to include the DSM-IIIR and DSM-IV-TR.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Background	p. 12 line 4: Does pharmacological treatment include complementary medication treatments (e.g., herbal products, supplements)? Currently that information only seems to relate to non-pharmacological approaches. It may be more clear to state: Interventions -- Pharmacologic treatments, non-pharmacological treatments and combinations of pharmacological and non-pharmacological treatments. Interventions also include complementary and integrative approaches. In addition, pharmacologic treatments are defined as any drug used to treat PTSD and can include herbal products, supplements, Schedule I drugs and any other medications regardless of whether approved by the US FDA for PTSD or for other indications.	In this section, the Background, we are giving a more general outline of the interventions included and how we categorized them. A further, more detailed, explanation is provided in the Methods section. Herbal and other supplements were considered under Complementary and Integrative Treatments, and categorized as non-pharmacological.
Peer Reviewer #4	Background	p. 12 lines 12-14: Lumping all of these interventions together as "control" interventions is problematic. Usual care may include active interventions making it difficult to compare findings with "control" conditions that lack active treatment (e.g., waitlist). Placebo and minimally active interventions fall in a continuum between these two treatment conditions since subjects receiving placebo will still have monitoring visits that could contribute to some benefit.	We can appreciate the distinctions the reviewer is making. We used "control" to categorize interventions that were being used as a control group within studies. The spreadsheet further details what constitutes a control, specifying the type of control in an individual cell. Ultimately, people wanting to work with the data set can stratify based on these characteristics and evaluate them individually.
Peer Reviewer #4	Background	p. 12 lines 20-21: This is a bit confusing as one might reduce specific symptoms of a concomitant psychiatric or medical diagnosis without reducing these diagnoses, per se.	Yes, we agree. In this first undertaking of abstracting data from PTSD treatment studies, we had to make decisions to make the work as useful as possible with the resources and timeframe available. Future expansions of this project may include adding data such as change in symptoms of concomitant psychiatric or medical diagnoses. With the current version, users will be alerted to the fact that these outcomes were measured and that further exploration may be necessary.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Background	p. 12 lines 25-26: Handling of missing data would be useful to extract for determining risk of bias but would not be a outcome in terms of patient-related outcomes that are specific to an intervention. Many other elements of study design also need to be extracted but are not mentioned here (nor should they be).	Thank you, we can appreciate this concern and agree that there are other elements that could be reported that relate to risk of bias. Our discussions with the sponsor of this work led us to include this item as relevant to users of the data set so that they understand the data they are seeing reported.
TEP Reviewer #5	Background	Page 2, Lines 3 - 13: There is a list of 6 uses for the data repository, none of them is explicitly written as to the repository's value to clinicians. #6 comes the closest, but it does not specify to whom it will serve as a resource.	Thank you for this comment. We have updated this section to highlight how this would be used by clinicians.
TEP Reviewer #6	Background	This read well.	Thank you, we appreciate this comment.
TEP Reviewer #7	Background	Provides a good description of the problem. It seems quite focused on military and veterans though the questions and scope seem to include the whole landscape of PTSD.	Thank you for this comment. We have tried to compare some of the research on civilians and Veterans in this section, highlighting data related to both populations.
TEP Reviewer #7	Background	Mention of sexual trauma and other high prevalence traumas that may result in PTSD could improve.	Thank you. We have added a mention of sexual abuse to this section.
	Introduction		
Peer Reviewer #1	Guiding Questions	Very good. These are clear.	Thank for your comment.
TEP Reviewer #3	Guiding Questions	none	NA
Peer Reviewer #4	Guiding Questions	The guiding questions seemed appropriate for the goals of the technical brief.	Thank for your comment.
TEP Reviewer #5	Guiding Questions	No Comments	NA
TEP Reviewer #6	Guiding Questions	These are very general, but work as the first step in creating the database.	Thank for your comment.
TEP Reviewer #7	Guiding Questions	Well done and not suggestions.	Thank for your comment.
Peer Reviewer #1	Methods	Very good. Rigorous searches included numerous databases.	Thank for your comment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Methods	Table 1. Inclusion and exclusion criteria includes “Studies reporting only individual symptoms or symptom clusters without overall PTSD outcome” are excluded yet the section discussing outcomes is very inclusive and seems to include what they say was excluded.	We have updated the inclusion criteria for the outcomes cell to better reflect the criteria.
TEP Reviewer #3	Methods	Table 1 interventions designed to simultaneously target ptsd and comorbid conditions excluded, but most treatments probably do address more than PTSD given high comorbidity. Authors do not need to change their methods but might provide a sentence or two on the limitations of measures typically reported. Also, given comment above, it may not be entirely clear that they were not always excluded.	We have updated the exclusion criteria to clarify as follows: "Interventions designed to simultaneously target PTSD and comorbid conditions if they cannot be standalone PTSD interventions (e.g., interventions targeting PTSD and a comorbidity such as depression are included if the intervention can be a treatment for PTSD alone)."
