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Internet-Delivered Cognitive Behavioral Therapy for Post-Traumatic Stress Disorder: A Review of Clinical Effectiveness

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Abbreviations

BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory-II
BSI	Brief Symptom Inventory
CAPS	Clinician Administered PTSD Scale
CBT	cognitive behavioural therapy
CES-D	Center for Epidemiological Studies-Depression Scale
CI	confidence interval
DSM	Diagnostic and Statistical Manual of Mental Disorders
EQ-5D	EuroQol 5 Dimensions Scale
FDAS	Four Dimensional Anxiety Scale
iCBT	internet-delivered cognitive behavioural therapy
IES-R	Impact of Event Scale – Revised
NRS	non-randomized study
PCL-C	PTSD Checklist – Civilian Version
PDS	Post-traumatic Stress Diagnostic Scale
PHQ-9	Patient Health Questionnaire
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTSD	post-traumatic stress disorder
PSS-IV	PTSD Symptom Scale-Interview Version
QOLI	Quality of Life Inventory
RCT	randomized controlled trial
SDS	Sheehan Disability Scale
SF-36	36-Item Short Form Survey
SR	systematic review
STTS-R	Satisfaction with Therapy and Therapist Scale-Revised
TES	Traumatic Event Scale

Context and Policy Issues

As much as 65% of the world's population experiences at least one traumatic event during their lifespan.[1-3] According to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)*, 5th Edition*, a traumatic event is defined as direct exposure, witnessing, or indirect exposure to death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence.[4] Although many individuals exposed to such trauma may recover naturally, persistent mental health conditions, such as post-traumatic stress disorder (PTSD) or depression may develop.[5,6] These conditions are associated with decreased quality of life, disability, and increase mortality.[7-10] Lifetime prevalence of PTSD in the US adult population is estimated to be around 11.7% in women and 4% in men,[11] with higher rates in high-risk groups such as military service members and first responders.[12-14] Individuals with PTSD may exhibit symptoms such as hyperarousal (i.e., irritability, concentration problems), nightmares, flashbacks, avoidance of reminders of trauma, numbing, and negative thoughts or feelings.[15]

Treatment of PTSD typically involves various psychotherapeutic or pharmacological approaches (e.g., paroxetine and sertraline).[16] Cognitive behavioural therapy (CBT) is one of the most commonly used psychotherapies and has a large volume of literature supporting its effectiveness for the treatment of PTSD.[8,17-19] By combining the principles of cognitive and behavioural therapies CBT aims to provide individuals with the coping strategies and mechanisms to solve current problems and to change dysfunctional

thoughts, behaviours, beliefs, and attitudes.[20] CBT for PTSD consists of psycho-education on common reactions to trauma, anxiety management strategies (e.g., breathing relaxation techniques), controlled confrontation (exposure) with trauma-associated memories, and cognitive restructuring of maladaptive cognitions, such as perceiving the world as dangerous and feelings of self-guilt or helplessness.[5,21]

CBT is traditionally delivered using face-to-face sessions between the individual and therapist. However, this mode of treatment is associated with barriers to access such as high financial costs, perceived stigma, potentially poor access to treatment in rural areas, and long wait times.[22-26] Several studies[27-29] have emphasized the discrepancy between the prevalence of PTSD (and other mental health conditions) and the number of individuals who are able to access mental health services, with some surveys estimating that over half of individuals meeting the diagnostic criteria for a mental health condition do not access or receive treatment.[27,28] Internet-delivered cognitive behavioural therapy (iCBT) has been proposed as a way to deliver an evidence-based psychotherapy while offering several advantages over traditional care. These advantages may include increased access to individuals living in remote areas or those with limited mobility due to physical or psychological barriers, decreased cost of treatment, increased flexibility in schedule, and iCBT may be more acceptable for individuals that fear possible stigmatization.[5,30-32]

The purpose of this report is to summarize the evidence on the clinical effectiveness of iCBT programs for the treatment of adults (≥16 years of age) diagnosed with PTSD. The findings of this report will be integrated into a larger project on the Optimal Use of iCBT for PTSD currently being conducted by CADTH.

Research Question

What is the clinical effectiveness of internet-delivered cognitive behavioural therapy for the treatment of post-traumatic stress disorder?

Key Findings

Three systematic reviews with meta-analyses and two additional randomized controlled trials were identified regarding the clinical effectiveness of internet-delivered cognitive behavioural therapy for patients (≥16 years of age) with a primary diagnosis of post-traumatic stress disorder. The features of the treatment programs (e.g., number of modules, duration, level of guidance, and frequency of support), scales used to assess clinical outcomes, and characteristics of patients (e.g., age, sex, type of trauma) examined in these studies were heterogeneous.

The evidence demonstrated that treatment with internet-delivered cognitive behavioural therapy resulted in improvement in severity of post-traumatic stress disorder symptoms compared to treatment with wait-list. There were generally no statistically significant differences between treatment with internet-delivered cognitive behavioural therapy and access to a psycho-educational website, internet-based supportive counselling, or optimized usual care for post-traumatic stress disorder symptom severity; however, these findings were based on one study per comparator. Additionally, one study reported no statistically significant differences between treatment with internet-delivered cognitive behavioural therapy that either included or did not include an exposure component for post-traumatic stress disorder symptom severity.

Evidence examining how iCBT compared to face-to-face CBT, video-delivered CBT, or to alternative frequently used psychotherapy interventions was not identified in this review. The limitations of the included studies highlighted in this review, such as their open-label nature and lack of detailed reporting on potential confounders (e.g., comorbid psychological condition, patient use of medication) should be considered when interpreting these results.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Medline, PsycINFO, PubMed (for non-Medline records), the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to randomized controlled trials (RCTs), non-randomized studies, health technology assessments, systematic reviews, and meta-analyses. The search was also limited to English language documents published between Jan 1, 2008 and Sep 25, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult outpatients, 16 and older, with a primary diagnosis of post-traumatic stress disorder[a] - Potential subgroups of interest: patients with comorbid mental health conditions versus those without
Intervention	Guided and unguided internet cognitive behavioral therapy (CBT delivered via the internet to the patient) - Excluding: Non-traditional CBT (e.g., mindfulness CBT); CBT delivered via bibliotherapy; CBT described as computerized (non-internet) - Potential subgroups of interest: guided versus unguided iCBT
Comparator	Alternative iCBT interventions[b]; face-to-face CBT; video-delivered or telehealth-delivered CBT; alternative psychotherapy interventions (e.g., EMDR); treatment as usual; wait list control; no treatment
Outcomes	Remission and prevention of relapse of trauma symptoms, depression symptoms, anxiety symptoms (as measured by validated scales or questionnaires; self-reported; clinical reported), or suicidality; response to therapy; safety; quality of life (quantitative scales); measures of functional disability; patient satisfaction (quantitative scales); drop-out rates; patient adherence
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies

CBT = cognitive behavioural therapy; EMDR = eye movement desensitization and reprocessing; iCBT = internet-delivered cognitive behavioural therapy.
[a] Studies on or including patients with symptoms of post-traumatic stress who have not undergone formal diagnosis will be excluded unless subgroup data is available for patients with a diagnosis. There were no restrictions applied to the measures used to assess diagnostic status; therefore, if the authors of the study considered their population to meet the criteria for a formal diagnosis the study was included.
[b] For example, guided vs. unguided iCBT; comparison of two different guided iCBT programs; comparison of two different unguided iCBT programs.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2008. Systematic reviews that were broad in scope (e.g., those that reviewed the effectiveness of all psychotherapeutic interventions for the treatment of anxiety or trauma disorders) and did not report sufficient study characteristics to assess primary study eligibility were also excluded provided all of their relevant studies were already included in this report. In addition, systematic reviews that had relevant included studies fully captured in other, more recent and comprehensive systematic reviews were excluded. Individual RCTs retrieved by the search were excluded if they were captured in one or more included systematic reviews. Studies that examined internet interventions that only consisted of a single component of CBT (e.g., exposure) and were not referred to by study authors as iCBT were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using AMSTAR 2,[33] and the included clinical studies were critically appraised using the Downs and Black checklist.[34] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 1,357 citations were identified in the literature search. Following screening of titles and abstracts, 1,284 citations were excluded and 73 potentially relevant reports from the electronic search were retrieved for full-text review. Ten potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 83 potentially relevant articles, 78 publications were excluded for various reasons, while five publications met the inclusion criteria and were included in this report. These comprised three systematic reviews with meta-analyses and two RCTs. Systematic reviews that contained at least one primary study that met our selection criteria and presented data at the individual study level were included. The eligibility of primary studies included in systematic reviews was assessed using the information provided within the systematic review (i.e., the full-texts of primary studies included within systematic reviews were not reviewed to confirm eligibility). Appendix 1 presents the PRISMA[35] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Three relevant systematic reviews with meta-analyses[5,14,21] and two additional relevant RCTs[36,37] were identified and included in this review. No relevant health technology assessments or non-randomized studies were identified. Study characteristics were extracted by one reviewer and are summarized below. Detailed characteristics are available in Appendix 2, Tables 2 and 3.

Study Design

All three systematic reviews with meta-analyses[5,14,21] had broad objectives and inclusion criteria; only information from studies relevant for our report is included here. The Kuester et al.[21] review searched for RCTs published up to April 7, 2015. The review by Olthuis et

al.[14] included RCTs published before July 28, 2016. The third systematic review[5] did not provide information on the date of their literature search (likely in 2015 or 2016 based on the year of publication), but did specify that they were only searching for RCTs. One systematic review[21] summarized four RCTs relevant under our inclusion criteria, while the systematic reviews by Olthuis et al.[14] and Sijbrandij et al.[5] each included five relevant RCTs. In total, the systematic reviews included eight unique relevant RCTs.[38-45] The relevant primary study overlap between these systematic reviews is summarized in Appendix 5, Table 9.

Two relevant clinical studies[36,37] were included, both of which were RCTs. One study[36] recruited patients through clinician referred and with media advertisements. The second RCT[37] used a series of advertising campaigns to recruit patients from four university or community college campuses. Due to the nature of the intervention and study designs, blinding of patient and therapist were not possible.

Year of Publication and Country of Origin

The included systematic reviews were from Germany,[21] Canada,[14] and the Netherlands.[5] All three reviews[5,14,21] were published in 2016. Relevant primary studies included in the systematic reviews were published between 2007 and 2016.

The included RCTs were conducted in the UK[36] and the US[37] and were published in 2016 and 2017, respectively.

Patient Population

One systematic review[21] included adults with subclinical or clinical PTSD. Primary studies were classified as including participants with clinical symptom levels of PTSD that were confirmed by diagnostic screening procedures, as subclinical samples, or as making no clear specification on the samples' symptom level. However, only primary studies in populations with clinical levels of PTSD were considered relevant for our review. The relevant RCTs included those who had experienced trauma including war, terror, or diverse events. The number of participants in the individual RCTs ranged between 44 and 159, with a total of 373 participants included. The mean age, sex, use of medication, and comorbidities of the patients were not reported. The review by Olthuis et al.[14] included adults (≥18 years of age) with a primary diagnosis of PTSD or subclinical PTSD according to the DSM. Diagnostic status was determined using a validated diagnostic instrument. Studies including participants with comorbid diagnoses were included. The number of included participants in the relevant individual RCTs ranged between 44 and 80, with a total of 287. The proportion of female participants ranged between 19% and 100%. The mean age, type of trauma experienced, and number or type of comorbidities of patients were not reported. The third systematic review[5] included patients with a clinician-obtained diagnosis of PTSD or with elevated levels of PTSD symptoms based on a PTSD self-report instrument; however, only results from studies of participants with a full diagnosis of PTSD were relevant to our review (and will be further discussed). The relevant studies included patients who experienced trauma resulting from pregnancy loss, terrorism, combat, or mixed events. A total of 475 participants were included in the relevant studies, with individual studies recruiting between 18 and 228. The mean age, sex, and comorbidities of patients were not reported.

