BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038951
Article Type:	Protocol
Date Submitted by the Author:	31-Mar-2020
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Keywords:	MENTAL HEALTH, THERAPEUTICS, Depression & mood disorders < PSYCHIATRY

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Study protocol for network meta-analysis of digital-technology-based psychotherapies for PTSD in adults

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Abstract

Introduction Post-traumatic stress disorder (PTSD) is a type of stress disorder common among adults who have been exposed to various forms of trauma events. Studies on various types of digital-technology-based psychotherapies (DTPs) have indicated that these DTPs are effective for PTSD among adults, and more accessible than face-to-face therapies, for multiple reasons. The intervention efficacy hierarchy, however, is still not clear. Therefore, we propose to conduct a network meta-analysis to assess the efficacy hierarchy of various psychotherapies based on digital technology for PTSD in adults.

Methods and Analyses We will search Embase, CINAHL, MEDLINE, HealthSTAR, the Cochrane Library, PsycINFO, PubMed, the Chinese biomedical literature database, clinical trials (e.g., ClinicalTrials.gov), and other academic platforms for relevant studies, mainly in English and Chinese. Randomised controlled trials (RCTs) and meta-analyses, regardless of publication year or type, investigating the efficacy of

any DTP for PTSD patients (clinically diagnosed or self-diagnosed) for any controlled condition will be included. The number of intervention sessions and the research duration are unlimited; the effects for different durations will be tested via sensitivity analysis. In this project, the end-point score of PTSD symptoms is extracted as the primary outcome measure (various PTSD scales are acceptable). Secondary outcome measures will include (1) dropout rate; (2) efficacy at longest follow-up, but not more than 12 months; and (3) patients' functional recovery ratio (such as return-to-work ratio or sick-leave percentage). Bayesian network meta-analysis will be conducted for all outcome measures. We will perform subgroup analysis and sensitivity analysis to see whether the results are influenced by study characteristics. The Grading of Recommendations, Assessments, Development, and Evaluation (GRADE) framework will be adopted to grade the quality of evidence of the network estimates so that more accurate recommendations regarding the DTP effect hierarchy can be made for future medical and health practices. The network estimates of the primary outcome measure will be evaluated in order to make more effective recommendations.

Strengths and limitations of this study

- This study will help guide practitioners and service providers in providing efficient and effective interventions for many different types of PTSD patients (especially useful for those resulting from the COVID-19 pandemic) that traditional face-to-face psychotherapies could not normally reach.

- Network meta-analysis can compare various types of digital-technology-based psychotherapy for PTSD among adults by integrating indirect and direct comparisons.
- Potential moderators for efficacy can be found through subgroup and sensitivity analysis.
- Since PTSD often co-occurs with other mental or physical illnesses, we will include trials and meta-analyses in which patients with comorbidity were recruited. However, this will increase risk of bias even though it broadens the pooled sample. Relevant subgroup analysis will be applied to examine this impact.
- The project will use the Cochrane risk-of-bias tool to assess the degree of bias of the studies included, and the GRADE framework will be adopted to grade the quality of evidence for network estimates of the primary outcome, in order to provide practical recommendations with high-quality evidence.

Keywords

PTSD; digital-technology-based psychotherapy; network meta-analysis;

Introduction

The outbreak of COVID-19 starting in China has spawned a wide range of reflections upon psychological distress in the face of a national and global trauma event. It has been found that public health outbreaks such as SARS are likely to cause acute stress

disorder during the outbreak and post-traumatic stress disorder after it, especially in the context of nationwide quarantine[1,2].

The World Health Organization (1992) defined trauma as resulting from "an exceptionally stressful life event producing an acute stress reaction, or a significant life change leading to continued unpleasant circumstances that result in an adjustment disorder"[3]. According to the American Psychological Association's *Diagnostic and Statistical Manual of Mental Disorders 5* (DSM-5), stress disorder usually begins within the first three months, although there may be a delay of months or even years before a full diagnosis can be made[4]. Post-traumatic stress disorder (PTSD) usually features four symptom groups: (1) relived experiences of the trauma (such as nightmares, flashbacks, and intrusive thoughts), often invasive; (2) persistent hyperreaction (such as insomnia, difficulty in concentration, and increased startle reflex); (3) active avoidance of things related to the traumatic event; and (4) negative cognition and behaviours (loss of social function, absence from work, etc.) that were initiated by the trauma or that worsened after it[5,6]. Other comorbidities, such as anger management issues, drug and alcohol abuse, depression, and anxiety, may occur with the development of PTSD symptoms, thereby aggravating the patient's mental illness[7]. PTSD is a common mental disorder worldwide. Epidemiological studies have shown that more than half of the population (usually more men than women) experience at least one traumatic event in their lifetime that may lead to PTSD[8,9]. After experiencing traumatic events, more than 10% of people may develop PTSD[10]; a Chinese study also showed that SARS patients and their family members

had a 10% chance of acquiring PTSD[11]. About one-third of PTSD patients never recover, and of those that do, the median relapse period is 14 years[12]. PTSD places a serious burden on individuals and on society[13].

In view of the breadth and depth of the impacts of PTSD, it is very important to study the available effective interventions for PTSD patients. The debate on which treatments work the best is ongoing[14]. Many systematic reviews and meta-analyses have shown no significant difference between the majority of drug treatment methods (except phenylethylhydrazine) and the control group (e.g.[14,15]). The five most prestigious professional organisations internationally—the American Psychological Association (APA), International Society for Traumatic Stress Studies (ISTS), National Institute for Health and Care Excellence (NICE), Phoenix Australia Centre for Posttraumatic Mental Health (PACPMH), and US Department of Veterans Affairs/Department of Defense (VA/DoD)—have all claimed that psychotherapies are significantly effective for PTSD symptom relief[16–20]. The latter three clearly stated that exposure psychotherapies are much more effective than drug therapies[18–20].

There are many factors that may interfere with a patient's access to necessary and appropriate psychotherapies for PTSD[21]. An epidemiological study showed that only 53% of people globally with a history of PTSD receive any type of treatment[22]. The main barriers to treatment seem to occur at two levels: the individual patient level and the health service level[23]. Barriers at the individual patient level include cost (such as travel expenses, childcare, payments for face-to-face psychotherapies, and time investment in travel), limited physical

mobility, lack of transportation, and fear of being ostracised or stigmatised for having a mental illness[24]; many of these barriers are particularly important for patients living in remote communities[25]. At the health service level, the lack of availability of high-quality evidence-based psychotherapy guidelines or qualified psychotherapists might prevent patients from accessing treatments[26, 27]. These barriers have prompted interest in new ways of delivering effective psychotherapies and new technologies for doing so. For example, one way of facilitating PTSD patients' access to treatments might be through digital technology[28].

Digital-technology-based psychotherapy (DTP) usually uses internet-based platforms such as Web-based services and PC and smartphone apps to deliver psychotherapies to the patients[29]. Compared with traditional face-to-face psychotherapy, digital-technology-based psychotherapy has many advantages, such as lower cost, higher flexibility, and better protection of privacy[30]; various studies have also confirmed several disadvantages, such as a higher dropout rate, increased risk of leaking of patient information, lower level of patient participation in the programme, and requiring patients to acquire technical skills[31–33]. During a public health outbreak the use of digital technology is more appropriate over face-to-face therapies for PTSD patients, who are often resistant to face-to-face contact due to fear of imagined infection, even long after the trauma event[2, 34, 35]. For other kinds of mental illnesses, such as anxiety disorder and depression, the efficacy of DTP has been well studied and confirmed[6]. However, research on DTP for PTSD has only begun to emerge in recent years. For example, a systematic review of DTP for PTSD

in veterans found that in most instances, DTP was as effective as traditional face-to-face interventions in reducing PTSD symptoms[31, 36].

Three weaknesses were identified in the existing systematic reviews and meta-analyses on DTP for PTSD (e.g.,[37–43]). First, the trials included are not comprehensive. Most of the meta-analyses focused on cognitive behavioural therapy (CBT) trials; for example, two different meta-analyses proved the efficacy of CBT delivered through digital technology but did not include other types of psychotherapies[14, 44]. Also, in all the meta-analyses the criteria for trauma event types did not include public health outbreaks such as SARS and Ebola. Additionally, smartphone-app-based psychotherapies were excluded in most meta-analyses[e.g. 26, 45]. Second, the trials examined had very high heterogeneity or high risk of bias, so the quality of evidence is questionable[14, 44]. Third, most of meta-analyses focused on the effects of specific psychotherapies rather than exploring the comparative efficacy of different DTPs [e.g., 24, 26, 37–43, 46]. For instance, Olthuis et al.'s meta-analysis confirmed that DTP was more effective when compared to effects on the waiting control group, and did not compare efficacy among various types of DTP[26]. Moreover, the efficacy of DTP for PTSD patients compared to traditional face-to-face psychotherapy has also been questioned. Several scholars concluded that the efficacy of DTP cannot be confirmed due to the lack of sufficient comparative efficacy evidence with face-to-face therapies for PTSD[41, 47].

Not only has the effect-size classification for various types of DTP for PTSD not been confirmed, we also found that the recommendation hierarchy for various forms

of traditional face-to-face psychotherapies for PTSD is inconsistent among the guidelines for the treatment of PTSD in adults from the five prestigious organisations mentioned above. APA and ISTS in particular did not provide a clear recommendation hierarchy for various forms of psychotherapies[16, 17]. Although all the organisations strongly recommend exposure-focused therapy as a choice for PTSD treatment, the recommendations for specific exposure-focused therapy and non-exposure therapy are inconsistent; for example, different guidelines may grade eclectic psychotherapy and narrative exposure therapy vastly differently. Three organisations strongly recommended DTP but generally classified all kinds of DTP into a single treatment group[16–20].

As a newly developed method, network meta-analysis, through appropriate research design, can easily fill the gaps identified above. Although the assumptions of network meta-analysis are similar to those of regular meta-analysis, the key additional assumptions are transitivity (no effect-modifying factors affecting indirect comparison) and coherence (direct and indirect effect estimates are similar)[6]. Therefore, network meta-analysis can integrate direct evidence from comparative studies of different interventions and indirect evidence from studies of individual interventions with common control conditions, and assess the efficacy hierarchy among various interventions[48]. This method can provide meaningful evidence for clinical practice guides by comparing multiple treatments at the same time[49]. By also using GRADE (Grading of Recommendations, Assessments, Development, and Evaluation) to rate the quality of evidence synthesised through network meta-analysis,

the aim of this research is to provide high-quality clinical guidance on DTP for PTSD in adults[50].

Research on traditional PTSD psychotherapy through network meta-analysis is limited. For example, a network meta-analysis in 2019 compared the effectiveness of different psychotherapies for PTSD[51]. However, the study focused on young people, not adult patients, and the psychotherapies were not based on digital technology. Network meta-analysis of traditional psychotherapies for PTSD in adults is also limited. There are no such studies published in Chinese[52] and only a few articles published in English[6, 45, 53–55]. One study concentrated on traditional face-to-face psychotherapy, with very outdated data extraction (January 2011)[6]; another article compared the efficacy of different traditional psychotherapies and conducted a subgroup analysis between patients with clinical diagnosis and those without[53]. Network meta-analysis research is even more limited on digital-technology-based PTSD psychotherapy for adults. Moreover, these studies also have inconsistencies with the guidelines mentioned above. For example, a network meta-analysis of DTP indicated that the efficacy of various psychotherapies, such as cognitive behavioural therapy, comfort counselling, and eye movement desensitisation and reprocessing, does not significantly differ between them, and most of the trials included had a low quality of evidence[54]. Two research protocols of network meta-analysis published in 2018 advocated for examination of the comparative efficacy of different DTPs for PTSD in adults[45, 50].

Therefore, we endeavour to conduct a network meta-analysis of studies on

digital-technology-based psychotherapies for PTSD in adults, specifically studies that incorporate trials in a comprehensive manner and with special consideration for quality of evidence, in order to better compare the efficacy hierarchy for different DTPs (including an effectiveness comparison with traditional face-to-face psychotherapy).

Methods

This network meta-analysis will be conducted in accordance with the PRISMA-P checklist[56].

1. Search strategy

Longtao He and Geng will search Embase, CINAHL, MEDLINE, HealthSTAR, the Cochrane Library, PsycINFO, PubMed, the Chinese biomedical literature database, clinical trials (e.g., ClinicalTrials.gov), and other academic platforms for studies on various DTPs for PTSD in adults, mainly in English and Chinese. The studies included will be randomised controlled trials (RCTs) and systematic meta-analyses on DTP psychotherapies for PTSD (some meta-analyses may have included RCTs we did not find otherwise). An experienced medical librarian will be consulted to improve the search strategy for each database, and any differences will be resolved through discussion; in case of disagreement we will consult another expert.