TEP Reviewer #3	Methods	Table 1 “Selected systematic reviews will be considered as reference check sources of studies to be reviewed for possible inclusion; however, data will be abstracted from individual studies, rather than from systematic reviews”— suggest editing for clarity --- “Selected systematic reviews will be considered as an additional referene check to ensure comprehensive nature of the review to identify any additional individual studies for data abstraction.	We have revised this sentence to be more clear by removing the word "check".
TEP Reviewer #3	Methods	P 5 literature search strategy—define “gray literature search” if this report is for public audience who are unlikely to be familiar with that term	We have added a definition to this sentence.
Peer Reviewer #4	Methods	The methods are generally strong. The literature search is well-described and the systematic review methodology is also excellent. There were some aspects of the categorization of interventions that might be improved (e.g., including herbal products and supplements with medications). It is also unfortunate that studies of interventions for specific PTSD symptoms (e.g., nightmares) were only included if they also assessed response to overall PTSD symptoms or diagnosis. Please see the attached document for other specific comments.	Thank you, we can appreciate these comments. Our decision on how to categorize herbals and supplements was based on the FDA's categorization of these products.
Peer Reviewer #4	Methods	p. 13 line 20, inclusion criteria should add DSM-IIIR.	Thank you. We have updated this section to include the DSM-IIIR and DSM-IV-TR.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Methods	The introductory information also noted that there are many studies that use rating scale thresholds to define the population of subjects. Given that information, it seems that limiting the population to those with DSM defined PTSD may exclude potentially important and relevant studies. If there are reasonable rating scale thresholds that define populations that are similar to DSM defined PTSD, those would be worth adding to the inclusion criteria as an alternative.	Thank you. The section on population now states, "Adults (≥18 years old) with a PTSD diagnosis (DSM-III, DSM-IIIR, DSM-IV, DSM-IV-TR, or DSM-5) diagnosed by a clinician or through the administration of a validated clinician-administered or patient-reported assessment tool."
Peer Reviewer #4	Methods	p. 13 line 26: See comments above related to intervention description. Also, the exclusion criteria of "Interventions designed to simultaneously target PTSD and comorbid conditions" seems unnecessary and confusing to apply. If an SSRI is given to subjects with PTSD and major depressive disorder and helps with both, it seems problematic to exclude such a study from the data base, particularly given the high rates of comorbid PTSD and depression.	Thank you for this comment. We have clarified these exclusion criteria as described above.
Peer Reviewer #4	Methods	p. 13 lines 36-39: See prior comments on the classification of interventions as "controls".	We can appreciate the distinctions the reviewer is making. We used "control" to categorize interventions that were being used as a control group within studies. Further on in the spreadsheet we present details of what constitutes the control. Ultimately, people wanting to work with the data set can stratify based on these characteristics and evaluate them individually.
Peer Reviewer #4	Methods	p. 13 lines 40-42: From a clinical decision-making standpoint, it is problematic to exclude interventions that focus on a single symptom or symptom cluster. For patients with prominent nightmares and sleep disturbance, any improvement in this symptom alone could be extremely meaningful. Eliminating studies that focus only on these symptoms reduces the information that is available to patients and clinicians on a topic of considerable interest and importance.	Thank you for this comment. We agree, and given resources available for this project, we worked with the Technical Expert Panel to focus on certain types of interventions for this initial group of studies. Later stages of this project will hopefully be able to expand to the valuable areas of individual symptoms and symptom clusters.

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Peer Reviewer #4	Methods	p. 14 line 31: If complementary treatments such as herbal products and supplements are included, it would be worth mentioning them in this list either as a distinct bullet point or in the list of miscellaneous treatments. Convulsive therapy, electric shock therapy and shock therapy are outmoded terms for electroconvulsive therapy and can be deleted from this list to avoid confusion. Also, rTMS is typically referred to as TMS nowadays in the psychiatric literature.	Please see Table 3, where the bullet on natural products lists herbs; there is also a bullet for Dietary supplements. We included the older terms on electroconvulsive therapy in the list because they will have been used to describe these therapies in older trial reports. We have removed the "r" from "rTMS".
Peer Reviewer #4	Methods	p. 15 Table 3: Supplements and Natural products are complementary therapies but do not fall neatly into the category of a Non-pharmacologic intervention. (See comments above).	Thank you, we can appreciate this viewpoint. As noted, we made the decision on categorizing herbs and supplements based on the way that the FDA categorizes and regulates them.
Peer Reviewer #4	Methods	p. 16 line 8: If not already included, the data template should also be able to include information on sex (e.g., proportion of sample that is male) given the many differences in men and women with respect to PTSD development, comorbidities, and potentially treatment responses in addition to differences in typical trauma experienced. Inclusion/exclusion of individuals with a substance use disorder would also be important to note, given the significant comorbidity with PTSD and substance use disorders and the impact of such comorbidity on outcomes. Funding source and issues with investigator conflicts of interest are also important elements to extract.	Yes, these are important and were abstracted. Please see the abstraction table headings.