The RCT conducted by Lewis et al.[36] included adults (≥18 years of age) who met the diagnostic criteria for DSM-5 PTSD of mild to moderate severity after a two week period of symptom monitoring. Participants with psychosis, previous trauma-focused psychological

therapy, DSM-5 severe major depressive episode, substance dependence, inability to read and write English fluently, inability to access the internet, and those who had changes in their psychotropic medication within the previous month were not eligible for the study. A total of 42 patients were recruited and randomized in the study. Participants had experienced a wide variety of trauma contributing to their PTSD, including transportation accidents, witnessing a sudden, violent, or accidental death, traumatic childbirth or stillbirth, sexual assault or rape, physical attack, life threatening illness or injury, serious accident, learning of the violent death of a loved one, seeing a mutilated body, and being held hostage and detained. The mean age of participants was 39.29 years (range = 20–65). The proportion of female participants was 59.5%. The RCT by Littleton et al.[37] included women who were enrolled as a student at one of four universities or community colleges, had suffered rape-related trauma, and met the diagnostic criteria for PTSD. Exclusion criteria were current treatment with psychotherapy, change in participant's use of psychotropic medication within the previous three months, active suicidality, or comorbid substance dependence according to the DSM-4. The number of participants randomized was 87. The mean age of women was 22 years (range = 18 to 42). All participants had experienced a completed rape (as described by the authors of the study) since the age of 14.

None of the included studies[5,14,21,36,37] examined how treatment with iCBT programs may differ in patients with comorbid mental health conditions versus those without.

Interventions and Comparators

The three included systematic reviews[5,14,21] investigated a variety of treatments. One systematic review[21] included studies that compared internet-based interventions including iCBT to active or passive comparison groups for the treatment of post-traumatic stress. Interventions were broadly classified as being based on either expressive writing or CBT, and could be either therapist-guided or unguided (self-help); however, all studies relevant to our review examined therapist-guided iCBT programs. The second systematic review[14] investigated the effectiveness of therapist-guided, distance-delivered interventions for PTSD including iCBT compared to inactive control (e.g., waiting list, delayed treatment) or active intervention. The systematic review by Sijbrandij et al.[5] included studies that compared iCBT versus inactive control or active interventions.

Within the three included systematic reviews[5,14,21] there were a total of eight relevant primary studies (all RCTs)[38-45] that investigated a variety of individual iCBT programs (relevant primary study overlap is described in Appendix 5, Table 9). The iCBT programs examined in these primary studies included DESTRESS,[43,44] programs based on Interapy,[41] or were not named.[38-40,42,45] The number of treatment modules included in the iCBT programs ranged between 6 and 18 and the length of treatment was typically between 5 to 8 weeks based on the information provided in the three systematic reviews.[5,14,21] The comparators used in the relevant RCTs[38-45] from the systematic reviews[5,14,21] were internet-based supportive counselling,[44] iCBT without an exposure component,[38] optimized usual care,[43] or waiting list.[39-42,45]

One RCT[36] included in this review compared a therapist-guided, self-help iCBT program to a delayed treatment control group. The iCBT group was allowed up to three hours of therapist assistance provided by a psychiatrist, a clinical psychologist, and three cognitive behavioral therapists who were experienced in the delivery of trauma-focused CBT. The purpose of the assistance was to offer continued support, monitoring, motivation, and problem solving. The treatment consisted of eight modules delivered over a 10 week period. Participants allocated to the delayed treatment control group did not receive any

therapist contact until they crossed over to the treatment arm (after the study). The RCT by Littleton et al.[37] investigated the effectiveness of the From Survivor to Thriver program, an interactive, therapist-guided iCBT program for rape-related PTSD. The program consisted of nine modules to be completed over 14 weeks. Therapist-guidance was provided by doctoral students in the form of scheduled check-in phone calls approximately once every two weeks. The purpose of these calls was to assess the participants' mood, substance use, suicidal or self-harming thoughts, frequency of logging into the program, time spent in enjoyable activities, and to discuss technical problems or distress related to the program. The control group received access to a psycho-educational website that contained informational content from the first three treatment modules (which focused on relaxation, grounding, and coping strategies). The website did not contain multimedia content or interactive exercises from the iCBT program.

None of the included studies[5,14,21,36,37] examined unguided iCBT programs for the treatment of individuals with PTSD.

Outcomes

The RCTs in the included systematic reviews[5,14,21] reported outcomes measured with several different scales for PTSD symptom severity, functioning, or quality of life, including: the Impact of Event Scale – Revised (IES-R), PTSD Checklist – Civilian Version (PCL-C), Post-traumatic Stress Diagnostic Scale (PDS), PTSD Symptom Scale – Interview Version (PSS-IV), Traumatic Event Scale (TES), 36-Item Short Form Survey (SF-36), Quality of Life Inventory (QOLI), EuroQol 5 Dimensions Scale (EQ-5D), Sheehan Disability Scale (SDS), Clinician Administered PTSD Scale (CAPS), Beck Depression Inventory – II (BDI–II), Brief Symptom Inventory (BSI), and Patient Health Questionnaire (PHQ-9). A list of the scales used in the included systematic reviews[5,14,21] is provided in Appendix 2, Table 2, and a brief description of some of the commonly used scales is available in Appendix 2, Table 4. The results were presented as standardized mean differences, typically a Hedges' *g* or Cohen's *d* value. A commonly used (although arbitrary) interpretation for Hedges' *g* or Cohen's *d* values are small (*d* = 0.2), medium (*d* = 0.5), and large (*d* = 0.8), as proposed by Cohen in 1988.[46-49] However, Cohen did suggest caution for this rule of thumb as these thresholds may vary based on the context in which the Cohen's *d* value is being applied.[47] Two systematic reviews[14,21] reported on dropouts as an outcome of interest.

It is important to note that the eight unique primary studies[38-45] summarized from the three systematic reviews[5,14,21] likely examined additional outcomes that were not discussed within the systematic reviews. It is typical for systematic reviews to consolidate data on primary outcomes or a specific outcome of interest (in this case PTSD symptom severity), rather than completely summarizing all findings from primary studies.

The included RCTs[36,37] assessed PTSD symptom severity using the CAPS-5, the PTSD Checklist for DSM-5 (PCL-5), and the PSS-IV. In addition, symptoms of depression and anxiety, functional impairment, perceived social support, working alliance, and treatment satisfaction were assessed using various scales. A list of the scales used in both included RCTs[36,37] is provided in Appendix 2, Table 3, and a brief explanation of some of the commonly used scales is provided in Appendix 2, Table 4. The RCT by Littleton et al.[37] evaluated whether participants in either treatment arm experienced clinically significant change on their study measures from pre-treatment to post-treatment using the reliable change index, as described by Jacobson and Truax.[50] The reliable change index is a measure of statistically and clinically significant improvement in scores following treatment that considers the outcome measure's reliability and variability in pre-treatment scores.[37]

While it is possible that the authors of the relevant primary studies included in the systematic reviews provided some discussion on minimal clinically importance differences (minimal clinically important score changes), this aspect was not discussed in the three included systematic reviews[5,14,21] or the Lewis et al. RCT[36] for any of the outcome scales used. Both RCTs[36,37] provided information on the number of dropouts or attritions rates in each treatment arm. Therapists participating in the Lewis et al.[36] study were asked to record any adverse event arising during the trial.

Summary of Critical Appraisal

Critical appraisal of the included studies is summarized below and detailed in Appendix 3, Tables 5 and 6.

Systematic Reviews

The three identified systematic reviews[5,14,21] were generally well-conducted but had some important limitations, based on the assessment using AMSTAR 2.[33] All three systematic reviews[5,14,21] clearly stated their objectives and inclusion criteria, searched multiple databases, provided key search terms, described the article selection process, provided a list of included studies and summarized their characteristics, and conducted quality assessment of included studies. The three systematic reviews[5,14,21] performed a meta-analysis using appropriate methods for the statistical combination of results and assessed heterogeneity when suitable (using Q and I^2 statistics). However, pooled estimates from two systematic reviews[5,14] could not be extracted for our report as the pooled data presented in the Forest plots included RCTs that were not relevant under our inclusion criteria. It was unclear whether the methods used in the systematic reviews[5,14,21] were established prior to the conduct of the review as none of the reviews made reference to a study protocol. Although two included reviews[14,21] provided dates for their literature searches, the review by Sijbrandij et al.[5] did not. Two systematic reviews[14,21] performed study selection in duplicate, decreasing the likelihood that relevant studies were excluded. None of the reviews[5,14,21] included a list of excluded studies; however, reasons for exclusion were described. In addition, the systematic reviews[5,14,21] did not include information on adverse events associated with treatment; therefore, the safety of iCBT is unclear from the systematic reviews. The authors of two systematic reviews[5,21] stated they had no conflicts of interest and received no financial support for this work. One systematic review[14] made no mention of conflicts of interest and the source of funding was unclear.

In addition to the strengths and limitation identified as part of our review using AMSTAR 2,[33] the authors of all three systematic reviews[5,14,21] included some form of quality appraisal to assess their included RCTs. Kuester et al.[21] suggested that the studies' quality was "overall sufficient"; however, the authors did note several studies did not provide adequate information on blinding, reasons for attrition, or inclusion/exclusion criteria. In the second systematic review,[14] Olthuis et al. assessed risk of bias for each included study using the Cochrane Collaboration's risk of bias tool. The authors concluded that the included studies were of relatively low risk of bias with a few exceptions. All of the included RCTs were unable to blind study participants or clinicians; however, outcome assessors were blind in some studies. Additionally, the methods for allocation concealment and the severity of selective reporting were unclear within the majority of included RCTs. The systematic review by Sijbrandij et al.[5] coded methodological quality as high or low based on four criteria from the Cochrane Handbook for Systematic Reviews of Interventions (i.e., adequate sequence generation, allocation concealment, blinded assessments, and the use

of an intention-to-treat analysis). Of the RCTs relevant to our review, one RCT met all four criteria,[45] two RCTs met three criteria,[39,42] and two RCTs met two criteria.[38,44]

RCTs

The strengths and limitations of the two included RCTs[36,37] were identified based on the assessment using the Downs and Black Checklist.[34] Both RCTs[36,37] had clearly described objectives, interventions, controls, main outcomes, inclusion/exclusion criteria, and patient recruitment methodology. Randomization was done using appropriate computer-assisted methods that could not be influenced by study investigators, decreasing the risk for a biased allocation process (selection bias). Sample size calculations were conducted in one study,[36] where study authors then recruited the number of participants predicted to be needed. The second study[37] did not report sample size calculations. Study participants in both RCTs[36,37] were aware of their allocation to treatment arms (open-label), creating a serious risk of bias. Outcome assessors were blind to the treatment received in the Lewis et al. study,[36] but not in the Littleton et al.[37] RCT. Patient and outcome assessor knowledge of treatment allocation may have influenced responses to symptom questionnaires or may have caused patients to drop out of the study (the two RCTs[36,37] reported dropout rates of 28.8% and 43.5% in the iCBT groups, which were higher than the 19.0% and 29.3% that dropped out of control groups), creating a risk for bias in either direction depending on the perceptions and expectations of participants and therapists involved. In both studies[36,37] the baseline patient characteristics, which included age, sex, ethnicity, education, employment, type of trauma, time since trauma, and baseline symptom severity scores were well-balanced between treatment and control groups and any differences were documented (increasing confidence in the randomization process); however, number of patients with comorbid mental health conditions in each group was not described. The length of follow-up was consistent between the treatment and control groups in both RCTs.[36,37] As for the validity of the outcomes, the tools used as primary outcomes in the two RCTs (i.e., CAPS-5[36] and PSS-IV[37]) are well-studied in the literature and are valid for symptom measurement.[51,52] Significant conflicts of interest were reported in the RCT by Lewis et al.[36] The study was a collaborative project between the company who developed the software and Cardiff University. If the program was marketed, royalties would be paid to Cardiff University, Cardiff and Vale University Health Board, and to five of the seven authors. The remaining two authors had no conflicts of interest to disclose. The sources of funding for either study[36,37] were unclear.

