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Augmentation of trauma-focused psychotherapy for post-traumatic stress disorder: A protocol of a systematic review and meta-analysis.

Lisa Mewes[1,**], Till Langhammer[1,*,**], Jonathan Torbecke[1], Johannes C. Fendel[2], Ulrike Lueken[1,3]

[1] Department of Psychology, Humboldt-Universität zu Berlin, Berlin, Germany.

[2] Department of Psychosomatic Medicine and Psychotherapy, Medical Center - University of Freiburg, Medical Faculty, University of Freiburg, Freiburg, Germany.

[3] German Center for Mental Health (DZPG), PartnerSite Berlin/Potsdam, Berlin, Germany.

Running title: TFP augmentation for PTSD

Abstract: 248 words, text: 2.012 words, tables: 1, supplemental digital appendix: PRISMA-P checklist, search syntaxes for all databases

Keywords: Stress Disorders, Post-Traumatic; Psychotherapy; Treatment Outcome; Meta-Analysis; Systematic Review

***Corresponding author**:

Till Langhammer, Department of Psychology, Humboldt-Universität zu Berlin, Berlin, Germany.

Unter den Linden 6, 10099 Berlin, Germany

till.langhammer@hu-berlin.de

**both authors contributed equally

Abstract

Introduction: Despite the established status of trauma-focused psychotherapy (TFP) as a first-line treatment for post-traumatic stress disorder (PTSD), a substantial proportion of individuals does not achieve clinically significant improvement or discontinues treatment. Exploring augmentation strategies to enhance treatment outcomes is essential to reduce the overall burden PTSD puts on individuals and the society. This protocol outlines a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating the efficacy of nonpharmacological augmentation strategies in addition to TFP for PTSD treatment.

Methods and Analysis: We will comprehensively search PubMed, Embase, CENTRAL, PTSDpubs, PsycArticles, PsycINFO, PSYNDEX, and CINAHL for RCTs without restrictions on publication dates or languages. Additionally, we will perform forward-and-backward searches of included studies and relevant reviews. Two reviewers will independently screen and select studies, extract data, and assess the risk of bias. We will conduct a narrative review to qualitatively synthesize data and a meta-analysis to quantitatively compare the treatment efficacy of augmented TFP with TFP alone or TFP plus placebo. Primary outcomes will be both symptom severity and response rates. The secondary outcome will be dropout rates. We will explore sources of between-study heterogeneity and potential moderators through subgroup and meta-regression analyses. We will assess the overall quality of the included studies with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.

Ethics and dissemination: Ethical approval is not required. We intend to publish results in a peer-reviewed journal and provide materials and data through the Open Science Framework (OSF).

PROSPERO registration number: CRDANONYMIZED.

Strengths and limitations of this study

- We will conduct the first systematic review to include a meta-analysis of randomized controlled trials on nonpharmacological augmentation strategies for the treatment of post-traumatic stress disorder.
- We will investigate whether treatment augmentation can further reduce symptom severity, increase response rates, and decrease dropout rates beyond trauma-focused psychotherapy, as well as explore potential moderators of these effects.
- We adhere to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) guidelines and will evaluate the quality of evidence with the Grading o Recommendations Assessment, Development and Evaluation (GRADE) system.
- We will include only randomized controlled trials to strengthen internal validity, mitigate bias, and enhance the reliability of our findings.
- However, this approach excludes valuable insights from alternative study designs and could limit generalizability of results to real-world clinical settings.

1 Introduction

Rationale

Post-traumatic stress disorder (PTSD) is a prevalent and serious condition resulting from traumatic experiences, leading to health risks and societal costs that necessitate effective treatment. Most individuals experience at least one traumatic event during their lifetime, with varying exposure rates across nations and specific demographics, such as military personnel [1]. The risk for developing a PTSD following a traumatic event, defined as 'actual or threatened death, serious injury, or sexual violence' [2], is estimated at approximately 4% [3]. The risk varies depending on the type of trauma experienced, with risk rates up to 19% following interpersonal trauma incidents like rape [4]. Beyond the substantial burden of PTSD symptoms, the disorder is associated with numerous adverse outcomes, including increased mortality rate [5], elevated risks of cardiovascular and metabolic diseases [6], as well as substantial societal costs, e.g. due to health care and unemployment [7]. Untreated PTSD often persists for many years [8], underscoring the need for effective treatments to address the individual and societal burden associated with the disorder.

Available first-line treatments are effective for many PTSD patients, but their impact remains insufficient. International treatment guidelines uniformly recommend trauma-focused psychotherapy (TFP) as the first-line treatment for PTSD [9,10]. Conversely, recommendations for pharmacotherapy vary [9,10], reflecting smaller sustained treatment effects for pharmacotherapy compared with TFP [11,12]. The umbrella term TFP encompasses various trauma-focused evidence-based treatments such as trauma-focused cognitive behavioral therapy (TF-CBT) and Eye Movement Desensitization and

Reprocessing (EMDR) [10,13]. While their specific treatment rationales may differ, TFPs typically target memories of the traumatic event or trauma-related thoughts and emotions using exposure-based and/or cognitive techniques. Several meta-analyses [11,14–16] report moderate to large effect sizes for TFPs in reducing PTSD symptom severity compared with different control groups, including active psychological therapies (e.g. supportive psychotherapy), treatment-as-usual, and waitlist controls. These treatment effects demonstrate stability over time, indicating enduring efficacy [17,18]. However, approximately one in five patients discontinues TFP treatment [19]. Further, inadequate treatment response, which is usually defined as loss of diagnosis or reduction of PTSD symptom severity [20], persists as a prevalent issue. Meta-analyses have found that pooled response rates for TFP vary between 35% and 59% [21,22], depending on factors such as differing definitions for response. Consequently, a substantial proportion of patients continues to experience residual symptoms despite undergoing a first-line treatment.

Current research addresses inadequate treatment response to TFP by developing and evaluating additional treatment components, often referred to as augmentation strategies. Stage models for PTSD chronification and treatment resistance [13,23] propose integrating augmentation strategies to enhance established first-line treatments – particularly for the patients at risk of nonresponse. In the future, these could be identified early in TFP treatment with promising personalized care approaches [24,25]. Recent systematic reviews and meta-analyses indicate that most previously examined pharmaco-agents (e.g. selective serotonin reuptake inhibitors, D-cycloserine) have yet failed to demonstrate a robust augmentation effect [26–28]. To the best of our knowledge, two systematic reviews [28,29] compiled evidence on nonpharmacological augmentation strategies in TFP (e.g. neurostimulation [30], acupoint stimulation [31],

and exercise [32]). However, at the time of their investigations, most of these strategies have been evaluated in a single randomized controlled trial (RCT) only, with no accompanying meta-analysis conducted. Given the increasing number of RCTs examining integrative, complementary, and alternative TFP augmentations for PTSD [33], it is imperative to update the existing reviews and evaluate proposed categories of augmentation strategies. To examine whether nonpharmacological augmentation strategies can improve treatment outcomes for patients who typically do not respond to TFP, it is essential to assess not only mean symptom reduction but also response rates and dropout rates.