Peer Reviewer #4	Methods	p. 16 line 13: ICD-10 is noted here but is not listed as one of the allowable inclusion criteria for a PTSD diagnosis	Thank you. We have updated all sections to reflect that ICD-9 and ICD-10 diagnoses were included.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Methods	p. 16 line 17 ff: It would be useful to consider these data elements in the design of the database even if the current extraction efforts don't include them. Since many of the PTSD studies have already been rated for quality and risk of bias in prior reviews (including some done by AHRQ), it would be very useful for the database to include a field for Quality and for Risk of Bias that could be filled in and marked as taken from a prior review. This should not be that difficult or time-consuming. If built into the data model, a clerical staff person should be able to look at the prior AHRQ review and type the information into the database at rather low-cost. This would make the value to the field much greater.	The current scope of the project does not include assessing or reporting the risk of bias of the studies, but this issue is of high importance to the sponsors. Future efforts on expanding this data set may include risk of bias assessments.
Peer Reviewer #4	Methods	p. 16 line 29: Is Excel being planned for use in the full implementation or just for the current evidence tables? As written, the implication is that the entire database will be in Excel whereas one would hope that the full implementation would use a more robust and technologically sophisticated data management approach. If so, it would be helpful to state specific information at the start of this paragraph (e.g., "For the fully implemented project, we will develop a SQL database and associated web interface to permit easy searching, filtering and downloading of information by stakeholders. However, for purposes of this technical brief we have extracted information from included studies into Microsoft Excel.")	The final deliverable for this project is a set of evidence tables in Excel. However, the reviewer is correct that the information provided within the evidence tables is intended for translation into a fully functional database. How this is handled is outside our scope of work and will be a decision for the NCPTSD. We have clarified this section to note that, "Future plans for this project including converting the abstracted data into searchable databases will be handled by the NCPTSD."

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Methods	p. 16 line 40-41: It would be helpful to know which studies were identified in the overall search but excluded prior to the level of the full text review. Although such a list would be prohibitive to include in a paper publication, it should be straightforward to include in a database. Researchers could then know if a publication was excluded at any point or whether it was missed in the original search.	At the abstract level, exclusions are made only for citations that are clearly not eligible. Broad searches such as these will bring in many citations that are not eligible, such as narrative reviews, commentaries, epidemiological studies, etc. Any that may potentially be eligible are reviewed with a full-text version. Because of this, the AHRQ EPC Methods Guide (https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview) does not recommend providing lists of citations excluded based on the abstract.
TEP Reviewer #5	Methods	I note in Appendix F and G that studies conducted outside the U.S. use the abbreviations VA/DoD and non-VA/DoD. The use of the former is possibly confusing or misleading to the user as VA/DoD refers to the Departments of Veterans Affairs and Defense, respectively. For non- U.S. studies would military (MIL) and nonmilitary (Non-MIL) be better choices? See App F. Akuchekian and Manteghi.	The decision to clearly identify studies conducted at VA/DoD centers was made in consultation with the sponsor. Studies of military or veteran populations outside of the US (non-VA/DoD) are recorded separately (MIL).
TEP Reviewer #6	Methods	The literature search was done carefully and the exclusions are carefully documented. A very large set of data were coded from the studies, which is a remarkable achievement, but also possibly makes errors and omissions somewhat more likely. I noticed for example, that even if drop out rates and completer rates were given in a paper, these were not always entered in the data base and recorded as NR. There is a possible problem in that the extraction of the results is not informative as it could be. This is due to the rule that effect sizes are not calculated from data available in the paper. This inflates the number of not reported codes and information on group differences is lost even though the paper reported the statistics for this comparison. At least the significance levels should be recorded from the group comparison statistics. This was not done in cases I found. Furthermore, for changes in diagnostic status 2x2 tables effect sizes could be calculated from the information reported in the papers.	Thank you for the insight and attention to this matter. Our intent in extracting study data was to capture as much complete information as possible in a manner that is applicable across studies. However, calculating effect sizes and other types of data not originally reported within a study can be very resource intensive. This is an item of note and will be considered for possible expansion for the next phase of database development.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #7	Methods	Page 27, line 10- Can some of the "missing" data that may not be reported in a single RCT be recovered from Clinical Trials.gov? or from methods publications for the study? Many authors intentionally leave out some of these details from a main outcome paper if they are published in a methods paper already.	We included published methods papers and abstracted any relevant data found in those. For this version of the data set, we did not additionally search out protocols or results that may be found in ClinicalTrials.gov.
TEP Reviewer #7	Methods	Why was the Cigrang et al 2017 PE-PC RCT not included? Is it due to inclusion of subsyndromal PTSD? For the PC setting requiring 80% PTSD diagnosis is not consistent with the PC model of care that works from brief assessment and intervention and not a full diagnostic interview. Thus, if a patient reports significant PTSD symptoms on PCL and a desire for PC treatment, they should be included in trials in this setting. I think this may warrant expansion if the database plans to represent PTSD treatment in the PC setting.	We appreciate your concern regarding this study. The Cigrang 2017 study was determined eligible for inclusion in our technical brief. However, information from this study was not yet extracted at the time of our submission. It will appear in the final report appendices.
Peer Reviewer #1	Findings	1. Pg 9 under Included Studies. Last sentence. Consider adding explanation/reasons for why 5 exemplars were excluded.	We have added a reference to the location of this information in the appendix.