As for external validity, both RCTs[36,37] included study participants (patients with clinically diagnosed PTSD), care providers (therapists with relevant training and experience), and health care setting appear to be representative of the "real-world". However, it is important to consider that all patients included in these studies met the clinical diagnosis for PTSD, and many patients that seek help for symptoms of post-traumatic stress may not meet the same threshold. Additionally, the study by Littleton et al.[37] completely relied on individuals to contact study investigators through posted advertisements, which may have selected for a motivated subset of people with PTSD that are more likely to complete iCBT programs and to apply their learning in their lives (potentially overestimating the treatment effect of iCBT).

Summary of Findings

The overall findings of the included literature are summarized below. A detailed summary of the main findings are available in Appendix 4, Tables 7 and 8.

Clinical Effectiveness of Internet-Delivered Cognitive Behavioural Therapy for Post-Traumatic Stress Disorder

PTSD Symptoms

Information on the effectiveness of iCBT for PTSD symptoms was available from two systematic reviews[5,14] and two RCTs.[36,37] The systematic review by Kuester et al.[21] provided pooled results on PTSD symptom severity, rather than results from individual included studies. Because of this it was not possible to extract PTSD symptom severity data from only the relevant primary studies and these findings are not discussed further.

The review by Olthuis et al.[14] included three relevant primary studies[39,40,45] comparing iCBT to waiting list, one relevant primary study[43] comparing iCBT to usual care, and one relevant primary study[44] comparing iCBT to internet-based supportive counselling. The results suggested that iCBT outperformed waiting list and internet-based supportive counselling with respect to PTSD symptoms at post-treatment and at three to six month follow-up. This difference reached statistical significance in two[40,45] of the four[39,40,44,45] relevant RCTs at post-treatment. There was no statistically significant difference between iCBT and usual care for symptoms of PTSD at post-treatment or at three to six month follow-up in the single relevant RCT[43] that made this comparison (95% confidence intervals [CIs] overlapped the null).

The systematic review by Sijbrandij et al.[5] included three primary relevant studies[39,42,45] comparing iCBT to waiting list, one relevant primary study[44] comparing iCBT to internet-based supportive counselling, and one primary study[38] comparing iCBT with an exposure component to iCBT without an exposure component. Three of these RCTs[39,44,45] were included in the Olthuis et al.[14] review. Compared to waiting list control, iCBT was statistically superior for the reduction of PTSD symptoms. Two primary studies[38,44] showed that treatment with iCBT did not statistically differ from treatment with internet-based supportive counselling or iCBT without an exposure component.

The RCT by Lewis et al.[36] monitored symptoms of PTSD using the CAPS-5 and the PCL-5. Participants allocated to iCBT treatment demonstrated statistically significantly lower levels of PTSD symptoms at post-treatment (and at 14 week follow-up compared to those on the delayed treatment waiting list.

The study by Littleton et al.[37] measured symptoms of PTSD using the PSS-IV. In addition, interference was measured by asking participants to indicate how much their PTSD symptoms were interfering with their academic performance, relationships with others, job or volunteer work, and life overall on a scale of zero (does not interfere at all) to three (interferes very much). Both the interactive, therapist-guided iCBT group and the psycho-educational website group reported statistically significant reductions in symptoms of PTSD at post-treatment and at three month follow-up compared to pre-treatment (based on PSS-IV scores). A large number of participants (approximately 75%) in each treatment group also experienced clinically significant reduction in symptoms of PTSD, while no participants reported a clinically significant increase in symptoms of PTSD (as assessed with the reliable change index). There was also an improvement in interference scores observed for both treatment groups between pre-treatment and post-treatment, although these changes did not always reach statistical significance.

Depression Symptoms

Information on the effectiveness of iCBT for symptoms of depression was available from one systematic review[14] and two RCTs.[36,37]

The systematic review by Olthuis et al.[14] included five relevant primary RCTs that monitored depression symptoms over the course of iCBT treatment using the PHQ-9 or the BDI-II.[39,40,43-45] At post-treatment, two[39,45] of the three[39,40,45] RCTs that compared iCBT to waiting list control reported a statistically significant decrease in symptoms of depression, while the third RCT[40] favoured iCBT but did not reach statistical significance. There were no statistically significant differences between iCBT and treatment as usual or internet-based supportive counseling for depression symptoms at post-treatment in the other two relevant studies.[43,44]

The RCT by Lewis et al.[36] monitored symptoms of depression using the BDI. Compared to the delayed treatment control group (waiting list), the participants treated with iCBT demonstrated statistically significant improvements in symptoms of depression at post-treatment and at 14 week follow-up.

The Littleton et al.[37] RCT measured symptoms depression using the Center for Epidemiological Studies-Depression Scale (CES-D). Participants in both treatment programs experienced significant reductions in symptoms of depression at post-treatment and thee month follow-up compared to baseline. There were no statistically significant differences between the iCBT and psycho-educational website groups at any time point. The authors also noted that over one-third of participants in both programs experienced a clinically significant reduction in depression symptoms, as assessed with the reliable change index.

Anxiety Symptoms

No relevant evidence regarding the effectiveness of iCBT for the treatment of anxiety symptoms in patients with PTSD was identified from the included systematic reviews.[5,14,21]

Symptoms of anxiety were assessed using the Beck Anxiety Inventory (BAI) in the RCT by Lewis et al.[36] The authors reported that participants treated with iCBT experienced statistically significantly improvements in symptoms of anxiety at post-treatment and 14 week follow-up compared to the delayed treatment control group.

The RCT by Littleton et al.[37] measured symptoms of anxiety using the Four Dimensional Anxiety Scale (FDAS). Both the iCBT and psycho-educational website groups reported statistically significant decreases in symptoms of anxiety at post-treatment and three month follow-up compared to pre-treatment scores. There were no statistically significant differences in anxiety symptoms between groups at any time point. In addition, over half of the participants in either treatment group reported a clinically significant decrease in anxiety symptoms (measured using the reliable change index).

Suicidality

No relevant evidence regarding the clinical effectiveness of iCBT for suicidality in patients with PTSD was identified.

Safety

No relevant evidence regarding the safety of iCBT in patients with PTSD was identified from the included systematic reviews.[5,14,21]

One RCT[36] stated that there were no adverse events reported for any of the 42 patients randomized to receive iCBT or delayed treatment waiting list. The RCT by Littleton et al.[37] noted that 4.3% of participants (2/46) who were assigned to their interactive iCBT program reported clinically significant increases in depression at post-treatment (measured using the reliable change index). The authors did report that two of these participants experienced the death of an immediate family member while completing the intervention and speculated that this may have contributed to the observed increase in symptomology. Similarly, 8.7% (4/46) of individuals in the iCBT group reported a clinically significant increase in symptoms of anxiety at post-treatment. None of the 41 participants allocated to the psycho-educational website reported clinically significant increase in their symptoms of depression or anxiety. Additionally, no participants in either treatment group reported a clinically significant increase in PTSD symptoms.

Functional Disability

The systematic review by Olthuis et al.[14] reported on outcomes relating to functioning or quality of life from four primary studies.[39,40,43,45] Three studies[39,40,45] compared iCBT to wait list control, all of which were unable to detect statistically significant differences between the two groups for functioning or quality of life. The fourth primary study[43] reported higher SF-36 scores for patients treated with iCBT compared to those given treatment as usual; however, this difference did not reach statistical significance.

The RCT conducted by Lewis et al.[36] used the SDS to assess functional impairment. The participants treated with guided iCBT demonstrated a statistically significant reduction in their SDS scores compared to participants in the delayed treatment waiting list at post-treatment and at the 14 week follow-up.

Patient Satisfaction

No relevant evidence regarding patient satisfaction with iCBT for the treatment of PTSD was identified from the included systematic reviews.[5,14,21]

The RCT by Littleton et al.[37] evaluated participant satisfaction with the interactive iCBT program and their therapist using the Satisfaction with Therapy and Therapist Scale-Revised (STTS-R). Participants in the iCBT group reported high levels of satisfaction with their treatment program and their online therapist. Seven of the 21 participants (33.3%) allocated to the iCBT treatment reported the maximum possible satisfaction rating for the online program, while nine (42.9%) of these patients reported the maximum satisfaction rating with their online therapist.

Patient Adherence and Dropout

Information regarding adherence and dropout rates of patients treated with iCBT for PTSD was available from one systematic review[21] and two RCTs.[36,37] The systematic review by Olthuis et al.[14] provided an average dropout rate for all of their included studies (which included studies ineligible under our inclusion criteria); however, the data from individual studies was not presented and could therefore not be extracted from only the studies relevant to our review.

The systematic review by Kuester et al.[21] reported the dropout rates observed for patients treated with either iCBT or control interventions from four relevant primary studies.[38,39,41,44] Three of these studies[38,39,41] reported less than a 2% difference in dropout rates between iCBT and waiting list[39,41] or between iCBT with an exposure component and iCBT without an exposure component.[38] The two RCTs[39,41] comparing iCBT to waiting list control reported dropout rates of 40.5% and 8.7% in the iCBT groups compared to 41.2% and 9.5% in the waiting list control groups, respectively. The RCT[38] comparing iCBT with an exposure component to iCBT without an exposure component reported a dropout rate of 12% in the exposure group and 14% in the group without an exposure component. The remaining primary study[44] reported a 41.7% dropout rate in the iCBT group compared to 19% in the internet supportive counselling group.

Lewis et al.[36] reported that of the 42 participants randomized, six (6/21, 28.6%) from the treatment group and four (4/21, 19.0%) from the delayed treatment control group were not available at post-treatment (10 weeks). In the RCT by Littleton et al.,[37] 20 of the 46 (43.5%) participants allocated to interactive iCBT and 12 of the 41 (29.3%) participants allocated to the psycho-educational website were not available at post-treatment. These patients failed to initiate the program, withdrew from the study, or discontinued the intervention.

Limitations

A number of limitations were identified in the critical appraisal (Appendix 3, Tables 5 and 6), however, additional limitations exist.

There was variability in the way that PTSD diagnosis was reported in the systematic reviews. This may have been a result of the primary study authors not providing sufficient information on diagnostic status of participants at baseline. The complexity of the condition and the availability of multiple tools or interviews used to diagnose PTSD may have also contributed. In addition, while all studies[5,14,21,36,37] investigated iCBT, the interventions were heterogeneous with respect to program content, number of modules, duration, type of support (e.g., phone, email, combination), and frequency of support. The appropriateness of combining such heterogeneous studies is unclear.

No data was available comparing iCBT to traditional face-to-face CBT (individual or group format), video-delivered or telehealth-delivered CBT, or to alternative frequently used psychotherapy interventions (e.g., Eye Movement Desensitization and Reprocessing).

All of the iCBT programs examined in the included literature provided some form of clinician support, guidance, or assistance. Therefore, the effectiveness of unguided iCBT is unclear. Several studies[53-55] not included in this review have investigated the use of unguided iCBT for the treatment of post-traumatic stress; however, the participants comprised those without a clinical diagnosis of PTSD.

As outlined in our inclusion criteria, all studies[5,14,21,36,37] examined in this review only included patients that met the clinical threshold for diagnosis of PTSD. It is important to note that mental health conditions are complex and that many people that may seek help for symptoms of post-traumatic stress may be of sub-clinical threshold; however, the effectiveness of iCBT in these populations is outside of the scope of this report.

A potentially major limitation that should be considered when interpreting these results is that participants and outcome assessors were aware of treatment allocation in a majority of the reviewed studies. Given that a large number of outcomes reported in these trials were based on subjective questionnaires this may have had an effect on the reliability of the

results. In addition, participant knowledge of their treatment allocation may have been relayed to health professionals (e.g., psychiatrists or family physicians) who the individuals were seeing outside of the context of the study, potentially influencing prescription decisions and creating a source of confounding that may have biased treatment effects in either direction (e.g., clinicians may have increased the prescription of psychotropic medication to patients who were allocated to waiting list controls in an attempt to prevent deterioration or other adverse events). This is particularity important to consider given studies did not control for use of medication throughout the course of trials.