Objectives

Through a systematic review and meta-analysis, we aim to fill this gap by offering researchers, practitioners, and policymakers a comprehensive overview of nonpharmacological augmentation strategies in addition to TFP for PTSD. We will explore the characteristics of different nonpharmacological augmentation strategies evaluated in RCTs and assess their overall impact on different aspects of treatment efficacy for PTSD. Specifically, we will evaluate whether augmentation strategies lead to reduced post-treatment PTSD symptom severity, increased response rates, and reduced dropout rates. We will carefully analyze potential moderators and factors contributing to between-study heterogeneity, including different types of augmentation strategies, TFPs, trauma types, treatment resistance at baseline, treatment delivery format, treatment setting, control type, age group, proportion of female participants, proportion of medicated participants, as well as length and dosage of both treatment components (TFP and augmentation).

2 Methods

We prepared this protocol adhering to the guidelines for Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [34] and provide the PRISMA-P checklist in the Supplemental Digital Appendix 1. The subsequent systematic review and meta-analysis will comply with the updated Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines [35]. We registered the study with the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRDANONYMIZED). We will document important amendments to this protocol within PROSPERO.

2.1 Eligibility criteria

We utilized the PICOS framework to determine inclusion and exclusion criteria, as outlined in Table 1. Eligible TFPs for this review will be EMDR, TF-CBT, and their variants, such as Cognitive Processing Therapy and Prolonged Exposure. In this review, augmentation is defined as any (nonpharmacological) intervention 'delivered prior to, concurrently, or after a first-line PTSD treatment, where the focus of the augmentation was to improve PTSD symptoms and/or improve readiness for treatment, engagement, or retention in the first-line treatment' [28]. The primary outcomes comprise post-intervention PTSD symptom severity and response rates. If studies used multiple measures to assess symptom severity, we will use the studies' primary outcome. We anticipate that included RCTs of first-line PTSD treatments will have varying definitions of treatment response [20]. Following Cuijpers et al. [22], we will estimate the number of responders from means and standard deviations using the

method by Furukawa et al. [36]. As recommended by Varker et al. [20], we will define response as a 30% reduction in baseline symptom severity to ensure comparability across different measures. Further, we will conduct a sensitivity analysis using the response rates as defined in the respective study. As the secondary outcome, we will assess dropout rates as defined in the respective study.

Table 1 – Inclusion and exclusion criteria

Criterion	Inclusion criteria	Exclusion criteria
Population	- patients with PTSD diagnosed by a clinician according to DSM or ICD criteria - no or stable concurrent psychotropic medication	- Non-clinical or undiagnosed samples - samples in which PTSD is not primary diagnosis - changes in psychotropic medication during the trial
Intervention	TFP combined with at least one additional nonpharmacological treatment component (augmentation)	- No TFP - pharmacological augmentation strategy only
Comparator	TFP only or with a placebo-augmentation control condition	- No TFP - augmentation strategy only
Outcomes	PTSD symptom severity, assessed with a clinician-administered PTSD scale (e.g. CAPS-5 [37]) or validated self-repots (e.g. PCL-5 [38])	Self-reports without validation
Study design	Randomized controlled trials	non-randomized trials, including non-controlled before–after studies, case–control studies, single/ clinical case studies, systematic reviews, meta-analyses

Note. CAPS = Clinician-Administered PTSD Scale, DSM = Diagnostic and Statistical Manual of Mental Disorders, ICD = International Classification of Disease, PCL = PTSD checklist, PTSD = Post-traumatic stress disorder, TFP = Trauma-focused psychotherapy.

2.2 Search strategy

We will systematically search the following electronic bibliographic databases: PubMed, Embase (Ovid interface), Cochrane Register of Controlled Trials (CENTRAL), PTSDpubs (ProQuest interface), as well as PsycArticles, PsycINFO, PSYNDEX, and CINAHL (previous four via EBSCOhost interface), without restrictions regarding publication date or language. Given the absence of a standardized terminology in the emerging field of augmentation approaches in addition to psychotherapy treatments (e.g. augmentation, enhancement, add-on etc.), we will prioritize high sensitivity in our

search strategy. Our search terms will be related to (1) PTSD, (2) evidence-based TFPs, and (3) RCT study design. Search syntaxes for all bibliographic databases are provided in the Supplemental Digital Appendix 2. Additionally, we will conduct backward-and-forward literature searches of included studies and relevant reviews on PTSD treatment. If full texts are unavailable or pertinent information within the scope of this systematic review and meta-analysis is missing, we will contact the corresponding authors of the respective studies and wait eight weeks for their response.

2.3 Study selection

Two reviewers (XX and XX) will independently conduct software-based study selection in a hierarchical manner. If either reviewer considers the study eligible based on title and abstract screening, we will comprehensively screen the full text. Finally, studies will be included if a consensus can be reached. If no consensus is reached, a third reviewer will be consulted (XX). We will document the study selection process in a flowchart adhering to the updated PRISMA guidelines [35].

2.4 Data extraction

Two interviewers (XX and XX) will independently extract relevant information from the eligible studies using a standardized extraction form, which will be pilot tested and adjusted if necessary. Information to be extracted includes: (1) the study: authors, publication year, country, type of TFP, type of control; (2) the population: sample size, age, sex, ethnicity, trauma type, comorbidities, medication, treatment resistance at baseline, inclusion and exclusion criteria; (3) the intervention and the comparator: delivery format (face-to-face/online/hybrid), setting (individual/ group), augmentation strategy, proposed mechanism of augmentation, treatment characteristics for TFP and

augmentation strategy (including session duration, number and frequency of sessions, treatment duration, homework, schedule (prior to, concurrently, or after TFP)), use of measurement tools for intervention integrity including adherence to the protocol, clinical and program experience of the facilitating therapist; (4) the outcomes: means and standard deviations for PTSD symptoms (pre- and post-treatment, follow-up if assessed), time points of assessment, measure of symptom severity, response rates (including absolute numbers of response/ non-response), response operationalization, dropout rate (including absolute numbers of completion/ non-completion), dropout operationalization, adverse events.