Peer Reviewer #1	Findings	2. Pg 10. Lines 13-17 seem speculative and more like material one would expect to see in Discussion section rather than Results (and the same thing shows up again later in Discussion). Also, the figure appears to show that research increased each decade after 1988, not just in the last decade.	We agree and have moved this to the section on summary and implications.
Peer Reviewer #1	Findings	3. In general, the figures and drafts of future figures are good.	Thank you for this comment.
Peer Reviewer #1	Findings	4. Figure 6. Consider changing "Foreign" to give more detailed breakdown there, listing specific countries (at least for the top 10 or so, and then maybe an "Other" category). I would suggest that applicability considerations should drive the categories there, and that lumping all non-US into a single category oversimplifies it a lot.	We will make this change in the final report.
TEP Reviewer #3	Findings	Figure 1 suggest authors clarify why interventions deemed ineligible (perhaps provide common examples of why studies were found ineligible)	Figure 1 provides categories of reasons why articles reviewed at full text were excluded (e.g., ineligible population).

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TEP Reviewer #3	Findings	Figure 2 suggest converting into a stacked bar chart showing the types of treatment studies in the various years to show if there are trends in funding different types of interventions	We have modified this chart to show pharmacologic treatments versus nonpharmacologic treatments.
TEP Reviewer #3	Findings	P 12 There appears to be a typo (emphasis to indicate where typo is believed to be) “In addition to the two overarching categories (pharmacologic and nonpharmacologic), each represented by a separate the evidence table in this technical brief, each intervention arm was also classified by intervention categories that align with the 2017 Veterans Affairs/Department of Defense clinical practice guideline,9 as recommended by the TEP and NCPTSD”	Thank you, this typo has been corrected.
Peer Reviewer #4	Findings	The findings are generally clear and provide a useful high-level overview of the data that was extracted. Please see the attached document for specific comments.	Thank you for your comments.
Peer Reviewer #4	Findings	p. 20 line 3 ff. This information seems almost identical to that on p. 18. It could be kept there and simply include the first sentence of this paragraph on p. 20	This change has been made in the report.
Peer Reviewer #4	Findings	p. 20 table 3: This graph seems unnecessary. A simple statement would suffice. (e.g., Pharmacologic treatments were used in 30% of studies (108/360) and nonpharmacologic treatments were used in 70% (252/360).)	We have made this change.
Peer Reviewer #4	Findings	p. 21 Figure 4: Consider splitting the complementary medications out of the complementary category as noted earlier and placing with pharmacotherapy. At least in other areas of medicine, the phrase "biological therapies" focuses on immune modulating treatments, antibody-based treatments, etc. (see for example https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/bio-therapies-fact-sheet). Thus, consider renaming Nonpharm-Biological as Nonpharm-Somatic Therapies. It would also be possible to eliminate the pharmacotherapy vs. non-pharmacotherapy distinction and just have 4 groups: Psychotherapies, Complementary/Integrative, pharmacotherapy, other somatic therapies.	We can appreciate the concern over categorization of herbs and supplements as complementary and not as pharmacologic agents. As noted, we made a decision to consider these in this manner based on the FDA's handling of them. The immunotherapy noted here for cancer treatments are not herbs and dietary supplements. Immune-modulating drugs (biologic or not) would be included as pharmacologic therapies here, as they are also considered drugs by the FDA.
Peer Reviewer #4	Findings	p. 26 Figure 10. This table would be better placed with the other figures on population characteristics and before the figure on rating scales used.	Thank you for the insight on this. We have moved the figure to be placed with the other population characteristic graphs.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Findings	p. 27 line 13: Knowing the education of the providers seems non-specific as compared to knowing the skill of the provider in delivering the specific intervention and knowing whether there were assessments of treatment fidelity incorporated into the study design.	Thank you for this comment. This is an important consideration. Skill was not abstracted because it is infrequently reported in studies. Similarly, we noted if studies reported treatment fidelity, although most did not, and this was abstracted in comments rather than as a specific data element.
Peer Reviewer #4	Findings	p. 27 line 16: It's not clear what is meant by "allowed PTSD and other psychotherapy co-intervention."	Clarification of this information has been added to Appendix B.
Peer Reviewer #4	Findings	p. 27 line 19: Does this apply to any diagnostic instrument or only to specific rating scales with a numerical score?	This refers to instruments with a numeric score.
Peer Reviewer #4	Findings	p. 27 lines 22-24: These are definitely important comorbidities but were not mentioned earlier in the document. Other comorbidities such as depression may also be worth noting here.	We agree that depression is important to note. This data element is captured in outcomes, as we abstracted data on depression measures. These other comorbidities are reported as part of population characteristics when studies reported them.
Peer Reviewer #4	Findings	p. 27 line 32: In addition to pharmacologic adherence, adherence with psychotherapies and other treatments would also be important to note. With psychotherapy, for example, studies sometimes report proportions of sessions attended even for those who complete the study.	We appreciate this comment. Our data template captures number of sessions attended for psychotherapeutic interventions as a mean and standard deviation in a separate category called "Sessions Completed". However, this characteristic was not included in the Lack of Reporting table (Table 5) as this information was often reported.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Findings	p. 27 line 46: CDC recommends that the term "suicidality" not be used since it conflates suicidal thoughts, behaviors (including attempts) and death by suicide.	We agree that the term "suicidality" conflates these constructs; however, we purposely grouped these together in the data abstraction to reflect the many ways individual studies discussed outcomes and adverse events related to suicide.