With the exception of the RCT by Littleton et al.,[37] the included studies[5,14,21,36] aimed to find a statistically significant, and not clinically significant, difference between treatment with iCBT and control intervention on various scales that measure symptom severity, quality of life, or other outcomes (see Appendix 2, Table 4 for brief descriptions of some of the scales). A statistically significant difference in scores does not necessarily indicate a clinically significant change in symptom severity, quality of life, or other outcomes. While there is literature that examines the relationship between statistically and clinically significant changes, this was not discussed in detail within four[5,14,21,36] of the included studies.

Five[39,40,43-45] of the eight[38-45] unique relevant primary studies included in the systematic reviews[5,14,21] and both additional RCTs[36,37] had small sample sizes (< 100) and were of variable quality.

The eight relevant primary studies[38-45] from the systematic reviews and the two RCTs[36,37] were not conducted in Canada; hence the results of these studies may not be generalizable for the Canadian setting. However, four studies[37,42-44] were conducted in North America (in the US) and there was no strong indication that the findings from any included would not generalize to individuals from Canada. Based on the reported information, the majority of participants in most studies were female (patient populations ranged from 19%[14] to 100% female[37]), although this is likely a result of the higher prevalence of PTSD in women.[56]

Our review relied on the information presented in identified systematic reviews to assess the eligibility of their included primary studies (i.e., the full-texts of primary studies included within systematic reviews were not reviewed to confirm eligibility). In general, the information used to assess the eligibility of overlapping primary studies was described by the authors of the systematic reviews consistently; however, there were three instances where a primary study was determined to be eligible based on the information presented in one systematic review but ineligible based on the information presented in another systematic review. In these cases, we extracted and summarized the outcome data reported in the systematic review based on the eligibility information presented in each systematic review. Outcome data from primary studies assessed as eligible from one systematic review was not extracted from another systematic review in which the authors presented the study as ineligible for our review. Details on these instances are presented in in Appendix 5, Table 9.

Conclusions and Implications for Decision or Policy Making

Three systematic reviews with meta-analyses[5,14,21] and two relevant RCTs[36,37] were identified regarding the clinical effectiveness of iCBT for adults with PTSD.

Evidence from two included systematic reviews[5,14] and one RCT[37] demonstrated that adults (≥16 years of age) with PTSD treated with iCBT may experience a larger decrease in

severity of PTSD symptoms than those put on a waiting list. Similarly, evidence from one included primary study[44] suggested that treatment with iCBT may lead to larger decreases in PTSD symptom severity scores compared to treatment with internet-based supportive counselling (this difference did not reach statistical significance). The systematic review by Sijbrandij et al.[5] reported that treatment with iCBT with an exposure component resulted in a larger decrease in PTSD symptom severity scores than treatment with iCBT without an exposure component; however, this result was based on data from one primary study[38] and a statistically significant difference was not reached. One study[43] reported that iCBT was equivalent to optimized usual care for PTSD symptom severity. Additional clinical outcomes, including severity of depression and anxiety symptoms, functional disability, and satisfaction with treatment also generally favoured iCBT groups.[5,14,21,36,37] Evidence examining how iCBT compared to face-to-face CBT, video-delivered CBT, or to alternative frequently used psychotherapy interventions was not identified in this review. However, there may be data comparing these treatments available in the future from trials currently underway.[57]

The reviewed iCBT interventions were heterogeneous in program content and it is unclear which features may be most beneficial to patients (e.g., number of modules, duration of program, frequency and type of support). Additionally, patient characteristics such as age, gender, type of trauma experienced, comfort with technology, level of education, use of psychotropic medication, and comorbidity with other mental health conditions may have an unknown effect on treatment success.[36]

The limitations of the included studies and of this report should be considered when interpreting the results. Important risks of bias include the absence of reported strategies to blind outcome assessors and the lack of control over significant confounding characteristics (e.g., comorbidity with other mental health conditions, use of medication). In addition, many included studies used small sample sizes that generally lacked power to detect statistically significant differences in several outcomes of interest. Further research investigating the effectiveness of iCBT compared to face-to-face CBT or video-delivered CBT and the use of unguided iCBT to treat PTSD would help to reduce uncertainty.

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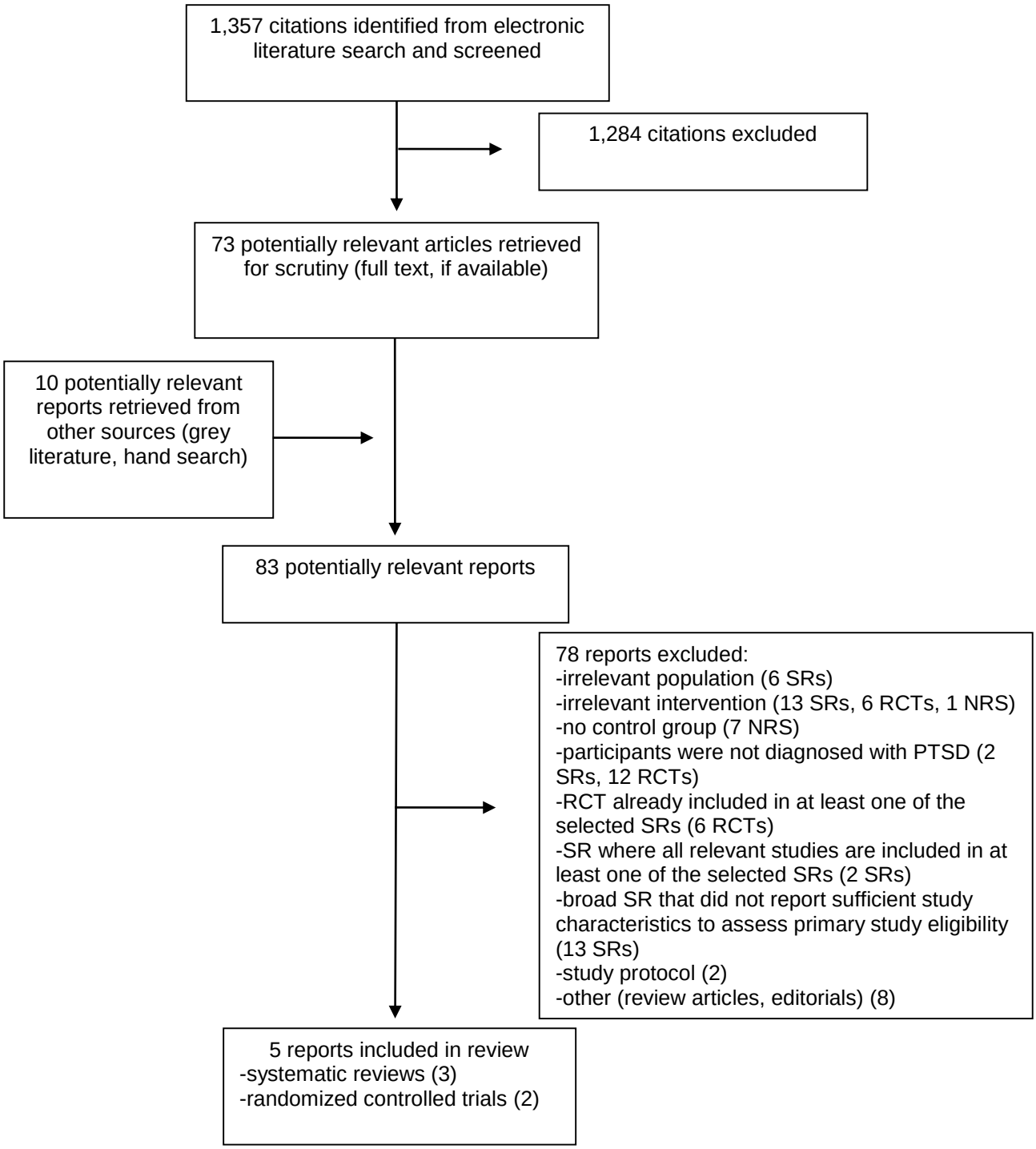
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs, Search Strategy, Numbers of Primary Studies Included, and Objective	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Kuester, 2016[21] Germany	**Study design**: SR and MA that included RCTs **Literature search strategy**: *"We screened the databases Medline, CINAHL, PsycARTICLES, PsycINFO, Psyndex, PubMed, Web of Science, PILOTS and SCOPUS for articles that had been published and for references of unpublished dissertations in English or German language up to 24th February 2015"*[21] (page 4) **Number of primary studies**: In total, 20 RCTs were included, with 4 RCTs relevant for our report. **Objective**: to conduct a comprehensive MA of all RCTs that evaluate internet-based interventions for the treatment of subclinical or clinical PTSD in adults	Adults with subclinical or clinical PTSD (only information on patients with clinical PTSD was included in our review) **Number of patients**: relevant RCTs recruited between 44 and 159 (total of 373 in relevant studies) **Mean age**: NR **Sex**: NR **Type of trauma**: War or terror (2 RCTs) and mixed (2 RCTs)	Internet based intervention programs The iCBT programs relevant to our report were Interapy based, DESTRESS, or were not named. All were iCBT that included therapist support. **Number of sessions**: 6 to 10 **Treatment duration**: 5 to 8 weeks	Active or passive comparison groups Studies relevant to our report used alternative iCBT programs, psycho-education, or WL	**Outcome measures from relevant studies:** - PDS - PSS-IV - IES-R - PCL-C **Follow-up:** up to 24 weeks Note: the systematic review was not limited to these outcomes
Olthuis, 2016[14] Canada	**Study design**: SR and MA that included RCTs **Literature search strategy**: *"A comprehensive search for studies meeting the inclusion criteria was conducted in PsycINFO, PubMed, and Embase to August 19, 2015. An update search employing*	Adults (≥18 years of age) with a primary diagnosis of PTSD or subclinical PTSD according to the DSM. Diagnostic status must have been determined using a validated diagnostic instrument (only information on patients with clinical PTSD was included in our	Therapist-guided, distance-delivered interventions for PTSD (including five relevant studies that used iCBT) **Number of sessions**: 7 to 18	Inactive control (e.g., WL) or active interventions Studies relevant to our report used usual care, internet-based supportive	**Outcome measures from relevant studies:** - IES-R - PDS - PSS-IV - TES - PCL-C - SF-36 - EQ-5D - QOLI

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs, Search Strategy, Numbers of Primary Studies Included, and Objective	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-Up
	an identical search strategy was conducted to January 29, 2016 and a second update search was conducted to July 28, 2016."[14] (page 13) **Number of primary studies**: In total, 19 RCTs were included, with 5 RCTs relevant for our report. **Objective**: *"To comprehensively review the outcomes from therapist-guided, distance-delivered interventions for PTSD"*[14] (page 11)	review) **Number of patients**: relevant RCTs recruited between 44 and 80 (total of 287 in relevant studies) **Mean age:** NR **Sex**: populations from relevant RCTs were 19% to 100% female participants **Type of trauma**: NR	**Treatment duration**: 6 to 8 weeks	counselling, or WL as comparators	- PHQ-9 - BDI-II **Follow-up:** 3 to 12 months Note: the systematic review was not limited to these outcomes
Sijbrandij, 2016[5] Netherlands	**Study design**: SR and MA that included RCTs **Literature search strategy**: Authors searched the Cochrane Central Register of Controlled Trials, PsychINFO, PubMed, Web of Science, and Embase **Number of primary studies**: In total, 12 RCTs were included, with 5 RCTs relevant for our report. **Objective**: To assess the effectiveness of iCBT compared to inactive control (e.g., WL, TAU) or active interventions (e.g., psychoeducation, supportive counselling, face-to-face therapy) in reducing PTSD	Adults with a clinician-obtained diagnosis of PTSD or with elevated levels of PTSD symptoms based on a PTSD self-report instrument (only information on PTSD diagnosed patients was included in our review) **Number of patients**: relevant RCTs recruited between 18 and 228 (total of 475 in relevant studies) **Mean age**: NR (all studies relevant for our report only included adults) **Sex**: NR **Type of trauma:** Pregnancy loss (1 RCT),	iCBT All studies relevant to our report used therapist-assisted iCBT **Number of sessions**: 6 to 10 **Treatment duration**: NR	Inactive control (e.g., WL, TAU) or active interventions (e.g., iCBT without exposure, psycho-education, supportive counselling, face-to-face therapy) Studies relevant to our report used	**Outcome measures from relevant studies**: - CAPS - IES-R - PDS - BDI-II - BSI - PSS-IV - PCL-C - PHQ-9 **Follow-up**: NR Note: the systematic review was not limited to these outcomes

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs, Search Strategy, Numbers of Primary Studies Included, and Objective	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-Up
	symptoms	terrorism or combat (1 RCT), and mixed (3 RCTs)			

BDI-II = Beck Depression Inventory – II; BSI = Brief Symptom Inventory; CAPS = Clinician Administered PTSD Scale; CBT = cognitive behavioural therapy; DSM = Diagnostic and Statistical Manual of Mental Disorders; EQ-5D = EuroQol 5 Dimensions Scale; iCBT = internet-delivered cognitive behavioural therapy; IES-R = Impact of Event Scale – Revised; MA = meta-analysis; NR = not reported; PCL-C = PTSD Checklist – Civilian Version; PDS = Posttraumatic Stress Diagnostic Scale; PHQ-9 = Patient Health Questionnaire; PSS-IV = PTSD Symptom Scale – Interview Version; QOLI = Quality of Life Inventory; RCT = randomized controlled trial; SF-36 = 36-Item Short Form Survey; SR = systematic review; TAU = treatment as usual; TES = Traumatic Event Scale; WL = waiting list.