2. Selection Criteria

2.1 Inclusion criteria:

- The patients recruited in an individual RCT or in RCTs in meta-analyses are adults diagnosed with primary or secondary PTSD (according to DSM-III, IV, and V, the International Classification of Diseases, and other similar standards);
- Trauma events will include all types, with special attention to public health outbreaks;
- The diagnosis may be either clinical diagnosis (e.g., using the Clinician-Administered PTSD Scale [CAPS] according to DSM-IV) or self-diagnosis (e.g., using the Post-traumatic Stress Disorder Checklist—Civilian Version [PCL-C]); the efficacy of independent studies with informal diagnosis will be tested via sensitivity analysis;
- The study of secondary PTSD must focus on the treatment of PTSD;
- If the PTSD patients recruited in the RCT also suffer from other comorbidities, such as physical disease, they will be included in the database, and these groups of patients will be tested via sensitivity analysis;
- DTP will include various technologies (e.g., Web-based services, PC and smartphone apps), but there must be elements of interaction between programmes and patients;

- The selection of various types of psychotherapy is mainly based on the comprehensive analysis of PTSD therapy guidelines of the five authoritative societies and organisations mentioned above (see Table 1), along with types of control group;
- The research duration is unlimited, but the effects for different durations will be tested by subgroup analysis. The number of DTP sessions is also unlimited.

Table 1: Description of Psychotherapies and Control Conditions

Type of Psychotherapy	Abbrev.	Brief Description
Exposure-Based Psychotherapy		
Trauma-Focused Cognitive Behavioural Therapy (undifferentiated)	TF-CBT	Implemented through cognitive remodelling and behavioural change techniques; focuses on trauma, and usually deals with trauma-related thoughts and behaviours through exposure-to-trauma situations or cognition.
Prolonged Exposure Therapy	PET	Uses specific methods to guide patients to gradually make contact and deal with cognitive thoughts, behaviours, and scenes about trauma.
Narrative Exposure Therapy	NET	Encourages the patients to focus on the traumatic events and piece together a coherent life story to deal with the fragmentation of life memories caused by trauma.
Eye Movement Desensitization and Reprocessing	EMDR	Pays less attention to the traumatic event itself than to the disturbing emotions and thoughts caused by the event. Treatment involves the therapist using techniques to guide the patient's eye movement from side to side.
Cognitive Processing Therapy	CPT	Socratic questioning often used to help patients learn how to challenge their misconceptions and behaviours around trauma. Written assignments may be given to encourage patients to develop new cognitive skills.
Cognitive Therapy	CT	Focuses solely on challenging patients' old ways of thinking about trauma from a cognitive perspective.
Non-Exposure-Based Psychotherapy		
Non-Trauma-Focused Cognitive Behavioural Therapy	NTF-CBT	Implemented through cognitive remodeling and behaviour change techniques; the focus is not on trauma itself but rather on behavior and cognition skills.
Present-Centred Therapy (mindfulness)	PCT	Instructs patients to learn skills for focusing on the "present" and letting go of bad memories from the past.
Relaxation Therapy	RT	Mainly uses a series of relaxation methods, such as deep breathing, to teach patients to deal with the recurrence of traumatic memories.
Supportive Counselling	SC	The therapist mainly provides emotional support, listening to the patient's difficulties, sadness, etc.
Brief Eclectic Therapy	BET	Integrates CBT, SC, and other treatment skills to treat patients over a short period of time.

Type of Psychotherapy	Abbrev.	Brief Description
Psychodynamic Therapy	PDT	Focuses mainly on revealing the subconscious in the patient's heart, so as to relieve their mental tension.
Psychoeducation	PE	Treats patients by enhancing their understanding of PTSD.
Control Group		
Treatment as Usual	TAU	Refers to the usual treatment method at the research site, which may contain many components of psycho-interventions, as well as drug treatment.
Waitlist	WL	Patients do not receive any treatment during the study but will receive treatment after the study.
No Treatment	NT	Patients receive no treatment during or after the study.
Active Therapeutic Treatment	ATT	Patients receive some kind of traditional face-to-face psychological intervention.
Digital-Technology-Based Active Therapeutic Treatment	DTATT	Patients receive some kind of psychotherapy based in digital technology.

2.2 Exclusion Criteria:

- The RCT has an intervention group or control group of fewer than 10 participants (of the five organisations, NICE and VA/DoD guidelines exclude RCTs with fewer than 10 participants[18, 20]; we think adopting this exclusion criterion is an appropriate way to increase quality of evidence);
- It is a pilot study, feasibility study, or crossover trial;
- The recruitment criteria are for severe PTSD, which includes excessively high willingness to commit suicide, high dissociative disorder, severe mania, and psychosis;
- If a small number of participants in a RCT meet the above exclusion criteria, we

will try our best to abstract and exclude the data of those independent participants, and include the trial; if we are not able to exclude these individual data, but the number of these participants does not exceed 20% of the total enrolled, the trial will still be included.

3. **Data Extraction and Bias Analysis**

3.1 Data extraction

a. *RCT and meta-analysis data extraction:* In order to ensure the reliability of independent data extraction, a data extraction Excel form will be designed and the following calibration exercises will be conducted among project researchers (Longtao He, Tian, and Pan). The data extraction form will include study characteristics (first author, year of publication, source of funding, and so on) and patient and trial characteristics such as patient demographic information (age, gender, occupation, disability status, type of trauma, and related comorbidity status), sample size, and intervention- and control-group characteristics.

b. *Independent patient data provided by RCT and meta-analysis authors:* If the complete data cannot be downloaded from the database, the authors of the selected trials or studies will be contacted and asked to share their independent patient data (including baseline measurement and other information); the corresponding author will be contacted first, and if not available, the other authors will be contacted in turn; if there is no response from the authors within two weeks, a second email will be sent;

if there is no response within one month from any of the authors contacted, the RCT or meta-analysis will only be included in the analysis at the aggregate data level. Two researchers (Longtao He and Geng) will separately test the consistency of the independent patient data with the data summary published in the article. The validity of this project would be compromised if the trials with independent patient data were systematically and statistically different from those without. Therefore, we will divide data into two groups for analysis according to source origin, and compare the differences between the two groups; if there are statistical differences, we will include this result in our later assessment of the quality of evidence.

3.2 Primary outcome measure

In this project, the end-point score of PTSD symptoms is extracted as the primary outcome measure (various professional PTSD scales are acceptable). If the patient has more than one outcome measure, the project will select the most common, most effective, or most accurate one according to the sequence shown in Table 2. If there are different outcome raters in a study, we will choose the results of self-checking by patients themselves because they are generally more conservative than those measured by clinicians. If the two studies use different outcome measures, we will use the established conversion algorithms[57]. If the outcome is a dichotomy outcome, the authors of the RCT study or meta-analysis will be contacted and asked to provide relevant primary data; if there is no response, the study will not be considered.

3.3 Secondary outcome measures

(1) dropout rate—the rate of patients who discontinued the trial for any reason at any time before the end of trial; (2) efficacy at the longest follow-up period, but not more than 12 months; (3) patients' functional recovery ratio (such as return-to-work ratio or sick-leave percentage).

Table 2: Primary Outcome Hierarchy

Ranking	Name	Abbrev.	Brief Introduction
1	PTSD Checklist —Civilian Version	PCL-C	According to DSM-5's diagnostic criteria for PTSD, 17 items were designed to measure the symptoms of PTSD.
2	Post-traumatic Stress Disorder Self-Rating Scale	PTSD-SS	This consists of 24 items including 17 standard symptoms of PTSD, and adopts a 5-level scoring method.
3	Clinician-Administered PTSD Scale for DSM-5	CAPS-5	According to DSM-5's diagnostic criteria for PTSD, clinicians conduct semi-structured interviews to measure the symptoms of PTSD.
4	PTSD Symptom Scale Interview	PSS-I	The questionnaire is composed of 17 standard items regarding the symptoms of PTSD, and is graded according to four grades of 0–3. The completion time is about 20 minutes.
5	Impact of Event Scale —Revised	IES-R	The scale contains 22 questions, including three core symptoms of PTSD. The questionnaire normally takes 20–30 minutes to complete.
6	Post-traumatic Diagnosis Scale	PTDS	The first 12 items examine the possible traumatic events that individuals may have suffered. The frequency of each symptom over the past 30 days is then assessed using a four-level grading of 17 types of symptoms.
7	PTSD Checklist —Veteran Version	PCL-V	According to DSM-5's diagnostic criteria for PTSD, 17 items were designed to measure the symptoms of PTSD among veterans.
8	Penn Inventory for Post-Traumatic Stress	PIP	26 items for accident victims and veterans.
9	Other Types of Scale		

3.4 Risk of bias

The project will use the Cochrane risk-of-bias tool, version 2.0, to assess the degree of bias of the study by assessing random sequence generation, allocation concealment, blinding of participants, blinding of personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting.

4. Data synthesis and analysis

Bayesian network meta-analysis will be conducted for all outcome measures. For dichotomous outcomes (e.g., the disappearance ratio of a symptom), the project will calculate the odds ratio (OR) using the baseline risk estimates of the high-quality control group, as well as the relevant 95% confidence interval (CIs); if the sample pool is big enough, absolute risk (AR) will also be calculated. For continuous outcomes (such as severity of PTSD or quality-of-life scale score), if the scales are different, the project will calculate the standard mean difference (SMD) and the related 95% confidence interval (CIs); if the scales are the same, we will also use the weighted mean difference (WMD). For tests using different tools for the same outcome measure, the project will convert all outcomes into a common tool according to Thorlund et al.'s recommendations[58]. If *p* value, *t* value, CIs, range, or standard error (SE) are reported in the trials and meta-analysis, the project will use the method recommended by the Cochrane manual to estimate the missing standard deviation (MSD)[45].

4.1 Direct comparison

The project will use the DerSimonian-Laird random-effects model to conduct standard pairwise meta-analyses (for at least two studies) for all outcomes[59]. The Q statistic and I^2 were used to evaluate the statistical heterogeneity. Each direct comparison will report study and patient characteristics, risk of bias, and aggregate estimates of related outcomes.

4.2 Indirect comparison

This project will settle inconsistency by comparing direct evidence with indirect evidence of efficacy hierarchy, and use the Wald test to test any statistical difference between direct and indirect estimates[60]. The project will report the probability of each DTP efficacy level. After using a rankogram to show rank probability, the SUCRA value will be used to explain the comparative efficacy of the DTP (a SUCRA value of 100 is the best and 0 the worst). The software package R, version 3.4.3, will be applied for statistical analysis.

5. Quality of evidence assessment

The project will use GRADE to rate the quality of both direct and indirect evidence and will classify the evidence as “high”, “moderate”, “low”, or “very low”. The

starting point for RCT quality of evidence is very high, yet could be downgraded due to risk of bias, imprecision, inconsistency, indirectness, and publication bias according to GRADE.

6. Subgroup and sensitivity analysis

This project will adopt subgroup and sensitivity analysis to test six hypotheses: 1) compared with the trials with low risk of bias, trials with high risk of bias will show a greater effect size; 2) occupational groups such as medical staff, military, or police will show a smaller effect size than the civilian samples for the same DTP; 3) RCT or meta-analysis of formal diagnosis will show less efficacy than those with informal diagnosis; 4) the longer the follow-up period, the smaller the DTP efficacy; and 5) the efficacy of DTPs with the participation of therapists is better than that of those without therapists; and 6) different trauma events may trigger different levels of symptom severity (and duration); for instance, public health emergencies may have a stronger influence than one-off events such as earthquakes.

7. Patient and Public Involvement

No patient or public involved.

Ethics and dissemination

No ethics approval is needed in this protocol study. The network meta-analysis results of this project will be disseminated to organisations supporting PTSD patients and hospitals with psychiatry or psychology departments.

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Author's Contribution He (Longtao) conceived the project design and drafted the article. Geng and Tian assisted with design and revision. He (Longtao) and Tian will conduct most data abstraction and the risk-of-bias assessment. Tian, Geng, and Pan participated in the design of data synthesis and analysis. Geng, He (Xinyu), and Pan will conduct statistical analysis. All authors have agreed to publish this protocol.

Funding Statement This research was funded by the Youth Project of Humanities and Social Sciences (project No.: 20XJC840001) of the MOE (Ministry of Education in China).

Disclaimer This funder has no role in the protocol design, the writing of the protocol, or the decision to submit the protocol.

Competing interests statement The Author(s) declare(s) that there is no conflict of interest.

Patient consent Not required.

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Reporting checklist for protocol of a systematic review.