TEP Reviewer #5	Findings	The graphics are helpful.	Thank you for this comment.
TEP Reviewer #6	Findings	The authors report preliminary descriptive findings, which are mostly straightforward. However, I think there is a possible problem with Table 5, which states lack of reporting. This table includes a mixture of true missing data with coding missing effect sizes even if other statistics are included in the paper. I think it would be worthwhile to calculate the effect sizes from the information provided in the papers. An analysis of outcomes would also be helpful.	We agree that this would be valuable information to capture. Though we were limited by resources allocated at this stage of the project, these calculated data may be included in future portions of this larger project.
TEP Reviewer #7	Findings	Tables appears to be pretty useful and informative. It is difficult to predict what other information a reader may want as this may come out of the patterns of data presented and a desire to clarify. That being said, the current tables appear to cover the key items I would want to see up front. They are understandable and categories are well differentiated.	Thank you, we appreciate this comment.
Peer Reviewer #1	Summary and Implications	Good.	Thank you.
TEP Reviewer #3	Summary and Implications	P 19 -Might acknowledge how funding can influence numbers of projects—increase after 2008 also coincides with large appropriation to DoD for PTSD research	Agreed. We have noted this in the revised summary and implications section.
TEP Reviewer #3	Summary and Implications	Evidence tables will eventually be formatted for public accessibility—please provide timeline	Thank you for this comment. Creation of the publicly accessible database is beyond the scope of work for this portion of the project and will be handled by the NCPTSD within approximately one year.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Summary and Implications	The sections on "summary and implications" and "next steps" refer to the creation of a database repository. It is still not clear to me, even after reading through the whole document, whether this will be based in Excel or a more sophisticated database. If based in Excel, this is of concern. If data is entered in Excel with the subsequent intent to transfer it into a more robust database, this is also problematic. However, at the very least, the document should be clear about what is actually planned.	We certainly appreciate this reviewers concern and will take it into consideration when preparing the final draft. Our product (the Excel file) is not intended for the end user but rather as a precursor for our sponsors to implement a data repository. The method of construction (e.g., relational or object-based) and intended platform are up to them. While this is briefly mentioned under the Next Steps section it will be elaborated on for the final report.
TEP Reviewer #5	Summary and Implications	No Comments.	Thank you.
TEP Reviewer #6	Summary and Implications	No comments.	Thank you.
TEP Reviewer #7	Summary and Implications	Summary and Implications: If we are covering PTSD treatment in PC, the requirement of full diagnostic status at 80% is inconsistent with clinic practice. For this setting, I would suggest a modified entry criterion based on use of an adequate self report/interview PTSD scale.	We agree that broader inclusion is an important possible next step. We have added this to the "Next Steps" section.
Peer Reviewer #1	Next Steps	Good	Thank for your comment.
TEP Reviewer #3	Next Steps	none	No response.
Peer Reviewer #4	Next Steps	See comments for section f.	Thank for your comment.
Peer Reviewer #4	Next Steps	p. 29 line 13: suggest changing "substance abuse disorders" to "substance use disorders" throughout the document for consistency with current DSM terminology.	Thank you for bringing this to our attention. This phrase has been changed to match the current nomenclature as set forth in the DSM 5.
TEP Reviewer #5	Next Steps	No Comments	NA
TEP Reviewer #6	Next Steps	These made sense.	Thank you.
TEP Reviewer #7	Next Steps	I look forward to abstraction of these studies and examination of the new database.	Thank you very much.
Peer Reviewer #1	Clarity and Usability	The report is clear and well structured.	Thank you for this comment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Clarity and Usability	yes.	Thank you.
Peer Reviewer #4	Clarity and Usability	The organization of the report itself is good. The main points are clear, except for the concerns noted above about describing the plans for the database. There were a few sentences in the document that would benefit from revision or additional clarification and those are outlines in the attachment.	Thank you for your comments, we will review the other documents you supplied.
Peer Reviewer #4	Clarity and Usability	Since the full extraction of evidence is not yet complete, the conclusions are not yet intended for direct application. I would expect that the extracted data would be useful for future research if it were extracted into a technologically robust database that supported searching, filtering and aggregating of study details. Plans for frequent literature updates would also be essential to maintain the utility of the data for stakeholders.	Thank you for these comments, we will pass them along to the sponsors.
TEP Reviewer #5	Clarity and Usability	The report is well structured and organized. The main goal and uses of the repository is well communicated. I think the conclusions reflect the current state of knowledge, gaps in research and what is needed in the future.	Thank you.
TEP Reviewer #6	Clarity and Usability	The report is well structured and the writing is clear. Conclusions for future research would require an analysis of more categories of the data base. For example, outcomes are not yet presented.	Thank you for your comments.
TEP Reviewer #7	Clarity and Usability	With the exception of the PC practice issue mentioned above, I think this is very clear, well structured and organized and will be quite informative.	Thank you.