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design, Setting, and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Lewis, 2017[36] UK	**Study design**: RCT, single blind (the outcome assessor was blinded), 1:1 ratio **Setting**: Participants were recruited from mental health services at a primary care level and at a specialist secondary care Traumatic Stress Service. 95% of participants were referred by treating clinicians and 5% were recruited by advertisements in the media **Objective**: *"To evaluate a novel trauma-focused internet-based guided self-help program for PTSD"*[36] (page 556)	Adults (≥18 years of age) who met the diagnostic criteria for DSM-5 PTSD of mild to moderate severity after a 2-week period of symptom monitoring **Number of patients**: 42 (21 in iCBT group, 21 in WL) **Mean age**: 39.29 years (SD = 12.7, range = 20–65) **Sex**: 59.5% female **Type of trauma:** *"Transportation accidents (n = 9); witnessing a sudden, violent, or accidental death (n = 9); traumatic childbirth or stillbirth (n = 8); sexual assault or rape (n = 5); physical attack (n = 4); life threatening illness or injury (n = 3); serious accident (n = 1); learning of the violent death of a loved one (n = 1); seeing a mutilated body (n = 1); and being held hostage/detained (n = 1)."*[36] (page 559). The average time since trauma was 37.33 months (SD = 46.95, range = 3–228 months).	Therapist-guided self-help iCBT **Number of sessions**: 8 modules **Treatment duration**: 10 weeks The intervention allowed up to 3 hours of therapist assistance, which was offered to provide support, monitoring, motivation, and problem solving. This guidance was provided by a psychiatrist, a clinical psychologist, and three cognitive behavioral therapists who were experienced in the delivery of trauma-focused CBT	WL control (delayed treatment group) This group did not receive any therapist contact until they crossed over	**Primary outcomes**: - CAPS-5 **Secondary outcomes**: - PTSD symptoms (PCL-5) - Depression symptoms (BDI) - Anxiety symptoms (BAI) - Signs of harmful drinking or dependence (AUDIT) - Perceived social support (SSQ) - Functional impairment (SDS) **Follow-up**: 10 weeks (post-treatment), 14 weeks (1 month post-treatment), and 22 weeks (3 months post-treatment)
Littleton, 2016[37] US	**Study design**: RCT, open-label, 1:1 ratio **Setting**: *"Participants were recruited via posted advertisements*	Women who were enrolled as a student at one of four universities or community colleges, had suffered rape-related trauma, and met the diagnostic criteria for PTSD	Therapist-guided iCBT (The From Survivor to Thriver Program) **Number of**	Access to a psycho-educational website that contained informational	**Outcomes**: - PSS-IV - Interference (at school, work, relationships, and overall; scored

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design, Setting, and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-Up
	on all four campuses (e.g., fliers, campus bus advertisements, advertisements in campus newspapers), postings on university psychology department participant management websites, as well as via social media (e.g., a study Facebook page, postings in student Facebook groups)"[37] (page 3) **Objective**: To determine the effectiveness of a therapist-facilitated, online CBT program tailored to meet the needs of rape victims with PTSD	(according to PSS-I) **Number of patients**: 87 (46 in iCBT group, 41 in psycho-educational website group) **Mean age**: 22 years (range = 18–42) **Sex**: 100% female **Type of trauma**: All participants had experienced a completed rape since the age of 14	**sessions**: 9 modules **Treatment duration**: 14 weeks Therapist-guidance was provided by doctoral students in the form of scheduled check-in phone calls approximately once every two weeks. The aim of these calls was to assess the participants' mood, substance use, suicidal or self-harming thoughts, frequency of logging into the program, time spent in enjoyable activities, and to discuss technical problems or distress related to the program.	content from the first three treatment modules (which focused on relaxation, grounding, and coping strategies). The website did not contain multimedia content or interactive exercises from the iCBT program. Patients in both groups received scheduled check-in phone calls from study staff (doctoral students in psychology) generally once every two weeks.	between 0-3) - CES-D - FDAS - Therapist competence - Therapist and treatment satisfaction (STTS-R) - Working alliance (WAI-S) **Follow-up**: 14 weeks (post-treatment) and 3 months

AUDIT = Alcohol Use Disorders Identification Test; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CAPS = Clinician Administered PTSD Scale; CBT = cognitive behavioural therapy; CES-D = Center for Epidemiological Studies-Depression Scale; DSM = Diagnostic and Statistical Manual of Mental Disorders; FDAS = Four Dimensional Anxiety Scale; iCBT = internet-delivered cognitive behavioural therapy; NR = not reported; PCL-5 = PTSD Checklist for DSM-5; PSSI = PTSD Symptom Scale-Interview; RCT = randomized controlled trial; PSS-IV = PTSD Symptom Scale Interview; SD = standard deviation; SDS = Sheehan Disability Scale; SSQ = Social Support Questionnaire; STTS-R = Satisfaction with Therapy and Therapist Scale-Revised; WAI-S = Working Alliance Inventory-Short Form; WL = waiting list.

Table 4: Description of Outcome Assessment Scales

Outcome Assessment Scale	Reference	Description
BAI	Julian, 2011[58]	A 21-question multiple-choice self-report inventory used to evaluate the severity of anxiety symptoms. The total score (sum of the 21 items) classifies anxiety severity: 0-9 (normal to minimal anxiety), 10-18 (mild to moderate anxiety), 19-29 (moderate to severe anxiety) and ≥30 (severe anxiety).
BDI (I or II)	Beck, 1961[59]	A 21-question multiple-choice self-report inventory used to evaluate the severity of depressive symptoms. Each answer is scored on a value of 0 to 3. A total score is calculated: 0-13 (minimal depression), 14-19 (mild depression), 20-28 (moderate depression), and ≥29 (severe depression).
BSI	Knaevelsrud, 2017[60]	An 18-item inventory that consists of three 6-item subscales (focusing on depression, anxiety, somatization). Each item is rated on a 5-point Likert scale (0 = not at all, 4 = extremely), with higher scores indicating increased symptom severity.
CAPS (CAPS-5)	Lewis, 2017[36]	A 30-item structured interview that corresponds to the DSM-5 criteria for PTSD. This scale has been considered the “gold standard” for PTSD assessment. Higher scores indicate more severe PTSD symptoms.
CES-D	Littleton, 2016[37]	A 20-item, self-report measure of depressive symptoms occurring within the past week. Total scores can range from 0 to 60. A total score above 12 suggest clinically significant depressive symptoms.
EQ-5D	Devlin, 2017[61]	A simple, generic, and standardized measure of health status (quality of life and functioning) developed by the EuroQol Group that can be used in a wide range of health conditions and treatment. It typically includes a visual analogue scale on which patients rate their health states between 100 (best possible) and zero (worst possible).
FDAS	Littleton, 2016[37]	A 35-item measured used to quantify physiological, cognitive, emotional, and behavioral anxiety symptoms occurring within the past week. Total scores can range between 35 and 175. Higher scores indicate more severe symptoms of anxiety.
IES-R	Kersting, 2013[42]	A 22-item scale used to assess post-traumatic stress symptoms categorized into three symptom clusters (intrusions, avoidance, and hyperarousal). Frequency of symptoms over the past week is scores on a 4-point measurement scale. Higher scores indicate increased symptom severity.
PCL-C	Cernvall, 2017[62]	A 17-item self-report instrument used to measure PTSD symptoms. Each item is rated between1 (not at all) and 5 (extremely). Higher scores indicate increased PTSD symptom severity. A score of 44 has been suggested as a cut-off for the depression of PTSD.
PDS	Franklin, 2017[63]	A 48-item self-report measure of PTSD symptom severity. Total scores can range between 0 and 51, with higher scores indicating higher symptom severity.
PHQ-9	Johnston, 2011[64]	A 9-item measure of the symptoms and severity of major depressive disorder based on the DSM-IV criteria. Each question is scored on a value of 0 to 3, with higher scores indicating more severe symptoms. A total score of 10 on the PHQ-9 has been identified as an important threshold for identifying major depression that meets the DSM-IV criteria.

Table 4: Description of Outcome Assessment Scales

Outcome Assessment Scale	Reference	Description
PSS-IV	Littleton, 2016[37]	An interview measure that consists of 17 items, each rated on a scale of 0 (does not interfere at all) to 3 (interferes very much). Total score ranges from 0 to 51, with higher scores indicating more severe PTSD symptoms.
TES	Nieminen, 2016[40]	A scale consisting of 24 questions used to assess the severity of traumatic stress symptom. Total scores range from 0 to 51, with higher scores indicating more severe symptoms. A cut-off score of ≥30 is considered to indicate a PTSD diagnosis.
SF-36	Ware, 1992[65]	A multipurpose survey consisting of 36 questions that is used to evaluate mental and physical functioning and overall health-related quality of life. Responses are weighted between 0 (lowest level of health) and 100 (highest level of health) and combined to yield a physical health composite score and a mental health composite score
STTS-R	Littleton, 2016[37]	A 12-item measure used to quantify an individual's satisfaction with their therapist and with the treatment received. The Individual as asked to rate their agreement with each measure between 1 (strong disagree) and 5 (strongly agree). Higher scores indicate increased patient satisfaction.
WAI-S	Littleton, 2016[37]	A 12-item questionnaire used to assess working alliance. It investigates three areas: agreement on therapeutic tasks, mutual endorsement of therapeutic goals, and bond between therapist and client. The individual is asked to rate the extent to which each item is true between 1 (never) and 7 (always). Higher scores indicate a stronger therapeutic alliance between therapist and client.

BDI-II = Beck Depression Inventory – II; BSI = Brief Symptom Inventory; CAPS = Clinician Administered PTSD Scale; CES-D = Center for Epidemiological Studies-Depression Scale; EQ-5D = EuroQol 5 Dimensions Scale; FDAS = Four Dimensional Anxiety Scale; IES-R = Impact of Event Scale – Revised; PCL-C = PTSD Checklist – Civilian Version; PDS = Posttraumatic Stress Diagnostic Scale; PHQ-9 = Patient Health Questionnaire; PSS-IV = PTSD Symptom Scale – Interview Version; PTSD = post-traumatic stress disorder; SF-36 = 36-Item Short Form Survey; STTS-R = Satisfaction with Therapy and Therapist Scale-Revised; TES = Traumatic Event Scale; WAI-S = Working Alliance Inventory-Short Form.