2.5 Risk of bias and quality assessment in individual studies

Two reviewers (XX and XX) will independently assess the risk of bias in the included studies using the second version of the Cochrane risk-of-bias assessment tool for randomized trials (RoB2) [39]. We will resolve any discrepancies through discussion; if no consensus can be reached, a third reviewer will be consulted (XX). Within the RoB2 tool, risk of bias is rated as 'low risk of bias', 'some concerns', or 'high risk of bias' regarding five domains: (1) bias arising from the randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported result. Based on the rating in these domains, an overall rating is derived for each outcome.

2.6 Risk of Bias across studies

To examine publication bias, we will visually inspect funnel plots, compute Egger's regression test [40] and Rosenthal's fail-safe N [41], and conduct the 'trim and fill' method [42]. We will use the Grading of Recommendations Assessment, Development

and Evaluation (GRADE) approach [43] to assess the overall quality of evidence for each outcome, separately for different augmentation approaches and across all included studies. Two reviewers (XX and XX) will independently rank the quality of evidence as 'high', 'moderate', 'low', or 'very low' for each of the following dimensions: (1) risk of bias, (2) inconsistency of results, (3) indirectness of evidence, (4) imprecision of effect size, and (5) publication bias.

2.7 Data Synthesis

We will conduct a narrative review to qualitatively synthesize data on key characteristics of the included studies. This synthesis will involve categorizing augmentation strategies into relevant groups based on proposed frameworks [28] and insights from the reviewed literature, among other aspects. Pertinent results will be reported in a comprehensive 'summary of findings' table.

We will conduct quantitative data synthesis to generate pooled effect sizes for augmentation effects and examine between-study heterogeneity. Due to the inclusion of studies with diverse characteristics, we anticipate considerable between-study heterogeneity. We will evaluate this assumption by calculating the Q-Test, I^2-statistic [44], and prediction intervals [45] within a random-effects meta-analytical framework. To quantify standardized mean difference for symptom severity between-groups (augmented TFP vs. TFP only/with placebo) post-treatment, we will calculate pooled Hedges' *g* [46]. For between-group differences in response rates and dropout rates, we will calculate pooled risk ratios. All effect sizes will be calculated with their 95% confidence intervals and associated *p* values. Sensitivity analyses will address risk of bias, follow-up outcomes, study population (intention-to-treat vs. completers), different response operationalizations, and outliers using the "non-overlapping confidence

interval" approach [47]. We will explore sources of heterogeneity with subgroup and meta-regression analyses using mixed-effects models, if we can include at least ten studies in total and three studies per subgroup [48]. Subgroups will be formed regarding augmentation approach, TFP approach, trauma type, treatment resistance at baseline, treatment delivery format, treatment setting, control type, and age group. We will examine potential continuous moderators, such as proportion of female participants, proportion of medicated participants, length and dosage of both treatment components (TFP and augmentation) using meta-regression analyses. All analyses will be conducted in R.

2.8 Patient and public involvement

Neither patients nor the public will be involved in the study design, conduct, reporting, or dissemination plans of this research.

3 Ethics and dissemination

Ethical approval is not considered necessary for this study. Results will be published in peer-reviewed journals. We will provide materials and data within the Open Science Framework (OSF).

Author Contributions XX, XX, XX, and XX drafted the work and made substantial contributions to the conception. XX, XX, and XX wrote and approved the submitted version of the protocol and account for accuracy and integrity of any part of the work. XX and XX read, edited, and approved several versions of the manuscript. XX consulted in all stages of the conception.

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Competing interests None declared.

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Supplemental Digital Appendix 1

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page number(s)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1, 12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	7
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4 - 6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7 - 8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8 - 9
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	supplement
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9

Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9 - 10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7 - 8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11 - 12
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10 - 11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

This checklist has been adapted from: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplemental Digital Appendix 2

Search Strategy for PubMed, Embase, CENTRAL, PTSDpubs, PsycArticles, PsycINFO, PSYNDEX, and CINAHL

PubMed

No.	Search Terms
#1	PTSD [tiab] OR “posttraumatic stress disorder” [tiab] OR “post traumatic stress disorder” [tiab] OR stress disorders, post traumatic [mesh]
#2	“trauma focused” [tiab] OR psychotherap* [tiab] OR “cognitive therapy” [tiab] OR “cognitive behavio* therapy” [tiab] OR CBT [tiab] OR “cognitive processing therapy” [tiab] OR CPT [tiab] OR “exposure therapy” [tiab] OR “prolonged exposure” [tiab] OR “narrative exposure” [tiab] OR “eye movement desensiti*” [tiab] OR EMDR [tiab] OR Psychotherapy [mesh]
#3	RCT [tiab] OR”clinical trial” [tiab] OR “parallel design” [tiab] OR “controlled trial” [tiab] OR randomi* [tiab] OR randomly [tiab] OR “treatment trial” [tiab] OR Randomized Controlled Trials [Publication Type]
#4	#1 AND #2 AND #3

Note. We include textwords in title and abstract (tiab) and keywords with controlled vocabulary (MeSH terms).

Embase via Ovid

No.	Search Terms
#1	(PTSD or "posttraumatic stress disorder" or "post traumatic stress disorder").ti,ab. or exp posttraumatic stress disorder/
#2	("trauma focused*" or psychotherap* or "cognitive therapy" or "cognitive behavioural therapy" or CBT or "cognitive processing therapy" or CPT or "exposure therapy" or "prolonged exposure" or "narrative exposure" or "eye movement desensiti*" or EMDR).ti,ab. OR exp trauma-focused cognitive behavioral therapy/ OR exp cognitive processing therapy/ OR exp exposure therapy
#3	(RCT or "clinical trial" or "parallel design" or "controlled trial" or randomi* or randomly or "treatment trial").ti,ab. or exp randomized controlled trial/
#4	#1 AND #2 AND #3

Note. We include text words in title and abstract (.ti,ab.) and keywords with controlled vocabulary (Emtree terms).

CENTRAL

No.	Search Terms
#1	PTSD OR “posttraumatic stress disorder” OR “post traumatic stress disorder”
#2	"trauma focused" OR psychotherap* OR "cognitive therapy" OR cognitive NEXT behavio* NEXT therapy OR CBT OR "cognitive processing therapy" OR CPT OR "exposure therapy" OR "prolonged exposure" OR "narrative exposure" OR eye NEXT movement NEXT desensiti* OR EMDR
#3	RCT OR “clinical trial” OR “parallel design” OR “controlled trial” OR randomi* OR randomly OR “treatment trial”
#4	#1 AND #2 AND #3

Note. We include text words in title, abstract, and keywords.