Peer Reviewer #1	Quality of the Report:	Good	Thank you for reviewing our report.
TEP Reviewer #3	Quality of the Report:	Good	Thank you for reviewing our report.
Peer Reviewer #4	Quality of the Report:	Fair	Thank you for reviewing our report.
TEP Reviewer #5	Quality of the Report:	Superior	Thank you for reviewing our report.
TEP Reviewer #6	Quality of the Report:	Good	Thank you for reviewing our report.
TEP Reviewer #7	Quality of the Report:	Good	Thank you for reviewing our report.
Peer Reviewer #1	Appendix	NA	NA

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Appendix	NA	NA
Peer Reviewer #4	Appendix	Table B-1: If the database is to be used by non-VA/DoD providers and patients, it would be helpful to have other categories of site type such as academic center or community based facility.	Thank you. This was a semantic decision on our part. We used the words "Site Type" to differentiate between VA/DoD and Non-VA/DoD after discussions with our stakeholders. We used the word "Setting" to indicate where the study with participants physically took place. Additional site categories such as academic center are located in our Clinical Setting column under "Other (brief description)".
Peer Reviewer #4	Appendix	Table B-1: For study design, to make the data fields appropriate for later expansion, it would be useful to include other study designs besides RCTs.	We do appreciate this reflection. The scope of work for this project required that we focus primarily on RCTs. We will pass this along to our sponsors though.
Peer Reviewer #4	Appendix	Table B1: If there are questions about the skill of the clinical staff who are providing psychotherapies, it seems as if it would be helpful to distinguish between master's level clinicians and doctorate level clinicians.	We agree that this would be valuable information to capture. Because of the variability in how these data are reported in studies, it was more feasible to report whether or not graduate level clinicians were providing psychotherapies since this is often the only level of granularity reported in studies.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Appendix	Table B2: On the threshold, it seems hard to interpret the measure score cutoff without a direct link to the specific measure that is use. The continuous rating scale measures would be worth categorizing in a separate field rather than mixing them together with the DSM or ICD version that was used.	Thank you, we agree. The specific measure being used is indicated in the previous cell of the evidence table under "PTSD Diagnostic Instruments". This data element was added to capture the variability of cutoff scores within different studies using the same diagnostic instrument. Links between data elements will be considered by the NCPTSD as they develop the user-friendly database.
Peer Reviewer #4	Appendix	Table B2: The text that states "Participants may be excluded if they meet exclusion criteria during study" is confusing. Once the subjects are randomized, they are typically not excluded from later analyses. This is different from an initial screening for study eligibility in which individuals would be excluded prior to the study starting.	Thank you for making this point. The confusing wording here was removed. The items in appendix B are meant to guide readers of the evidence table, through our abtraction process. However, *n* per intervention and per outcome analyzed appear in elsewhere our evidence table. So, this particular statement is not needed.
Peer Reviewer #4	Appendix	Table B2: From a database design standpoint, it would be preferable to have separate data elements: one for the duration in years, one for measure of central tendency that was used and one for the measure of spread.	Thank you for the comment and we do respect this point of view. We understand that the current format of this information is limited in usability. Our data abstraction is intended as an intermediate step to developing something larger. Comments such as these are very helpful and will be sent along to our sponsors.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Appendix	Table B2: The same comment applies to age calculations as to duration of PTSD symptoms: Having discrete data element is better than noting other units of measure as part of a single data element.	Thank you for the comment and we do respect this point of view. We do understand that the current format of this information is limited in usability. Our data abstraction is intended as an intermediate step to developing something larger. Comments such as these are very helpful and will be sent along to our sponsors.
Peer Reviewer #4	Appendix	Table B-2: It isn't clear how the data element will handle multiple different races. It would be preferable to have separate data elements for each of the most commonly reported races rather than lumping all of the data into a single data element.	Our team agreed to stick with Census defined categories for race. We used carriage returns within a single cell so this data could be potentially reformatted in future database development.
Peer Reviewer #4	Appendix	Table B-2: in the % with depression data element, the text describing abstraction for MDD vs. general depressive symptoms isn't clear. It sounds as if users would not be able to infer whether patients only had depressive symptoms or met full MDD criteria. Again, if it seems that some studies will include lifetime diagnoses rather than current diagnoses, then a separate data element should be created to hold that information.	Thank you. We do appreciate and agree with this perspective. Future iterations of the abtracted data may see separate data elements for these categories as this information is translated into a functional database. We will pass along this information to our sponsors.
Peer Reviewer #4	Appendix	Table B-2: Comments for the % substance use data elements mirror those above. If multiple disorders will be reported, separate data elements should be created. Similarly, separate data elements should be created for lifetime vs. current diagnoses.	Thank you. We do appreciate and agree with this perspective. Future iterations of the extracted data may see separate data elements for these categories as this information is translated into a functional database. We will pass along this information to our sponsors.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Appendix	Table B-2: Suggest that the word "suicidality" not be used as per CDC recommendations. In addition, it would be helpful to have a separate data element noting whether subjects were excluded for severe physical health conditions. Typically, individuals enrolled in a research study would be terms subjects or participants rather than patients.	We agree that the term "suicidality" conflates constructs related to ideation, behaviors, etc. However, we purposely grouped these together in the data abstraction to reflect the many ways individual studies discussed outcomes and adverse events related to suicide. Adding information on physical health conditions is a data abstraction element that can be considered in future abstraction efforts for this project. Finally, we agree that the term participant should be used in place of subject and have made this change in the two instances we used this term in the appendices to be consistent with the rest of the report.