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		Reporting Item	Page Number
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	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	n/a
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page 1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	Title page 2
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	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	17-22
Sponsor	#5b	Provide name for the review funder and / or sponsor	Title page 2
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	Title page 2
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3-9
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	9
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	10-11
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	10
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	10
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	12
Study records - 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)	12-13
Study records - data	#11c	Describe planned method of extracting data from reports (such as	12-13

collection process		piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	
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	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	13-14
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	14
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	15
Data synthesis	#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 I2, Kendall's τ)	15
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	15
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	15
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	16
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	16

Notes:

- 3a: Title page 1
- 3b: Title page 2
- 5b: Title page 2
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BMJ Open

Study protocol for network meta-analysis of digital-technology-based psychotherapies for PTSD in adults

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038951.R1
Article Type:	Protocol
Date Submitted by the Author:	24-Jun-2020
Complete List of Authors:	he, longtao; Southwestern University of Finance and Economics, Research Institute of Social Development Geng, Yanling; Northwest University, Department of Social Work Pan, Yangu; Southwest University of Finance and Economics, Research Institute of Social Development Tian, Jinhui; Lanzhou University, Evidence-Based Medicine Centre & School of Basic Science he, xinyu; Xihua University, School of Social Development
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Evidence based practice
Keywords:	MENTAL HEALTH, THERAPEUTICS, Depression & mood disorders < PSYCHIATRY

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Study protocol for network meta-analysis of digital-technology-based psychotherapies for PTSD in adults

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Abstract

Introduction Post-traumatic stress disorder (PTSD) is a type of stress disorder common among adults who have been exposed to various forms of trauma events. Studies on various types of digital-technology-based psychotherapies (DTPs) have indicated that they are effective for PTSD symptom relief among adults, and more accessible than face-to-face therapies, for multiple reasons. The intervention efficacy or effectiveness hierarchy, however, is still not clear. Therefore, we propose to conduct a network meta-analysis to assess the relative effectiveness of various types of therapies based on digital technology for PTSD in adults, and establish the differential effectiveness of these therapies in terms of symptom reduction.

Methods and Analyses We will search an array of databases for relevant studies, mainly in English and Chinese (as we plan to conduct a trial on PTSD patients in Wuhan, China, based on the results of this network meta-analysis). Randomised controlled trials (RCTs) and meta-analyses investigating the effectiveness of any DTP for PTSD patients (clinically diagnosed or self-diagnosed) for any controlled condition will be included. The number of intervention sessions and the research

duration are unlimited; the effects for different durations will be tested via sensitivity analysis. For this project, the primary measure of outcome will be PTSD symptoms at the end of treatment using endpoint scores for PTSD scales. Secondary outcome measures will include (1) dropout rate; (2) effectiveness at longest follow-up, but not more than 12 months; and (3) patients' functional recovery ratio (such as the return-to-work ratio or percentage of sick leave). Bayesian network meta-analysis will be conducted for all relative outcome measures. We will perform subgroup analysis and sensitivity analysis to see whether the results are influenced by study characteristics. The Grading of Recommendations, Assessments, Development, and Evaluation (GRADE) framework will be adopted to evaluate the quality of evidence contributing to network estimates of the primary outcome.

Ethics and dissemination The researchers of the primary trials will have already had ethical approval for the data used in our study.

PROSPERO registration number CRD42020173253

Strengths and limitations of this study

- Network meta-analysis can compare various types of digital-technology-based psychotherapy for PTSD among adults by integrating indirect and direct comparisons to establish the relative effectiveness of treatments.
- Potential moderators for effectiveness can be found through subgroup and sensitivity analysis.

- The project will use the Cochrane risk-of-bias tool to assess the degree of bias of the studies included, and adopt the GRADE framework to evaluate the quality of evidence for network estimates of the primary outcome.
- Trials and meta-analyses in which patients with comorbidities might increase risk of bias will be included even though this broadens the pooled sample; this impact will be examined through relevant subgroup analysis.
- The lack of an evidence base for psychotherapies delivered through smartphone apps in general limits the probability of an RCT having been conducted on them and thereby hinders the search for relevant studies with a high quality of evidence.

Keywords

PTSD; digital-technology-based psychotherapy; network meta-analysis

Introduction

The outbreak of COVID-19 starting in China has spawned a wide range of reflections on psychological distress in the face of a national and global trauma event. It has been found that public health outbreaks are likely to induce post-traumatic stress disorder among a wide range of people, especially in the context of nationwide quarantine[1, 2, 3]. According to the American Psychological Association's *Diagnostic and Statistical Manual of Mental Disorders 5* (DSM-5), post-traumatic stress disorder (PTSD) usually features four symptom groups: (1) relived experiences of the trauma (such as nightmares and flashbacks), often invasive; (2) persistent hyperreaction (such as insomnia, difficulty concentrating, and increased startle reflex); (3) active avoidance of things related to the traumatic event; and (4) negative cognition and behaviours (loss of social function, absence from work, etc.) that were initiated by the trauma or that worsened after it[4–6].

Although the debate on which treatments work the best is ongoing[7, 8], the world's five most prestigious professional organisations have all claimed that psychotherapies are significantly effective for PTSD symptom relief[9–13]. Three of them clearly stated that psychotherapies, especially exposure psychotherapies, are much more effective than drug therapies[11–13]. There are many factors or barriers that may interfere with a patient's access to necessary and appropriate psychotherapies for PTSD, such as cost (travel expenses, childcare, professional charges for face-to-face psychotherapies, and time investment in travel), limited physical mobility, lack of transportation, fear of being ostracised or stigmatised for

having a mental illness, and the lack of qualified psychotherapists[14–20]. These barriers have prompted interest in new ways of delivering effective psychotherapies and in new (digital) technologies for doing so[21].

Digital-technology-based psychotherapy (DTP) usually uses internet-based platforms such as Web-based services or PC or smartphone apps to deliver psychotherapies to patients, which may potentially compensate for many of the abovementioned disadvantages of traditional face-to-face psychotherapies[22, 23]. Various studies have also confirmed several disadvantages, such as a higher dropout rate, increased risk of leaking of patient information, a lower level of patient participation in the programme, and requiring patients to acquire technical skills[24–26]. During a public health outbreak the use of digital technology is more appropriate than face-to-face therapies for PTSD patients, who are often resistant to face-to-face contact due to fear of imagined infection, even long after the trauma event[2, 27, 28]. For other kinds of mental illnesses, such as anxiety disorder and depression, the effectiveness of DTP has been well studied and confirmed[6]. However, research on DTP for PTSD has only begun to emerge in recent years. For example, a systematic review of DTP for PTSD in veterans found that in most instances, DTP was as effective as traditional face-to-face interventions in reducing PTSD symptoms[24, 29].

Three weaknesses were identified in the existing systematic reviews and meta-analyses on the effectiveness of DTP for PTSD (e.g.,[30–36]). First, the trials included are not comprehensive. Most of the meta-analyses only focused on cognitive

behavioural therapy (CBT) trials (e.g.,[7, 37]). Also, in all the meta-analyses the criteria for trauma event types did not include public health outbreaks such as SARS and Ebola. Additionally, smartphone-app-based psychotherapies were excluded in most meta-analyses (e.g.,[19, 38]). In a 2016 study a search of the smartphone app stores (in English) turned up 28 apps essentially targeted at PTSD symptom relief or general education on PTSD[39]. We conducted a search of the Chinese Android app store and found one mindfulness app targeting PTSD symptom relief and another 10 apps providing general mental health information that includes PTSD as a subcategory. PTSD Coach, an English-language app, has been used in 106 countries and downloaded more than 350,000 times (the most for any app targeted at PTSD symptom relief) as of March 2018[40]; two trials evaluated its effectiveness and both found no significant effects in favour of intervention versus the control group[41, 42]. Indeed, like PTSD Coach, many mental health apps are not evidence-based, and this would be considered as one limitation of this study[43].

Second, the trials examined had very high heterogeneity or high risk of bias, so the quality of evidence is questionable[7, 37]. Third, most of meta-analyses focused on the effects of certain specific psychotherapies rather than exploring the comparative effectiveness of different DTPs (e.g.,[17, 19, 30–36, 44]). For instance, Olthuis et al.'s meta-analysis confirmed that DTP was more effective when compared to effects on the waiting control group, and did not compare effectiveness among various types of DTP[19]. Moreover, the effectiveness of DTP for PTSD patients compared to traditional face-to-face psychotherapy has also been questioned. Several

scholars concluded that the effectiveness of DTP cannot be confirmed due to the lack of sufficient comparative effectiveness evidence with face-to-face therapies for PTSD[34, 45]. Furthermore, not only has the effect-size classification for various types of DTP for PTSD not been confirmed, we also found that the recommendation hierarchy for various forms of traditional face-to-face psychotherapy for PTSD is inconsistent among the guidelines for the treatment of PTSD in adults from the five prestigious organisations mentioned above. Three of these organisations strongly recommended DTP but generally classified all kinds of DTP into a single treatment group[9–13].

As a newly developed method, network meta-analysis, through appropriate research design, can easily fill the gaps identified above. Although the assumptions of network meta-analysis are similar to those of regular meta-analysis, the key additional assumptions are transitivity (no effect-modifying factors affecting indirect comparison) and coherence (direct and indirect effect estimates are similar)[6]. Therefore, network meta-analysis can integrate direct evidence from comparative studies of different interventions and indirect evidence from studies of individual interventions with common control conditions, and assess the effectiveness hierarchy among various interventions[46]. This method can provide meaningful evidence for clinical practice guides by comparing multiple treatments at the same time[47]. By also using the Grading of Recommendations, Assessments, Development, and Evaluation (GRADE) framework to rate the quality of evidence synthesised through network meta-analysis, the aim of this research is to provide high-quality clinical guidance on DTP for PTSD

in adults[48].

Research on traditional PTSD psychotherapy through network meta-analysis is very limited. For example, a network meta-analysis in 2019 compared the effectiveness of different psychotherapies for PTSD[49]. However, the study focused on young people, not adult patients, and the psychotherapies were not based on digital technology. Network meta-analysis of traditional psychotherapies for PTSD in adults is also limited. There are no such studies published in Chinese[50] and only a few articles on research conducted in China published in English[6, 38, 51–53]. One study concentrated on traditional face-to-face psychotherapy, with very outdated data extraction (January 2011)[6]; another article compared the effectiveness of different traditional psychotherapies and conducted a subgroup analysis between patients with clinical diagnosis and those without[51]. Network meta-analysis research on digital-technology-based PTSD psychotherapy for adults is even more limited. Moreover, these studies also present inconsistencies with the guidelines mentioned above. For example, a network meta-analysis of DTP indicated that the effectiveness of various psychotherapies, such as cognitive behavioural therapy, comfort counselling, and eye movement desensitisation and reprocessing, does not significantly differ between them, and most of the trials included had a low quality of evidence[52]. Two research protocols of network meta-analysis published in 2018 advocated for examination of the comparative effectiveness of different DTPs for PTSD in adults[38, 48].

Therefore, we endeavour to conduct a network meta-analysis of studies on

digital-technology-based psychotherapies for PTSD in adults, specifically studies that incorporate trials in a comprehensive manner and with special consideration for quality of evidence, in order to better compare relative effectiveness for different DTPs (including an effectiveness comparison with traditional face-to-face psychotherapies) and establish the differential effectiveness of these therapies for symptom reduction.

Methods

This network meta-analysis will be conducted in accordance with the PRISMA-P checklist[54].

1. Search strategy

L. He and Geng will search Embase, CINAHL, MEDLINE, HealthSTAR, the Cochrane Library, PsycINFO, PubMed, the Chinese biomedical literature database, clinical trials (e.g., ClinicalTrials.gov), and other academic platforms for studies on various DTPs for PTSD in adults, mainly in English and Chinese, using the keywords and phrases detailed in Table 1. The studies included will be randomised controlled trials (RCTs) and systematic meta-analyses on DTPs for PTSD (some meta-analyses may have included RCTs we did not find otherwise). An experienced medical librarian will be consulted to improve the search strategy for each database, and any differences will be resolved through discussion; in case of disagreement we will consult another expert.