PTSDpubs via ProQuest

No.	Search Terms
#1	PTSD or "posttraumatic stress disorder" or "post traumatic stress disorder"
#2	"trauma focused*" or psychotherap* or "cognitive therapy" or "cognitive behavio* therapy" or CBT or "cognitive processing therapy" or CPT or "exposure therapy" or "prolonged exposure" or "narrative exposure" or "eye movement desensiti*" or EMDR
#3	RCT or "clinical trial" or "parallel design" or "controlled trial" or randomi* or randomly or "treatment trial"
#4	#1 AND #2 AND #3

Note. We include text word search in all fields except from full text (noft).

PsycArticles, PsycInfo, PSYNDEX via EBSCOhost

No.	Search Terms
#1	TI "ptsd" OR AB "ptsd" OR TI "posttraumatic stress disorder" OR AB "posttraumatic stress disorder" OR TI "post traumatic stress disorder" OR AB "post traumatic stress disorder" OR DE "Posttraumatic Stress Disorder" OR DE "Complex PTSD"
#2	TI "trauma focused" OR AB "trauma focused" OR TI "psychotherap*" OR AB "psychotherap*" OR TI "cognitive therapy" OR AB "cognitive therapy" OR TI "cognitive behavio* therapy" OR AB "cognitive behavio* therapy" OR TI “cbt” or AB “cbt” OR TI "cognitive processing therapy" OR AB "cognitive processing therapy" OR TI “cpt” OR AB “cpt” OR TI "exposure therapy" OR AB "exposure therapy" OR TI "prolonged exposure" OR AB "prolonged exposure" OR TI "narrative exposure" OR AB "narrative exposure" OR TI "eye movement desensiti*" OR AB "eye movement desensiti*" OR TI "EMDR" OR AB "EMDR" OR - DE "Psychotherapy" OR DE "Trauma Treatment" OR DE "Trauma-Focused Cognitive Behavior Therapy" OR DE "Cognitive Behavior Therapy" OR DE "Cognitive Therapy" OR DE "Behavior Therapy" OR DE "Exposure Therapy" OR DE "Imaginal Exposure" OR DE "Prolonged Exposure Therapy" OR "Narrative Therapy" OR DE "Eye Movement Desensitization Therapy"
#3	TI "rct" OR AB "rct" OR TI "clinical trial" OR AB "clinical trial" OR TI "parallel design" OR AB "parallel design" OR TI "controlled trial" OR AB "controlled trial" OR TI "randomi*" OR AB "randomi*" OR TI "randomly" OR AB "randomly" OR TI "treatment trial" OR AB "treatment trial" OR DE "Randomized Controlled Trials" OR DE "Randomized Clinical Trials"
#4	#1 AND #2 AND #3

Notes. We include text words in title (TI) and abstract (AB) and keywords with controlled vocabulary (DE).

CINAHL via EBSCOhost

No.	Search Terms
#1	TI "ptsd" OR AB "ptsd" OR TI "posttraumatic stress disorder" OR AB "posttraumatic stress disorder" OR TI "post traumatic stress disorder" OR AB "post traumatic stress disorder"OR MH "Stress Disorders, Post-Traumatic+"
#2	TI "trauma focused" OR AB "trauma focused" OR TI "psychotherap*" OR AB "psychotherap*" OR TI "cognitive therapy" OR AB "cognitive therapy" OR TI "cognitive behavio* therapy" OR AB "cognitive behavio* therapy" OR TI “cbt” or AB “cbt” OR TI "cognitive processing therapy" OR AB "cognitive processing therapy" OR TI “cpt” OR AB “cpt” OR TI "exposure therapy" OR AB "exposure therapy" OR TI "prolonged exposure" OR AB "prolonged exposure" OR TI "narrative exposure" OR AB "narrative exposure" OR TI "eye movement desensiti*" OR AB "eye movement desensiti*" OR TI "EMDR" OR AB "EMDR" OR MH "Psychotherapy+"
#3	TI "rct" OR AB "rct" OR TI "clinical trial" OR AB "clinical trial" OR TI "parallel design" OR AB "parallel design" OR TI "controlled trial" OR AB "controlled trial" OR TI "randomi*" OR AB "randomi*" OR TI "randomly" OR AB "randomly" OR TI "treatment trial" OR AB "treatment trial" OR MH "Randomized Controlled Trials+"
#4	#1 AND #2 AND #3

Notes. We include text words in title (TI) and abstract (AB) and keywords with controlled vocabulary (MH+).

BMJ Open

Augmentation of trauma-focused psychotherapy for post-traumatic stress disorder: A protocol for a systematic review and meta-analysis.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-090571.R1
Article Type:	Protocol
Date Submitted by the Author:	06-Mar-2025
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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Complementary medicine, Evidence based practice, Patient-centred medicine
Keywords:	Systematic Review, Meta-Analysis, MENTAL HEALTH, PSYCHIATRY, TRAUMA MANAGEMENT

Augmentation of trauma-focused psychotherapy for post-traumatic stress disorder: A protocol for a systematic review and meta-analysis.

Lisa Mewes[1,2,**], Till Langhammer[1,*,**], Jonathan Torbecke[1], Johannes C. Fendel[3], Ulrike Lueken[1,2]

[1] Department of Psychology, Humboldt-Universität zu Berlin, Berlin, Germany.

[2] German Center for Mental Health (DZPG), PartnerSite Berlin/Potsdam, Berlin, Germany.

[3] Department of Psychosomatic Medicine and Psychotherapy, Medical Center - University of Freiburg, Medical Faculty, University of Freiburg, Freiburg, Germany.

Running title: TFP augmentation for PTSD

Abstract: 255 words, text: 2.584 words, tables: 1, supplemental digital appendix: PRISMA-P checklist, search syntaxes for all databases

Keywords: Stress Disorders, Post-Traumatic; Psychotherapy; Treatment Outcome; Meta-Analysis; Systematic Review

***Corresponding author**:

Till Langhammer, Department of Psychology, Humboldt-Universität zu Berlin, Berlin, Germany.

Unter den Linden 6, 10099 Berlin, Germany

till.langhammer@hu-berlin.de

**both authors contributed equally

Abstract

Introduction: Despite the established status of trauma-focused psychotherapy (TFP) as a first-line treatment for post-traumatic stress disorder (PTSD), a substantial proportion of individuals does not achieve clinically significant improvement or discontinues treatment. Exploring augmentation strategies to enhance treatment outcomes is essential to reduce the overall burden PTSD puts on individuals and society. This protocol outlines a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating the efficacy of nonpharmacological augmentation strategies in addition to TFP for PTSD treatment.