Peer Reviewer #4	Appendix	Table B-2: For intervention class and treatment name, see comments above on categorizations. The database design seems problematic in apparently listing only one data element for intervention, treatment name, etc. For each study, it is crucial to have a one-to-many database relationship to at least 2 different arms and then describe the intervention characteristics for each arm. Mixing different features in the same data element (e.g., dose and session length) is also problematic for aggreggating data unless there are unique data elements for each type of variable or unless there is one data element for the numerical entity and one for the units of measure (e.g., mg, minutes).	Thank you for the comment and we do respect this point of view. We understand that the current format of this information is limited in usability. Our data abstraction is intended as an intermediate step to developing something larger. Comments such as these are very helpful and will be sent along to our sponsors.
Peer Reviewer #4	Appendix	Table B2- For frequency, there needs to be some way to indicated variable frequencies using a separate free text field. Psychotherapy studies will sometimes begin with more frequent sessions and the taper off later in the study.	Information such as varying frequencies of psychotherapeutic session are added within the same cell as supportive text.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Appendix	Table B2: In terms of treatment duration, most studies have a designated number of weeks in the trial; however, there are some studies in which an average treatment duration may be listed.	Thank you, and yes this is an apt point. Studies that indicate averages are extracted as such with an indicator showing mean, median, or range.
Peer Reviewer #4	Appendix	Table B2: Completion implies that the subject finished the study. However, this is quite different from the proportion of psychotherapy sessions that were attended, even in individuals who "completed" the study. The wording should be fixed rather than trying to explain that % completed psychotherapy is not the same as study completion, which is inherently confusing.	We appreciate this distinction. The number of sessions completed is indicated in a separate column within our evidence table. We were interested in capturing the proportion of participants that finished a treatment schedule, as reported in the study. This includes individuals who may have missed sessions (or dosing). The "not the same as study completion" note is intended to indicate that we were looking at different things. However, the confusion is understandable and this has been removed from the table.
Peer Reviewer #4	Appendix	Table B-2: Under psychotherapy sessions completed, it may be better to describe this as psychotherapy sessions attended. Also it would be better to have separate data elements for psychotherapy and for study end point dose. For medication arms, it would be helpful to have a free text data element that would permit noting specifics of the medication titration approach (e.g., flexibly dosed, set increases at specific time points).	The reviewers point is understood and the wording has been changed to "Psychotherapy Sessions Attended". We also agree on the usefulness of having separate cells for psychotherapy versus medication (Dose at Study End). Our Evidence Table is formatted to capture separate intervention categories (up to four arms inclusive). However, headings are uniform in nature for ease and efficiency of data abtraction.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Appendix	Table B-3: Outcomes. I am not providing detailed comments on each of these data elements, however, each should be carefully examined for the issues noted above (e.g., one-to-many database relationships that are seemingly lumped in a single cell, issues with different possible measurement units being lumped together).	Thank you. We will look over each data element in a corresponding manner.
Peer Reviewer #4	Appendix	Table B-3: Lumping %, n and N into a single data element is not ideal. It is preferable to have discrete data elements. This also permits cross-checks on numerical accuracy without first having to extract the individual number using a string formula. Data entry errors are common so cross checks are important to do whenever possible.	Though this convention is standard with typical technical brief evidence tables, we do understand that it limits the usefulness of the table as a database. This comment will be passed along to our sponsors in case this table is translated into a functioning database during the future development phase of the project.
Peer Reviewer #4	Appendix	Table B-3: It's not clear what is meant by "Only abstract data for most number of variables adjusted."	We agree that the wording here isn't clear, and the text has been revised to "Abstract the most comprehensive list of variables adjusted for (e.g., if adjusting for 1, 2, then 3 variables, list all 3)"
Peer Reviewer #4	Appendix	Table B3: The plan to use carriage returns between elements is problematic and can cause major issues if exporting data and/or trying to sort data.	Thank you for the comment and we do respect this point of view. We understand that the current format of this information is limited in usability. Our data abstraction is intended as an intermediate step to developing something larger. Comments such as these are very helpful and will be sent along to our sponsors.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Appendix	Table 5-2: this format of table is problematic for exporting purposes because of having a single measure name in the far left column and multiple different arm comparisons in the other two columns with hard returns after each.	Thank you for the comment and we do respect this point of view. We understand that the current format of this information is limited in usability. Our data abstraction is intended as an intermediate step to developing something larger. Comments such as these are very helpful and will be sent along to our sponsors.
Peer Reviewer #4	Appendix	p. C-8 ff. I have not reproduced my comments from the prior pages in this section but they would still apply.	Please see our corresponding responses from above.