Table 1. Search strategy for databases

Search Lines	Search Items	Filter
Line 1	(post-trauma* OR posttrauma*) OR PTSD AND (stress OR disorder)	Title/Abstract
Line 2	(web* OR tele* OR computer* OR Mobile* OR internet* OR digital* OR remote* OR distance* OR e* OR online* OR on-line* OR smartphone* OR smart-phone* OR virtual* OR avatar* OR app*) AND (psychotherap* OR therap* OR treat* OR intervention* OR self-help OR exposure* OR CBT OR psychodynamic* OR pscychoeducation* OR eye movement desensitization and reprocessing OR eye movement desensitisation and reprocessing EMDR OR narrative exposure OR NET OR trauma-focused* OR trauma-focussed OR prolonged exposure OR cognitive processing OR cognitive therapy OR CT OR none-trauma-focused* OR non-trauma-focussed OR present-centred* OR mindfulness OR yoga OR relaxation* OR supportive counsellingOR supportive counseling OR counselling OR counseling OR brief eclectic therapy OR BET OR cCBT OR iCBT OR i-therapy OR e-therapy OR itherapy OR etherapy)	Title/Abstract

2. Selection Criteria

2.1 Inclusion criteria:

- The patients recruited in an individual RCT or in RCTs in meta-analyses are adults diagnosed with primary or secondary PTSD (according to DSM-III, IV, and V, the International Classification of Diseases, and other similar standards);

- Trauma events will include all types, with special attention to public health outbreaks;
- The diagnosis may be either clinical diagnosis (e.g., using the Clinician-Administered PTSD Scale [CAPS] according to DSM-IV) or self-diagnosis (e.g., using the Post-Traumatic Stress Disorder Checklist—Civilian Version [PCL-C]); the efficacy of independent studies with informal diagnosis will be tested via sensitivity analysis;
- The study of secondary PTSD must focus on the treatment of PTSD;
- If the PTSD patients recruited in the RCT also suffer from other comorbidities, such as physical disease, they will be included in the database, and these groups of patients will be tested via sensitivity analysis;
- DTP will include various technologies (e.g., Web-based services, PC and smartphone apps), but there must be elements of interaction between programmes and patients;
- The selection of various types of psychotherapy is mainly based on the comprehensive analysis of PTSD therapy guidelines of the five world's most prestigious professional societies and organisations mentioned above (see Figure 1), along with types of control group;
- The research duration is unlimited, but the effects for different durations will be tested by subgroup analysis. The number of DTP sessions is also unlimited.

2.2 Exclusion Criteria:

- The RCT has an intervention group or control group of fewer than 10 participants (of the five organisations, NICE and VA/DoD guidelines exclude RCTs with fewer than 10 participants[11, 13]; we think adopting this exclusion criterion is an appropriate way to increase quality of evidence);
- It is a pilot study, feasibility study, or crossover trial;
- The recruitment criteria are for severe PTSD, which includes excessively high intent to commit suicide, high dissociative disorder, severe mania, and psychosis;
- If a small number of participants in an RCT meet the above exclusion criteria, we will try our best to abstract and exclude the data of those independent participants and include the trial; if we are not able to exclude these individual data but the number of these participants does not exceed 20% of the total enrolled, the trial will still be included.

3. Data Extraction and Bias Analysis

3.1 Data extraction

a. *RCT and meta-analysis data extraction:* In order to ensure the reliability of independent data extraction, a data extraction Excel form will be designed and the following calibration exercises will be conducted among project researchers (L. He,

Tian, and Pan). The data extraction form will include study characteristics (first author, year of publication, source of funding, and so on) and patient and trial characteristics such as patient demographic information (age in years, gender, occupation, absence/presence of disability, type of trauma, and absence/presence of related comorbidity), sample size, and intervention- and control-group characteristics. Finally, type of trauma will be regarded as a dichotomous nominal variable between health-related and non-health-related type.

b. *Individual patient data provided by RCT and meta-analysis authors:* If the complete data cannot be downloaded from the database, the authors of the selected trials or studies will be contacted and asked to share their individual patient data (including baseline measurement and other information); the corresponding author will be contacted first, and if not available, the other authors will be contacted in turn; if there is no response from the authors within two weeks, a second email will be sent; if there is no response within one month from any of the authors contacted, the RCT or meta-analysis will only be included in the analysis at the aggregate data level. Two researchers (L. He and Geng) will separately test the consistency of the individual patient data with the data summary published in the article. The validity of this project would be compromised if the trials with individual patient data were systematically and statistically different from those without. Therefore, we will divide data into two groups for analysis according to source origin, and compare the differences between the two groups; if there are statistical differences, we will include this result in our later assessment of quality of evidence.

3.2 Primary outcome measure

In this project, PTSD symptoms at the end of treatment using endpoint scores for PTSD scales are extracted as the primary outcome measure (various professional PTSD scales are acceptable). If the patient has more than one outcome measure from these scales, the project will select the most common, most effective, or most accurate one according to the sequence shown in Figure 2. If there are different outcome raters in a study, we will choose the results of self-checking by patients themselves because they are generally more conservative than those measured by clinicians. If the two studies use different outcome measures, we will use the established conversion algorithms to convert one or both of them to the most commonly used scale, for instance the first one in Figure 2[55]. If the outcome is a dichotomy variable, the authors of the RCT study or meta-analysis will be contacted and asked to provide relevant primary data; if there is no response, the study will not be considered.

3.3 Secondary outcome measures

Secondary outcome measures include (1) dropout rate—the rate of patients who discontinued the trial for any reason at any time before the end of trial; (2) effectiveness at the longest follow-up period, but not more than 12 months; (3) patients' functional recovery ratio (such as the return-to-work ratio or percentage of sick leave).

3.4 Risk of bias

The project will use the Cochrane risk-of-bias tool, version 2.0, to assess the degree of bias of the study (as being at unclear risk of bias, low risk of bias, or high risk of bias) by assessing random sequence generation, allocation concealment, blinding of participants, blinding of personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting[56].

4. Data synthesis and analysis

Bayesian network meta-analysis will be conducted for all outcome measures[57]. For dichotomous outcomes (e.g., the disappearance ratio of a symptom), the project will calculate the odds ratio (OR) using the baseline risk estimates of the high-quality control group, as well as the relevant 95% confidence interval (CIs); if the sample pool is big enough, absolute risk (AR) will also be calculated. For continuous outcomes (such as severity of PTSD or quality-of-life scale score), if the scales are different, the project will calculate the standard mean difference (SMD) and the related 95% confidence interval (CIs); if the scales are the same, we will also use the weighted mean difference (WMD). For tests using different tools for the same outcome measure, the project will convert all outcomes into a common tool according to Thorlund et al.'s recommendations[58]. If *p* value, *t* value, CIs, range, or standard error (SE) are reported in the trials and meta-analysis, the project will use the method

recommended by the Cochrane manual to estimate the missing standard deviation (MSD)[38].

4.1 Direct comparison

The project will use the DerSimonian-Laird random-effects model to conduct standard pairwise meta-analyses (for at least two studies) for all outcomes[59]. The Q statistic and I^2 will be used to evaluate the statistical heterogeneity. Each direct comparison will report study and patient characteristics, risk of bias, and aggregate estimates of related outcomes.

4.2 Indirect comparison

This project will settle inconsistency by comparing direct evidence with indirect evidence of differential effectiveness of various treatments, and use the Wald test to test any statistical difference between direct and indirect estimates[60]. The project will report the probability of each DTP effectiveness level. After using a rankogram to show rank probability, the SUCRA value will be used to explain the comparative effectiveness of the DTP (a value of 100 is the best and 0 the worst). The software package R, version 3.4.3, will be applied for statistical analysis.

5. Quality of evidence assessment

The project will use GRADE to rate the quality of both direct and indirect evidence and will classify the evidence as “high”, “moderate”, “low”, or “very low”. The starting point for RCT quality of evidence is very high, yet could be downgraded due to risk of bias, imprecision, inconsistency, indirectness, and publication bias according to GRADE.

6. Subgroup and sensitivity analysis

This project will adopt subgroup and sensitivity analysis to test eight hypotheses: 1) trials with high risk of bias, compared with those with low risk, will show a greater effect size; 2) occupational groups such as medical staff, military, or police will show a smaller effect size than the civilian samples for the same DTP; 3) RCT or meta-analysis of formal diagnosis will show less effectiveness than those with informal diagnosis; 4) the longer the follow-up period, the smaller the DTP effectiveness; 5) the effectiveness of DTPs with the participation of therapists is better than that of those without therapists; 6) different trauma events may trigger different levels of symptom severity (and duration); for instance, public health emergencies may have a stronger influence than one-off events such as earthquakes; 7) the longer the duration of the treatment period, the greater the DTP’s effectiveness; and 8) studies on patients with comorbidities may contain a high risk of bias compared to those on patients without.

7. Patient and Public Involvement

No patients or members of the public are involved.

8. Study Status

We will officially commence data extraction in early July 2020 and finish at the end of that month. We will start our analysis from the beginning of August and expect to complete it within five months.

Ethics and dissemination

No ethics approval is needed in this protocol study. The network meta-analysis results of this project will be disseminated to organisations supporting PTSD patients and hospitals with psychiatry or psychology departments.

Author's Contribution L. He conceived the project design and drafted the article. Geng and Tian assisted with design and revision. L. He and Tian will conduct most of the data abstraction and the risk-of-bias assessment. Tian, Geng, and Pan participated in the design of data synthesis and analysis. Geng, X. He, and Pan will conduct the statistical analysis. All authors have agreed to publish this protocol.

Funding Statement This research was funded by the Youth Project of Humanities and Social Sciences (project no. 20XJC840001) of the MOE (Ministry of Education) in China.

Disclaimer This funder has no role in the protocol design, the writing of the protocol, or the decision to submit the protocol.

Competing interests statement The Author(s) declare(s) that there is no conflict of interest.

Patient consent Not required.

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Figure Captions

Figure1: Description of Psychotherapies and Control Conditions

Figure 2: Primary Outcome Hierarchy

Figure 1: Description of Psychotherapies and Control Conditions

Type of Psychotherapy	Abbrev.	Brief Description
Exposure-Based Psychotherapy		
Trauma-Focused Cognitive Bhavioural Therapy (undifferentiated)	TF-CBT	Implemented through cognitive remodelling and behavioural change techniques; focuses on trauma, and usually deals with trauma-related thoughts and behaviours through exposure-to-trauma situations or cognition.
Prolonged Exposure Therapy	PET	Uses specific methods to guide patients to gradually make contact and deal with cognitive thoughts, behaviours, and scenes about trauma.
Narrative Exposure Therapy	NET	Encourages the patients to focus on the traumatic events and piece together a coherent life story to deal with the fragmentation of life memories caused by trauma.
Eye Movement Desensitisation and Reprocessing	EMDR	Pays less attention to the traumatic event itself than to the disturbing emotions and thoughts caused by the event. Treatment involves the therapist using techniques to guide the patient's eye movement from side to side.
Cognitive Processing Therapy	CPT	Socratic questioning often used to help patients learn how to challenge their misconceptions and behaviours around trauma. Written assignments may be given to encourage patients to develop new cognitive skills.
Cognitive Therapy	CT	Focuses solely on challenging patients' old ways of thinking about trauma from a cognitive perspective.
Non-Exposure-Based Psychotherapy		
Non-Trauma-Focused Cognitive Behavioural Therapy	NTF-CBT	Implemented through cognitive remodeling and behavioural change techniques; the focus is not on trauma itself but rather on behaviour and cognition.
Present-Centred Therapy (mindfulness)	PCT	Instructs patients to learn skills for focusing on the "present" and letting go of bad memories from the past.
Relaxation Therapy	RT	Mainly uses a series of relaxation methods, such as deep breathing, to teach patients to deal with the recurrence of traumatic memories.
Supportive Counselling	SC	The therapist mainly provides emotional support, listening to the patient's difficulties, sadness, etc.
Brief Eclectic Therapy	BET	Integrates CBT, SC, and other treatment techniques to treat patients over a short period of time.
Psychodynamic Therapy	PDT	Focuses mainly on revealing how the past (e.g., unresolved conflicts, dysfunctional relationships) affects present behaviours, and thereby helps the clients to obtain self-awareness.
Psychoeducation	PE	Treats patients by enhancing their understanding of PTSD.
Control Group		
Treatment as Usual	TAU	Refers to the usual treatment method at the research site, which may contain many components of psychointerventions, as well as drug treatment.
Waitlist	WL	Patients do not receive any treatment during the study but will receive treatment after the study.
No Treatment	NT	Patients receive no treatment during or after the study.
Active Therapeutic Treatment	ATT	Patients receive some kind of traditional face-to-face psychotherapeutic intervention.
Digital-Technology-Based Active Therapeutic Treatment	DTATT	Patients receive some kind of psychotherapy based in digital technology.