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[33]

Strengths	Limitations
Kuester, 2016[21]	
• The objectives and inclusion/exclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes • Multiple databases were searched (Medline, CINAHL, PsycARTICLES, PsycINFO, Psyndex, PubMed, Web of Science, PILOTS, and SCOPUS). In addition, grey literature searching was done by examining abstracts of conference contributions, posters and commentaries, and trial registries (clinicaltrials.gov) • Search terms and dates were provided (February 24, 2015 and April 7, 2015) • Study selection process was described and conducted in duplicate • A flow chart of study selection was provided • A list of included studies was provided • Characteristics of included studies were described in detail • Meta-analysis was conducted with random effects model. Subgroup analyses were conducted using mixed effects analysis • Heterogeneity was assessed and considered for the interpretation of results • Publication bias was assessed and although there was a minor tendency toward bias, the authors concluded it had no significant effect on the efficacy of iCBT in the data sets under scrutiny • The authors stated that they had no conflicts of interest and that no financial support had been received for this review	• It is unclear whether the review methods were established prior to the conduct of the review (no mention of a protocol) • It is unclear if data extraction or quality assessment were done in duplicate • A list of excluded studies was not provided (although the reasons for exclusion were) • Details on the methods used to assess quality of included studies were lacking • It is unclear if there were any adverse events resulting from the intervention in any of the included studies • Review authors did not report on source of funding for the included studies • Risk of bias was not considered when conducting the meta-analysis
Olthuis, 2016[14]	
• The objectives and inclusion/exclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes • Multiple databases (PsycINFO, PubMed, and Embase) and the reference lists of identified studies and relevant reviews were searched. In addition, authors searched trial registries (clinicaltrials.gov and the Australian New Zealand Clinical TrialsRegistry) and the Journal of Medical Internet Research (www.jmir.org) databases to locate trials that may have been registered but never published • Search terms and dates were provided (August 19, 2015, January 29, 2016, and July 28, 2016) • Study selection, data extraction, and assessment of risk of bias were completed in duplicate and described in detail • Justification for only including RCTs was provided • A flow chart of study selection was provided	• It is unclear whether the review methods were established prior to the conduct of the review (no mention of a protocol) • A list of excluded studies was not provided (although the reasons for exclusion were) • It is unclear if there were any adverse events resulting from the intervention in any of the included studies • Review authors did not report on source of funding for the included studies • The source of funding for the review is unclear (one author acknowledges support by the University of Regina President's Chair for Academic Excellence in Adult Mental Health Research) • There was no mention of conflicts of interest

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[33]

Strengths	Limitations
• A list of included studies was provided • Details on the methods used to assess quality of included studies were presented (Cochrane Collaboration's risk of bias tool) • Characteristics of included studies were described in detail • Meta-analysis was conducted with random effects model due to the high degree of heterogeneity expected in the included studies. Within-group and between-group effects were analyzed separately • Heterogeneity was assessed by calculating the *Q* statistic. Where heterogeneity was present the I^2 statistic was used to determine the variability due to heterogeneity rather than chance • Publication bias was assessed and the results did not indicate concern	
Sijbrandij, 2016[5]	
• The objectives and inclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes • Multiple databases (the Cochrane Central Register of Controlled Trials, PsychINFO, PubMed, Web of Science, and Embase) and the reference lists of previous meta-analyses and reviews were considered and searched for relevant articles were searched • Search terms were provided • A list of included studies was provided • Details on the methods used to assess quality of included studies were presented (assessed with four criteria of the Cochrane Handbook for Systematic Reviews of Interventions) • Quality assessment of included studies was completed in duplicate and described in detail • Characteristics of included studies were described in detail • Meta-analysis was conducted with random effects model. The *Q* and I^2 statistics were calculated when appropriate • Publication bias was assessed using funnel plot and Egger's test and did not indicate the presence of publication bias • The authors stated that they had no conflicts of interest or financial disclosure related to this review	• It is unclear whether the review methods were established prior to the conduct of the review (no mention of a protocol) • The exclusion criteria were not explicitly stated • Search dates were not provided • A list of excluded studies was not provided (although the reasons for exclusion were) • It is unclear if there were any adverse events resulting from the intervention in any of the included studies • It is unclear if study selection or data extraction were done in duplicate • Review authors did not report on source of funding for the included studies

iCBT = internet-delivered cognitive behavioural therapy.

Table 6: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[34]

Strengths	Limitations
Lewis, 2017[36]	
• The objectives, interventions, controls, and main outcomes are clearly described • Detailed methodology on patient recruitment and assessment of inclusion/exclusion criteria is included • Randomization was done through a system of sealed, opaque envelopes containing an allocation code generated by an independent statistician • Treatment and control groups were overall balanced in baseline patient characteristics • Sample size calculations were undertaken and the appropriate number of patients recruited (42 estimated vs. 42 randomized) • Intention-to-treat analysis was undertaken (missing data was imputed using values uniformly sampled between a last observation last observation carried forward method and a missing at random method) • Because participants were recruited from both the primary care level and specialist secondary care services study participants, care providers, and setting appear to be representative of the population and care setting of interest • Outcome assessors were blind to the treatment received • Adverse events were recorded as part of the study (there no events reported) • Length of follow-up was consistent between the treatment and control groups (10 weeks, 14 weeks, and 22 weeks) • Authors noted that dropout was not significantly associated with age, gender, education, baseline PTSD symptoms, or baseline social support • Estimates of random variability (standard deviations) were reported	• Due to the nature of the intervention, patients were not blinded to treatment assignment • The number of patients with comorbid mental health conditions (e.g., generalized anxiety disorder, depression, social anxiety disorder) was not described as part of the baseline patient characteristics (potential confounder) • The dropout rates in the treatment and control groups were substantial (28.6% in the iCBT group compared to 19.0% in the control group at post-treatment) • Conflicts of interest were stated by all study authors. The study was a collaborative project between the company who developed the software and Cardiff University. If the program was marketed, royalties would be paid to Cardiff University, Cardiff and Vale University Health Board, and to five of the seven authors. The remaining two authors had no conflicts of interest to disclose • The source of funding was unclear
Littleton, 2016[37]	
• The objectives, interventions, controls, and main outcomes are clearly described • Detailed methodology on patient recruitment and assessment of inclusion/exclusion criteria is included • Randomization was done based on a computerized coin flip following assessment of eligibility criteria • Treatment groups were overall balanced in baseline patient characteristics and any differences were well-documented • Adverse events were recorded as part of the study (clinically significant increases in PTSD symptoms was assessed by the reliable change index) • Intention-to-treat analysis was undertaken (data missing at post-treatment and follow-up were imputed using the R package mice) • Care providers and setting appear to be representative of those of interest	• Due to the nature of the intervention, patients and assessors were not blinded to treatment assignment • The number of patients with comorbid mental health conditions (e.g., generalized anxiety disorder, depression, social anxiety disorder) was not described as part of the baseline patient characteristics (potential confounder) • The dropout rates in the treatment and control groups were substantial (43.5% in the iCBT group compared to 29.3% in the control group at post-treatment) • Attempts were made to gather data on patients lost to follow-up; however, only 2 of 7 patients could be contacted to complete post-treatment assessments • It is unclear if sample size calculations were conducted • Participant recruitment relied on individuals to reach out to study investigators through posted advertisements, which may have selected for a motivated subset of people with

Table 6: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[34]

Strengths	Limitations
• Authors noted that there were no differences between dropouts and completers on demographics or other baseline characteristics • Length of follow-up was consistent between treatment groups (post-treatment and at 3 month follow-up) • Estimates of random variability (standard errors/deviations) and actual probability values (*P*-values) were reported	PTSD that are more likely to complete iCBT programs and to apply their learning in their lives • Source of funding and potential conflicts of interest were not disclosed

iCBT = internet-delivered cognitive behavioural therapy; PTSD = post-traumatic stress disorder.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 7: Summary of Findings Included Systematic Reviews and Meta-Analyses

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Kuester, 2016[21]</td></tr>
<tr><td>Systematic review investigating the effectiveness of internet-based interventions for posttraumatic stress.

Relevant individual studies: The systematic review included 4 relevant RCTs on the use of iCBT for the treatment of clinically diagnosed PTSD in adults.

Findings: The systematic review did not conduct a subgroup analysis for the studies that are relevant for our review; therefore, no information on outcomes relating to PTSD symptom severity was available. However, information on the number of dropouts was available.

Comparison of iCBT groups and control groups with respect to dropout rates
<table>
<tr><th>Primary study citation</th><th>Treatment group</th><th>Dropout rate</th></tr>
<tr><td>Knaevelsrud, 2015</td><td>iCBT (N = 79)
WL (N = 80)</td><td>40.5%
41.2%</td></tr>
<tr><td>Litz, 2007</td><td>iCBT (N = 24)
Internet supportive counselling (N = 21)</td><td>41.7%
19%</td></tr>
<tr><td>Spence, 2014</td><td>iCBT with exposure (N = 59)
iCBT without exposure (N = 66)</td><td>12%
14%</td></tr>
<tr><td>Spence, 2011</td><td>iCBT (N = 23)
WL (N = 21)</td><td>8.7%
9.5%</td></tr>
</table>
iCBT = internet-delivered cognitive behavioural therapy; N = number of patients; WL = waiting list.</td><td>"Our meta-analysis provides promising initial evidence for the efficacy of CBT-IBIs in the treatment of PTSD. IBIs have the potential to add new and beneficial options for interventions to mental health care and may address challenges associated with the provision of conventional psychotherapy. CBT-based IBIs in particular significantly reduce PTSD symptoms, and dropout rates indicate that treatment through the internet is well accepted among participants with various trauma types. Our findings are an initial step that highlights the overall promising avenues for internet-based programs for the treatment of PTSD, but more systematic research is necessary to strengthen the evidence and disentangle the impact of particular program characteristics, in order to increase the knowledge about the optimal internet-based delivery of treatment."[21] (page 14)</td></tr>
<tr><td colspan="2">Olthuis, 2016[14]</td></tr>
<tr><td>Systematic review investigating the effectiveness of distance-delivered interventions for PTSD.

Relevant individual studies: The systematic review included 5 relevant RCTs on the use of iCBT for the treatment of clinically diagnosed PTSD in adults.

Findings: The systematic review presented results on PTSD symptoms, depression symptoms, and functioning or quality of life that could be extracted for the relevant studies.

Comparison of iCBT versus waiting list with respect to several outcomes
<table>
<tr><th>Primary study citation</th><th>Outcome measures</th><th>Within-group effect sizes (Hedges' g [95% CI])</th><th>Between-group effect sizes (Hedges' g [95% CI])</th></tr>
<tr><td colspan="4">PTSD Symptoms</td></tr>
<tr><td>Ivarsson, 2014 (N = 62)</td><td>IES-R, PDS
Post-treatment</td><td>1.48 (0.92 to 2.04)</td><td>0.89 (0.37 to 1.41)</td></tr>
<tr><td>Nieminen, 2016</td><td>IES-R, TES</td><td></td><td></td></tr>
</table></td><td>"Despite the aforementioned limitations, the present findings highlight some promising reasons to continue to explore distance-delivered interventions for PTSD. Taken together, the 19 included studies suggest that this type of intervention can reduce PTSD symptoms. Moreover, the Internet- and printed materials-based (with email or telephone support) delivery approach produces superior outcomes to a waiting list control. Future research that</td></tr>
</table>

Table 7: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings				Authors' Conclusion
(N = 56)	Post-treatment	1.33 (0.73 to 1.93)	0.58 (0.02 to 1.14)	*compares the Internet delivery approach to face-to-face delivery and investigates whether the Internet delivery approach works best as a stand-alone approach or as a complement or adjunct to face-to-face care is needed."*[14] (page 24)
Spence, 2011 (N = 44)	**PCL-C** Post-treatment Follow-up	 0.78 (0.18 to 1.38) 0.81 (0.21 to 1.41)	 0.46 (−0.16 to 1.08) NR	
Depression Symptoms				
Ivarsson, 2014 (N = 62)	**BDI-II** Post-treatment	 0.92 (0.40 to 1.44)	 0.57 (0.06 to 1.08)	
Nieminen, 2016 (N = 56)	**BDI-II, PHQ-9** Post-treatment	 0.69 (0.13 to 1.25)	 0.25 (−0.30 to 0.80)	
Spence, 2011 (N = 44)	**PHQ-9** Post-treatment Follow-up	 0.83 (0.23 to 1.43) 0.73 (0.13 to 1.33)	 0.69 (0.06 to 1.32) NR	
Functioning or Quality of Life				
Ivarsson, 2014 (N = 62)	**QOLI** Post-treatment	 0.59 (0.08 to 1.10)	 0.30 (−0.20 to 0.80)	
Nieminen, 2016 (N = 56)	**QOLI, EQ-5D** Post-treatment	 0.41 (−0.14 to 0.96)	 −0.07 (−0.62 to 0.48)	
Spence, 2011 (N = 44)	**SDS** Post-treatment Follow-up	 0.54 (−0.05 to 1.13) 0.73 (0.13 to 1.33)	 0.61 (−0.01 to 1.23) NR	

BDI-II = Beck Depression Inventory, Second Edition; CI = confidence interval; EQ-5D = EuroQol 5 Dimensions Scale; iCBT = internet-delivered cognitive behavioural therapy; IES-R = Impact of Events Scale, Revised; N = number of patients; NR = not reported; PCL-C = PTSD Checklist Civilian version; PSD = Post-traumatic Stress Diagnostic Scale; PHQ–9 = Patient Health Questionnaire, 9-item; QOLI = Quality of Life Inventory; SDS = Sheehan Disability Scale; TES = Traumatic Event Scale.

Comparison of iCBT versus optimized usual care with respect to several outcomes

Primary study citation	Outcome measures	Within-group effect sizes (Hedges' *g* [95% CI])	Between-group effect sizes (Hedges' *g* [95% CI])
PTSD Symptoms			
Engel, 2015 (N = 80)	**PCL-C** Post-treatment Follow-up	 0.31 (−0.11 to 0.74) 0.72 (0.28 to 1.16)	 −0.13 (−0.57 to 0.31) −0.12 (−0.56 to 0.32)
Depression Symptoms			
Engel, 2015 (N = 80)	**PHQ-9** Post-treatment Follow-up	 0.35 (−0.08 to 0.78) 0.41 (−0.01 to 0.84)	 −0.13 (−0.57 to 0.31) −0.20 (−0.64 to 0.24)
Functioning or Quality of Life			
Engel, 2015 (N = 80)	**SF-36** Post-treatment Follow-up	 0.25 (−0.17 to 0.67) 0.37 (−0.06 to 0.80)	 0.21 (−0.23 to 0.65) 0.31 (−0.13 to 0.75)

CI = confidence interval; iCBT = internet-delivered cognitive behavioural therapy; PCL-C = PTSD Checklist Civilian version; PHQ–9 = Patient Health Questionnaire, 9-item; SF-36 = 36-Item Short Form Survey.

Comparison of iCBT versus internet-based supportive counselling with respect to several outcomes

Primary study citation	Outcome measures	Within-group effect sizes (Hedges' *g* [95% CI])	Between-group effect sizes (Hedges' *g* [95% CI])
PTSD Symptoms			
Litz, 2007 (N = 45)	**PSS-IV** Post-treatment Follow-up	 0.85 (0.16 to 1.54) 1.81 (0.89 to 2.73)	 0.40 (−0.31 to 1.11) 0.90 (−0.08 to 1.88)
Depression Symptoms			

Table 7: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings				Authors' Conclusion
Litz, 2007 (N = 45)	**BDI-II** Post-treatment Follow-up	 0.66 (−0.02 to 1.34) 0.92 (0.08 to 1.76)	 0.49 (−0.23 to 1.21) 0.97 (−0.01 to 1.95)	

BDI-II = Beck Depression Inventory, Second Edition; CI = confidence interval; iCBT = internet-delivered cognitive behavioural therapy; PSS-I = PTSD Symptom Scale – Interview Version.

Sijbrandij, 2016[5]

Systematic review investigating the effectiveness of iCBT for PTSD or post-traumatic stress.

Relevant individual studies: The systematic review included 5 relevant RCTs on the use of iCBT for the treatment of clinically diagnosed PTSD in adults.

Findings: The systematic review presented results on PTSD symptoms that could be extracted for the relevant studies. Data on the effectiveness of iCBT for the reduction of comorbid symptoms of depression was also available; however, this data were not presented in a way that allowed for the extraction of results from relevant studies.

Comparison of iCBT versus waiting list with respect to several outcomes

Primary study citation	Outcome measures	Between-group effect sizes (Hedges' *g* [95% CI])	*P*-value
PTSD Symptoms			
Ivarsson, 2014 (N = 62)	CAPS, IES-R, PDS	0.89 (0.37 to 1.41)	0.02
Kersting, 2013 (N = 228)	IES-R, BSI	0.88 (0.61 to 1.15)	0.00
Spence, 2011 (N = 42)	PCL-C, PHQ-9	0.44 (−0.16 to 1.04)	0.15
Three studies combined (N = 332)	CAPS, IES-R, PDS, BSI, PCL-C, PHQ-9	0.77 (0.34 to 1.20)	NR

BSI = Brief Symptom Inventory; CI = confidence interval; iCBT = internet-delivered cognitive behavioural therapy; IES-R = Impact of Events Scale, Revised; N = number of patients; NR = not reported; PCL-C = PTSD Checklist Civilian version; PDS = Post-traumatic Stress Diagnostic Scale; PHQ–9 = Patient Health Questionnaire, 9-item.

Comparison of iCBT versus internet-based supportive counselling with respect to several outcomes

Primary study citation	Outcome measures	Between-group effect sizes (Hedges' *g* [95% CI])	*P*-value
PTSD Symptoms			
Litz, 2007 (N = 18)	PSS-IV	0.40 (−0.29 to 1.10)	0.25

CI = confidence interval; iCBT = internet-delivered cognitive behavioural therapy; N = number of patients; PSS-IV = PTSD Symptom Scale – Interview Version.

Comparison of iCBT with exposure versus iCBT without exposure with respect to several outcomes

Primary study citation	Outcome measures	Between-group effect sizes (Hedges' *g* [95% CI])	*P*-value
PTSD Symptoms			
Spence, 2014 (N = 125)	PSS-IV, IES-R, PHQ-9	0.24 (−0.11 to 0.59)	0.18

CI = confidence interval; iCBT = internet-delivered cognitive behavioural therapy; IES-R = Impact of Events Scale, Revised; N = number of patients; PSS-IV = PTSD Symptom Scale – Interview Version.

"This meta-analysis promotes the use of iCBT in clinical settings, potentially as part of blended care strategies. Preferably, iCBT interventions are therapist-assisted, and measures should be taken to enhance uptake and ensure patients' motivation to finish iCBT intervention of longer duration. Note, however, that self-help iCBT showed a moderate effect size in our meta-analysis, and it may still be offered to clients preferring self-help treatments or in situations where therapist support is unavailable."[5] (page 790)

"The findings of this systematic review and meta-analysis supplement understanding of Internet-delivered interventions by showing that iCBT, particularly with some component of therapist-support, is an effective treatment for individuals with PTSD symptoms. Accordingly, iCBT may be a promising alternative to traditional PTSD treatments."[5] (page 790)

CBT = cognitive behavioural therapy; IBI = internet-based intervention; iCBT = internet-delivered cognitive behavioural therapy; PTSD = post-traumatic stress disorder.

Table 8: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Lewis, 2017[36]	

RCT investigating the effectiveness of a therapist-guided self-help iCBT program (N = 21) compared to a delayed treatment control group (DT; N = 21) for the treatment of patients with mild to moderate PTSD.

Comparison of iCBT and delayed treatment control (DT) with respect to primary outcomes

Measure	Mean score (SD) Treatment group iCBT (N = 21)	Mean score (SD) Treatment group DT (N = 21)	Mean scores difference between groups (iCBT−DT) (95% CI)
CAPS			
Pre-treatment	35.99 (6.29)	37.12 (6.95)	−1.13 (NR)
Post-treatment (10 weeks)	17.93 (12.25)	36.53 (7.1)	−18.60 (−24.65 to −13.41)
Follow-up (14 weeks)	16.47 (13.22)	33.63 (8.42)	−17.16 (−23.78 to −10.68)
Follow-up (22 weeks)*	15.77 (13.01)	14.8 (13.71)	0.97 (−7.84 to 8.44)

*Both groups had received treatment by week 22 (week 22 was post-treatment for the delayed-treatment group).
CAPS = Clinician Administered PTSD Scale; CI = confidence interval; DT = delayed treatment control; iCBT = internet-delivered cognitive behavioural therapy; N = number of patients; NR = not reported; SD = standard deviation.

Between-group effect sizes (iCBT versus delayed treatment control) for CAPS score at post-treatment using various imputation methods to account for missing data

Imputation method	Between-group effect sizes (Cohen's *d*)
Multiple imputation method	1.86
Missing at random imputation	2.60
Last observation carried forward imputation	1.42

iCBT = internet-delivered cognitive behavioural therapy

Comparison of iCBT and delayed treatment control (DT) with respect to secondary outcomes

Measure	Mean score (SD) Treatment group iCBT (N = 21)	Mean score (SD) Treatment group DT (N = 21)	Mean scores difference between groups (iCBT−DT) (95% CI)
PCL			
Pre-treatment	50.78 (12.54)	49.87 (12.58)	0.91 (NR)
Post-treatment (10 weeks)	25.44 (15.84)	51.23 (9.97)	−25.79 (NR)
Follow-up (14 weeks)	22.26 (16.90)	44.74 (14.29)	−22.48 (NR)
Follow-up (22 weeks)*	21.30 (16.79)	21.81 (17.61)	−0.51 (NR)
BAI			
Pre-treatment	30.97 (13.60)	30.58 (15.72)	0.39 (NR)
Post-treatment (10 weeks)	17.10 (11.06)	30.05 (14.43)	−12.95 (NR)
Follow-up (14 weeks)	15.49 (11.63)	28.08 (15.10)	−12.59 (NR)
Follow-up (22 weeks)*	14.16 (11.75)	13.95 (12.94)	0.21 (NR)
BDI			
Pre-treatment	24.72 (10.36)	26.04 (8.47)	−1.32 (NR)
Post-treatment (10 weeks)	15.97 (10.42)	26.80 (9.08)	−10.83 (−16.66 to −5.14)
Follow-up (14 weeks)	14.66 (10.94)	23.61 (10.88)	−8.95 (NR)
Follow-up (22 weeks)*	15.24 (9.88)	15.85 (9.69)	−0.61 (NR)
SDS			
Pre-treatment	17.93 (7.14)	18.56 (5.73)	−0.63 (NR)
Post-treatment (10 weeks)	9.29 (8.09)	18.65 (6.95)	−9.36 (−13.56 to −3.93)
Follow-up (14 weeks)	9.55 (10.18)	16.24 (8.39)	−6.69 (NR)
Follow-up (22 weeks)*	9.35 (9.76)	9.87 (8.70)	−0.52 (NR)
AUDIT			
Pre-treatment	3.89 (4.18)	5.41 (5.47)	−1.52 (NS)

"The study findings suggest that internet-based guided self-help can be effective for the treatment of PTSD. Participants in the guided self-help group reported significant reductions in traumatic stress symptoms in comparison to the delayed treatment control group posttreatment and at 1-month follow up. Once the delayed treatment group had received treatment, their mean CAPS-5 scores reduced to the same degree as those of the immediate treatment group. The same pattern of results emerged in relation to symptoms of anxiety, depression, and functional impairment. These results were obtained with a mean of less than 2½ h of therapist input, around a fifth of that for the first-line face-to-face therapies currently recommended by NICE (NICE, 2005). The findings support the use of internet-based guided self-help as a potentially clinically and cost effective treatment option for PTSD of mild to moderate severity."[36] (page 561)

Table 8: Summary of Findings of Included Primary Clinical Studies

Main Study Findings				Authors' Conclusion
Post-treatment (10 weeks)	3.74 (3.64)	5.88 (6.51)	−2.13 (−6.02 to 1.63)	
Follow-up (14 weeks)	3.93 (4.40)	5.39 (5.67)	−1.46 (NS)	
Follow-up (22 weeks)*	4.00 (4.16)	5.19 (5.92)	−1.19 (NS)	
SSQ				
Pre-treatment	13.73 (9.01)	18.62 (10.88)	−4.89 (NS)	
Post-treatment (10 weeks)	15.25 (7.97)	15.43 (9.74)	−0.18 (−5.37 to 5.33)	
Follow-up (14 weeks)	14.32 (7.55)	16.23 (8.89)	−1.91 (NS)	
Follow-up (22 weeks)*	16.28 (9.23)	21.52 (11.73)	−5.24 (NS)	

*Both groups had received treatment by week 22 (week 22 was post-treatment for the delayed-treatment group).
AUDIT = Alcohol Use Disorders Identification Test; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CI = confidence interval; iCBT = internet-delivered cognitive behavioural therapy; N = number of patients; NS = non-significant; PCL = PTSD checklist; SD = standard deviation; SDS = Sheehan Disability Scale; SSQ = Social Support Questionnaire.

Comparison of iCBT and delayed treatment control (DT) with respect to dropout rate

	Treatment group	
Measure	iCBT (N = 21)	DT (N = 21)
Number of dropouts* (% of total)		
Post-treatment (10 weeks)	6 (28.6%)	4 (19.0%)

*The number of patients who were randomized to an intervention group but did not complete post-treatment questionnaires.
DT = delayed treatment; iCBT = internet-delivered cognitive behavioural therapy; N = number of patients.

Adverse events: No adverse events were reported for any patient in either treatment group.

Littleton, 2016[37]

RCT investigating the effectiveness of an interactive, therapist-guided iCBT program (the From Survivor to Thriver Program; N = 46) compared to access to a psycho-educational website (N = 41) for the treatment of patients with rape-related PTSD.

Comparison of interactive, therapist-guided iCBT (iCBT) versus psycho-educational website (PE) with respect to several outcomes

	Treatment group					
	iCBT (N = 38[a], 23[b], 20[c], 18[d], 20[e], 37[f], 20[g], 19[h])			PE (N = 35[a], 28[b], 21[c], 24[d], 17[e], 33[f], 23[g], 17[h])		
Measure	Mean score (SD)	*d**	% RCI†	Mean score (SD)	*d**	% RCI†
PSS-IV						
Pre-treatment[a]	23.7 (6.5)			23.0 (7.3)		
Post-treatment[b]	11.2 (5.8)	0.88	73.9	10.4 (8.5)	0.86	75.0
Follow-up (3 month)[c]	7.9 (6.3)	1.80	80.0	6.8 (5.7)	1.80	70.0
Interference (school)						
Pre-treatment[a]	1.2 (0.9)			1.3 (1.0)		
Post-treatment[b]	0.7 (0.8)	0.28	—	0.8 (1.0)	0.32	—
Interference (work)						
Pre-treatment[a]	0.8 (0.9)			0.7 (0.9)		
Post-treatment[b]	0.3 (0.7)	0.05	—	0.4 (0.8)	0.13	—
Interference (relationships)						
Pre-treatment[a]	2.5 (0.6)			2.2 (0.7)		
Post-treatment[b]	1.3 (1.0)	0.51	—	1.6 (0.9)	0.79	—
Interference (overall)						
Pre-treatment[a]	2.1 (0.6)			2.1 (0.6)		

"Initial comparisons of the efficacy of these two interventions supported that the programs were equally efficacious at reducing symptoms of PTSD, depression, and general anxiety."[37] (page 15)

"Bearing these limitations in mind, results provide support for the efficacy of tailored cognitive-behaviorally oriented online interventions for rape-related PTSD presented in either a self-help or therapist-facilitated format. Future trials are necessary to evaluate the efficacy and effectiveness of such interventions when delivered to more diverse populations and when delivered in multiple practice settings (e.g., college counseling centers, VA outpatient clinics, sexual assault resource centers). Additionally, future research is necessary to determine which individuals are

Table 8: Summary of Findings of Included Primary Clinical Studies

Main Study Findings							Authors' Conclusion
Post-treatment[b]	1.5 (0.8)	0.60	—	1.3 (0.7)	0.50	—	*most likely to benefit from a self-help or therapist-facilitated format, including utilizing a treatment matching protocol. Finally, future research should focus on strategies to increase engagement in online treatments, as well as to determine the necessary effective treatment dose for different groups of individuals. Work in these areas is necessary in order to develop beneficial, therapist-resource efficient online interventions for PTSD."*[37] (page 16)
CES-D							
Pre-treatment[a]	22.0 (9.7)			22.6 (9.1)			
Post-treatment[d]	14.7 (9.6)	0.68	40.0	13.2 (7.5)	0.39	37.5	
Follow-up (3 month)[e]	14.4 (10.7)	0.84	40.0	10.8 (7.2)	0.62	52.9	
FDAS							
Pre-treatment[f]	78.7 (18.4)			81.5 (23.4)			
Post-treatment[g]	68.9 (23.3)	0.75	55.0	58.7 (16.4)	0.63	52.2	
Follow-up (3 month)[h]	60.7 (16.0)	0.78	68.4	59.7 (17.2)	0.68	52.9	
STTS-R (Program)							
Post-treatment	4.33 (0.64)	NA	NA	NA	NA	NA	
STTS-R (Therapist)							
Post-treatment	4.43 (0.62)	NA	NA	NA	NA	NA	

*Within-group effect sizes (Cohens' *d*) from the intention-to-treat analysis. Cohens' *d* values were also presented for the completers; however, this data was not extracted.
†Percentage of participants with statistically significant Reliable Change Index scores at post-treatment.
CES-D = Center for Epidemiological Studies- Depression Scale; FDAS = Four Dimensional Anxiety Scale; iCBT = internet-delivered cognitive behavioural therapy; NA = not applicable; PSS-IV = PTSD Symptom Scale – Interview Version; RCI = reliable change index; SD = standard deviation; STTS-R = Satisfaction with Therapy and Therapist Scale-Revised.

Comparison of interactive, therapist-guided iCBT (iCBT) versus psycho-educational website (PE) with respect dropout rate

Measure	Treatment group	
	iCBT (N = 46)	PE (N = 41)
Number of dropouts* (% of total)		
Post-treatment	20 (43.5%)	12 (29.3%)

*The number of patients who were randomized to an intervention group but did not complete post-treatment questionnaires. This includes patients who failed to initiate the program and those that were lost to follow-up.
iCBT = internet-delivered cognitive behavioural therapy; N = number of patient; PE = psycho-educational website.

Adverse events: No participants reported a clinically significant increase in PTSD symptoms from pre-treatment to follow-up (according to the reliable change index). Two participants from the interactive iCBT group reported clinically significant increase in depression symptoms. One of these participants also reported clinically significant increase in anxiety symptoms. No participants in the psycho-educational website group reported clinically significant increase in depression or anxiety symptoms.

CAPS = Clinician Administered PTSD Scale; CBT = cognitive behavioural therapy; iCBT = internet-delivered cognitive behavioural therapy; NICE = National Institute for Health and Care Excellence; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; VA = Veteran's Affairs.

Appendix 5: Overlap between Included Systematic Reviews

Table 9: Relevant Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation		
	Kuester, 2016[21]	Olthuis, 2016[14]	Sijbrandij, 2016[5]
Engel, 2015		X	
Ivarsson, 2014		X	X
Kersting, 2013	▪		X
Knaevelsrud, 2015	X	▪	
Litz, 2007	X	X	X
Nieminen, 2016		X	
Spence, 2014	X	▪	X
Spence, 2011	X	X	X

X = the primary study was included in the systematic review and relevant data was extracted for our review.
▪ = the primary study was included in the systematic review; however, the primary study did not meet the inclusion criteria for our review based on the information summarized by the authors of the systematic review. In the case of the Keuster et al.[21] systematic review the Kersting, 2013 study population was characterized as having a symptom level of "not otherwise specified". Data from this study was therefore not extracted as participants were not classified as meeting the criteria for PTSD. In the case of the Olthuis et al.[14] systematic review, the participant populations from the Knaevelsrud, 2015 and Spence, 2014 studies consisted of a mixture of participants with a clinical diagnosis of PTSD (88% in the Knaevelsrud, 2015 study; 86% in the Spence, 2014 study) and those with a subclinical level of PTSD (12% in the Knaevelsrud, 2015 study; 14% in the Spence, 2014 study). Therefore data from these studies were not extracted from the Olthuis et al.[14] review as all patients did not meet our inclusion criteria.

Appendix 6: Additional References of Potential Interest

Previous CADTH Reports

e-Therapy interventions for the treatment of post-traumatic stress disorder: clinical evidence. *(CADTH Rapid response report: summary with critical appraisal)*. Ottawa (ON): CADTH; 2018. Available from: https://www.cadth.ca/sites/default/files/pdf/htis/2018/RC0985%20e-therapy%20for%20PTSD%20Final.pdf. Accessed 2018 Oct 31.

Telehealth for the assessment and treatment of depression, post-traumatic stress disorder, and anxiety: clinical evidence. *(CADTH Rapid response report: summary with critical appraisal)*. Ottawa (ON): CADTH; 2018. Available from: https://www.cadth.ca/sites/default/files/pdf/htis/2018/RC0980%20TelePsychotherapy%20Final.pdf. Accessed 2018 Oct 31.

Treatment for post-traumatic stress disorder, operational stress injury, or critical incident stress: a summary of clinical practice guidelines. Ottawa (ON): CADTH; 2015. Available from: https://www.cadth.ca/sites/default/files/pdf/PTSD_Treatment_A_Summary_of_Clinical_Practice_Guidelines.pdf. Accessed 2018 Oct 31.

Cognitive behavioural therapy for post-traumatic stress disorder: a review of the clinical and cost-effectiveness. *(CADTH Rapid response report: summary with critical appraisal)*. Ottawa (ON): CADTH; 2010. Available from: https://www.cadth.ca/sites/default/files/pdf/L0148_CBT_PTSD.pdf. Accessed 2018 Oct 31.

Randomized Controlled Trials

Study Protocols

Lehavot K, Litz B, Millard SP, Hamilton AB, Sadler A, Simpson T. Study adaptation, design, and methods of a web-based PTSD intervention for women Veterans. *Contemp Clin Trials*. 2017 02;53:68-79.
PubMed: PM27940187

Nollett C, Lewis C, Kitchiner N, et al. Pragmatic RAndomised controlled trial of a trauma-focused guided self-help Programme versus InDividual trauma-focused cognitive Behavioural therapy for post-traumatic stress disorder (RAPID): trial protocol. *BMC Psychiatry*. 2018 Mar 27;18(1):77.
PubMed: PM29580220

Gawlytta R, Niemeyer H, Bottche M, Scherag A, Knaevelsrud C, Rosendahl J. Internet-based cognitive-behavioural writing therapy for reducing post-traumatic stress after intensive care for sepsis in patients and their spouses (REPAIR): study protocol for a randomised-controlled trial. *BMJ Open*. 2017 Feb 22;7(2):e014363.
PubMed: PM28232467

Kunovski I, Donker T, Driessen E, Cuijpers P, Andersson G, Sijbrandij M. Internet-delivered cognitive behavioral therapy for posttraumatic stress disorder in international humanitarian

aid workers: study protocol. *Internet Interv*. 2017 Dec;10:23-28.
PubMed: PM30135749

Allen AR, Newby JM, Smith J, Andrews G. Internet-based cognitive behavioural therapy (ICBT) for posttraumatic stress disorder versus waitlist control: study protocol for a randomised controlled trial. *Trials*. 2015 Dec 01;16:544.
PubMed: PM26628268