Peer Reviewer #4	Appendix	Table 5-5 and subsequent tables: Again the format here is extremely problematic for any reuse of data. Not only are multiple different types of data clustered in a single cell and separated by carriage returns, but the time-related information wraps across several lines and there is misalignment across columns (the 3 month data starts on different lines in each column)	We do recognize that this as a potential issue for end users seeking to do meta-analysis or study comparisons. However, resource constraints required efficient use of our spreadsheets. We will pass this comment along to our sponsors as they intend to translate this information into a database format.
Peer Reviewer #4	Appendix	Table 5-10: Having multiple different adverse events clustered in a single cell also is very problematic in terms of doing comparisons across interventions and in terms of summarizing data across studies.	Thank you for the comment and we do respect this point of view. We understand that the current format of this information is limited in usability. Our data abstraction is intended as an intermediate step to developing something larger. Comments such as these are very helpful and will be sent along to our sponsors.
TEP Reviewer #5	Appendix	Originally included in Methods Comments: I note in Appendix F and G that studies conducted outside the U.S. use the abbreviations VA/DoD and non-VA/DoD. The use of the former is possibly confusing or misleading to the user as VA/DoD refers to the Departments of Veterans Affairs and Defense, respectively. For non- U.S. studies would military (MIL) and nonmilitary (Non-MIL) be better choices? See App F. Akuchekian and Manteghi.	Thank you for the additional insight on this. We have added the designation of "MIL" to those studies conducted at military sites in foreign countries. We will keep the designation of VA/DoD for studies conducted by these U.S. agencies.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #6	Appendix	Originally included in Methods Comments: Appendix C3: Cognitive Therapy for PTSD is missing from table 2-1. It is one of the APA recommended treatments for PTSD and should thus be listed. It is not the same as CR	Thank you for pointing this out. We have added it to our list in table 2-1.
TEP Reviewer #7	Appendix	NA	NA
Public Reviewer #1	Appendix	Appendix e--you might consider adding the grant(s) numbers for funding source where applicable. Future efforts for expanding the data set might focus on pulling in the information that is not reported in several columns for studies by exploring the content of the other publications related to the studies that might contain additional information about the protocol or looking at clinical trials.org that may similarly have additional information.	Thank you for the comments. This is certainly a consideration and we did try to pull grant numbers when available directly from the study. However, this was not a requirement for our data extraction. We will propose this and your other recommendations for future expansion to our funding partners as they look forward to the next phase of this project.
Peer Reviewer #1	General Comments	Very nice work on this so far and good luck with finishing it up. This work will result in a very useful database. I suggest changing the title (probably by adding to it) to make it clear that this is developing a publicly accessible database or data repository for the VA national center for PTSD	We appreciate this comment, and we have expanded the title to be more descriptive.
TEP Reviewer #3	General Comments	I was disappointed to see Interventions designed to prevent PTSD and Interventions designed to simultaneously target PTSD and comorbid conditions were excluded.	We appreciate this comment, and agree that these are important. The initial scope of work was set based on resource and time-frame limitations. Future expansion of this project may include adding such studies.
Peer Reviewer #4	General Comments	Please see the attached documents. I have included a Word document that includes general and line-by-line comments on the draft document and the appendices.	Thank you. We have integrated those comments into this table and have addressed each accordingly.
Peer Reviewer #4	General Comments	I have also included the pdf files with line-by-line comments incorporated in case this format is easier for you to review. I did not review the appendices of the extracted studies for content or extraction errors; I only examined them to get an idea of the proposed layouts. However, the attachments do include my comments on the layouts and other aspects of the evidence extraction framework.	Thank you. We have reviewed the comments in the attachments and made revisions as needed.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	General Comments	The technical brief is well written and obviously represents a huge amount of work in fine-tuning all of the crucial data elements that are relevant to studies of PTSD. Overall, however, I am extremely concerned that the potential benefits of the project will not be realized because of the way in which the data apparently will be recorded and stored. In the current technological era, it seems unconscionable to rely on Excel spreadsheets for organizing study details given the variety of different database structures (e.g., relational, non-relational) that exist and the potential for web-based data querying, filtering and synthesizing of data.	We appreciate this comment, thank you. The intent of capturing the trials data on Excel sheets is to allow future conversion to an advanced database structure that allows for flexible interfaces and data manipulation capabilities.
TEP Reviewer #5	General Comments	I found the report well thought out and constructed, very complete and thorough. I can appreciate the amount of time and effort it took to compile the data base and report. Well done.	We appreciate this comment, thank you.
TEP Reviewer #6	General Comments	The authors can be congratulated on this project. A lot of thought has gone into the literature search and data extraction, and the data base will be a valuable resource.	We appreciate this comment, thank you.
TEP Reviewer #7	General Comments	Very well done structure and start! I do have one issue in mind about ensuring the database will represent PC practice that includes subsyndromal PTSD.	Thank you. The first round of eligibility for creating this data set did not include subsyndromal PTSD, but we are aware that there is high interest in this population, and it may be added in the future. While screening studies for this project, we noted any studies that were excluded only for this reason so we can identify them easily in the future.
Public Reviewer #1	General Comments	This is a worthwhile and useful report in support of an effort that will be of tremendous benefit to many in the field.	Thank you, we appreciate this comment.