Figure 1: Descriptions of Psychotherapies and Control Conditions

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Figure 2: Primary Outcome Hierarchy

Ranking	Name	Abbrev.	Brief Introduction
1	PTSD Checklist —Civilian Version	PCL-C	According to DSM-5's diagnostic criteria for PTSD, 17 items were designed to measure the symptoms of PTSD. The descriptive categories are numerically coded, and a sum score (or alternatively, symptom indicators) for using the DSM criteria for diagnosis will be used.
2	Post-Traumatic Stress Disorder Self-Rating Scale	PTSD-SS	This consists of 24 items including 17 standard symptoms of PTSD, and adopts a five-level scoring method.
3	Clinician-Administered PTSD Scale for DSM-5	CAPS-5	According to DSM-5's diagnostic criteria for PTSD, clinicians conduct structured interviews to measure the symptoms of PTSD by asking structured questions and numerically code each into categories.
4	PTSD Symptom Scale – Interview	PSS-I	The questionnaire is composed of 17 standard items regarding the symptoms of PTSD, and is graded according to four grades of 0–3. The completion time is about 20 minutes.
5	Impact of Event Scale —Revised	IES-R	The scale contains 22 questions that are related to PTSD symptoms. Each question is graded from 0 to 4. The sum score can be clinically meaningful (PTSD becomes a clinical concern) if it exceeds 24.
6	Post-Traumatic Diagnosis Scale	PTDS	The first 12 items examine the possible traumatic events that individuals may have suffered. The frequency of each symptom over the past 30 days is then assessed using a four-level grading of 17 types of symptoms.
7	PTSD Checklist —Veteran Version	PCL-V	According to DSM-5's diagnostic criteria for PTSD, 17 items were designed to measure the symptoms of PTSD among veterans.
8	Penn Inventory for Post-Traumatic Stress Disorder	PIP	There are 26 items for accident victims and veterans to measure PTSD symptoms using a sum score.
9	Other Types of Scale		

Figure 2: Primary Outcome Hierarchy

210x267mm (300 x 300 DPI)

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

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		Reporting Item	Page Number
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	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	n/a
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page 1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	Title page 2
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	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	17-22
Sponsor	#5b	Provide name for the review funder and / or sponsor	Title page 2
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	Title page 2
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3-9
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	9
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	10-11
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	10
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	10
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	12
Study records - 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)	12-13
Study records - data	#11c	Describe planned method of extracting data from reports (such as	12-13

collection process		piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	
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	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	13-14
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	14
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	15
Data synthesis	#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 I2, Kendall's τ)	15
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	15
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	15
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	16
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	16

Notes:

- 3a: Title page 1
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BMJ Open

Study protocol for a network meta-analysis of digital-technology-based psychotherapies for PTSD in adults

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038951.R2
Article Type:	Protocol
Date Submitted by the Author:	11-Sep-2020
Complete List of Authors:	he, longtao; Southwestern University of Finance and Economics, Research Institute of Social Development Geng, Yanling; Northwest University, Department of Social Work Pan, Yangu; Southwest University of Finance and Economics, Research Institute of Social Development Tian, Jinhui; Lanzhou University, Evidence-Based Medicine Centre & School of Basic Science he, xinyu; Xihua University, School of Social Development
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Evidence based practice
Keywords:	MENTAL HEALTH, THERAPEUTICS, Depression & mood disorders < PSYCHIATRY

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Study protocol for a network meta-analysis of digital-technology-based psychotherapies for PTSD in adults

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Abstract

Introduction Studies on various types of digital-technology-based psychotherapies (DTPs) have indicated that they are effective for PTSD symptom relief among adults. The intervention efficacy or effectiveness hierarchy, however, is still not clear. Therefore, we propose to conduct a network meta-analysis to assess the relative effectiveness of various types of DTPs. We aim to establish the differential effectiveness of these therapies in terms of symptom reduction and provide high-quality evidence for treating PTSD.

Methods and Analyses We will search Embase, CINAHL, MEDLINE, HealthSTAR, the Cochrane Library, PsycINFO, PubMed, the Chinese biomedical literature database, clinical trials (e.g., ClinicalTrials.gov), and other academic platforms for relevant studies, mainly in English and Chinese (as we plan to conduct a trial on PTSD patients in Wuhan, China, based on the results of this network meta-analysis). Randomised controlled trials (RCTs) and meta-analyses investigating the effectiveness of any DTPs for PTSD patients for any controlled condition will be included. The number of intervention sessions and the research duration are unlimited;

the effects for different durations will be tested via sensitivity analysis. For this project, the primary measure of outcome will be PTSD symptoms at the end of treatment using raw scores for one widely used PTSD scale, PCL-C. Secondary outcome measures will include (1) dropout rate; (2) effectiveness at longest follow-up, but not more than 12 months; and (3) patients' functional recovery ratio (such as the return-to-work ratio or percentage of sick leave). Bayesian network meta-analysis will be conducted for all relative outcome measures. We will perform subgroup analysis and sensitivity analysis to see whether the results are influenced by study characteristics. The Grading of Recommendations, Assessments, Development, and Evaluation (GRADE) framework will be adopted to evaluate the quality of evidence contributing to network estimates of the primary outcome.

Ethics and dissemination The researchers of the primary trials will already have had ethical approval for the data used in our study.

PROSPERO registration number CRD42020173253

Strengths and limitations of this study

- Network meta-analysis can compare various types of digital-technology-based psychotherapies for PTSD among adults by integrating indirect and direct comparisons to establish the relative effectiveness of treatments.
- Potential moderators for effectiveness can be found through subgroup and sensitivity analysis.

- The project will use the Cochrane risk-of-bias tool to assess the degree of bias of the studies included, and adopt the GRADE framework to evaluate the quality of evidence for network estimates of the primary outcome.
- Trials and meta-analyses in which patients with comorbidities might increase risk of bias will be included even though this broadens the pooled sample; this impact will be examined through relevant subgroup analysis.
- The lack of an evidence base for psychotherapies delivered through smartphone apps in general limits the probability of an RCT having been conducted on them and thereby hinders the search for relevant studies with a high quality of evidence.

Keywords

PTSD; digital-technology-based psychotherapy; network meta-analysis

Introduction

The outbreak of COVID-19 starting in China has spawned a wide range of reflections on psychological distress in the face of a national and global trauma event. It has been found that public health outbreaks are likely to induce post-traumatic stress disorder among a wide range of people, especially in the context of nationwide quarantine[1, 2, 3]. According to the American Psychological Association's *Diagnostic and Statistical Manual of Mental Disorders 5* (DSM-5), post-traumatic stress disorder (PTSD) usually features four symptom groups: (1) relived experiences of the trauma (such as nightmares and flashbacks), often invasive; (2) persistent hyperreaction (such as insomnia, difficulty concentrating, and increased startle reflex); (3) active avoidance of things related to the traumatic event; and (4) negative cognition and behaviours (loss of social function, absence from work, etc.) that were initiated by the trauma or that worsened after it[4–6].

Although the debate on which treatments work the best is ongoing[7, 8], the world's five most prestigious professional organisations have all claimed that psychotherapies are significantly effective for PTSD symptom relief[9–13]. Three of them clearly stated that psychotherapies, especially exposure psychotherapies, are much more effective than drug therapies[11–13]. There are many factors or barriers that may interfere with a patient's access to necessary and appropriate psychotherapies for PTSD, such as cost (travel expenses, childcare, professional charges for face-to-face psychotherapies, and time investment in travel), limited physical mobility, lack of transportation, fear of being ostracised or stigmatised for

having a mental illness, and the lack of qualified psychotherapists[14–20]. These barriers have prompted interest in new ways of delivering effective psychotherapies and in new (digital) technologies for doing so[21].

Digital-technology-based psychotherapy (DTP) usually uses internet-based platforms such as Web-based services or PC or smartphone apps to deliver psychotherapies to patients, which may potentially compensate for many of the abovementioned disadvantages of traditional face-to-face psychotherapies[22, 23]. Various studies have also confirmed several disadvantages, such as a higher dropout rate, increased risk of leaking of patient information, a lower level of patient participation in the programme, and requiring patients to acquire technical skills[24–26]. During a public health outbreak the use of digital technology is more appropriate than face-to-face therapies for PTSD patients, who are often resistant to face-to-face contact due to fear of imagined infection, even long after the trauma event[2, 27, 28]. For other kinds of mental illnesses, such as anxiety disorder and depression, the effectiveness of DTP has been well studied and confirmed[6]. However, research on DTP for PTSD has only begun to emerge in recent years. For example, a systematic review of DTP for PTSD in veterans found that in most instances, DTP was as effective as traditional face-to-face interventions in reducing PTSD symptoms[24, 29].

Three weaknesses were identified in the existing systematic reviews and meta-analyses on the effectiveness of DTP for PTSD (e.g.,[30–36]). First, the trials included are not comprehensive. Most of the meta-analyses only focused on cognitive

behavioural therapy (CBT) trials (e.g.,[7, 37]). Also, in all the meta-analyses the criteria for trauma event types did not include public health outbreaks such as SARS and Ebola. Additionally, smartphone-app-based psychotherapies were excluded in most meta-analyses (e.g.,[19, 38]). In a 2016 study a search of the smartphone app stores (in English) turned up 28 apps essentially targeted at PTSD symptom relief or general education on PTSD[39]. We conducted a search of the Chinese Android app store and found one mindfulness app targeting PTSD symptom relief and another 10 apps providing general mental health information that includes PTSD as a subcategory. PTSD Coach, an English-language app, has been used in 106 countries and downloaded more than 350,000 times (the most for any app targeted at PTSD symptom relief) as of March 2018[40]; two trials evaluated its effectiveness and both found no significant effects in favour of intervention versus the control group[41, 42]. Indeed, like PTSD Coach, many mental health apps are not evidence-based, and this would be considered as one limitation of this study[43].

Second, the trials examined had very high heterogeneity or high risk of bias, so the quality of evidence is questionable[7, 37]. Third, most of meta-analyses focused on the effects of certain specific psychotherapies rather than exploring the comparative effectiveness of different DTPs (e.g.,[17, 19, 30–36, 44]). For instance, Olthuis et al.'s meta-analysis confirmed that DTP was more effective when compared to effects on the waiting control group, and did not compare effectiveness among various types of DTPs[19]. Moreover, the effectiveness of DTP for PTSD patients compared to traditional face-to-face psychotherapy has also been questioned. Several

scholars concluded that the effectiveness of DTP cannot be confirmed due to the lack of sufficient comparative effectiveness evidence with face-to-face therapies for PTSD[34, 45]. Furthermore, not only has the effect-size classification for various types of DTP for PTSD not been confirmed, we also found that the recommendation hierarchy for various forms of traditional face-to-face psychotherapy for PTSD is inconsistent among the guidelines for the treatment of PTSD in adults from the five prestigious international organisations. Three of these organisations strongly recommended DTP but generally classified all kinds of DTPs into a single treatment group[9–13].

As a newly developed method, network meta-analysis, through appropriate research design, can easily fill the gaps identified above. Although the assumptions of network meta-analysis are similar to those of regular meta-analysis, the key additional assumptions are transitivity (no effect-modifying factors affecting indirect comparison) and coherence (direct and indirect effect estimates are similar)[6]. Therefore, network meta-analysis can integrate direct evidence from comparative studies of different interventions and indirect evidence from studies of individual interventions with common control conditions, and assess the effectiveness hierarchy among various interventions[46]. This method can provide meaningful evidence for clinical practice guides by comparing multiple treatments at the same time[47]. By also using the Grading of Recommendations, Assessments, Development, and Evaluation (GRADE) framework to rate the quality of evidence synthesised through network meta-analysis, the aim of this research is to provide high-quality clinical guidance on DTP for PTSD

in adults[48].

Research on traditional PTSD psychotherapy through network meta-analysis is very limited. For example, a network meta-analysis in 2019 compared the effectiveness of different psychotherapies for PTSD[49]. However, the study focused on young people, not adult patients, and the psychotherapies were not based on digital technology. Network meta-analysis of traditional psychotherapies for PTSD in adults is also limited. There are no such studies published in Chinese[50] and only a few articles on research conducted in China published in English[6, 38, 51–53]. One study concentrated on traditional face-to-face psychotherapy, with very outdated data extraction (January 2011)[6]; another article compared the effectiveness of different traditional psychotherapies and conducted a subgroup analysis between patients with clinical diagnosis and those without[51]. Network meta-analysis research on digital-technology-based PTSD psychotherapy for adults is even more limited. Moreover, these studies also present inconsistencies with the guidelines mentioned above. For example, a network meta-analysis of DTPs indicated that the effectiveness of various psychotherapies, such as cognitive behavioural therapy, comfort counselling, and eye movement desensitisation and reprocessing, does not significantly differ between them, and most of the trials included had a low quality of evidence[52]. Two research protocols of network meta-analysis published in 2018 advocated for examination of the comparative effectiveness of different DTPs for PTSD in adults[38, 48].

Therefore, we endeavour to conduct a network meta-analysis of studies on DTPs

for PTSD in adults, specifically studies that incorporate trials in a comprehensive manner and with special consideration for quality of evidence, in order to better compare relative effectiveness for different DTPs (including an effectiveness comparison with traditional face-to-face psychotherapies) and establish the differential effectiveness of these therapies for symptom reduction.

Methods

This network meta-analysis will be conducted in accordance with the PRISMA-P checklist[54].