Methods and Analysis: We comprehensively searched PubMed, Embase, CENTRAL, PTSDpubs, PsycArticles, PsycINFO, PSYNDEX, and CINAHL for RCTs without restrictions on publication dates or languages in October 2024. Study screening is currently ongoing. Additionally, we will perform forward and backward searches of included studies and relevant reviews. Two reviewers will independently screen and select studies, extract data, and assess the risk of bias. We will conduct a narrative review to qualitatively synthesize data and a meta-analysis to quantitatively compare the treatment efficacy of augmented TFP with TFP alone or TFP plus placebo. Primary outcomes will be both symptom severity and response rates. The secondary outcome will be dropout rates. We will explore sources of between-study heterogeneity and potential moderators through subgroup and meta-regression analyses. We will assess the overall quality of the included studies with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.

Ethics and dissemination: Ethical approval is not required. We intend to publish results in a peer-reviewed journal and provide materials and data through the Open Science Framework (OSF).

PROSPERO registration number: CRD42024549435.

Strengths and limitations of this study

- We employ a comprehensive search strategy across eight bibliographic databases that include grey literature to maximize sensitivity in study identification.
- We will evaluate three key outcomes - symptom severity, response rates, and dropout rates – while exploring potential moderators through subgroup analyses and meta-regression.
- We will systematically assess individual study quality and overall strength of evidence through standardized evaluation tools, including the Cochrane Risk of Bias tool version 2 (RoB2), and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.
- We will include only randomized controlled trials to strengthen internal validity, mitigate bias, and enhance the reliability of our findings.
- However, this approach excludes valuable insights from alternative study designs and could limit generalizability of results to real-world clinical settings.

1 Introduction

1.1 Rationale

Post-traumatic stress disorder (PTSD) is a prevalent and serious condition resulting from traumatic experiences, leading to health risks and societal costs that necessitate effective treatment. Most individuals experience at least one traumatic event during their lifetime, with varying exposure rates across nations and specific demographics, such as military personnel [1]. The risk for developing PTSD following a traumatic event, defined as 'actual or threatened death, serious injury, or sexual violence' [2], is estimated at approximately 4% [3]. The risk varies depending on the type of trauma experienced, with risk rates up to 19% following interpersonal trauma incidents such as rape [4]. Beyond the substantial burden of PTSD symptoms, the disorder is associated with numerous adverse outcomes, including increased mortality rate [5], elevated risks of cardiovascular and metabolic diseases [6], as well as substantial societal costs, e.g. due to health care and unemployment [7]. Untreated PTSD often persists for many years [8], underscoring the need for effective treatments to address the individual and societal burden associated with the disorder.

Available first-line treatments are effective for many PTSD patients, but their impact remains insufficient. International treatment guidelines uniformly recommend trauma-focused psychotherapy (TFP) as the first-line treatment for PTSD [9,10]. The umbrella term TFP encompasses various trauma-focused evidence-based treatments such as variants of trauma-focused cognitive behavioral therapy (TF-CBT) and eye movement desensitization and reprocessing (EMDR) [10,13]. While their specific treatment rationales may differ, TFPs typically target trauma memories, trauma-related thoughts

and emotions, and responses to environmental triggers using exposure-based and/or cognitive techniques. These interventions share several core therapeutic mechanisms: fear extinction learning, cognitive processing and restructuring, and emotional processing of the traumatic experience [14]. Several meta-analyses [11,15–17] report moderate to large effect sizes for TFPs in reducing PTSD symptom severity compared with different control groups, including active psychological therapies (e.g. supportive psychotherapy), treatment-as-usual, and waitlist controls. These treatment effects demonstrate stability over time, indicating enduring efficacy [18,19]. Conversely, recommendations for pharmacotherapy vary [9,10], reflecting smaller sustained treatment effects for pharmacotherapy compared with TFP [11,12]. However, dropout in TFPs remains a concern, with meta analyses reporting that approximately one-fifth of patients discontinue TFP treatment [20,21]. Findings on dropout patterns vary: while Lewis et al. (2020) found higher dropout rates for TFP (18%) compared with non-TFP (14%), Varker et al. (2021) reported similar dropout rates between TFPs and active control conditions overall (20.9% vs. 20.3%), though rates were notably higher for TFPs in military populations (32.9% vs. 23.3%). Further, inadequate treatment response remains a significant challenge at the individual patient level [22,23]. The definition of treatment response varies across PTSD treatment trials but is most commonly operationalized as loss of diagnosis or reduction of PTSD symptom severity [24]. Meta-analyses report different response rates for TFP ranging from 35% using standardized 50% symptom reduction thresholds [23] to 59% when aggregating studies' diverse author-defined criteria [22]. Recent systematic evidence suggests that treatment response to trauma-focused psychotherapy is moderated by diverse factors including biological mechanisms, comorbidities, cognitive functioning, social support, and trauma characteristics [25]. Though these findings primarily reflect correlational relationships with mean post-treatment symptom severity,

they suggest that a 'one-size-fits-all' approach to PTSD treatment is insufficient. Enhancement of standard TFP approaches appears necessary for the substantial proportion of patients who currently derive insufficient benefit.

Current research addresses inadequate treatment response to TFP by developing and evaluating additional treatment components, often referred to as augmentation strategies. The recently introduced four-stage model for PTSD chronification and treatment [26] proposes matching interventions to the progression of the disorder – from early neuroprotective strategies in subsyndromal stages to complex, multi-modal treatments for chronic presentations. This model suggests integrating augmentation strategies to enhance established first-line treatments, particularly for patients at risk of nonresponse, who may be identified early in TFP treatment through promising personalized care approaches [27,28]. Recent systematic reviews and meta-analyses indicate that most previously examined pharmaco-agents (e.g. selective serotonin reuptake inhibitors, D-cycloserine) have yet failed to demonstrate a robust augmentation effect [29–31]. These limited effects may reflect that pharmacological approaches often target specific fear extinction mechanisms [31], potentially overlooking the complex nature of treatment response [25]. In contrast, nonpharmacological augmentation strategies could offer advantages through their more comprehensive therapeutic pathways: First, they could enhance different core TFP mechanisms, as demonstrated for example by exercise promoting neural plasticity [32], and breathing feedback supporting emotional arousal regulation during exposure [33]. Second, they could address additional therapeutic targets not explicitly included in TFPs and hereby interact with the overall therapy process rather than specific mechanisms, such as sleep-directed interventions addressing common comorbid difficulties [34]. To the best of our knowledge, two systematic reviews

[31,35] compiled evidence on nonpharmacological augmentation strategies in TFP. However, at the time of their investigations, most of these strategies have been evaluated in a single randomized controlled trial (RCT) only, with no accompanying meta-analysis conducted. Given the increasing number of RCTs examining integrative, complementary, and alternative TFP augmentations for PTSD [36], it is imperative to update the existing reviews and evaluate proposed categories of augmentation strategies. To examine whether nonpharmacological augmentation strategies can improve treatment outcomes for patients who typically do not respond to TFP or drop out of treatment, it is essential to assess not only mean symptom reduction but also response rates and dropout rates. However, these effects are unlikely to be uniform across all conditions, as the success of augmentation strategies may depend on factors such as type, dosage, integration within TFP, and patient characteristics. To gain insights for whom and under which conditions what specific augmentation could be most effective, we will explore potential moderators.