1. Search Strategy

L. He and Geng will search Embase, CINAHL, MEDLINE, HealthSTAR, the Cochrane Library, PsycINFO, PubMed, the Chinese biomedical literature database, clinical trials (e.g., ClinicalTrials.gov), and other academic platforms for studies on various DTPs for PTSD in adults, mainly in English and Chinese, using the keywords and phrases detailed in Table 1. The studies included will be randomised controlled trials (RCTs) and systematic meta-analyses on DTPs for PTSD (some meta-analyses may have included RCTs we did not find otherwise). An experienced medical librarian will be consulted to improve the search strategy for each database, and any differences will be resolved through discussion; in case of disagreement we will consult another expert.

Table 1. Search strategy for databases

Search Lines	Search Items	Filter
Line 1	(post-trauma* OR posttrauma*) OR PTSD AND (stress OR disorder)	Title/Abstract
Line 2	(web* OR tele* OR computer* OR mobile* OR internet* OR digital* OR remote* OR distance* OR e* OR online* OR on-line* OR smartphone* OR smart-phone* OR virtual* OR avatar* OR app*) AND (psychotherap* OR therap* OR treat* OR intervention* OR self-help OR exposure* OR CBT OR psychodynamic* OR psychoeducation* OR eye movement desensitization and reprocessing OR eye movement desensitisation and reprocessing EMDR OR narrative exposure OR NET OR trauma-focused* OR trauma-focussed OR prolonged exposure OR cognitive processing OR cognitive therapy OR CT OR non-trauma-focused* OR non-trauma-focussed OR present-centred* OR present-centered OR mindfulness OR yoga OR relaxation* OR supportive counselling OR supportive counseling OR counselling OR counseling OR brief eclectic therapy OR BET OR cCBT OR iCBT OR i-therapy OR e-therapy OR itherapy OR etherapy)	Title/Abstract

2. Selection Criteria

2.1 Inclusion criteria:

- The patients recruited in an individual RCT or in RCTs in meta-analyses are adults diagnosed with primary or secondary PTSD (according to DSM-III, IV, and 5, the International Classification of Diseases, and other similar standards);

- Trauma events will include all types, with special attention to public health outbreaks;
- The study of secondary PTSD must focus on the treatment of PTSD;
- If the PTSD patients recruited in the RCT also suffer from other comorbidities, such as physical disease, they will be included in the database, and these groups of patients will be tested via sensitivity analysis;
- DTP will include various technologies (e.g., Web-based services, PC and smartphone apps), but there must be elements of interaction between programmes and patients;
- The selection of various types of psychotherapy is mainly based on the comprehensive analysis of PTSD therapy guidelines of the five world's most prestigious professional societies and organisations (see Figure 1), along with types of control group;
- The research duration is unlimited, but the effects for different durations will be tested by subgroup analysis; the number of DTP sessions is also unlimited.

2.2 Exclusion criteria:

- The RCT has an intervention group or control group of fewer than 10 participants (of the five organisations, NICE and VA/DoD guidelines exclude RCTs with fewer than 10 participants[11, 13]; we think adopting this exclusion criterion is an

appropriate way to increase quality of evidence);

- It is a pilot study, feasibility study, or crossover trial;
- The recruitment criteria are for severe PTSD, which includes excessively high intent to commit suicide, high dissociative disorder, severe mania, and psychosis;
- If a small number of participants in an RCT meet the above exclusion criteria, we will try our best to abstract and exclude the data of those independent participants and include the trial; if we are not able to exclude these individual data but the number of these participants does not exceed 20% of the total enrolled, the trial will still be included.

3. **Data Extraction and Bias Analysis**

3.1 Data extraction

a. *RCT and meta-analysis data extraction:* In order to ensure the reliability of independent data extraction, a data extraction Excel form will be designed and the following calibration exercises will be conducted among project researchers (L. He, Tian, and Pan). The data extraction form will include study characteristics (first author, year of publication, source of funding, and so on) and patient and trial characteristics such as patient demographic information (age in years, gender, occupation, absence/presence of disability, type of trauma, and absence/presence of related comorbidity), sample size, and intervention- and control-group characteristics. Finally, type of trauma will be regarded as a dichotomous nominal variable between

health-related and non-health-related type.

b. *Individual patient data provided by RCT and meta-analysis authors:* If the complete data cannot be downloaded from the database, the authors of the selected trials or studies will be contacted and asked to share their individual patient data (including baseline measurement and other information); the corresponding author will be contacted first, and if not available, the other authors will be contacted in turn; if there is no response from the authors within two weeks, a second email will be sent; if there is no response within one month from any of the authors contacted, the RCT or meta-analysis will only be included in the analysis at the aggregate data level. Two researchers (L. He and Geng) will separately test the consistency of the individual patient data with the data summary published in the article. The validity of this project would be compromised if the trials with individual patient data were systematically and statistically different from those without. Therefore, we will divide data into two groups for analysis according to source origin, and compare the differences between the two groups; if there are statistical differences, we will include this result in our later assessment of quality of evidence.

3.2 Primary outcome measure

In this project, PTSD symptoms at the end of treatment using raw scores for one of the most widely used PTSD scales are extracted as the primary outcome measure. The scale we chose is PTSD Checklist—Civilian Version (PCL-C). PCL-C contains 17

items designed to measure PTSD symptoms according to DSM-5's diagnostic criteria, based on answers provided by the patients; the descriptive categories are numerically coded, and a sum score (or alternatively, symptom indicators) will be calculated. If the outcome is a dichotomy variable, the authors of the RCT study or meta-analysis will be contacted and asked to provide relevant primary raw scores; if there is no response, the study will not be considered.

3.3 Secondary outcome measures

Secondary outcome measures include (1) dropout rate—the rate of patients who discontinued the trial for any reason at any time before the end of trial; (2) effectiveness at the longest follow-up period, but not more than 12 months; and (3) patients' functional recovery ratio (such as the return-to-work ratio or percentage of sick leave).

3.4 Risk of bias

The project will use the Cochrane risk-of-bias tool, version 2.0, to assess the degree of bias of the study (as being at unclear risk of bias, low risk of bias, or high risk of bias) by assessing random sequence generation, allocation concealment, blinding of participants, blinding of personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting[55, 56].

4. Data Synthesis and Analysis

Bayesian network meta-analysis will be conducted for all outcome measures[57]. For the primary outcome measure, the project will calculate the weighted mean difference (WMD) and the related 95% confidence interval (CI). For the secondary outcome measure, if the tools for the same outcome measure are the same, we will also use the WMD and the related 95% CI[57, 58]; for studies using different tools for the same outcome measure, the project will convert all outcomes into a common tool according to Thorlund et al.'s recommendations, and calculate the standard mean difference (SMD) and the related 95% CI[58]. If *p* value, *t* value, CI, range, or standard error (SE) are reported in the trials and meta-analysis, the project will use the method recommended by the Cochrane manual to estimate the missing standard deviation (MSD)[38].

4.1 Direct comparison

The project will use the DerSimonian-Laird random-effects model to conduct standard pairwise meta-analyses (for at least two studies) for all outcomes[59]. The Q statistic and I^2 will be used to evaluate the statistical heterogeneity. Each direct comparison will report study and patient characteristics, risk of bias, and aggregate estimates of related outcomes.

4.2 Indirect comparison

This project will settle inconsistency by comparing direct evidence with indirect evidence of differential effectiveness of various treatments, and use the Wald test to test any statistical difference between direct and indirect estimates[60]. The project will report the probability of each DTP effectiveness level. After using a rankogram to show rank probability, the SUCRA value will be used to explain the comparative effectiveness of the DTP (a value of 100 is the best and 0 the worst). The software package R, version 3.4.3, will be applied for statistical analysis.

5. Quality of Evidence Assessment

The project will use GRADE to rate the quality of both direct and indirect evidence and will classify the evidence as “high”, “moderate”, “low”, or “very low”. The starting point for RCT quality of evidence is very high, yet could be downgraded due to risk of bias, imprecision, inconsistency, indirectness, and publication bias according to GRADE.

6. Subgroup and Sensitivity Analysis

This project will adopt subgroup and sensitivity analysis to test seven hypotheses: 1) trials with high risk of bias, compared with those with low risk, will show a greater effect size; 2) occupational groups such as medical staff, military, or police will show

a smaller effect size than the civilian samples for the same DTP; 3) the longer the follow-up period, the smaller the DTP effectiveness; 4) the effectiveness of DTPs with the participation of therapists is better than that of those without therapists; 5) different trauma events may trigger different levels of symptom severity (and duration); for instance, public health emergencies may have a stronger influence than one-off events such as earthquakes; 6) the longer the duration of the treatment period, the greater the DTP's effectiveness; and 7) studies on patients with comorbidities may contain a high risk of bias compared to those on patients without.

7. Patient and Public Involvement

No patients or members of the public are involved.

8. Study Status

We will officially commence data extraction in early September 2020 and finish at the end of that month. We will start our analysis from the beginning of October and expect to complete it within five months.

Ethics and Dissemination

No ethics approval is needed in this protocol study. The network meta-analysis results of this project will be disseminated to organisations supporting PTSD patients and

hospitals with psychiatry or psychology departments.

Author's Contribution L. He conceived the project design and drafted the article. Geng and Tian assisted with design and revision. L. He and Tian will conduct most of the data abstraction and the risk-of-bias assessment. Tian, Geng, and Pan participated in the design of data synthesis and analysis. Geng, X. He, and Pan will conduct the statistical analysis. All authors have agreed to publish this protocol.

Funding Statement This research was funded by the Youth Project of Humanities and Social Sciences (project no. 20XJC840001) of the MOE (Ministry of Education) in China.

Disclaimer This funder has no role in the protocol design, the writing of the protocol, or the decision to submit the protocol.

Competing interests statement The Author(s) declare(s) that there is no conflict of interest.

Patient consent Not required.

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Figure Captions

Figure1: Description of Psychotherapies and Control Conditions

Figure 1: Description of Psychotherapies and Control Conditions

Type of Psychotherapy	Abbrev.	Brief Description
Exposure-Based Psychotherapy		
Trauma-Focused Cognitive Behavioural Therapy (undifferentiated)	TF-CBT	Implemented through cognitive remodelling and behavioural change techniques; focuses on trauma, and usually deals with trauma-related thoughts and behaviours through exposure-to-trauma situations or cognition.
Prolonged Exposure Therapy	PET	Uses specific methods to guide patients to gradually make contact and deal with cognitive thoughts, behaviours, and scenes about trauma.
Narrative Exposure Therapy	NET	Encourages the patients to focus on the traumatic events and piece together a coherent life story to deal with the fragmentation of life memories caused by trauma.
Eye Movement Desensitisation and Reprocessing	EMDR	Pays less attention to the traumatic event itself than to the disturbing emotions and thoughts caused by the event. Treatment involves the therapist using techniques to guide the patient's eye movement from side to side.
Cognitive Processing Therapy	CPT	Socratic questioning often used to help patients learn how to challenge their misconceptions and behaviours around trauma. Written assignments may be given to encourage patients to develop new cognitive skills.
Cognitive Therapy	CT	Focuses solely on challenging patients' old ways of thinking about trauma from a cognitive perspective.
Non-Exposure-Based Psychotherapy		
Non-Trauma-Focused Cognitive Behavioural Therapy	NTF-CBT	Implemented through cognitive remodelling and behavioural change techniques; the focus is not on trauma itself but rather on behaviour and cognition.
Present-Centred Therapy (mindfulness)	PCT	Instructs patients to learn skills for focusing on the "present" and letting go of bad memories from the past.
Relaxation Therapy	RT	Mainly uses a series of relaxation methods, such as deep breathing, to teach patients to deal with the recurrence of traumatic memories.
Supportive Counselling	SC	The therapist mainly provides emotional support, listening to the patient's difficulties, sadness, etc.
Brief Eclectic Therapy	BET	Integrates CBT, SC, and other treatment techniques to treat patients over a short period of time.
Psychodynamic Therapy	PDT	Focuses mainly on revealing how the past (e.g., unresolved conflicts, dysfunctional relationships) affects present behaviours, and thereby helps the clients to obtain self-awareness.
Psychoeducation	PE	Treats patients by enhancing their understanding of PTSD.
Control Group		
Treatment as Usual	TAU	Refers to the usual treatment method at the research site, which may contain many components of psychointerventions, as well as drug treatment.
Waitlist	WL	Patients do not receive any treatment during the study but will receive treatment after the study.
No Treatment	NT	Patients receive no treatment during or after the study.
Active Therapeutic Treatment	ATT	Patients receive some kind of traditional face-to-face psychotherapeutic intervention.
Digital-Technology-Based Active Therapeutic Treatment	DTB-ATT	Patients receive some kind of psychotherapy based in digital technology.

Figure1: Description of Psychotherapies and Control Conditions

210x297mm (300 x 300 DPI)

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
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	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	n/a
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page 1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	Title page 2
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	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	17-22
Sponsor	#5b	Provide name for the review funder and / or sponsor	Title page 2
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	Title page 2
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3-9
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	9
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	10-11
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	10
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	10
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	12
Study records - 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)	12-13
Study records - data	#11c	Describe planned method of extracting data from reports (such as	12-13

collection process		piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	
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	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	13-14
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	14
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	15
Data synthesis	#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 I2, Kendall's τ)	15
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	15
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	15
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	16
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	16

Notes:

- 3a: Title page 1
- 3b: Title page 2
- 5b: Title page 2
- 5c: Title page 2 The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution License CC-BY 4.0. This checklist was completed on 27. March 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Study protocol for a network meta-analysis of digital-technology-based psychotherapies for PTSD in adults

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038951.R3
Article Type:	Protocol
Date Submitted by the Author:	15-Oct-2020
Complete List of Authors:	he, longtao; Southwestern University of Finance and Economics, Research Institute of Social Development Geng, Yanling; Northwest University, Department of Social Work Pan, Yangu; Southwest University of Finance and Economics, Research Institute of Social Development Tian, Jinhui; Lanzhou University, Evidence-Based Medicine Centre & School of Basic Science he, xinyu; Xihua University, School of Social Development
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Evidence based practice
Keywords:	MENTAL HEALTH, THERAPEUTICS, Depression & mood disorders < PSYCHIATRY

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Study protocol for a network meta-analysis of digital-technology-based psychotherapies for PTSD in adults

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Abstract

Introduction Studies on various types of digital-technology-based psychotherapies (DTPs) have indicated that they are effective for PTSD symptom relief among adults. The intervention efficacy or effectiveness hierarchy, however, is still not clear. Therefore, we propose to conduct a network meta-analysis to assess the relative effectiveness of various types of DTPs. We aim to establish the differential effectiveness of these therapies in terms of symptom reduction and provide high-quality evidence for treating PTSD.

Methods and Analyses We will search Embase, CINAHL, MEDLINE, HealthSTAR, the Cochrane Library, PsycINFO, PubMed, the Chinese biomedical literature database, clinical trials (e.g., ClinicalTrials.gov), and other academic platforms for relevant studies, mainly in English and Chinese (as we plan to conduct a trial on PTSD patients in Wuhan, China, based on the results of this network meta-analysis), from inception to October 2020. Randomised controlled trials (RCTs) and meta-analyses investigating the effectiveness of any DTPs for PTSD patients for any controlled condition will be included. The number of intervention sessions and the research

duration are unlimited; the effects for different durations will be tested via sensitivity analysis. For this project, the primary measure of outcome will be PTSD symptoms at the end of treatment using raw scores for one widely used PTSD scale, PCL-5. Secondary outcome measures will include (1) dropout rate; (2) effectiveness at longest follow-up, but not more than 12 months; and (3) patients' functional recovery ratio (such as the return-to-work ratio or percentage of sick leave). Bayesian network meta-analysis will be conducted for all relative outcome measures. We will perform subgroup analysis and sensitivity analysis to see whether the results are influenced by study characteristics. The Grading of Recommendations, Assessments, Development, and Evaluation (GRADE) framework will be adopted to evaluate the quality of evidence contributing to network estimates of the primary outcome.

Ethics and dissemination The researchers of the primary trials will already have had ethical approval for the data used in our study.

PROSPERO registration number CRD42020173253

Strengths and limitations of this study

- Network meta-analysis can compare various types of digital-technology-based psychotherapies for PTSD among adults by integrating indirect and direct comparisons to establish the relative effectiveness of treatments.
- Potential moderators for effectiveness can be found through subgroup and sensitivity analysis.

- The project will use the Cochrane risk-of-bias tool to assess the degree of bias of the studies included, and adopt the GRADE framework to evaluate the quality of evidence for network estimates of the primary outcome.
- Trials and meta-analyses in which patients with comorbidities might increase risk of bias will be included even though this broadens the pooled sample; this impact will be examined through relevant subgroup analysis.
- The lack of an evidence base for psychotherapies delivered through smartphone apps in general limits the probability of an RCT having been conducted on them and thereby hinders the search for relevant studies with a high quality of evidence.

Keywords

PTSD; digital-technology-based psychotherapy; network meta-analysis

Introduction

The outbreak of COVID-19 starting in China has spawned a wide range of reflections on psychological distress in the face of a national and global trauma event. It has been found that public health outbreaks are likely to induce post-traumatic stress disorder among a wide range of people, especially in the context of nationwide quarantine[1, 2, 3]. According to the American Psychological Association's *Diagnostic and Statistical Manual of Mental Disorders 5* (DSM-5), post-traumatic stress disorder (PTSD) usually features four symptom groups: (1) relived experiences of the trauma (such as nightmares and flashbacks), often invasive; (2) persistent hyperreaction (such as insomnia, difficulty concentrating, and increased startle reflex); (3) active avoidance of things related to the traumatic event; and (4) negative cognition and behaviours (loss of social function, absence from work, etc.) that were initiated by the trauma or that worsened after it[4–6].

Although the debate on which treatments work the best is ongoing[7, 8], the world's five most prestigious professional organisations have all claimed that psychotherapies are significantly effective for PTSD symptom relief[9–13]. Three of them clearly stated that psychotherapies, especially exposure psychotherapies, are much more effective than drug therapies[11–13]. There are many factors or barriers that may interfere with a patient's access to necessary and appropriate psychotherapies for PTSD, such as cost (travel expenses, childcare, professional charges for face-to-face psychotherapies, and time investment in travel), limited physical mobility, lack of transportation, fear of being ostracised or stigmatised for

having a mental illness, and the lack of qualified psychotherapists[14–20]. These barriers have prompted interest in new ways of delivering effective psychotherapies and in new (digital) technologies for doing so[21].

Digital-technology-based psychotherapy (DTP) usually uses internet-based platforms such as Web-based services or PC or smartphone apps to deliver psychotherapies to patients, which may potentially compensate for many of the abovementioned disadvantages of traditional face-to-face psychotherapies[22, 23]. Various studies have also confirmed several disadvantages, such as a higher dropout rate, increased risk of leaking of patient information, a lower level of patient participation in the programme, and requiring patients to acquire technical skills[24–26]. During a public health outbreak the use of digital technology is more appropriate than face-to-face therapies for PTSD patients, who are often resistant to face-to-face contact due to fear of imagined infection, even long after the trauma event[2, 27, 28]. For other kinds of mental illnesses, such as anxiety disorder and depression, the effectiveness of DTP has been well studied and confirmed[6]. However, research on DTP for PTSD has only begun to emerge in recent years. For example, a systematic review of DTP for PTSD in veterans found that in most instances, DTP was as effective as traditional face-to-face interventions in reducing PTSD symptoms[24, 29].

Three weaknesses were identified in the existing systematic reviews and meta-analyses on the effectiveness of DTP for PTSD (e.g.,[30–36]). First, the trials included are not comprehensive. Most of the meta-analyses only focused on cognitive

behavioural therapy (CBT) trials (e.g.,[7, 37]). Also, in all the meta-analyses the criteria for trauma event types did not include public health outbreaks such as SARS and Ebola. Additionally, smartphone-app-based psychotherapies were excluded in most meta-analyses (e.g.,[19, 38]). In a 2016 study a search of the smartphone app stores (in English) turned up 28 apps essentially targeted at PTSD symptom relief or general education on PTSD[39]. We conducted a search of the Chinese Android app store and found one mindfulness app targeting PTSD symptom relief and another 10 apps providing general mental health information that includes PTSD as a subcategory. PTSD Coach, an English-language app, has been used in 106 countries and downloaded more than 350,000 times (the most for any app targeted at PTSD symptom relief) as of March 2018[40]; two trials evaluated its effectiveness and both found no significant effects in favour of intervention versus the control group[41, 42]. Indeed, like PTSD Coach, many mental health apps are not evidence-based, and this would be considered as one limitation of this study[43].

Second, the trials examined had very high heterogeneity or high risk of bias, so the quality of evidence is questionable[7, 37]. Third, most of meta-analyses focused on the effects of certain specific psychotherapies rather than exploring the comparative effectiveness of different DTPs (e.g.,[17, 19, 30–36, 44]). For instance, Olthuis et al.'s meta-analysis confirmed that DTP was more effective when compared to effects on the waiting control group, and did not compare effectiveness among various types of DTPs[19]. Moreover, the effectiveness of DTP for PTSD patients compared to traditional face-to-face psychotherapy has also been questioned. Several

scholars concluded that the effectiveness of DTP cannot be confirmed due to the lack of sufficient comparative effectiveness evidence with face-to-face therapies for PTSD[34, 45]. Furthermore, not only has the effect-size classification for various types of DTP for PTSD not been confirmed, we also found that the recommendation hierarchy for various forms of traditional face-to-face psychotherapy for PTSD is inconsistent among the guidelines for the treatment of PTSD in adults from the five prestigious international organisations. Three of these organisations strongly recommended DTP but generally classified all kinds of DTPs into a single treatment group[9–13].

As a newly developed method, network meta-analysis, through appropriate research design, can easily fill the gaps identified above. Although the assumptions of network meta-analysis are similar to those of regular meta-analysis, the key additional assumptions are transitivity (no effect-modifying factors affecting indirect comparison) and coherence (direct and indirect effect estimates are similar)[6]. Therefore, network meta-analysis can integrate direct evidence from comparative studies of different interventions and indirect evidence from studies of individual interventions with common control conditions, and assess the effectiveness hierarchy among various interventions[46]. This method can provide meaningful evidence for clinical practice guides by comparing multiple treatments at the same time[47]. By also using the Grading of Recommendations, Assessments, Development, and Evaluation (GRADE) framework to rate the quality of evidence synthesised through network meta-analysis, the aim of this research is to provide high-quality clinical guidance on DTP for PTSD

in adults[48].

Research on traditional PTSD psychotherapy through network meta-analysis is very limited. For example, a network meta-analysis in 2019 compared the effectiveness of different psychotherapies for PTSD[49]. However, the study focused on young people, not adult patients, and the psychotherapies were not based on digital technology. Network meta-analysis of traditional psychotherapies for PTSD in adults is also limited. There are no such studies published in Chinese[50] and only a few articles on research conducted in China published in English[6, 38, 51–53]. One study concentrated on traditional face-to-face psychotherapy, with very outdated data extraction (January 2011)[6]; another article compared the effectiveness of different traditional psychotherapies and conducted a subgroup analysis between patients with clinical diagnosis and those without[51]. Network meta-analysis research on digital-technology-based PTSD psychotherapy for adults is even more limited. Moreover, these studies also present inconsistencies with the guidelines mentioned above. For example, a network meta-analysis of DTPs indicated that the effectiveness of various psychotherapies, such as cognitive behavioural therapy, comfort counselling, and eye movement desensitisation and reprocessing, does not significantly differ between them, and most of the trials included had a low quality of evidence[52]. Two research protocols of network meta-analysis published in 2018 advocated for examination of the comparative effectiveness of different DTPs for PTSD in adults[38, 48].

Therefore, we endeavour to conduct a network meta-analysis of studies on DTPs

for PTSD in adults, specifically studies that incorporate trials in a comprehensive manner and with special consideration for quality of evidence, in order to better compare relative effectiveness for different DTPs (including an effectiveness comparison with traditional face-to-face psychotherapies) and establish the differential effectiveness of these therapies for symptom reduction.

Methods

This network meta-analysis will be conducted in accordance with the PRISMA-P checklist[54].

1. Search Strategy

L. He and Geng will search Embase, CINAHL, MEDLINE, HealthSTAR, the Cochrane Library, PsycINFO, PubMed, the Chinese biomedical literature database, clinical trials (e.g., ClinicalTrials.gov), and other academic platforms for studies on various DTPs for PTSD in adults, mainly in English and Chinese, using the keywords and phrases detailed in Table 1, from inception to October 2020. The studies included will be randomised controlled trials (RCTs) and systematic meta-analyses on DTPs for PTSD (some meta-analyses may have included RCTs we did not find otherwise). An experienced medical librarian will be consulted to improve the search strategy for each database, and any differences will be resolved through discussion; in case of disagreement we will consult another expert.