1.2 Objectives

Through a systematic review and meta-analysis, we aim to fill this gap by offering researchers, practitioners, and policymakers a comprehensive overview of nonpharmacological augmentation strategies in addition to TFP for PTSD. We will explore the characteristics of different nonpharmacological augmentation strategies evaluated in RCTs and assess their overall impact on different aspects of treatment efficacy for PTSD. Specifically, we will evaluate whether augmentation strategies lead to reduced post-treatment PTSD symptom severity, increased response rates, and reduced dropout rates. We will carefully analyze potential moderators and factors contributing to between-study heterogeneity, including different types of augmentation strategies, TFPs, trauma types,

treatment resistance at baseline, treatment delivery format, treatment setting, control type, age group, length and dosage of both treatment components (TFP and augmentation).

2 Methods

We prepared this protocol adhering to the guidelines for Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [37] and provide the PRISMA-P checklist in the Supplemental Digital Appendix 1. The subsequent systematic review and meta-analysis will comply with the updated Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines [39]. We registered the study with the International Prospective Register of Systematic Reviews (PROSPERO registration number CRD42024549435). We will document important amendments to this protocol within PROSPERO.

2.1 Eligibility criteria

We utilized the PICOS framework to determine inclusion and exclusion criteria, as outlined in Table 1. Eligible TFPs for this review will include established treatments endorsed by current international PTSD treatment guidelines [9,10]: TF-CBTs, EMDR, cognitive processing therapy (CPT), prolonged exposure (PE), and other exposure-driven approaches specifically addressing trauma memories or environmental triggers (e.g. narrative exposure therapy (NET)). In this review, augmentation is defined as any (nonpharmacological) intervention 'delivered prior to, concurrently, or after a first-line PTSD treatment, where the focus of the augmentation was to improve PTSD symptoms and/or improve readiness for treatment, engagement, or retention in the first-line

treatment' [31]. The primary outcomes comprise (1) post-intervention PTSD symptom severity compared between groups (augmented TFP vs. TFP only/ placebo), and (2) response rates based on individual pre-to-post treatment changes. Follow-up data will be examined in sensitivity analyses to assess the durability of treatment effects. If studies used multiple measures to assess symptom severity, we will use the studies' primary outcome. We anticipate that included RCTs of first-line PTSD treatments will have varying definitions of treatment response [24]. Following Cuijpers et al. [23], we will estimate the number of responders from means and standard deviations using the method by Furukawa et al. [40]. Following Varker et al. [24], who recommended thresholds between 30-50% symptom reduction, we will define response as a 30% reduction in baseline symptom severity to ensure comparability across different measures while maintaining sensitivity. We will then conduct sensitivity analyses using the response rates as defined in the respective study and using a more conservative 50% symptom reduction threshold, aligned with recent meta-analytical approaches [23]. As the secondary outcome, we will assess dropout rates. Following recent meta-analyses [20,21], we will calculate the number of dropouts as the difference between the number of randomized participants and those providing post-treatment assessment data.

Table 1

Inclusion and exclusion criteria

Criterion	Inclusion criteria	Exclusion criteria
Population	Patients with PTSD diagnosed by a clinician according to DSM or ICD criteria; no or stable concurrent psychotropic medication	Non-clinical or undiagnosed samples; samples in which PTSD is not the primary diagnosis; changes in psychotropic medication during the trial
Intervention	TFP combined with at least one additional nonpharmacological treatment component (augmentation)	No TFP; pharmacological augmentation strategy only

Comparator	TFP only or with a placebo-augmentation control condition	No TFP; augmentation strategy only
Outcomes	PTSD symptom severity, assessed with a clinician-administered PTSD scale (e.g. CAPS-5 [41]) or validated self-reports (e.g. PCL-5 [42])	Self-reports without validation
Study design	Randomized controlled trials	Non-randomized trials, including non-controlled before-after studies, case-control studies, single/clinical case studies, systematic reviews, meta-analyses

Note. CAPS = Clinician-Administered PTSD Scale; DSM = Diagnostic and Statistical Manual of Mental Disorders; ICD = International Classification of Disease; PCL = PTSD checklist; PTSD = Post-traumatic stress disorder; TFP = Trauma-focused psychotherapy.

2.2 Search strategy

We systematically searched the following electronic bibliographic databases: PubMed, Embase (Ovid interface), Cochrane Register of Controlled Trials (CENTRAL), PTSDpubs (ProQuest interface), as well as PsycArticles, PsycINFO, PSYNDEX, and CINAHL (previous four via EBSCOhost interface), without restrictions regarding publication date or language in October 2024. The competition of the systematic review is anticipated for the second half of 2025. Given the absence of standardized terminology in the emerging field of augmentation approaches in addition to psychotherapy treatments (e.g. augmentation, enhancement, add-on etc.), we will prioritize high sensitivity in our search strategy. Our search terms will be related to (1) PTSD, (2) evidence-based TFPs, and (3) RCT study design. Search syntaxes for all bibliographic databases are provided in the Supplemental Digital Appendix 2. Additionally, we will conduct backward-and-forward literature searches of included studies and relevant reviews on PTSD treatment. If full texts are unavailable or pertinent information within the scope of this systematic review

and meta-analysis is missing, we will contact the corresponding authors of the respective studies and wait eight weeks for their response. Further, we will reach out to all corresponding authors of included studies to identify any existing but unpublished data. This applies to both published studies with missing data and to identified study protocols, conference abstracts, or trial registrations, for which we will contact investigators to inquire about study completion and data availability.

2.3 Study selection

The study selection process began in November 2024 and is currently ongoing. Two reviewers (LM and TL) are independently conducting software-based study selection. If either reviewer considers the study eligible based on title and abstract screening, we proceed with comprehensive full-text-screening. Finally, studies are included when a consensus is reached. If no consensus is reached, a third reviewer is consulted (UL). We document the study selection process in a flowchart adhering to the updated PRISMA guidelines [39].

2.4 Data extraction

One reviewer (LM) will extract relevant information from the eligible studies. A second reviewer (TL) will independently extract data from a random sample 10 studies to ensure reliability and minimize bias. We will use a standardized extraction form, which will be pilot tested and adjusted if necessary. Information to be extracted includes: (1) the study: authors, publication year, country, type of TFP, type of control; (2) the population: sample size (at randomization, pre- and post-treatment assessment), age, sex, ethnicity, trauma

type, comorbidities, medication, treatment resistance at baseline (study-defined status, criteria, and measures used), inclusion and exclusion criteria; (3) the intervention and the comparator: delivery format (face-to-face/online/hybrid), setting (individual/ group), augmentation strategy, proposed mechanism of augmentation, treatment characteristics for TFP and augmentation strategy (including session duration, number and frequency of sessions, treatment duration, homework, schedule (prior to, concurrently, or after TFP)), use of measurement tools for intervention integrity including adherence to the protocol, clinical and program experience of the facilitating therapist; (4) the outcomes: means and standard deviations for PTSD symptoms (pre- and post-treatment, follow-up if assessed), time points of assessment, measure of symptom severity, response rates (including absolute numbers of response/ non-response), response operationalization, dropout reasons, adverse events.

2.5 Risk of bias and quality assessment in individual studies

Two reviewers (LM and TL) will independently assess the risk of bias in the included studies using the second version of the Cochrane risk-of-bias assessment tool for randomized trials (RoB2) [43]. We will resolve any discrepancies through discussion; if no consensus can be reached, a third reviewer will be consulted (UL). Within the RoB2 tool, risk of bias is rated as 'low risk of bias', 'some concerns', or 'high risk of bias' regarding five domains: (1) bias arising from the randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported result. Based on the rating in these domains, an overall rating is derived for each outcome.

2.6 Risk of Bias across studies

To examine publication bias, we will visually inspect funnel plots, compute Egger's regression test [44] and Rosenthal's fail-safe N [45], and conduct the 'trim and fill' method [46]. We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [47] to assess the overall quality of evidence for each outcome, separately for different augmentation approaches and across all included studies. Two reviewers (LM and TL) will independently rank the quality of evidence as 'high', 'moderate', 'low', or 'very low' for each of the following dimensions: (1) risk of bias, (2) inconsistency of results, (3) indirectness of evidence, (4) imprecision of effect size, and (5) publication bias.

2.7 Data Synthesis

We will conduct a narrative review to qualitatively synthesize data on key characteristics of the included studies. This synthesis will involve categorizing augmentation strategies into relevant groups based on proposed frameworks [28] and insights from the reviewed literature. Building on Metcalf and colleagues (2020), we aim to categorize augmentation strategies based on their proposed primary mechanisms of action. If mechanism-based categorization proves challenging, alternative organizing principles, such as application methods, will be considered to ensure meaningful clinical distinctions. Pertinent results will be reported in a comprehensive 'summary of findings' table.

We will conduct quantitative data synthesis to generate pooled effect sizes for augmentation effects and examine between-study heterogeneity. Due to the inclusion of studies with diverse characteristics, we anticipate considerable between-study heterogeneity. We will evaluate this assumption by calculating the Q-Test, I^2-statistic [48],

and prediction intervals [49] within a random-effects meta-analytical framework. To quantify standardized mean difference for symptom severity between-groups (augmented TFP vs. TFP only/with placebo) at post-treatment, we will calculate pooled Hedges' *g* [50]. For between-group differences in response rates and dropout rates, we will calculate pooled risk ratios. All effect sizes will be calculated with their 95% confidence intervals and associated *p* values. Sensitivity analyses will address risk of bias, follow-up outcomes, study sample (intention-to-treat vs. completers), different response operationalizations, and outliers using the "non-overlapping confidence interval" approach [51]. We will explore sources of heterogeneity with subgroup and meta-regression analyses using mixed-effects models, if we can include at least ten studies in total and three studies per subgroup [52]. Subgroups will be formed regarding augmentation approach, TFP approach, trauma type, treatment resistance at baseline, treatment delivery format, treatment setting, control type, and age group. We will examine potential continuous moderators, such as length and dosage of both treatment components (TFP and augmentation) using meta-regression analyses. Analyses with insufficient available studies (defined as fewer than 10 times the number of planned analyses) will be considered as exploratory and used to generate hypotheses for future research rather than to draw definitive conclusions. All analyses will be conducted in RStudio [53].

2.8 Patient and public involvement

Neither patients nor the public will be involved in the study design, conduct, reporting, or dissemination plans of this research.

3 Ethics and dissemination

Ethical approval is not considered necessary for this study. Results will be published in peer-reviewed journals. We will provide materials and data within the Open Science Framework (OSF).

Author Contributions TL is the guarantor. LM, TL, JCF, and UL drafted the work and made substantial contributions to the conception. LM, and TL wrote and approved the submitted version of the protocol and account for accuracy and integrity of any part of the work. JCF, JT and UL read, edited, and approved several versions of the manuscript. JT consulted in all stages of the conception.

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Competing interests LM, TL, JT, JCF, and UL have no competing interests to declare. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Supplemental Digital Appendix 1

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page number(s)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1, 14 - 15
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	8
Support:			
Sources	5a	Indicate sources of financial or other support for the review	15
Sponsor	5b	Provide name for the review funder and/or sponsor	15
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	15
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4 - 8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7 - 8
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8 - 9
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8 - 9
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplement 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	11

Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10 - 12
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11 - 12
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8 - 9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	12 - 13
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	13
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	13
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13 - 14
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	13
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13 - 14

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

This checklist has been adapted from: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplemental Digital Appendix 2

Search Strategy for PubMed, Embase, CENTRAL, PTSDpubs, PsycArticles, PsycINFO, PSYNDEX, and CINAHL

PubMed

No.	Search Terms
#1	PTSD [tiab] OR “posttraumatic stress disorder” [tiab] OR “post traumatic stress disorder” [tiab] OR stress disorders, post traumatic [mesh]
#2	“trauma focused” [tiab] OR psychotherap* [tiab] OR “cognitive therapy” [tiab] OR “cognitive behavio* therapy” [tiab] OR CBT [tiab] OR “cognitive processing therapy” [tiab] OR CPT [tiab] OR “exposure therapy” [tiab] OR “prolonged exposure” [tiab] OR “narrative exposure” [tiab] OR “eye movement desensiti*” [tiab] OR EMDR [tiab] OR Psychotherapy [mesh]
#3	RCT [tiab] OR”clinical trial” [tiab] OR “parallel design” [tiab] OR “controlled trial” [tiab] OR randomi* [tiab] OR randomly [tiab] OR “treatment trial” [tiab] OR Randomized Controlled Trials [Publication Type]
#4	#1 AND #2 AND #3

Note. We include textwords in title and abstract (tiab) and keywords with controlled vocabulary (MeSH terms).

Embase via Ovid

No.	Search Terms
#1	(PTSD or "posttraumatic stress disorder" or "post traumatic stress disorder").ti,ab. or exp posttraumatic stress disorder/
#2	("trauma focused*" or psychotherap* or "cognitive therapy" or "cognitive behavioural therapy" or CBT or "cognitive processing therapy" or CPT or "exposure therapy" or "prolonged exposure" or "narrative exposure" or "eye movement desensiti*" or EMDR).ti,ab. OR exp trauma-focused cognitive behavioral therapy/ OR exp cognitive processing therapy/ OR exp exposure therapy
#3	(RCT or "clinical trial" or "parallel design" or "controlled trial" or randomi* or randomly or "treatment trial").ti,ab. or exp randomized controlled trial/
#4	#1 AND #2 AND #3

Note. We include text words in title and abstract (.ti,ab.) and keywords with controlled vocabulary (Emtree terms).

CENTRAL

No.	Search Terms
#1	PTSD OR “posttraumatic stress disorder” OR “post traumatic stress disorder”
#2	"trauma focused" OR psychotherap* OR "cognitive therapy" OR cognitive NEXT behavio* NEXT therapy OR CBT OR "cognitive processing therapy" OR CPT OR "exposure therapy" OR "prolonged exposure" OR "narrative exposure" OR eye NEXT movement NEXT desensiti* OR EMDR
#3	RCT OR “clinical trial” OR “parallel design” OR “controlled trial” OR randomi* OR randomly OR “treatment trial”
#4	#1 AND #2 AND #3

Note. We include text words in title, abstract, and keywords.

PTSDpubs via ProQuest

No.	Search Terms
#1	PTSD or "posttraumatic stress disorder" or "post traumatic stress disorder"
#2	"trauma focused*" or psychotherap* or "cognitive therapy" or "cognitive behavio* therapy" or CBT or "cognitive processing therapy" or CPT or "exposure therapy" or "prolonged exposure" or "narrative exposure" or "eye movement desensiti*" or EMDR
#3	RCT or "clinical trial" or "parallel design" or "controlled trial" or randomi* or randomly or "treatment trial"
#4	#1 AND #2 AND #3

Note. We include text word search in all fields except from full text (noft).

PsycArticles, PsycInfo, PSYNDEX via EBSCOhost

No.	Search Terms
#1	TI "ptsd" OR AB "ptsd" OR TI "posttraumatic stress disorder" OR AB "posttraumatic stress disorder" OR TI "post traumatic stress disorder" OR AB "post traumatic stress disorder" OR DE "Posttraumatic Stress Disorder" OR DE "Complex PTSD"
#2	TI "trauma focused" OR AB "trauma focused" OR TI "psychotherap*" OR AB "psychotherap*" OR TI "cognitive therapy" OR AB "cognitive therapy" OR TI "cognitive behavio* therapy" OR AB "cognitive behavio* therapy" OR TI “cbt” or AB “cbt” OR TI "cognitive processing therapy" OR AB "cognitive processing therapy" OR TI “cpt” OR AB “cpt” OR TI "exposure therapy" OR AB "exposure therapy" OR TI "prolonged exposure" OR AB "prolonged exposure" OR TI "narrative exposure" OR AB "narrative exposure" OR TI "eye movement desensiti*" OR AB "eye movement desensiti*" OR TI "EMDR" OR AB "EMDR" OR - DE "Psychotherapy" OR DE "Trauma Treatment" OR DE "Trauma-Focused Cognitive Behavior Therapy" OR DE "Cognitive Behavior Therapy" OR DE "Cognitive Therapy" OR DE "Behavior Therapy" OR DE "Exposure Therapy" OR DE "Imaginal Exposure" OR DE "Prolonged Exposure Therapy" OR "Narrative Therapy" OR DE "Eye Movement Desensitization Therapy"
#3	TI "rct" OR AB "rct" OR TI "clinical trial" OR AB "clinical trial" OR TI "parallel design" OR AB "parallel design" OR TI "controlled trial" OR AB "controlled trial" OR TI "randomi*" OR AB "randomi*" OR TI "randomly" OR AB "randomly" OR TI "treatment trial" OR AB "treatment trial" OR DE "Randomized Controlled Trials" OR DE "Randomized Clinical Trials"
#4	#1 AND #2 AND #3

Notes. We include text words in title (TI) and abstract (AB) and keywords with controlled vocabulary (DE).

CINAHL via EBSCOhost

No.	Search Terms
#1	TI "ptsd" OR AB "ptsd" OR TI "posttraumatic stress disorder" OR AB "posttraumatic stress disorder" OR TI "post traumatic stress disorder" OR AB "post traumatic stress disorder"OR MH "Stress Disorders, Post-Traumatic+"
#2	TI "trauma focused" OR AB "trauma focused" OR TI "psychotherap*" OR AB "psychotherap*" OR TI "cognitive therapy" OR AB "cognitive therapy" OR TI "cognitive behavio* therapy" OR AB "cognitive behavio* therapy" OR TI “cbt” or AB “cbt” OR TI "cognitive processing therapy" OR AB "cognitive processing therapy" OR TI “cpt” OR AB “cpt” OR TI "exposure therapy" OR AB "exposure therapy" OR TI "prolonged exposure" OR AB "prolonged exposure" OR TI "narrative exposure" OR AB "narrative exposure" OR TI "eye movement desensiti*" OR AB "eye movement desensiti*" OR TI "EMDR" OR AB "EMDR" OR MH "Psychotherapy+"
#3	TI "rct" OR AB "rct" OR TI "clinical trial" OR AB "clinical trial" OR TI "parallel design" OR AB "parallel design" OR TI "controlled trial" OR AB "controlled trial" OR TI "randomi*" OR AB "randomi*" OR TI "randomly" OR AB "randomly" OR TI "treatment trial" OR AB "treatment trial" OR MH "Randomized Controlled Trials+"
#4	#1 AND #2 AND #3

Notes. We include text words in title (TI) and abstract (AB) and keywords with controlled vocabulary (MH+).