Table 1. Search strategy for databases

Search Lines	Search Items	Filter
Line 1	(post-trauma* OR posttrauma*) OR PTSD AND (stress OR disorder)	Title/Abstract
Line 2	(web* OR tele* OR computer* OR mobile* OR internet* OR digital* OR remote* OR distance* OR e* OR online* OR on-line* OR smartphone* OR smart-phone* OR virtual* OR avatar* OR app*) AND (psychotherap* OR therap* OR treat* OR intervention* OR self-help OR exposure* OR CBT OR psychodynamic* OR psychoeducation* OR eye movement desensitization and reprocessing OR eye movement desensitisation and reprocessing EMDR OR narrative exposure OR NET OR trauma-focused* OR trauma-focussed OR prolonged exposure OR cognitive processing OR cognitive therapy OR CT OR non-trauma-focused* OR non-trauma-focussed OR present-centred* OR present-centered OR mindfulness OR yoga OR relaxation* OR supportive counselling OR supportive counseling OR counselling OR counseling OR brief eclectic therapy OR BET OR cCBT OR iCBT OR i-therapy OR e-therapy OR itherapy OR etherapy)	Title/Abstract

2. Selection Criteria

2.1 Inclusion criteria:

- The patients recruited in an individual RCT or in RCTs in meta-analyses are adults diagnosed with primary or secondary PTSD (according to DSM-III, IV, and 5, the International Classification of Diseases, and other similar standards);

- Trauma events will include all types, with special attention to public health outbreaks;
- The study of secondary PTSD must focus on the treatment of PTSD;
- If the PTSD patients recruited in the RCT also suffer from other comorbidities, such as physical disease, they will be included in the database, and these groups of patients will be tested via sensitivity analysis;
- DTP will include various technologies (e.g., Web-based services, PC and smartphone apps), but there must be elements of interaction between programmes and patients;
- The selection of various types of psychotherapy is mainly based on the comprehensive analysis of PTSD therapy guidelines of the five world's most prestigious professional societies and organisations (see Figure 1), along with types of control group;
- The research duration is unlimited, but the effects for different durations will be tested by subgroup analysis; the number of DTP sessions is also unlimited.

2.2 Exclusion criteria:

- The RCT has an intervention group or control group of fewer than 10 participants (of the five organisations, NICE and VA/DoD guidelines exclude RCTs with fewer than 10 participants[11, 13]; we think adopting this exclusion criterion is an

appropriate way to increase quality of evidence);

- It is a pilot study, feasibility study, or crossover trial;
- The recruitment criteria are for severe PTSD, which includes excessively high intent to commit suicide, high dissociative disorder, severe mania, and psychosis;
- If a small number of participants in an RCT meet the above exclusion criteria, we will try our best to abstract and exclude the data of those independent participants and include the trial; if we are not able to exclude these individual data but the number of these participants does not exceed 20% of the total enrolled, the trial will still be included.

3. **Data Extraction and Bias Analysis**

3.1 Data extraction

a. *RCT and meta-analysis data extraction:* In order to ensure the reliability of independent data extraction, a data extraction Excel form will be designed and the following calibration exercises will be conducted among project researchers (L. He, Tian, and Pan). The data extraction form will include study characteristics (first author, year of publication, source of funding, and so on) and patient and trial characteristics such as patient demographic information (age in years, gender, occupation, absence/presence of disability, type of trauma, and absence/presence of related comorbidity), sample size, and intervention- and control-group characteristics. Finally, type of trauma will be regarded as a dichotomous nominal variable between

health-related and non-health-related type.

b. *Individual patient data provided by RCT and meta-analysis authors:* If the complete data cannot be downloaded from the database, the authors of the selected trials or studies will be contacted and asked to share their individual patient data (including baseline measurement and other information); the corresponding author will be contacted first, and if not available, the other authors will be contacted in turn; if there is no response from the authors within two weeks, a second email will be sent; if there is no response within one month from any of the authors contacted, the RCT or meta-analysis will only be included in the analysis at the aggregate data level. Two researchers (L. He and Geng) will separately test the consistency of the individual patient data with the data summary published in the article. The validity of this project would be compromised if the trials with individual patient data were systematically and statistically different from those without. Therefore, we will divide data into two groups for analysis according to source origin, and compare the differences between the two groups; if there are statistical differences, we will include this result in our later assessment of quality of evidence.

3.2 Primary outcome measure

In this project, PTSD symptoms at the end of treatment using raw scores for one of the most widely used PTSD scales are extracted as the primary outcome measure. The scale we chose is the PTSD Checklist (PCL-5). PCL-5 contains 20 items designed to

measure 4 PTSD symptom clusters according to DSM-5's diagnostic criteria, based on answers provided by the patients; the symptom indicators are numerically coded, generating a total symptom severity score of between 0 and 80[55]. If the outcome is a dichotomy variable, the authors of the RCT study or meta-analysis will be contacted and asked to provide relevant primary raw scores; if there is no response, the study will not be considered.

3.3 Secondary outcome measures

Secondary outcome measures include (1) dropout rate—the rate of patients who discontinued the trial for any reason at any time before the end of trial; (2) effectiveness at the longest follow-up period, but not more than 12 months; and (3) patients' functional recovery ratio (such as the return-to-work ratio or percentage of sick leave).

3.4 Risk of bias

The project will use the Cochrane risk-of-bias tool, version 2.0, to assess the degree of bias of the study (as being at unclear risk of bias, low risk of bias, or high risk of bias) by assessing random sequence generation, allocation concealment, blinding of participants, blinding of personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting[56].

4. Data Synthesis and Analysis

Bayesian network meta-analysis will be conducted for all outcome measures[57]. For the primary outcome measure, the project will calculate the weighted mean difference (WMD) and the related 95% confidence interval (CI). For the secondary outcome measure, if the tools for the same outcome measure are the same, we will also use the WMD and the related 95% CI[57, 58]; for studies using different tools for the same outcome measure, the project will convert all outcomes into a common tool according to Thorlund et al.'s recommendations, and calculate the standard mean difference (SMD) and the related 95% CI[58]. If *p* value, *t* value, CI, range, or standard error (SE) are reported in the trials and meta-analysis, the project will use the method recommended by the Cochrane manual to estimate the missing standard deviation (MSD)[38].

4.1 Direct comparison

The project will use the DerSimonian-Laird random-effects model to conduct standard pairwise meta-analyses (for at least two studies) for all outcomes[59]. The Q statistic and I^2 will be used to evaluate the statistical heterogeneity. Each direct comparison will report study and patient characteristics, risk of bias, and aggregate estimates of related outcomes.

4.2 Indirect comparison

This project will settle inconsistency by comparing direct evidence with indirect evidence of differential effectiveness of various treatments, and use the Wald test to test any statistical difference between direct and indirect estimates[60]. The project will report the probability of each DTP effectiveness level. After using a rankogram to show rank probability, the SUCRA value will be used to explain the comparative effectiveness of the DTP (a value of 100 is the best and 0 the worst). The software package R, version 3.4.3, will be applied for statistical analysis.

5. Quality of Evidence Assessment

The project will use GRADE to rate the quality of both direct and indirect evidence and will classify the evidence as “high”, “moderate”, “low”, or “very low”. The starting point for RCT quality of evidence is very high, yet could be downgraded due to risk of bias, imprecision, inconsistency, indirectness, and publication bias according to GRADE.

6. Subgroup and Sensitivity Analysis

This project will adopt subgroup and sensitivity analysis to test seven hypotheses: 1) trials with high risk of bias, compared with those with low risk, will show a greater effect size; 2) occupational groups such as medical staff, military, or police will show

a smaller effect size than the civilian samples for the same DTP; 3) the longer the follow-up period, the smaller the DTP effectiveness; 4) the effectiveness of DTPs with the participation of therapists is better than that of those without therapists; 5) different trauma events may trigger different levels of symptom severity (and duration); for instance, public health emergencies may have a stronger influence than one-off events such as earthquakes; 6) the longer the duration of the treatment period, the greater the DTP's effectiveness; and 7) studies on patients with comorbidities may contain a high risk of bias compared to those on patients without.

7. Patient and Public Involvement

No patients or members of the public are involved.

8. Study Status

We will officially commence data extraction in early September 2020 and finish at the end of that month. We will start our analysis from the beginning of October and expect to complete it within five months.

Ethics and Dissemination

No ethics approval is needed in this protocol study. The network meta-analysis results of this project will be disseminated to organisations supporting PTSD patients and

hospitals with psychiatry or psychology departments.

We will present the results of this meta-analysis at academic conferences and publish them in peer-reviewed journals. Authors who make essential contributions to the generation of the final report will be granted with authorship. Moreover, we will disseminate results to health service receivers. The results will be implemented and reported according to the CONSORT statement.

Author's Contribution L. He conceived the project design and drafted the article. Geng and Tian assisted with design and revision. L. He and Tian will conduct most of the data abstraction and the risk-of-bias assessment. Tian, Geng, and Pan participated in the design of data synthesis and analysis. Geng, X. He, and Pan will conduct the statistical analysis. All authors have agreed to publish this protocol.

Funding Statement This research was funded by the Youth Project of Humanities and Social Sciences (project no. 20XJC840001) of the MOE (Ministry of Education) in China.

Disclaimer This funder has no role in the protocol design, the writing of the protocol, or the decision to submit the protocol.

Competing interests statement The Author(s) declare(s) that there is no conflict of interest.

Patient consent Not required.

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Figure Captions

Figure1: Description of Psychotherapies and Control Conditions

Figure 1: Description of Psychotherapies and Control Conditions

Type of Psychotherapy	Abbrev.	Brief Description
Exposure-Based Psychotherapy		
Trauma-Focused Cognitive Behavioural Therapy (undifferentiated)	TF-CBT	Implemented through cognitive remodelling and behavioural change techniques; focuses on trauma, and usually deals with trauma-related thoughts and behaviours through exposure-to-trauma situations or cognition.
Prolonged Exposure Therapy	PET	Uses specific methods to guide patients to gradually make contact and deal with cognitive thoughts, behaviours, and scenes about trauma.
Narrative Exposure Therapy	NET	Encourages the patients to focus on the traumatic events and piece together a coherent life story to deal with the fragmentation of life memories caused by trauma.
Eye Movement Desensitisation and Reprocessing	EMDR	Pays less attention to the traumatic event itself than to the disturbing emotions and thoughts caused by the event. Treatment involves the therapist using techniques to guide the patient's eye movement from side to side.
Cognitive Processing Therapy	CPT	Socratic questioning often used to help patients learn how to challenge their misconceptions and behaviours around trauma. Written assignments may be given to encourage patients to develop new cognitive skills.
Cognitive Therapy	CT	Focuses solely on challenging patients' old ways of thinking about trauma from a cognitive perspective.
Non-Exposure-Based Psychotherapy		
Non-Trauma-Focused Cognitive Behavioural Therapy	NTF-CBT	Implemented through cognitive remodelling and behavioural change techniques; the focus is not on trauma itself but rather on behaviour and cognition.
Present-Centred Therapy (mindfulness)	PCT	Instructs patients to learn skills for focusing on the "present" and letting go of bad memories from the past.
Relaxation Therapy	RT	Mainly uses a series of relaxation methods, such as deep breathing, to teach patients to deal with the recurrence of traumatic memories.
Supportive Counselling	SC	The therapist mainly provides emotional support, listening to the patient's difficulties, sadness, etc.
Brief Eclectic Therapy	BET	Integrates CBT, SC, and other treatment techniques to treat patients over a short period of time.
Psychodynamic Therapy	PDT	Focuses mainly on revealing how the past (e.g., unresolved conflicts, dysfunctional relationships) affects present behaviours, and thereby helps the clients to obtain self-awareness.
Psychoeducation	PE	Treats patients by enhancing their understanding of PTSD.
Control Group		
Treatment as Usual	TAU	Refers to the usual treatment method at the research site, which may contain many components of psychointerventions, as well as drug treatment.
Waitlist	WL	Patients do not receive any treatment during the study but will receive treatment after the study.
No Treatment	NT	Patients receive no treatment during or after the study.
Active Therapeutic Treatment	ATT	Patients receive some kind of traditional face-to-face psychotherapeutic intervention.
Digital-Technology-Based Active Therapeutic Treatment	DTB-ATT	Patients receive some kind of psychotherapy based in digital technology.

Figure1: Description of Psychotherapies and Control Conditions

210x297mm (300 x 300 DPI)

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
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	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	n/a
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page 1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	Title page 2
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	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	17-22
Sponsor	#5b	Provide name for the review funder and / or sponsor	Title page 2
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	Title page 2
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3-9
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	9
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	10-11
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	10
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	10
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	12
Study records - 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)	12-13
Study records - data	#11c	Describe planned method of extracting data from reports (such as	12-13

collection process		piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	
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	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	13-14
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	14
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	15
Data synthesis	#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 I2, Kendall's τ)	15
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	15
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	15
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	16
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	16

Notes:

- 3a: Title page 1
- 3b: Title page 2
- 5b: Title page 2
- 5c: Title page 2 The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution License CC-BY 4.0. This checklist was completed on 27. March 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai