CADTH

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Internet-Delivered Cognitive Behavioural Therapy for Post-Traumatic Stress Disorder: A Health Technology Assessment

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Abbreviations

AMSTAR II	A Measurement Tool to Assess Systematic Reviews II
APA	American Psychological Association
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
CAPS	Clinician-Administered Post-Traumatic Stress Disorder Scale
CBT	cognitive behavioural therapy
CBT-T	cognitive behavioural therapy with a trauma focus
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CPT	cognitive processing therapy
DMA	Diagnostic and Statistical Manual of Mental Disorders
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, Third Edition
DSM-IIIR	Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	health technology assessment
iCBT	internet-delivered cognitive behavioural therapy
ICD-9	International Classification of Diseases, Ninth Revision
ICD-10	International Classification of Diseases, Tenth Revision
ICUR	incremental cost-utility ratio
IES-R	Impact of Event Scale – Revised
i-non-CBT	internet-delivered non-cognitive behavioural therapy
ISTSS	International Society of Traumatic Stress Studies
MCID	minimal clinically important difference
MD	mean difference
MeSH	Medical Subject Headings
PCL	Post-Traumatic Stress Disorder Checklist
PCL-C	Post-Traumatic Stress Disorder Checklist – Civilian Version

PCL-M	Post-Traumatic Stress Disorder Checklist – Military Version
PDS	Post-Traumatic Stress Diagnostic Scale
PE	prolonged exposure
PHQ	Patient Health Questionnaire
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS-I	Post-Traumatic Stress Disorder Symptom Scale – Interview
PTSD	post-traumatic stress disorder
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RR	relative risk
SMD	standardized mean difference

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gave their insights into and experiences of post-traumatic stress disorder and cognitive behavioural therapy treatment (confidentially). These perspectives and feedback were carefully considered by CADTH in developing the report.

Conflicts of Interest

The authors declared no conflicts of interest relevant to this report.

Table of Contents

Tables

Figures

Protocol Amendments

Section	Amendment	Protocol Page Number
Perspectives and Experiences	Broadened research question from specific focus on internet cognitive behavioural therapy for post-traumatic stress disorder to psychotherapies for post-traumatic stress disorder.	8 and 17

Executive Summary

Background

Issue

Post-traumatic stress disorder (PTSD) is a debilitating mental health condition that is associated with decreased quality of life, disability, and increased mortality. In Canada, one study published in 2008 estimated the lifetime prevalence of PTSD to be 9.2% among the population of those aged 18 years and older. Military personnel are a known high-risk group for PTSD and in 2013, the lifetime and 12-month rates of this condition among Canadian service members were, respectively, 11.1% and 5.3%. Cognitive behavioural therapy (CBT) is one of the most frequently used psychotherapies for treating PTSD; it is traditionally delivered through face-to-face sessions between the individual and a therapist. However, access to traditional CBT can be impeded by a number of factors such as financial costs and the ability to pay, perceived stigma, potentially scarce geographic availability (e.g., in rural or remote areas), and long wait times. Overall, insufficient access to traditional mental health treatment and services is a known challenge facing Canada's health care system. As such, in Canada and elsewhere, internet-delivered cognitive behavioural therapy (iCBT) is increasingly being considered or implemented as a way to improve access to treatment and services for mental health conditions, including PTSD. In this context, there is broad interest in Canada in understanding the appropriate use of iCBT in the care of patients with PTSD and a need to systematically evaluate relevant evidence. Specfically, this Health Technology Assessment (HTA) aimed to address the following questions that articulate the decision problems:

- Should internet-delivered cognitive behavioural therapy (iCBT) be used to treat individuals with PTSD?
- If so, what factors and considerations should guide the implementation of iCBT in the treatment of individuals with PTSD?

Objectives and Research Questions

The purpose of this HTA is to inform the decision problems through an assessment of the clinical effectiveness and safety; cost-effectiveness; perspectives and experiences of patients, families, and health care providers; and ethical and implementation issues associated with the use of iCBT in the treatment of individuals with PTSD. Accordingly, the HTA explores the following research questions:

Clinical Review

1) What is the clinical effectiveness and safety of iCBT for the treatment of patients, aged 16 years or older, with a primary diagnosis of PTSD?

Economic Evaluation

2) What is the cost-effectiveness of iCBT compared with face-to-face CBT, alternative psychotherapy intervention(s), treatment as usual, and no treatment in patients 16 years of age or older with a primary diagnosis of PTSD?

Perspectives and Experiences Review

3) How do patients, their families, and their health care providers experience engaging with treatments for PTSD?

Ethical Issues Analysis

4) What are the major ethical issues raised by the provision, development, and use of iCBT for PTSD?
5) How might these major ethical issues or concerns be addressed?

Implementation Issues Analysis

6) What are issues relating to the acceptability, feasibility, and capacity for implementing iCBT for the treatment of PTSD at micro (i.e., individuals living with the diagnosis of PTSD and their health care providers), meso (e.g., health care organizations, community mental health agencies, educational institutions), and macro (i.e., provincial, territorial, and federal) levels?

Clinical Evidence

Methods

An update of a Cochrane systematic review and meta-analysis on the effectiveness of iCBT for the treatment of PTSD (published in December of 2018) was conducted. The update consisted of reporting on the methods of the Cochrane review, performing literature search updates to capture any new relevant evidence, summarizing the findings of the Cochrane review, planning to reanalyze results with data from any relevant studies identified in the search updates, and conducting a quality assessment of the Cochrane review and of newly included literature. Literature search updates for clinical studies were performed by an information specialist using the search strategies provided in the Cochrane review. Studies were eligible for inclusion if they compared the clinical effectiveness or safety of iCBT with that of face-to-face psychological therapy, wait-list, repeated assessment, usual care, internet psychoeducation, or internet psychological therapy in adults (aged 16 years or older) with traumatic stress symptoms. At least 70% of participants in any given study were required to meet the diagnostic criteria for PTSD. Additionally, a supplemental search created and peer-reviewed by CADTH information specialists was conducted to identify studies with designs other than randomized or controlled clinical trials, consistent with the usual CADTH approach, to identify additional literature for consideration in the discussion section of this HTA. Study screening was conducted in duplicate; data extraction was conducted by one reviewer and verified by a second independent reviewer. The quality of the Cochrane systematic review was assessed in duplicate using A MeaSurement Tool to Assess systematic Reviews II. Quality assessment of primary studies identified in the updates to the Cochrane search was planned using the revised Cochrane risk-of-bias tool for randomized trials. Narrative syntheses were performed and updates to the meta-analyses from the Cochrane review were planned to incorporate data from any eligible studies identified in the search updates.

Findings

No publications from the search update and alerts met the eligibility criteria and were included in this review; therefore, the review was comprised of the 10 relevant clinical studies included in the Cochrane review (eight studies compared iCBT versus wait-list, delayed treatment, or usual care alone; two studies compared iCBT versus internet-delivered-non-CBT interventions). Of these ten RCTs, four studies recruited individuals who had experienced war or terrorism-related trauma, one study recruited females who experienced sexual trauma, and five studies did not restrict their study population by type of trauma. A total of 720 participants were included in the 10 primary studies, with individual studies recruiting between 34 and 159 participants. The proportion of female participants in

studies ranged from 18.75% to 100%. The mean time since primary traumatic event (index trauma) in the patient populations of included studies ranged from 2.72 years to 9.88 years, although the time since index trauma was not reported in eight primary studies. iCBT treatment durations ranged between four weeks and 14 weeks (the median treatment duration was eight weeks). Clinical outcomes were assessed at baseline and post-treatment in all studies; however, some studies conducted additional subsequent follow-up measurements. The time from treatment initiation to final follow up ranged from one month to one year; however, most studies did not measure outcomes beyond three months. The quality of the evidence ranged from “very low” to “low” across outcomes and comparisons. The most common limitations of the evidence were: 1) high risk of bias that reduced the certainty in the treatment effect size (particularity due to lack of blinding of study participants, personnel, and outcome assessors), 2) inconsistency and high levels of heterogeneity, and 3) imprecision due to small sample size. In light of these limitations, there was a high level of uncertainty in the findings of the meta-analyses.

In the context of these limitations, overall, the findings of the clinical review suggest that iCBT may be more effective than wait-list for adult patients with PTSD post-treatment. There was evidence for the effectiveness of iCBT in comparison with wait-list with respect to severity of PTSD symptoms, depressive symptoms, anxiety symptoms, and quality of life. However, the magnitude of the benefit to PTSD symptomology may not translate into clinically meaningful change according to minimal clinically important difference values from the literature. In addition, there was low-quality evidence that participants treated with iCBT were at an increased risk for dropout compared with those allocated to wait-list; although the mechanism driving this increased risk was unclear, this finding warrants consideration and future investigation. There were no statistically significant differences between treatment with iCBT and internet non-CBT (i-non-CBT) interventions with respect to severity of PTSD symptoms. Evidence regarding experienced adverse events, such as the need for hospitalization or worsening of symptoms, was unavailable from a majority of the included primary studies.

Economic Evidence

Methods

A cohort-level state-transition model was constructed to examine the clinical outcomes and costs associated with the treatment of PTSD in patients 16 years of age or older with iCBT compared with no additional treatment (i.e., wait-list, usual care, or delayed treatment control group). The decision-analytic model was developed by reviewing existing clinical and economic literature, and its structure was subsequently validated by a clinical expert with experience in the treatment and management of patients with PTSD. The model included health states relevant to the natural history of PTSD and the long-term effects of treatment. Health states included remission, active PTSD with or without comorbidities (i.e., depression or substance abuse), and death. Relative treatment effects, reported as standardized mean difference in severity of PTSD symptoms in the Cochrane review, were incorporated into the model to inform the transition probability from active PTSD to remission. The primary outcome was the cost per quality-adjusted life-years (QALYs) gained, in 2019 Canadian dollars, from the Canadian public health care payer perspective. As the clinical and cost consequences of PTSD can persist indefinitely, a lifetime time horizon was adopted.

Results

The results of the economic evaluation suggest iCBT was dominant compared with no additional treatment (i.e., iCBT was associated with lower total costs and greater QALYs). The results were primarily driven by the cost of treatment with iCBT and the extrapolation of the impact of iCBT compared with no additional treatment over a lifetime time horizon. Much of the estimated QALY gains were observed beyond the first year of treatment (more than 93%). When a one-year time horizon was considered, iCBT was no longer dominant and was associated with an incremental cost-utility ratio of $17,435 per QALY gained. The incremental QALYs for this scenario was marginal (i.e., 0.028, which would be equivalent to just more than 10 days of perfect health over one year). Results were robust to changes in other parameters and assumptions in sensitivity and scenario analyses, including across various scenarios altering the price and efficacy associated with iCBT. In a scenario analysis against i-non-CBT as the comparator intervention, iCBT remained cost-effective in comparison with i-non-CBT ($8,624 per QALY gained).

It was not possible to conduct analyses of iCBT compared with the current standard of care (including face-to-face CBTs), due to a lack of clinical data and, as a result, the cost-effectiveness of iCBT in comparison with other psychotherapy interventions in the care pathway remains uncertain. Additionally, a lack of subgroup data precluded any analysis of cost-effectiveness of iCBT in patients who experienced a single exposure to trauma versus repeat exposure, or those who have experienced different types of trauma (i.e., interpersonal trauma versus non-interpersonal trauma). As a result, it was not possible to identify subgroups in which iCBT may be more or less cost-effective.

Perspectives and Experiences

Methods

A rapid qualitative evidence synthesis and best-fit framework analysis of primary qualitative studies describing the perspectives and experiences of psychotherapy for people living with a diagnosis of PTSD, and those of the families and care providers, was conducted. Patient engagement with five people living with PTSD occurred throughout the protocol development and the early stages of evidence synthesis as a way of gaining insight on what it might be like to live with PTSD and engage in subsequent treatment, like iCBTs, for PTSD. Due to the large body of eligible literature, concepts that arose during these conversations also assisted with sampling decisions.

Findings

Thirteen publications were included that reported on qualitative research of patients' and care providers' perspectives of or experiences with various psychotherapies for PTSD. It should be noted that none focused on perspectives of or experiences with iCBT. Following critical appraisal these studies were judged to be of moderate-to-high quality.

Results from the analysis generally pivoted around the concept of relationality and demonstrated how experiences living with, coming to know, and engaging in treatment for PTSD were described as neither isolated nor stable events in the lived worlds of PTSD. Strong therapeutic relationships and the freedom to play a collaborative role in one's treatment decisions were indicated as helpful to fostering a sense of achievability and providing a comfortable space to work through therapy. The opportunity to draw on the experiences of peers engaged in similar treatment protocols or invite loved ones to

contribute to treatment plans could have similar effects. While it is possible that individuals interested in engaging with iCBTs for PTSD might place less of an emphasis on these sorts of external relationships, it seems important to provide the space within iCBT protocols for them to flourish if that is desired.

When considering the role an individual might play in their own therapy, terms like *readiness* and *motivation* were used to describe the self-work involved in preparing for and successfully completing psychotherapies for PTSD. As this frequently involves elements of re-exposure to traumatic thoughts or spaces, readiness often implied a pairing of emotional management skills and safe coping mechanisms with a strong desire to change. Ensuring that iCBTs help to develop these skills and mechanisms prior to exposure elements (if included in the program) would likely be beneficial to the overall treatment plan.

Due to the lack of literature focused on experiences or perspectives of iCBT for PTSD, our broadened review of experiences and perspectives of psychotherapies for PTSD was unable to provide further direction on specific content or procedural elements that would be considered beneficial, or not, for iCBT programs. Nonetheless, from the included body of literature it is evident that a one-size-fits-all approach to iCBT for PTSD would be inappropriate and neglect the need for tailoring emphasized throughout the included studies.

Ethical Issues

Methods

The ethics analysis involved reviewing the ethics, clinical, and public health literatures to identify existing ethical analyses of the technology, and conducting a novel ethical analysis based on gaps identified in the ethics literature and the results of concurrent reviews conducted as part of this HTA. The ethical issues identified, values described, and solutions proposed in the literature were evaluated using the methods of ethical (applied philosophical) analysis, which included applying standards of logical consistency and rigour in argumentation. The purpose was to identify and reflect upon key ethical issues that should be contemplated when considering the provision, development, and use of iCBT for PTSD in Canada.

Findings

The central themes identified in the literature were: trauma-informed care, the therapeutic alliance, and trust; beneficence and the uncertainty of new treatment modalities; nonmaleficence, limitations to client safety, and the prevention of retraumatization; justice and enhanced access; respect for autonomy and informed consent; privacy and confidentiality in the context of internet-delivered therapies; and professional and legal issues.

In addition to identifying ethical issues that can be expected to arise in the context of many, if not all, internet-delivered mental health therapies, this report also identified and discussed several ethical issues specifically relevant to the provision, development, and use of iCBT for PTSD in Canada. These ethical issues include the extent to which trauma-informed care (and associated ethical commitments to prioritize client safety and prevent retraumatization) can be sufficiently realized in the context of iCBT, particularly where iCBT is not therapist supported; the consideration and proper balancing of the justice-enhancing and justice-diminishing features of iCBT; and the prospect of a trusting alliance to be established in the

context of iCBT such that iCBT providers are capable of effectively fulfilling their ethical obligations.

Implementation Analysis

Methods

A qualitative descriptive study, using a framework approach to analysis, was conducted to explore the implementation issues associated with the use of iCBT in the treatment of PTSD. In addition to engaging with literature that included things like guidelines for PTSD care and Canadian policy documents oriented around PTSD care, we spoke with fifteen individuals representing eleven stakeholder groups representing various levels of decision-making and health care delivery in mental health. Stakeholders were engaged as a way of gaining a better understanding of the context and relevant issues of implementing iCBT for PTSD in Canada.

Findings

For jurisdictions interested in implementing iCBTs as an option in PTSD care, our analysis identified six key points to consider.

1) There may be a role for a regulatory framework or licensing body oversight in terms of what qualifies as an iCBT and how this is determined or evaluated. As such, a blanket recommendation or set of policies for iCBTs understood generally may not be appropriate.
2) iCBT interventions will not be appropriate for everyone presenting with PTSD. Whom they are appropriate for will be dependent on factors such as severity and form of PTSD, patient goals, and the presence of comorbidities.
3) Where iCBT for PTSD could fit into a current care pathway depends largely on what gap iCBT is meant to fill in terms of mental health care. Stakeholders identified four potential places where they perceived iCBTs may be useful: prevention, assessment and triage, first-line therapy, and maintenance therapy. Of note, long wait-lists were identified as tied to ineffective and inefficient triaging strategies. As many people living with PTSD in Canada undergo assessment through someone other than a specialist, upon referral to a specialist it is possible that some individuals are “lost” to treatment due, at least in part, to subsequent wait times. Providing access to iCBT programs with built-in assessment procedures was identified as a possible way to break up these wait-lists as they can follow assessment with rapid triage to the iCBT program if appropriate for that individual.
4) Which professionals are deemed appropriate to provide iCBTs is tied both to where it is proposed to fit in a care pathway and what professions (e.g., psychologists, social workers, trained paraprofessionals) payers are willing to engage.
5) There is a need for more comparative research around the effectiveness of iCBTs in relation to active comparators like face-to-face CBTs.
6) In order for iCBTs to be successfully implemented into care for PTSD, several structural concerns may need to be addressed. These concerns include those of the “digital divide” in Canada, wherein it is recognized that neither digital literacy nor access to online technologies are everywhere equal in Canada; IT control around data security (e.g., privacy and confidentiality); and funding or provision fragmentations inherent in Canada’s two-tiered mental health system.

Conclusion

Overall, based on primarily “very low-” to “low-” quality evidence, the findings from the clinical review suggested that treatment with iCBT improved severity of PTSD symptoms compared with wait-list for patients aged 16 years or older with a primary diagnosis of PTSD; however, the magnitude of the improvement did not translate into a clinically meaningful change (using minimal clinically important difference values from the literature). Additionally, treatment with iCBT improved the severity of depressive symptoms, the severity of anxiety symptoms, and quality of life compared with wait-list. There were no statistically significant differences between treatment with iCBT and i-non-CBT interventions with respect to severity of PTSD symptoms. In the economic evaluation, iCBT was less costly and produced more QALYs over a lifetime compared with no additional treatment and, compared with i-non-CBT, iCBT was associated with an incremental cost-utility ratio of $8,624 per QALY gained. The results were primarily driven by the cost of treatment and the extrapolation of the impact of iCBT over a lifetime time horizon. These estimates remain uncertain due to limitations with the clinical efficacy data, as well as uncertainty with the natural history inputs (i.e., variability in the progression of PTSD that could not be modelled); though results remained robust in the extensive scenario and sensitivity analyses conducted. No evidence that directly compared treatment with iCBT and face-to-face CBT or other psychotherapies was identified in the clinical literature; therefore, the comparative clinical and cost-effectiveness of iCBT and face-to-face psychotherapies is unknown.

The potential implementation of iCBTs for PTSD across jurisdictions in Canada is likely to be influenced by several factors, including whether a regulatory or licensing body can provide oversight on which iCBT programs provide care that aligns with the principles of CBT, which gaps in the provision of PTSD care iCBTs are meant to fill and whether there is research supporting the use of iCBTs to fill these gaps, which providers are (or are not) allowed to provide care with iCBTs, and how iCBTs fit within current mental health funding and provision structures across jurisdictions. Similarly, how iCBTs align (or do not align) with individual patient treatment goals or values and the opportunity to develop and maintain strong therapeutic relationships would seem important to consider when deliberating on the implementation of particular programs.

Mental health conditions like PTSD are complex. Treatment modalities for PTSD and the research around them are constantly evolving. As substantial new evidence regarding iCBT programs emerges, reassessment may be warranted, particularly with respect to complex traumas and comparisons with current standards of care.

Introduction and Rationale

Approximately 65% of the world's population experiences at least one traumatic event in their lifetime.[1-3] The *Diagnostic and Statistical Manual of Mental Disorders*, *Fifth Edition (DSM-5)* defines a traumatic event as direct exposure, witnessing, or indirect exposure to death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence.[4] Although it is possible to recover naturally from the psychological effects of trauma exposure, some affected individuals may develop prolonged symptoms and mental health afflictions such as post-traumatic stress disorder (PTSD) or depression.[5,6] These conditions are associated with decreased quality of life, disability, and increased mortality.[7-10] Specifically, PTSD is a debilitating condition which, according to the *DSM-5*, is characterized by four main groups of symptoms:

- intrusive thoughts depicted by repeated, involuntary, and distressing recollections of the traumatic event
- persistent avoidance of situations and elements that may trigger memories of the traumatic event
- negative thoughts and feelings about oneself or others deriving from the traumatic experience
- ongoing state of hyperarousal, which can include symptoms such as irritability, the tendency to be startled easily; insomnia and concentration problems; or the inclination toward aggressive, reckless, and self-destructive behaviour.[4]

The lifetime prevalence of PTSD in the adult US population is approximately 11.7% in women and 4% in men,[11] and prevalence is typically greater in high-risk groups such as military personnel and first responders.[12-14] In Canada, one study published in 2008 estimated the lifetime prevalence of PTSD to be 9.2% among the population aged 18 years and older.[15] In 2013, the lifetime and 12-month rates of PTSD among Canadian service members were, respectively, 11.1% and 5.3%.[16]

Treatment strategies for PTSD commonly include pharmacotherapy (e.g., selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors) and psychotherapy, which are used separately or in combination with one another.[17] Cognitive behavioural therapy (CBT) is one the most frequently used psychotherapies for treating PTSD and its effectiveness is supported by a large body of evidence.[8,18-20] CBT combines the principles of cognitive and behavioural therapies; the aim of CBT is to provide individuals with coping strategies and mechanisms to solve current problems and to change dysfunctional thoughts, behaviours, beliefs, and attitudes.[21] CBT for PTSD consists of psychoeducation 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.[5,22]

Like other established psychotherapies, the traditional form of CBT is delivered through face-to-face sessions between the individual and a therapist. However, access to traditional CBT can be impeded by a number of factors such as financial costs and the ability to pay, perceived stigma, potentially scarce geographic availability (e.g., in rural or remote areas), and long wait times.[23-27] Specifically, some estimates propose that more than half of individuals who meet the diagnostic criteria for a mental health condition do not use mental health services.[28,29]

Insufficient access to traditional mental health treatment and services is a known challenge facing Canada's health care system.[16,30] In a survey conducted in 2015, around 4.9 million Canadians aged 15 years and older said they had had a need for mental health care in the past 12 months, with 600,000 reporting that this need was left unmet and more than one million reporting that it was partially met.[30] In Canada and elsewhere, internet-delivered cognitive behavioural therapy (iCBT) is increasingly being considered or implemented as a way to improve access to treatment and services for mental health conditions, including PTSD.[16,31,32] Essentially, iCBT involves the delivery of CBT through an online platform with or without the support of a therapist (or other practitioner).[22] Using iCBT to address the psychotherapeutic needs of individuals with PTSD and other mental health conditions has been suggested to offer several benefits for patients and the health care system. These benefits are assumed to 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 decreased risk for possible stigmatization.[5,33-35] However, there may be challenges associated with iCBT programs such as the limited, or no, interaction with a therapist, which may make it difficult to monitor patients and adjust the treatment to their needs, and the potential for an increased risk of adverse events.[5,36] Other potential challenges that are commonly suggested for iCBT include low adherence to the therapy; a lack of computer skills or proper internet service, which could exclude some individuals from receiving iCBT; and the varying quality of existing iCBT programs, which put patients at risk of receiving suboptimal or improper care.[5,36]

CADTH, in collaboration with Health Quality Ontario, recently completed an Optimal Use project on the use of iCBT in patients with mild and moderate major depressive disorder and anxiety disorders.[37,38] PTSD is a distinct condition and the findings from a previous Optimal Use report may not generalize to people living with this condition. While iCBT treatment options may be structurally similar (e.g., modular approaches, treatment goals) across diagnoses, how these programs fit into and act upon the lives of individuals living with PTSD might be different than for individuals living with mild-to-moderate major depressive disorder or anxiety disorders. With previous traumatic experience situated as a central feature of a PTSD diagnosis, efforts at reframing or restructuring maladaptive thoughts and behaviours stemming from this particular traumatic experience (or experiences) could pose a different set of challenges for individuals living with PTSD than for individuals working through other diagnoses. Similarly, exposure — in which the patient is led to confront the traumatic memory — is considered a key element of many psychotherapies for PTSD[5] and it is unclear whether this step can be implemented safely and reliably in remotely delivered interventions like iCBT. Although iCBT may be less costly than interventions currently in use for the treatment of other mental health indications (e.g., major depressive disorder and anxiety),[39] whether iCBT is cost-effective in the context of PTSD, taking into account the costs and utilities throughout a patient's lifetime when compared with these other interventions, remains to be determined. Moreover, while there may be some overlap in implementation issues across mental health disorders, such as those identified in a previous CADTH report,[37,38] there may be unique implementation considerations for some populations at high risk of PTSD (e.g., veterans of war, first responders, and police officers).

There is broad interest in Canada in understanding the appropriate use of iCBT in the care of patients with PTSD and a need to systematically evaluate relevant evidence. Specifically, the clinical effectiveness and safety, cost-effectiveness, perspectives and experiences of patients and their families and health care providers, and ethical and implementation issues associated with the use of iCBT in the treatment of individuals with PTSD need to be

assessed. Overall, there is a need for evidence to guide policy and the appropriate use of iCBT in the context of caring for patients with PTSD in Canada.

Decision Problems

This Health Technology Assessment (HTA) addresses the following questions that articulate the decision problems:

- Should internet-delivered cognitive behavioural (iCBT) therapy be used to treat individuals with PTSD?
- If so, what factors and considerations should guide the implementation of iCBT in the treatment of individuals with PTSD?

Objective

The purpose of this HTA was to inform the decision problems through an assessment of the clinical effectiveness and safety; cost-effectiveness; perspectives and experiences of patients, families, and health care providers; and ethical and implementation issues associated with the use of iCBT in the treatment of individuals with PTSD.

Research Questions

This HTA informs the decision problems by exploring the following research questions (details on the specific interventions and outcomes are included in Table 1):

Clinical Review

1. What is the clinical effectiveness and safety of iCBT for the treatment of patients, aged 16 years or older, with a primary diagnosis of PTSD?

Economic Evaluation

2. What is the cost-effectiveness of iCBT compared with face-to-face CBT, alternative psychotherapy intervention(s), treatment as usual, and no treatment in patients 16 years of age or older with a primary diagnosis of PTSD?

Perspectives and Experiences Review

3. How do patients, their families, and their health care providers experience engaging with treatments for PTSD?

Ethical Issues Analysis

4. What are the major ethical issues raised by the provision, development, and use of iCBT for PTSD?
5. How might these major ethical issues or concerns be addressed?

Implementation Issues Analysis

6. What are issues relating to the acceptability, feasibility, and capacity for implementing iCBT for the treatment of PTSD at micro (i.e., individuals living with the diagnosis of PTSD and their health care providers), meso (e.g., health care organizations, community mental health agencies, educational institutions), and macro (i.e., provincial, territorial, and federal) levels?
    - What are the current or potential pathways of care for individuals living with a diagnosis of PTSD and where or how could iCBT fit within these pathways?

- Given existing and potential pathways of care for individuals, what resources and infrastructure would be needed to continue, expand, or optimize its delivery?
- How do stakeholders (e.g., practitioners and current payers) and people living with a diagnosis of PTSD understand the technology of iCBT and its application to the treatment of PTSD, and how could these understandings or perspectives influence the uptake of iCBT?

Clinical Review

The objective of the clinical review was to address the following research question:

- What is the clinical effectiveness and safety of iCBT for the treatment of patients, aged 16 years or older, with a primary diagnosis of PTSD?

Study Design

To address the clinical research question, we conducted an update of a Cochrane systematic review and meta-analysis[40] on the effectiveness of iCBT for the treatment of PTSD, which was published in December 2018. This Cochrane review[40] was identified through scoping activities that included an unpublished scoping review of existing literature and a CADTH Rapid Response report[41] (published in November of 2018) that examined the clinical effectiveness of iCBT programs for the treatment of adults diagnosed with PTSD. Details on the complete methodology for the Rapid Response report — including literature search methods, detailed article selection, and eligibility criteria, and the processes used for study screening, data extraction, critical appraisal, and data analysis and synthesis — are available in the Rapid Response report.[41] A preliminary quality assessment using A MeaSurement Tool to Assess systematic Reviews II[42] — or AMSTAR II — indicated that the Cochrane review[40] provided an accurate and comprehensive summary of the results of the available studies that address the question of interest. The Cochrane review[40] also accurately aligned with the objectives of the clinical review of this HTA.

The update to the Cochrane review[40] consisted of reporting on the methods of the Cochrane review,[40] performing literature search updates to capture any new relevant evidence, summarizing the findings of the Cochrane review,[40] planning to reanalyze meta-analytic results with data from any relevant studies identified in the search updates, and conducting a quality assessment of the Cochrane review[40] and of newly included literature.

A protocol for the clinical review (CRD42019140614) was written a priori and followed throughout the review process.

Methods

Literature Search Strategy

An update of the literature search for clinical studies was performed by an information specialist using the search strategies provided in the appendices of the 2018 Cochrane review.[40]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, PsycINFO (1806–) via Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's Medical Subject Headings (MeSH), and keywords. The main search concepts were iCBT

and PTSD. Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Search Portal (ICTRP).

Search filters were applied to limit retrieval to randomized controlled trials (RCTs) and controlled clinical trials. Retrieval was limited to documents published since January 1, 2017 (to ensure appropriate overlap with the searches conducted by the authors of the Cochrane review),[40] but not limited by language.

In addition to this search, a supplemental search created and peer-reviewed by CADTH information specialists was conducted to identify studies with designs other than RCTs or controlled clinical trials, consistent with the usual CADTH approach. The purpose of this search was to identify additional literature for consideration in the discussion section of the HTA. The databases searched included MEDLINE, PsycINFO, PubMed, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, the Health Technology Assessments database, 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 HTAs, systematic reviews, meta-analyses, RCTs, clinical controlled trials, and non-randomized studies. The search was also limited to English- or French-language documents published since January 1, 2008. The search strategy is available on request.

Regular alerts updated both the Cochrane search and the supplemental search until the publication of the final report.

Grey literature (literature that is not commercially published) was identified by searching sources listed in relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters),[43] which includes the websites of HTA agencies, clinical guideline repositories, systematic review repositories, and professional associations. Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with experts and industry, as appropriate. Additional information on the grey literature search strategy is provided in Appendix 1.

Selection Criteria

The inclusion criteria for the Cochrane review (as described in the publication)[40] were used to assess the eligibility of studies identified in the search updates for the Cochrane review. Studies were included if they were published in English or French and met the selection criteria presented in Table 1, which were reproduced from the Cochrane review.[40] Additionally, studies identified in the Cochrane search and the supplemental search were screened using the eligibility criteria described in a previously published CADTH Rapid Response report.[41] In short, the Rapid Response criteria were less restrictive with respect to comparator (i.e., alternative iCBT interventions were also eligible) and study design (i.e., HTAs, systematic reviews, meta-analyses, and non-randomized studies were also eligible), and more restrictive for population (all study participants, rather than 70%, were required to meet diagnostic criteria for PTSD); the remaining criteria were consistent with the Cochrane search. Any studies that met the eligibility criteria for the Rapid Response but not the Cochrane review[40] for any reason, as well as the primary studies summarized in the Rapid Response[41] but not the Cochrane review,[40] were mentioned in the discussion section of this HTA.

Table 1: Selection Criteria for the Clinical Review

Population	Adults, aged 16 years or older, with traumatic stress symptoms. At least 70% of participants in any given study were required to meet the diagnostic criteria for PTSD according to the *DSM-III, DSM-IIIR, DSM-IV, DSM-V, ICD-9, or ICD-10*, as assessed by clinical interview or a validated questionnaire. • There were no restrictions placed on sex or gender, ethnicity, comorbidities, setting, type of traumatic event, severity of symptoms, or length of time since trauma.
Intervention	Guided and unguided internet-based cognitive behavioral therapies delivered via a computer or mobile device • Excluded: Interventions based on EMDR or online psychoeducation alone, and interventions using mindfulness-based approaches, apart from mindfulness-based iCBT.
Comparator	Face-to-face psychological therapy (CBT based); face-to-face psychological therapy (non-CBT based; e.g., EMDR, supportive therapy, non-directive counselling, psychodynamic therapy, and present-centred therapy); wait-list; repeated assessment; usual care; internet psychoeducation; internet psychological therapy (non-CBT).
Outcomes	Severity of PTSD symptoms (as measured by standardized scales; e.g., CAPS-5, PCL-5; primary outcome); dropout rates (primary outcome); diagnosis of PTSD after treatment (i.e., number of participants who met diagnostic criteria for PTSD in each arm of the study); depression symptoms (as measured by standardized scales; e.g., BDI); anxiety symptoms (as measured by standardized scales; e.g., BAI); cost-effectiveness; adverse events (e.g., symptoms worsening, relapses to substance use, hospitalizations, suicide attempts, work absenteeism); quality of life (using any measures): • Studies that met the aforementioned inclusion criteria were included regardless of whether they reported on these outcomes.
Study Designs	Randomized controlled trials, randomized crossover trials, and cluster-randomized trials.

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CAPS = Clinician-Administered Post-Traumatic Stress Disorder Scale; CBT = cognitive behavioural therapy; *DSM* = *Diagnostic and Statistical Manual of Mental Disorders*; EMDR = eye movement desensitization and reprocessing; iCBT = internet-delivered cognitive behavioural therapy; *ICD* = *The International Statistical Classification of Diseases and Health Related Problems*; PCL = Post-Traumatic Stress Disorder Checklist; PTSD = post-traumatic stress disorder.

Source: Lewis et al. (2018).[40]

Selection Methods

Two reviewers independently screened titles and abstracts of all the citations retrieved in search updates for the Cochrane review and in the supplemental search against the eligibility criteria in Table 1 for inclusion in the body of the clinical review and against the eligibility criteria described in the Rapid Response report[41] for consideration in the discussion section of this HTA. Exclusion by both reviewers was required for a record to be excluded at the title and abstract level. Full-text versions of all other articles were retrieved for the second level of screening. The same reviewers independently examined all full-text articles, and consensus was required for inclusion in the review. Discrepancies between reviewers were resolved by discussion between the reviewers or by consultation with a third reviewer, if necessary.

Data Extraction

Data extraction was performed by one reviewer in structured tables in Microsoft Word, and independently checked for accuracy by a second reviewer. Disagreements were resolved through discussion until consensus was reached or through adjudication by a third reviewer, if necessary. Data from the primary studies included in the Cochrane review[40] were primarily summarized from the Cochrane review[40] itself; however, the primary studies were retrieved and examined to ensure consistency and completeness. Relevant information was extracted, where available, including:

- study characteristics (e.g., first author's name, publication year, country where the study was conducted, funding sources)
- methodology (e.g., study design, analytical approach, follow-up duration, inclusion and exclusion criteria)
- population (e.g., number of patients, age, sex, type of trauma, method of PTSD diagnosis)
- intervention (e.g., description of the iCBT program, type and level of therapist support, number of sessions, treatment duration)
- comparators (e.g., wait-list, non-CBT internet interventions)
- results (including exact *P* values, confidence intervals [CIs], and estimates of random variability, where available) regarding the outcomes of interest (and their method of measurement, where available).

If numerical values were discrepant throughout a study (e.g., different values reported in the abstract, results tables, and/or results text), all values were extracted and reported. Study findings were considered statistically significant at $P < 0.05$, irrespective of how significance was interpreted in the Cochrane review.[40]

Methodological Quality Assessment

Quality Assessment: The Cochrane Review

Critical appraisal of the Cochrane review[40] was conducted by two independent reviewers using the AMSTAR II tool.[42] Any disagreements were resolved by discussion with a third reviewer, if required.

The AMSTAR II tool allowed for the assessment of risk of bias in the systematic review using 16 questions that were answered using "yes," "partial yes," "no," or "unclear." These 16 items were used as a guide to identify the strengths and weaknesses of the Cochrane review.[40]

The overall quality of the evidence (i.e., the certainty of the evidence) and the risk of bias in the primary studies included in the systematic review were summarized from the assessments made by authors of the Cochrane review,[40] using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework and the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions,*[44] respectively.

According to GRADE, evidence from RCTs begins with a rating of "high" quality, but can be downgraded (to "moderate," "low," or "very low") if there is serious or very serious risk of bias,[45] inconsistency (e.g., unexplained heterogeneity in the effect),[46] indirectness (e.g., use

of a surrogate measure instead of a direct measure of an outcome),[47] imprecision (e.g., wide CIs leading to uncertainty about the true magnitude of the effect),[48] or publication bias,[49] because these characteristics reduce the certainty in the estimated effect.

The criteria in the *Cochrane Handbook for Systematic Reviews of Interventions*[44] were applied to each included primary study by the authors of the Cochrane review[40] to judge each potential source of bias as high, low, or unclear. The sources of bias considered by the Cochrane review[40] authors included random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (report bias), and other bias (e.g., baseline imbalances, early termination of the trial, researcher allegiance). The results of this assessment were summarized based on the information available in the Cochrane review.[40]

Quality Assessment: Primary Studies from the Search Updates

The quality assessment of the primary studies identified in the updates to the Cochrane search was planned using the revised Cochrane risk-of-bias tool for randomized trials, the revised Cochrane risk-of-bias tool for randomized trials;[50] however, no new studies were identified for inclusion, precluding the planned assessments.

No formal quality appraisal was planned for studies identified in the supplementary search that were intended for the discussion only.

Data Analysis Methods

Narrative syntheses were performed, including the presentation of study characteristics and findings by outcome within summary tables, on studies identified in the update and primary studies summarized in the Cochrane review.[40] The direction and size of any observed effects were summarized across comparisons, including an assessment of the likelihood of clinical benefit (i.e., clinical effectiveness) or harm (i.e., safety, including worsening of PTSD). Studies identified in the updated Cochrane search or in the supplemental search that compared iCBT interventions with alterative iCBT interventions, or that met the eligibility criteria described in a previously published CADTH Rapid Response report[41] but not the Cochrane review[40] (and therefore the update) for any reason, were mentioned in the discussion section of the HTA.

In addition to the narrative syntheses, we had planned to conduct updates to the meta-analyses from the Cochrane review[40] with data from any eligible studies identified in the search updates. No eligible primary studies were identified in the search updates; however, we conducted a reanalysis of data from one outcome in the Cochrane review[40] (severity of PTSD symptoms at a second follow up at less than six months in the iCBT versus wait-list comparison). This reanalysis was conducted with the methods established in the Cochrane review,[40] using a random-effects meta-analysis of continuous data analyzed using standardized mean differences (SMD). Statistical heterogeneity was assessed using graphical presentations (e.g., forest plots) and calculations of Cochrane's Chi^2 test and the I^2 statistic standardized mean. The reanalysis was carried out using Cochrane Review Manager software (version 5.3). No further updates or reanalyses were conducted. Additional details on planned analyses (that were not conducted as a result of no new eligible primary studies being identified) are found in the protocol.[51]

Minimal Clinically Important Difference

In order to further interpret the findings relating to PTSD symptom severity (the primary outcome) following treatment, we conducted a post hoc investigation into the clinical significance of the results (using minimal clinically important difference [MCID] values). In brief, the SMD for PTSD symptom severity was back-transformed into mean differences (MDs) using typical among-person standard deviations for the Clinician-Administered Post-Traumatic Stress Disorder Scale (CAPS) (6.63; retrieved from the Lewis et al.[52] study) and for the Post-Traumatic Stress Disorder Checklist (PCL) (10.70; retrieved by pooling the standard deviations from three studies),[53] according to guidance provided by the *Cochrane Handbook for Systematic Reviews of Interventions*.[44] The Lewis et al.[52] study was chosen as it was the only included study to provide baseline CAPS scores for participants, while the Kuhn et al.,[53] Engel et al.,[54] and Spence et al.[55] studies were chosen for pooling because they were the only included studies that provided baseline total PCL scores. The resulting MDs were compared against MCID values from the literature,[56-62] retrieved using a supplemental search, to assess whether SMDs from the meta-analysis indicated a clinically meaningful change in the severity of PTSD symptoms. This supplemental literature search was conducted in MEDLINE and PsycINFO for studies relating to MCIDs of various PTSD assessment instruments. The search was limited to English-language documents but was not limited by publication date.

Results

Quantity of Research Available

A total of 515 unique citations were identified in the update to the Cochrane literature search. Following screening of titles and abstracts, 505 citations were excluded and 10 potentially relevant reports were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search for full-text review. In addition, six potentially relevant reports were retrieved from the search alerts. Of these 17 potentially relevant articles, all 17 publications were excluded for various reasons, and no publications from the search update and alerts met the inclusion criteria and were included in this review. The study selection process is outlined in Appendix 2 using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses[63] (PRISMA) diagram. Lists of excluded citations, with details describing the rationale for those excluded, are presented in Appendix 4.

As part of the literature screening process, a subsequent publication[64] of the Cochrane review[40] was identified and retrieved. This publication[64] included two additional subgroup analyses. One, studies that used trauma-focused iCBT programs, and two, studies that provided therapist guidance with iCBT treatment. The results of these analyses are discussed in the summary of findings section of the clinical review.

There were no additional publications identified in the updated Cochrane search or supplemental search for exclusive mention in the discussion section of the HTA. However, one study that was included in the previously published Rapid Response[41] was identified for mention in the discussion. This RCT, which was published in 2014 by Spence et al.,[65] compared the efficacy and safety of a trauma-focused iCBT program with and without exposure components, and was not eligible for inclusion in the body of the review due to comparator criteria (i.e., alternative iCBT programs were ineligible).

Study Characteristics

The characteristics of the Cochrane review[40] are summarized in Table 14 in Appendix 5.

Although there were no eligible primary studies identified in the search updates, study characteristics from the 10 primary studies[52-55,66-71] included and summarized in the Cochrane review[40] are described here. A list of the included primary studies is available in Appendix 3, and additional details regarding the characteristics of the included studies are available in Table 16 in Appendix 7.

Study Design, Year of Publication, and Source of Funding

The Cochrane review,[40] published in 2018, was designed as a systematic review and meta-analysis of RCTs, randomized crossover trials, and cluster-randomized trials. The literature search was last updated March 1st, 2018, and was not restricted by publication date, language, or publication status. The authors acknowledged the editorial team of the Cochrane Common Mental Disorder Group, whose single largest funder is the National Institute for Health Research (NIHR). Support was also received internally from Cardiff University.

Ten relevant clinical studies[52-55,66-71] were included in the Cochrane review,[40] all of which were RCTs. All ten of these studies recruited patients to intervention and control groups in a 1:1 ratio and were of an open-label nature, although four studies[52,54,69,71] stated that the outcome assessors were blinded. The RCT by Krupnick et al.[66] was funded by a grant from the Telemedicine and Advanced Technology Research Center, Lewis et al.[52] received financial support from the Knowledge Transfer Partnerships (KTP008512), the Ivarrson et al.[69] study received a grant from Linköping University, Spence et al.[55] were supported by a research fellowship from the New Wales Institute of Psychiatry, and the RCT by Litz et al.[71] was supported by a grant from the National Institute of Mental Health. The five remaining studies[53,54,67,68,70] did not report their sources of funding.

Country of Origin

Based on the location of the corresponding authors, Lewis et al.[40] were based in the UK.

RCTs included in the Cochrane review[40] were conducted in Australia,[55] Iraq,[68] Sweden,[69] the UK,[52] and the US.[53,54,66,67,70,71]

Patient Population

In order to be eligible for the Cochrane review,[40] primary studies were required to have enrolled adults (16 years of age or older) with traumatic stress symptoms with at least 70% meeting diagnostic criteria for PTSD (according to the *Diagnostic and Statistical Manual of Mental Disorders [DSM]-III, DSM-IIIR, DSM-IV, DSM-V*, *The International Statistical Classification of Diseases and Health Related Problems [ICD]-9*, or the *ICD-10*, as assessed by clinical interview or a validated questionnaire). There were no additional restrictions on sex or gender, ethnicity, comorbidities, setting, type of traumatic event, severity of symptoms, length of time since trauma, or previous or concurrent psychotherapy or pharmacotherapy.

Of the ten RCTs[52-55,66-71] included in the Cochrane review,[40] four studies recruited individuals who had experienced war or terrorism-related trauma,[54,66,68,71] one study recruited females who experienced sexual trauma,[70] and five studies did not restrict their study population by

type of trauma.[52,53,55,67,69] The Krupnick et al.[66] study enrolled veterans (18 years of age or older) who served in Iraq or Afghanistan with a PCL score of greater than 50, a cut-off score often cited as important for the diagnosis of PTSD in military populations (total range = 17 to 85).[72,73] The Engel et al.[54] RCT included war veterans who reported war-related trauma (including sexual military trauma) and screened positive on a four-item PTSD screener and met the criteria for PTSD on the CAPS). Knaevelsrud et al.[68] recruited Arabic-speaking adults (18 years of age and older and 65 years of age and younger) with a history of trauma, symptoms of post-traumatic stress, and who screened positive for PTSD using the Post-Traumatic Stress Diagnostic Scale (PDS). The RCT by Litz et al.[71] included Department of Defense service members (21 years of age and older and 65 years of age and younger) who had PTSD (according to *DSM-IV* criteria) as a result of the Pentagon attack on September 11th, 2001, or combat in Iraq or Afghanistan. Littleton et al.[70] enrolled college or university students who had experienced rape-related trauma and met the diagnostic criteria for PTSD according to the PTSD Symptom Scale Interview (PSS-I). Kuhn et al.[53] recruited adults (18 years of age and older) who had exposure to a traumatic event (of any nature) and who had a PTSD Checklist – Civilian Version (PCL-C) score of 35 or greater. The Lewis et al.[52] RCT included adults (18 years of age and older) who met the diagnostic criteria for *DSM-V* PTSD (as measured by CAPS-5) of mild to moderate. Miner et al.[67] enrolled adults (18 years of age and older) who had a PCL-C score of 25 or higher, with none of the included participants having a PCL-C score lower than the recommended range (i.e., 30 to 35) for PTSD screening in the general population. Ivarsson et al.[69] recruited adults (18 years of age and older) living in Sweden who met the *DSM-IV* criteria for chronic PTSD. Finally, Spence et al.[55] enrolled adult (18 years of age and older) residents of Australia who met the DSM-IV criteria for PTSD, as assessed with the Mini International Neuropsychiatric Interview.

The primary studies applied various exclusion criteria based on concurrent or previous treatment, such as excluding participants who had previous treatment with trauma-focused therapy,[52,54] or were currently receiving CBT,[55,66] psychological therapy,[52,69,70] psychiatric treatment,[71] or any treatment for PTSD.[53,67,68]

A total of 720 participants were included in the 10 primary studies,[52-55,66-71] with individual studies recruiting between 34[66] and 159[68] participants. The proportion of female participants in studies ranged from 18.75%[54] to 100%.[70] The mean time since primary traumatic event (index trauma) in the patient populations of included studies ranged from 2.72 years[52] to 9.88 years,[53] although the time since index trauma was not reported in eight primary studies.[54,55,66-71]

Interventions and Comparators

The Cochrane review[40] included studies that compared guided and unguided iCBT delivered via a computer or mobile device with face-to-face psychological therapy (either CBT based or non-CBT based; e.g., supportive therapy, non-directive counselling, psychodynamic therapy, and present-centred therapy), wait-list, repeated assessment, usual care, internet psychoeducation, or internet psychological therapy (internet-delivered non-CBT interventions [i-non-CBT]) (e.g., supportive therapy, non-directive counselling, psychodynamic therapy, and present- centred therapy). The authors of the Cochrane review did not apply their own criteria to classify interventions and comparators, but rather accepted the descriptions provided by the primary study authors (e.g., “face-to-face CBT therapy” was not required to contain specific components, but qualified as such if it was described as face-to-face CBT by the primary study authors).

Of the 10 primary studies in the Cochrane review,[40] eight studies[52-55,66-69] compared iCBT versus wait-list, delayed treatment, or usual care alone. Specifically, five RCTs used a wait-list or delayed treatment control,[52,53,55,67,68] one RCT used treatment as usual,[66] one RCT used optimized usual care alone,[54] and one RCT used minimal support via the internet.[69] Usual care and optimized usual care consisted of treatment as usual with no restrictions (i.e., participants may have received pharmacotherapy, psychotherapy, other treatments for PTSD, or no treatment). Both studies[54,66] also provided access to these options for individuals receiving iCBT treatment. These eight studies[51-55,66-6] were collectively analyzed in the iCBT versus wait-list or usual care comparison. The remaining two studies[70,71] compared iCBT versus i-non-CBT. One study used access to a psycho-educational website that contained informational content as the comparator intervention,[70] while the second RCT provided internet-delivered supportive counselling to participants in the control group.[71] The iCBT programs examined in these primary studies were PTSD Coach,[53,67] DESTRESS,[54,71] the From Survivor to Thriver Program,[70] were based on interapy,[66,68] or were not named.[55,69,74] All of the iCBT programs[54,55,66,68-71,74] included some form of therapist or nurse guidance, with the exception of PTSD Coach,[53,67] which was unguided. Treatment durations were four weeks,[67] five weeks,[68] six weeks,[67] eight weeks,[52,55,69,71] 12 weeks,[53] 14 weeks,[70] or was not reported.[66] The number of treatment sessions included in the iCBT programs ranged between seven[55,71] and 18.[54]

Outcome Measures

The following description is of the outcomes for which data were extracted, summarized, and used in the meta-analyses conducted by the authors of the Cochrane review.[40] The RCTs included in the Cochrane review[40] primarily reported on symptoms of PTSD, which were measured with several different scales, including: the PTSD Checklist – Military Version (PCL-M),[66] the PCL-C,[53-55,67] the CAPS-5,[52] the PCL-5,[52] the PDS,[68,69] the Impact of Event Scale – Revised (IES-R),[69] and the PSS-I.[70,71] Additionally, the Ivarsson et al.[69] study reported on the number of participants with a diagnosis of PTSD after treatment. The severity of depressive symptoms was measured in seven studies using the Beck Depression Inventory,[52,71] the Patient Health Questionnaire (PHQ-7, PHQ-8, PHQ-9, PHQ-15),[53,55,69] the Center for Epidemiologic Studies Depression Scale,[70] and the Hopkins Symptom Checklist-25.[68] Anxiety symptoms were measured in six studies with the Beck Anxiety Inventory (BAI)[52,69,71] the Generalized Anxiety Disorder 7-Item Scale,[55] the Four Dimensional Anxiety Scale,[70] and the Hopkins Symptom Checklist-25.[68] Quality of life was measured in two studies using the Quality of Life Inventory[69] and the EUROHIS-QUOL.[68] A brief description of some of the commonly used scales is available in Table 17 in Appendix 7. All 10 primary studies[52-55,66-71] provided information on the number of dropouts in each treatment arm within their study population. Outcome measurement occurred at baseline in all studies[52-55,66-71] (prior to the initiation of iCBT), with follow-up measurements at one month,[67] five weeks,[68] six weeks,[54] eight weeks,[55,69,71] 10 weeks,[52] 12 weeks (or three months),[53-55,66,68,71] 14 weeks,[52,70] 18 weeks,[54] 22 weeks,[52] 24 weeks,[66,70] six months,[53,71] or one year[69] after treatment initiation.

Critical Appraisal

Quality of the Cochrane Review

The quality assessment of the Cochrane review,[40] as assessed using the AMSTAR II tool,[42] is presented in Table 15 in Appendix 6.

A number of strengths of the Cochrane review[40] were identified through the critical appraisal process. The research questions, objectives, and eligibility criteria were clearly described and included components of population, intervention, comparators, and outcomes. The review included a reference to a protocol, published in 2015,[74] providing confidence that review methods were established a priori. Additionally, the authors provided justification for any significant deviations between the methods in the protocol and in the final publication (the only difference between the protocol and the review was that “attrition” was removed as an outcome measure of adverse events to avoid duplication with “dropout”). The review used a comprehensive literature search strategy, which was conducted in multiple databases and trial and study registries. The search also involved examination of reference lists and bibliographies of included studies, a search for grey literature, and consultation with experts in the field. The search strategy was described in detail and search terms were provided in the appendices of the report.

The methods for article selection, data extraction, and quality assessment were well-documented and all three were conducted in duplicate, decreasing the likelihood for inconsistency in these processes. The review included a flow chart illustrating study selection and provided reasons for articles that were excluded after full-text review. The review authors provided a detailed description of the included studies, including populations (inclusion and exclusion criteria), interventions, comparators, outcomes, study designs, sources of funding, and the contact information of authors.

The risk of bias in included primary studies was appropriately assessed using the criteria in the *Cochrane Handbook for Systematic Reviews of Interventions*,[44] and these risks were considered when interpreting and discussing the results of the review (particularly when evaluating the overall quality of the evidence using GRADE considerations).

Meta-analyses were performed using appropriate methods for the statistical combination of results (using a random-effects model when there was expected substantial heterogeneity between trials) and assessed and described heterogeneity when suitable (using Q and I^2 statistics). The authors planned to assess the potential causes of methodological heterogeneity and to examine the relationships between risk of bias and estimates of effectiveness using sensitivity analysis; however, the relatively low number of included studies per outcome and lack of variability in study quality (all of the included studies were of similar low quality) precluded the analyses.

Publication bias was adequately discussed in the Cochrane review. Although the authors were unable to use funnel plots to visually explore the possibility of publication bias,[44] they searched clinical trial registries and contacted experts in the field with the aim of identifying unpublished trials. The authors of the Cochrane review[40] disclosed their conflicts of interest (three authors were involved in the development and evaluation of an online, guided iCBT program for the treatment of PTSD in conjunction with Healthcare Learning Smile-on) and their sources of funding, none of which were considered likely to have influenced their findings.

As for limitations, the authors of the Cochrane review[40] did not explain the decision to restrict eligible study designs to RCTs, randomized crossover trials, and cluster-randomized trials. Although it may be assumed that this decision was related to study quality, this was never explicitly stated in the publication. It is possible that relevant non-randomized studies exist that were published prior to the search update and supplemental search; it is unknown whether such studies might have impacted the findings of the review.

A second limitation was the authors' decision to combine data across different follow-up durations in intervals of six months (which appeared to be an arbitrarily chosen length of time, rather than a follow-up duration with clinical meaning or importance). Using this approach, the findings of any studies that conducted a follow up at less than six months were combined in the meta-analysis. This led to studies with substantially different lengths of follow up (ranging from four weeks[67] to 18 weeks[54]) being combined to provide a single point estimate. This combination of data may have contributed to the substantial heterogeneity in several of the meta-analyses, an additional limitation to consider. For example, heterogeneity for the primary outcome (severity of PTSD symptoms) ranged between I^2 = 76% (post-treatment) and I^2 = 88% (at a second follow up less than six months later) for the comparison of iCBT versus waiting list or usual care alone. According to the *Cochrane Handbook for Systematic Reviews of Interventions*,[44] both of these I^2 values indicate considerable heterogeneity. An additional factor that may have contributed to the observed heterogeneity was the combination of wait-list and usual care alone within the same comparator condition (analysis 1 in the Cochrane review).[40] Participants treated with usual care (or optimized usual care) alone may have had increased access to PTSD treatment versus participants allocated to wait-list groups, where they would generally not have scheduled contact with clinicians. The authors of the Cochrane review[40] intended to explore the potential causes of clinical heterogeneity, including the level of therapist assistance (e.g., unguided or guided interventions), type of therapist assistance (e.g., guidance face-to-face, by telephone, by video conference, by email, by instant messaging), participant subgroups (e.g., veterans, female victims of sexual abuse, police officers), methods of participant recruitment (e.g., from media adverts or from health care services), type of CBT (e.g., predominantly cognitive therapy or predominantly behavioural therapy), baseline symptom severity (e.g., high versus low baseline mean symptom severity), trauma type and context (e.g., war, childhood abuse, motor vehicle accident), trauma focus (e.g., trauma-focused iCBT, which places specific emphasis on emotions, thoughts, and behaviours relating to a traumatic event, versus non-trauma focused iCBT, which may incorporate cognitive reframing techniques and educational information about PTSD, stress, depression, anger management, sleep hygiene, and relaxation techniques), and type of device (e.g., computer, smartphone); however, there were insufficient data to perform these subgroup analyses. As a result, the affect that clinical heterogeneity may have on the findings of the review is uncertain.

Some of the outcomes included in the meta-analysis were conducted on primary studies that had effect estimates moving in opposite directions. One example of this is analysis 1.5 from the Cochrane review[40] (re-created in Figure 4), which compared iCBT with wait-list for the severity of depression symptoms post-treatment. The appropriateness of the statistical combination of these results should be considered when interpreting the findings of the meta-analysis.

The Cochrane review did not include any discussion regarding MCID values for any of the outcomes (i.e., severity of PTSD symptoms, severity of depression symptoms, severity of anxiety symptoms, quality of life). A statistically significant difference in scores does not

necessarily indicate a clinically meaningful difference, and it is unclear if any of the statistically significant findings in the review translate into clinically meaningful differences.

Quality of Primary Studies Included in the Cochrane Review

The results of the quality assessment of the included primary studies, as judged by Lewis et al.[40] using the criteria in the *Cochrane Handbook for Systematic Reviews of Interventions*,[44] are presented in Table 18 in Appendix 8.

The risk of selection bias due to random sequence generation was unclear in three studies[66,67,71] and low in seven studies.[52-55,68-70] The risk of selection bias due to allocation concealment was unclear in nine studies[42,53-55,66,68-71] that did not provide information to make a judgment, and low in one study (where sealed, opaque envelopes were used to conceal the allocation of treatment).[52] The risk of performance bias was high in all ten studies[52-55,66-71] due to a lack of blinding of participants and personnel. Performance bias may have overestimated the treatment effects for iCBT as clinicians conducting the study and participants who agreed to enter the study are more likely to have a bias favouring treatment success.[75] The risk of detection bias was high in two studies[55,70] due to unblinded outcome assessors and low in eight studies[52-54,66-69,71] that reported adequate blinding of outcome assessors. The risk of attrition bias was high in four studies[55,66,68,71] due to incomplete outcome data and low in six studies.[52-54,67,69,70] In a majority of included studies, participants allocated to iCBT groups were at a higher risk for dropout than those in control groups (Figure 3). If the mechanism driving this imbalance was lack of treatment effect with iCBT, the effect estimates may have been overestimated (as patients who were successful with iCBT treatment would have been more likely to remain until the final follow up and provide data for analysis). The risk of selective outcome reporting bias was low for all ten studies[52-55,66-71] because the authors either published a study protocol or they reported on pre-specified outcomes that are expected in trials of this type in the field of PTSD (e.g., severity of PTSD, depression, and anxiety). The risk of bias from other biases was high in four studies,[52,66,69,71] unclear in one study,[55] and low in five studies.[53,54,67,68,70] Specifically, the risk of other bias was high in the following studies: Ivarsson et al.[69] as the intervention was evaluated by its developers; Krupnick et al.[66] due to small sample size and the risk for confounding due to participants receiving other interventions during the trial; Lewis et al.[52] due to small sample size and the fact that the intervention was evaluated by the originators; and Litz et al.[71] due to small sample size, large numbers lost to follow up, and the fact that the intervention was evaluated by the originators. This risk of other bias was judged as unclear in Spence et al.[55] due to small sample size, the termination of recruitment due to staff availability, the inability to meet recruitment targets, that the intervention was evaluated by the originators, and the lack of information on time since trauma in participants.

Summary of Findings

Clinical Effectiveness and Safety of iCBT for the Treatment of Patients, Aged 16 Years or Older, With a Primary Diagnosis of PTSD

iCBT Versus Wait-List or Usual Care

Severity of Post-Traumatic Stress Disorder Symptoms

Very low-quality evidence suggested that iCBT was more effective than wait-list or usual care alone with respect to the severity of PTSD symptoms post-treatment (SMD [95% CI] = −0.60 [−0.97 to −0.24]; participants = 560; 8 RCTs). There was considerable heterogeneity in study results (I^2 = 76%). These results are shown in Figure 1.

In order to further contextualize this result, an investigation into the clinical significance of this finding was conducted, as previously described. Back calculation of the SMD yielded MD values for both the CAPS-5 (MD = −3.98) and the PCL (MD = −6.42). A supplemental search on MCID literature suggested that there is currently no widely accepted threshold for defining clinically significant change on the CAPS or the PCL; however, a few thresholds have been proposed. Starting with the CAPS instrument, several studies[56,57] have used a decrease of at least 10 points as indicating clinically significant change, one study[58] used a decrease of 15 points, and Hien et al.[59] used a change of 30 points. As for the PCL, Polusny et al.[60] and Krystal et al.[61] considered a reduction of 10 points or more as an MCID. According to all of these thresholds, and taking into account the CIs, the estimated SMD would not indicate a clinically meaningful change. Additionally, Stefanovics et al.[62] conducted a study to derive MCID values for both the CAPS and the PCL instruments in a population of veterans with PTSD. Their findings estimated MCID values with midpoints of 10.4 for the CAPS and 7.9 points for the PCL. Comparison with these values suggests that the estimated MDs were clinically insignificant for both the CAPS and the PCL. According to this estimation procedure, with the assumption that the utilized among-person standard deviations are representative, the estimated SMD does not appear to indicate a clinically significant change in the severity of PTSD symptoms (despite being statistically significant) between iCBT and wait-list or usual care alone.

This result was further investigated by Lewis et al.[64] in a subsequent publication of the Cochrane review,[40] which was identified within the search updates. As part of this second publication, the authors conducted two additional subgroup analyses: one, studies that used trauma-focused iCBT programs, and two, studies that provided therapist guidance with iCBT treatment. Their findings indicated that the post-treatment effect size was greater for studies that that used trauma-focused iCBT programs (SMD [95% CI] = −1.04 [−1.57 to −0.51] versus non-trauma focused; participants = 177; 4 RCTs). Their analysis on the effect of therapist guidance suggested that guided iCBT programs had greater effect post-treatment (SMD [95% CI] = −0.86 [−1.25 to −0.47]; participants = 391; 6 RCTs) than both guided and unguided iCBT interventions combined (SMD [95% CI] = −0.60 [−0.97 to −0.24]; participants = 560; 8 RCTs) versus wait-list.

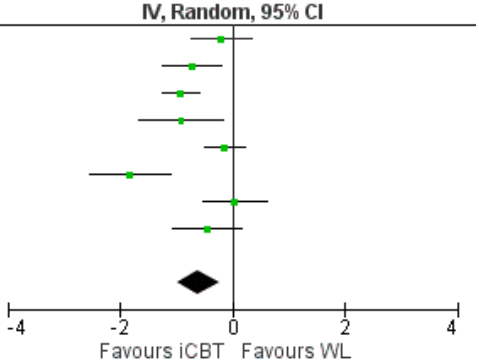
According to a reanalysis of the Cochrane results, there were no statistically significant differences between the iCBT and wait-list or usual care alone groups for severity of PTSD symptoms at a second follow up at less than six months (SMD [95% CI] = −0.84 [−2.15 to 0.47]; participants = 95; 2 RCTs; Figure 2). There was once again considerable heterogeneity in the study results (I^2 =88%). Two modifications were made in our analysis compared with analysis 1.2 from the Cochrane review.[40] To start, the Miner et al.[67] study

was removed from our analysis as participants in the wait-list group were crossed over to treatment with iCBT prior to the second follow up at less than six months. Therefore, this data point was not comparing iCBT-treated individuals with a wait-list group and was not relevant for the analysis. Second, the mean scores and standard deviations for both treatment groups from the Engel et al.[54] study were adjusted to reflect PCL scores at second follow up of less than six months, rather than the PHQ-8 scores used in the Cochrane analysis. These modifications did not alter the statistical significance of the findings, but the point estimate and CIs shifted as a result (from SMD [95% CI] = −0.43 [−1.41 to 0.56] in the Cochrane review to SMD [95% CI] = −0.84 [−2.15 to 0.47] in our analysis).

Figure 1: Comparison of Internet-Delivered Cognitive Behavioural Therapy and Wait-List — Outcome: Severity of Post-Traumatic Stress Disorder Symptoms (Post-Treatment)

	iCBT			Wait list				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Engel 2015	43.8	18.33	30	47.36	17.45	25	12.7%	-0.20 [-0.73, 0.34]
Ivarsson 2014	17.32	9.86	31	25.04	11.14	31	12.9%	-0.72 [-1.24, -0.21]
Knaevelsrund 2015	20.29	12.45	79	30.17	8.7	80	15.2%	-0.92 [-1.24, -0.59]
Krupnick 2017	3.58	0.3	16	3.91	0.4	15	10.1%	-0.91 [-1.66, -0.17]
Kuhn 2017	51.93	14.04	62	53.9	13.78	58	14.8%	-0.14 [-0.50, 0.22]
Lewis 2017	17.93	12.25	21	36.53	7.1	21	10.3%	-1.82 [-2.55, -1.09]
Miner 2016	56.31	10.51	25	55.77	12.99	24	12.3%	0.05 [-0.52, 0.61]
Spence 2011	44.78	17.29	23	51.79	12.51	19	11.6%	-0.45 [-1.06, 0.17]
Total (95% CI)			**287**			**273**	**100.0%**	**-0.60 [-0.97, -0.24]**

Heterogeneity: Tau² = 0.20; Chi² = 28.96, df = 7 (P = 0.0001); I² = 76%
Test for overall effect: Z = 3.22 (P = 0.001)



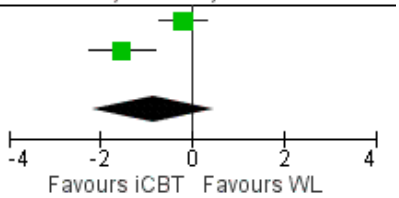
CI = confidence interval; iCBT = internet-delivered cognitive behavioural therapy; IV = inverse variance; SD = standard deviation; WL = wait-list.

Source: Lewis et al. (2018).[40]

Figure 2: Comparison Of Internet-Delivered Cognitive Behavioural Therapy And Wait-List — Outcome: Severity of Post-Traumatic Stress Disorder Symptoms (Follow Up Less Than Six Months)

	iCBT			Wait list				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Engel 2015	43.8	18.33	30	47.36	17.45	25	51.7%	-0.20 [-0.73, 0.34]
Lewis 2017	16.47	13.22	19	33.63	8.42	21	48.3%	-1.53 [-2.25, -0.82]
Total (95% CI)			**49**			**46**	**100.0%**	**-0.84 [-2.15, 0.47]**

Heterogeneity: Tau² = 0.79; Chi² = 8.68, df = 1 (P = 0.003); I² = 88%
Test for overall effect: Z = 1.26 (P = 0.21)



CI = confidence interval; iCBT = internet-delivered cognitive behavioural therapy; IV = inverse variance; SD = standard deviation; Std. = standard; WL = wait-list.

Source: Lewis et al. (2018).[40]

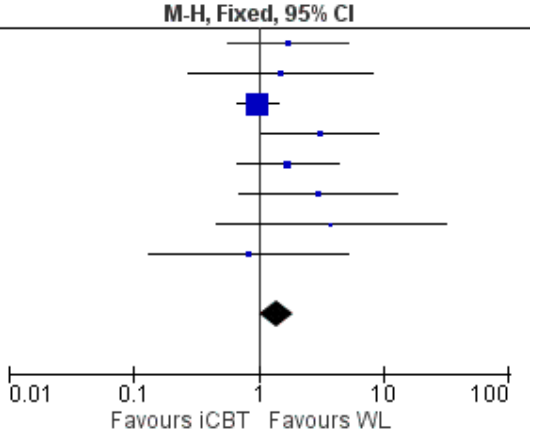
Dropouts

Low-quality evidence indicated that there was a statistically significant difference in dropout rates between participants in the iCBT and wait-list or usual care alone control groups, with an increased risk for dropout in those treated with iCBT (relative risk [RR]) [95% CI] = 1.39 [1.03 to 1.88]; participants = 585; 8 RCTs; I^2 = 13%; Figure 3). Participants who did not complete post-treatment assessments for any reason (e.g., individuals who discontinued the intervention, withdrew from the study, were lost to follow up, did not respond to requests from study conductors) were considered to have dropped out.

Figure 3: Comparison of Internet-Delivered Cognitive Behavioural Therapy and Wait-List — Outcome: Dropouts

	iCBT		Wait list			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Engel 2015	8	43	4	37	8.0%	1.72 [0.56, 5.26]
Ivarsson 2014	3	31	2	31	3.7%	1.50 [0.27, 8.36]
Knaevelsrund 2015	32	79	33	80	61.2%	0.98 [0.68, 1.43]
Krupnick 2017	10	16	3	15	5.8%	3.13 [1.06, 9.21]
Kuhn 2017	11	62	6	58	11.6%	1.72 [0.68, 4.34]
Lewis 2017	6	21	2	21	3.7%	3.00 [0.68, 13.20]
Miner 2016	4	25	1	24	1.9%	3.84 [0.46, 31.94]
Spence 2011	2	23	2	19	4.1%	0.83 [0.13, 5.32]
Total (95% CI)		**300**		**285**	**100.0%**	**1.39 [1.03, 1.88]**
Total events	76		53			

Heterogeneity: Chi² = 8.05, df = 7 (P = 0.33); I² = 13%
Test for overall effect: Z = 2.18 (P = 0.03)



CI = confidence interval; df = degrees of freedomiCBT = internet-delivered cognitive behavioural therapy; M-H = Mantel–Haenszel; WL = wait-list.

Source: Lewis et al. (2018).[40]

Diagnosis of Post-Traumatic Stress Disorder After Treatment

There was very low-quality evidence of no statistically significant difference between iCBT and wait-list for the risk of continued PTSD diagnosis (i.e., PTSD diagnosis retained following treatment) post-treatment (RR [95% CI] = 0.53 [0.28 to 1.00]; participants = 62; 1 RCT; I^2 = not applicable). The study[69] that measured this outcome assessed the diagnostic status of patients at post-treatment using the PDS (a self-report measure following the *DSM-IV* diagnosis criteria for PTSD).

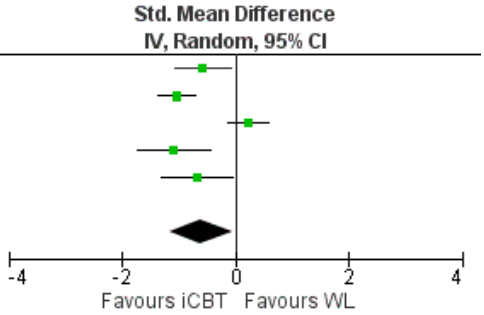
Severity of Depressive Symptoms

Very low-quality evidence suggested that iCBT was more effective than wait-list or usual care alone for the reduction of depressive symptoms from pre- to post-treatment (SMD [95% CI] = −0.61 [−1.17 to −0.05]; participants = 425; 5 RCTs; Figure 4). There was considerable heterogeneity in the study results (I^2 = 86%). There was very low-quality evidence that iCBT was still more effective than wait-list or usual care alone at a second follow up at less than six months (MD [95% CI] = −8.95 [−15.57 to −2.33]; participants = 42; 1 RCT; I^2 = not applicable).

Figure 4: Comparison of Internet-Delivered Cognitive Behavioural Therapy and Wait-List — Outcome: Severity of Depressive Symptoms (Post-Treatment)

	iCBT			Wait list				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Ivarsson 2014	16.11	10.49	31	22.19	10.5	31	19.9%	-0.57 [-1.08, -0.06]
Knaevelsrund 2015	2.36	0.9	79	3.11	0.5	80	22.0%	-1.03 [-1.36, -0.70]
Kuhn 2017	13.62	5.55	62	12.31	5.88	58	21.7%	0.23 [-0.13, 0.59]
Lewis 2017	15.97	10.42	21	26.8	9.08	21	18.0%	-1.09 [-1.74, -0.43]
Spence 2011	10.17	5.65	23	13.84	4.95	19	18.3%	-0.67 [-1.30, -0.05]
Total (95% CI)			**216**			**209**	**100.0%**	**-0.61 [-1.17, -0.05]**

Heterogeneity: Tau² = 0.34; Chi² = 28.74, df = 4 (P < 0.00001); I² = 86%
Test for overall effect: Z = 2.14 (P = 0.03)



CI = confidence interval; df = degrees of freedom; iCBT = internet-delivered cognitive behavioural therapy; IV = inverse variance; SD = standard deviation; Std. = standard; WL = wait-list.

Source: Lewis et al. (2018).[40]

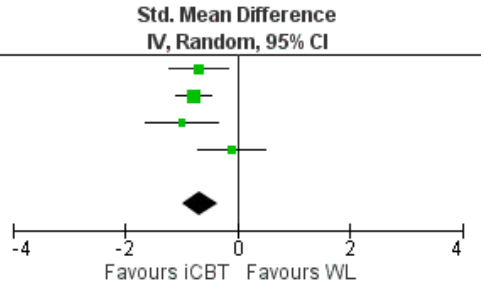
Severity of Anxiety Symptoms

There was very low-quality evidence that iCBT was more effective than wait-list or usual care alone at reducing symptoms of anxiety from pre- to post-treatment (SMD [95% CI] = −0.67 [−0.98 to −0.36]; participants = 305; 4 RCTs; I^2 = 35%; Figure 5). Very low-quality evidence suggested that iCBT was still more effective than wait-list or usual care alone at a second follow up at less than six months, as measured with the BAI (MD [95% CI] = −12.59 [−20.74 to −4.44]; participants = 42; 1 RCT; I^2 = not applicable).

Figure 5: Comparison of Internet-Delivered Cognitive Behavioural Therapy and Wait-List — Outcome: Severity of Anxiety Symptoms (Post-Treatment)

	iCBT			Wait list				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Ivarsson 2014	13.57	8.15	31	20.08	10.26	31	23.9%	-0.69 [-1.21, -0.18]
Knaevelsrund 2015	2.29	0.81	79	2.85	0.61	80	39.8%	-0.78 [-1.10, -0.46]
Lewis 2017	17.1	11.06	21	30.05	14.43	21	17.4%	-0.99 [-1.63, -0.34]
Spence 2011	7.26	5.94	23	7.91	5.98	19	18.9%	-0.11 [-0.72, 0.50]
Total (95% CI)			**154**			**151**	**100.0%**	**-0.67 [-0.98, -0.36]**

Heterogeneity: Tau² = 0.04; Chi² = 4.64, df = 3 (P = 0.20); I² = 35%
Test for overall effect: Z = 4.23 (P < 0.0001)



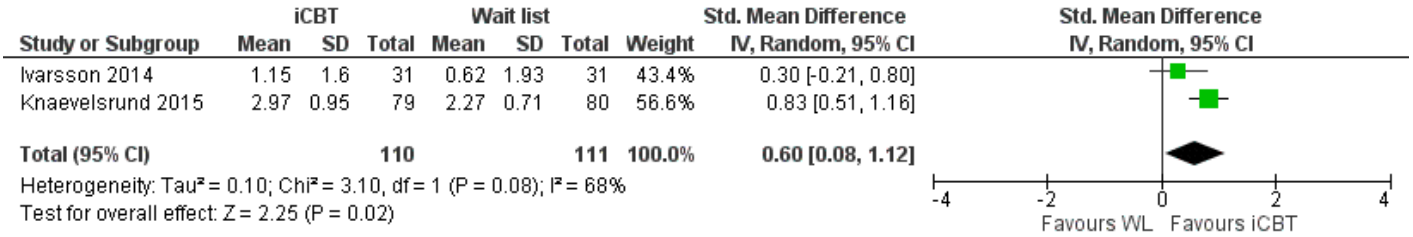
CI = confidence interval; df = degrees of freedom; iCBT = internet-delivered cognitive behavioural therapy; IV = inverse variance; SD = standard deviation; Std. = standard; WL = wait-list.

Source: Lewis et al. (2018).[40]

Quality of Life

Very low-quality evidence from two studies showed that iCBT was more effective than wait-list or control (reported as insignificant in the Cochrane review) for improving quality of life post-treatment (SMD [95% CI] = 0.60 [0.08 to 1.12]; participants = 221; 2 RCTs; Figure 6). There was substantial heterogeneity in the study results (I^2 = 68%).

Figure 6: Comparison of Internet-Delivered Cognitive Behavioural Therapy and Wait-List — Outcome: Quality of Life (Post-Treatment)



CI = confidence interval; df = degrees of freedom; iCBT = internet-delivered cognitive behavioural therapy; IV = inverse variance; SD = standard deviation; Std. = standard; WL = wait-list.

Note: The x-axis for this figure is reversed (i.e., favours iCBT is on the right side of zero) as this outcome is the only instance where a positive standard mean difference indicated improvement (e.g., increased quality of life scores indicated improvement while decreased PTSD symptom severity scores indicated improvement).

Source: Lewis et al. (2018).[40]

Adverse Events

The RCT by Lewis et al.[52] stated that there were no adverse events reported by any study participants (in both the iCBT and wait-list groups). Similarly, the Krupnick et al.[66] study noted an absence of adverse incidents, such as the need for hospitalization, in their participant population. The remaining six included primary studies[53-55,67-69] that compared iCBT versus wait-list or usual care alone and reported no adverse event data.

iCBT Versus Internet Non-Cognitive Behavioural Therapy Interventions

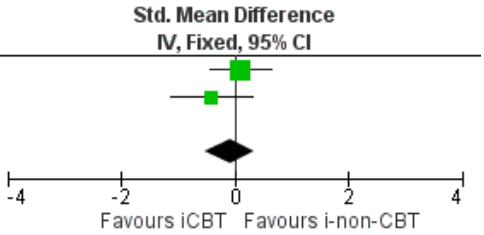
Severity of Post-Traumatic Stress Symptoms

Very low-quality evidence suggested that there was no difference between iCBT and i-non-CBT groups with respect to the severity of PTSD symptoms post-treatment (SMD [95% CI] = −0.08 [−0.57 to 0.35]; participants = 82; 2 RCTs; I^2 = 19%; Figure 7) or at a second follow up of less than six months (SMD [95% CI] = 0.08 [−0.41 to 0.57]; participants = 65; 2 RCTs; I^2 = 0%; Figure 8). However, there was a significant difference in favour of iCBT at follow up between six and 12 months, as measured with the PSS-I (MD [95% CI] = −8.83 [−17.32 to −0.34]; participants = 18; 1 RCT; I^2 = not applicable).This result should be interpreted with caution as the number of patients lost prior to the follow up between six and 12 months in this study[71] was greater than 50%.

Figure 7: Comparison of Internet-Delivered Cognitive Behavioural Therapy and Internet Non-Cognitive Behavioural Therapy — Outcome: Severity of Post-Traumatic Stress Disorder Symptoms (Post-Treatment)

	iCBT			i-non-CBT				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Littleton 2016	11.2	5.8	23	10.4	8.5	28	62.7%	0.11 [-0.45, 0.66]
Litz 2007	14.86	13.35	14	20	11.5	17	37.3%	-0.40 [-1.12, 0.31]
Total (95% CI)			**37**			**45**	**100.0%**	**-0.08 [-0.52, 0.35]**

Heterogeneity: Chi² = 1.23, df = 1 (P = 0.27); I² = 19%
Test for overall effect: Z = 0.38 (P = 0.71)



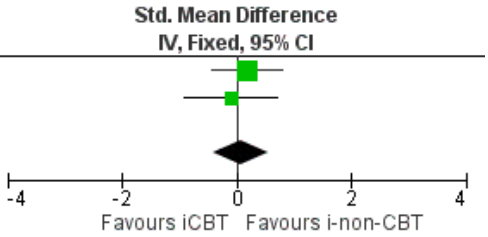
CI = confidence interval; df = degrees of freedom; iCBT = internet-delivered cognitive behavioural therapy; i-non-CBT = internet-delivered non-cognitive behavioural therapy; IV = inverse variance; SD = standard deviation; Std. = standard; WL = wait-list.

Source: Lewis et al. (2018).[40]

Figure 8: Comparison of Internet-Delivered Cognitive Behavioural Therapy and Internet Non-Cognitive Behavioural Therapy — Outcome: Severity of Post-Traumatic Stress Disorder Symptoms (Follow Up of fewer than Six Months)

	iCBT			i-non-CBT				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Littleton 2016	7.9	6.3	20	6.8	5.7	21	63.6%	0.18 [-0.43, 0.79]
Litz 2007	13.2	7.05	10	13.96	8.63	14	36.4%	-0.09 [-0.90, 0.72]
Total (95% CI)			**30**			**35**	**100.0%**	**0.08 [-0.41, 0.57]**

Heterogeneity: Chi² = 0.27, df = 1 (P = 0.60); I² = 0%
Test for overall effect: Z = 0.32 (P = 0.75)



CI = confidence interval; df = degrees of freedom; iCBT = internet-delivered cognitive behavioural therapy; i-non-CBT = internet-delivered non-cognitive behavioural therapy;
IV = inverse variance; SD = standard deviation; Std. = standard; WL = wait-list.

Source: Lewis et al. (2018).[40]

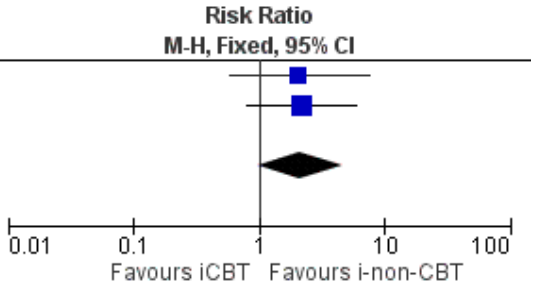
Dropouts

Very low-quality evidence indicated that there were no statistically significant differences in dropout rates between participants in the iCBT and i-non-CBT groups (RR [95% CI] = 2.14 [0.97 to 4.73]; participants = 1,325; 2 RCTs; I^2 = 0%). Data are shown in Figure 9.

Figure 9: Comparison of Internet-Delivered Cognitive Behavioural Therapy and Internet Non-Cognitive Behavioural Therapy — Outcome: Dropouts

Study or Subgroup	iCBT Events	iCBT Total	i-non-CBT Events	i-non-CBT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Littleton 2016	7	46	3	41	42.6%	2.08 [0.58, 7.52]
Litz 2007	10	24	4	21	57.4%	2.19 [0.80, 5.95]
Total (95% CI)		**70**		**62**	**100.0%**	**2.14 [0.97, 4.73]**
Total events	17		7			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.88 (P = 0.06)



CI = confidence interval; df = degrees of freedom; iCBT = internet-delivered cognitive behavioural therapy; i-non-CBT = internet-delivered non-cognitive behavioural therapy; M-H = Mantel–Haenszel; WL = wait-list.

Source: Lewis et al. (2018).[40]

Diagnosis of Post-Traumatic Stress Disorder After Treatment

None of the included primary studies that compared iCBT with i-non-CBT reported diagnosis of PTSD after treatment.

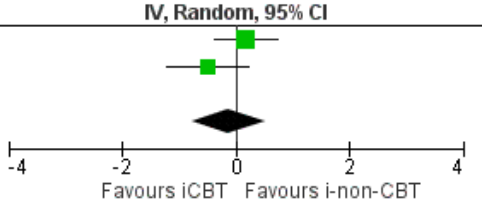
Severity of Depressive Symptoms

There was very low-quality evidence for no statistically significant difference in severity of depressive symptoms between participants treated with iCBT and i-non-CBT interventions post-treatment (SMD [95% CI] = −0.12 [−0.78 to 0.54]; participants = 84; 2 RCTs; I^2 = 52%; Figure 10) or at a second follow up of less than six months (SMD [95% CI] = 0.20 [−0.31 to 0.71]; participants = 61; 2 RCTs; I^2 = 0%; Figure 11). However, there was a statistically significant difference in the severity of depressive symptoms between iCBT and i-non-CBT groups (favouring iCBT) when follow up was between six and 12 months, as measured with the Beck Depression Inventory II (MD [95% CI] = −8.34 [−15.83 to −0.85]; participants = 18; 1 RCT; I^2 = not applicable). This result should be interpreted with caution as the number of patients lost prior to the follow up between six and 12 months in this study[71] was greater than 50%.

Figure 10: Comparison of Internet-Delivered Cognitive Behavioural Therapy and Internet Non-Cognitive Behavioural Therapy — Outcome: Severity of Depressive Symptoms (Post-Treatment)

Study or Subgroup	iCBT Mean	iCBT SD	iCBT Total	i-non-CBT Mean	i-non-CBT SD	i-non-CBT Total	Weight	Std. Mean Difference IV, Random, 95% CI
Littleton 2016	14.7	9.6	18	13.2	7.5	35	55.5%	0.18 [-0.39, 0.75]
Litz 2007	12.14	9.56	14	17.47	11.19	17	44.5%	-0.49 [-1.21, 0.22]
Total (95% CI)			**32**			**52**	**100.0%**	**-0.12 [-0.78, 0.54]**

Heterogeneity: Tau² = 0.12; Chi² = 2.07, df = 1 (P = 0.15); I² = 52%
Test for overall effect: Z = 0.36 (P = 0.72)



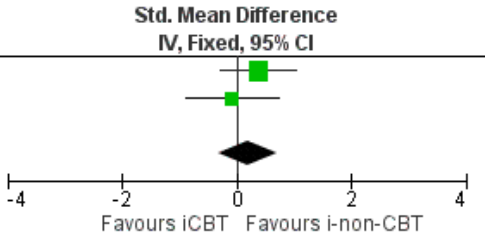
CI = confidence interval; df = degrees of freedom; iCBT = internet-delivered cognitive behavioural therapy; IV = inverse variance; SD = standard deviation; STD. = standard; WL = wait-list.

Source: Lewis et al. (2018).[40]

Figure 11: Comparison of Internet-Delivered Cognitive Behavioural Therapy and Internet Non-Cognitive Behavioural Therapy — Outcome: Severity of Depressive Symptoms (Follow Up of Fewer than Six Months)

Study or Subgroup	iCBT Mean	iCBT SD	iCBT Total	i-non-CBT Mean	i-non-CBT SD	i-non-CBT Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Littleton 2016	14.4	10.7	20	10.8	7.2	17	60.7%	0.38 [-0.27, 1.03]
Litz 2007	12.51	6.53	10	13.23	9.08	14	39.3%	-0.09 [-0.90, 0.73]
Total (95% CI)			**30**			**31**	**100.0%**	**0.20 [-0.31, 0.71]**

Heterogeneity: Chi² = 0.77, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 0.76 (P = 0.45)



CI = confidence interval; df = degrees of freedom; iCBT = internet-delivered cognitive behavioural therapy; i-non-CBT = internet-delivered non-cognitive behavioural therapy; IV = inverse variance; SD = standard deviation; STD. = standard; WL = wait-list.

Source: Lewis et al. (2018).[40]

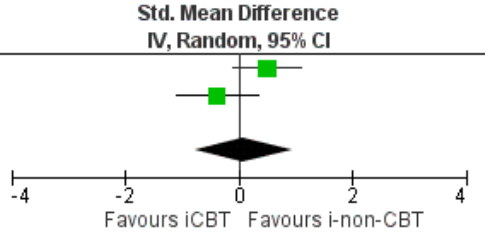
Severity of Anxiety Symptoms

Very low-quality evidence suggested that there were no statistically significant differences in severity of anxiety symptoms between the iCBT and i-non-CBT groups post-treatment (SMD [95% CI] = 0.08 [−0.78 to 0.95]; participants = 74; 2 RCTs; I^2 = 70%; Figure 12) or at a second follow up of less than six months (SMD [95% CI] = −0.16 [−0.67 to 0.35]; participants = 60; 2 RCTs; I^2 = 9%; Figure 13). However, there was very low-quality evidence for a significant difference in the severity of anxiety symptoms between the iCBT and i-non-CBT groups (favouring iCBT) when follow up was between six and 12 months, as measured with the BAI (MD [95% CI] = −8.05 [−15.20 to −0.90]; participants = 18; 1 RCT; I^2 = not applicable). This result should be interpreted with caution as the number of patients lost prior to the follow up between six and 12 months in this study[71] was greater than 50%.

Figure 12: Comparison of Internet-Delivered Cognitive Behavioural Therapy and Internet Non-Cognitive Behavioural Therapy — Outcome: Severity of Anxiety Symptoms (Post-Treatment)

Study or Subgroup	iCBT Mean	iCBT SD	iCBT Total	i-non-CBT Mean	i-non-CBT SD	i-non-CBT Total	Weight	Std. Mean Difference IV, Random, 95% CI
Littleton 2016	68.9	23.3	20	58.7	16.4	23	52.3%	0.50 [-0.11, 1.11]
Litz 2007	8.43	5.93	14	12.59	13.45	17	47.7%	-0.38 [-1.09, 0.34]
Total (95% CI)			**34**			**40**	**100.0%**	**0.08 [-0.78, 0.95]**

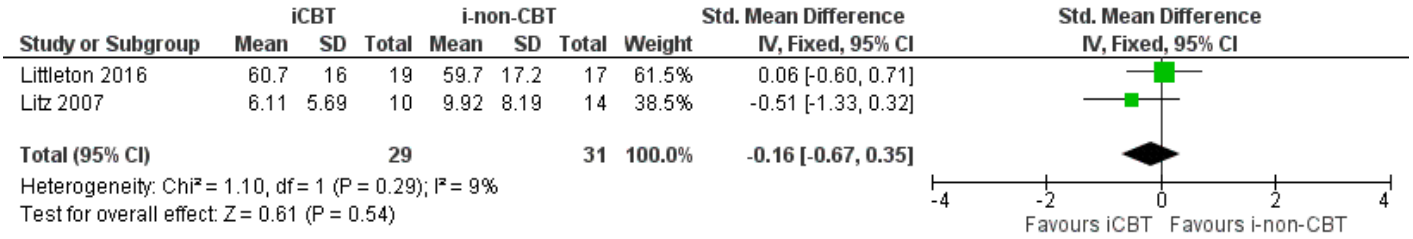
Heterogeneity: Tau² = 0.27; Chi² = 3.37, df = 1 (P = 0.07); I² = 70%
Test for overall effect: Z = 0.19 (P = 0.85)



CI = confidence interval; df = degrees of freedom; iCBT = internet-delivered cognitive behavioural therapy; i-non-CBT = internet-delivered non-cognitive behavioural therapy; IV = inverse variance; SD = standard deviation; STD. = standard; WL = wait-list.

Source: Lewis et al. (2018).[40]

Figure 13: Comparison of Internet-Delivered Cognitive Behavioural Therapy and Internet Non-Cognitive Behavioural Therapy — Outcome: Severity of Anxiety Symptoms (Follow Up of Fewer Than Six Months)



CI = confidence interval; df = degrees of freedom; i-non-CBT = internet-delivered non-cognitive behavioural therapy; IV = inverse variance; SD = standard deviation; STD. = standard;
WL = wait-list.

Source: Lewis et al. (2018).[40]

Quality of Life

None of the included primary studies that compared iCBT versus i-non-CBT reported on quality of life.

Adverse Events

The RCT by Littleton et al.[70] noted that 4.3% of participants (2 out of 46) who were assigned to treatment with iCBT reported clinically significant increases in depression at post-treatment (measured using the Reliable Change Index). The authors reported that these two 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 out of 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 i-non-CBT intervention reported a 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. The Litz et al.[71] RCT did not report data relating to adverse events.

Overall Summary of Findings and Quality of the Evidence

The overall findings of the included studies (estimated with the meta-analyses) and the quality (certainty) of the evidence, as assessed by the authors of the Cochrane review[40] using the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) are summarized in Table 2.

Overall, there was a high level of uncertainty in the findings of the meta-analyses. Evidence for eight out of the nine outcomes for which data were available were rated as being of very low quality. Evidence for one outcome (dropouts for the comparison of iCBT versus wait-list or usual care alone) was rated as low quality. One of the main reasons for rating down the quality of the evidence was the high risk of bias in the primary studies, which was considered to have potentially overestimated the treatment effects. For example, all included primary studies were open-label and at a risk for bias depending on the perceptions and expectations of the participants and clinicians involved. Although blinding of participants and practitioners may not be feasible for psychotherapeutic interventions, it is expected that both the treating clinicians (i.e., the study authors) and the individuals willing to participate in the

iCBT studies would have a bias favouring treatment success.[75] Other reasons for quality downgrades included imprecision (due to small sample size) and inconsistency in effect estimates between studies. These concerns limit the internal validity of the reviewed studies.

As for external validity, the study participants, clinicians, and care setting largely appear to be representative of the population and care setting of interest; however, the recruitment of participants into the included primary studies often relied on individuals to reach out to study investigators through advertisements in newspapers, websites, university campuses, or primary care centres. This method of recruitment through self-selection may have resulted in the enrolment of a motivated subset of individuals with PTSD who were more likely to complete iCBT programs and to apply their learning in their lives. In addition, there were high levels of clinical variability between iCBT programs with respect to program content, number of modules, duration, type of support (e.g., phone, email, face-to-face, combination), and frequency of support. Given the available data, it is unclear which components and features of iCBT programs may be most beneficial to patients. Finally, none of the included primary studies were conducted in Canada, and although there was no strong indication that the findings from any of the primary studies would not apply to the people accessing the Canadian health system, this remains possible. In summary, there are numerous concerns regarding the certainty and quality of the evidence that limit the extent to which the conclusions of the meta-analyses are internally and externally valid; the true effect that would be observed in the "real world" may be substantially different from the estimates described in this report.

Table 2: Overall Summary of Evidence

Outcome	Anticipated Absolute Effects (95% CI)		Relative Effect (95% CI)	Number of Participants and Studies	Certainty of the Evidence (GRADE)
	Control Group	iCBT Group			
iCBT Versus Wait-List or Usual Care Alone					
Severity of PTSD symptoms (post-treatment; measured with the IES-R, CAPS-5, PCL, and PDS; higher score indicate increased severity)	The mean severity of PTSD symptoms (post-treatment) was 0	SMD = −0.60 (−0.97 to −0.24)	–	560 8 RCTs[52-55,66-69]	⊕OOO VERY LOW • Downgraded two levels due to high risk of performance bias (8 RCTs),[52-55,66-69] high risk of attrition bias (2 RCTs),[66,68] and high risk of other biases (3 RCTs)[52,66,69] • Downgraded one level for inconsistency and high levels of heterogeneity
Dropouts	186 per 1,000	258 per 1,000 (192 to 350)	RR = 1.39 (1.03 to 1.88)	585 8 RCTs[52-55,66-69]	⊕⊕OO LOW • Downgraded two levels due to high risk of performance bias (8 RCTs),[52-55,66-69] high risk of attrition bias (2 RCTs),[66,68] and high risk of other biases (3 RCTs)[52,66,69]
Diagnosis of PTSD (post-treatment)	548 per 1,000	291 per 1,000 (154 to 548)	RR = 0.53 (0.28 to 1.00)	62 1 RCT[9]	⊕OOO VERY LOW

Outcome	Anticipated Absolute Effects (95% CI)		Relative Effect (95% CI)	Number of Participants and Studies	Certainty of the Evidence (GRADE)
	Control Group	iCBT Group			
					• Downgraded two levels due to high risk of performance bias and other bias (1 RCT)[69] • Downgraded one level for imprecision due to small sample size and the CI around the effect estimate includes both little or no effect
Severity of depressive symptoms (post-treatment; measured with the BDI, PHQ, and CES-D; higher score indicates increased severity)	The mean depression (post-treatment) was 0	SMD = −0.61 (−1.17 to −0.05)	–	425 5 RCTs[52,53,55,68,69]	⊕OOO VERY LOW • Downgraded two levels due to high risk of performance bias (5 RCTs),[52,53,55,68,69] high risk of attrition bias (1 RCT),[68] and high risk of other bias (2 RCTs)[52,69] • Downgraded one level for inconsistency and high levels of heterogeneity
Severity of anxiety symptoms (post-treatment; measured with the BAI and GAD-7; higher score indicates increased severity)	The mean anxiety (post-treatment) was 0	SMD = −0.67 (−0.98 to −0.36)	–	305 4 RCTs[52,55,68,69]	⊕OOO VERY LOW • Downgraded two levels due to high risk of performance bias (4 RCTs),[52,55,68,69] high risk of attrition bias (1 RCT),[68] and high risk of other bias (2 RCTs)[52,55] • Downgraded one level for imprecision due to small sample size
iCBT Versus i-non-CBT Interventions					
Severity of PTSD symptoms (post-treatment; measured with the IES-R, CAPS-5, PCL, and PDS; higher score indicates increased severity)	The mean severity of PTSD symptoms (post-treatment) was 0	SMD = −0.08 (−0.52 to 0.35)	–	82 2 RCTs[70,71]	⊕OOO VERY LOW • Downgraded two levels due to high risk of performance bias due to lack of blinding study participants and personnel (2 RCTs),[70,71] high risk of detection bias due to lack of blinding of outcome assessors (1 RCT),[70] and high risk of attrition bias and other bias (1 RCT)[71] • Downgraded two levels for imprecision due to small sample size and the CI of the effect estimate includes no effect
Dropouts	113 per 1,000	242 per 1,000	RR = 2.14	132	⊕OOO

Outcome	Anticipated Absolute Effects (95% CI)		Relative Effect (95% CI)	Number of Participants and Studies	Certainty of the Evidence (GRADE)
	Control Group	iCBT Group			
		(110 to 534)	(0.97 to 4.73)	2 RCTs[70,71]	VERY LOW • Downgraded two levels due to high risk of performance bias due to lack of blinding study participants and personnel (2 RCTs),[70,71] high risk of detection bias due to lack of blinding of outcome assessors (1 RCT),[70] and high risk of attrition bias and other bias (1 RCT)[71] • Downgraded two levels for imprecision due to small sample size and the CI of the effect estimate includes no effect
Diagnosis of PTSD (post-treatment)	None of the included primary studies reported on diagnosis of PTSD at post-treatment				
Severity of depressive symptoms (post-treatment; measured with the BDI, PHQ, and CES-D; higher score indicates increased severity)	The mean depression (post-treatment) was 0	SMD = −0.12 (−0.78 to 0.54)	–	84 2 RCTs[70,71]	⊕OOO VERY LOW • Downgraded two levels due to high risk of performance bias due to lack of blinding study participants and personnel (2 RCTs),[70,71] high risk of detection bias due to lack of blinding of outcome assessors (1 RCT),[70] and high risk of attrition bias and other bias (1 RCT)[71] • Downgraded two levels for imprecision due to small sample size and the CI of the effect estimate includes no effect
Severity of anxiety symptoms (post-treatment; measured with the BAI and GAD-7; higher score indicates increased severity)	The mean anxiety (post-treatment) was 0	SMD = 0.08 (−0.78 to 0.95)	–	74 2 RCTs[70,71]	⊕OOO VERY LOW • Downgraded two levels due to high risk of performance bias due to lack of blinding study participants and personnel (2 RCTs),[70,71] high risk of detection bias due to lack of blinding of outcome assessors (1 RCT),[70] and high risk of attrition bias and other bias (1 RCT)[71] • Downgraded two levels for imprecision due to small sample

Outcome	Anticipated Absolute Effects (95% CI)		Relative Effect (95% CI)	Number of Participants and Studies	Certainty of the Evidence (GRADE)
	Control Group	iCBT Group			
					size and the CI of the effect estimate includes no effect • Downgraded one level for inconsistency due to high levels of heterogeneity

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CAPS = Clinician-Administered Post-Traumatic Stress Disorder Symptom Scale; CBT = cognitive behavioural therapy; CES-D = Center for Epidemiologic Studies Depression Scale; CI = confidence interval; GAD-7 = Generalized Anxiety Disorder 7-Item Scale; GRADE = Grading of Recommendations Assessment, Development and Evaluation; iCBT = internet-delivered cognitive behavioural therapy; i-non-CBT = internet-delivered non- cognitive behavioural therapy; IES-R = Impact of Event Scale; PCL = Post-Traumatic Stress Disorder Checklist; PDS = Post-Traumatic Diagnostic Scale; PHQ = Patient Health Questionnaire; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; RR = risk ratio; SMD = standardized mean difference.

Note: Definitions of Quality of Evidence Grades from the GRADE Handbook:[76] High = we are very confident that the true effect lies close to that of the estimate of the effect; Moderate = we are moderately confident in the effect estimate, the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low = our confidence in the effect estimate is limited, the true effect may be substantially different from the estimate of the effect; Very Low = we have very little confidence in the effect estimate, the true effect is likely to be substantially different from the estimate of effect.

Source: Lewis et al. (2018).[40]

Economic Analysis

Methods

Economic Evaluation

An economic evaluation addressing the following research question was conducted to help determine if iCBT for PTSD should be publicly reimbursed:

- What is the cost-effectiveness of iCBT compared with face-to-face CBT, alternative psychotherapy intervention(s), treatment as usual, and no treatment in patients 16 years of age or older, with a primary diagnosis of PTSD?

Literature Review

A focused, peer-reviewed literature search for economic studies was conducted using the following bibliographic databases: MEDLINE All (1946–) via Ovid, PsycINFO (1806–) via Ovid, the NHS Economic Evaluation Database (NHS EED) via the Centre for Reviews and Dissemination (CRD), and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH, and keywords. The main search concept was post-traumatic stress disorder. Methodological filters were applied to limit retrieval to economic studies. The search was limited to English- or French-language documents. No date limits were used. The initial search was completed on May 23, 2019. Regular alerts updated the search until project completion.

Grey literature (literature that is not commercially published) was identified by searching sources listed in relevant sections of the Grey Matters: A Practical Tool For Searching Health-Related Grey Literature checklist (https://www.cadth.ca/grey-matters).[43]

The medical literature was screened for economic evaluations comparing iCBT with face-to-face CBT, alternative psychotherapy intervention(s), treatment as usual, and no treatment in patients with a primary diagnosis of PTSD. No economic evaluations addressing this research question were identified.

Primary Economic Analysis

Given the lack of published literature addressing the research question of interest, a de novo decision-analytic model was developed to assess the costs and health outcomes associated with interventions for the treatment of PTSD in patients 16 years of age or older. A protocol for the economic evaluation was written a priori and adhered to during the conduct of this review.[51]

Type of Economic Evaluation

Due to the impact of PTSD, and the potential impact of the resolution of PTSD symptoms, on quality of life, a cost-utility analysis was deemed most appropriate. Health outcomes were expressed as quality-adjusted life-years (QALYs) to capture the impacts of the condition and treatment options. The primary outcome of the economic evaluation was the incremental cost per QALY gained in the form of the incremental cost-utility ratio (ICUR).

Target Populations and Setting

The target population in the economic analysis aligned with the clinical review and reflected patients 16 years of age or older with a primary diagnosis of PTSD treated in the community or outpatient setting. Patients were assumed to be those who were seeking out therapy for PTSD. The analysis excluded patients who experienced spontaneous recovery within the first three months following exposure to trauma and development of PTSD as these individuals would not require further treatment with psychotherapy to treat PTSD symptoms. Cohort age at model entry was reflective of the weighted mean age of the trial participants from the meta-analysis used to inform relative treatment effects, as subsequently discussed. The clinical expert consulted by CADTH for this review indicated that the results from this population (mean age: 37) would be generalizable to that of the target population for this economic evaluation. A literature search was conducted to identify the proportion of patients experiencing a comorbidity of either depression or substance abuse at baseline.[77]

Subgroup analyses stratifying patients by number of traumas (i.e., single or repeat trauma) and type of exposure, noted to be of interest in the protocol,[51] were not possible to conduct given the lack of clinical data on these subgroups.

Interventions

The interventions included within this economic evaluation were based on the findings from the clinical review. As noted in the research question, the economic evaluation aimed to compare iCBT with face-to-face CBT, alternative psychotherapy intervention(s), treatment as usual, and no treatment. As much of the clinical evidence involved the comparison with wait-list, usual care (Appendix 7 provides the definitions of usual care used in the trials), or delayed treatment control group, the reference case in the economic analysis compared iCBT with no additional treatment (i.e., wait-list, usual care, or delayed treatment control group). The clinical data informing the reference case included a mix of guided and unguided iCBT interventions, and separate scenario analyses were conducted assessing guided iCBT compared with no additional treatment and unguided iCBT compared with no additional treatment. A scenario analysis comparing guided iCBT with i-non-CBT (i.e., access to a psycho-educational website, along with symptom logging) was also conducted. iCBT was assumed to be provided only once, at the start of the model, with no booster sessions in subsequent cycles. It was assumed there would be no barriers to treatment access, with equal and immediate access to all treatments included in the base case, and scenario and sensitivity analyses.

It was noted in the protocol that the optimal sequencing of iCBT with other currently available interventions for PTSD may be of interest.[51] We were unable to conduct such an analysis as no relevant clinical data related to sequencing of interventions, or stepped care, were identified.

Perspective

The primary perspective in the reference case was that of a publicly funded health care system (i.e., provincial ministry of health), focusing only on direct medical costs. This was in accordance with *CADTH Guidelines for the Economic Evaluation of Health Technologies: Canada*.[78] Costs captured from this perspective included costs of in-patient visits, outpatient visits, medical services, and medication that would be covered by the public health care system.

A secondary analysis was undertaken from a societal perspective, and captured additional costs related to loss of productivity from the patient's perspective.

Time Horizon and Discounting

Given that PTSD is a potentially life-long condition and interventions to treat PTSD may impact both short- and long-term morbidity, a lifetime time horizon was selected to best account for resulting differences in lifetime costs and benefits between included interventions. A cycle length of six months was selected as this was an appropriate amount of time to observe meaningful changes in a patient's PTSD status according to the input of the clinical expert consulted by CADTH. A short-term, one-year time horizon was further assessed in a scenario analysis.

Discounting of costs and health outcomes was set at 1.5% per year as per CADTH's guidelines for economic evaluations.[78]

Model Structure

A cohort-level state-transition (Markov) model was developed to describe the movement of patients between health states, reflecting the typical clinical progression of PTSD. Over the course of patients' lifetimes, their PTSD and related comorbidities may improve or remain at the same disease severity, depending on the effectiveness of the treatment for PTSD. This in turn may impact the clinical progression of the disease. The clinical expert consulted for this review indicated that there was no consensus on an appropriate classification system for the severity of PTSD symptoms. As a result, worsening of PTSD symptoms was not modelled as patients were assumed to not progress any further than their baseline condition. The clinical pathway and decision-analytic model were developed by reviewing existing clinical literature, and the conceptualization of the model was validated with a clinical expert.

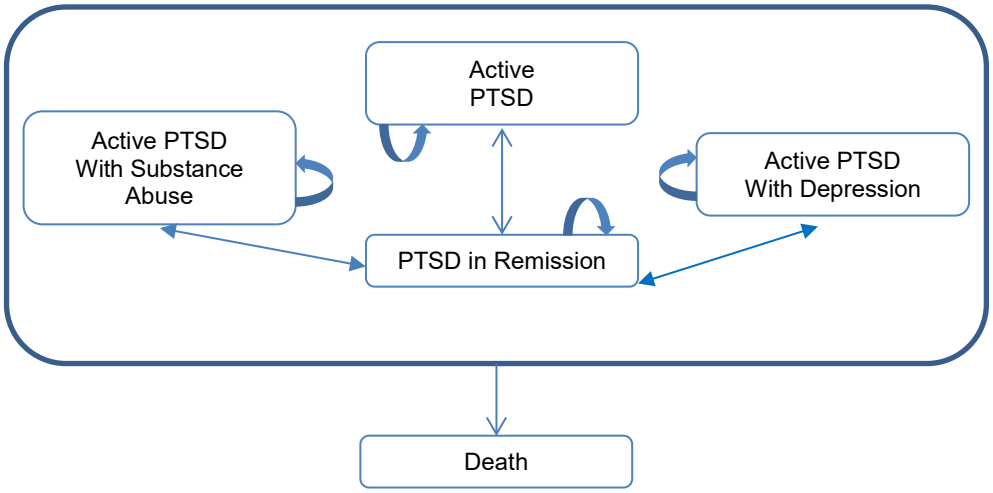
The model structure is depicted in Figure 14. The Markov model includes health states relevant to the natural history of PTSD and the long-term effects of treatment. Health states included remission (i.e., no longer meeting the threshold for a diagnosis of active PTSD), active PTSD (i.e., a diagnosis of PTSD) with or without comorbidities (i.e., depression or substance abuse), and death. At the start of the model, all patients entered the Markov model with active PTSD. The proportion of patients with either comorbid depression or comorbid substance abuse entered directly into their respective comorbid health states (i.e., entered "active PTSD with substance abuse" or "active PTSD with depression" health states). While the clinical review included studies assessing the impact of treatment on

symptoms of anxiety, in addition to depression, only depression and substance abuse were selected for inclusion in the model based on feedback from the clinical expert consulted by CADTH as comorbidities that are common with PTSD and which have the greatest impact on patient quality of life. No combined comorbid state (e.g., substance abuse and depression) was included in the model due to an absence of data specific to patients with PTSD. Every six months, patients could become asymptomatic (i.e., PTSD in remission health state); otherwise they remained in their current active disease state (i.e., active PTSD or its equivalent combined comorbid health state should a comorbidity be present at baseline). It was also assumed that patients with comorbidities would continue to have a comorbidity until the PTSD was resolved, and as such they could not move to the active PTSD state. Patients who achieved remission could either remain asymptomatic or experience a recurrence to active PTSD with the same natural history data as assumed in the PTSD incident event. All living patients were further at risk of death, which was the absorbing state in the model.

The effects of treatment with iCBT were applied only in the first two model cycles. This assumption was based on feedback from the clinical expert consulted for this review indicating that there may be a latent effect of treatment, which demonstrates the need to extend the treatment effect beyond the first cycle. However, no long-term follow-up data beyond one year were identified in the clinical review. As treatment effect was unknown beyond such a point in time, it was assumed that patients who had not recovered from PTSD by the first year would follow the expected natural history of disease with no further gains from the effect of iCBT treatment.

In the reference case, comorbidities were present at baseline or were reassigned upon disease recurrence with the same probabilities of comorbidity applied as those at baseline. Comorbidities were present at baseline as clinical expert feedback indicated comorbidities were likely to be present at the time of treatment initiation. The model was programmed with the capability to depict comorbidities as time varying (i.e., varying risk of developing a comorbidity within the first year of treatment [at model entry] or recurrence of PTSD symptoms [at subsequent cycles]). This was implemented in the model via tunnel states and the impact of this structural feature was explored in scenario analyses. Additionally, the model was programmed with the ability to modify the likelihood of recurrence, including having all patients at risk, having none at risk, or a mixture of both. This functionality was used in scenario analyses, as well. In the reference case, all patients were at risk of recurrence. This assumption was used as it was deemed to be the most conservative of the available options.

Figure 14: Conceptual Design of the Markov Model for Post-Traumatic Stress Disorder



PTSD = post-traumatic stress disorder.

Data Inputs

Clinical Parameters

Natural History: Mortality

The annual mortality rate from Canadian Life Tables was applied to all health states to reflect baseline mortality.[79] No clinical data related to differences in risk of mortality due to PTSD compared with the general population was identified. The clinical expert consulted by CADTH for this review indicated that patients with active PTSD were not at increased risk of death compared with the general population but did indicate patients with comorbidities were likely to be at an increased risk of death. As a result, baseline mortality for patients in the active PTSD states with comorbidities were adjusted by the relative risk of death reported among patients with psychological distress compared with the general population.[77]

Natural History: Other Outcomes

Inputs relating to patient transitions between health states for the no treatment arm of the model reflected the expected natural history of the condition. These were identified via a literature search.

Probability of self-recovery were identified from a prospective cohort study in the US with five years of follow up.[80] The characteristics of the patient population from this prospective cohort study were similar to that of the target population for this economic evaluation, and the rates of self-recovery and remission observed were aligned with what was expected to be observed in Canadian clinical practice according to the clinical expert consulted for this economic evaluation. These values were similar to those reported in a systematic review by Morina et al.[81] The rate of self-recovery for patients with a comorbidity was further modified using a hazard ratio from the same study that reported the risk of recovery for patients with each comorbidity compared with patients without comorbidities.[80] It was assumed that patients with comorbidities would continue to have a comorbidity until the PTSD was resolved.

The probability of recurrence of PTSD for patients with a comorbidity was assumed to be the same as the probability of recurrence of PTSD for patients without a comorbidity in the absence of clinical data specific to this subpopulation. The probability of recurrence similarly came from the aforementioned US cohort study.[80]

All transition probabilities were adjusted to match the six-month cycle length using the appropriate rate-to-probability conversion. Table 3 presents the natural history and baseline demographic inputs used in the reference case.

Table 3: Natural History and Baseline Demographic Inputs

Input	Value	Distribution	Source
Age at model entry	37	NA	CADTH clinical review — mean age of trial participants
Probability of comorbid substance abuse (12 month)	0.25 (Alpha: 28; Beta: 84)	Beta	Kessler (2005)[77]
Probability of comorbid major depressive disorder (12 month)	0.50 (Alpha: 56; Beta: 56)	Beta	Kessler (2005)[77]
Probability of self-recovery, no treatment (5 year)	0.38 (Alpha: 76; Beta: 123)	Beta	Perez Benitez (2012)[80]
Probability of recurrence of PTSD (5 year)	0.295 (Alpha: 18; Beta: 78)	Beta	Perez Benitez (2012)[80]
Hazard ratio, self-recovery rate due to substance abuse versus self-recovery rate without substance abuse	0.773 (95% CI, 0.508 to 1.176)	Log-normal	Perez Benitez (2012)[80]
Hazard ratio, self-recovery rate due to major depressive disorder versus self-recovery without major depressive disorder	0.871 (95% CI, 0.760 to 0.998)	Log-normal	Perez Benitez (2012)[80]
Relative risk of mortality for active PTSD with comorbidity compared with active PTSD without comorbidity	1.57 (95% CI, 1.14 to 2.15)	Log-normal	Chiu et al. (2018)[82]

CI = confidence interval; NA = not applicable; PTSD = post-traumatic stress disorder.

Treatment Effects

To estimate the transition from active PTSD (with or without comorbidity) to PTSD in remission for patients in the iCBT arm, the relative treatment effects of iCBT compared with no additional treatment (i.e., wait-list) were identified from the clinical review. The clinical review included a meta-analysis of eight studies assessing the mean difference in PTSD symptom scores and pooled studies with both guided and unguided iCBT interventions. The SMD of iCBT compared with no additional treatment was estimated to be –0.60 (95% CI, –0.97 to –0.24) according to the meta-analysis (see Figure 1).[37] To apply relative treatment effects within the model, the SMD was converted to an odds ratio (OR) using the approach described in the Cochrane handbook (chapter 10.6).[43] This required the assumption that differences in PTSD symptom score changes correspond to equivalent differences in remission from PTSD between interventions. The OR was directly applied to the probability of self-recovery to derive the probability of remission for patients treated with iCBT. This approach would assume that OR approximates relative risk.

The clinical review did not identify data relating to adverse treatment effects and these were excluded from the evaluation.

The clinical review did identify data related to patient dropouts for iCBT compared with no treatment, but this was excluded from the model as it was unclear if the associated efficacy data accounted for patient dropout. Additionally, there were no data available on the natural history of patient recovery and remission following dropout from treatment. As a result, it was assumed that treatment efficacy values accounted for the differences in dropout rates.

When the trials included in the meta-analysis were assessed individually, a trend in treatment effect was identified among trials with no therapist support provided as part of iCBT arms of the trials. As a result, a scenario analysis incorporating the treatment effects from a trial with limited therapist guidance was also conducted (SMD, –0.14; 95% CI, –0.50 to 0.22).[53] A similar scenario analysis was conducted using the meta-analyzed value for guided iCBT only (see Appendix 9).

The Cochrane review also identified a single study that reported the relative risk of PTSD diagnosis after treatment for patients on iCBT compared with wait-list. A study by Ivarsson et al. indicated that patients on iCBT were at lower odds of a PTSD diagnosis post-treatment than patients on wait-list (OR, 0.12; 95% CI, 0.06 to 0.71). This clinical outcome is different from those previously reported as it refers to the probability of remaining in the PTSD state rather than the probability of achieving remission. Given that this clinical data would provide an alternative methodological approach to incorporate treatment effects, this OR was incorporated into the model in a scenario analysis.

The clinical review further identified a comparison of guided iCBT with i-non-CBT in the Cochrane review.[40] The studies included in this comparison were not included as part of the meta-analysis used to inform the reference case analysis. Given that i-non-CBT could not be compared indirectly with the other set of literature on iCBT versus no additional treatment, a separate scenario analysis comparing guided iCBT with i-non-CBT was conducted. The meta-analyzed results from Lewis et al. were used (SMD, –0.08; 95% CI, –0.52 to 0.35),[40] while the baseline characteristics and natural history data remained unchanged in the absence of long-term follow-up data specific to i-non-CBT. The clinical efficacy values used for the reference case and scenario analyses are presented in Table 4.

Table 4: Clinical Efficacy Values Used

Input	SMD (95% CI)	OR [a] (95% CI)	Source
Reference case — iCBT vs. wait-list	–0.60 (–0.97 to –0.24)	2.97 (1.55 to 5.81)	Lewis et al. (2018)[40]
Scenario analysis — therapist-guided iCBT vs. internet-delivered non-CBT interventions	–0.08 (–0.52 to 0.35)	1.16 (0.36 to 1.89)	Lewis et al. (2018)[40]
Scenario analysis — unguided iCBT vs. wait-list	–0.14 (–0.50 to 0.22)	1.28 (0.67 to 2.48)	Kuhn et al. (2017)[53]
Scenario analysis — guided iCBT vs. wait-list	–0.80 (–1.18 to –0.42)	4.27 (2.14 to 8.50)	Adapted from Lewis et al. (2018);[40] See Appendix 9.
Scenario analysis — odds of continuing to have a diagnosis of PTSD	Odds ratio: 0.12 (0.06 to 0.70)	NA	Ivarsson et al. (2014)[69]

CBT = cognitive behavioural therapy; CI = confidence interval; iCBT = internet-based cognitive behavioural therapy; NA = not applicable; OR = odds ratio; PTSD = post-traumatic stress disorder; SMD = standardized mean difference; vs. = versus.

[a] Reported odds ratio were calculated based on the approach described in the Cochrane handbook chapter 10.6.

Utilities

Each health state in the model was assigned a utility weight. Although the preference was for Canadian-specific utility values, a literature search did not identify utility weights corresponding to the modelled health states from a Canadian population.

For the health states of active PTSD, PTSD with comorbid depression, and PTSD in remission, utility values were derived from an Australian study by Gospodarevskaya et al. that assessed health-related quality of life according to PTSD symptom status using the Assessment of Quality of Life instrument in patients (n = 993) according to PTSD and comorbidity status.[83] The Assessment of Quality of Life instrument is a multi-attribute generic quality-of-life instrument. Answers were converted to utility scores based on a published algorithm that was reported to show logical discrimination by health status, with a high correlation between instrument and self-evaluated preferences, and an association with other utility instruments.[84] A separate utility value for substance abuse elicited via the EuroQol 5-Dimensions from patients diagnosed with alcohol dependence was identified in the literature,[85] and this was combined multiplicatively with the utility value for active PTSD alone to determine the combined health state utility value for this joint health state. Table 5 summarizes the utility values used in the model. These were converted from utilities into disutilities before being applied into the model and were adjusted to the six-month cycle length. The death state was ascribed a utility value of zero.

Table 5: Utility Inputs

Health State	Mean (SD)	Distribution[a]	Source
Active PTSD	0.68 (0.28)	Log-normal	Gospodarevskaya et al. (2013)[83]
PTSD in remission	0.87 (0.17)	Log-normal	
PTSD with major depressive disorder	0.53 (0.26)	Log-normal	
Substance abuse	0.58 (0.20)	Log-normal	Gunther et al. (2007)[85]
Death	0	–	Assumption

PTSD = post-traumatic stress disorder; SD = standard deviation.

[a] Log-normal distribution used as utilities were converted into disutilities before being applied in the model.

Costs

Costs are described in Table 6. All costs were reported in Canadian dollars and, where appropriate, were inflated to 2019 costs using the Consumer Price Index for health care items in Canada.[86]

Treatment Costs

It was assumed that iCBT would be implemented as a new stand-alone iCBT program and costs of intervention were derived from a previous economic evaluation by Health Quality Ontario.[37] Such a program was assumed to include costs related to licence fees for online iCBT modules, salaries for e-therapist guidance, as well as maintenance costs of the online program. Details on these cost components can be found elsewhere.[37,39] The number of therapist support hours per patient was derived from the range of therapist support hours that was reported within the clinical trials that informed the treatment efficacy value used in the model. It was further assumed that 40% to 60% of patients would receive a referral from their primary care physician to an iCBT program. In the reference case, it was assumed the therapist support would be provided by an e-therapist, and scenario analyses were

conducted to determine the impact of assuming a registered non-physician therapist (higher hourly rate) as the provider of therapist guidance instead. The previously noted assumptions noted relating to treatment costs were based on feedback from a clinical expert consulted by CADTH as part of a previous economic evaluation assessing the use of iCBT for major depressive disorder and anxiety (which was written in collaboration with Health Quality Ontario and validated by the clinical expert involved in this review). Separate scenario analyses assessing the implications of limited therapist support or reimbursing an existing iCBT program for PTSD (i.e., the Beacon program) were also conducted. The total costs of the intervention in the reference case and scenarios analyses are available in Table 7.

It was conservatively assumed that no intervention costs would be incurred for patients receiving no treatment. The costs of the i-non-CBT interventions, considered in a scenario analysis, were assumed to be the same as those for iCBT without therapist guidance.

Health State Costs

Patients with active PTSD incurred an annual cost of $838 based on a study that assessed the incremental costs of patients with post-traumatic stress symptoms to patients without such symptoms using health administrative databases in Quebec.[87] This cost included all in-patient and outpatient medical costs, as well as medication costs.

For patients with a comorbid condition, it was assumed there would be no additional costs to avoid double counting of health care resource use. In support of this, we compared the resource utilization reported in a study of patients with PTSD[87] to a study of a patient population with major depression, which indicated resource use for patients with PTSD was greater. This supports the reference case assumption that additional costs due to depression may not be warranted;[88] limited evidence was identified for substance abuse. The comparability of the severity of depression from the study of patients used to compare resource use with that typically present in patients with comorbid PTSD and depression is unknown. To account for this, we tested the assumption that there would be no additional costs due to comorbidities in a scenario analysis by adding costs related to comorbidities.

Patients with PTSD in remission were assumed to incur costs related to one physician visit per year.

Table 6: Cost and Resource Utilization Inputs

Input	Value (SD, Range)	Distribution Used	Source
Physician and Other Labour Costs			
Primary care physician	$80.30	NA	Ontario Schedule of Benefits[89]
E-therapist hourly salary rate	$42.70	NA	CADTH and HQO economic evaluation of iCBT for major depressive disorder and anxiety disorders[38,39]
Regulated non-physician therapist	$86.25	NA	
Psychotherapies Programs			
A. Licence costs, per patient	$5	NA	CADTH and HQO economic evaluation of iCBT for major depressive disorder and anxiety disorders[37,39]
Proportion of patients receiving referral to iCBT from primary care physician	0.5 (0.4 to 0.6)	Beta	Assumption. CADTH and HQO economic evaluation of iCBT for major depressive disorder and anxiety disorders[37,39]
B. Total referral costs	$40.15 ($32.12 to $48.18)	NA	Ontario Schedule of Benefits[90]

Input	Value (SD, Range)	Distribution Used	Source
Therapist support hours provided	3 (0 to 6)	Gamma	CADTH clinical review
C. Total E-therapist salary costs	$128.1 ($0 to $258.23)	NA	CADTH and HQO economic evaluation of iCBT for major depressive disorder and anxiety disorders[37,39]
D. iCBT program maintenance costs, per patient	$77	NA	
Total cost of iCBT – reference case (A + B + C + D)	$250.86 ($122.12 to $380.34)	NA	NA
Health State Costs			
Active PTSD	$838 ($167.6)	Gamma	Lamoureux-Lamarche et al. (2016)[87]
Active PTSD with comorbid condition	No additional costs	NA	Chan et al. (2011)[91]

iCBT = internet-delivered cognitive behavioural therapy; HQO = Health Quality Ontario; NA = not available; PTSD = post-traumatic stress disorder; SD = standard deviation.

Table 7: Intervention Costs, Reference Case, and Scenarios

Input	Mean Value (Range)	Notes
Reference case	$250.86 ($122.12 to $380.34)	
Guided iCBT	$272.75 ($165.15 to $380.34)	Modified therapist costs of guided iCBT in the reference case to 1 to 6 hours of support, otherwise all other costs remain identical
Unguided iCBT	$122.12 to $165.15	Modified therapist costs of guided iCBT in the reference case to 0 to 1 hours of support, otherwise all other costs remain identical
Beacon program	$595	Obtained from https://www.mindbeacon.com/pricing/.[92] This is the standard offering
Internet-delivered non-CBT interventions	$122.12	Assumed a publicly run Web portal with psycho-educational materials requiring the same resources as an unguided iCBT portal without any support hours

iCBT = internet-delivered cognitive behavioural therapy.

Societal Costs

As previously noted, a scenario analysis including costs related to unemployment due to PTSD was conducted. Six-month costs due to unemployment were calculated by first determining the difference in proportion of unemployment rate among patients with PTSD from a Canadian cross-sectional survey compared with the general census results (Table 8).[15] This value was then multiplied by the average individual income in Canada,[93] adjusted to 2019 Canadian prices and a six-month cycle length. As a simplifying assumption, these costs were applied to all active PTSD states, with or without comorbidities, throughout the entire model time horizon.

Table 8: Employment Costs Included as Part of Societal Perspective

Input	Value (Range)	Distribution Used	Source
Proportion of patients unemployed compared with general population	0.027 (0.0203 to 0.0338)	Uniform	Van Ameringen et al. (2008)[15]
Average annual individual income in Canada (16 years of age or older)	$46,403	NA	Statistics Canada[93]
Loss of employment costs (6 month)	$626.45 ($469.84 to $783.06)	NA	NA

NA = not applicable.

Statistical Analysis and Sensitivity Analysis

The reference case reflects the probabilistic results based on 5,000 Monte Carlo simulations. The probabilistic results characterize the extent to which parameter uncertainty impacts the cost-effectiveness estimates in the model. Standard distributional forms were taken to describe the probability distribution functions relating to input parameters: transition probabilities were characterized by beta distributions, utilities and relative risks and hazard ratios were characterized by a log-normal distribution, and costs were characterized by gamma distributions. Results of the probabilistic analysis are presented on a cost-effectiveness acceptability curve. This graph presents the probability that each treatment is optimal given different willingness-to-pay values for an additional QALY gained.

Sensitivity analyses were conducted to evaluate the degree to which uncertainty in the model parameters (i.e., parameter uncertainty) and its assumptions (i.e., structural uncertainty) would impact the results. They are presented in Table 9.

Table 9: Scenario and Sensitivity Analyses

Scenario or Sensitivity Analysis	Reference Case Value	Scenario Analysis Value	Notes
Clinical efficacy (and costs) for iCBT with no therapist guidance	Efficacy (SMD): –0.60 (95% CI: –0.97 to –0.24) Cost: $251.23 (Range: $122.12 to $380.34)	Efficacy (SMD): –0.14 (95% CI: –0.50 to 0.22) Cost: $143.64 (Range: $122.12 to $165.15)	Modified therapist costs of guided iCBT above to 0 to 1 hours of support, otherwise costs are identical
Clinical efficacy (and costs) for iCBT with therapist guidance only	Efficacy (SMD): –0.60 (95% CI, –0.97 to –0.24) Cost: $251.23 (Range: $122.12 to $380.34)	Efficacy (SMD): –0.80 (95% CI, –1.18 to –0.42) Cost: $272.75 ($165.15 to $380.34)	Modified therapist costs of guided iCBT above to 1 to 6 hours of support, otherwise costs are identical
Clinical efficacy from Ivarsson et al.,[69] — odds of having a diagnosis of PTSD post-treatment	Efficacy (SMD): –0.60 (95% CI, –0.97 to –0.24)	Efficacy (OR): 0.12 (95% CI, 0.06 or 0.70)	Probability of remaining in the Active PTSD states was altered instead of the probability of achieving remission
iCBT costs based on reimbursement of Beacon per person cost (with reference case efficacy)	Efficacy (SMD): –0.60 (95% CI, –0.97 to –0.24) Cost: $251.23 (Range: $122.12 to $380.34)	Efficacy (SMD): –0.60 (95% CI, –0.97 to –0.24) Cost: $595	This is the base offering of Beacon. Sourced from their website: https://www.mindbeacon.com/pricing/[92]

Scenario or Sensitivity Analysis	Reference Case Value	Scenario Analysis Value	Notes
iCBT costs based on reimbursement of Beacon per person cost (with efficacy for no therapist guidance)	Efficacy (SMD): –0.60 (95% CI, –0.97 to –0.24) Cost: $251.23 (Range: $122.12 to $380.34)	Efficacy (SMD): –0.14 (95% CI, –0.50 to 0.22) Cost: $595	
Therapist support is assumed to be provided by a registered non-physician therapist	Therapist salary costs: $129.12 ($0 to $258.23)	Therapist salary costs: $260.80 ($0 to $521.61)	This is the base offering of Beacon. Sourced from their website: https://www.mindbeacon.com/pricing/[92]
Comparison with internet-delivered non-CBT interventions instead of wait-list	NA	Efficacy (SMD): –0.08 (95% CI, –0.52 to 0.35) Cost of internet-delivered non-CBT: $122.12	Costs of internet-delivered non-CBT assumed a publicly run Web portal with psycho-educational materials requiring the same resources as the iCBT portal, without therapist costs
Addition of lost productivity costs as part of societal perspective	None applied	Loss of employment costs applied to all active PTSD health states: $1231.20 (Range: $925.68 to $1541.28)	
All patients receive referral to iCBT as part of intervention costs	Referral costs: $40.15 ($32.12 to $48.18)	Referral costs: $80.30	
Comorbidities develop after entry into model over course of one year	Comorbidities present at baseline or upon recurrence	Comorbidities not present at baseline, develop during two cycles following model entry or recurrence	
Additional costs for comorbid conditions applied	No additional costs applied to patients with comorbidities	Additional health state costs applied — Major depressive disorder: $243.5 Substance abuse: $172.5	Major depressive disorder costs obtained from: Chiu et al., 2017[88] Substance abuse costs obtained from: https://www.ccsa.ca/sites/default/files/2019-04/CSUCH-Canadian-Substance-Use-Costs-Harms-Report-2018-en.pdf[94]
No change in recovery for patients with comorbidities compared with patients without comorbidities	Hazard ratio for patients with comorbid major depressive disorder and substance abuse applied to self-recovery rate	No hazard ratio applied	
One-year time horizon	Lifetime time horizon	One-year time horizon	Based on feedback to implementation team that this would be an intervention provided when no face-to-face options exist as a stop-gap measure
Assumed any recurrence was not related to initial trauma	All patients at risk of recurrence	No patients at risk of recurrence	

CBT = cognitive behavioural therapy; CI = confidence interval; iCBT = internet-delivered cognitive behavioural therapy; NA = not applicable; OR = odds ratio; SMD = standardized mean deviation.

To account for the uncertainties associated with the clinical evidence that informed the efficacy of iCBT compared with no additional treatment, a threshold analysis was also conducted. The analysis was conducted deterministically, holding all parameters constant, save for the efficacy of iCBT compared with no additional treatment to determine the minimum level of effectiveness required for iCBT to remain cost-effective at a commonly cited willingness-to-pay threshold ($50,000 per QALY).

Model Validation

The model structure and data inputs were presented to a Canadian clinical expert to ensure that the model, its parameters, and its assumptions reflected Canadian clinical practice and the available body of literature (i.e., face validity). Internal validity was assessed by ensuring that the mathematical calculations were performed correctly and were consistent with the model specification, and logical discrepancies were assessed by evaluating the model under hypothetical and extreme conditions. The model further underwent external technical peer review.

Model Assumptions

Several assumptions needed to be made, either to supplement missing information or to simplify the model. The assumptions used in the reference case are as follows:

- no barriers to treatment access
- iCBT is provided at only one single point in time
- active PTSD health states referred to patients with a diagnosis of PTSD; differences in severity were not explicitly modelled
- patients entering model are those who have not recovered in three months post-trauma and would be seeking out therapy
- changes in PTSD status are observed every six months
- rates of comorbidity do not vary by age or with recurrence
- differences in PTSD symptom score changes identified in the clinical review corresponded to equivalent changes in remission from PTSD
- treatment effect only applies in cycle during which treatment is provided and one cycle after (i.e., two cycles; 12 months)
- treatment effectiveness is not dependent on type of trauma or the number of exposures experienced
- comorbidity is resolved with remission of PTSD, and patients may only have one of the two included comorbidities, not both
- no additional health care costs are borne by patients with comorbidities
- there are no differences in adverse events between comparators
- the impact of dropouts was captured via treatment outcome; the full cost of therapy is incurred for all patients.

Results

Reference Case

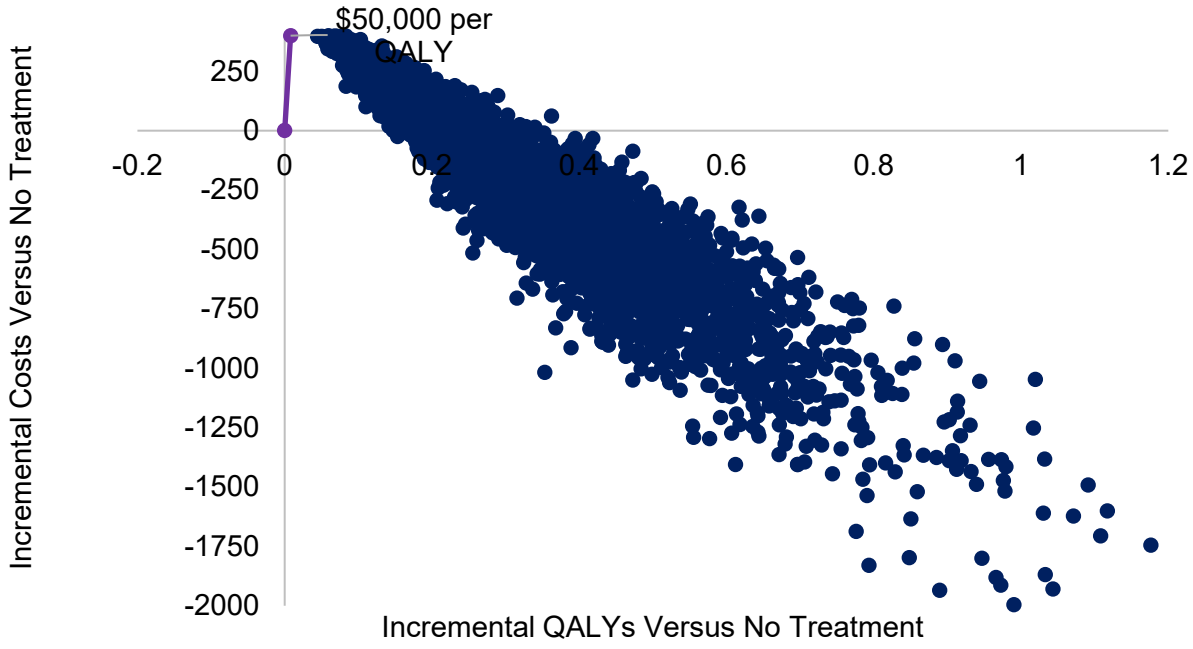
iCBT had fewer expected costs ($15,998) and higher QALYs (23.12) compared with no additional treatment ($16,501 and 22.81, respectively), resulting in incremental costs of –$504 and incremental QALYs of 0.31 (see Table 10). This resulted in iCBT being dominant compared with no additional treatment as it was both less expensive and produced more QALYs, which was the case in more than 95% of simulations. The cost-effectiveness scatter plot and acceptability curve can be found in Figure 15 and Figure 16, respectively. Figures describing patient movement between health states over the full model time horizon for both comparators are presented in Appendix 10.

Table 10: Reference Case Results

Strategies	Expected Costs, $	Expected QALYs	Incremental Costs, $	Incremental QALYs	Incremental LYs	Sequential ICUR, $/QALY gained
No additional treatment	16,501	22.81	Reference			
iCBT	15,998	23.12	–504	0.31	0.02	Dominant

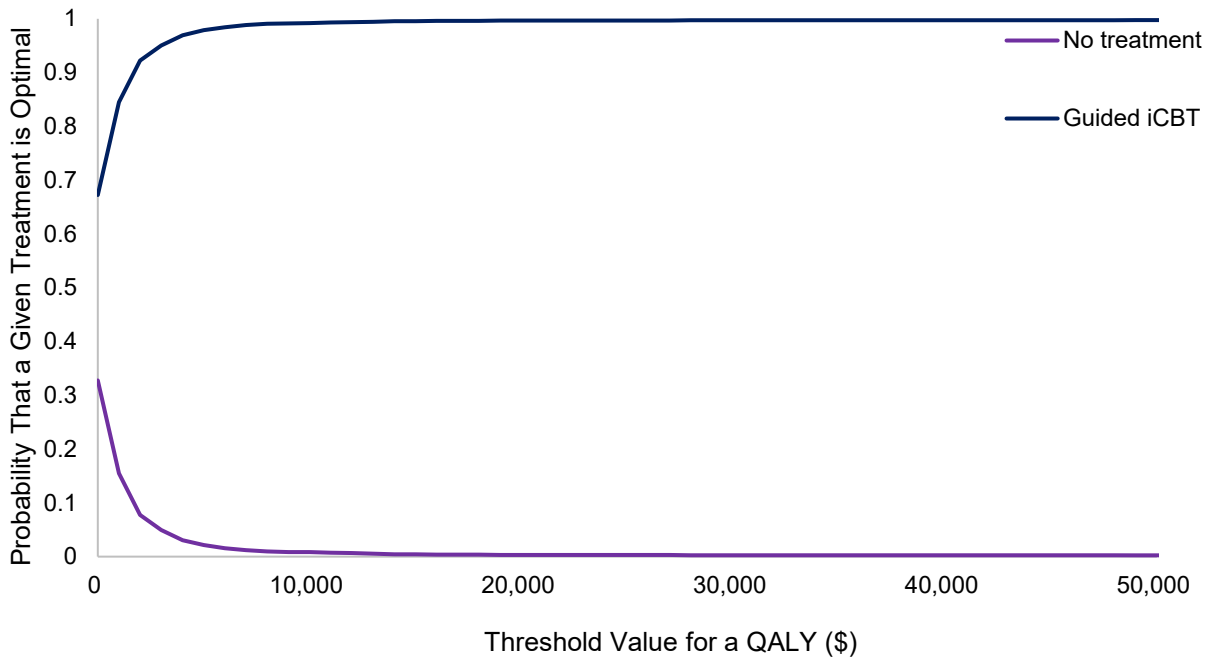
iCBT = internet-based cognitive behavioural therapy; ICUR = incremental cost-utility ratio; LY = life-year; QALY = quality-adjusted life-year.

Figure 15: Cost-effectiveness Scatterplot (Reference Case)



iCBT = internet-delivered cognitive behavioural therapy; QALY = quality-adjusted life-year.

Figure 16: Cost-Effectiveness Acceptability Curve (Reference Case)



iCBT = internet-delivered cognitive behavioural therapy; QALY = quality-adjusted life-year.

A breakdown of costs and QALYs by categories is presented in Table 11. Costs were disaggregated into health state costs and treatment costs, as well as costs in year 1 and beyond year 1. iCBT compared with no additional treatment resulted in lower health state costs ($15,750 versus $16,501) but required higher treatment costs ($248 versus 0). As identified in the breakdown of the costs of the interventions, the primary driver of iCBT costs is the amount of therapist guidance provided. iCBT was also associated with greater costs in year 1 ($998 versus $511) but fewer costs beyond year 1 ($14,972 versus $15,662). The majority of the incremental QALYs were generated in the long-term period (i.e., beyond year 1, whereby clinical benefits were extrapolated).

Table 11: Breakdown of Costs and Quality-Adjusted Life-Years by Health State and/or Assessment Time

Strategies	Costs				QALYs	
	Health State, $	Treatment, $	Total Costs, Year 1, $	Total Costs, Beyond Year 1, $	Year 1	Beyond Year 1
No additional treatment	16,501	0	511	15,662	0.60	22.22
iCBT	15,750	248	998	14,972	0.62	22.51
Incremental	–751	248	487	–690	0.027	0.29

iCBT = internet-based cognitive behavioural therapy; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Sensitivity Analysis

Scenario and sensitivity analyses were used to assess the impact of alternative efficacy values (guided iCBT, unguided iCBT), alternative treatment costs, different comparators (iCBT versus i-non-CBT), inclusion of lost productivity, a one-year time horizon, and changes to assumptions around recurrence and comorbidities. Of the scenario analyses, iCBT continued to dominate no treatment in most scenarios.

In the scenario comparing unguided iCBT with no additional treatment, iCBT was no longer dominant, with higher costs, while continuing to have higher associated QALYs, for an ICUR of $6,042 per QALY gained. In the two scenarios assessing the cost of the Beacon program with efficacy estimates from either the reference case or unguided iCBT, iCBT was no longer dominant, with an ICUR of $439 and $13,645 per QALY, respectively (Table 12).

The comparison of iCBT with i-non-CBT programs also resulted in higher costs ($16,634 versus $16,291) and higher QALYs (22.88 versus 22.84), for an ICUR of $8,624 per QALY gained.

When the OR for remaining in the PTSD health state[69] was used as the relative treatment effect measure, iCBT remained dominant over wait-list. This scenario analysis suggested greater cost savings and incremental QALY gains than the base case.

Results were robust to the sensitivity analyses conducted. No additional treatment continued to be dominated by iCBT in all sensitivity analyses except for when a one-year time horizon was modelled. In this sensitivity analysis, guided iCBT had higher costs ($999 versus $511) but also produced higher QALYs (0.62 versus 0.61) compared with no treatment, for an ICUR of $17,435 per QALY gained. The results of this scenario analysis, along with additional scenario and sensitivity analyses with limited impact on results, are presented in Appendix 11.

Table 12: Scenario and Sensitivity Analysis Results

Scenario or Sensitivity Analysis	Strategies	Expected Costs, $	Expected QALYs	Incremental Costs, $	Incremental QALYs	ICUR, $/QALY gained	Probability of Being Cost-Effective at Willingness-to-Pay Threshold of $50,000/QALY
Scenarios							
Clinical efficacy (and costs) for iCBT with no therapist guidance	No additional treatment	16,199	22.79	Reference			28%
	Unguided iCBT	16,524	22.85	325	0.05	6,042	72%
Clinical efficacy (and costs) for iCBT with therapist guidance only	No additional treatment	16,201	22.79	Reference			0%
	Guided iCBT	15,549	23.30	–652	0.51	Dominant	100%
	Wait-list	16,166	25.10	Reference			0%

Scenario or Sensitivity Analysis	Strategies	Expected Costs, $	Expected QALYs	Incremental Costs, $	Incremental QALYs	ICUR, $/QALY gained	Probability of Being Cost-Effective at Willingness-to-Pay Threshold of $50,000/QALY
Clinical efficacy from Ivarsson et al.,[69] — odds of having a diagnosis of PTSD post-treatment	Guided iCBT	11,342	22.81	–4,824	2.29	Dominant	100%
iCBT costs based on reimbursement of Beacon per person cost (with base-case efficacy)	No additional treatment	16,156	22.81	Reference			0%
	iCBT	16,296	23.13	140	0.32	439	100%
iCBT costs based on reimbursement of Beacon per person cost (with efficacy for no therapist guidance)	No additional treatment	16,165	22.81	Reference			30%
	Unguided iCBT	16,929	22.87	765	0.06	13,645	70%
Comparison with internet-delivered non-CBT interventions instead of wait-list	Internet-delivered non-CBT interventions	16,292	22.84	Reference			42%
	iCBT	16,634	22.88	342	0.04	8,624	58%

CBT = cognitive behavioural therapy; iCBT = iCBT internet-based cognitive behavioural therapy; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Threshold Analysis

The threshold analysis to determine at which level of effectiveness the ICUR of iCBT compared with no additional treatment would cross the willingness-to-pay threshold of $50,000 per QALY indicated that this threshold would be exceeded when an SMD of worse than –0.039 (OR, 1.073) for iCBT compared with no additional treatment was used.

Summary of Economic Results

The economic evaluation previously presented is, to our knowledge, the first assessment of the cost-effectiveness of iCBT for PTSD in Canada. In the reference case analysis, we assessed the long-term costs and QALYs associated with iCBT compared with no additional treatment. The reference case results suggested that iCBT was dominant compared with no additional treatment (i.e., fewer costs and higher QALYs). The results were primarily driven by the cost of treatment with iCBT and the extrapolation of the impact of iCBT compared

with no additional treatment using a lifetime time horizon. Much of the estimated QALY gain was observed beyond the first year of treatment (more than 93%). When a one-year time horizon was considered, iCBT was no longer dominant and an ICUR of $17,435 per QALY gained was observed. The incremental QALYs for this scenario were 0.028 (i.e., equivalent to just more than 10 days of perfect health), which is in alignment with the findings from the clinical review, which indicate that the treatment effect may not be clinically significant based on the clinical result not surpassing its MCID for the primary outcome of PTSD symptom severity.

The conclusions of the economic analyses were robust. Drivers of the model were highlighted via extensive sensitivity and scenario analyses to test the assumptions and parameters informing the model. Scenario analyses were conducted varying the type of intervention and/or the comparator. iCBT continued to dominate no additional treatment, except for the scenarios in which the iCBT program was unguided or reflected the public cost for the Beacon program. In these scenarios, iCBT was no longer dominant; instead, the cost of the iCBT programs were higher and therefore these strategies resulted in higher costs compared with a no additional treatment, but still produced higher QALYs. The resulting ICURs were $6,042, $439, and $13,645 per QALY, respectively. Additionally, the scenario comparing iCBT with i-non-CBT resulted in an ICUR of $8,624 per QALY gained. These scenarios highlight the impact when higher treatment costs and/or reduced treatment efficacy are applied to the economic model on the potential cost-effectiveness of iCBT. Yet while iCBT was no longer dominant in such scenarios, the ICURs remained below conventional willingness-to-pay thresholds (i.e., $50,000 per QALY), indicating that in comparison to no additional treatment or psychoeducation alone, iCBT is likely to be cost-effective.

Treatment effects in the reference case were based on CADTH's clinical review, which identified a meta-analysis on PTSD symptom that were pooled and reported as standardized mean measures. As noted in the clinical review, there are numerous concerns regarding the certainty and quality of the clinical evidence, limiting the extent to which the conclusions of the meta-analyses are internally and externally valid, particularly related to the assumption of the SMD of PTSD symptom scores corresponding to increased odds of remission from PTSD. Furthermore, to derive the clinical effects of iCBT, ORs were assumed to approximate relative risk. To account for some of this methodological uncertainty, a scenario analysis was conducted based on a clinical study that reported on a different clinical outcome: risk of still having a PTSD diagnosis after treatment. This efficacy measure provided an alternative approach to incorporate treatment response and, in taking this alternative methodological approach, conclusions remained consistent. It was not possible to conduct analyses of iCBT compared with the current standard of care, including face-to-face CBTs and, as a result, the cost-effectiveness of iCBT in comparison with other psychotherapy interventions in the care pathway remains uncertain. Additionally, a lack of subgroup data precluded any analysis of cost-effectiveness of iCBT in patients who experienced a single exposure to trauma versus repeat exposure, or those who have experienced interpersonal trauma versus non-interpersonal trauma. As a result, the identification of subgroups in which iCBT may be more or less cost-effective remains unknown.

Perspectives and Experiences Review

This section addresses the following research question:

- How do patients, their families, and their health care providers experience engaging with treatments for post-traumatic stress disorder?

Exploration of this question was guided by reflection on how understandings of PTSD and experiences with various treatment options might influence expectations toward iCBT as a treatment option.

Study Design

We conducted a rapid qualitative review of empirical studies examining ways in which people living with PTSD understand their condition and subsequently navigate the health care spaces afforded them. Studies that include the perspectives of family members and health care providers were also included. Following an iterative approach consistent with the inductive principles of qualitative research, the a priori planned methods[51] were actively refined and amended at a few stages. In particular, while a research question was established a priori, given the scarcity of qualitative evidence on experiences with iCBT for the treatment of PTSD, and to ensure a sufficient evidence base to inform the decision problem, our research question was modified and the scope of this review accordingly expanded to include experiences with any form of treatment for PTSD.

Literature Search Methods

The literature search was performed by an information specialist, using a peer-reviewed search strategy according to the Peer Review of Electronic Search Strategies (PRESS) checklist (https://www.cadth.ca/resources/finding-evidence/press).

Information related to patient preferences was identified by searching the following bibliographic databases: MEDLINE All (1946–) and PsycINFO (1806–) via Ovid, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO, and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH, and keywords. The main search concepts were iCBT and PTSD.

Methodological filters were applied to limit retrieval to qualitative studies. Retrieval was also limited to English- or French-language documents published since January 1, 2008. The search was completed on May 23, 2019.

As the initial search found no literature focused specifically on iCBT, a second search was conducted on July 17, 2019. The main search concepts were CBT and PTSD. Methodological filters were applied to limit retrieval to qualitative studies. Retrieval was also limited to English- or French-language documents published since January 1, 2014. Regular alerts updated both searches until the publication of the final report.

Grey literature (literature that is not commercially published) was identified by searching sources listed in relevant sections of the Grey Matters: A Practical Tool For Searching Health-Related Grey Literature checklist (https://www.cadth.ca/grey-matters),[43] which includes the websites of regulatory agencies, HTA agencies, clinical guideline repositories, systematic review repositories, patient-related groups, and professional associations. Google was used to search for additional internet-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with

appropriate experts and industry, as appropriate. The complete search strategy is presented in Appendix 1.

Eligibility Criteria

Studies published in English or French that used qualitative data collection (e.g., interviews or participant observation) and analysis methods to explore the experiences of people living with a diagnosis of PTSD, or their families or health care providers, or about engaging with treatment of PTSD, were eligible. While iCBT is the focus of this review, studies exploring experiences with other therapeutic interventions to treat PTSD were eligible with the aim to capture analytical concepts specifically relevant to our research question.

Theses and dissertations, data presented in abstract form only, commentaries, case reports, and editorials were excluded. In addition, studies focused primarily on the experiences of people living with comorbidities (e.g., depression, substance use, anxiety) rather than PTSD were excluded.

Table 13: Eligibility Criteria

Sample	Adults, aged 16 years or older, with traumatic stress symptoms; family and professional caregivers of people living with a diagnosis of PTSD
Phenomena of Interest	How a diagnosis of PTSD is understood, lived and experienced; experiences and expectations when engaging with treatment of PTSD; experiences providing treatment for patients with a diagnosis of PTSD
Design	Qualitative studies (primary or syntheses) of any design (e.g., phenomenology, grounded theory, qualitative description)
Evaluation	Perspectives and experiences of people living with a diagnosis of PTSD, and those of their family and professional caregivers
Research Type	Studies using any qualitative methodology; mixed-methods studies with a qualitative component

PTSD = post-traumatic stress disorder.

Screening and Selecting Studies for Inclusion

Titles and abstracts of retrieved citations from both literature searches were screened by one reviewer in Endnote according to the final eligibility criteria (Table 13). The full text of all potentially eligible citations were retrieved and subsequently screened by the same reviewer.

Article Sampling

Once the eligibility of all citations retrieved through the literature searches had been determined (n = 59), the number of included studies (i.e., sample size) was deemed too large to analyze adequately within the time constraints of a rapid qualitative review. Accordingly, we determined that a purposefully selected sample of the eligible studies would allow for more detailed engagement with the data and result in a more relevant analysis. To develop our sample of included articles for analysis, based on the list of eligible full-text articles, we used a purposeful sampling strategy that applied the technique of critical case sampling.[95] The critical case sampling strategy helped ensure that our sample would “yield the most information and have the greatest impact on the development of knowledge.” (p. 276)[96]

To assist with sampling decisions, we drew from key concepts that arose during conversation with five individuals living with a diagnosis of PTSD. We engaged with these individuals throughout the course of the HTA as a way of gaining insight on what it might be like to live with PTSD and partake in subsequent treatment for that PTSD. Individuals were led in conversation by the CADTH patient engagement officer and the primary qualitative research officer on the project. Following the discussions, notes from the conversations were summarized, with personal identifiers removed, and shared with the review team. The patient engagement officer and qualitative research officer then met with a second qualitative researcher and a qualitative methodologist to identify and develop critical case sampling criteria that addressed key issues raised during patient engagement. The concepts identified as our critical case sampling criteria were access, catalysts for diagnosis, relationality, and treatment burden. In addition, we endeavoured to include key populations such as parents of medically fragile children, experiences reflecting various sources of trauma (e.g., medical trauma, traumatic childbirths, victims of violence including sexual violence, or work-related PTSD), and any reports specifically on the topic of iCBT for PTSD.

To minimize the potential for bias in selection, two reviewers jointly reviewed the eligible full-text articles and sampled for critical cases. Disagreements were resolved by discussion.

Data Analysis

A “best-fit” framework approach to data analysis was used to analyze data relating to the perspectives and experiences of people living with a diagnosis of PTSD, as well as those of their families and health care providers, with a specific lens on how these perspectives and experiences might be relevant to the uptake of iCBT.[97] While the best-fit method suggests a systematic search to identify models or theories that could form a foundational framework, the thematic categories identified within the patients’ perspectives and experiences section of CADTH’s Optimal Use project on iCBT for the treatment of mild-to-moderate major depressive disorder and anxiety disorders were chosen for this purpose.[38] As iCBT is the intervention of interest in both reviews, these categories were perceived as an appropriate framework without the need to undergo an extra systematic search under abbreviated timelines. These thematic categories include experiences related to:

Content: This involves experiences with iCBT’s modules and how these are designed to facilitate knowledge transfer (or not) to the participant. It also involves experiences regarding modes of communication within the intervention, the adaptability of the intervention to the participant, and the navigation skills necessary to use the intervention.

Process: This involves experiences with iCBT’s accessibility, convenience, flexibility, anonymity, and privacy (or not). It also involves participants’ perceptions on what is required for them to successfully engage with iCBT (or not), and experiences with completing these requirements in the given time frame.

Relationality: This involves perceptions of and experiences with a therapist or supporter throughout the use of iCBT.

Context: This involves experiences with the ways in which both personal (e.g., severity of condition) and structural (e.g., availability of intervention) situations influence engagement with iCBT.

Articles were imported into NVivo 11[98] for data analysis. The primary reviewer began by coding the results sections of documents, line by line, using an initial set of codes defined by the foundational framework. New codes and subsequent thematic categories were

developed to accommodate findings emerging from the included literature not accommodated within the initial framework and that may highlight differences in experiences in relation to PTSD. Codes were refined and organized into concepts and findings through ongoing and frequent discussions between the review team, and supported by the use of diagramming and memoing. This iterative and conversational approach aided in ensuring that the primary reviewer was engaging with the material in an appropriately reflexive mode of inquiry.

Results

Quantity of Research Available

A total of 1,009 citations were identified in the two literature searches (with duplicates removed). Following screening of titles and abstracts, 941 citations were excluded and 68 potentially relevant reports from the electronic search were retrieved for full-text review. An additional potentially relevant publication was identified through hand searching of bibliographies and was retrieved for full text review. Of these 69 potentially relevant articles, three were excluded due to an irrelevant study design and seven were excluded as they did not focus on an intervention. Therefore, 59 publications met the eligibility criteria.

Following sampling, 13 publications were included in this report. Appendix 12 presents the PRISMA[63] flowchart of the study selection process.

Summary of Study Characteristics

Details regarding the characteristics of included publications and their participants are provided in Appendix 13.

Study Design and Data Collection

Of the thirteen included publications, twelve were primary qualitative studies[99-110] and one was a mixed-methods study.[111] Five studies used grounded theory analysis techniques,[99-101,105,110] five used phenomenological approaches,[102,103,106,108,109] two did not specify particular qualitative designs or analysis strategies,[104,107] and the qualitative component of the mixed-methods study was analyzed using content analysis.[111]

Twelve studies used interviews as the method of qualitative data collection, while one used focus groups.[111]

Country of Origin

Seven studies were conducted in the US.[99-101,104,105,107,111] Two studies each were conducted in Australia[103,106] and the UK[108,109] and one each in Canada[110] and Norway.[102]

Intervention Type

Eight of the included studies explored perspectives and experiences with various forms of CBT. Of these, six were oriented around experiences with prolonged exposure (PE) and cognitive processing therapy (CPT). The American Psychological Association (APA) defines CPT as a “therapy that focuses on the cognitions developed as a result of the trauma and the role that inaccurate or distorted cognitions have on emotional responses and on behavior.” (p. 125)[112] The APA defines PE as a “therapy designed to help PTSD sufferers emotionally process their traumatic experiences through repeated revisiting and recounting of their trauma memories (imaginal exposure) and repeated, gradual confrontation of feared

situations, places, and things that are objectively safe but feel more dangerous following the traumatic event (in vivo exposure)." (p. 125)[112] Another study focused on experiences with trauma-focused CBT. Another specified the intervention as under development but drawing on the principles of CBT.

Of the remaining studies, one focused on compassion-focused therapy, another on experiences from skills training in a stabilization group, and three did not specify the types of interventions being engaged by their participants. Of note, no studies specifically examined experiences with iCBT.

Patient and Clinician Characteristics

The thirteen included publications reported the experiences of 119 individuals living with a diagnosis of PTSD, of which 80 were veterans. Health care providers' experiences included a variety of professions: psychologists (n = 242), psychiatrists (n = 13), social workers (n = 133), nurses (n = 14), traditional counsellors (n = 5), traditional healers or medicine people (n=3), traditional counsellor and teacher (n = 1), Elders (n = 1), and "other" (n = 10).

Summary of Critical Appraisal

In general, the included publications were assessed to be of moderate-to-high quality. Details of the critical appraisal can be found in Appendix 14

The primary issue affecting the quality of the individual studies was their relevance to the current review. As there were no studies included that dealt directly with perspectives and experiences surrounding the use of iCBT for PTSD, the degree to which definitive statements can be made regarding this HTA's decision problem is limited. While this does not lessen the significance of the review's findings, it should be considered when deliberating on its generalizability. Further, seven studies failed to adequately consider the relationship between study authors, study participants, and study findings, which could impact the credibility of the overall findings.[99-101,104,105,107,109]

Summary of Findings

Relationality

As a thematic finding for this review, the concept of relationality demonstrated how experiences living with, coming to know, and engaging in treatment for PTSD are neither isolated nor stable events in the lived worlds of PTSD. These experiences are, at least in part, dependent upon how (or from where) one stands in relation to others and self. While what qualifies as PTSD and its potential treatments were couched within the clinical languages of the *DSM* or evidence-based psychotherapies, how those diagnoses or treatments were enacted was often described as contingent on the forms of internal and external relations at play. Our engagement with the concept of relationality reflected on this contingency and worked to draw out how descriptions of things like therapeutic relationships, relationships with others outside of therapy, and relationships with one's self interacted with the effects or values placed on the variety of included therapies.

In the previous review of iCBT for major depressive disorder and anxiety, we found that patients were often concerned with elements like the pace of treatment, communication or monitoring features, and the demands of fully engaging with treatment.[38] However, the variability in focus of these concerns and their suggested solutions made it difficult to identify generally appreciated aspects of iCBT programs intended to treat major depressive disorder

or anxiety. As such, our primary conclusion pivoted around the idea that assuming a one-size-fits-all model of iCBT would disregard this variability and "neglect the importance of tailoring emphasized within patient experiences." (p. 39).[38]

Our broadened reading of relationality for the current review supports this overall conclusion and may help to provide further insight into where or how this tailoring might happen when considering the potential uses of iCBT for PTSD. While it is recognized in the sections on "content" and "process" that treatment success relies on the internal makeup, logic, and course of a chosen intervention, our analysis of the forms and importance of relationships described throughout the included literature suggests that these components are already well situated within larger fields of relations. Simply put, our analysis suggests how concerns with treatment content or processes can more easily rise to the fore and become addressable through an attentive appraisal of how one stands in their relations.

The value of being attentive to relations is reflected in the way strong therapeutic relationships can provide the grounds for providers and their patients to navigate disparate preconceptions of interventions (like iCBTs) or encourage sticking with chosen interventions by instilling a sense of being heard, respected, and of a "shared humanity." Even if not pursued, having the opportunity to actively collaborate in one's own treatment decisions, and thus the opportunity to tailor treatment, could further establish a sense of comfort with treatment and foster the sense that "I can do this." With higher dropout rates from iCBT programs meant to treat PTSD, as compared with wait-lists, it is possible these programs could benefit by re-evaluating the touchpoints between patient and provider, as well as the overall space provided to develop strong relationships.

This is important when working through which patients might be appropriate for iCBT (or how to adapt particular iCBTs to an individual patient), but also when thinking through the asks being placed on the shoulders of the individual undergoing treatment. The included literature tended to work through notions of "readiness" or "motivation" by situating the responsibility "to be ready" on the patient. Interventions, particularly those focused on exposure, were understood as stable objects that anyone could engage in given the right level of preparedness and motivation. As such, readiness and treatment were seemingly understood as activities of "doing" or "knowing." Doing (or having done) work to develop the right affect management skills (which is typical of early iCBT modules) and positive coping strategies (again, typical of early iCBT modules) were considered necessary components of the exposure-ready patient. For iCBT programs that include exposure elements, one way of supporting patients and building awareness of how difficult this might be for them could be to ensure a clear understanding of the relationship between how the development of these skills or strategies is connected to the thoughts or behaviours they are meant to address, and why this matters for the exposure elements of treatment.

The notion of readiness also included conversations around a third component of the exposure-ready patient: motivation. What it meant to be motivated, or how motivation was felt to play a role in successful treatment, could be different depending on whether people were considering their treatment goals in the moment, or contemplating what a new life might look like after successful treatment. This temporal shifting of notions of motivation has the potential to reframe motivation from questions of "How do I stand in relation to myself? (Am I ready to do this?)" to "How do I stand in relation to myself in the world? What does (hopefully) successful treatment change about the world I live in?" When readiness is considered as primarily coming from a space of patient characteristics making them ready to

engage with a therapy (or not), we lose sight of the way in which patients, treatments, and their providers are situated within larger worlds. As such, assessing an individual's readiness to engage in a treatment like iCBT may benefit from broader conversations than whether an individual has the appropriate skill set or willingness to change.

Therapeutic Relationships

Patients and providers consistently described the development and maintenance of a strong therapeutic relationship as an important component of treatment for PTSD.[99-101,105,106,108,109] Descriptions of the work these relationships could do and what they might look like in practice took on multiple forms, but most hinged around the assumption that stronger relationships meant stronger results. In its simplest form, a well-established relationship could help to bridge potentially differing valuations of treatment purpose or utility of treatment held by providers and their patients.[99,100,105] And while bridging often took the form of providers garnering buy-in for a suggested course of treatment from their patients,[99,100,105] it could also indicate interest in pursuing collaborative approaches to treatment.[106,109] Being a collaborative partner in treatment helped to develop a sense of respect and provided patients with the opportunity to engage with therapy "at my pace." (p. 227).[109]This could help them feel more capable of incorporating the techniques being shared during therapy into their lives and more aware of what they might be achieving (or not) through treatment.[109]

Fostering this relationship early on (whether based on collaboration or not) could establish the groundwork from which to comfortably have difficult conversations regarding veering off track from the treatment goals,[101,109] or whether chosen treatments still felt right and should continue to be pursued.[101,105,108] The asks associated with successful completion of treatments for PTSD, particularly those engaging with re-exposure to traumatic memories or situations (i.e., PE and CPT), can be quite challenging and require a lot of active participation on the part of patients.[100,107] Feeling as though a provider understood this and could recognize when they (as in the patient) were struggling, could "make it a little bit easier to show up." (p. 53).[101]

While this could be as straightforward (and imprecise) as developing a "good working relationship," (p. 9),[100] it could also be caught up within notions of shared humanity,[106,108] feeling heard,[109] and being acknowledged as more than just another patient downloading expert knowledge.[106,108,109] In this way, some practitioners saw a strong relationship as a way of sharing in their patients' journeys rather than directing them from a removed space of objective expertise.[106]

"You notice that the clients are different… How they respond to you when you're not trying to be technically perfect…or when you're not trying to be the expert…you know. I think that's…a mistake we all make, this idea that we have to be the expert all the time…and that's not what they're looking for… You can get that out of a book." (p. 198).[106]

Concerned with the felt restrictions placed on them in an in-patient setting oriented toward eight 12-week intervention time frames, this provider suggests that caring for their clients happens somewhere outside of the space of expert knowledge. Knowledge can (and should) certainly be passed along but situating themselves in a space outside of expertise with their clients could open the door for a "shift then in therapy." (p.197).[106] Not doing this could make the treatment feel packaged and like something you can get "out of a book."

Developing these types of relationships, however, can take time and is often easier said than done. This could be particularly true of residential programs where rigid timelines[100,106] and structural pressures to pursue a one-size fits all, "diagnose-treat-discharge" model to

care provides little room to build anything more than an "artificial therapeutic relationship." (p. 196).[106] This could not only be damaging to the patient's desire or ability to pursue and continue treatment, but it could also leave providers feeling disconnected, desensitized, deskilled, and ultimately "complicit in their patient's distress." (p. 196).[106] This could be further exacerbated by a lack of continuity in care. Speaking of the lengthy referral process in the US Veterans Affairs system, one veteran explained, "Then she tells me, okay I'm going to assign you a new therapist. I'm thinking, shit I gotta go through this again. That's when I quit, yeah, that day." (p. 539).[99] Hopping from provider to provider could be difficult for patients as with each new provider there was a renewed need to describe their traumatic experience(s).

If we are to take seriously the value placed on therapeutic relationships described here, ensuring iCBTs are able to be engaged in ways that permit the development of these relationships is important. Given the described importance of these relationships it seems less likely that unguided iCBTs for PTSD would be considered as useful or chosen over guided iCBTs by both providers and patients. While expected or desired ideas of what a relationship might look like, and how one goes about developing it, can certainly vary by person (e.g., there may be individuals who prefer unguided or minimal guidance), implementing and engaging in iCBT programs that take this variability into account would also need to be considered. The freedom for patients and their providers to collaboratively adapt chosen iCBT programs to suit relationship needs or desired outcomes would help alleviate the difficulties of this variability.

That being said, relying on the iCBT program alone to foster this relationship and successfully treat PTSD is not sufficient. The uptake and, hopefully, subsequent positive effect of an intervention like iCBT is, at least partially, already situated within a relationship established on trust, respect, empathy, shared humanity, and active listening.[99,105,106,108,109] With this in mind, it is important to acknowledge that using iCBTs to treat PTSD is likely not appropriate for everyone. Even if concerns over adaptability and collaboration are satisfied, it is possible that the modular design and limited timeframes of iCBTs could limit the opportunity for providers to downshift from expert to listener. Of course, it is possible that the movement between expert and listener could be more related to the provider's own ability to navigate the needs of their patient within the treatment paramenters rather than the design of any intervention. Simply put, some providers may struggle with meeting patients needs of desiring this depth and form of relationship regardless of intervention (e.g., be that iCBT or face-to-face CBT), and responsibility for fostering this sort of relationship should not be situated squarely on the intervention alone.

In many ways this resonates with how some traditional healers understood their role in caring for their clients. One healer noted,

"The way healers work — or medicine people work — is they don't actually do anything themselves. They build their connection through their teachings, through their way of life, through how they live. And their connection becomes very strong. So what they do is, they do ceremony. And in that ceremony they actually are consulting with some of these spirits that people are experiencing. They consult with the people's spirits. And when they do that consulting…those spirits know how to help this person heal." (p. 71).[110]

In this example, while healers are indeed holders of expert knowledge, this knowledge is grounded in their ways of life — this knowledge implicates the healer as more than expert knower. To successfully care for their clients, a healer needs to consult with something other

than themselves. Then, and only then, does the healer know how to help this person heal. In this way, caring is grounded in that relational aspect of a therapeutic relationship.

Relationships With Family, Friends, and Other Peers

A growing awareness of the shifting relations between family, friends, and peers was articulated as playing an active role in coming to realize something was off, eventual pursuit of treatment, and desired forms of treatment.[101,108,109] Living with PTSD can be disruptive to the daily norms of family life and for some people it took their loved one's expressing concern to initiate treatment. "I mean a couple of times I'd go upstairs and lock the door and I would stay upstairs for two days… It was my partner who picked up on it. It was causing a lot of rifts between me and her. But I was like yeah, let's go and give it a go and see what happens." (p. 226).[109] Understood as a problem situated within a larger field of relations than themselves, some individuals even expressed a desire for their friends and family to be collaborative participants in therapy.[109] While a desire for collaboration was often tied to notions of developing independence or control over their lives, it was also considered important to the development of lives outside of active therapy.[109]

The presence of strong ties to family or peers also contributed to the will to stick with treatment.[101,108] While some indicated being driven by the commitment they had made to their peers regarding treatment completion,[101] for others, knowing that they were not alone throughout treatment[108] and could count on loved ones was integral to treatment success. "My other half was supportive of it. She was here every day. If she hadn't've been here every day I think I'd've walked out." (p. 53).[101]

Given the largely individualized space of iCBT programs that are built around a patients' drive to develop their own relationships or skills to build these relationships, it could be important to consider ways of incorporating participation from family and friends. While not every person living with PTSD will need their family, friends, or peers to be involved, finding a way to recognize the importance of these relationships could help to maintain treatment goals for some patients.

Relationship With One's Self

As a diagnostic category marked by clinically recognizable poor relations with one's self (e.g., criteria C, D and E in *DSM-V*),[4] the commonality of conversations concerned with how that self might be implicated in treatment is perhaps unsurprising. While these conversations were typically situated within a language of readiness, it is important to note how the use (and meaning) of terms like "readiness" or "motivation" shifted among participants. Most providers and many of their patients interpreted and used these terms as a way of articulating both *patient* suitability (or not) for certain forms of PTSD treatments,[100,104,107] and desires to change or "do" something about how one was living.[102,109] For others living with PTSD, being ready could be a reflection on *treatment* suitability (or not) for their lives,[99,105] and an engagement with just what treatment might mean for their lives.[102,108,109] One asked, "What do I need right now to make myself ready for treatment?" and the other, "How will being ready for, and engaging in, treatment ask me to live differently in the world?" While subtle, the shifting inflection point between these two uses draws attention to the temporal frames involved in seeking, receiving, and completing treatment for PTSD.

Though it is important to note that concerns with readiness "to do" tended to be situated within clinical frames of treatment, they were not the exclusive domain of providers as they were often shared by patients, as well. That being said, we do take our framing of this understanding of readiness from providers working within the US Department of Veterans

Affairs. As such, readiness for evidence-based psychotherapies, like PE and CPT, was described as reflective of a patient's "affect management skills," "psychiatric and external stability," and an individual "readiness to change."[100,104,107] In this way, treatment success is tied to a form of readiness that happens when a patient's ability to self-manage is paired with their "hunger"[100] to change. As trauma-focused treatments predicated on the therapeutic importance of re-exposure to traumatic memories, feelings, or situations, without this base, practitioners worried that treatment could ultimately be unsuccessful.[100,104,107] Following an eight-week PE or CPT protocol is "fast and furious and so it can feel, I think in some ways, and we've seen this with some of our veterans, kind of like 'whoa, I don't know if I can do this.'" (p. 6).[100] Without knowing that "I can do this," the fast-ness and furious-ness might overwhelm the veteran and render a treatment unsuccessful. While a number of stopgaps had been established in these programs to develop readiness in their clientele (i.e., psycho-educational and skill building groups),[100,104] dropout rates were often still linked to patient readiness — "About a third are dropping out and typically they're not dropping because they don't need it." (p. 93–94).[104]

In this reading, it is possible to make statements like "I think there's probably no bad client for CPT and PE. It's just getting clients to be willing to do those treatments that's the challenge." (p. 139).[107] The interventions themselves are seen as stable objects full of therapeutic potential, ready and waiting for the motivated individual. While this was indeed echoed by many individuals living with PTSD across intervention types,[99,101,102,105,108,109] it was, at times, complicated by slightly disparate understandings of what qualified as motivation or "a willing[ness] to do those treatments."

For some, a desire "to do" was caught up within feelings of deservingness. This is not surprising given that an "exaggerated blame on self or others" is a possible indication under criterion D for PTSD.[4] Questioning whether one deserves to heal makes it possible to say, "I still felt that I didn't deserve to be happy or to have nice thoughts or to be kind to myself. I thought that by [being compassionate], there were things that would make me smile and I felt, well, I know it sounds silly, as if I wasn't allowed to smile." (p. 499).[108] Describing motivation as a "willingness to do" or "hunger" to change fails to recognize a potential disconnect between what might be wanted and what is able to be done.

For others, that motivation is simply a matter of wanting "to do" something devalues the extent of the ask being passed along to individuals engaging in treatment. Knowing that something feels off and wanting to address that something can butt up against concerns of what it means to face that something — "Am I going to like the person that I've become? Because I've been like this, with these memories and these thoughts for so long." (p. 499).[108] For this individual, the question was less about do I want to "do it," (as they had "done it" in the form of compassion-focused therapy) and more, "Who am I without these memories and thoughts?" As such, assessing readiness or motivation might be less about wanting "to do" and rather something more like a reflection on the aftereffects of that doing and how it can upend one's lived world.

Again, this is not to say that providers and their clients were universally at odds when describing notions of readiness or motivation. Many patients aligned with providers by describing a sort of upfront desire to do, "Yes, I need motivation! Help me see the goal. Because I felt, in the group too, I need help to see the goals! 'What does this do?' 'What does it help me?' 'Where are we going?' 'What is happening?'" (p. 576).[102] Even when tied to a need to understand the point of treatment, the focus for motivation here is situated around that act of change rather than the aftereffects of that change. While these concerns

are indeed distinct, they are not in opposition. The first seems primarily to be oriented toward those "techniques of self" necessary to successfully engage with treatment, but the second situates the development of these techniques within a larger plain of relations. Both ask questions about that relationship one has with one's self, but one drags the relationship with one's self out into the way therapy could have an effect both within one's self and the world.

Descriptions of how one's relationship with one's self is implicated in treatment becomes important to thinking through the use of iCBTs for PTSD in a few ways. On the one hand, this relationship was actively tied to the techniques or tools one needed to be ready to engage in certain forms of treatment. Studies oriented around PE and CPT qualified this as "affect management skills." As exposure is often a component of iCBT, it is important that individuals engaging in the exposure elements of iCBT have appropriate affect management skills. This is valid and, according to our reading, would seemingly be appreciated by providers and patients alike. The development of and ability to apply these skills in one's daily life could be liberating and can open the door for those living with PTSD to begin "relat[ing] differently to their problems." (p. 577).[102]

This relationship also comes to bear when thinking through the relationality of interventions like iCBT. As interventions existing and being engaged within the lived worlds of patients, iCBTs and the asks associated with successful completion of an iCBT program do not stand in isolation from these lived worlds. The techniques and tools being developed, or exposure elements being worked through, in these programs only have practical effect when applied to the lived worlds of those patients engaging with them. As such, it would be helpful to remember that notions of "motivation" apply to more than a willingness "to do" an iCBT. Knowing that one is ready and motivated to engage in treatment is not the same as knowing what happens once one has completed treatment.

The importance of understanding this situating in the world was also prevalent in Reeves and Stewart's[110] study with Indigenous counsellors, healers, and Elders. Some expressed the wounds of trauma as a broken spirit. While it was first important to understand the context of their Indigenous clients (situated within histories of colonial violence) it is then important to understand how this can play out on their daily lives with new, non-historical, traumas. If one such wound is a broken spirit in which a lost connection with the spiritual worlds around them is manifested, one Elder asks, "So how do you re-Aboriginalize ourselves [sic]? In terms of utilization of spirit? Which is probably the weakest part of ourselves that we didn't grow with and nurture… Healing has to reflect the cultural paradigm." (p. 69).[110]

Content

Given that there were no studies found engaging with either patients' or providers' experiences of iCBT for PTSD, the thematic category of "content" as taken from the previous report on the use of iCBT for major depressive disorder and anxiety required some adaptation to meet the objectives of this review. As the studies included in this review engage with therapies ranging from skills training in stabilizing groups to more intensive ones like PE or CPT, it was neither possible, nor practical, to capture the breadth of commentary surrounding intervention-specific content concerns as was done in the prior report. Rather, "content" for the purpose of the current review was explored from a high-level reading that considered how participants described the value, rather than makeup, of the types of content being engaged. As such, content here highlights the value placed on skill

building programs and the importance of a program's content to be adapted to patient needs.

The importance of a strong set of tools or skills with which to face the daily stressors of life with PTSD was widely recognized among both practitioners and patients.[100,102,104,107] Such skill building programs were highly valued as a way of reorienting an individual to the world around them and their life with PTSD. These programs were described as helping to foster a sense of control over affective responses by building a connection between understanding the "cause of their problems" and how tools might help them enact that desired control.[102] "My feelings have controlled me a lot… I have, in a way, existed. Floated along. And that is a really big difference from now, when I see that I have a choice, and if I choose that it has a consequence, and if I don't choose that it gets another consequence." (p. 575).[102] As described previously, the importance of this control was reiterated by providers situated around treatments like PE or CPT.[100,104,107] Providing iCBT programs with approachable content that helps to deepen an individual's knowledge of PTSD, while articulating the relevance of how that specific treatment is meant to address PTSD, would seem important.

Similarly, homework was described as helpful, though could be difficult to engage with at times due to time constraints or inappropriate language.[102] For example, some individuals described that it could be difficult to relate to some of the language used in treatment. "I used this safe place [but] What the hell, safe place, what is a safe place? I didn't really experience a lot of safety, so it became: 'Hm…ok, yes. I like to be outdoors, in the nature, it helps me relax. Calm place. So rather that." (p. 576). While the term "safe place" itself may have been useful for others engaging in this treatment, for this individual it was difficult to identify what a safe place could be as they had not experienced the feeling of safety very often in their own life. As such, they needed to adjust the language to suit their own situation and needs. Though it seems as if this individual was able to do this successfully, it is possible that it may be restrictive for others[102] and could prevent them from successfully engaging with treatment. While this is a minor example, it does reiterate the potential importance of tailoring iCBT programs to the individuals engaging with them that has been noted throughout this review. Ensuring that appropriate language throughout iCBT modular work and homework activities would seem important when deciding whether a particular program is appropriate for the patient.

Traditional counsellors, healers, and Elders included in Reeves and Stewart's[110] study, spoke to the importance of providing healing oriented around an understanding of spirituality as "a cornerstone of wellness" for their Indigenous clients. Similarly, while these providers unanimously considered Western and traditional forms of healing as compatible, it was important that clients decided which content was considered important to their healing. As such, they noted the value of being able to track back and forth between traditional and Western forms of healing. One counsellor noted that this could take the form of "doing some basic psycho-educational training with clients and maybe using some grounding techniques and tuning into the fives senses, and then we suggested praying with a grandfather or rock, help to ground them when they're triggered."[110]

Process

Similar to the way in which the thematic category of "content" did not directly fit into this review from the previous review of iCBT for major depressive disorder and anxiety,[38] the thematic category of "process" likewise needed refinement. Again, as it was neither possible nor useful for this report to engage in the details of each intervention, we present here a high-level understanding of the important procedural pieces for successful treatment of

PTSD. As such, process here highlights the value placed on buy-in to treatment and flexibility in things like scheduling or location of treatment.

Across interventions, respondents repeatedly commented on how difficult it could be to engage in treatment for PTSD.[99-102,105] Recognizing, responding to, and treating PTSD is neither intuitive nor as simple as following a series of steps. A host of relational (as previously described) and practical issues can complicate the procedural quality of therapy. As such, an initial buy-in to therapy was described as dramatically helping improve the likelihood of successful engagement with therapy. Buy-in, in large part, can be motivated relationally through the development of strong therapeutic relationships built on trust and empathy,[106,108,109] peers vouching for particular modes of treatment,[101,105] or individual alignment with the goals, ideals, and problems couched within treatment protocols.[99,101,102,108] Again, while buy-in to (or collaborative agreement upon) suggested treatment may happen through relationships with providers or others, for an iCBT to be successful it is likely that those engaging with the program would need to agree with the reason for engaging in the program.

More practically, some patients spoke to the difficulties of attending face-to-face therapies. Being unable to take time off of work, the difficulties associated with the frequency and distance of travelling to therapy, and poor scheduling flexibility could mitigate any effect treatment might have.[99,111] This could be further exacerbated in care settings where patients' had previous negative experiences. This was particularly true in settings like VA hospitals where US veterans receive the majority of care for their medical needs. "I've got everything wrong with my back, but you can't even give me a damn MRI. That's why I'm done with the VA…the doctor telling me that it costs too much for him to put in a order for me to have an MRI… My trust is not there with the VA." (p. 540).[99] Others could feel out of place or simply uncomfortable in their particular care setting. "I despise going to the VA like with every fiber of my being. There are people everywhere, just hordes of people everywhere. I think that I was the only female in there, and I was just, I almost left… Usually I sit there with my purse clutched like I'm at the subway station in New York or something." (p. 540).[99] As iCBTs are able to be engaged with at one's convenience, and in one's own home, their value in potentially alleviating these concerns would likely be appreciated by individuals engaging with them.

Clear access to and communication with providers was also considered a helpful component of treatment.[111] For some patients, the opportunity to communicate with their providers online was understood as helping provide a more detailed and thorough description of their day-to-day lives. "When I was on active duty my psychiatrist and psychologist used email and it was good for them when I could express how I felt at that time; for them to gauge my overall health status and not just what I say when I'm sitting in their chair."[111] Even when replies from their provider were asynchronous, being able to reach out and describe what was happening in the moment was understood as a valuable addition to treatment. The features of most iCBT programs may already be well suited to this form of communication and could provide further benefit for those who might find expressing themselves in person daunting.[111]

Context

Unlike content and process, it was appropriate to port the thematic finding of "context" into this review from the previous report on iCBT for major depressive disorder and anxiety.[38] In the previous report, context was understood as involving experiences with the ways in which both personal (e.g., severity of condition) and structural (e.g., availability of intervention)

situations influence engagements with treatment. While both of these have been previously articulated and are highly relevant to thematic categories like relationality and process, there is more nuance to ways that context influences experiences with treatment.

Providers repeatedly articulated the ways in which the presence of psychiatric comorbidities could limit the effectiveness of interventions like PE or CPT.[100,104,107] One way of approaching comorbidities was to address them prior to treatment for PTSD, "Whether it may be substance-related issues or severe personality pathology or bipolar, they probably need a degree of stabilization in those areas before they can really focus in and do the type of trauma-focused work that we would need them to do in a CPT or PE." (p. 138).[107] Another was to potentially treat them together, "Maybe PE and a combination with other things but PE alone, when you're dealing with more than one psychiatric condition, you have to treat all of them." (p. 138).[107] Some patients experiencing both first-episode psychosis and PTSD found treating them together difficult even if eventually valuable.[103]

Though minor, some patients did note that treatments that they would have liked to engage with rather than those available through their care provider (e.g., PE and CPT) were unviable and one reason for not engaging with treatment.[99] Implicit here is that iCBT could provide another option to the standard treatments available.

Traditional Indigenous healers, counsellors, and Elders described the exploration and understanding of context as a primary need when thinking of healing from trauma. Context was largely presented in conversations around "loss" that included themes of colonization, "trauma as a constellation of losses," and "wounds." Participants described colonization as the policies and systemic injustices meant to assimilate Indigenous culture into Western culture and was understood as a fundamental driver in many of the mental health issues facing their clientele. Forms of colonial oppression like the residential schooling system and adoption policies of the Sixties Scoop were described as having been disruptive to the transmission of culture across generations and were considered responsible for a host of negative outcomes, including complex trauma and sexual abuse.

As such, participants described their clientele's traumas as situated within a "constellation of losses" rather than the result of a single event. Whether referring to poor social determinates of health or the notion of "historical trauma," this constellation of loss was considered important for participants to acknowledge as it allowed them to demarcate the complexity that would need to be spoken to. "I can show you four generations of residential school issues, where, you know, the kid hasn't gone, his parents haven't gone, his grandparents never went, but his great-grandparents did. But the kid has all the same symptoms that the great-grandparent had…because no cycle was broken." (p. 66–67).[110] The manifestations of these ongoing and reinforced cycles of trauma as well as any new traumatic experiences were described as "wounds." One of the forms a wound could take was described as a "broken spirit." (p. 67).[110] A broken spirit was someone who was "lost spiritually…and I think that's what people feel, is that general sense of loss and not feeling connected to anything around them. And people can get stuck in there for years and years — their whole lives!" (p. 67).[110]

Limitations

The included publications focused on providers' and patients' perspectives regarding decisions of whether or not to engage with various psychotherapies for PTSD, as well as experiences providing or undergoing these psychotherapies. While the original intent of this review was to include perspectives and experiences of engaging with iCBTs for PTSD, as

no literature was identified that specifically focused on iCBTs, we broadened our focus to perspectives and experiences with any psychotherapy treatment for PTSD.

The lack of literature specific to experiences with and perspectives of iCBT for PTSD raises a few concerns. The included literature potentially privileges the value of the therapeutic relationship because all of the interventions that patients and providers had experienced in the included studies were face to face. While this does not invalidate the findings represented under the theme of relationality (indeed the importance of a strong therapeutic relationship remains clear for participants included in the studies), it does encourage reflection on how the results of this review may be used.

This review is not meant to provide descriptions of “preferences” of patients and providers engaging in treatment for PTSD. Rather, the type of work presented here provides potential glimpses into what it might be like to engage with treatment for PTSD. These glimpses should not be understood as representative of the complete and uniform perspective or experience, but should rather be understood as part of a patchwork of perspectives or experiences across a range of individuals living with, or caring for people living with, PTSD.

The findings in this review are meant to inform a deliberative process that recognizes the potential diversity of human experience and can provide balance to the generalizations of clinical outcomes data and QALY evaluations. Knowing that the people participating in studies included in this review found a strong therapeutic relationship valuable and effective in their treatment regimen does not imply that all people engaging in treatment for PTSD will feel similarly. Rather, this finding raises the question of how, if interested in providing iCBTs as a treatment option for PTSD, we implement iCBT programs that can adapt to the diversity of relational needs or desires involved in the care of PTSD.

Given the lack of primary qualitative studies directly exploring experiences with iCBT for PTSD, it is unclear which, if any, findings from CADTH’s previous HTA on the use of iCBT for depression and anxiety[38] are transferrable to the PTSD context. While we know that participants included in the studies in that review valued the adaptability of iCBT programs they had engaged with and, generally, though not always, appreciated the involvement of a therapist in their treatment, the applicability of the nuance of these findings (e.g., what aspects need to be adaptable or how therapist was involvement helpful) is uncertain in relation to the current policy problem.

Of the 13 included studies, seven were conducted with US veterans or their care providers. Differences in the organization of psychiatric care across jurisdictions could not only influence the types of therapies available, but also the forms of traumatic experiences being lived.

Similarly, at least one issue described in our conversations with individuals living with PTSD through patient engagement work was absent from the literature — how varied forms of trauma might be recognized, diagnosed, treated, and experienced differently. In these conversations, it was made clear that the experience of PTSD is not universal across forms and that part of this has to do with the likelihood that traumatic experiences will be recognized as potentially developing into clinical diagnosable PTSD. While our literature search did return some studies exploring the experiences of people living with PTSD resulting from events such as childbirth or caring for sick children, none explored how these individuals engaged with treatment; thus, these were excluded according to our inclusion criteria.

Ethical Issues Analysis

The purpose of this analysis was to identify and reflect upon key ethical issues that should be contemplated when considering the provision, development, and use of iCBT for PTSD in Canada. Although other sections of this HTA implicitly touch upon ethical concerns, the aim of this analysis was to make such issues explicit and to identify others that may be relevant to any decisions in this regard.

The questions which guided this inquiry were:

- What are the major ethical issues raised by the provision, development, and use of iCBT for PTSD?
- How might these major ethical issues or concerns be addressed?

Inquiry

Bioethical analysis requires a two-step approach to identify potential issues. The first is a review of the ethics, clinical, and public health literatures to identify existing ethical analyses of the technology. The second is a novel ethical analysis based on gaps identified in the ethics literature and the results of concurrent reviews conducted as part of this HTA. This typically requires further selective literature searches to provide the basis in theoretical ethics, in applied ethical analyses of similar technologies, and in evidence for the ethical analysis of emerging issues specific to iCBT generally and for PTSD in particular. Using this approach, we identified and assessed the relative importance and strength of the identified concerns and proposed solutions, identified and assessed ethics issues that have not yet been identified in the iCBT literature, and delineated ethical desiderata for possible solutions to the issues where such solutions have not yet been proposed.

Insofar as this process involved ethical concerns in applied ethics, in the course of the analysis we reflected on the specific details of community and patients' perspectives, clinical utility, economic analysis, and implementation considerations. As such, the ethical review involved an iterative process whereby the analysis was responsive to results emerging from clinical, implementation, patients' perspectives, and economic reviews also conducted as part of this HTA.

In particular, this report presents a review of literature that provides normative analyses of ethical issues arising in the use of iCBT, whether for the treatment of PTSD or for the use of iCBT more generally, and of literature that presents empirical research directly addressing an ethical issue arising in the use of iCBT.

Literature Search Methods

The search for literature identifying explicit ethical considerations was performed by an information specialist using a peer-reviewed search strategy according to the PRESS checklist (https://www.cadth.ca/resources/finding-evidence/press). The search strategy is available on request.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) and PsycINFO (1806–) via Ovid, the Cumulative Index to CINAHL via EBSCO, and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH, and keywords. The main search concepts were iCBT and PTSD or therapy for PTSD.

Methodological filters were applied to limit retrieval to studies relevant to ethical issues. Retrieval was also limited to English- or French-language documents published since January 1, 2008. The initial search was completed in June 2019. Regular alerts updated the search until the publication of the final report.

Grey literature (literature that is not commercially published) was identified by searching sources listed in relevant sections of the Grey Matters: A Practical Tool For Searching Health-Related Grey Literature checklist (https://www.cadth.ca/grey-matters),[43] which includes the websites of regulatory agencies, HTA agencies, clinical guideline repositories, systematic review repositories, patient-related groups, and professional associations. Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers.

Literature Screening and Selection

The selection of relevant literature proceeded in two stages. In the first stage, the title and abstracts of citations were screened for relevance by a single reviewer. Articles were categorized as "retrieve" if they:

- provided normative analysis of an ethical issue arising in the provision, development, and use of iCBT, whether for the treatment of PTSD or more generally
- presented empirical research directly addressing an ethical issue arising in the provision, development, and use of iCBT, whether for the treatment of PTSD or more generally.

The goal in a review of bioethics literature is to canvass what arises as an ethical issue from a broad range of relevant perspectives. As such, the quality of normative analysis did not figure into the article selection criteria; any identification of an issue by members of the public, patients, health care providers, researchers, or policy-makers was of interest, whether presented through rigorous ethical argumentation or not. For example, academic ethicists may focus on certain issues because these relate to theoretical trends in their discipline, whereas an opinion piece by a clinical or policy leader, or a patient's experience, may bring to the fore ethical questions that were neglected by academic ethicists but highly pertinent to the assessment of the technology in the relevant context.

In the second stage, the full-text reports were reviewed by a single reviewer with ethics expertise. Reports meeting the previously mentioned criteria were included in the analysis, and reports that did not meet these criteria were excluded.

This review incorporated and built upon the results of a recently completed review[38] of ethical issues arising in the provision, development, and use of iCBT for major depressive disorder and anxiety disorders in Canada, which included an analysis of literature assessing ethical issues arising in the use of iCBT more generally. A key finding of that review was that a paucity of literature exists that directly and explicitly provides a normative or empirical analysis of ethical issues related to iCBT, let alone for the provision, development, and use of iCBT for particular conditions like major depressive disorder or anxiety disorders. Part of that review therefore involved canvassing a broader literature which engaged with the ethics of internet-delivered therapies, "Web-counselling," "eMH," "mHealth," "email therapy," and "telemedicine" in order to capture ethical issues that emerged in, and may be shared across, e-mental health practice. Rather than duplicate that search and analysis, for the purposes of this review we chose to, first, include previously reported ethical themes related to iCBT more generally; second, identify additional literature and novel ethical themes, if any, by locating and analyzing literature focused on ethical issues raised by iCBT for PTSD in particular; third, identify additional literature and novel ethical themes, if any, by locating and

analyzing literature focused on iCBT more generally that had been published following the publication of the previously conducted review on iCBT for major depressive disorder and anxiety disorders; and finally, provide an analysis that was responsive to the novel results emerging from concurrent reviews conducted as part of this HTA. In addition to reporting novel ethical themes related to the provision, development, and use of iCBT for PTSD, this review included literature identified in the previously completed review and reported general themes from that review when they were deemed ethically relevant. Given that existing literature tended to discuss ethical issues associated with iCBT in general and not in terms of particular conditions, and due to the significant overlap of these issues as they relate to major depressive disorder and anxiety disorders, this review is largely similar to the review previously conducted for major depressive disorder and anxiety disorders, with minor modifications and references made to PTSD where appropriate.

Analysis

The ethical issues identified, values described, and solutions proposed in the literature were at this stage evaluated using the methods of ethical (applied philosophical) analysis, which included applying standards of logical consistency and rigour in argumentation, particularly where specific implications were identified and specific solutions advocated; evaluating their responsiveness to important values of health care and health care policy in the field in which the technology is proposed for implementation; evaluating their adequacy to the context for which the technology is being considered; and evaluating the representation of perspectives from diverse relevant communities, particularly marginalized and vulnerable populations. The ethical issues identified, values described, and solutions proposed in the literature were analyzed in relation to key ethical values or principles (e.g., respect for autonomy, beneficence, nonmaleficence, and justice). In addition, where appropriate, the analysis drew most directly on two classic perspectives that are well-established in the health ethics literature, namely the utilitarian and consequentialist approach and the deontological and duty-based approach. The former focuses more directly on the overall consequences of a particular course of action and deals with questions of individual rights and duties, and considerations of social justice, only indirectly. Conversely, the deontological and duty-based approach gives priority to considerations of individual rights and concomitant duties while treating overall utility (i.e., the greatest good for the greatest number) as of only secondary importance. While these two theoretical approaches are often treated as opposed, there is a well-established tradition within contemporary health care ethics that treats them as complementary. Depending on the nature of the issue and the context in which it arose, other normative ethical considerations and perspectives were invoked in the analysis.

Results

Literature Sources

In total, after the previously completed review on iCBT for major depressive disorder and anxiety disorders,[38] 1,335 new citations were available for screening. An additional 88 citations were identified from regular alert updates, which resulted in a total of 1,423 citations identified. An analysis of the titles and abstracts of the identified citations led to the inclusion of 43 reports for full-text analysis. After full-text analysis was completed, 38 reports were excluded, leaving five for inclusion. These five reports formed the basis of the analysis, in addition to the 57 reports included in the prior review on iCBT for major depressive disorder and anxiety disorders.[38]

Substantive Results

The central themes identified in the literature are presented here according to the key ethical principles or values that they primarily invoke or implicate, in addition to the primary ethical issue or domain in which that principle or value applies. The themes are trauma-informed care, the therapeutic alliance, and trust; beneficence and the uncertainty of new treatment modalities; nonmaleficence, limitations to client safety, and the prevention of retraumatization; justice and enhanced access; respect for autonomy and informed consent; privacy and confidentiality in the context of internet-delivered therapies; and professional and legal issues.

Trauma-Informed Care, the Therapeutic Alliance, and Trust

It is widely appreciated that the **therapeutic alliance** between clients and their health care providers is of critical importance to mental health care.[113-115] Indeed, evidence suggests that the therapeutic alliance is significantly associated with health outcomes across different treatments.[116,117] The therapeutic alliance may be especially important for therapies that aim to realize the principles of trauma-informed care, such as approaches commonly used to treat PTSD, which require relational collaboration that works to develop safety and trust (also described in the Perspectives and Experiences Review section).[118-121] Approaches to **trauma-informed care** can differ in a number of respects, but for these purposes these approaches can be defined as "an understanding of and responsiveness to the impact of trauma, that emphasizes physical, psychological, and emotional safety for both providers and survivors, and that creates opportunities for survivors to rebuild a sense of control and empowerment." (p. 81–82).[122] Prioritizing client safety, choice, and control, as well as understanding the unique ways that violence or trauma impacts the lives of clients, are viewed as essential in reducing possibility of retraumatization.[120,121]

Hence, it is important to note that, while there is substantial empirical investigation of the therapeutic alliance in this context (to be discussed shortly), some concerns have been raised regarding the presence and quality of the therapeutic alliance in the context of iCBT irrespective of the condition for which it is being used.[113,118,123-127] Such concerns have been raised because iCBT, or, more generally, internet-delivered therapies, are variably seen as limited, remote, and often asynchronous;[113,124] as potentially unable to provide individuality and respect to clients;[124] and as mechanical, impersonal, generic, isolating, or dehumanizing.[123,128-131] As a result, some argue that it is unclear whether such therapies are capable of conveying features like empathy, emotional responsiveness, and other interpersonal collaborative features of human-delivered therapy that are crucial for establishing and maintaining a therapeutic alliance.[123,132]

Further potentially jeopardizing the therapeutic alliance are the boundary issues possibly raised by iCBT and other internet-delivered therapies. With an internet mode of delivery comes the possibility of being able to instantly message one's therapist, which may result in clients feeling closer to the therapist than in traditional face-to-face settings, which may in turn foster dependence.[115,133-139] However, the ability of clients to communicate with their therapist more frequently could also be beneficial for clients. iCBT applications (and in particular, applications that passively collect data) may also have the capacity to unexpectedly reveal information about inappropriate and perhaps even illegal client behaviour, which may impair the therapeutic alliance between the client and therapist (and which may have implications for confidentiality and liability, as detailed in the Privacy and

Confidentiality in the Context of Internet-Delivered Therapies and Professional and Legal Issues sections).[140]

Of course, the presence and quality of the therapeutic alliance in iCBT may be affected by many factors, not least of which is the degree of involvement and supportive contact of the therapist: does “internet-delivered” mean that the internet is used as a tool by a therapist to support therapeutic objectives, or does it mean that the internet is used with minimal or no therapeutic contact?[128,141,142] Hypothetically, increased therapist contact, even through the implementation of video communication to retain communicative features, could affect the quality of the therapeutic alliance.[124]

In addition to its impact on clinical effectiveness, concerns regarding the quality of the therapeutic alliance should be viewed as being ethical in nature for the following two reasons. First, if it were the case that iCBT renders it difficult for therapists to act in accordance with the ethical principles of mental health practice (e.g., principles of beneficence, nonmaleficence, and so forth), then the integrity of the therapeutic alliance may be threatened. For example, if therapists are unable or less able to effectively fulfill their ethical obligations of privacy or confidentiality when using iCBT, then clients may be less inclined to engage in therapy openly and honestly, which may in turn threaten the therapeutic alliance, and perhaps the capacity to engage in trauma-informed care. Second, and conversely, if it were the case that it is difficult to establish or sustain a therapeutic alliance using iCBT, then it may be difficult for therapists to discharge their ethical obligations or act in accordance with ethical principles of mental health care. For example, if therapists are less capable or incapable of establishing or sustaining a therapeutic alliance given limited interpersonal contact with their clients (relative to traditional face-to-face CBT), and clients are as a result less inclined to share and engage with the therapist during the course of their therapy, then the therapist may be unable to effectively fulfill their ethical obligations of nonmaleficence by adequately monitoring and managing clients’ distress. Similarly, if therapists are less capable or incapable of engaging in trauma-informed care via iCBT, then they may be less able to emphasize the physical, psychological, and emotional safety of their clients. Each of the ethical concerns and issues identified in the remainder of this report (e.g., conflicts of interest, privacy and confidentiality, limitations to client safety, and so forth) might therefore have important implications for the quality and extent of the therapeutic alliance in iCBT.

Ultimately, though, the extent to which internet-delivered therapies like iCBT are capable of embodying the critical features of the therapeutic alliance is an empirical question that has generated considerable debate.[113,119,123,124,128,131,141,143-146] With the previous concerns noted, some studies have found that it is indeed possible to establish a therapeutic alliance in the context of iCBT; for instance, one study found that some clients ranked the therapeutic alliance higher in internet-delivered therapy as compared with traditional face-to-face therapy.[147] Other studies have nuanced these findings. For instance, one study found that, while there was variation among programs in whether features of the therapeutic alliance were present, iCBT programs were capable of emulating those features designed to *establish* a therapeutic alliance, but there may ultimately be fewer features associated with *developing* and *maintaining* the alliance.[123] Moreover, some have questioned the extent to which the therapeutic alliance is even as important in iCBT as it is in traditional CBT given the shift of responsibilities from therapists to clients.[113,124,131] Though, given the importance of trustworthy relationships to practising trauma-informed care,[120,148] it is unclear whether this would hold true in the case of iCBT for PTSD. Furthermore, some studies suggest that the therapeutic alliance may be especially important for certain populations, such as women

who have experienced sexual abuse[149] (a particularly relevant patient population in the context of PTSD), and less so for others (e.g., those experiencing social phobia with a preference of minimal therapist contact).[146,150] The degree to which different forms of iCBT are capable of, and effective at, establishing and maintaining a therapeutic alliance is beyond the scope of this review. From an ethical standpoint, a crucial question hitherto neglected in this literature is not whether a therapeutic alliance is present or capable of being present in the context of iCBT for PTSD, but rather whether a therapeutic alliance *ought* to be present in this therapeutic context.

Fully answering this question is itself beyond the scope of this review. With that said, it is worth noting that there is a lack of literature identifying or meaningfully analyzing the significance and role of what is widely considered to be of central ethical value to the therapeutic alliance: **trust**.[151-154] Trust is a relational value that is complex and has many dimensions, but for these purposes it may be defined as "an attitude that we have toward people whom we hope will be trustworthy," where a "trustworthy person" is someone who is competent and committed to do what he or she is trusted to do.[155] Indeed, therapists' demonstration of "facilitative attitudes" of a therapeutic alliance, like empathy, positive regard, and unconditional regard, has been shown to be associated with clients' trust in their therapists (and appears to be significant in the context of treatment for PTSD, see the Perspectives and Experiences Review section).[154] A lack of trust, or distrust, in mental health services can act as a barrier to care,[153] and as previously mentioned, may render it difficult or impossible for therapists to fulfill their ethical obligations to their clients. For example, confidentiality assumes a relationship based on trust.[156] Additionally, trust may be particularly important (and difficult to establish) in the therapeutic context of PTSD where clients' trust in people may be generally compromised as a result of previous traumatic events, or because clients' willingness to revisit painful memories or traumas may be predicated on trusting their therapist.[148,157-159]

A trusting relationship between therapist and client may be critical to the therapeutic process not only because of its ostensible association with therapeutic outcomes, but perhaps also because it establishes and renders it possible to fulfill the ethical responsibilities that each party has in relation to one another. As a result, features or concerns that challenge or erode the therapeutic alliance, and therefore trust, in iCBT might be viewed as ethical challenges for iCBT, particularly given the presence of non-traditional therapist–client interactions in this context.[153] Conversely, the degree to which trust and trustworthiness can be promoted and established in the context of iCBT should be viewed as an important, yet hitherto underexamined, ethical question.

Beneficence and the Uncertainty of New Treatment Modalities

A core principle of bioethics is **beneficence**, which requires that health care providers act in the best interests of their patients or clients.[160] As such, if iCBT is not effective in treating PTSD, or if there is uncertainty as to its effectiveness (Clinical Review section), then it may not be ethically justifiable to support or promote this treatment modality for PTSD.

Several themes in this literature speak to the challenges that may exist for iCBT providers to adequately fulfill their duty of beneficence, including concerns over limited rigorous testing; a limited or equivocal evidence base for the effectiveness of iCBT (for PTSD and more generally); and limited regulatory oversight, safeguards, guidelines, and consistency for the development and implementation of iCBT applications.[37,161] In other words, in order to act in accordance with the principle of beneficence, iCBT providers must be able to weigh the benefits and risks associated with iCBT for each of their clients.[124] While the evidence base

and regulatory environment associated with iCBT is rapidly changing, if providers are uncertain or unclear as to whether iCBT (or a particular iCBT application) has firm empirical support regarding its effectiveness for the treatment of PTSD, or more generally whether iCBT will benefit their clients (in absolute terms or relative to traditional face-to-face CBT), then it will be unclear whether iCBT is in the best interests of patients. As such, treating clients with iCBT may run against therapists' duties of beneficence.[134,140,162] As noted in the Clinical Review section, there is indeed a high level of uncertainty regarding the effectiveness of iCBT for PTSD. The effectiveness of iCBT for PTSD is also muddied by the sheer number of applications on the market, which may each vary in terms of effectiveness, quality, safety,[118,133,134,162,163] not to mention their capacity to address the many ethical concerns raised in this review (e.g., privacy and confidentiality).

It is reasonable to believe that at least some perceived uncertainty regarding the effectiveness of iCBT for PTSD could be addressed through the provision of professional guidelines and/or regulatory oversight regarding the development of iCBT applications and the practice of iCBT insofar as these mechanisms could provide monitoring as well as quality and safety standards enforcement, or because they might simply promote consistency across platforms.[152] Currently, however, the expansion of internet-delivered therapies has outpaced regulatory bodies' capacity to provide guidance or oversight for their provision.[135,136,141,147,164] No matter the safeguards and regulatory mechanisms in place, iCBT providers themselves must also be adequately trained and competent to practice in this unique modality if they are to be able to act in their clients' best interests.[128] And, while professional guidelines and regulatory oversight would help to lessen uncertainty regarding the effectiveness of any particular iCBT application for PTSD, the general effectiveness of iCBT for PTSD would still need to be established in order to claim that iCBT is in the best interests of clients experiencing PTSD.

While not necessarily framed as such in the literature, **conflicts of interest** might motivate developers or iCBT providers to act in a manner that does not always align with the best interests of clients. Simply, where new technologies exist, there also exists the potential for those who have a financial stake in those technologies to profit from their use.[128,133,161] Such financial interests may in turn impair a provider's objectivity, competence, or ability to effectively perform their role.[165] Potential also exists for those with financial interests in iCBT to attempt to influence guideline development or research in this area.[166] And while such conflicts will not always run counter to clients' best interests, clients ought to be fully informed of any potentially or perceived competing interests of their therapist (and for similar reasons, of application developers or funders).[126,163]

Ultimately, limited regulatory oversight and safeguards in this area may render it more likely that iCBT developers or therapists fail to disclose or manage conflicts of interest. As such, to prevent, mitigate, and manage conflicts of interest, efforts ought to made to promote the transparent disclosure of the individuals or organizations involved in the development and funding of iCBT applications.[162] Such transparency is critical for fostering trust between clients and iCBT providers (and their platforms) (Trauma-Informed Care, the Therapeutic Alliance, and Trust section). Ultimately, it may be challenging for therapists to reconcile their duty of beneficence with iCBT until these concerns are allayed (i.e., whether it can be demonstrated and in which cases iCBT is in the best interests of their individual clients).

Given the rapidly changing evidence base for iCBT, it is worth considering whether iCBT ought to be supported if there was, in fact, sufficient evidence supporting its effectiveness. If iCBT *is* effective for the treatment of PTSD, then it should be seen as a viable alternative

that may benefit clients with this disorder. In addition, compared with traditional face-to-face CBT, iCBT may have features that allow for more individualized therapy. While consistency and standardization are often considered as key advantages of iCBT relative to traditional face-to-face CBT,[161] some suggest that iCBT can be highly personalized based on demographic information, personal goals, and other types of data that clients provide.[167] As a result, the ability to individualize treatment could render it more possible to act in the best interests of one's client (and to have clients' best interests met) given the modality's ability to be responsive to clients' unique needs. In addition, it may be that iCBT is a preferable mode of delivery for clients,[168,169] or that this modality is more appropriate or suitable for some clients who are dealing with body image concerns, social anxiety, avoidance symptoms, or phobias, or if they are unable to attend a face-to-face session due to mobility issues (Respect for Autonomy and Informed Consent section).[128,141] iCBT may be a preferable modality for other reasons, as well; some suggest that because traumatic events are identifiable etiological factors, they may be more amenable to being treated via a "less-intensive" internet-based mode of delivery.[118] Finally, iCBT may increase opportunities for social interaction and serve as a source of connectedness that would not otherwise exist or be possible to access, which may be in the best interests of some clients.[128]

iCBT could perhaps more readily promote or meet the best interests of clients if iCBT applications can be more readily and routinely updated to reflect the best evidence for therapy,[170] or if iCBT renders it easier to systematically collect client data and adapt treatment plans accordingly.[171] And, on a population level, if such therapies are better capable of producing datasets of digital biomarkers, the potential may exist to promote the interests of all clients by being better able to predict outcomes and further our understanding of mental health conditions.[153]

For clients experiencing barriers to traditional face-to-face CBT, the provision of CBT via the internet may redress inequities of access, which will be in those clients' best interests should the online medium be appropriate for their particular therapeutic circumstances. Though, the extent to which iCBT is in fact justice-enhancing, and therefore beneficence-enhancing, is not a foregone conclusion (Justice and Enhanced Access section).

Finally, left outstanding is the question of whether clients should be able to access iCBT for PTSD even in the absence of strong evidence supporting its effectiveness. For instance, consider a situation where traditional face-to-face CBT is inaccessible but that iCBT applications could be made accessible (e.g., for individuals in rural or remote communities). One may argue—perhaps on the grounds of beneficence or justice—that clients who cannot access traditional face-to-face CBT should at least have the option to access iCBT, even if its effectiveness is doubted or is uncertain, because "some therapy is better than no therapy." Indeed, given the burden of unmet need faced by those experiencing PTSD in Canada, and iCBT may be a treatment modality that is favoured by some clients, such an argument appears at first blush to have some force and so should not be dismissed. While there are good ethical reasons to enable clients to access iCBT, especially when the alternative is often simply no therapy at all, there are still ethical concerns that ought to be carefully considered. First, we may not necessarily be able to assume that "some therapy" will be better than no therapy (e.g., in cases where "some therapy" is ineffective). Second, if there is a possibility that iCBT could harm clients without proper supports in place, then there may be an ethical reason to support restricting access to iCBT for PTSD until the scientific community and, indeed, individual therapists, are satisfied by the evidence of its effectiveness. This reason is grounded in therapists' obligation to do no harm.

Nonmaleficence, Limitations to Client Safety, and the Prevention of Retraumatization

One of the therapist's primary ethical obligations is to do no harm.[172] As such, any potential benefits of iCBT must be carefully balanced and weighed against any possible risks.[164] Due to the possibility of significant geographical distance between therapist and client, in addition to possible time delays resulting from the often asynchronous nature of the therapy delivered in iCBT, it may be challenging for iCBT providers to fulfill this ethical obligation of **nonmaleficence**, which means that **limitations to client safety** may be present in the iCBT context.[125] In addition, insofar as fulfilling ethical obligations of nonmaleficence in the context of PTSD therapy requires an approach that is trauma-informed,[173] iCBT applications that fail to be sensitive or responsive to individuals and their unique traumatic stressors and stress symptoms may lead to **retraumatization**, thus violating this obligation to do no harm. Though, it should be noted that, of the limited clinical evidence on iCBT for PTSD, there is very little evidence of adverse events associated with iCBT (Clinical Review section).

Many suggest that it may be more challenging to perceive, monitor, and adequately respond to safety issues (e.g., risk of suicide, suicidal ideation, aggressive behaviour to others, and so forth) in the context of iCBT (though, there is lack of evidence regarding the actual safety of iCBT, as outlined in the Clinical Review section). This concern has been raised for a number of reasons. First, it may be more challenging to perceive safety issues that may otherwise be identified in traditional face-to-face therapies given the possible absence of non-verbal clues, clothing and hygiene indicators, or other aspects of a client's appearance that may signal the type and severity of pathology.[130,133,136,163,174,175] Second, different mechanisms may exist for iCBT applications with respect to how client information is monitored and provided to the therapist (if such applications are therapist supported), if it is monitored and reviewed at all, potentially rendering it difficult to automatically or synchronously monitor safety signals should they arise.[140] Third, iCBT may use unique therapeutic modalities that warrant enhanced monitoring given the risks of harm to clients (notably, retraumatization), such as exposure therapy conducted via virtual reality.[173,175] Fourth, treatment modalities used specifically for PTSD may be particularly important to closely monitor due to related risks of harm to clients (notably, retraumatization), such as the act of confronting, working through, and integrating traumatic memories, or treating related moral injury via adaptive disclosure.[115,176] Finally, an internet mode of delivery may render it more difficult or impossible to ethically act in response to safety signals, such as evidence of client risk to themselves or others, even when there is a legal obligation to do so.[124,125,127,131,132,136,138,139,171,177-179] Thus, if a therapist recommends iCBT, or a particular iCBT application, and an adverse outcome occurs in the course of therapy in this modality, one might be inclined to argue that the applicable standard of care was not met (Professional and Legal Issues section).[140] With that said, given that iCBT may include more frequent interactions than traditional face-to-face CBT, it is possible that iCBT could have the potential to be more effective in identifying and monitoring risks of client self-harm or harm to others.

Some suggest that a possible solution to providers' potential inability to monitor, review, and act upon safety signals is to ensure that clients are made fully aware of these inherent limitations to client safety.[129,140] This is indeed important; yet, from an ethical standpoint, a crucial question hitherto largely neglected in this literature is not how liabilities might be avoided where adequate monitoring of client distress or risk of harm is not feasible, but rather whether therapies *ought* to be offered when by their very nature it might be more challenging to prevent retraumatization or otherwise prevent harm to clients. In other words,

while it is certainly ethically necessary to inform clients of a therapist's potential inability to ethically act on certain information divulged in the course of therapy, simply informing clients of this should not necessarily be seen as altogether avoiding the ethical issue at hand; namely, that those seeking therapy may be at risk of harm to themselves or others, and that it may not be possible or feasible for internet-delivered therapies to prevent or be sufficiently responsive to these risks of harm. One must therefore ask whether this is an acceptable state of affairs given the unique nature of the mode of therapy, or whether an ethical obligation exists in this context to actually ensure that mechanisms are in place to anticipate, mitigate, or prevent such risks.

Arguably, in addition to duly informing clients of potential limitations to preventing or assessing harm or risks of harm in the context of iCBT, the principle of nonmaleficence may reasonably be seen as requiring sufficiently robust screening to identify clients for whom internet-delivered therapy may be inappropriate (i.e., preventing "unscreened access"),[135,177,180] strictly defined management protocols that address therapist responses to such risks should they arise,[135] and perhaps even the restriction of some treatment approaches from being used in the online platform if they risk retraumatization and are difficult to manage in the absence of appropriate supports. This may be particularly significant in the case of PTSD, where a client's "readiness" to begin therapy appears to be critical for successful treatment given that therapies are often predicated on re-exposure to traumatic memories.[5] The ability to adequately monitor and assess a client's "readiness" to return to work (e.g., first responders), combat (e.g., military personnel), or otherwise, is also particularly important in the context of PTSD — which can also have implications for clients' long-term disability or compensation claims — which may be limited with inadequate monitoring and assessment. As such, nonmaleficence in this context arguably requires that vigilant risk assessment be a part of iCBT both in terms of the initiation of therapy and when assessing client readiness to return to work or combat.[124,162,167,170,174] In any case, risk monitoring mechanisms should be present throughout the therapeutic encounter.

iCBT's digital mode of delivery may facilitate these assessment and monitoring activities; for example, iCBT may integrate ecological momentary assessment as a form of monitoring and assessment[181,182] (which involves repeated sampling of clients' behaviours and experiences in real time within their natural environments),[183] and clients' digital footprints may reveal important information about client behaviour,[152] perhaps leading to a digital phenotype for PTSD.[181] Ultimately, though, the principle of nonmaleficence may be supportive of the idea that treatment approaches involving exposing clients to feelings, memories, or situations that remind them of the trauma they have experienced only be included when the iCBT application is therapist supported and synchronously monitored so as to best avoid the risk of retraumatization.

Importantly, it may be less possible, or altogether impossible, to fulfill these obligations if the identity and contact information of the client is unknown, which may suggest that clients' identities and contact information should be known (or at least be accessible) to the iCBT provider.[151,184] Multiple mechanisms exist that could conceivably support adequate risk assessment and monitoring, including having discussions with the client regarding the plans for addressing potential crises that occur during or between sessions[164] or establishing in-person supports in the client's geographic location (perhaps through a network of crisis counsellors[135,179] or a telephone hotline that is responsive to urgent client issues).[131] Such obligations may also extend to the responsibility to follow up with clients who stop participating in iCBT with no prior notice, which may be particularly important given rates of loss to follow up associated with iCBT[144] (as described in the Clinical Review section).

Finally, while much has been said here about the concerns for (and limitations to) client safety, less has been said about the exercise of client autonomy in light of these concerns. For many reasons discussed in this report (most notably, in the Respect for Autonomy and Informed Consent and Justice and Enhanced Access sections), clients may prefer or choose to pursue iCBT as a treatment for their PTSD. There are good ethical reasons to support the self-determination of clients in this regard rather than merely considering the ethical reasons that might support paternalistic actions to prevent client access to iCBT due to risks of harm, or for other reasons. As such, this should perhaps be cause to re-cast concerns around nonmaleficence as reasons to ensure iCBT applications exist in their safest form should clients wish to pursue iCBT as a treatment modality, rather than as reasons against the provision of iCBT for PTSD.

Justice and Enhanced Access

The provision of mental health care in Canada requires significant investments of time and resources, which may unfortunately limit the availability of services.[185] The introduction of alternative modes of therapy, like iCBT, may therefore generally lead to **enhanced access** by expanding service capacity and by reducing waiting lists for mental health care, which would address a substantial unmet need.[123,144,161,162,178] And, given its unique mode of delivery, iCBT may provide access to those who might otherwise not be able to access psychotherapy.[5,118,124,126,144,150,152,163,169,171,186,187] iCBT has the potential to increase access to critical mental health services given that it is not restricted to location or time,[123,124,126,131,144,162,167,169,177,179] because it may reduce barriers related to immobility, lack of transportation, pain symptoms, cost, and personal, family, or work obligations,[126,141,144,161,178,185] and because it may reduce treatment-seeking barriers due to stigma,[5,123,124,135,141,152,162,188,189] which may be particularly salient and significant for populations who are already marginalized or vulnerable.[141,189] This is particularly important in the case of PTSD, where disparities (e.g., disadvantaging women and ethnic minorities) already exist with respect to PTSD diagnosis and treatment.[190,191] In addition, because symptoms inherent to some psychological disorders, such as avoidance symptoms experienced by those with PTSD, may prevent individuals from seeking traditional face-to-face CBT, iCBT may offer a preferable and potentially more appropriate therapeutic alternative.[5,144] For these reasons, insofar as it is effective, iCBT should be viewed as enhancing **justice**, as it makes substantial, positive steps toward the reduction of disparities of access to mental health services.

iCBT may not be a panacea capable of effectively remediating disparities in access to traditional face-to-face CBT; yet, relative to the perceived justice-enhancing features of iCBT, considerations that may attenuate or otherwise restrict access to iCBT are given scarce attention in this context. As such, while iCBT may tend to generally reduce common barriers to mental health services, if due attention is not paid to the barriers that may remain in this context for some populations, new inequities may be created and existing inequities may be exacerbated.[152,178,187]

In particular, given its internet mode of delivery, the digital divide is implicated in this context.[118,128,180] For instance, internet-delivered services may tend to target, and be viewed as more acceptable, to younger populations who may be more familiar and comfortable with such technologies.[152] In addition, it may be required that those participating in iCBT be familiar with using a computer, be competent typists, and have literacy and digital literacy skills.[5,125] Ultimately, these factors point to the social determinants of access to internet-delivered mental health services, and illustrate how economic and social inequalities may

preclude certain populations from accessing, and ultimately benefiting from, iCBT.[124,126,133,152,178] In particular, individuals with lower income, lower educational attainment, who lack digital literacy, or who cannot afford a computer or reliable internet access may not meaningfully benefit from the "increased access" ostensibly on offer by iCBT.

Attending to the social determinants of access to internet-delivered mental health services is multifaceted and complex. With that said, one of the principal mechanisms that may limit the availability and access to mental health services is the cost to the client. While iCBT for PTSD may be cost-effective (at least when compared with no treatment, as shown in the Economic Evaluation section), this does not necessarily preclude iCBT from remaining inaccessible to those of lower socio-economic status when such populations are unable to afford it.[185] Indeed, funding and reimbursement policies may affect the successful implementation of iCBT. Yet, iCBT is generally not included in public health insurance schemes, and may also not be covered under private insurance or employee assistance programs, depending on the organization.[124,186] For this reason, as Hadjistavropoulos et al. argue, successfully scaling up iCBT to increase its accessibility would require that iCBT become part of the permanent basket of health care services funded and provided to provincial residents.[186] On their analysis, iCBT has the added benefit of having the capacity to reduce at least some provincial health care expenditures, so this may count as a reason in favour of providing public coverage for such therapies. As an alternative, Hadjistavropoulos et al. also raise the possibility of establishing a national collaborative unit to increase access to iCBT and provide a mechanism for cost sharing among provinces. A national collaborative unit may also align with the perceived need for the national coordination of licensing for those practising across jurisdictions (Professional and Legal Issues section). Yet, apart from raising the question as to whether iCBT should be included in the basket of publicly insured services, none of the literature identified examined the ethical advantages or disadvantages of doing so.

That iCBT provides a relatively standardized therapeutic approach may be assessed as a justice-enhancing feature insofar as such standardization could hypothetically remove the biases or variation that may exist among and across therapists, which may in turn be capable of producing inequities in client outcomes, how clients are treated, and so forth. In effect, standardization may work to ensure that all clients receive the same standard of care, and thereby militate against inequities that might manifest from variable therapy quality across providers or geographies. Yet, one must also consider the potential threats to justice that standardization might raise. First, standardization may simply systematize biases rather than remove them. Ethical guidelines for application development will therefore be crucial in remedying this possible outcome.[162] Second, standardization may render iCBT applications unable to be meaningfully sensitive and responsive to important client characteristics, such as language, culture, Indigeneity, religious beliefs, sex, gender, individual traumas, or comorbid symptoms.[125,131,133,138,139,150,162,174,180,192] This may be particularly important given the diverse Canadian context and because iCBT may expand the traditional geographical scope of practice. In addition, this is especially significant in the context of PTSD where trauma and responses to trauma typically occur within a cultural context.[115,193,194] In other words, to be trauma-informed is to "understand clients and their symptoms in the context of their life experiences and cultures."[195] As such, a failure to meaningfully adapt treatment to these characteristics, including clients' unique traumatic stressors and stress symptoms, may represent a failure in providing trauma-informed care.[120,196] And while some suggest that one could attempt to resolve this issue by asking new clients to provide such information to their therapists upon intake,[131] it remains to be seen the degree to which iCBT

applications are capable of being meaningfully responsive to such information and, ultimately, whether trauma-informed care is possible in the absence of a therapist. As such, standardization, which may be more applicable in iCBT than it is in traditional face-to-face CBT, may conflict with the individualization or cultural adaptation viewed as conducive to a healthy and productive therapeutic alliance (and which may also conflict with respecting client autonomy —Respect for Autonomy and Informed Consent section).[166,193]

In summary, iCBT clearly shows the potential to enhance access to sorely needed mental health services. This should count as a strong ethical reason in support of enabling access to this treatment modality. With that said, it should be noted that iCBT is not *necessarily* more accessible, convenient, or appropriate than traditional face-to-face CBT simply due to the fact that it may reduce common barriers to access.[178] In order to make substantial gains in an area where there is a significant unmet need, and to not entirely work against the justice-enhancing features of iCBT (which could occur if it were predominantly available to middle- to upper-class, well-educated, young- to middle-aged individuals),[124] careful attention ought to be paid to introducing mechanisms, such as public coverage, that will meaningfully enable underserved, marginalized, and vulnerable individuals and populations to access its benefits.

Respect for Autonomy and Informed Consent

A central principle in bioethics is that, insofar as is possible, one should respect and promote client **autonomy**.[160] Respecting and promoting client autonomy may mean many things, but at its core it requires that "persons ought to have independence, that is, be free from coercion and other similar interferences."[197] Client autonomy in the context of iCBT is implicated in a number of ways. First, rather straightforwardly, iCBT may be the preferred mode of delivery of CBT for some clients,[168,169] and so the very fact that iCBT exists as an alternative to traditional face-to-face CBT can be counted as autonomy enhancing, provided that iCBT is at least as available, accessible, and effective as is traditional face-to-face CBT (Justice and Enhanced Access section). Indeed, iCBT can be considered unique insofar as it is rather flexible in terms of where, when, and how therapy is accessed,[123] which may enhance clients' self-determination and control when seeking therapy. Second, if iCBT shifts much of the responsibility for treatment from the therapist to the client, as is commonly touted with iCBT, then clients may have increased autonomy in determining and controlling their treatment (e.g., how and when to do the treatment, at what pace and intensity to pursue the treatment, and so forth).[169]

Despite the previously noted possible benefits to client choice and control, therapies that fail to be sufficiently sensitive and responsive to clients' unique traumatic stressors and stress symptoms arguably limit clients' choice and control in decisions affecting their treatment. Empowering clients to revisit their traumas requires paying special attention to client "readiness," including when clients are ready to explore past abuse or trauma, at what speed they wish to explore past abuse or trauma, and so forth. For this reason, iCBT may limit this degree of client choice and control in decisions affecting their treatment, and so therefore could be viewed as autonomy diminishing. With that said, if iCBT truly shifts much of the responsibility from the therapist to the client, then it is possible that the client could retain greater control over their therapy and therapeutic objectives (e.g., they could proceed at their own pace when ready to do so).

Client autonomy may also be threatened when clients are unaware of the details of a given treatment, including the expected benefits and risks (e.g., retraumatization) and the likelihood that the benefits and risks will occur. As such, challenges in obtaining **informed**

consent in the context of iCBT may threaten the ability of clients to make autonomous choices about their care. There is a dearth of research that explains how informed consent is obtained and whether such consent is truly informed in the context of iCBT.[124] This is particularly ethically problematic given the importance of the informed consent process when asking (or expecting) clients to revisit traumatic memories, feelings, or situations.[120]

Several challenges for informed consent have been raised by a number of scholars in the literature.[124,126,130-132,135-137,139,147,151,164,165,168,175,178,184,187,198] The central challenge raised is the inability of iCBT providers to determine and verify the identities and ages of clients. In addition to the practical challenges of verifying age and identity,[126,130,131,135,137,139,147,151,164,165,175,184] concerns abound that clients may willfully misrepresent their age or identity in this context.[124,136,178] The inability to verify the identity of clients is important for a number of reasons, not least of which is because this may render it impossible to intervene in cases of emergency or in situations where a duty to warn or report arises (Nonmaleficence, Limitations to Client Safety, and the Prevention of Retraumatization section).[147] An additional related concern not explicitly raised in the literature is the possibility for clients to commit insurance fraud by misrepresenting their identity in order to receive covered (either publicly or privately) mental health services. At the same time, concerns have also been raised regarding the ability of clients and regulators to determine and verify the identity and certifications of iCBT providers (Professional and Legal Issues section).[131,198] Indeed, a 2003 study found that of 136 Web-counselling websites, only 38% had some means for detecting imposter clients or counsellors, and that even the steps that existed to do so were minimal.[199]

Verifying the identity of clients and iCBT providers is a critical step in both the informed consent process and in the delivery of therapeutic services. Yet, rather straightforward mechanisms may be installed to facilitate these verification processes, including the presentation of photo identification or a birth certificate, requiring an initial in-person or video meeting, or using the verification services of third-party organizations.[126,175] What is perhaps more ethically troubling is the related challenge of determining a client's **decisional capacity** to consent to services.[178] Adequately evaluating a client's capacity to consent may in some instances require the assessment of verbal and non-verbal cues,[178] which may be difficult in the context of iCBT. Similarly, iCBT may limit the ability to ensure that informed consent processes meet the linguistic, cultural, and literacy needs of clients and provide opportunities for clients to ask questions or raise concerns.[124,187]

Privacy and Confidentiality in the Context of Internet-Delivered Therapies

Privacy and confidentiality are critical ethical values in mental health practice, and both are widely viewed as being potentially more challenging to establish and maintain in the context of internet-delivered therapies, irrespective of mental health condition, largely due to concerns over data security and the transfer of data to third parties.[140,184] Privacy and confidentiality can be distinguished insofar as privacy generally applies to the person, whereas confidentiality generally applies to the person's data.

Given the online mode of delivery for iCBT, multiple risks to data security exist, which raises ethical concerns regarding the quality and extent of privacy and confidentiality for this mode of therapy.[125,126,134,140,161,163,165,168,174,177,178,198,200] Depending on the data security protocols in place for any given iCBT application, risks regarding unauthorized access to client data exist at multiple levels: at the therapist's end, at the client's end, and during the electronic transmission of information.[140,164,177,200] To prevent unauthorized access to client data, many suggest that providers of iCBT use a secure user environment that encrypts therapist–client

communications at both ends, password-protected log-ins (with the possibility of pseudonyms to protect users' identities should a data security breach occur), and secure mechanisms for the storage of data.[126,152,164,170,177,200]

Even where robust data security protocols exist to address the aforementioned sites of data insecurity, iCBT applications may remain vulnerable to what are referred to as "dependency insecurities." Dependency insecurities exist because most software depend on a range of external components and applications in order for them to function (e.g., operating systems, Web browsers), which themselves may be vulnerable to data breaches. Such vulnerabilities may render iCBT applications vulnerable to unauthorized access even when the latter's internal security is robust. As such, iCBT applications are recommended to be developed by those with the knowledge and expertise necessary to sufficiently manage data security issues that may arise with applications' external components.[200] Moreover, even when robust data security protocols are installed at the launch of an iCBT application, they may need to be routinely updated as security risks will change over time.[200]

Ultimately, data security in the context of iCBT is of critical ethical importance given the ethical obligation that therapists have to keep any information generated within the therapeutic relationship confidential. **Confidentiality** requires that precautions be taken to respect and safeguard information generated within the therapeutic relationship, and that therapists refrain from disclosing certain information to those outside the therapeutic relationship without the client's expressed authorization, or unless required by law.[201]

Perhaps more than any other ethical issue, concerns regarding the quality and extent of confidentiality in the context of iCBT abound.[118,124-127,130,132,133,135,137-141,151,152,164-167,170,171,174,175,177-180,184,188,198,202,203] First, such concerns are ubiquitous in this context given the aforementioned data security concerns; breaches in data security may translate into breaches in confidentiality. As such, given the inability to issue guarantees against data breaches, providers of iCBT cannot entirely guarantee confidentiality to their clients.[152] While ethically worrisome for any client, this may have particularly problematic implications for those seeking treatment for traumas resulting from combat, the workplace, or abuse. However, unqualified guarantees to protect client confidentiality are likely not possible even in traditional face-to-face therapeutic contexts.

Ultimately, given that risks of data breaches will invariably exist no matter the sophistication of data security protocols and safeguards, a critical risk mitigation measure in this context would involve collecting only the data that is necessary and appropriate to achieve therapeutic objectives.[177,200] Potential harms to clients might also be mitigated by summarizing themes generated from therapy sessions and destroying raw data.[124]

Breaches in confidentiality may also occur in cases unrelated to data breaches, including when client information is intentionally shared with, or sold to, third parties,[140,166] in addition to when client information is disclosed to other parties given therapists' legal obligations. Importantly, data intentionally shared or sold may include that which is actively collected (i.e., through the course of therapy) and that which is passively collected (e.g., location data and social network data collected by the application),[140,153] which may each have many intended uses, including research, quality improvement, and marketing.[200] Indeed, CBT delivered via the internet presents many opportunities to passively collect data that may reveal a great deal of personal and behavioural information, which may be commercially lucrative if sold to third parties. Unless adequately protected and controlled, data brokers may end up indefinitely owning client data and using it for a number of purposes not authorized by the client.[140] To some, this emphasizes the need for informed, user-controlled

data collection.[153] At the very least, it signals the need for iCBT applications and providers to be explicit and transparent regarding the expected collection, use, and disclosure of client information (Respect for Autonomy and Informed Consent section).[140]

Providers of iCBT have the ethical responsibility to safeguard clients from unauthorized disclosures of information generated in the course of the therapeutic relationship.[152] With that said, providers are legally permitted or required to disclose certain information should it arise in the course of therapy, and some information may be subjected to legal subpoena.[137,140,165,198] As such, providers of iCBT ought to take reasonable steps to anticipate the circumstances where information generated while using an app might require disclosure, and ensure that clients are informed of these limits to confidentiality (limitations to disclosure stemming from limitations on client monitoring are described in the Nonmaleficence, Limitations to Client Safety, and the Prevention of Retraumatization section).

The **privacy** of clients using iCBT may be compromised when the confidentiality of their data is breached, and as such many have raised privacy concerns in response to internet-delivered therapies.[118,124-126,130-132,135,140,153,161,168,177,180,184,202] While some wellness applications may escape the scope of privacy legislation (like the Personal Health Information Protection Act), given that much of the information generated via iCBT applications will count as personal health information, much of the information generated from such applications will fall squarely within the scope of such legislation.[124,140] In addition, iCBT administered to clients outside of Canada will be subject to foreign privacy laws (Professional and Legal Issues section).[124] As such, iCBT applications and providers must ensure that the collection, use, and disclosure of personal health information complies with existing privacy legislation in both the therapist's and client's jurisdictions. And, while iCBT applications themselves may come with privacy policies that discuss the measures in place to protect clients' privacy and the limitations of such measures, the presence of such policies may not necessarily mean that measures to protect privacy are in place, or that privacy concerns have been taken seriously and been addressed.[140,204]

Interestingly, despite the many concerns over privacy and confidentiality raised by internet-delivered therapies, the degree of privacy and confidentiality afforded by such therapies might actually be perceived as an advantage over traditional face-to-face therapies. Indeed, given the opportunity to participate in therapy without the knowledge of family and friends, in addition to the opportunity to discuss sensitive topics that might otherwise be difficult in face-to-face settings, internet-delivered therapies may supply a degree of privacy not on offer with face-to-face therapies.[126,167,170,205] Given this possible perception and expectation of privacy and confidentiality, there is arguably an added imperative to ensure that iCBT applications have adequate measures in place to protect the privacy and confidentiality of clients.

Clearly, many limits to privacy and confidentiality are likely to exist in the context of iCBT. As a result, such limits and their attendant risks must be discussed with clients (in the informed consent process and as circumstances change) (Respect for Autonomy and Informed Consent section).[175] Providers of iCBT ought to be transparent with clients regarding who their data will be shared with, what type of information will be shared, how that information will be shared, and the expected use of their data.[126,162,165,170,200,203] Providers who use or recommend an app for iCBT but fail to inform clients of known limitations to privacy or confidentiality could plausibly be held liable based on the failure to obtain proper informed consent (Professional and Legal Issues section).[140] Unfortunately, codes of ethics may be ill-

equipped to adequately guide iCBT providers in these areas. For instance, as Lawlor-Savage and Prentice argue, the Canadian Code of Ethics for Psychologists has been updated in recent years and addresses ethical issues regarding confidentiality and privacy, but it largely fails to "adequately address the increasingly complex relationship between electronic media and psychological practice." (p. 231).[124]

Finally, an idea related to privacy and confidentiality that is of increased relevance in the context of iCBT is that of **anonymity**.[124,131,138,161,175,178,206] Where clients can participate in such therapies anonymously (or where their participation is perceived as sufficiently anonymous or privacy-enhancing), feelings of discomfort, embarrassment, and stigma may be reduced, which may promote treatment seeking and provide clients with increased disinhibition, empowering them to disclose and discuss their deeply personal behaviours, experiences, issues, and thoughts (Justice and Enhanced Access section).[131,178,206] This may be particularly significant in the context of PTSD, where stigma stemming from experiences in war, trauma, and abuse may be especially pronounced, and where military personnel experiencing PTSD have concerns about being seen as "weak" for seeking treatment.[99,207] However, anonymity in internet-delivered therapies may be a double-edged sword; in group-based therapies, for instance, perceived anonymity may decrease social pressure or guilt, which may otherwise discourage clients from compromising confidentiality in these settings.[124] In addition, anonymous participation in any psychotherapy may be problematic for establishing the therapeutic alliance (Trauma-Informed Care, the Therapeutic Alliance, and Trust section), and may present challenges for therapists to fulfill other ethical obligations (e.g., duties to report and warn) (see the Nonmaleficence, Limitations to Client Safety, and the Prevention of Retraumatization section).[138,178,206]

In summary, compromises to privacy and confidentiality may occur in different ways in the context of iCBT as compared with traditional face-to-face therapy,[184] and the prospects of such compromises may affect the uptake of iCBT.[141,167] Given that assurances of privacy and confidentiality are key ethical features of the therapeutic alliance and of ethical mental health practice more generally,[125,208] mechanisms to prevent breaches of privacy and confidentiality are crucial, as is informing clients of any limitations to realizing these values.

Professional and Legal Issues

iCBT should be delivered by trained and qualified mental health practitioners,[124] and these practitioners should practice only within the realm of their expertise.[128] Yet, given its relative novelty, limited training programs, and lack of consistency and regulatory oversight, concerns exist regarding practitioners' competence in using iCBT, that qualified or unqualified providers may outsource their work to other unqualified colleagues,[134] or that the mode of delivery renders it easier for untrained or unqualified individuals to provide such services or otherwise promote themselves as being competent to do so.[138]

While risks related to unqualified or unlicensed providers exist across all treatment modalities, internet-delivered therapies may render it easier to deceive clients in this regard. Indeed, previous studies have found that many providers of internet-delivered therapy may be unlicensed. While not a panacea, one mechanism to better ensure that iCBT providers are trained and qualified to provide such therapy is for them to make their training, qualifications, or credentials transparent and available in any iCBT application.[124]

The competence of therapists in providing iCBT is critical not only for positive therapeutic outcomes but also to fulfill their ethical obligations in practice.[165] For example, lack of competence in monitoring client distress or installing data security safeguards in this

modality may render it more likely that a therapist will be unable to discharge their ethical obligation of nonmaleficence. Yet, therapist competence in providing iCBT is a major concern in the literature.[124,129,132,134,135,137-139,164,165,179,180,184,187] These concerns arise because the skills cultivated through training for traditional face-to-face interactions are viewed as not automatically transferable to the digital environment,[133] and because of the great deal of variability in iCBT applications, which signals the importance of iCBT providers understanding the functions and limits of different applications.[135] Furthermore, because iCBT applications may reach diverse populations, iCBT providers ought to be competent in providing services to clients with different ethnic, racial, cultural, linguistic, geographic, socio-economic, and sexual orientation and gender backgrounds, which may be particularly important in the Canadian context.[124,128,133,135] Ongoing training opportunities to educate future practitioners in competent and ethical iCBT use are particularly important in this area given how such technologies are constantly evolving.[128] Unfortunately, research has found that the majority of online therapists report not having formal training in online therapy during their education.[178] As such, some suggest that it would be reasonable for iCBT providers to demonstrate, perhaps to a licensing board, their abilities to competently practice CBT in a digital medium.[174]

Several professional and legal issues may arise with any internet-delivered therapy given the potential for services to be delivered to clients residing, or who may travel, outside of the jurisdiction(s) within which their therapists are licensed to practice.[132,135,136,141,175] iCBT providers are expected to be aware of and comply with all relevant laws and regulations from both their jurisdiction and their clients' jurisdictions.[131,135,151] In such cases of interjurisdictional practice, legal issues may arise with regard to licensure (i.e., whether providers have legal authority to practice in a client's jurisdiction).[132,133,137,139,171,174,178,188] Issues of licensure may be addressed at a systems level by installing a transferable, national licensing system.[136]

In addition to issues of licensure that may arise when practising across jurisdictions, several other issues may exist with regard to accountability and liability.[130,131,136] For instance, different jurisdictions will have varying legal requirements for permitted and mandatory disclosure (e.g., of child abuse and self-harm).[130,137,167,178] In addition, it is unclear where liability will or should lie if an iCBT provider mismanages a client's condition due to an application providing inaccurate data, or due to a mistake made by a client when using the application.[140,161] What is clear, however, is that failing to consider and address such issues of liability may leave the provider uncovered in the event of an interjurisdictional malpractice lawsuit.[168] With respect to accountability, providing clients using iCBT with the opportunity to raise and have their grievances redressed, and making clients aware of the regulatory agencies and/or professional associations that oversee such grievances may be considered.[137] Yet, the limitations that would be imposed by distance, differing jurisdictions, or the financial resources required to raise and pursue grievances may render these opportunities impractical.[137,164]

Summary of Results and Limitations

Despite a paucity of literature that directly and explicitly engaged in the normative or empirical analysis of ethical issues that can be expected to arise in the context of iCBT for PTSD, this review raised several key ethical issues that require normative reflection. In addition to identifying ethical issues that can be expected to arise in the context of many, if not all, internet-delivered mental health therapies (including limits to privacy and confidentiality, challenges to the informed consent process, and an assortment of professional and legal issues related to professional competence and liability), it has also identified and discussed several ethical issues that pose challenges to the provision, development, and use of iCBT for PTSD in Canada. On this assessment, these ethical issues include the extent to which trauma-informed care (and associated ethical commitments to prioritize client safety and prevent retraumatization) can be sufficiently realized in the context of iCBT, particularly where iCBT is not therapist supported; the consideration and proper balancing of the justice-enhancing and justice-diminishing features of iCBT; and the prospect of a trusting alliance to be established in the context of iCBT such that iCBT providers are capable of effectively fulfilling their ethical obligations. Considered together, while iCBT has the capacity to enhance access to needed mental health services, the justice-enhancing features of iCBT may perhaps only be viewed as virtues where the prospect of increased access extends to those less privileged, and where the therapeutic environment does not entirely eliminate an alliance between the practitioner and the client where ethical, trauma-informed practice is possible.

This review has a number of limitations. As noted at the outset of this section, there is a paucity of literature that directly and explicitly engages in the normative or empirical analysis of ethical issues that can be expected to arise in the context of internet-delivered CBT, let alone iCBT for PTSD, in particular. Common ethical issues may be relevant to all internet-delivered therapies (e.g., confidentiality). Yet, what is left largely unexamined or underexamined in the literature are the potentially unique ethical considerations and issues that may arise in the development and delivery of iCBT, and, in particular, those considerations and issues that arise in the treatment of PTSD via iCBT. Efforts were made in this review to situate frequently cited ethical issues associated with internet-delivered therapies within the context of iCBT and PTSD.

Second, as is typical in ethics literature reviews, the vast majority of the literature identified in this review merely enumerated ethical issues associated with iCBT or, more generally, internet-delivered therapies, and thus failed to actually examine or provide substantive normative analyses of these issues. Thus, many of the ethical issues one would expect to appear in a list of ethical issues associated with anything internet-delivered or psychotherapy-related unsurprisingly emerged (e.g., confidentiality, privacy, informed consent), but they did so with limited insight into to the degree to which their manifestation might be unique (practically or ethically) in the context of iCBT. Efforts were made to synthesize and analyze these findings in order to examine their normative implications for the use of iCBT for PTSD.

Third, while ethical issues and considerations emerging from the perspectives of clients, app developers, organizations, funders, and health regulators were variably raised in this literature, the ethical issues and considerations identified predominantly reflected those that emerge in relation to iCBT providers and the delivery of iCBT. As such, much of this literature was framed in relation to the ethical obligations of providers (e.g., to protect confidentiality, obtain informed consent, and so forth). Efforts were therefore made to

illuminate the ways in which many of the ethical issues and considerations discussed in this report might impact or be viewed by different stakeholders; however, future research exploring the ethical dimensions of iCBT emerging from other stakeholders' perspectives will be important.

Fourth, it must be noted that the ethical issues raised in this report do not necessarily reflect the perspectives of clients simply given the authorship of the literature reviewed. As a result, the literature (and the themes identified in the literature) may tend to reflect the ethical issues, concerns, and perspectives of mental health practitioners, ethicists, or other scholars in this area, and not the ethical issues, concerns, and perspectives of clients. As such, the characterization of the issues and themes discussed may be biased in favour of the sorts of concerns and remedies seen as most important to those who do not necessarily represent the client perspective.

Finally, and as a result of the findings expressed in the prior remarks, many of the ethical concerns raised in the reviewed literature in large part reflect practical, technical, or logistical challenges (e.g., compromises to confidentiality due to the spectre of data insecurity; jurisdictional licensing) that may be addressed with relatively straightforward measures and due attention (e.g., data security protocols and informing clients of limits to confidentiality; creative licensing arrangements across jurisdictions). This is not to say that such ethical issues and their solutions are of little or no importance. Rather, the motivation for this remark is to indicate that, on this assessment, the more intractable ethical concerns raised by iCBT for PTSD have received limited attention. The conclusions drawn in this review should therefore reflect the central ethical issues that do not simply require future technical solutions, but rather require normative reflection.

Implementation Analysis

Research Question

The implementation analysis was guided by the following research question:

- What are issues relating to the acceptability, feasibility, and capacity for implementing iCBT for the treatment of PTSD at micro (i.e., individual living with diagnosis of PTSD and their health care provider), meso (e.g., health care organizations, community mental health agencies, educational institutions), and macro (i.e., provincial, territorial, and federal) levels?

Exploration of this question was guided by three sub-questions:

- What are the current or potential pathways of care for individuals living with a diagnosis of PTSD and where or how could iCBT fit within these pathways?
- Given the existing and potential pathways of care for individuals, what resources and infrastructure would be needed to continue, expand, or optimize its delivery?
- How do stakeholders (e.g., practitioners and current payers) and people living with a diagnosis of PTSD understand the technology of iCBT and its application to the treatment of PTSD, and how could these understandings or perspectives influence the uptake of iCBT?

Study Design

A qualitative descriptive study was conducted to explore the implementation issues associated with the use of iCBT in the treatment of PTSD.

Data Collection

Literature Review

Literature Search Methods

The search for literature describing implementation considerations was performed by an information specialist using a peer-reviewed search strategy according to the PRESS checklist (https://www.cadth.ca/resources/finding-evidence/press). The search strategy is available on request.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–), PsycINFO (1806–), and the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, the Health Technology Assessment database, CINAHL via EBSCO, and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH, and keywords. The main search concepts were iCBT and PTSD.

No search filters were applied. Retrieval was limited to English- or French-language documents published since January 1, 2008. The initial search was completed in May 2019. Regular alerts updated the search until the publication of the final report.

Grey literature (literature that is not commercially published) was identified by searching sources listed in relevant sections of the Grey Matters: A Practical Tool For Searching Health-Related Grey Literature checklist (https://www.cadth.ca/grey-matters),[43] which includes the websites of regulatory agencies, HTA agencies, clinical guideline repositories, systematic review repositories, patient-related groups, and professional associations.

Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with experts and industry, as appropriate. Appendix 1 provides more information on the grey literature search strategy.

Eligibility Criteria

Articles that provide insights on acceptability, feasibility, or capacity issues associated with the use of iCBT for the treatment of PTSD from the perspectives of Canadian patients, health care providers, and decision-makers were eligible for this review. The categories included in the INTEGRATE-HTA Context and Implementation of Complex Interventions Framework,[209] as well as stakeholder consultation were used to sensitize the reviewer to particular points of concern. For example, the issues included although were not limited to the following:

- technical requirements, resource needs, and other operational considerations
- staffing, training, and accreditation or licensing issues (e.g., clinical specialties)
- referral pathways and multidisciplinary patient management schemes
- design of public or private funding programs, including eligibility and prioritization criteria.

Screening and Selecting Articles for Inclusion

English- or French-language documents meeting the previously noted eligibility criteria were considered for inclusion in this analysis regardless of publication type, although conference abstracts were excluded. The titles and abstracts of the retrieved citations were screened by a single reviewer in Endnote. First-level screening excluded all citations that are not primarily about or include substantive discussion about iCBT, particularly in relation to the treatment of PTSD. Full texts of all remaining potentially eligible citations were then screened by the same reviewer using the eligibility criteria.

Stakeholder Consultations

To gain a better understanding of the context and relevant issues of implementing iCBT for PTSD in Canada, we consulted with stakeholders representing various levels of decision-making and health care delivery in mental health.

CADTH's Implementation Support and Knowledge Mobilization team identified potential stakeholders through existing CADTH networks and other relevant national or provincial stakeholder groups using a purposive sampling strategy. The goal was to obtain a sample of stakeholders that is inclusive of the range of decision-makers involved in the delivery and use of iCBT for PTSD in Canada. Potential participants included policy-makers (e.g., at the ministry level), clinicians (e.g., psychologists, psychiatrists, and social workers), researchers, insurance providers, online platform developers, and administrators of health care facilities across Canada. Representatives of national groups of interest such as Veterans Affairs Canada, police, and other first responders were also approached. We continued with stakeholder consultations until no new information was emerging (i.e., data saturation); however, sample size was ultimately limited due to time and resource constraints.

The consultations were facilitated by two CADTH staff members, a knowledge mobilization officer and a qualitative research officer, and a semi-structured interview questionnaire was used to guide the discussions with stakeholders around the context and implementation of iCBT for PTSD in Canada. Depending on which stakeholder we were speaking with,

questions touched on areas such as how PTSD is currently cared for in the stakeholder's jurisdiction, what sort of conversations or concerns are currently surrounding the use of iCBT for PTSD, has iCBT for PTSD been used in their jurisdiction already, and how will or does funding for iCBT currently happen.

Stakeholders were asked to provide informed consent on the purpose and process of the consultations as well as permission to use any relevant information they provided as part of the final HTA results.

Data Analysis

The findings of the literature review, stakeholder consultations, and information from the analyses of other sections of this HTA were synthesized using a framework approach.[210]

A framework approach involves a five-stage process to data analysis: familiarization, indexing, charting, mapping, and interpretation. While analysis was led by the primary reviewer (the qualitative research officer), conversations with a second reviewer as well as the project's knowledge mobilization and patient engagement officers provided clarity and depth to the analysis.

Stage 1: Familiarization

Familiarization involved gaining an understanding of the breadth, richness, diversity, and range of stakeholders, perspectives, and types of data and findings before any sorting or categorizing. This process is akin to the qualitative approach of immersion in the data, which enables the research team to be oriented and versed in the breadth of available material prior to analysis. Familiarization was done through team discussion, review of the retrieved literature and draft reports from other sections of this HTA, and stakeholder consultations. During the process of familiarization, the researchers aimed to draw out any initial ideas and concepts through diagramming, memoing, and discussion. Categories included in the Context and Implementation of Complex Interventions Framework were also used to aid in the development of these ideas and concepts, though not as strictly followed as the primary categories of import.

Stage 2: Identifying a Thematic Framework

This stage involved returning to the key concepts and ideas that started emerging during the familiarization stage, and setting up a framework with which the data were sorted for analysis. The framework was guided by the research questions and allowed for implementation issues to be mapped across the pathway of care, by levels of implementation (i.e., micro, meso, and macro), and by stakeholder perspectives (e.g., patient, provider, and health care system).

Stage 3: Indexing

This stage involved applying the framework to the results of all data sources. Attention was paid to who raised the issue, the potential implications of the issue, and potential solutions.

It was possible that more than one concept or idea was applied to a piece of text or single passage to allow full exploration of the relationship of themes within the data. While applying a framework involves using researcher judgment to explore the meaning and significance of the data, indexing provided transparency to this process. During indexing, changes were made to the framework to improve its clarity and relevance to research objectives.

Stage 4: Charting

The process of charting involved the visualization of the data as a whole set. Ritchie and Spencer describe charts as such: “Charts are devised with headings and subheadings which may be drawn from the thematic framework, from a priori research questions, or according to considerations about how best to present and write up the study.” (p. 182).[210]

Charting helped to visualize the data across cases or themes; data were sorted into charts based on key ideas or concepts. This process aided in comparing and contrasting key findings across data types and sources (e.g., literature, stakeholder interviews, and other HTA results and analyses).

Findings from the literature review, stakeholder consultations, and information from other sections of the HTA were mapped onto this framework, progressing through the steps of indexing and charting using memoing and diagramming.

Stage 5: Mapping and Interpretation

This stage involved mapping and interpreting the analytic results of the previous stages to describe the implementation issues (including acceptability, feasibility, and capacity considerations), across the pathways of care (i.e., diagnosis, treatment, outcome, follow up) and by perspective (i.e., patient, provider, payer). Mapping and interpretation were supported by frequent discussion among researchers involved in all components of the implementation analysis and through larger team discussions.

Results

Literature

We engaged with literature that included clinical guidelines for PTSD care,[211-215] not-for-profit reports focused on the states of mental health care and digital literacy in Canada,[216,217] policy documents highlighting strategic plans for PTSD care across Canadian jurisdictions, academic literature situated around iCBTs,[218,219] and other analyses conducted as part of this HTA.

Stakeholders

We spoke with fifteen individuals that represented eleven stakeholders groups, which included program developers, care providers and payers for military personnel, private insurance providers, public safety personnel (e.g., firefighters), and PTSD researchers.

Summary of Findings

There may be a role for a regulatory framework or licensing body oversight in terms of what qualifies as an iCBT and how this is determined or evaluated. As such, a blanket recommendation or set of policies for iCBTs (as generally understood) may not be appropriate.

To understand the potential benefit (or not) of an iCBT program developed to treat individuals living with PTSD, it is important to first understand what qualifies as an iCBT and the intended goals or objectives of these programs. As the name implies, a straightforward definition of iCBT would simply indicate that iCBTs are CBTs delivered via some form of online mediation. These programs can be guided, unguided, or a mixture of both, and while communication with providers tends to be asynchronous, some programs may provide the

opportunity for live communication via telephone, online messaging, or the occasional face-to-face meeting.[219] Providers can range from technicians, peer mentors, or paraprofessionals trained in specific iCBT protocols, to social workers or fully accredited psychologists experienced with a range psychotherapies.[219]

In any of these scenarios, an iCBT program is meant to be understood as drawing on the tenants of CBT to successfully treat individuals living with clinically defined mental health disorders. This begs another question: What are CBTs? Cognitive behavioral therapy refers both to a theoretical orientation in psychology and a number of therapeutic approaches situated within this theoretical orientation.[220] As such, while CBT as a therapeutic approach may be diverse, CBTs share the following three propositions: cognitive activity affects behaviour, cognitive activity may be monitored and altered, and desired behaviour change may be effected through cognitive change. (p. 4).[220] Even so, how approaches are meant to work on the problem or disorder at hand (in our case PTSD) can vary.

Generally, according to the APA, when using CBT to treat PTSD, the work tends to include elements like psychoeducation and stress management, evaluation and correction of maladaptive thought patterns (i.e., cognitive restructuring), and re-exposure to trauma narratives.[212] Which elements are used, how they are used, and when they are used may vary across CBTs or according to the provider and patient's needs or desired course of action.[212] For example, in the International Society of Traumatic Stress Studies' (ISTSS) 2019 update to their guidelines for the prevention and treatment of PTSD, their strong recommendation for individual CBT with a trauma focus (CBT-T) includes nine subgroup therapies as distinct as virtual reality therapy and CPT.[211] While these, and the remaining seven therapies, may have similar aims and objectives, how they go about achieving them are distinct.

Guided internet-based CBT-T qualifies as one of the therapies subsumed within ISTSS's broad CBT-T category. That being said, the provided definition is circular and refers to it as a CBT-T with less therapist interaction than traditional face-to-face CBT-T,[211] which raises the question again — What is iCBT (trauma focused or not)? A quick look at other guidelines or recommendations does not clarify the definition. Similar to the ISTSS, the APA notes in its 2017 guidelines for the treatment of PTSD that the included trial evaluating internet application of CBT[69] was considered a match "for the recommendations for efficacy of CBT." (p. 53).[212] The Veteran's Affairs guidelines, which do cite weak evidence in their recommendation of guided iCBT (trauma focused or not) as an alternative to no treatment,[214] do not provide a definition of iCBT. They do, however, qualify this recommendation by stating that "clinicians should carefully review the content of any Web-based materials to ensure their accuracy and ethical application before recommending their use to patients." (p. 70).[214] Phoenix Australia follows a similar course in its recommendation of iCBT.[213] England's National Institute for Health and Care Excellence's updated 2018 guidelines include no recommendations on iCBTs (trauma focused or not).[215]

While the scope of this analysis is not to provide a detailed and definitive overview of what does or should qualify as an iCBT meant to treat PTSD, it is important to note that some stakeholders were concerned with the ambiguity surrounding iCBTs and PTSD — particularly how exposure elements may come to bear on asynchronously delivered iCBTs. As such, it seems important to consider the diversity of CBTs (particularly CBT-Ts) meant to treat PTSD and the variety of ways in which common elements may be used or engaged differently throughout iCBT programs.

This is notable in light of the heterogeneity of interventions included in our own clinical review. Out of ten included studies, there were at least seven different, self-described iCBT programs (i.e., we did not classify programs as iCBT or not, but rather accepted the descriptions provided by primary study authors) that varied in things like treatment duration and number of treatment sessions or modules. While the presence of diverse iCBTs is not problematic in and of itself (and may even be considered valuable by patients seeking out tailored treatment), some stakeholders were concerned with the possible proliferation of apps or programs being pitched as founded on the tenants of CBT without any clear evaluation of their effectiveness.

As such, and due to other inconsistencies across programs in areas like safety standards (e.g., privacy and confidentiality) or diverse jurisdictional requirements in professional credentialing (e.g., paraprofessionals, registered social workers, or licensed psychologists), it could be important that a regulatory framework or licensing body provide oversight in these areas, among others (e.g., necessary components of iCBTs, and appropriate assessment and referral components). The ethics analysis included in this HTA describes similar concerns and finds that even were a regulatory body in place, more research would need to be conducted to detail issues such as which elements of an iCBT provide therapeutic effect.

iCBT interventions will not be appropriate for everyone presenting with PTSD. Whom they are appropriate for will be dependent upon factors such as the severity and form of PTSD, patient goals, and the presence of comorbidities.

Severity and Form of Post-Traumatic Stress Disorder

Some stakeholders reflected that iCBTs may not be appropriate for people with more severe forms of PTSD or for those individuals living with forms of PTSD associated with feelings of moral injury or guilt as the complexity of their trauma was imagined as outside the reach of exposure elements traditionally included in CBT interventions. While it is unclear if these stakeholders imagined CBTs as unable to address complex trauma generally, a position statement on complex trauma released with the 2019 ISTSS guidelines suggest that it is possible that established treatments like many CBTs (inclusive of exposure elements) could be beneficial with some adaptation.[221] What this means for iCBT is currently unclear.

Patient Alignment With Treatment Goals

There is a need to ensure that iCBT is offered to those patients who have treatment goals congruent with those possible through iCBT. As noted in the perspectives and experiences review conducted as part of this HTA, it is not simply a question of whether patients have the appropriate skill sets in place to engage in therapy — there is also a need to ensure a fit with what they are seeking from treatment and their understanding of what treatment might be asking of them. Some stakeholders indicated that part of this alignment could involve understanding where patients feel comfortable receiving care and noted that many patients may feel more comfortable accessing iCBT on their own time at home.

Presence and Form of Comorbidities

Several stakeholders consulted for this review suggested that there is little consensus among practitioners of the appropriate approach to treatment for people living with comorbidities. As such, some of the suggested options include to treat in tandem with multiple interventions, treat in tandem with a transdiagnostic intervention, or treat in succession with multiple interventions. To further demonstrate treatment uncertainty, of the 10 primary studies included in CADTH's clinical review, six excluded individuals with active

suicidal ideation, seven excluded individuals with either substance dependence or substance abuse, and one excluded patients with severe major depressive episodes.

Where iCBT for PTSD could fit into a current care pathway depends largely on what gap(s) iCBT is meant to fill in terms of mental health care.

Stakeholders identified four potential places where they perceived that iCBTs may be useful: prevention, assessment and triage, first-line therapy, and maintenance therapy. Of note, all but one place the potential for exposure therapy outside of an iCBT. While it is understood that PE elements are typical components of CBTs meant to treat PTSD, there is some discomfort around the safety an individual undergoing exposure therapy at a distance without face-to-face or synchronous therapist support.

Prevention

Stakeholders representing private insurance programs spoke to the possibility of iCBTs being available as an early prevention tool. From their perspective, iCBTs could be offered as part of a routine suite of services that individuals access at their discretion, and/or following potentially traumatizing situations (particularly for public safety personnel like firefighters, police, and paramedics). Used as a prevention tool, the idea was that iCBTs could catch individuals struggling to manage traumatic experiences early enough to prevent the development of clinical PTSD and thereby potentially averting financial costs associated with disability leave.

In cases where insurers are considering this model for depression and anxiety, the iCBTs being engaged seem focused around return-to-work protocols. It is unclear whether insurers would similarly be interested in iCBTs for PTSD that incorporated return-to-work protocols. That being said, when this was described as an option, attention seemed largely focused on the ability of iCBTs to quickly address symptomatic problems associated with PTSD rather than the trauma itself. This makes sense coming from insurance schemes whose customers are employers rather than employees.

While it does seem there is some evidence for the clinical effects of prevention strategies using other interventions (e.g., CPT and PE), as noted in the National Institute for Health and Care Excellence's guidelines for the treatment of PTSD,[215] how this translates to iCBTs is uncertain. We did not address this in our own clinical review.

Assessment and Triage

Stakeholders repeatedly articulated wait-lists as one of the primary concerns for delivering effective PTSD care. Long wait-lists were identified as, in part, tied to ineffective and inefficient triaging strategies. As many people living with PTSD in Canada undergo assessment through someone other than a specialist, upon referral to a specialist it is possible that some individuals are "lost" to treatment due, at least in part, to subsequent wait times. Providing access to iCBT programs with built-in assessment procedures was identified as a possible way to break up these wait-lists as patients could follow assessment with rapid triage to the iCBT program if appropriate for that individual.

For some, the potential for iCBTs to be used in this manner was couched within an understanding of CBTs for PTSD that described three distinct phases of treatment. In the first, there is no work on the actual trauma itself, but instead the focus is placed on psychoeducation and developing affect management skills and healthier coping techniques. In the second, individuals work through their trauma by way of imaginal or in vivo exposure.

In the third, the focus is placed on relapse prevention and getting back into life. Though not delineated in the same stepwise manner, this seems to align with the APA's understanding of the use of CBT for PTSD, wherein providers engage in various levels of psychoeducation, cognitive restructuring, and exposure to trauma narratives.[212] Due to variability in the protocols across the CBT-oriented interventions noted previously, we assumed this was a fair categorization of the phases of CBT, though certainly not one that is representative of all CBTs.

With these phases in mind, some stakeholders suggested that iCBTs could provide a strong alternative to standard face-to-face treatments for those who need to build up their skills and techniques throughout this first phase. It was further acknowledged that some individuals may never make it past the first stage, but developing a strong set of skills there can still help them live more comfortably. Moving individuals straight from assessment and directly into this first phase was considered advantageous for two reasons. One, individuals that only need, or primarily need, psychoeducation and skill building work could do this under therapeutic supervision while simultaneously freeing up their spots on waiting lists for face-to-face therapy with specialists. Two, this had the added effect of allowing the possibility of face-to-face therapy to really focus in on the trauma work that is common to CBTs for PTSD.

First-Line Therapy

Similar to how assessment and triage are identified, many stakeholders articulated that it could be appropriate to suggest the use of iCBT for patients who were either at a distance from and unable to seek standard face-to-face care, or they declined standard care. While many acknowledged the limited state of evidence on the use of iCBTs for PTSD, some stated the opinion that providing some treatment was better than providing no treatment.

Step Down From Face-to-Face Therapy and Maintenance Therapy

Again, similar to the way the three phases associated with CBTs for PTSD are described for assessment and triage, some stakeholders suggested that iCBT could be a beneficial addition to provisions offered following standard care. For those who have already gone through a trauma-focused therapy but want to re-engage with symptom control strategies, iCBT was seen as providing a possible "refresher."

Which professionals are deemed appropriate to provide iCBTs is tied both to where it is proposed to fit in a care pathway and what professions payers are willing to engage.

While stakeholders generally agreed that both licensed psychologists and registered social workers were appropriate to provide iCBTs with the goal of alleviating resourcing concerns, some stakeholders noted that there is currently a discussion around the role of the social worker in the provision of care. While none of the stakeholders included in this review were uncomfortable with using social workers to provided iCBTs themselves, it was indicated that some other stakeholders may be unfamiliar with the current reality that social workers with certification in CBTs are already able to provide them.

There is a need for more comparative research around active comparators.

By and large, stakeholders agreed that prior to providing iCBT as standard first-line option, more research is needed to compare iCBTs with active interventions like face-to-face CBT. This resonates with the findings of the clinical review, which did not identify any includable studies comparing iCBTs for PTSD with anything other than inactive comparators or other

internet-based interventions, including wait-list and i-non-CBT controls. As has been noted previously in this analysis, the limited research around iCBT was not restrictive for all stakeholders as many thought iCBT would be better than nothing if evidence were available that demonstrated its effectiveness over wait-list.

In order for iCBTs to be successfully implemented into care for PTSD, several structural concerns may need to be addressed.

These include structural concerns around the "digital divide" in Canada, IT control around data security (e.g., privacy and confidentiality), and funding or provision fragmentations inherent in Canada's two-tiered mental health system.

Digital Divide

While stakeholders generally felt that digital literacy has developed to the point that iCBT programs may easily be implemented in most circumstances, it is important to recognize that neither digital literacy or access to online technologies are equal across Canada's diverse geography.[216]

Though stakeholders recognized iCBTs technological foundations as able to facilitate better access to care, some who had experience with telehealth noted that while program interruptions had been minimal, when they occurred, they had the potential to be very disruptive to treatment.

A recent Brookfield report on the status of digital literacy in Canada describes access to technological hardware, software, and the internet (all important for iCBTs) as "deeply intertwined with income/wealth, geography, and other socio-economic factors including housing stability." (p. 44).[216] As the value of iCBTs is often articulated along the lines of access, it is important to consider who might not be able to access this sort of intervention and how that might influence the equitable distribution of care for PTSD (of note, the Ethics Analysis section also contains a discussion on equity and access).

Data Security

As online technologies, iCBTs are vulnerable to privacy and confidentiality concerns that could potentially limit their scope, reach, and ethical use (see also Ethics Analysis section).

Stakeholders engaging with the potential to develop and provide iCBTs internally, rather than through a third-party provider, suggested that data security could be easily resolved in light of the security measures that are already employed in such instances as online banking and alternate modes of telehealth. As such, the primary concern was not how to address online security, but rather how to instigate this growth and the development of strong IT measures inside of institutions described as risk averse. Some stakeholders felt that risk assessments focused on the potential for security or data breaches failed to engage with the risks posed to individuals who may not be able to access care were iCBTs not available.

Where iCBT providers are external to the paying institution, concerns with data security may be resituated on how client information will be used (e.g., shared with or sold to third parties) in addition to standard concerns with storage security. As raised within the ethics analysis, it is clear that providers have an ethical obligation to protect their client's information and mechanisms to protect this information would need to be in place prior to the provision of an iCBT program.

This is connected with previously articulated concerns around establishing a regulatory framework that would be able to evaluate data security of a given iCBT prior to approving public use and distribution.

Funding and Provision

While concerns around the stigma of attending face-to-face therapy or the burdens associated with taking time off work and travelling to therapy may well be addressed through the implementation of iCBTs, it is possible that structural pressures associated with face-to-face delivery of mental health care across Canada may not be rectified by providing online forms of access to care. As such, in Canada's two-tiered system oriented largely around private access (e.g., out-of-pocket or employer insurance benefits) to mental health care[217] there is a need to consider who might actually be able to access iCBTs.

Were iCBTs for PTSD considered a viable option for treatment, individuals who are unemployed and not receiving disability benefits, for example, may face the same financial challenges in accessing care as are already present in face-to-face treatment strategies. To fulfill iCBTs claims of improving access to mental health care, alternative funding models may need to be considered.[217]

Discussion

Treatment Impact

In general, in patients aged 16 years or older with a primary diagnosis of PTSD, there was evidence for the effectiveness of iCBT in comparison with wait-list with respect to severity of PTSD symptoms, depressive symptoms, anxiety symptoms, and quality of life. While there was evidence for a statistically significant improvement in the severity of PTSD symptoms with iCBT compared with wait-list or usual care alone, this did not translate into a clinically meaningful change (using MCID values from the literature). There were no statistically significant differences between treatment with iCBT and i-non-CBT interventions with respect to severity of PTSD symptoms. The magnitude and precision of the results were uncertain given the limitations of the available literature (e.g., very low-quality evidence, and heterogeneity of included iCBT programs and patient populations). No evidence was identified that directly compared treatment with iCBT with face-to-face CBT or other psychotherapies; therefore, the comparative clinical effectiveness of iCBT and face-to-face psychotherapies is unknown. Overall, the findings of the clinical review suggest that iCBT may be more effective than wait-list or usual care for adult patients with PTSD.

The results of the clinical review impacted the approach taken in the economic evaluation; the economic model mirrored the comparisons for which there was evidence from the clinical review. Overall, the results of our economic evaluation found that iCBT dominated no additional treatment (i.e., iCBT was less costly and more effective). These results were likely driven by the low cost of treatment and the extrapolation of the impact of iCBT compared with no additional treatment over a lifetime time horizon, as much of the estimated QALY (more than 93%) gains were observed beyond the first year of treatment. These results should be interpreted with caution given the limitations of the underlying clinical data, as well as taking into account the assumption necessary to apply treatment effects to the model (i.e., the SMD identified in the clinical review corresponds to equivalent differences in remission rates).

It is worth noting that the clinical review found that participants treated with iCBT were at a statistically higher risk for dropout than those allocated to wait-list or usual care groups (RR [95% CI] = 1.39 [1.03 to 1.88]). In total, the dropout rate for all participants treated with iCBT in the reviewed studies was 25.1% (93 out of 370) versus 18.6% (53 out of 285) for patients allocated to wait-list. The mechanisms driving this increased risk of treatment discontinuation in the iCBT group remain unclear, but may be partially attributable to poorly developed therapeutic relationships within treatment or divergent treatment goals. The value placed on the therapeutic alliance were highlighted throughout the qualitative and ethics literature, stakeholder consultations, and patient engagement. As such, investigating how or where iCBTs may foster and contribute to a sustained therapeutic relationship developed along the principles of trauma-informed care may, in the long run, help to ameliorate difficulties with dropout rates and clinically insignificant treatment effects over wait-list controls.

The value of therapeutic alliance is further supported by the reported different treatment effects observed between guided (i.e., therapist provides support throughout the program; e.g., therapist guided, clinician guided, coach guided) and unguided (i.e., no therapist support; e.g., self guided, self help) iCBT. Two studies included within the clinical review examined the use of an unguided iCBT program (PTSD Coach) and did not identify statistically significant differences in PTSD symptoms between this program and wait-list controls. While there was no formal sensitivity analysis conducted as part of the clinical review on the role of therapist support, this does seem to align with the value placed on therapeutic relationships across the qualitative and ethics portions of our review. Scenario analyses assessing the cost-effectiveness of guided or unguided iCBT compared with no additional treatment found that the psychotherapy was no longer dominant to usual care (i.e., less costly and more effective) when the intervention was unguided iCBT. This evidence suggests that the cost-effectiveness of iCBT may differ depending on whether guidance is provided as part of the intervention.

Other factors that may contribute to the overall impact of treatment with iCBT include the content and procedural elements of an iCBT program (e.g., the provision of psychoeducation materials, relaxation exercises, cognitive restructuring of maladaptive thoughts, exposure therapy). Engaging in treatment for PTSD, particularly through interventions that include exposure elements like many iCBT programs, can be quite difficult and challenging for many individuals. One publication comparing different elements of an iCBT program is the RCT by Spence et al.,[65] which investigated the efficacy and safety of the same guided iCBT program with and without exposure components for the treatment of adults (aged 18 years of age or older) with a principal complaint of PTSD. The authors found no significant differences between the exposure and no exposure treatment groups on any monitored safety or effectiveness outcomes throughout the trial.[65] Note that this study[65] was not formally included in the clinical review because the comparison of one type of iCBT versus another iCBT did not meet the inclusion criteria, and its findings should be interpreted with caution due to its methodological limitations (e.g., open-label nature and relatively limited number of participants). Given the limited research on the different elements that would increase the success of an iCBT program, further research is required.

Place in Therapy

Various stakeholders consulted as part of the implementation analysis were keen to note several places within the care pathway where iCBTs may be considered for adoption. While these did seem contingent on what sort of care provision gaps iCBTs were meant to fill (e.g.,

long wait-lists, extended disability leave, options for rural clientele), suggestions ranged from prevention following potentially traumatizing experiences (though it should be noted that our review did not examine the effectiveness of using iCBT preventatively) to first-line therapy for rural patients or those expressing an interest in receiving iCBT. Some stakeholders described the possibility for iCBT programs that include assessment and triage to help create efficiencies within PTSD care and suggested that there may be value in placing them earlier within the care pathway. That being said, the placement of iCBT within the treatment pathway for PTSD was often couched within a larger concern for patient safety given the potential exposure elements of iCBTs. One suggestion for navigating this concern around exposure was to begin treatment by providing iCBTs that focused primarily on elements such as psychoeducation and emotional regulation without the necessity for patients to then engage in exposure elements. Clinical and economic evidence regarding the optimal role and place of iCBT in therapy are limited. While primary studies in the clinical review included participants with wide-ranging time since the index trauma (e.g., six months to 10 years), studies did not explicitly describe whether participants were using iCBT as a first-line therapy or whether they had previous experience with psychologic or pharmacologic treatments for PTSD. The economic analyses therefore did not specify whether the patient population was seeking iCBT as first-line or subsequent lines of therapy and could not assess the specific cost-effectiveness of iCBT in each of its potential places in the line of therapy. The potential clinical and cost-effectiveness of iCBT delivered within a stepped-care model (e.g., iCBT followed by face-to-face CBT) is not addressed within this review.

This concern for various components of iCBTs and when or how they might be appropriate for various patients was not surprising given the importance placed on engaging in trauma-informed care within the PTSD literature. As a central tenet of trauma-informed care is the prioritization of client safety and being sensitive to client “readiness” to begin therapy in order to avoid retraumatization, it seems that the initiation (and placement) of therapy via iCBT should only proceed following a rigorous assessment of client readiness in order to prevent harm (notably, retraumatization). Given that client readiness is closely associated with clients’ unique traumatic stressors and stress symptoms, it may be difficult to assess client readiness and initiate treatment without therapist support if there is not a mechanism whereby therapist refer patients to treatment. When it was assumed that all patients would receive a referral to iCBT in a scenario analysis of the economic model, iCBT continued to dominate no additional treatment, indicating that iCBT would likely remain cost-effective compared with no additional treatment should this be a requirement. The act of clients revisiting their traumas may require paying special attention to whether and when clients are ready to explore past abuse or trauma, at what speed they wish to explore past abuse or trauma, and so forth. From this, it is possible to suggest that iCBT could supplement therapist-supported treatment, but perhaps not entirely replace it.

Access

In the implementation review, it was apparent that iCBTs are assumed to improve access to treatment due to their online form of mediation. This assumption becomes problematic, however, when considering the realities of a digital divide in Canada that tends to be demarcated along geographic boundaries and socio-economic factors such as housing stability. Disparities in download and upload speeds across regions of Canada or the distribution of electronic devices capable of accessing the internet have the potential to disrupt iCBT delivery and should be taken into account when considering where and for whom iCBTs might be appropriate. This disparity is exacerbated by current modes of funding and providing mental health care services across Canada. As the majority of

Canadians accessing mental health care presently do so through employer-provided insurance schemes or as an out-of-pocket expense, were iCBTs considered optimal those without these resources may still be unable to access them without reimbursement or coverage from public payers.

As such, despite its internet mode of delivery, iCBT is not necessarily more accessible, convenient, or appropriate than traditional face-to-face CBT simply due to the fact that it may reduce common barriers to access. In order to make substantial gains in an area where there is a significant unmet need, and to not entirely work against the access-enhancing features of iCBT, careful attention ought to be paid to introducing mechanisms (such as public coverage) that would meaningfully enable underserved, marginalized, and vulnerable individuals and populations to access the benefits of iCBTs well supported by empirical evidence.

Aside from these structural components and concerns regarding access, it is important to consider the assumption that clients who cannot access traditional face-to-face CBT should at least have the option to access iCBT. Even where iCBT's effectiveness is doubted or uncertain, some may propose the use of iCBT in these populations because "some therapy is better than no therapy." Indeed, given the burden of unmet need faced by those experiencing PTSD in Canada, such an argument may have some merit, as supported by the findings of the Clinical Review and Economic Evaluation sections. However, such an argument is dubious in its own right (i.e., "some therapy" will often not be better than no therapy if "some therapy" is ineffective) and may run counter to a therapist's obligation to do no harm considering the absence of evidence exploring whether iCBT has the potential to retraumatize clients.

Special Considerations

The studies included in the clinical review recruited participants from diverse backgrounds who had experienced various types of trauma, including war or terrorism-related trauma, sexualized trauma, physical assault, torture, traumatic childbirth or stillbirth, life-threatening illness or injury, and trauma resulting from natural disasters. Despite this, the clinical review was unable to investigate the appropriateness of iCBT in many specific populations (e.g., immigrants; refugees; First Nations, Inuit, and Metis' populations; people living with disabilities; people of diverse genders and sexual identities) due to the limited quantity of identified literature. This is a limitation given the reality that trauma and responses to trauma typically occur within a cultural context and to provide trauma-informed care is to "understand clients and their symptoms in the context of their life experiences and cultures."[195] As such, a failure to meaningfully adapt treatment to client characteristics and identities such as language, culture, religious beliefs, Indigeneity, sex, sexuality, gender, individual traumas, or comorbid symptoms may represent a failure in providing trauma-informed care.

Not only this, but what it means to make something "culturally appropriate" may have as much to do with how care happens (e.g., who is the provider, where does it happen, on which cultural grounds is it based) as it does with the material included in a program. One study[110] included in the perspectives and experiences review that examined how Western modes of healing for sexualized trauma are incorporated into traditional Anishnawbe modes of healing describes cultural appropriateness as situated within a thorough understanding of the contextual factors of trauma. Providers in this study described the importance of working through histories of ongoing colonial aggression in Canada and demonstrating the way in

which historical traumas enacted through this aggression are related to and provide a stage of sorts for an individual's present trauma.

Additionally, it was not possible to make specific conclusions regarding the effectiveness or cost-effectiveness of iCBT for individuals who had experienced various types of trauma (e.g., natural disasters, sexual abuse, medical injury, historical trauma, sudden and unexpected loss of a loved one, domestic violence, military or terror-related trauma, repeated trauma, interpersonal trauma) due to the limited evidence in these populations, precluding the planned subgroup analyses in the clinical review and the economic evaluation.

The type of trauma may also play a role in the implementation of iCBT programs. In clients who have experienced work-related trauma, the ability to adequately monitor and assess client "readiness" to return to work (e.g., first responders), combat (e.g., military personnel), or otherwise, may be particularly important in the context of PTSD — which can also have implications for clients' long-term disability or compensation claims — which may be limited without therapist support or adequate monitoring and assessment mechanisms in the iCBT application.

With all of this in mind, our central concern ought to be whether iCBT is in the best interests of clients experiencing PTSD. This would require that therapists weigh the benefits and risks of iCBT generally, as well as specifically, for their particular clients. Where evidence of iCBT's effectiveness for PTSD is limited or simply uncertain, it would be ethically troubling for a therapist to refer a client to iCBT as they cannot be confident that it would be in their best interest. Even in the absence of therapist referral, the availability or public coverage of iCBT may suggest to clients that it is at least potentially in their best interest, which would be problematic given the limited evidence base.

Generalizability

In general, the studies reviewed as part of the clinical review included study participants, care providers, and health care settings that appear to be representative of the "real world" and did not apply inappropriate or excessive patient exclusion criteria. For example, participants with cormorbid depression or anxiety were generally accepted into the clinical trials, and care providers were reflective of those who would treat individuals with PTSD in practice (i.e., mental health professionals with training in the provision of CBT). Though these factors give some confidence in the generalizability of the findings, a majority of the studies relied on participant recruitment through advertising campaigns (in newspapers, websites, university campuses, or primary care centres). This method of self-referral may have selected for a motivated subset of individuals with PTSD who were more likely to complete iCBT programs and to apply their learning in their lives. Additionally, none of the primary studies were conducted in Canada; however, the majority of the evidence was from developed countries (e.g., the US, Australia, Sweden, the UK), and is likely to generalize to the Canadian context. Individual study populations were comprised of individuals who had experienced war- or terrorism-related trauma (four studies[54,66,68,71]), females who experienced sexual trauma (one study),[70] and diverse populations that did not restrict their inclusion into the study by type of trauma (five studies).[52,53,55,67,69] There were no studies specific to first responders, young adults (e.g., participants between 16 and 21 years of age), individuals with repeated trauma, Indigenous populations, refugees, immigrants, or people living with disabilities; therefore, the generalizability of the findings summarized in the clinical review to these populations is unclear.

The data used to populate the economic evaluation were the best data that could be identified. Despite the limitations associated with the clinical evidence, as previously noted, the analysis likely represented the average Canadian patient with PTSD who is motivated to seek out treatment. That being said, it is important to remember that treatment for PTSD is highly individualized and some patients may not be as motivated. As such, the results for iCBT compared with no additional treatment from the base case may not be generalizable to all patients with PTSD.

As none of the studies included in the perspectives and experiences review focused specifically on engagements with iCBTs for PTSD, it is possible that some distinctions of engaging in care through this modality have been missed and that the emphasis on relationships found in this review may not apply to all patients (or providers) interested in iCBTs. This does not necessarily limit the finding of relationality, but rather points to the general importance of tailoring iCBTs (or other PTSD interventions, for that matter) to the individual patient to the extent that is possible.

The implementation analysis was comprised of consultations with Canadian stakeholders and included input from Canadian literature. As such, the analysis is generalizable to the Canadian context, though it should certainly not be understood as providing a complete picture of stakeholder perspectives.

Limitations and Sources of Uncertainty

The findings of the clinical review should be interpreted with consideration for the substantial limitations and sources of uncertainty that exist. To start, the quality of the evidence was rated as “very low” for eight outcomes and as “low” for one outcome (dropouts for the comparison of iCBT versus wait-list or usual care, which favoured the wait-list or usual care group) using the five GRADE considerations. Each of the included primary studies were rated as being at a high or unclear risk for several types of bias, most notably performance bias due to the open-label nature of all included studies and selection bias due to poor reporting on the methods of allocation concealment. In general, it is expected that the risks of bias described as part of quality assessment may have potentially overestimated the treatment effects of iCBT. In addition, although the meta-analysis suggested that treatment with iCBT resulted in statistically significant improvements in PTSD symptom severity compared with wait-list, further exploration into this finding suggested the difference was not likely to be clinically significant. The clinical significance of other outcomes of interest (e.g., severity of depressive symptoms, severity of anxiety symptoms, quality of life) were not investigated due to the expected limited availability of literature regarding clinically important differences on the remaining outcome scales in populations diagnosed with PTSD.

There was substantial clinical heterogeneity in the clinical review. Specifically, sources of heterogeneity included differences across studies in population characteristics (e.g., age, sex, baseline symptom severity, trauma type, and context), iCBT interventions (e.g., level of therapist guidance, type of therapist guidance, therapist training and credentials, type of CBT, type of device used to access iCBT), outcomes (e.g., scales used to assess PTSD severity or depression severity), and duration of follow up (which ranged between five weeks[68] and six months[71]). It is unclear which components and features of iCBT programs or which specific iCBT programs (e.g., DESTRESS, the From Survivor to Thriver Program) may be most beneficial to patients.

The findings from the economic evaluation suggested that iCBT was cost-effective for the treatment of PTSD when compared with no treatment, though there were a number of

limitations with the model contributing to uncertainty with the obtained estimates of cost-effectiveness. There was considerable uncertainty with the clinical pathway and natural history of PTSD. Limited natural history data were identified, and there was structural uncertainty within the clinical pathway of PTSD, which led to the requirement of a number of assumptions that increased uncertainty with the results of the economic evaluation. Despite these limitations, extensive scenario and sensitivity analyses were conducted that indicated that the model was quite robust, with iCBT associated with an ICUR below $50,000 per QALY or being dominant in all scenario and sensitivity analyses.

No evidence was identified in the clinical review relating to the harms of iCBT for PTSD, so their impact on the economic results is uncertain as we were unable to account for them within the economic evaluation. It should also be noted that no studies identified a worsening of PTSD symptoms, though this would have been accounted for via the clinical efficacy inputs derived from the clinical review.

Conversations with stakeholders included as part of the implementation analysis were necessarily constrained by the limitations noted for the clinical review and economic evaluation. While stakeholders could imagine ways in which iCBTs for PTSD may be incorporated into current care pathways, it is important to remember that these are situated within a limited evidence base and were often couched within a desire for more comparative research with active comparators.

There was a paucity of literature that directly and explicitly engaged in the normative or empirical analysis of ethical issues that can be expected to arise in the context of iCBT, let alone iCBT for PTSD, in particular. If it were clear that iCBT was effective in treating clients with PTSD, then one would have to carefully consider whether existing ethical concerns and issues provide enough reason to object to the development, provision, and use of iCBT for PTSD. Yet, it was unclear whether iCBT was effective in treating clients with PTSD, and so the cumulative force of the ethical concerns and issues noted provide a stronger reason to be cautious about the development, provision, and use of iCBT for PTSD.

Research Gaps and Future Directions

There were significant evidence gaps identified as part of the clinical review that further impacted the economic evaluation. There was no literature identified that directly compared iCBT with face-to-face CBT or other forms of psychotherapy; therefore, the relative clinical and cost-effectiveness of these interventions is unknown. The literature summarized in the clinical review was limited to iCBT versus wait-list or usual care and i-non-CBT interventions. As such, the base-case results of the economic model could only consider no additional treatment as the comparator, with i-non-CBT assessed in a separate scenario analysis. Future research on the comparative clinical effectiveness of iCBT versus active treatments (e.g., face-to-face CBT or other psychotherapies) would provide further insight into the place of iCBT in the treatment of PTSD and allow comparative cost-effectiveness assessment of iCBT against other active psychotherapy programs such as face-to-face CBT. Additionally, the clinical review did not identify any harms data reporting on rates of adverse events (e.g., worsening of PTSD symptoms, suicidality, mortality). The safety of PTSD treatment with iCBT is unclear.

Further longitudinal studies assessing the natural history of patients with PTSD by type of trauma, the number of events, or other characteristics of interest, along with clinical studies assessing iCBT by these same characteristics would allow for assessment of the cost-effectiveness of iCBT compared with other relevant interventions by subgroups of interest.

Given the ostensible centrality of engaging in trauma-informed care when it comes to the treatment of PTSD, an important future direction concerns whether trauma-informed care is actually possible in the context of iCBT. Either iCBT needs to be able to incorporate and reflect the principles of trauma-informed care, or good reasons need to exist that iCBT for PTSD need not be trauma-informed.

Within the HTA, there were limited studies and evidence specific to several populations (e.g., immigrants, refugees, Indigenous populations, people living with disabilities, or other socio-demographic groups). Future research should examine the clinical effectiveness; cost-effectiveness; perspectives and experiences of patients, families, and health care providers; and ethical and implementation issues of iCBT in these specific subpopulations to facilitate appropriate patient selection for iCBT treatment interventions.

Conclusions

Overall, based on primarily “very low” to “low” quality evidence, the findings from the clinical review suggested that treatment with iCBT improved severity of PTSD symptoms compared with wait-list for patients aged 16 years or older with a primary diagnosis of PTSD; however, the magnitude improvement did not translate into a clinically meaningful change (using MCID values from the literature). Additionally, treatment with iCBT improved severity of depressive symptoms, severity of anxiety symptoms, and quality of life compared with wait-list. There were no statistically significant differences between treatment with iCBT and i-non-CBT interventions with respect to severity of PTSD symptoms. In the economic evaluation, iCBT was less costly and produced more QALYs over a lifetime compared with no additional treatment and, compared with i-non-CBT, iCBT was associated with an ICUR of $8,624 per QALY gained. The results were primarily driven by the cost of treatment and the extrapolation of the impact of iCBT over a lifetime time horizon. These estimates remain uncertain due to limitations with the clinical efficacy data, as well as uncertainty with the natural history inputs (i.e., variability in the progression of PTSD which could not be modelled); though results remained robust in the extensive scenario and sensitivity analyses conducted.

No evidence that directly compared treatment with iCBT with face-to-face CBT or other psychotherapies was identified in the clinical literature; therefore, the comparative clinical and cost-effectiveness of iCBT and face-to-face psychotherapies is unknown.

The potential implementation of iCBTs for PTSD across jurisdictions in Canada is likely to be influenced by several factors, including whether a regulatory or licensing body can provide oversight on which iCBT programs provide care that aligns with the principles of CBT, which gaps in the provision of PTSD care iCBTs are meant to fill and whether there research supporting the use of iCBTs to fill these gaps, which providers are (or are not) allowed to provide care with iCBTs, and how iCBTs fit within current mental health funding and provision structures across jurisdictions. Similarly, how iCBTs align (or do not) with individual patient treatment goals or values and the opportunity to develop and maintain strong therapeutic relationships would seem important to consider when deliberating on the implementation of particular programs.

Mental health conditions like PTSD are complex. Treatment modalities for PTSD and the research around them are constantly evolving. As substantial new evidence regarding the clinical effectiveness and safety, cost-effectiveness, perspectives and experiences, ethical issues, and implementation issues of iCBT programs emerges, reassessment will be needed, particularly with respect to complex traumas and comparisons to current standards of care.

References

1. Galea S, Nandi A, Vlahov D. The epidemiology of post-traumatic stress disorder after disasters. *Epidemiol Rev.* 2005;27:78-91.
2. Norris FH. Epidemiology of trauma: frequency and impact of different potentially traumatic events on different demographic groups. *J Consult Clin Psychol.* 1992;60(3):409-418.
3. Breslau N, Kessler RC, Chilcoat HD, Schultz LR, Davis GC, Andreski P. Trauma and posttraumatic stress disorder in the community: the 1996 Detroit Area Survey of Trauma. *Arch Gen Psychiatry.* 1998;55(7):626-632.
4. Diagnostic and statistical manual of mental disorders. 5th ed. Washington (DC): American Psychiatric Association; 2013.
5. Sijbrandij M, Kunovski I, Cuijpers P. Effectiveness of internet-delivered cognitive behavioral therapy for posttraumatic stress disorder: a systematic review and meta-analysis. *Depress Anxiety.* 2016;33(9):783-791.
6. Barlow DH, Keane TM, Marx BP, Sloan DM, DePrince A. Trauma, dissociation, and post-traumatic stress disorder. In: Barlow DH, ed. *The Oxford handbook of clinical psychology*. 1st ed. New York (NY): Oxford University Press; 2010.
7. Klein B, Mitchell J, Gilson K, et al. A therapist-assisted Internet-based CBT intervention for posttraumatic stress disorder: preliminary results. *Cogn Behav Ther.* 2009;38(2):121-131.
8. Kar N. Cognitive behavioral therapy for the treatment of post-traumatic stress disorder: a review. *Neuropsychiatr Dis Treat.* 2011;7:167-181.
9. Saarni SI, Suvisaari J, Sintonen H, et al. Impact of psychiatric disorders on health-related quality of life: general population survey. *Br J Psychiatry.* 2007;190:326-332.
10. Cuijpers P, Smit F. Excess mortality in depression: a meta-analysis of community studies. *J Affect Disord.* 2002;72(3):227-236.
11. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *Int J Methods Psychiatr Res.* 2012;21(3):169-184.
12. Sareen J, Henriksen CA, Bolton SL, Afifi TO, Stein MB, Asmundson GJ. Adverse childhood experiences in relation to mood and anxiety disorders in a population-based sample of active military personnel. *Psychol Med.* 2013;43(1):73-84.
13. Skeffington PM, Rees CS, Mazzucchelli T. Trauma exposure and post-traumatic stress disorder within fire and emergency services in Western Australia. *Aust J Psychol.* 2017;69(1):20-28.
14. Olthuis JV, Wozney L, Asmundson GJ, Cramm H, Lingley-Pottie P, McGrath PJ. Distance-delivered interventions for PTSD: a systematic review and meta-analysis. *J Anxiety Disord.* 2016;44:9-26.
15. Van Ameringen M, Mancini C, Patterson B, Boyle MH. Post-traumatic stress disorder in Canada. *CNS Neurosci Ther.* 2008;14(3):171-181.
16. E-mental health in Canada: transforming the mental health system using technology. *A briefing document*. Ottawa (ON): Mental Health Commission of Canada; 2014: https://www.mentalhealthcommission.ca/sites/default/files/MHCC_E-Mental_Health-Briefing_Document_ENG_0.pdf. Accessed 2019 Sep 6.
17. Jonas DE, Cusack K, Forneris CA, et al. Psychological and pharmacological treatments for adults with posttraumatic stress disorder (PTSD). *(Comparative effectiveness review no. 92)*. Rockville (MD): Agency for Healthcare Research and Quality; 2013: https://www.ncbi.nlm.nih.gov/books/NBK137702/. Accessed 2019 Sep 3.
18. Sin J, Spain D, Furuta M, Murrells T, Norman I. Psychological interventions for post-traumatic stress disorder (PTSD) in people with severe mental illness. *Cochrane Database Syst Rev.* 2017;1:CD011464.
19. Katzman MA, Bleau P, Blier P, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry.* 2014;14(1):S1.
20. Mendes DD, Mello MF, Ventura P, Passarela C, Mari J. A systematic review on the effectiveness of cognitive behavioral therapy for posttraumatic stress disorder. *Int J Psychiatry Med.* 2008;38(3):241-259.
21. Benjamin CL, Puleo CM, Settipani CA, et al. History of cognitive-behavioral therapy in youth. *Child Adolesc Psychiatr Clin N Am.* 2011;20(2):179-189.
22. Kuester A, Niemeyer H, Knaevelsrud C. Internet-based interventions for posttraumatic stress: a meta-analysis of randomized controlled trials. *Clin Psychol Rev.* 2016;43:1-16.
23. Mohr DC, Ho J, Duffecy J, et al. Perceived barriers to psychological treatments and their relationship to depression. *J Clin Psychol.* 2010;66(4):394-409.
24. Ringle VA, Read KL, Edmunds JM, et al. Barriers to and facilitators in the implementation of cognitive-behavioral therapy for youth anxiety in the community. *Psychiatr Serv.* 2015;66(9):938-945.
25. Bekker MJ, Griffiths KM, Barrett PM. Improving accessibility of cognitive behavioural therapy for children and adolescents: review of evidence and future directions. *Clin Psychol.* 2017;21(3):157-164.
26. Collins KA, Westra HA, Dozois DJ, Burns DD. Gaps in accessing treatment for anxiety and depression: challenges for the delivery of care. *Clin Psychol Rev.* 2004;24(5):583-616.

27. Hundt NE, Mott JM, Cully JA, Beason-Smith M, Grady RH, Teng E. Factors associated with low and high use of psychotherapy in veterans with PTSD. *Psychol Trauma.* 2014;6(6):731-738.

28. Sareen J, Cox BJ, Afifi TO, et al. Combat and peacekeeping operations in relation to prevalence of mental disorders and perceived need for mental health care: findings from a large representative sample of military personnel. *Arch Gen Psychiatry.* 2007;64(7):843-852.

29. Topper K, van Rooyen K, Grobler C, van Rooyen D, Andersson L. Posttraumatic stress disorder and barriers to care in Eastern Cape Province, South Africa. *J Trauma Stress.* 2015;28(4):375-379.

30. Accessing mental health care in Canada. Ottawa (ON): Statistics Canada; 2018: http://www.statcan.gc.ca/pub/11-627-m/11-627-m2017019-eng.pdf. Accessed 2019 Sep 6.

31. Ascribe Marketing Communications Inc. Addressing the access gap: leveraging the potential of e-mental health in Canada. Summary report. Ottawa (ON): Mental Health Commission of Canada; 2017: https://www.mentalhealthcommission.ca/sites/default/files/2017-07/MHCC%20January%20Roundtable_FINAL%20EN.pdf. Accessed 2019 Apr 18.

32. McGrath P, Newton A, Hartling L, et al. Advancing the evolution: insights into the state of e-mental health services in Canada. Ottawa (ON): Mental Health Commission of Canada; 2017: https://www.mentalhealthcommission.ca/sites/default/files/2017-08/eMH%20Environmental%20Scan_FINAL%20EN.pdf. Accessed 2019 Apr 18.

33. Andersson G, Titov N. Advantages and limitations of Internet-based interventions for common mental disorders. *World Psychiatry.* 2014;13(1):4-11.

34. Amstadter AB, Broman-Fulks J, Zinzow H, Ruggiero KJ, Cercone J. Internet-based interventions for traumatic stress-related mental health problems: a review and suggestion for future research. *Clin Psychol Rev.* 2009;29(5):410-420.

35. Mojtabai R, Olfson M, Sampson NA, et al. Barriers to mental health treatment: results from the National Comorbidity Survey Replication. *Psychol Med.* 2011;41(8):1751-1761.

36. Gratzer D, Khalid-Khan F. Internet-delivered cognitive behavioural therapy in the treatment of psychiatric illness. *CMAJ.* 2016;188(4):263-272.

37. Health Quality Ontario. Internet-delivered cognitive behavioural therapy for major depression and anxiety disorders: a health technology assessment. *Ont Health Technol Assess Ser.* 2019;19(6):1-199. https://www.hqontario.ca/Portals/0/documents/evidence/reports/hta-internet-delivered-cognitive-behavioural-therapy.pdf. Accessed 2019 Apr 16.

38. Internet-delivered cognitive behavioural therapy for major depressive disorder and anxiety disorders: patients' experiences and perspectives, implementation, and ethical issues. *(CADTH Optimal use report; vol. 8, no. 2b)*. Ottawa (ON): CADTH; 2019: https://cadth.ca/sites/default/files/pdf/OP0534%20iCBT%20for%20MDD%20and%20Anxiety%20Disorders%20Final%20Report.pdf. Accessed 2019 Apr 18.

39. Internet-delivered cognitive behavioural therapy for major depressive disorder and anxiety disorders: recommendations. *(CADTH Optimal use report; vol. 8, no. 2c)*. Ottawa (ON): CADTH; 2019: https://cadth.ca/sites/default/files/ou-tr/op0534-iCBT-recommendations.pdf. Accessed 2019 Apr 18.

40. Lewis C, Roberts NP, Bethell A, Robertson L, Bisson JI. Internet-based cognitive and behavioural therapies for posttraumatic stress disorder (PTSD) in adults. *Cochrane Database Syst Rev.* 2018(12):CD011710.

41. Young C, Campbell K. Internet-delivered cognitive behavioral therapy for post-traumatic stress diorder: a review of clinical effectiveness. *(CADTH rapid response report: peer-reviewed summary with critical appraisal)*. Ottawa (ON): CADTH; 2018: https://www.cadth.ca/sites/default/files/pdf/htis/2018/RD0048%20iCBT%20for%20PTSD%20Final.pdf. Accessed 2019 Sep 3.

42. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008. http://www.bmj.com/content/bmj/358/bmj.j4008.full.pdf. Accessed 2019 Apr 10.

43. Grey matters: a practical tool for searching health-related grey literature. Ottawa (ON): CADTH; 2018: https://www.cadth.ca/resources/finding-evidence. Accessed 2019 Sep 3.

44. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. Version 5.1.0. London (UK): Cochrane Collaboration; 2011: http://handbook-5-1.cochrane.org/. Accessed 2019 Sep 3.

45. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *J Clin Epidemiol.* 2011;64(4):407-415.

46. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. *J Clin Epidemiol.* 2011;64(12):1294-1302.

47. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *J Clin Epidemiol.* 2011;64(12):1303-1310.

48. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. *J Clin Epidemiol.* 2011;64(12):1283-1293.

49. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. *J Clin Epidemiol.* 2011;64(12):1277-1282.

50. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.

51. Internet-delivered cognitive behavioural therapy for post-traumatic stress disorder: a health technology assessment — project protocol. *(CADTH Optimal use report; Vol. 9, No. 3a)*. Ottawa (ON): CADTH; 2019: https://cadth.ca/sites/default/files/ou-tr/op0537-internet-delivered-cognitive-behavioural-therapy-for-post-traumatic-stress-disorder-protocol.pdf. Accessed 2019 Jul 31.

52. Lewis CE, Farewell D, Groves V, et al. Internet-based guided self-help for posttraumatic stress disorder (PTSD): randomized controlled trial. *Depress Anxiety.* 2017;34(6):555-565.

53. Kuhn E, Kanuri N, Hoffman JE, Garvert DW, Ruzek JI, Taylor CB. A randomized controlled trial of a smartphone app for posttraumatic stress disorder symptoms. *J Consult Clin Psychol.* 2017;85(3):267-273.

54. Engel CC, Litz B, Magruder KM, et al. Delivery of self training and education for stressful situations (DESTRESS-PC): a randomized trial of nurse assisted online self-management for PTSD in primary care. *Gen Hosp Psychiatry.* 2015;37(4):323-328.

55. Spence J, Titov N, Dear BF, et al. Randomized controlled trial of Internet-delivered cognitive behavioral therapy for posttraumatic stress disorder. *Depress Anxiety.* 2011;28(7):541-550.

56. Schnurr PP, Friedman MJ, Engel CC, et al. Cognitive behavioral therapy for posttraumatic stress disorder in women: a randomized controlled trial. *JAMA.* 2007;297(8):820-830.

57. Schnurr PP, Friedman MJ, Foy DW, et al. Randomized trial of trauma-focused group therapy for posttraumatic stress disorder: results from a department of Veterans Affairs cooperative study. *Arch Gen Psychiatry.* 2003;60(5):481-489.

58. Hinton DE, Chhean D, Pich V, Safren SA, Hofmann SG, Pollack MH. A randomized controlled trial of cognitive-behavior therapy for Cambodian refugees with treatment-resistant PTSD and panic attacks: a cross-over design. *J Trauma Stress.* 2005;18(6):617-629.

59. Hien DA, Wells EA, Jiang H, et al. Multisite randomized trial of behavioral interventions for women with co-occurring PTSD and substance use disorders. *J Consult Clin Psychol.* 2009;77(4):607-619.

60. Polusny MA, Erbes CR, Thuras P, et al. Mindfulness-based stress reduction for posttraumatic stress disorder among veterans: a randomized clinical trial. *JAMA.* 2015;314(5):456-465.

61. Krystal JH, Rosenheck RA, Cramer JA, et al. Adjunctive risperidone treatment for antidepressant-resistant symptoms of chronic military service-related PTSD: a randomized trial. *JAMA.* 2011;306(5):493-502.

62. Stefanovics EA, Rosenheck RA, Jones KM, Huang G, Krystal JH. Minimal Clinically Important Differences (MCID) in assessing outcomes of post-traumatic stress disorder. *Psychiatr Q.* 2018;89(1):141-155.

63. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.

64. Lewis C, Roberts NP, Simon N, Bethell A, Bisson JI. Internet-based cognitive behavioural therapy (i-CBT) for post-traumatic stress disorder (PTSD): systematic review and meta-analysis. *Acta Psychiatr Scand.* 2019 [Epub ahead of print 2019 Jul 29].

65. Spence J, Titov N, Johnston L, Jones MP, Dear BF, Solley K. Internet-based trauma-focused cognitive behavioural therapy for PTSD with and without exposure components: a randomised controlled trial. *J Affect Disord.* 2014;162:73-80.

66. Krupnick JL, Green BL, Amdur R, et al. An Internet-based writing intervention for PTSD in veterans: a feasibility and pilot effectiveness trial. *Psychol Trauma.* 2017;9(4):461-470.

67. Miner A, Kuhn E, Hoffman JE, Owen JE, Ruzek JI, Taylor CB. Feasibility, acceptability, and potential efficacy of the PTSD Coach app: a pilot randomized controlled trial with community trauma survivors. *Psychol Trauma.* 2016;8(3):384-392.

68. Knaevelsrud C, Brand J, Lange A, Ruwaard J, Wagner B. Web-based psychotherapy for posttraumatic stress disorder in war-traumatized Arab patients: randomized controlled trial. *J Med Internet Res.* 2015;17(3):e71.

69. Ivarsson D, Blom M, Hesser H, et al. Guided internet-delivered cognitive behavior therapy for post-traumatic stress disorder: a randomized controlled trial. *Internet Interv.* 2014;1(1):33-40.

70. Littleton H, Grills AE, Kline KD, Schoemann AM, Dodd JC. The From Survivor to Thriver program: RCT of an online therapist-facilitated program for rape-related PTSD. *J Anxiety Disord.* 2016;43:41-51.

71. Litz BT, Engel CC, Bryant RA, Papa A. A randomized, controlled proof-of-concept trial of an Internet-based, therapist-assisted self-management treatment for posttraumatic stress disorder. *Am J Psychiatry.* 2007;164(11):1676-1683.

72. Spoont M, Arbisi P, Fu S, et al. Screening for post-traumatic stress disorder (PTSD) in primary care: a systematic review. *VA Evidence-based synthesis program report*. Washington (DC): Department of Veterans Affairs; 2013.

73. Blanchard EB, Jones-Alexander J, Buckley TC, Forneris CA. Psychometric properties of the PTSD Checklist (PCL). *Behav Res Ther.* 1996;34(8):669-673.

74. Lewis C, Roberts NP, Bethell A, Bisson JI. Internet-based cognitive and behavioural therapies for post-traumatic stress disorder (PTSD) in adults [protocol]. *Cochrane Database Syst Rev.* 2015(5).

75. Kakhnovets R. Relationships among personality, expectations about counseling, and help-seeking attitudes. *J Couns Dev.* 2011;89(1):11-19.

76. Schünemann H, Brożek J, Guyatt GH, Oxman AD, eds. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013. 2013: https://gdt.gradepro.org/app/handbook/handbook.html. Accessed 2019 Sep 3.

77. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry.* 2005;62(6):617-627.

78. Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Ottawa (ON): CADTH; 2017: https://www.cadth.ca/dv/guidelines-economic-evaluation-health-technologies-canada-4th-edition. Accessed 2019 Sep 3.

79. Life tables, Canada, provinces and territories, 1980/1982 to 2014/2016. Ottawa (ON): Statistics Canada; 2018.

80. Perez Benitez CI, Zlotnick C, Stout RI, et al. A 5-year longitudinal study of posttraumatic stress disorder in primary care patients. *Psychopathology.* 2012;45(5):286-293.

81. Morina N, Wicherts JM, Lobbrecht J, Priebe S. Remission from post-traumatic stress disorder in adults: a systematic review and meta-analysis of long term outcome studies. *Clin Psychol Rev.* 2014;34(3):249-255.

82. Chiu M, Vigod S, Rahman F, Wilton AS, Lebenbaum M, Kurdyak P. Mortality risk associated with psychological distress and major depression: a population-based cohort study. *J Affect Disord.* 2018;234:117-123.

83. Gospodarevskaya E. Post-traumatic stress disorder and quality of life in sexually abused Australian children. *J Child Sex Abuse.* 2013;22(3):277-296.

84. Hawthorne G, Richardson J, Osborne R. The Assessment of Quality of Life (AQoL) instrument: a psychometric measure of health-related quality of life. *Qual Life Res.* 1999;8(3):209-224.

85. Gunther O, Roick C, Angermeyer MC, Konig HH. The EQ-5D in alcohol dependent patients: relationships among health-related quality of life, psychopathology and social functioning. *Drug Alcohol Depend.* 2007;86(2-3):253-264.

86. Bank of Canada. Inflation calculator. 2019; http://www.bankofcanada.ca/rates/related/inflation-calculator/. Accessed 2019 May 26.

87. Lamoureux-Lamarche C, Vasiliadis HM, Preville M, Berbiche D. Healthcare use and costs associated with post-traumatic stress syndrome in a community sample of older adults: results from the ESA-Services study. *Int Psychogeriatr.* 2016;28(6):903-911.

88. Chiu M, Lebenbaum M, Cheng J, de Oliveira C, Kurdyak P. The direct healthcare costs associated with psychological distress and major depression: a population-based cohort study in Ontario, Canada. *PLoS One.* 2017;12(9):e0184268.

89. Ontario Ministry of Health Long-Term Care. Ontario drug benefit formulary/comparative drug index. 2019; https://www.formulary.health.gov.on.ca/formulary/. Accessed 2019 May 26.

90. Schedule of benefits for physician services under the Health Insurance Act: (December 22, 2015 (effective March 1, 2016)). Toronto (ON): Ontario Ministry of Health and Long-Term Care; 2015: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/sob_master20181115.pdf. Accessed 2019 Sep 16.

91. Chan D, Fan MY, Unutzer J. Long-term effectiveness of collaborative depression care in older primary care patients with and without PTSD symptoms. *Int J Geriatr Psychiatry.* 2011;26(7):758-764.

92. Beacon. Affordable pricing for therapy that works. 2019; https://www.mindbeacon.com/pricing/. Accessed 2019 Sep 16.

93. Income of individuals by age group, sex and income source, Canada, provinces and selected census metropolitan areas. Ottawa (ON): Statistics Canada; 2018: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1110023901. Accessed 2019 May 13.

94. Canadian Substance Use Costs and Harms Scientific Working Group. Canadian substance use costs and harms (2007–2014). Ottawa (ON): Canadian Institute for Substance Use Research, Canadian Centre on Substance Use and Addiction; 2018: https://www.ccsa.ca/sites/default/files/2019-04/CSUCH-Canadian-Substance-Use-Costs-Harms-Report-2018-en.pdf. Accessed 2019 Sep 16.

95. Suri H. Purposeful sampling in qualitative research synthesis. *Qual Res J.* 2011;11(2):63-75.

96. Patton MQ. Qualitative research & evaluation methods : integrating theory and practice. 4th ed. Thousand Oaks (CA): SAGE; 2015.

97. Carroll C, Booth A, Leaviss J, Rick J. "Best fit" framework synthesis: refining the method. *BMC Med Res Methodol.* 2013;13(1):37.

98. *NVivo: qualitative data analysis software.* Burlington (MA): QSR International; 2015.

99. Hundt NE, Helm A, Smith TL, Lamkin J, Cully JA, Stanley MA. Failure to engage: a qualitative study of veterans who decline evidence-based psychotherapies for PTSD. *Psychol Serv.* 2018;15(4):536-542.

100. Cook JM, Simiola V, Hamblen JL, Bernardy N, Schnurr PP. The influence of patient readiness on implementation of evidence-based PTSD treatments in Veterans Affairs residential programs. *Psychol Trauma.* 2017;9(Suppl 1):51-58.

101. Hundt NE, Barrera TL, Arney J, Stanley MA. "It's worth it in the end": veterans' experiences in prolonged exposure and cognitive processing therapy. *Cogn Behav Pract.* 2017;24(1):50-57.

102. Stige SH, Binder PE. From painstaking work to a new way of meeting the world-trauma clients' experiences with skill training in a stabilization group approach. *Psychother Res.* 2017;27(5):571-582.

103. Tong J, Simpson K, Alvarez-Jimenez M, Bendall S. Distress, psychotic symptom exacerbation, and relief in reaction to talking about trauma in the context of beneficial trauma therapy: perspectives from young people with post-traumatic stress disorder and first episode psychosis. *Behav Cogn Psychother.* 2017;45(6):561-576.

104. Hamblen JL, Bernardy NC, Sherrieb K, et al. VA PTSD clinic director perspectives: how perceptions of readiness influence delivery of evidence-based PTSD treatment. *Prof Psychol Res Pr.* 2015;46(2):90-96.

105. Hundt NE, Mott JM, Miles SR, Arney J, Cully JA, Stanley MA. Veterans' perspectives on initiating evidence-based psychotherapy for posttraumatic stress disorder. *Psychol Trauma.* 2015;7(6):539-546.

106. McCormack L, White S, Cuenca J. A fractured journey of growth: making meaning of a 'broken' childhood and parental mental ill-health. *Community Work Fam.* 2017;20(3):327-345.

107. Cook JM, Dinnen S, Simiola V, Thompson R, Schnurr PP. VA residential provider perceptions of dissuading factors to the use of two evidence-based PTSD treatments. *Prof Psychol Res Pr.* 2014;45(2):136-142.

108. Lawrence VA, Lee D. An exploration of people's experiences of compassion-focused therapy for trauma, using interpretative phenomenological analysis. *Clin Psychol Psychother.* 2014;21(6):495-507.

109. Lowe C, Murray C. Adult service-users' experiences of trauma-focused cognitive behavioural therapy. *J Contemp Psychother.* 2014;44(4):223-231.

110. Reeves A, Stewart S. Exploring the integration of indigenous healing and western psychotherapy for sexual trauma survivors who use mental health services at Anishnawbe Health Toronto. *Can J Couns Psychother.* 2014;49(1).

111. Whealin JM, Jenchura EC, Wong AC, Zulman DM. How veterans with post-traumatic stress disorder and comorbid health conditions utilize eHealth to manage their health care needs: a mixed-methods analysis. *J Med Internet Res.* 2016;18(10):e280.

112. Clinical practice guideline for the treatment of PTSD: appendices. Washington (DC): American Psychological Association; 2017: https://www.apa.org/ptsd-guideline/appendices.pdf. Accessed 2019 Sep 3.

113. Cavanagh K, Belnap BH, Rothenberger SD, Abebe KZ, Rollman BL. My care manager, my computer therapy and me: the relationship triangle in computerized cognitive behavioural therapy. *Internet Interv.* 2018;11:11-19.

114. Beck A, Dozois D. Cognitive therapy: current status and future directions. *Annu Rev Med.* 2011;62:397-409.

115. Ducharme EL. Best practices in working with complex trauma and dissociative identity disorder. *Pract Innov.* 2017;2(3):150-161.

116. Martin DJ, Garske JP, Davis MK. Relation of therapeutic alliance with outcome and other variables: a meta-analytic review. *J Consult Clin Psychol.* 2000;68:438-450.

117. Shirk S, Karver M. Prediction of treatment outcome from relationship variables in child and adolescent therapy. *J Consult Clin Psychol.* 2003;71:462-471.

118. Jain S. Treating posttraumatic stress disorder via the Internet does therapeutic alliance matter? *J Am Med Assoc.* 2011;306(5):543-544.

119. Theodore Z. The relationship between the therapeutic alliance and treatment outcome in prolonged exposure therapy for PTSD. *Diss Abstr Int Sect B Sci Eng.* 2018;79(1-B(E)).

120. Poole N. Trauma-informed Care. *The essentials of ... series*. Ottawa (ON): Canadian Centre on Substance Abuse; 2012: http://bccewh.bc.ca/wp-content/uploads/2014/05/PT-Trauma-informed-Care-2012-01-en.pdf. Accessed 2019 Sep 3.

121. Elliot DE, Bjelajac P, Fallot RD, Markoff LS, Reed BG. Trauma-informed or trauma-denied: principles and implementation of trauma-informed services for women. *J Community Psychol.* 2005;33(4):461-477.

122. Hopper EK, Bassuk EL, Olivet J. Shelter from the storm: trauma-informed care in homelessness service settings. *Open Health Policy Serv J.* 2010;3:80-100.

123. Barazzone N, Cavanagh K, Richards DA. Computerized cognitive behavioural therapy and the therapeutic alliance: A qualitative enquiry. *Br J Clin Psychol.* 2012;51(4):396-417.

124. Lawlor-Savage L, Prentice JL. Digital cognitive behaviour therapy (CBT) in Canada: ethical considerations. *Can Psychol.* 2014;55(4):231-239.

125. Dunne N. Evaluation of psychology clinicians' attitudes towards computerized cognitive behavior therapy, for use in their future clinical practice, with regard to treating those suffering from anxiety and depression. *Diss Abstr Int Sect B Sci Eng.* 2018;79(5-B(E)).

126. Fitzgerald TD, Hunter PV, Hadjistavropoulos T, Koocher GP. Ethical and legal considerations for internet-based psychotherapy. *Cogn Behav Ther.* 2010;39(3):173-187.

127. Shapiro DE, Schulman CE. Ethical and legal issues in e-mail therapy. *Ethics Behav.* 1996;6(2):107-124.

128. Anderson P, Jacobs C, Rothbaum BO. Computer-supported cognitive behavioral treatment of anxiety disorders. *J Clin Psychol.* 2004;60(3):253-267.

129. Berry RR, Lai B. The emerging role of technology in cognitive-behavioral therapy for anxious youth: a review. *J Ration Emot Cogn Behav Ther.* 2014;32(1):57-66.

130. Satalkar P, Shrivastava S, De Souza A. Internet-mediated psychotherapy: are we ready for the ethical challenges? *Indian J Med Ethics.* 2015;12(4):220-227.

131. Manhal-Baugus M. e-Therapy: practical, ethical, and legal issues. *CyberPsychol Behav.* 2001;4(5):551-563.

132. Eells TD, Barrett MS, Wright JH, Thase M. Computer-assisted cognitive-behavior therapy for depression. *Psychotherapy.* 2014;51(2):191-197.

133. Karcher NR, Presser NR. Ethical and legal issues addressing the use of mobile health (mHealth) as an adjunct to psychotherapy. *Ethics Behav.* 2018;28(1):1-22.

134. Norris L, Swartz L, Tomlinson M. Mobile phone technology for improved mental health care in South Africa: possibilities and challenges. *S Afr J Psychol.* 2013;43(3):379-388.

135. Sansom-Daly UM, Wakefield CE, McGill BC, Wilson HL, Patterson P. Consensus among international ethical guidelines for the provision of videoconferencing-based mental health treatments. *JMIR Ment Health.* 2016;3(2):e17.

136. Sprague G. Telehealth implementation in rural communities. *Diss Abstr Int Sect B Sci Eng.* 2017;78(6-B(E)).

137. Childress CA. Ethical issues in providing online psychotherapeutic interventions. *J Med Internet Res.* 2000;2(1):e5.

138. Hughes RS. Ethics and regulations of cybercounseling. *ERIC/CASS Digest.* 2000.

139. Li LP, Jaladin RAM, Abdullah HS. Understanding the two sides of online counseling and their ethical and legal ramifications. *Procedia Soc Behav Sci.* 2013;103(26):1243-1251.

140. Armontrout J, Torous J, Fisher M, Drogin E, Gutheil T. Mobile mental health: navigating new rules and regulations for digital tools. *Curr Psychiatry Rep.* 2016;18(10):91.

141. Wodarski J, Frimpong J. Application of e-therapy programs to the social work practice. *J Hum Behav Soc Environ.* 2013;23(1):29-36.

142. Titzler I, Saruhanjan K, Berking M, Riper H, Ebert DD. Barriers and facilitators for the implementation of blended psychotherapy for depression: a qualitative pilot study of therapists' perspective. *Internet Interv.* 2018;12:150-164.

143. Knaevelsrud C, Maercker A. Does the quality of the working alliance predict treatment outcome in online psychotherapy for traumatized patients? *J Med Internet Res.* 2006;8(4):e31.

144. Woods AP, Stults CB, Terry RL, Rego SA. Strengths and limitations of internet-based cognitive-behavioral treatments for anxiety disorders. *Pragmat Case Stud Psychother.* 2017;13(3):271-283.

145. Barak A, Hen L, Boniel-Nissim M, Shapira N. A comprehensive review and a meta-analysis of the effectiveness of Internet-based psychotherapeutic interventions. *J Technol Human Ser.* 2008;26:109-160.

146. Capaldi S, Asnaani A, Zandberg LJ, Carpenter JK, Foa EB. Therapeutic alliance during prolonged exposure versus client-centered therapy for adolescent posttraumatic stress disorder. *J Clin Psychol.* 2016;72(10):1026-1036.

147. Lovejoy T, Demireva P, Grayson J, McNamara J. Advancing the practice of online psychotherapy: an application of Rogers' diffusion of innovations theory. *Psychother Theory Res Pract Train.* 2009;46(1):112-124.

148. McLaughlin AA, Keller SM, Feeny NC, Youngstrom EA, Zoellner LA. Patterns of therapeutic alliance: rupture-repair episodes in prolonged exposure for posttraumatic stress disorder. *J Consult Clin Psychol.* 2014;82(1):112-121.

149. Cloitre M, Chase Stovall-McClough K, Miranda R, Chemtob C. Therapeutic alliance, negative mood regulation, and treatment outcome in child abuse-related posttraumatic stress disorder. *J Consult Clin Psychol.* 2004;72(3):411–416.

150. Caspar F. Case studies of clinician-guided, online therapy: towards a fuller understanding of how and under what conditions such therapy works. *Pragmat Case Stud Psychother.* 2017;13(3):265-270.

151. Finn J, Barak A. A descriptive study of e-counsellor attitudes, ethics, and practice. *Couns Psychother Res.* 2010;10(4):268-277.

152. Shaw HE, Shaw SF. Critical ethical issues in online counseling: Assessing current practices with an ethical intent checklist. *J Couns Dev.* 2006;84(1):41-53.

153. Nicholas J, Huckvale K, Larsen ME, et al. Issues for eHealth in psychiatry: results of an expert survey. *J Med Internet Res.* 2017;19(2):e55.

154. Peschken WE, Johnson M. Therapist and client trust in the therapeutic relationship. *Psychother Res.* 1997;7(4):439-447.

155. McLeod C. Trust. In: Zalta E, ed. *The Stanford encyclopedia of philosophy*. Fall 2015 ed. Stanford (CA): Stanford University; 2015: https://plato.stanford.edu/archives/fall2015/entries/trust/. Accessed 2019 Sep 3.

156. Winslade W. Confidentiality. In: Jennings B, ed. *Bioethics*. 4 ed. New York (NY): Macmillan Reference USA; 2014:671-676.

157. Eidlitz L. Therapeutic alliance and age of trauma onset in treatment of comorbid posttraumatic stress disorder and alcohol use disorder. *Diss Abstr Int Sect B Sci Eng.* 2018;79(2-B(E)).

158. Soltis K, Acierno R, Gros DF, Yoder M, Tuerk PW. Post-traumatic stress disorder: ethical and legal relevance to the criminal justice system. *J Law Med Ethics.* 2014;42(2):147-154.

159. Foa EB, Chrestman KR, Gilboa-Schechtman E. Prolonged exposure therapy for adolescents with PTSD: emotional processing of traumatic experiences. New York (NY): Oxford University Press; 2009.

160. Beauchamp TL, Childress JF. Principles of Biomedical Ethics. New York (NY): Oxford University Press; 2012.

161. Lal S. E-mental health: promising advancements in policy, research, and practice. *Healthc Manage Forum.* 2019;32(2):56-62.

162. Zelmer J, van Hoof K, Notarianni M, van Mierlo T, Schellenberg M, Tannenbaum C. An assessment framework for e-mental health apps in Canada: results of a modified Delphi process. *JMIR Mhealth Uhealth.* 2018;6(7):e10016.

163. Ebert DD, Van Daele T, Nordgreen T, et al. Internet- and mobile-based psychological interventions: applications, efficacy, and potential for improving mental health: a report of the EFPA E-Health Taskforce. *Eur Psychol.* 2018;23(2):167-187.

164. Hill C, Creswell C, Vigerland S, et al. Navigating the development and dissemination of internet cognitive behavioral therapy (iCBT) for anxiety disorders in children and young people: a consensus statement with recommendations from the #iCBTLorentz Workshop Group. *Internet Interv.* 2018;12:1-10.

165. Fisher CB, Fried AL. Internet-Mediated Psychological Services and the American Psychological Association Ethics Code. *Psychotherapy.* 2003;40(1/2):103-111.

166. van der Feltz-Cornelis CM. Economical framework of psychiatric care. In: Helmchen H, Sartorius N, eds. *Ethics in psychiatry: European contributions*. New York (NY): Springer Science + Business Media; 2010.

167. Finfgeld DL. Computer-assisted therapy: harbinger of the 21st century? *Arch Psychiatr Nurs.* 1999;13(6):303-310.

168. Recupero PR, Rainey SE. Informed consent to e-therapy. *Am J Psychother.* 2005;59(4):319-331.

169. Lenhard F, Vigerland S, Engberg H, Hallberg A, Thermaenius H, Serlachius E. "On My Own, but Not Alone" - adolescents' experiences of Internet-delivered cognitive behavior therapy for obsessive-compulsive disorder. *PLoS One.* 2016;11(10):e0164311.

170. Cavanagh K, Grist R. The use of computer-aided cognitive behavioural therapy (CCBT) in therapeutic settings. In: Goss S, Anthony K, Sykes Stretch L, Merz Nagel D, eds. *Technology in mental health: applications in practice, supervision and training*. 2nd ed. Springfield (IL): Charles C Thomas Pub; 2016.

171. Mallen MJ, Vogel DL, Rochlen AB. The practical aspects of online counseling: ethics, training, technology, and competency. *Couns Psychol.* 2005;33(6):776-818.

172. Sheppard GW, Schulz WE, McMahon S-A. Code of Ethics. Ottawa (ON): Canadian Counselling and Psychotherapy Association; 2007: https://www.ccpa-accp.ca/wp-content/uploads/2014/10/CodeofEthics_en.pdf. Accessed 2019 Sep 3.

173. Schnurr PP. Focusing on trauma-focused psychotherapy for posttraumatic stress disorder. *Curr Opin Psychol.* 2017;14:56-60.

174. Midkiff DM, Wyatt WJ. Ethical issues in the provision of online mental health services (eTherapy). *J Technol Human Ser.* 2008;26(2-4):310-332.

175. Yellowlees PM, Holloway KM, Parish MB. Therapy in virtual environments--clinical and ethical issues. *Telemed J E Health.* 2012;18(7):558-564.

176. Litz BT, Lebowitz L, Gray MJ, Nash WP. Adaptive disclosure: a new treatment for military trauma, loss, and moral injury. New York (NY): Guilford Press; 2017.

177. Malhotra S, Chakrabarti S, Shah R. Telepsychiatry: promise, potential, and challenges. *Indian J Psychiatry.* 2013;55(1):3-11.

178. Harris B, Rachel B. Ethical and legal implications on the use of technology in counselling. *Clin Soc Work J.* 2014;43(2):133–141.

179. Frame MW. The ethics of counseling via the Internet. *Fam J Couns Ther Couples Fam.* 1997;5(4):328-330.

180. Bloom JW. The ethical practice of web counseling. *Br J Guid Counc.* 1998;26(1):53-59.

181. Bourla A, Mouchabac S, El Hage W, Ferreri F. e-PTSD: an overview on how new technologies can improve prediction and assessment of Posttraumatic Stress Disorder (PTSD). *Eur J Psychotraumatol.* 2018;9(Suppl 1):1424448.

182. Webb CA, Rosso IM, Rauch SL. Internet-based cognitive-behavioral therapy for depression: current progress and future directions. *Harv Rev Psychiatry.* 2017;25(3):114-122.

183. Shiffman S, Stone A, Hufford M. Ecological momentary assessment. *Ann Rev Clin Psych.* 2008;4:1-32.

184. Ragusea AS, VandeCreek L. Suggestions for the ethical practice of online psychotherapy. *Psychotherapy.* 2003;40(1/2):94-102.

185. Gratzer D, Goldbloom D. Making evidence-based psychotherapy more accessible in Canada. *Can J Psychiatry.* 2016;61(10):618-623.

186. Hadjistavropoulos HD, Alberts NM, Nugent M, Marchildon G. Improving access to psychological services through therapist-assisted, Internet-delivered cognitive behaviour therapy. *Can Psychol.* 2014;55(4):303-311.

187. Nelson E-L, Duncan AB. Cognitive behavioral therapy using televideo. *Cogn Behav Pract.* 2015;22(3):269-280.

188. Holmes K. How ethically we practice online: an exploration of potential online provider liability. *Annu Rev Cyberther Telemed.* 2008;6:99-104.

189. Wallin E, Maathz P, Parling T, Hursti T. Self-stigma and the intention to seek psychological help online compared to face-to-face. *J Clin Psychol.* 2018;74(7):1207-1218.

190. Lehavot K, Der-Martirosian C, Simpson TL, Sadler AG, Washington DL. Barriers to care for women veterans with posttraumatic stress disorder and depressive symptoms. *Psychol Serv.* 2013;10(2):203-212.

191. Spoont MR, Nelson DB, Murdoch M, et al. Are there racial/ethnic disparities in VA PTSD treatment retention? *Depress Anxiety.* 2015;32(6):415-425.

192. Mucic D, Hilty DM, Yellowlees PM. e-Mental health toward cross-cultural populations worldwide. In: Mucic D, Hilty DM, eds. *e-Mental health*. Cham (CH): Springer International; 2016.

193. Brooks E, Novins DK, Noe T, et al. Reaching rural communities with culturally appropriate care: a model for adapting remote monitoring to American Indian veterans with posttraumatic stress disorder. *Telemed J E Health.* 2013;19(4):272-277.

194. Huminuik K. Special competencies for psychological assessment of torture survivors. *Transcult Psychiatry.* 2017;54(2):239-259.

195. Butler LD, Critelli FM, Rinfrette ES. Trauma-informed care and mental health. *Dir Psychiatry.* 2011;31:197-210.

196. Bryant-Davis T. The cultural context of trauma recovery: considering the posttraumatic stress disorder practice guidelines and intersectionality. *Psychotherapy.* 2019;56(3):400-408.

197. Miller BL. Autonomy. In: Jennings B, ed. *Bioethics*. 4 ed. New York (NY): Macmillan Reference USA; 2014.

198. Heinlen KT, Welfel ER, Richmond EN, O'Donnell MS. The nature, scope, and ethics of psychologists' e-therapy web sites: what consumers find when surfing the web. *Psychotherapy.* 2003;40(1/2):112-124.

199. Heinlen KT, Welfel ER, Richmond EN, Rak CF. The scope of webcounseling: a survey of services and compliance with NBCC standards for the ethical practice of webcounseling. *J Couns Dev.* 2003;81(1):61–69.

200. Bennett K, Bennett AJ, Griffiths KM. Security considerations for e-mental health interventions. *J Med Internet Res.* 2010;12(5):e61.

201. Standards of practice. 5 ed. Ottawa (ON): Canadian Counselling and Psychotherapy Association; 2015: https://www.ccpa-accp.ca/wp-content/uploads/2015/07/StandardsOfPractice_en_June2015.pdf. Accessed 2019 Sep 3.

202. Marks I, Cavanagh K. Computer-aided psychological treatments: evolving issues. *Ann Rev Clin Psych.* 2009;5:121-141.

203. Newman MG, Koif DF, Przeworski A, Llera SJ. Anxiety disorders. In: Cucciare MA, Weingardt KR, eds. *Using technology to support evidence-based behavioral health practices: a clinician's guide*. New York (NY): Routledge/Taylor & Francis Group; 2010.

204. Glenn T, Monteith S. Privacy in the digital world: medical and health data outside of HIPAA protections. *Curr Psychiatry Rep.* 2014;16(11):494.

205. Young KS. An empirical examination of client attitudes towards online counseling. *Cyberpsychol Behav.* 2005;8:172-177.

206. Rehm IC, Foenander E, Wallace K, Abbott JM, Kyrios M, Thomas N. What role can avatars play in e-mental health interventions? Exploring new models of client-therapist interaction. *Front Psychiatr.* 2016;7:186.

207. Baldwin SL. Differences between younger and older male combat veterans with posttraumatic stress disorder in stressors, stigma, and barriers to care. *Diss Abstr Int Sect B Sci Eng.* 2018;79(9-B(E)).

208. Barak A. Psychological applications on the internet: a discipline on the threshold of a new millennium. *Appl Prev Psychol.* 1999;8:231-245.

209. Pfadenhauer L, Rohwer A, Burns J, et al. Guidance for the assessment of context and implementation in health technology assessments (HTA) and systematic reviews of complex interventions: the Context and Implementation of Complex Interventions (CICI) Framework. Bremen (DE): Integrated Health Technology Assessment for Evaluating Complex Technologies (INTEGRATE-HTA); 2016: http://www.integrate-hta.eu/wp-content/uploads/2016/02/Guidance-for-the-Assessment-of-Context-and-Implementation-in-HTA-and-Systematic-Reviews-of-Complex-Interventions-The-Co.pdf. Accessed 2019 Apr 11.

210. Ritchie J, Spencer L. Qualitative data analysis for applied policy research. In: Bryman A, Burgess RG, eds. *Analyzing qualitative data*. New York (NY): Routledge; 2002.

211. Berliner L, Bisson J, Cloitre M, et al. ISTSS PTSD prevention and treatment guidelines: methodology and recommendations. Oakbrook Terrace (IL): International Society for Traumatic Stress Studies; 2019: https://www.istss.org/getattachment/Treating-Trauma/New-ISTSS-Prevention-and-Treatment-Guidelines/ISTSS_PreventionTreatmentGuidelines_FNL.pdf.aspx. Accessed 2019 Sep 3.

212. Clinical practice guideline for the treatment of PTSD. Washington (DC): American Psychological Association; 2017: https://www.apa.org/ptsd-guideline/ptsd.pdf. Accessed 2019 Sep 3.

213. Australian guidelines for the treatment of acute stress disorder and posttraumatic stress disorder. Melbourne (AU): Phoenix Australia; 2013: https://www.phoenixaustralia.org/wp-content/uploads/2015/03/Phoenix-ASD-PTSD-Guidelines.pdf. Accessed 2019 Sep 3.

214. The Management of Posttraumatic Stress Disorder Work Group. VA/DOD clinical practice guideline for the management of posttraumatic stress disorder and accute stress disorder. Washington (DC): US Department of Veterans Affairs, US Department of Defense; 2017: https://www.healthquality.va.gov/guidelines/MH/ptsd/VADoDPTSDCPGFinal012418.pdf. Accessed 2019 Sept 3.

215. Post-traumatic stress disorder. London (UK): National Institute for Health Care Excellence (NICE); 2019: https://www.nice.org.uk/guidance/ng116/resources/posttraumatic-stress-disorder-pdf-66141601777861. Accessed 2019 Sep 3.

216. Huynh A, Malli N. Levelling up: the quest for digital literacy. Toronto (ON): Brookfield Institute; 2018: https://brookfieldinstitute.ca/report/levelling-up/. Accessed 2019 Jul 30.

217. Expanding access to psychotherapy: mapping lessons learned from Australia and the United Kingdom to the Canadian Context. Ottawa (ON): Mental Health Commission of Canada; 2018: https://www.mentalhealthcommission.ca/sites/default/files/2018-08/Expanding_Access_to_Psychotherapy_2018.pdf. Accessed 2019 Sep 3.

218. Belsher BE, Evatt DP, Freed MC, Engel CC. Internet and computer-based treatments for the management of PTSD. In: Benedek DM, Whnn GH, eds. *Complementary and alternative medicine for PTSD*. New York (NY): Oxford University Press; 2016:305-330.

219. Richards D, Enrique A, Palacios J, Duffy D. Internet-delivered cognitive behaviour therapy. In: Şenormancı O, Şenormancı G, eds. *Cognitive behaviour therapy and clinical applications*. London (UK): IntechOpen; 2017: https://www.intechopen.com/books/cognitive-behavioral-therapy-and-clinical-applications/internet-delivered-cognitive-behaviour-therapy. Accessed 2019 Sep 3.

220. Dobson K, Dozois D. Historical and philosophical bases of the cognitive-behavioural therapies. In: Dobson K, ed. *Handbook of cognitive behavioural therapies*. 3rd ed. New York (NY): Guilford Press; 2010.

221. Berliner L, Bisson J, Cloitre M, et al. ISTSS Guidelines position paper on complex PTSD in adults. Oakbrook Terrace (IL): International Society for Traumatic Stress Studies; 2019: https://www.istss.org/getattachment/Treating-Trauma/New-ISTSS-Prevention-and-Treatment-Guidelines/ISTSS_CPTSD-Position-Paper-(Adults)_FNL.pdf.aspx. Accessed 2019 Sep 3.

222. Julian LJ. Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). *Arthritis Care Res (Hoboken).* 2011;63(Suppl 11):S467-472.

223. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry.* 1961;4:561-571.

224. Kersting A, Dolemeyer R, Steinig J, et al. Brief Internet-based intervention reduces posttraumatic stress and prolonged grief in parents after the loss of a child during pregnancy: a randomized controlled trial. *Psychother Psychosom.* 2013;82(6):372-381.

225. Cernvall M, Carlbring P, Wikman A, Ljungman L, Ljungman G, von Essen L. Twelve-month follow-up of a randomized controlled trial of Internet-based guided self-help for parents of children on cancer treatment. *J Med Internet Res.* 2017;19(7):e273.

226. Franklin CL, Cuccurullo LA, Walton JL, Arseneau JR, Petersen NJ. Face to face but not in the same place: a pilot study of prolonged exposure therapy. *J Trauma Dissociation.* 2017;18(1):116-130.

227. Johnston L, Titov N, Andrews G, Spence J, Dear BF. A RCT of a transdiagnostic internet-delivered treatment for three anxiety disorders: examination of support roles and disorder-specific outcomes. *PLoS One.* 2011;6(11):e28079.

228. CASP qualitative checklist. Oxford (UK): Critical Appraisal Skills Programme; 2018: https://casp-uk.net/wp-content/uploads/2018/01/CASP-Qualitative-Checklist-2018.pdf. Accessed 2019 Aug 21.

Appendix 1: Literature Search Strategies

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-June 20, 2019) Embase (1974-2019 June 20) PsycINFO (1806 to June Week 2 2019) Cochrane Central Register of Controlled Trials (May 2019) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 21, 2019
Alerts:	Monthly search updates until project completion
Study Types:	Randomized controlled trials, controlled clinical trials
Limits:	Publication date limit: January 1, 2017-June 21, 2019 Humans

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase, Cochrane Cent)
.id.	Author keyword (PsycINFO)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.yr	Publication year
.jw	Journal word title
freq=#	Requires terms to occur # number of times in the specified fields
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials
psyh	Ovid database code: PsycINFO 1806 to present, updated weekly

MULTI-DATABASE STRATEGY	
Line #	**Search History**
1	Stress Disorders, Post-Traumatic/
2	Stress Disorders, Traumatic/
3	Combat Disorders/
4	Stress Disorders, Traumatic, Acute/
5	((posttrauma* or post-trauma*) adj3 (stress* or disorder* or psych* or symptom*)).ti,ab,kw.
6	PTSD.ti,ab,kw.
7	(acute stress disorder* or combat disorder* or war neuros*).ti,ab,kw.
8	or/1-7
9	(android or app or apps or audio* or blog or iCBT or cCBT or i-CBT or c-CBT or CD-ROM or cell phone* or cellphone or chat or computer* or cyber* or distance* or DVD or eHealth or e-health or electronic health* or e-Portal or ePortal or etherap* or etherap* or forum* or gaming or information technolog* or instant messag* or internet* or interapy or ipad or i-pad or iphone or i-phone or ipod or i-pod or web* or WWW or smart phone or smartphone or mobile phone* or e-mail* or email* or mHealth or m-health or mobile or multi-media or multimedia or online* or on-line or personal digital assistant* or PDA or SMS or social medi* or Facebook or software or telecomm* or telehealth* or telemed* or telemonitor* or telepsych*or teletherap* or text messag* or texting or tape or taped or video* or YouTube or podcast or virtual* or remote).ti,ab,kw.
10	(self adj3 (care or change or guide* or help or intervention or manag* or support* or train*)).ti,ab,kw.
11	9 or 10
12	8 and 11
13	limit 12 to yr="2017 -Current"
14	posttraumatic stress disorder/
15	(PTSD or ((posttrauma* or post-trauma* or post trauma*) adj3 (stress* or disorder* or psych* or symptom?)) or acute stress disorder* or combat disorder* or war neuros*).ti,ab,kw.
16	(((acute or traumatic) adj stress*) and (expos* or psyc*)).ti,ab,kw.
17	(traumati#ed adj (victim? or survivor?)).ti,ab,kw.
18	(trauma* adj2 (event? or memor* or flashback* or nightmare?)).ti,ab,kw.
19	((trauma* or posttrauma* or post-trauma* or victim* or survivor?) and (exposure adj3 (therap* or psychotherap* or training or counsel*))).ti,ab,kw.
20	or/14-19
21	(((internet or web or online) adj3 (cognitive or behavio*)) or iCBT or i-CBT or ePsych* or e-Psych* or cCBT or c-CBT).ti,ab,kw.
22	(android or app or apps or blog* or CD-ROMor cell phone or cellphone or chat room or computer* or cyber* or digital or technology based or DVD or eHealth or e-health or electronic health or e-mail* or email* or e-Portal or ePortal or eTherap* or e-therap* or forum* or gaming or information technolog* or instant messag* or messaging or internet* or ipad or i-pad or iphone or i-phone or ipod or i-pod or podcast or smart phone or smartphone or social network* site* or social networking or mHealth or m-health or mobile or multi-media or multimedia or online* or on-line or personal digital assistant or PDA or SMS or social medi* or software or telecomm* or telehealth* or telemed* or telemonitor* or telepsych* or teletherap* or tele-health* or tele-med* or tele-monitor* or tele-psych* or tele-therap* or text messag* or texting or virtual* or web* or WWW).ti,ab,kw,hw.
23	internet/
24	blogging/ or e-mail/ or social media/ or text messaging/ or videoconferencing/ or webcast/ or wireless communication/
25	telecommunication/ or teleconference/
26	telemedicine/ or telehealth/ or telepsychiatry/ or teletherapy/
27	mobile phone/ or smartphone/

28	mobile application.hw.
29	*technology/
30	computer program/ or digital computer/ or personal computer/ or computer assisted therapy/
31	*computer/
32	(telecomm* or tele-comm*).ti,ab,kw.
33	(eLearning or blended learning).ti,ab,kw.
34	(videoconferenc* or video conferenc*).ti,ab,kw.
35	(synchronous or asynchronous or (electronic adj2 deliver*)).ti,ab,kw.
36	or/22-35
37	(behavio* or cognitive).ti. or (psychotherap* or psychological therap* or cognitive behavio* or ((cognitive or behavio*) adj2 (activat* or component? or defusion or modif* or restructur* or technique* or intervention or treatment* or therap* or train*)) or ((acceptance* or commitment*) adj3 therap*) or rational emotive or RET or problem sol* or PST or problem focus* or solution focus* or trauma focus* or psychoeducat* or psycho-educat* or psychodrama or psycho-drama* or mindfulness* or third wave or self-control or (self* adj3 (control or efficacy)) or stress manage* or exposure or reality therap* or (anxiety adj3 (management or therap* or train*)) or relaxation or guided imagery or present cent* or person cent* or person* construct* or therapeutic process* or schema? or schemata or (thought* adj3 suppress*) or rumination).mp.
38	36 and 37
39	randomized controlled trial/
40	randomization.de.
41	controlled clinical trial/ and (Disease Management or Drug Therapy or Prevention or Rehabilitation or Therapy).fs.
42	*clinical trial/
43	placebo.de.
44	placebo.ti,ab.
45	trial.ti.
46	(randomi#ed or randomi#ation or randomi#ing).ti,ab,kw.
47	(RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*))).ti,ab,kw.
48	((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$ or dummy)).mp.
49	(control* and (trial or study or group) and (placebo or waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,kw,hw.
50	or/39-49
51	((animal or nonhuman) not (human and (animal or nonhuman))).de.
52	50 not 51
53	20 and (21 or 38) and 52
54	(2017* or 2018* or 2019*).yr,dp,dt,ed,ep.
55	53 and 54
56	"Trauma and Stressor Related Disorders"/ or stress disorders, traumatic/ or combat disorders/ or psychological trauma/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/
57	(PTSD or ((posttrauma* or post-trauma* or post trauma*) adj3 (stress* or disorder* or psych* or symptom?)) or acute stress disorder* or combat disorder* or war neuros*).ti,ab,kf.
58	(((acute or traumatic) adj stress*) and (expos* or psyc*)).ti,ab,kf.
59	(traumati#ed adj (victim? or survivor?)).ti,ab,kf.
60	(trauma* adj2 (event? or memor* or flashback* or nightmare?)).ti,ab,kf.

61	((trauma* or posttrauma* or post-trauma* or victim* or survivor?) and (exposure adj3 (therap* or psychotherap* or training or counsel*))).ti,ab,kf.
62	or/56-61
63	(((internet or web or online) adj3 (cognitive or behavio*)) or iCBT or i-CBT or ePsych* or e-Psych* or cCBT or c-CBT).ti,ab,kf.
64	(android or app or apps or blog* or CD-ROMor cell phone or cellphone or chat room or computer* or cyber* or digital or technology based or DVD or eHealth or e-health or electronic health or e-mail* or email* or e-Portal or ePortal or eTherap* or e-therap* or forum* or gaming or information technolog* or instant messag* or messaging or internet* or ipad or i-pad or iphone or i-phone or ipod or i-pod or podcast or smart phone or smartphone or social network* site* or social networking or mHealth or m-health or mobile or multi-media or multimedia or online* or on-line or personal digital assistant or PDA or SMS or social medi* or software or telecomm* or telehealth* or telemed* or telemonitor* or telepsych* or teletherap* or tele-health* or tele-med* or tele-monitor* or tele-psych* or tele-therap* or text messag* or texting or virtual* or web* or WWW).ti,ab,kf,hw.
65	computer communication networks/ or internet/ or blogging/ or social media/
66	cell phones/ or smartphone/ or text messaging/ or videoconferencing/ or webcasts as topic/ or wireless technology/
67	(telecomm* or tele-comm*).ti,ab,kf.
68	Telemedicine/
69	(eLearning or blended learning).ti,kf.
70	(videoconferenc* or video conferenc*).ti,kf.
71	(synchronous or asynchronous or (electronic adj2 deliver*)).ti,kf.
72	or/64-71
73	(behavio* or cognitive).ti. or (psychotherap* or psychological therap* or cognitive behavio* or ((cognitive or behavio*) adj2 (activat* or component? or defusion or modif* or restructur* or technique* or intervention or treatment* or therap* or train*)) or ((acceptance* or commitment*) adj3 therap*) or rational emotive or RET or problem sol* or PST or problem focus* or solution focus* or trauma focus* or psychoeducat* or psycho-educat* or psychodrama or psycho-drama* or mindfulness* or third wave or self-control or (self* adj3 (control or efficacy)) or stress manage* or exposure or reality therap* or (anxiety adj3 (management or therap* or train*)) or relaxation or guided imagery or present cent* or person cent* or person* construct* or therapeutic process* or schema? or schemata or (thought* adj3 suppress*) or rumination).mp.
74	72 and 73
75	controlled clinical trial.pt.
76	randomized controlled trial.pt.
77	(randomi#ed or randomi#ation or randomi#ing).ti,ab,kf.
78	(RCT or at random or (random* adj3 (assign* or allocat* or control* or crossover or cross-over or design* or divide* or division or number))).ti,ab,kf.
79	placebo*.ab,ti,kf.
80	trial.ab,ti,kf.
81	groups.ab.
82	(control* and (trial or study or group*) and (placebo or waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,kf,hw.
83	double-blind method/ or random allocation/ or single-blind method/
84	((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,kf.
85	or/75-84
86	exp animals/ not humans.sh.
87	85 not 86
88	62 and (63 or 74) and 87

89	(2017* or 2018* or 2019*).yr,dp,dt,ed,ep.
90	88 and 89
91	posttraumatic stress disorder/ or complex ptsd/ or acute stress disorder/ or combat experience/ or "debriefing (psychological)"/ or emotional trauma/ or post-traumatic stress/ or exp stress reactions/ or traumatic neurosis/
92	exp DISASTERS/
93	(PTSD or ((posttrauma* or post-trauma* or post trauma*) adj3 (stress* or disorder* or psych* or symptom?)) or acute stress disorder* or combat disorder* or war neuros*).ti,ab,id.
94	(((acute or traumatic) adj stress*) and (expos* or psyc*)).ti,ab,id.
95	(trauma* adj2 (event? or memor* or flashback* or nightmare?)).ti,ab,id.
96	((trauma* or posttrauma* or post-trauma* or victim* or survivor?) and (exposure adj3 (therap* or psychotherap* or training or counsel*))).ti,ab,id,hw.
97	(traumati#ed adj (victim? or survivor?)).ti,ab,id.
98	or/91-97
99	(((internet or web or online) adj3 (cognitive or behavio*)) or iCBT or i-CBT or ePsych* or e-Psych* or cCBT or c-CBT).ti,ab,kf.
100	(android or app or apps or blog* or CD-ROM or cell phone or cellphone or chat room or computer* or cyber* or digital or technology based or DVD or eHealth or e-health or electronic health or e-mail* or email* or e-Portal or ePortal or eTherap* or etherap* or forum* or gaming or information technolog* or instant messag* or messaging or internet* or ipad or i-pad or iphone or iphone or ipod or i-pod or podcast or smart phone or smartphone or social network* site* or social networking or mHealth or m-health or mobile or multi-media or multimedia or online* or on-line or personal digital assistant or PDA or SMS or social medi* or software or telecomm* or telehealth* or telemed* or telemonitor* or telepsych* or teletherap* or tele-health* or tele-med* or tele-monitor* or tele-psych* or tele-therap* or text messag* or texting or virtual* or web* or WWW).ti,ab,id,hw.
101	(telecomm* or tele-comm*).ti,ab,id.
102	(eLearning or blended learning).ti,ab,id.
103	(videoconferenc* or video conferenc*).ti,ab,id.
104	(synchronous or asynchronous or (electronic adj2 deliver*)).ti,ab,id.
105	internet/ or websites/
106	mobile devices/ or cellular phones/
107	social media/ or online social networks/ or blog/ or online community/ or text messaging/
108	electronic communication/ or exp computer mediated communication/ or electronic learning/
109	online therapy/ or telemedicine/
110	telecommunications media/
111	teleconferencing/
112	technology/ or information technology/ or exp computer applications/ or computer software/
113	computers/ or computer games/ or digital computers/ or microcomputers/
114	or/100-113
115	(behavio* or cognitive).ti. or (psychotherap* or psychological therap* or cognitive behavio* or ((cognitive or behavio*) adj2 (activat* or component? or defusion or modif* or restructur* or technique* or intervention or treatment* or therap* or train*)) or ((acceptance* or commitment*) adj3 therap*) or rational emotive or RET or problem sol* or PST or problem focus* or solution focus* or trauma focus* or psychoeducat* or psycho-educat* or psychodrama or psycho-drama* or mindfulness* or third wave or self-control or (self* adj3 (control or efficacy)) or stress manage* or exposure or reality therap* or (anxiety adj3 (management or therap* or train*)) or relaxation or guided imagery or present cent* or person cent* or person* construct* or therapeutic process* or schema? or schemata or (thought* adj3 suppress*) or rumination).ti,ab,id,hw.
116	(self adj (care or change or guide* or help or intervention or manag* or support* or train*)).ti,id.

117	114 and (115 or 116)
118	clinical trials.sh.
119	(randomi#ed or randomi#ation or randomi#ing).ti,ab,id.
120	(RCT or at random or (random* adj3 (assign* or allocat* or control* or crossover or cross-over or design* or divide* or division or number))).ti,ab,id.
121	(control* and (trial or study or group) and (placebo or waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,id,hw.
122	((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,id.
123	trial.ti.
124	placebo.ti,ab,id,hw.
125	treatment outcome.md.
126	treatment effectiveness evaluation.sh.
127	mental health program evaluation.sh.
128	or/118-127
129	98 and (99 or 117) and 128
130	(2017* or 2018* or 2019*).yr,an.
131	129 and 130
132	13 use cctr
133	55 use oemezd
134	90 use medal
135	131 use psyh
136	132 or 133 or 134 or 135
137	remove duplicates from 136

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials. Search: internet | post traumatic stress disorder | CBT	
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search: (internet or web or app or apps or mobile or self) AND ptsd AND CBT	

Patients' Preferences and Experiences Literature Search #1 (iCBT + PTSD)

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-May 21, 2019) PsycINFO (1806-May week 3, 2019) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid for the Ovid searches.
Date of Search:	May 23, 2019
Alerts:	Monthly search updates until project completion
Study Types:	Qualitative studies
Limits:	Publication date limit: January 1, 2008 – May 23, 2019 Language limit: English- and French-language

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.id	Author keyword (PsycINFO)
.pt	Publication type
.mp	Mapped term
.yr	Publication year
.dp	Date of publication
.dt	Create date
.ed	Entry date
.ep	Electronic date of publication
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
psyh	Ovid database code: PsycINFO, 1806 to present, updated weekly

MULTI-DATABASE STRATEGY	
Line #	**Search History**
1	Cognitive Behavioral Therapy/ or "Acceptance and Commitment Therapy"/ or Psychotherapy/ or Desensitization, Psychologic/ or Implosive Therapy/
2	(((cognitive or behavio* or facilitate* or guided or saturat* or unguided) adj2 (therap* or psychotherap* or psycho-therap*)) or cognitive behavio* or cognition therap* or CBT*).ti,ab,kf,kw,id.
3	(self-manag* or selfmanag* or self-help* or selfhelp*).ti,ab,kf,kw,id.
4	((psycholog* adj3 desensiti*) or imaginal flooding* or (imager* adj3 exposure*)).ti,ab,kf,kw,id.
5	((exposure or flooding* or implosive or saturation) adj3 therap*).ti,ab,kf,kw,id.
6	or/1-5
7	Internet/ or exp Computers/ or Therapy, Computer-Assisted/ or Computer-Assisted Instruction/ or Distance Counseling/ or Cell Phone/ or Mobile Applications/ or Remote Consultation/ or exp Telemedicine/ or exp Videoconferencing/
8	(internet* or Beacon or app or apps or computer* or cyber-therap* or cybertherap* or e mail* or email* or electronic mail* or "Information and communication technology" or "Information and communication technologies" or emedicine or e medicine or ehealth* or e health* or emental health* or e mental health* or etherap* or e therap* or epsychiatr* or e psychiatr* or epsychol* or e psychol* or media deliver* or mobile* or online* or smartphone* or smart phone* or telemedicine or tele medicine or telehealth* or tele health* or telemental health* or tele mental health* or telecare or tele care or teletherap* or tele therap* or telepsychiatr* or tele psychiatr* or telepsychol* or tele psychol* or telepsycho-therap* or tele-psycho-therap* or telepsychotherap* or tele-psychotherap* or tele-coach* or telecoach* or virtual or virtualist? or webbased or web based or web deliver* or webdeliver*).ti,ab,kf,kw,id.
9	or/7-8
10	exp Stress Disorders, Traumatic/
11	(PTSD or posttrauma* or post-trauma* or panic disorder* or panic attack* or shell shock or war neurosis or war neuroses or acute stress disorder* or operational stress or past trauma* or PTD or complex trauma* or traumatic stress or moral injur* or trauma-base* or trauma-focus*).ti,ab,kf,kw,id.
12	(combat* adj3 (neuroses* or neurosis* or stress* or fatigue* or disorder*)).ti,ab,kf,kw,id.
13	or/10-12
14	(cCBT* or iCBT* or eCBT*).ti,ab,kf,kw,id.
15	((computer* or cyber* or digital* or technolog* or web*) adj6 (CBT or coach* or deliver* or intervention* or psychiatr* or psycho-dynamic or psychodynamic or psycholog* or psycho-therap* or psychotherap* or therap* or technique* or training or treatment*)).ti,ab,kf,kw,id.
16	(MoodGym or Big White Wall or Beating the Blues or Fear Fighter or E compass or Ecompass or Deprexis or Moodkit or "Living Life to the Full" or Woebot).ti,ab,kf,kw,id.
17	(e-mental health or emental health).ti,ab,kf,kw,id.
18	(ACT Coach or (("Anger and Irritability Management Skills" or AIMS) adj5 app*) or Behavior Tracker Pro or Breathe2Relax or CBT-I Coach or CPT Coach or (cognitive processing therap* adj2 coach*) or Dream EZ or Life Armor or Mood Coach or Moving Forward or PE Coach or PTSD Coach or "T2 Mood Tracker" or Tactical Breather or VetChange or Interapy).ti,ab,kf,kw,id.
19	or/14-18
20	6 and 9 and 13
21	13 and 19
22	20 or 21
23	22 use medall
24	exp Cognitive Behavior Therapy/ or Cognitive Therapy/
25	(((cognitive or behavio* or facilitate* or guided or saturat* or unguided) adj2 (therap* or psychotherap* or psycho-therap*)) or cognitive behavio* or cognition therap* or CBT*).ti,ab,kf,kw,id.

26	(self-manag* or selfmanag* or self-help* or selfhelp*).ti,ab,kf,kw,id.
27	((psycholog* adj3 desensiti*) or imaginal flooding* or (imager* adj3 exposure*)).ti,ab,kf,kw,id.
28	((exposure or flooding* or implosive or saturation) adj3 therap*).ti,ab,kf,kw,id.
29	or/24-28
30	Telemedicine/ or Computer-Assisted therapy/ or Computer-Assisted Instruction/ or Internet/ or exp Mobile Devices/ or Online Therapy/
31	(internet* or Beacon or app or apps or computer* or cyber-therap* or cybertherap* or e mail* or email* or electronic mail* or "Information and communication technology" or "Information and communication technologies" or emedicine or e medicine or ehealth* or e health* or emental health* or e mental health* or etherap* or e therap* or epsychiatr* or e psychiatr* or epsychol* or e psychol* or media deliver* or mobile* or online* or smartphone* or smart phone* or telemedicine or tele medicine or telehealth* or tele health* or telemental health* or tele mental health* or telecare or tele care or teletherap* or tele therap* or telepsychiatr* or tele psychiatr* or telepsychol* or tele psychol* or telepsycho-therap* or tele-psycho-therap* or telepsychotherap* or tele-psychotherap* or tele-coach* or telecoach* or virtual or virtualist? or webbased or web based or web deliver* or webdeliver*).ti,ab,kf,kw,id.
32	or/30-31
33	exp Posttraumatic Stress Disorder/ or Combat Experience/ or Emotional Trauma/ or Post-Traumatic Stress/ or Traumatic Neurosis/
34	(PTSD or posttrauma* or post-trauma* or panic disorder* or panic attack* or shell shock or war neurosis or war neuroses or acute stress disorder* or operational stress or past trauma* or PTD or complex trauma* or traumatic stress or moral injur* or trauma-base* or trauma-focus*).ti,ab,kf,kw,id.
35	(combat* adj3 (neuroses* or neurosis* or stress* or fatigue* or disorder*)).ti,ab,kf,kw,id.
36	or/33-35
37	(cCBT* or iCBT* or eCBT*).ti,ab,kf,kw,id.
38	((computer* or cyber* or digital* or technolog* or web*) adj6 (CBT or coach* or deliver* or intervention* or psychiatr* or psycho-dynamic or psychodynamic or psycholog* or psycho-therap* or psychotherap* or therap* or technique* or training or treatment*)).ti,ab,kf,kw,id.
39	(MoodGym or Big White Wall or Beating the Blues or Fear Fighter or E compass or Ecompass or Deprexis or Moodkit or "Living Life to the Full" or Woebot).ti,ab,kf,kw,id.
40	(e-mental health or emental health).ti,ab,kf,kw,id.
41	(ACT Coach or (("Anger and Irritability Management Skills" or AIMS) adj5 app*) or Behavior Tracker Pro or Breathe2Relax or CBT-I Coach or CPT Coach or (cognitive processing therap* adj2 coach*) or Dream EZ or Life Armor or Mood Coach or Moving Forward or PE Coach or PTSD Coach or "T2 Mood Tracker" or Tactical Breather or VetChange or Interapy).ti,ab,kf,kw,id.
42	or/37-41
43	29 and 32 and 36
44	36 and 42
45	43 or 44
46	45 use psyh
47	23 or 46
48	47 and (english or french).la.
49	limit 48 to yr="2008 -Current"
50	exp Empirical Research/ or Interviews as Topic/ or Personal Narratives/ or Focus Groups/ or exp Narration/ or Nursing Methodology Research/ or Narrative Medicine/
51	Interview/
52	Qualitative Research/ or Grounded Theory/ or Narratives/ or Storytelling/ or exp Life Experiences/ or exp Interviews/
53	interview*.ti,ab,kf,id.

54	qualitative*.ti,ab,kf,jw,id.
55	(theme* or thematic).ti,ab,kf,id.
56	ethnological research.ti,ab,kf,id.
57	ethnograph*.ti,ab,kf,id.
58	ethnomedicine.ti,ab,kf,id.
59	ethnonursing.ti,ab,kf,id.
60	phenomenol*.ti,ab,kf,id.
61	(grounded adj (theor* or study or studies or research or analys?s)).ti,ab,kf,id.
62	(life stor* or women* stor*).ti,ab,kf,id.
63	(emic or etic or hermeneutic* or heuristic* or semiotic*).ti,ab,kf,id.
64	(data adj1 saturat$).ti,ab,kf,id.
65	participant observ*.ti,ab,kf,id.
66	(social construct* or postmodern* or post-structural* or post structural* or poststructural* or post modern* or post-modern* or feminis*).ti,ab,kf,id.
67	(action research or cooperative inquir* or co operative inquir* or co-operative inquir*).ti,ab,kf,id.
68	(humanistic or existential or experiential or paradigm*).ti,ab,kf,id.
69	(field adj (study or studies or research or work)).ti,ab,kf,id.
70	(human science or social science).ti,ab,kf,id.
71	biographical method.ti,ab,kf,id.
72	theoretical sampl*.ti,ab,kf,id.
73	((purpos* adj4 sampl*) or (focus adj group*)).ti,ab,kf,id.
74	(open-ended or narrative* or textual or texts or semi-structured).ti,ab,kf,id.
75	(life world* or life-world* or conversation analys?s or personal experience* or theoretical saturation).ti,ab,kf,id.
76	((lived or life) adj experience*).ti,ab,kf,id.
77	cluster sampl*.ti,ab,kf,id.
78	observational method*.ti,ab,kf,id.
79	content analysis.ti,ab,kf,id.
80	(constant adj (comparative or comparison)).ti,ab,kf,id.
81	((discourse* or discurs*) adj3 analys?s).ti,ab,kf,id.
82	(heidegger* or colaizzi* or spiegelberg* or merleau* or husserl* or foucault* or ricoeur or glaser*).ti,ab,kf,id.
83	(van adj manen*).ti,ab,kf,id.
84	(van adj kaam*).ti,ab,kf,id.
85	(corbin* adj2 strauss*).ti,ab,kf,id.
86	or/50-85
87	49 and 86
88	remove duplicates from 87

OTHER DATABASES	
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
CINAHL	Same MeSH, keywords, and limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for EBSCO platform, including the addition of CINAHL headings.

Patients' Preferences and Experiences Literature Search #2 (CBT + PTSD)

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-July 15, 2019) PsycINFO (1806-July week 2, 2019) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid for the Ovid searches.
Date of Search:	July 16, 2019
Alerts:	Monthly search updates until project completion
Study Types:	Qualitative studies
Limits:	Publication date limit: January 1, 2014 – July 16, 2019 Language limit: English- and French-language

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.id	Author keyword (PsycINFO)
.pt	Publication type
.mp	Mapped term
.yr	Publication year
.dp	Date of publication
.dt	Create date
.ed	Entry date
.ep	Electronic date of publication
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
psyh	Ovid database code: PsycINFO, 1806 to present, updated weekly

MULTI-DATABASE STRATEGY	
Line #	**Search History**
1	Cognitive Behavioral Therapy/ or "Acceptance and Commitment Therapy"/ or Psychotherapy/ or Desensitization, Psychologic/ or Implosive Therapy/
2	(((cognitive or behavio* or facilitate* or guided or saturat* or unguided) adj2 (therap* or psychotherap* or psycho-therap*)) or cognitive behavio* or cognition therap* or CBT*).ti,ab,kf,kw,id.
3	(self-manag* or selfmanag* or self-help* or selfhelp*).ti,ab,kf,kw,id.
4	((psycholog* adj3 desensiti*) or imaginal flooding* or (imager* adj3 exposure*)).ti,ab,kf,kw,id.
5	((exposure or flooding* or implosive or saturation) adj3 therap*).ti,ab,kf,kw,id.
6	or/1-5
7	exp Stress Disorders, Traumatic/
8	(PTSD or posttrauma* or post-trauma* or panic disorder* or panic attack* or shell shock or war neurosis or war neuroses or acute stress disorder* or operational stress or past trauma* or PTD or complex trauma* or traumatic stress or moral injur* or trauma-base* or trauma-focus*).ti,ab,kf,kw,id.
9	(combat* adj3 (neuroses* or neurosis* or stress* or fatigue* or disorder*)).ti,ab,kf,kw,id.
10	or/7-9
11	6 and 10
12	11 use medall
13	exp Cognitive Behavior Therapy/ or Cognitive Therapy/
14	(((cognitive or behavio* or facilitate* or guided or saturat* or unguided) adj2 (therap* or psychotherap* or psycho-therap*)) or cognitive behavio* or cognition therap* or CBT*).ti,ab,kf,kw,id.
15	(self-manag* or selfmanag* or self-help* or selfhelp*).ti,ab,kf,kw,id.
16	((psycholog* adj3 desensiti*) or imaginal flooding* or (imager* adj3 exposure*)).ti,ab,kf,kw,id.
17	((exposure or flooding* or implosive or saturation) adj3 therap*).ti,ab,kf,kw,id.
18	or/13-17
19	exp Posttraumatic Stress Disorder/ or Combat Experience/ or Emotional Trauma/ or Post-Traumatic Stress/ or Traumatic Neurosis/
20	(PTSD or posttrauma* or post-trauma* or panic disorder* or panic attack* or shell shock or war neurosis or war neuroses or acute stress disorder* or operational stress or past trauma* or PTD or complex trauma* or traumatic stress or moral injur* or trauma-base* or trauma-focus*).ti,ab,kf,kw,id.
21	(combat* adj3 (neuroses* or neurosis* or stress* or fatigue* or disorder*)).ti,ab,kf,kw,id.
22	or/19-21
23	18 and 22
24	23 use psyh
25	12 or 24
26	25 and (english or french).la.
27	limit 26 to yr="2014 -Current"
28	exp Empirical Research/ or Interview/ or Interviews as Topic/ or Personal Narratives/ or Focus Groups/ or exp Narration/ or Nursing Methodology Research/ or Narrative Medicine/
29	Interview/
30	Qualitative Research/ or Grounded Theory/ or Narratives/ or Storytelling/ or exp Life Experiences/ or exp Interviews/
31	interview*.ti,ab,kf,id.
32	qualitative*.ti,ab,kf,jw,id.
33	(theme* or thematic).ti,ab,kf,id.

34	ethnological research.ti,ab,kf,id.
35	ethnograph*.ti,ab,kf,id.
36	ethnomedicine.ti,ab,kf,id.
37	ethnonursing.ti,ab,kf,id.
38	phenomenol*.ti,ab,kf,id.
39	(grounded adj (theor* or study or studies or research or analys?s)).ti,ab,kf,id.
40	(life stor* or women* stor*).ti,ab,kf,id.
41	(emic or etic or hermeneutic* or heuristic* or semiotic*).ti,ab,kf,id.
42	(data adj1 saturat$).ti,ab,kf,id.
43	participant observ*.ti,ab,kf,id.
44	(social construct* or postmodern* or post-structural* or post structural* or poststructural* or post modern* or post-modern* or feminis*).ti,ab,kf,id.
45	(action research or cooperative inquir* or co operative inquir* or co-operative inquir*).ti,ab,kf,id.
46	(humanistic or existential or experiential or paradigm*).ti,ab,kf,id.
47	(field adj (study or studies or research or work)).ti,ab,kf,id.
48	(human science or social science).ti,ab,kf,id.
49	biographical method.ti,ab,kf,id.
50	theoretical sampl*.ti,ab,kf,id.
51	((purpos* adj4 sampl*) or (focus adj group*)).ti,ab,kf,id.
52	(open-ended or narrative* or textual or texts or semi-structured).ti,ab,kf,id.
53	(life world* or life-world* or conversation analys?s or personal experience* or theoretical saturation).ti,ab,kf,id.
54	((lived or life) adj experience*).ti,ab,kf,id.
55	cluster sampl*.ti,ab,kf,id.
56	observational method*.ti,ab,kf,id.
57	content analysis.ti,ab,kf,id.
58	(constant adj (comparative or comparison)).ti,ab,kf,id.
59	((discourse* or discurs*) adj3 analys?s).ti,ab,kf,id.
60	(heidegger* or colaizzi* or spiegelberg* or merleau* or husserl* or foucault* or ricoeur or glaser*).ti,ab,kf,id.
61	(van adj manen*).ti,ab,kf,id.
62	(van adj kaam*).ti,ab,kf,id.
63	(corbin* adj2 strauss*).ti,ab,kf,id.
64	or/28-63
65	27 and 64
66	remove duplicates from 65

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
CINAHL	Same MeSH, keywords, and limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for EBSCO platform, including the addition of CINAHL headings.	

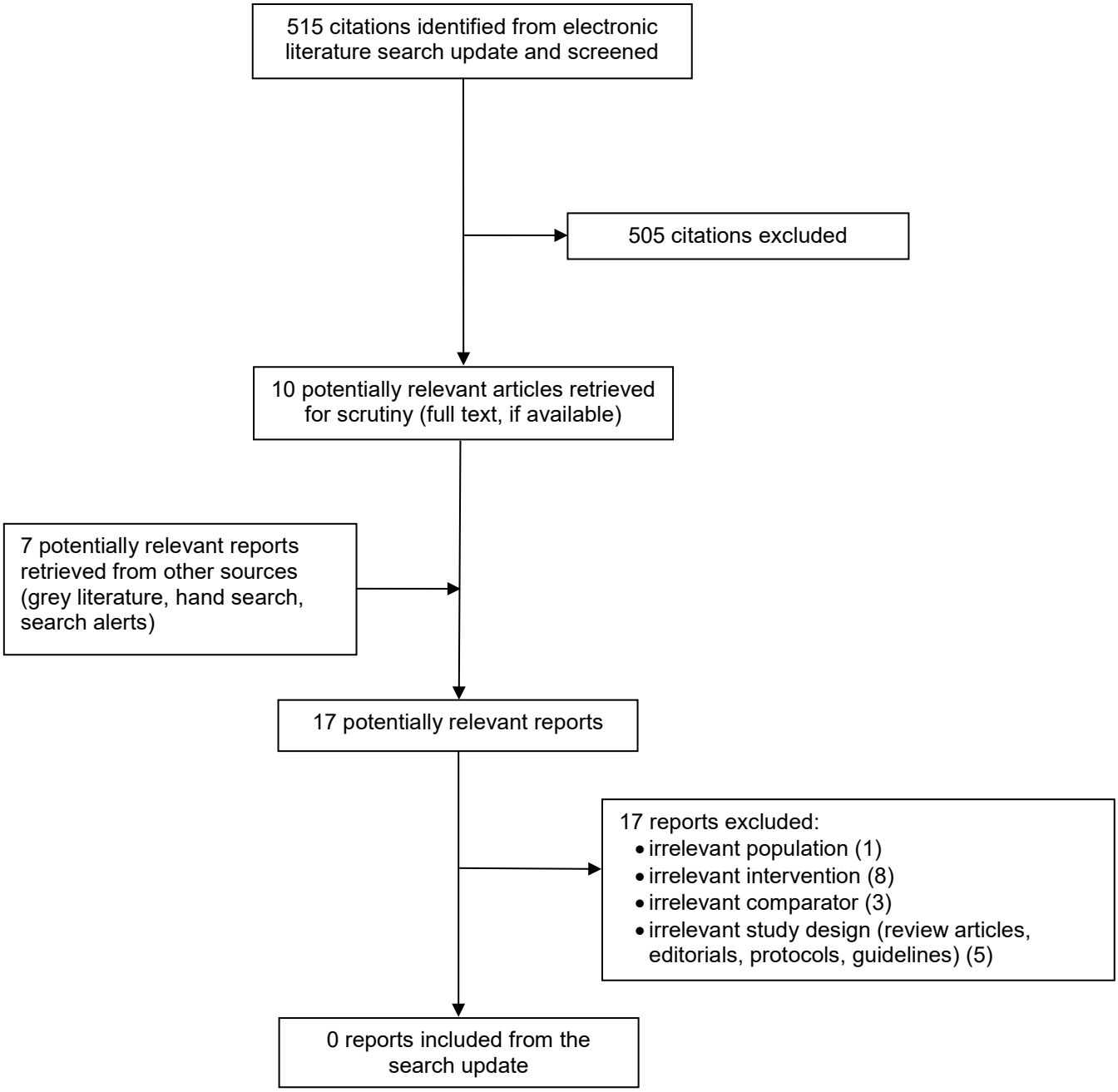
Grey Literature

Dates for Search:	June 10, 2019 - July 4, 2019
Keywords:	Internet, Cognitive Behavioural Therapy, PTSD
Limits:	Publication years: January 1, 2008 – present

Relevant websites from the following sections of the CADTH grey literature checklist, Grey Matters: A Practical Tool For Searching Health-Related Grey Literature (https://www.cadth.ca/grey-matters),[43] were searched:

- health technology assessment agencies
- health economics
- clinical practice guidelines
- clinical trial registries
- databases (free)
- Internet search
- open access journals.

Appendix 2: Study Selection Flow Diagram — Clinical Review



Appendix 3: List of Included Studies — Clinical Review

The citations provided in the following list are the primary studies that were included in the Cochrane review.[40] No additional studies eligible for inclusion were identified as part of our update to the Cochrane search.

1. Krupnick JL, Green BL, Amdur R, et al. An Internet-based writing intervention for PTSD in veterans: a feasibility and pilot effectiveness trial. Psychol Trauma. 2017;9(4):461-470.
2. Kuhn E, Kanuri N, Hoffman JE, Garvert DW, Ruzek JI, Taylor CB. A randomized controlled trial of a smartphone app for posttraumatic stress disorder symptoms. J Consult Clin Psychol. 2017;85(3):267-273.
3. Lewis CE, Farewell D, Groves V, et al. Internet-based guided self-help for posttraumatic stress disorder (PTSD): randomized controlled trial. Depress Anxiety. 2017;34(6):555-565.
4. Littleton H, Grills AE, Kline KD, Schoemann AM, Dodd JC. The From Survivor to Thriver program: RCT of an online therapist-facilitated program for rape-related PTSD. J Anxiety Disord. 2016;43:41-51.
5. Miner A, Kuhn E, Hoffman JE, Owen JE, Ruzek JI, Taylor CB. Feasibility, acceptability, and potential efficacy of the PTSD Coach app: a pilot randomized controlled trial with community trauma survivors. Psychol Trauma. 2016;8(3):384-392.
6. Engel CC, Litz B, Magruder KM, et al. Delivery of self training and education for stressful situations (DESTRESS-PC): a randomized trial of nurse assisted online self-management for PTSD in primary care. Gen Hosp Psychiatry. 2015;37(4):323-328.
7. Knaevelsrud C, Brand J, Lange A, Ruwaard J, Wagner B. Web-based psychotherapy for posttraumatic stress disorder in war-traumatized Arab patients: randomized controlled trial. J Med Internet Res. 2015;17(3):e71.
8. Ivarsson D, Blom M, Hesser H, et al. Guided internet-delivered cognitive behavior therapy for post-traumatic stress disorder: a randomized controlled trial. Internet Interv. 2014;1(1):33-40.
9. Spence J, Titov N, Dear BF, et al. Randomized controlled trial of Internet-delivered cognitive behavioral therapy for posttraumatic stress disorder. Depress Anxiety. 2011;28(7):541-550.
10. Litz BT, Engel CC, Bryant RA, Papa A. A randomized, controlled proof-of-concept trial of an Internet-based, therapist-assisted self-management treatment for posttraumatic stress disorder. Am J Psychiatry. 2007;164(11):1676-1683.

Studies Identified for the Discussion Section

The citations provided in the following list met the eligibility criteria for the CADTH Rapid Response report[41] but not for the body of the review. A brief summary of its findings was provided in the discussion section of the health technology assessment.

1. Spence J, Titov N, Johnston L, Jones MP, Dear BF, Solley K. Internet-based trauma-focused cognitive behavioural therapy for PTSD with and without exposure components: a randomised controlled trial. J Affect Disord. 2014;162:73-80.

Appendix 4: List of Excluded Studies and Reasons for Exclusion — Clinical Review

The citations provided in the following list are studies that were excluded after full-text assessment by two independent reviewers as part of the update to the Cochrane search. A list of articles excluded after full-text review from the original Cochrane search is available in the Cochrane review.[40]

Irrelevant Population

1. Taylor DJ, Peterson AL, Pruiksma KE, et al. Impact of cognitive behavioral therapy for insomnia disorder on sleep and comorbid symptoms in military personnel: a randomized clinical trial. Sleep. 2018;41(6):01.

Irrelevant Intervention

2. Capone C, Presseau C, Saunders E, Eaton E, Hamblen J, McGovern M. Is integrated CBT effective in reducing PTSD symptoms and substance use in Iraq and Afghanistan veterans? Results from a randomized clinical trial. Cognit Ther Res. 2018;42(6):735-746.
3. Darvish A, Khodadadi-Hassankiadeh N, Abdoosti S, Ghapandar Kashani M. Effect of text messaging-based psychiatric nursing program on quality of life in veterans with post-traumatic stress disorder: a randomized controlled trial. Int J Community Based Nurs Midwifery. 2019;7(1):52-62.
4. Elbogen EB, Dennis PA, Van Voorhees EE, et al. Cognitive rehabilitation with mobile technology and social support for veterans with TBI and PTSD: a randomized clinical trial. J Head Trauma Rehabil. 2019;34(1):1-10.
5. Elwy AR, Kim B, Plumb DN, et al. The connectedness of mental health providers referring patients to a treatment study for post-traumatic stress: a social network study. Adm Policy Ment Health. 2019.
6. Fonzo GA, Fine NB, Wright RN, et al. Internet-delivered computerized cognitive & affective remediation training for the treatment of acute and chronic posttraumatic stress disorder: two randomized clinical trials. J Psychiatr Res. 2019;115:82-89.
7. Gehrman P, Bellamy S, Medvedeva E, et al. Telehealth delivery of group CBT-I is noninferior to in-person treatment in veterans with PTSD. Sleep. 2018;41 (Suppl 1):A141-A142.
8. Laurel Franklin C, Walton JL, Raines AM, et al. Pilot study comparing telephone to in-person delivery of cognitive-behavioural therapy for trauma-related insomnia for rural veterans. J Telemed Telecare. 2018;24(9):629-635.
9. Nickerson A, Byrow Y, Pajak R, et al. 'Tell Your Story': a randomized controlled trial of an online intervention to reduce mental health stigma and increase help-seeking in refugee men with posttraumatic stress. Psychol Med. 2019.

Irrelevant Comparator

10. Murphy D, Turgoose D. Evaluating an Internet-based video cognitive processing therapy intervention for veterans with PTSD: a pilot study. J Telemed Telecare. 2019:1357633x19850393.
11. Smith SK, Kuhn E, O'Donnell J, et al. Cancer distress coach: Pilot study of a mobile app for managing posttraumatic stress. Psychooncology. 2018;27(1):350-353.
12. Tiet QQ, Duong H, Davis L, et al. PTSD coach mobile application with brief telephone support: a pilot study. Psychol Serv. 2019;16(2):227-232.

Irrelevant Study Design

13. 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;7(2):e014363.
14. Hoffmann R, Grosse J, Nagl M, Mehnert A, Kersting A. Internet-based therapy for bereaved persons after loss due to hematological cancer. Psychooncology. 2017;26 (Suppl 3):158.
15. Kuhn E, van der Meer C, Owen JE, et al. PTSD Coach around the world. Began with 2015. 2018;4:15.
16. Smith S. Evolution of a mobile app to manage cancer-related post-traumatic stress. *Psycho oncology.* 2019;28(19).
17. Post-traumatic stress disorder. *NICE guideline*. London (UK): National Institute for Health and Care Excellence (NICE); 2018.

Appendix 5: Summary of the Cochrane Review

Table 14: Study Characteristics of the Cochrane Systematic Review

Study Citation, Country, Funding Source	Study Designs, Search Time Frame, Number of Studies Included, Quality Assessment Tool, Objective	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes
Lewis et al., 2018[40] UK **Funding source:** The authors acknowledge the Cochrane Common Mental Disorder Group, whose single largest funder is the National Institute for Health Research (NIHR). Internal support was received from Cardiff University.	**Objective**: To evaluate the effectiveness of iCBT for the treatment of PTSD in adults. **Study design**: SR and MA of RCTs, randomized crossover trials, and cluster-randomized trials. **Literature search time frame**: Initial searches were conducted on September 24th, 2015, and May 6th, 2016. An update was performed on March 1st, 2018. The searches were not restricted by date, language, or publication status. **Number of studies included**: 10 studies were identified and included in the quantitative synthesis (MA). **Quality assessment tool**: The criteria in the *Cochrane Handbook for Systematic Reviews of Interventions*[44] were applied to each included primary study to judge each potential source of bias as high, low, or unclear. The overall quality of available evidence was evaluated using the GRADE approach.	Adults (≥ 16 years of age) with traumatic stress symptoms. At least 70% of participants in any given study were required to meet diagnostic criteria for PTSD according to the *DSM-III, DSM-IIIR, DSM-IV, DSM-V, ICD-9, or the ICD-10*, as assessed by clinical interview or a validated questionnaire. There were no restrictions placed on sex or gender, ethnicity, comorbidities, setting, type of traumatic event, severity of symptoms, or length of time since trauma.	**Intervention**: Guided or unguided iCBT delivered via a computer or mobile device. Interventions based on EMDR or online psychoeducation alone, and interventions using mindfulness-based approaches apart from mindfulness-based iCBT, were excluded. **Comparators**: Face-to-face psychological therapy (CBT based), face-to-face psychological therapy (non-CBT based; e.g., EMDR, supportive therapy, non-directive counselling, psychodynamic therapy, and present-centred therapy), wait-list, repeated assessment, usual care, internet psychoeducation, internet psychological therapy (non-CBT).	• Severity of PTSD symptoms (as measured by standardized scales, e.g., CAPS-5, PCL-5) • Dropout rates • Diagnosis of PTSD after treatment (i.e., number of participants who met diagnostic criteria for PTSD in each arm of the study) • Depression symptoms (as measured by standardized scales; e.g., BDI) • Anxiety symptoms (as measured by standardized scales; e.g., BAI) • Cost-effectiveness • Adverse events (e.g., symptoms worsening, relapses to substance use, hospitalizations, suicide attempts, work absenteeism) • Quality of life (using any measures) **Note**: Studies that met the inclusion criteria were included regardless of whether they reported on these outcomes.

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CAPS = Clinician-Administered Post-Traumatic Stress Disorder Scale; CBT = cognitive behavioural therapy; *DSM = Diagnostic and Statistical Manual of Mental Disorders*; EMDR = eye movement desensitization and reprocessing; GRADE = Grading of Recommendations Assessment, Development and Evaluation; iCBT = internet-delivered cognitive behavioural therapy; *ICD = The International Statistical Classification of Diseases and Health Related Problems*; MA = meta-analysis; PCL = Post-Traumatic Stress Disorder Checklist; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; SR = systematic review.

Appendix 6: Critical Appraisal of the Cochrane Review

Table 15: A Measurement Tool to Assess Systematic Reviews II Checklist

AMSTAR II Item	Lewis (2018)[40]
Did the research questions and inclusion criteria for the review include the components of PICO?	⊕
[a]Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	⊕
Did the review authors explain their selection of the study designs for inclusion in the review?	X
[a]Did the review authors use a comprehensive literature search strategy?	⊕
Did the review authors perform study selection in duplicate?	⊕
Did the review authors perform data extraction in duplicate?	⊕
[a] Did the review authors provide a list of excluded studies and justify the exclusions?	⊕
Did the review authors describe the included studies in adequate detail?	⊕
[a] Did the review authors use a satisfactory technique for assessing the RoB in individual studies that were included in the review?	⊕
Did the review authors report on the sources of funding for the studies included in the review?	⊕
[a] If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	⊕
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	⊕
[a] Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	⊕
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	⊕
[a] If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	⊕
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	⊕

⊕ = yes; X = no; AMSTAR = A Measurement Tool to Assess Systematic Reviews; RoB = risk of bias.

[a] = AMSTAR II critical domains.

Appendix 7: Characteristics of Included Primary Studies — Clinical Review

Table 16: Study and Patient Characteristics of Included Primary Clinical Studies

Author(s) (Publication Year), Country, Funding Source	Study Design, Setting, and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes; Length of Follow Up
iCBT Versus Wait-List or Usual Care					
Krupnick et al. (2017),[66] US **Funding source:** A grant from the Telemedicine and Advanced Technology Research Center, U.S. Department of Defense	**Study design**: RCT, open label, 1:1 ratio **Setting**: Participants were recruited from the Trauma Services Program, an outpatient program that specialized in the assessment and treatment of veterans with military-related PTSD **Objective**: To determine the feasibility, acceptability, safety, and preliminary effectiveness of an online writing intervention based on principles of CBT compared with treatment as usual	**Inclusion criteria**: Veterans (≥ 18 years of age) who served in Iraq or Afghanistan with a PCL-M score > 50 **Excluded**: Individuals with current substance dependence, acute suicidality, psychosis, gross cognitive impairment, or current participants in CBT **Number of participants**: 34 (18 in iCBT group, 16 in usual care group) **Mean age**: 35.44 (SD = NR) years in the iCBT + TAU group; 44.75 (SD = NR) years, in the TAU group **Sex**: 8.8% female; 91.2% male **Type of trauma**: Military trauma **Mean time since trauma**: NR **Baseline PTSD severity**: Baseline PCL-M score (mean item score) of 3.6 (SD = 0.3) in	Therapist-guided iCBT (WIRED, based on interapy) plus treatment as usual (details not provided). The program involved trauma confrontation, cognitive restructuring of maladaptive thoughts, and discussion of leave-taking and social sharing **Number of sessions**: 10 **Treatment duration**: NR **Guidance**: Support was provided by a psychologist as required by the study participants. A short response and further instructions were sent by the therapist after each writing session. Guidance was provided online	Treatment as usual with no restrictions. A chart review conducted at the end of the study showed that participants in this group received cognitive processing therapy (n = 4), antidepressant medication (n = 8), or acupuncture (n = 1)	**Outcomes**: • PCL-M • PHQ-9 • AUDIT **Follow up**: 12 weeks and 24 weeks

Author(s) (Publication Year), Country, Funding Source	Study Design, Setting, and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes; Length of Follow Up
		the iCBT + TAU group; baseline PCL-M score (mean item score) of 3.9 (SD = 0.4) in the TAU alone group **Comorbidities**: The study did not screen for comorbid conditions			
Kuhn et al. (2017),[53] US **Funding source:** NR	**Study design**: RCT, open label, 1:1 ratio **Setting**: Participants were recruited using advertisements through fliers, media coverage, social media, and websites (Craigslist) **Objective**: The aim of the study was to evaluate the efficacy of a freely available smartphone app (PTSD Coach), which includes CBT-based tools for the treatment of PTSD	**Inclusion criteria**: Adults (≥ 18 years of age) who were fluent in English, owned a mobile device capable of using PTSD Coach, had exposure to a traumatic event more than one month ago, and who had a PCL-C score of ≥ 35 **Excluded**: Individuals who were receiving any treatment for PTSD **Number of participants**: 120 (62 in iCBT group, 58 in WL group) **Mean age**: 39.43 (SD = 15.16) years in the iCBT group; 39.12 (SD = 14.08) years in the WL group **Sex**: 69.2% female, 30.8% male **Type of trauma**: Physical assault (n = 56), sexual assault (n = 17), serious accident (n = 25), life-threatening illness	Unguided internet program based on CBT (PTSD Coach). While PTSD Coach includes sections that provide participants with CBT-based tools, the program appears to be much less structured than other iCBT software **Number of sessions**: The program was not broken down into sessions **Treatment duration**: 12 weeks **Guidance**: The program did not include therapist guidance	WL control. Participants were on a wait-list for 14 weeks and then received information on PTSD Coach, allowing them to use it if they would like This group received no intervention during the treatment period	**Primary outcomes**: • PCL **Secondary outcomes**: • PTSD symptom coping self-efficacy • PHQ-8 • B-IPF **Follow up**: 3 months (post-treatment) and 6 months (there no data for the wait-list group available at second follow up)

Author(s) (Publication Year), Country, Funding Source	Study Design, Setting, and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes; Length of Follow Up
		or injury (n = 7), disaster exposure (n = 3), combat exposure (n = 4), and other events (n = 8) were reported as index traumas for participants in both groups **Mean time since trauma**: 9.88 (SD = 11.59) years in the iCBT group; 9.77 (SD = 10.22) years in the WL group **Baseline PTSD severity**: Mean PCL-C score of 63.19 (SD = 11.78) in the iCBT group; mean PCL-C score of 60.59 (SD = 10.24) in the WL group **Comorbidities**: NR			
Lewis et al. (2017),[52] UK **Funding source**: Knowledge Transfer Partnership (KTP008512)	**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	**Inclusion criteria**: Adults (≥ 18 years of age) who met the diagnostic criteria for *DSM-V* PTSD (as measured by CAPS-5) of mild-to-moderate severity after a two-week period of symptom monitoring **Excluded**: Individuals with psychosis, previous trauma-focused psychological therapy, severe major depressive episode (as defined in the *DSM-V*), substance dependence, inability to read and write fluent English, inability to access the internet, change in	Therapist-guided trauma-focused iCBT. The modules included psycho-educational materials, grounding techniques, relaxation exercises, imaginal exposure, cognitive techniques to address negative thoughts, and graded in vivo exposure work **Number of sessions**: 8 modules	WL control (delayed treatment group). Participants were on a wait-list for 14 weeks and then received the iCBT intervention 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)

Author(s) (Publication Year), Country, Funding Source	Study Design, Setting, and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes; Length of Follow Up
	Objective: "To evaluate a novel trauma-focused internet-based guided self-help program for PTSD"[52] (p. 556)	psychotropic medication in the previous month, concurrent psychological therapy, and suicidal intent **Number of participants**: 42 (21 in iCBT group, 21 in WL group) **Mean age**: 38.86 (SD = 11.91) years, range = 20 to 65 years in the iCBT group; 37.71 (SD = 13.8) years, range = 21-64 years in the WL (delayed treatment) group **Sex**: 59.5% female; 40.5% male **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 or detained (n = 1). The average time since trauma was 37.33 months (SD = 46.95, range = 3 to 228 months)	**Treatment duration**: 8 weeks **Guidance**: The intervention allowed up to three 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. Guidance was provided in face-to-face meetings, over the telephone, or by email		**Follow up**: 10 weeks (post-treatment), 14 weeks (1 month post-treatment), and 22 weeks (3 months post-treatment)

Author(s) (Publication Year), Country, Funding Source	Study Design, Setting, and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes; Length of Follow Up
		Mean time since trauma: 2.72 (SD = 4.34) years in the iCBT group; 3.54 (SD = 3.45) years in the WL (delayed treatment) group **Baseline PTSD severity**: Mean CAPS-5 score of 35.99 (SD = 6.29) in the iCBT group; mean CAPS-5 score of 37.12 (SD = 6.95) in the WL (delayed treatment) group **Comorbidities**: NR			
Miner et al. (2016),[67] US **Funding source**: NR	Study design: RCT, open label, 1:1 ratio **Setting**: Participants were recruited using fliers posted in the San Francisco Bay Area as well as through website postings (e.g., Craigslist) seeking volunteers who had experienced trauma, had PTSD symptoms from it, and were willing to use a mobile app **Objective**: To assess the feasibility, acceptability, and preliminary efficacy of the iCBT-based app (PTSD Coach) to inform a larger-scale trial	**Inclusion criteria**: Adults (≥ 18 years of age) who were fluent in English, had an active email address, and who had a PCL-C score of ≥ 25. None of the included participants had a PCL-C score lower than the recommended range (i.e., 30 to 35) for PTSD screening in general population **Excluded**: Individuals who were receiving any treatment for PTSD **Number of participants**: 49 (25 in the iCBT group, 24 in the WL group) **Mean age**: 45.7 (SD = 13.9) years in the total sample (age was NR by group)	Unguided internet program based on CBT (PTSD Coach). While PTSD Coach includes sections that provide participants with CBT-based tools, the program appears to be much less structured than other iCBT software **Number of sessions**: The program was not broken down into sessions **Treatment duration**: 4 weeks	WL control. Participants were on a wait-list for 4 weeks and then received information on PTSD Coach, allowing them to use it if they would like This group received no intervention during the treatment period	**Primary outcomes**: • PCL-C **Secondary outcomes**: • Acceptability • Feasibility **Follow up**: 1 month (post-treatment)

Author(s) (Publication Year), Country, Funding Source	Study Design, Setting, and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes; Length of Follow Up
		Sex: 81.6% female; 18.4% male **Type of trauma**: Various; details were NR **Mean time since trauma**: NR **Baseline PTSD severity**: Mean PSS-I score of 63.00 (SD = 11.28) in the iCBT group; mean PSS-I score of 59.33.4 (SD = 11.34) in the WL group **Comorbidities**: NR	**Guidance**: The program did not include therapist guidance		
Engel et al. (2015),[54] US **Funding source**: NR	**Study design**: RCT, single blind (the outcome assessor was blinded), 1:1 ratio **Setting**: Participants were referred from one of three Veterans Affairs and four Army clinics by their primary care providers after screening positive for PTSD **Objective**: To examine the effectiveness of a nurse-assisted online CBT intervention for war-related PTSD compared with optimized usual care PTSD treatment	**Inclusion criteria**: War veterans who reported war-related trauma (including military sexual trauma) that were seeking care at a participating Veterans Affairs or Department of Defense care clinics. Participants were required to screen positive on a four-item PTSD screener and meet criteria for PTSD on the CAPS using the 1 to 2 scoring rule **Excluded**: Individuals who received trauma-focused mental health treatment in the previous two months; had a recent history of failed specialty mental health treatment for PTSD or associated conditions; acute psychosis, psychotic episode, or psychotic disorder diagnosed	Nurse-guided trauma-focused iCBT (DESTRESS-PC) plus optimized usual primary care PTSD treatment. The program included educational information about PTSD, stress, trauma, depression, and survivors' guilt, as well as strategies to manage anger and promote better sleep hygiene and cognitive reframing techniques **Number of sessions**: 3 modules per week for 6 weeks (18 modules total)	Optimized usual PTSD care that consisted of usual primary care PTSD treatment augmented with low intensity care management, feedback to the primary care provider, and training of the clinic providers in management of PTSD. The treatment was designed to approximate the level of PTSD care normally available in primary care while incorporating nonspecific treatment elements of the DESTRESS intervention (e.g., participants received	**Primary outcomes**: • PCL-C **Secondary outcomes**: • PHQ-8 • PHQ-15 • SF-36 **Follow up**: 6 weeks, 12 weeks (post-treatment), and 18 weeks

Author(s) (Publication Year), Country, Funding Source	Study Design, Setting, and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes; Length of Follow Up
		within the past two years; active substance dependence in the past year; active suicidal or homicidal ideation within the past two months; current antipsychotic or mood-stabilizing medication; unstable administration schedule or dosing of any antidepressant, anxiolytic, or sedative-hypnotic during the last month; or acute or unstable physical illness. **Number of participants**: 80 (43 in iCBT group, 37 in optimized usual care group) **Mean age**: 36.2 (SD = 7.75) years in the iCBT group; 36.7 (SD = 9.75) years in the optimized usual care group **Sex**: 18.75% female; 81.25% male **Type of trauma**: War-related trauma (including military sexual trauma) **Mean time since trauma**: NR **Baseline PTSD severity**: Mean PCL-C score of 58.00 (SD = 9.95) in the iCBT group; mean PCL-C score of 54.48 (SD = 11.23) in the optimized usual care group	**Treatment duration**: 6 weeks with access to the program for 8 weeks (extended to 10 weeks in very rare cases) **Guidance**: Participants were encouraged to contact the study nurses for assistance if needed. The study nurses had access to a private portion of the website where they could monitor compliance and symptom severity	three 15 minute phone calls from the DESTRESS nurse)	

Author(s) (Publication Year), Country, Funding Source	Study Design, Setting, and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes; Length of Follow Up
		Comorbidities: The study did not screen for comorbid conditions			
Knaevelsrud et al. (2015),[68] Iraq **Funding source**: Unclear	**Study design**: RCT, open label, 1:1 ratio **Setting**: Participants were recruited between January 2009 and November 2011 using radio, TV, newspaper, and health-related websites in Iraq. Information about the study was regularly posted to a Facebook page **Objective**: To evaluate the effectiveness of an iCBT intervention for the treatment of PTSD in a highly unstable setting (Iraq)	**Inclusion criteria**: Arabic-speaking adults (≥ 18 and ≤ 65 years of age) with a history of trauma (according to the *DSM-IV* criteria) accompanied by post-traumatic stress symptoms. The PDS was used to identify if patients reported the minimum number of symptoms required by *DSM-IV* for each of the symptom clusters. The minimum score on the PDS to be included in the trial was 11 (indicating moderate symptom severity) **Excluded**: Individuals who were receiving treatment elsewhere, had substance abuse or dependence, high risk of suicide, psychotic symptoms, or low symptom severity **Number of participants**: 159 (79 in iCBT group, 80 in WL group) **Mean age**: 29.11 (SD = 8.20) years in the iCBT group; 27.15 (SD = 6.48) years in the WL group **Sex**: 76% female; 24% male	Therapist-guided trauma-focused iCBT (interapy, which was translated into Arabic and culturally adapted). Treatment involved structured writing activities over three phases: one, self-confrontation with the traumatic event; two, cognitive restructuring; and three, social sharing **Number of sessions**: 10 writing assignments **Treatment duration**: 5 weeks **Guidance**: Support was provided weekly either in face-to-face sessions of via Skype. Assignment reminders were provided by email and telephone	WL control. Participants were on a wait-list for six weeks (until after post-treatment assessments) and then received the iCBT intervention	**Primary outcomes**: • PDS **Secondary outcomes**: • HSCL-25 • SCL • EUROHIS-QOL **Follow up**: 5 weeks (post-treatment) and 3 months (there no data for the wait-list group available at second follow up)

Author(s) (Publication Year), Country, Funding Source	Study Design, Setting, and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes; Length of Follow Up
		Type of trauma: War-related; specifically killing of a family member (n = 24), sexual violence related to war or sexual abuse (n = 63), violence of war or torture (n = 30), others (e.g., kidnapping, witnessing bomb attacks; n = 42) **Mean time since trauma**: NR as a mean. Within the CBT group, 13%, 22%, and 65% of participants experienced trauma less than 6 months prior, 6 months to 3 years prior, or more than 3 years prior, respectively. Within the WL group, 10%, 18%, and 70% of participants experienced trauma less than 6 months prior, 6 months to 3 years prior, or more than 3 years prior, respectively **Baseline PTSD severity**: Mean PDS score of 30.87 (SD = 8.13) in the iCBT group; mean PDS score of 31.81 (SD = 7.13) in the WL group **Comorbidities**: NR			
Ivarsson et al. (2014),[69] Sweden **Funding source**: A grant from Linköping University	**Study design**: RCT, single blind (the outcome assessor was blinded), 1:1 ratio	Inclusion criteria: Adult (≥18 years of age) residents of Sweden who had access to a computer, were able to read and understand the Swedish language, were on a current	Therapist-guided trauma-focused iCBT. The program included psychoeducation, anxiety coping skill training, imaginal	Minimal support via the internet control group. Participants were presented with general questions on wellbeing, stress, and sleep on a	**Primary outcomes**: • IES-R • PDS **Secondary outcomes**: • BDI-II

Author(s) (Publication Year), Country, Funding Source	Study Design, Setting, and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes; Length of Follow Up
	Setting: Participants were recruited from the general population using advertisements in national and local newspapers that sought participants with PTSD willing to receive treatment over the internet **Objective**: To investigate the effectiveness of a guided iCBT program for the treatment of PTSD	stable dose of medication (for at least the last 3 months) or were medication-free, and who met the DSM-IV criteria for chronic PTSD **Excluded**: Individuals with imminent suicide risk, concurrent psychologic treatment, alcohol abuse, ongoing trauma or trauma within the past three months, or those who reported symptoms following childhood abuse **Number of participants**: 62 (31 in iCBT group; 31 in control group) **Mean age**: 44.8 (SD = 11.2) years in the iCBT group; 47.2 (SD = 12.2) years in the control group **Sex**: 82.3% female; 17.7% male **Type of trauma**: Sexual, physical, and/or psychological abuse by partner (n = 14); life-threatening disease (n = 8); severe offense by significant other (perceived as threatening to integrity; n = 6); life-threatening accident (n = 5); non-sexual assault by a stranger (n = 5); murder of close relative (n = 4); non-sexual assault by a	exposure, and cognitive restructuring **Number of sessions**: 8 text-based modules **Treatment duration**: 8 weeks **Guidance**: Support was provided by therapist students in their later semester of a five year clinical psychology program who had received clinical supervision in CBT. Support consisted of guidance, encouragement, and individual feedback on completed assignments. Therapist feedback was provided once every week via an encrypted web service (through emails). The average time spent with the participants was 28 minutes per week	weekly basis. The purpose of this group was to stay in touch and provide support during the waiting period. This group was offered the iCBT treatment after post-treatment measured were collected	• BAI • QOLI • CGI-I **Follow up**: 8 weeks (post-treatment) and 1 year (there no data for the wait-list group available at second follow up)

Author(s) (Publication Year), Country, Funding Source	Study Design, Setting, and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes; Length of Follow Up
		family member (n = 3); death of a close relative (n = 3); severe maltreatment in health care (n = 3); multiple stressors (n = 3); life-threatening disease of a close relative (n = 2); military combat (n = 2); torture (n = 1); rape by stranger (n = 1); rape by family member (n = 1); and tsunami disaster (n = 1) **Mean time since trauma**: NR **Baseline PTSD severity:** Mean IES-R score of 54.65 (SD = 13.16) in the iCBT group; mean IES-R score of 54.87 (SD = 15.48) in the control group **Comorbidities**: The study did not screen for comorbid conditions			
Spence et al. (2011),[55] Australia **Funding source**: Supported by a research fellowship from the New Wales Institute of Psychiatry	**Study design**: RCT, open-label, 1:1 ratio **Setting**: Participants were recruited from a website that offers participation in online psychological interventions (virtualclinic.org.au) and advertisements in a local newspaper and in an email newsletter sent by a government institution	**Inclusion criteria**: Adult (≥ 18 years of age) residents of Australia who had access to a computer and printer, were on a stable dose of medication for at least one month (with no intention of changing the dose throughout the study) or were medication-free, and met the DSM-IV criteria for PTSD (as assessed with the MINI) **Excluded**: Individuals who were currently participating in CBT,	Therapist-guided trauma-focused iCBT. The program included psycho-educational materials, strategies for monitoring and challenging thoughts, education, and guidelines about practising exposure and challenging dysfunctional beliefs, and information about relapse prevention	WL control. Participants were on a wait-list for eight weeks (until after post-treatment assessments) and then received the iCBT intervention	**Primary outcomes**: • PCL-C **Secondary outcomes**: • PHQ-9 • GAD-7 • SDS **Follow up**: 8 weeks (post-treatment) and 3 months (there no data for the wait-list group available at second follow up)

Author(s) (Publication Year), Country, Funding Source	Study Design, Setting, and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes; Length of Follow Up
	Objective: To explore the efficacy of an iCBT program for the treatment of PTSD	experiencing a psychotic mental illness, or who had severe symptoms of depression or were highly dissociative **Number of participants**: 42 (23 in iCBT group; 19 in WL group) **Mean age**: 43.0 (SD = 15.2) years in the iCBT group; 42.0 (SD = 10.4) years in the WL group **Sex**: 81% female; 19% male **Type of trauma**: Various; most participants had experienced multiple types of trauma. Most common traumas were physical assault (74%), unwanted sexual experience (70%), sexual assault (57%), transportation accidents (52%), and other stressful experiences (52%) **Mean time since trauma**: NR **Baseline PTSD severity**: Mean PCL-C score of 60.78 (SD = 10.03) in the iCBT group; mean PCL-C score of 57.00 (SD = 9.69) in the WL group **Comorbidities**: Participants were screened for comorbid depression, generalized anxiety disorder, panic disorder with or	**Number of sessions**: 7 modules **Treatment duration:** 8 weeks **Guidance**: Support was provided by a clinical psychologist via telephone, email, and forum posts. The purpose of the guidance was to monitor mood and provide support and encouragement. The mean therapist time per participant was 103.91 (SD = 96.53) minutes throughout the course of the program		

Author(s) (Publication Year), Country, Funding Source	Study Design, Setting, and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes; Length of Follow Up
		without agoraphobia, social phobia, and obsessive-compulsive disorder and pre-treatment and at three-month follow up			
iCBT Versus i-non-CBT Interventions					
Littleton et al. (2016),[70] US **Funding source**: NR	**Study design**: RCT, open-label, 1:1 ratio **Setting**: "Participants were recruited via posted advertisements 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)"[70] (p. 3). **Objective**: To determine the effectiveness of a therapist-facilitated, online CBT program tailored to meet the needs of rape victims with PTSD	**Inclusion criteria**: 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 (according to PSS-I) **Excluded**: Individuals currently receiving psychotherapy, change in psychotropic medication in past three months, active suicidality, or that met the DSM-IV criteria for current substance dependence **Number of participants**: 87 (46 in iCBT group; 41 in i-non-CBT group) **Mean age**: 22 years (range = 18 to 42 years) for the whole sample **Sex**: 100% female in both groups **Type of trauma**: All participants had experienced a completed rape since the age of 14	Therapist-guided iCBT (The From Survivor to Thriver Program). The program consisted of three phases: one, psychoeducation relating to PTSD; two, an introduction to the cognitive model and how to identify and respond to distorted or unhelpful automatic thoughts; three, the use of cognitive behavioural techniques to address specific concerns common among women following sexual assault (e.g., difficulties with trust, self-blame for the assault) **Number of sessions**: 9 modules **Treatment duration**: 14 weeks **Guidance**: Therapist guidance was provided	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 Patients in both groups received scheduled check-in phone calls from study staff (doctoral students in psychology) generally once every two weeks	**Primary outcomes**: • PSS-I **Secondary outcomes**: • Interference (at school, work, relationships, and overall; scored between 0 and 3) • CES-D • FDAS • Therapist competence • Therapist and treatment satisfaction (STTS-R) • Working alliance (WAI-S) **Follow up**: 14 weeks (post-treatment) and 24 weeks

Author(s) (Publication Year), Country, Funding Source	Study Design, Setting, and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes; Length of Follow Up
		Mean time since trauma: NR **Baseline PTSD severity**: Mean PSS-I score of 11.2 (SD = 5.8) in the iCBT group; mean PSS-I score of 10.4 (SD = 8.5) in the i-non-CBT group **Comorbidities**: NR	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		
Litz et al. (2007),[71] US **Funding source**: Supported by a grant from the National Institute of Mental Health	**Study design**: RCT, single blind (the outcome assessor was blinded), 1:1 ratio **Setting**: Participants were recruited through advertisements and presentations at Department of Defense websites **Objective**: To evaluate the effectiveness of a therapist-assisted iCBT program versus internet-based supportive counselling for the treatment of PTSD	**Inclusion criteria**: Department of Defense service members (≥ 21 and ≤ 65 years of age) who had PTSD (according to DSM-IV criteria) as a result of the Pentagon attack on September 11th or combat in Iraq or Afghanistan **Excluded**: Individuals with active substance dependence, current suicidal ideation, history of psychotic disorder, PTSD or depression prior to most recent trauma, current psychiatric treatment, marked ongoing stressors, inadequate social support, or recent changes in medication	Therapist-guided trauma-focused iCBT (DESTRESS). The program included stress management strategies and graduated, self-guided, in vivo exposure **Number of sessions**: 7 trauma writing sessions **Treatment duration**: 8 weeks **Guidance**: Support was provided by a therapist using initial face-to-face contact, telephone, and emails (both scheduled	Internet-delivered supportive counselling. This control group received monitoring of non–trauma-related concerns and online writing about these experiences. Psycho-educational materials were available. Participants were asked to visit the website daily to log their symptoms, read about stress and stress management, and to write about current concerns. Support was provided to the participants at their	**Primary outcomes**: • PSS-I **Secondary outcomes**: • BDI • BAI **Follow up**: 8 weeks (post-treatment), 3 months, and 6 months

Author(s) (Publication Year), Country, Funding Source	Study Design, Setting, and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes; Length of Follow Up
		Number of participants: 45 (24 in iCBT group; 21 in i-non-CBT group) **Mean age**: 38.63 (SD = 9.41) years in the iCBT group; 39.86 (SD = 7.72) years in the i-non-CBT group **Sex**: 22.2% female; 77.8% male **Type of trauma**: Combat exposure (9/11 attack on the Pentagon or combat in Iraq or Afghanistan) **Mean time since trauma**: NR **Baseline PTSD severity**: Mean PSS-I score of 26.72 (SD = 9.02) in the iCBT group; mean PSS-I score of 29.16 (SD = 9.93) in the i-non-CBT group **Comorbidities**: NR	and when requested by the participant)	request through initial face-to-face contact, telephone, and email. Therapists were instructed to be empathetic and validating, non-directive and supportive, and to focus on non-trauma-related present-day concerns	

AUDIT = Alcohol Use Disorders Identification Test; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; B-IPF = Brief Inventory of Psychosocial Functioning; CAPS = Clinician-Administered PTSD Scale; CBT = cognitive behavioural therapy; CES-D = Center for Epidemiological Studies – Depression Scale; CGI = Clinical Global Impression – Improvement; DESTRESS = Delivery of Self Training and Education for Stressful Situations; DESTRESS-PC = Delivery of Self Training and Education for Stressful Situations – Primary Care version; DSM = Diagnostic and Statistical Manual of Mental Disorders; FDAS = Four Dimensional Anxiety Scale; GAD-7 = Generalized Anxiety Disorder 7-Item Scale; HSCL = Hopkins Symptom Checklist; iCBT = internet-delivered cognitive behavioural therapy; i-non-CBT = internet-delivered non-CBT; IES-R = Impact of Event Scale – Revised; MINI = Mini International Neuropsychiatric Interview Version 5.0.0; NR = not reported; PCL-5 = Post-Traumatic Stress Disorder Checklist for *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; PCL-C = PTSD Checklist – Civilian; PCL-M = Post-Traumatic Stress Disorder Checklist – Military; PDS = Post-Traumatic Stress Diagnostic Scale; PHQ-8 = Patient Health Questionnaire – 8 Item; PHQ-9 = Patient Health Questionnaire – 9 Item; PSS-I = Post-Traumatic Stress Disorder Symptom Scale – Interview; PTSD = post-traumatic stress disorder; QOLI = Quality of Life Inventory; RCT = randomized controlled trial; SCL = The somatization subscale of the Symptom Checklist – 90; SD = standard deviation; SDS = Sheehan Disability Scale; SF-36 = Medical Outcomes Study Short Form-36; SSQ = Social Support Questionnaire; STTS-R = Satisfaction with Therapy and Therapist Scale – Revised; TAU = treatment as usual; WAI-S = Working Alliance Inventory – Short Form; WIRED = Warriors Internet Recovery & Education; WL = wait-list.

Source: Lewis et al. (2018).[40]

Table 17: Brief Description of Common Outcome Assessment Scales

Outcome Assessment Scale	Reference	Description
BAI	Julian, 2011[222]	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[223]	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).
CAPS (CAPS-5)	Lewis, 2017[52]	A 30-item structured interview that corresponds to the *DSM-V* 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[70]	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.
FDAS	Littleton, 2016[70]	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[224]	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 or PCL-M	Cernvall, 2017[225]	A 17-item self-report instrument used to measure PTSD symptoms. Each item is rated between 1 (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 diagnosis of PTSD. Total score ranges from 17 to 85, with higher scores indicating more severe PTSD symptoms.
PDS	Franklin, 2017[226]	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[227]	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.
PSS-I	Littleton, 2016[70]	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.

BDI-II = Beck Depression Inventory – II; CAPS = Clinician-Administered Post-Traumatic Stress Disorder Scale; CES-D = Center for Epidemiological Studies – Depression Scale; DSM = *Diagnostic and Statistical Manual of Mental Disorders*; FDAS = Four Dimensional Anxiety Scale; IES-R = Impact of Event Scale – Revised; PCL-C = Post-Traumatic Stress Disorder Checklist – Civilian Version; PCL-M = Post-Traumatic Stress Disorder Checklist – Military Version; PDS = Post-Traumatic Stress Diagnostic Scale; PHQ-9 = Patient Health Questionnaire; PSS-I = Post-Traumatic Stress Disorder Symptom Scale – Interview; PTSD = post-traumatic stress disorder.

Appendix 8: Critical Appraisal of Primary Studies

Table 18: Cochrane Risk of Bias Assessment for Included Randomized Controlled Trials

	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias
Study Citation	Risk of Bias in Sequence Generation	Risk of Bias in Allocation Concealment	Risk of Bias in Binding of Participants and Personnel	Risk of Bias in Binding of Outcome Assessment	Risk of Bias From Incomplete Outcome Data	Risk of Bias From Selective Outcome Reporting	Risk of Bias From Other Biases
Engel (2015)[54]	Low	Unclear	High	Low	Low	Low	Low
Ivarsson (2014)[69]	Low	Unclear	High	Low	Low	Low	High
Knaevelsrud (2015)[68]	Low	Unclear	High	Low	High	Low	Low
Krupnick (2017)[66]	Unclear	Unclear	High	Low	High	Low	High
Kuhn (2017)[53]	Low	Unclear	High	Low	Low	Low	Low
Lewis (2017)[52]	Low	Low	High	Low	Low	Low	High
Littleton (2016)[70]	Low	Unclear	High	High	Low	Low	Low
Litz (2007)[71]	Unclear	Unclear	High	Low	High	Low	High
Miner (2016)[67]	Unclear	Unclear	High	Low	Low	Low	Low
Spence (2011)[55]	Low	Unclear	High	High	High	Low	Unclear

Note: The assessment rating judgements in the table were made by the authors of the Cochrane review.

Source: Lewis et al. (2018).[40]

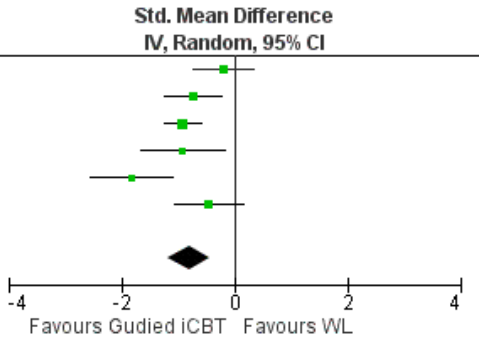
Appendix 9: Clinical Efficacy of Guided Internet-Delivered Cognitive Behavioural Therapy Versus Wait-List

In order to support the scenario analysis of guided internet-delivered cognitive behavioural therapy (iCBT) compared with wait-list or usual care, findings from the CADTH clinical review were reanalyzed using the six studies that examined nurse- or therapist-guided iCBT programs, excluding data from the two studies on PTSD Coach, an unguided iCBT program. This very low-quality evidence indicated that guided iCBT was more effective than wait-list or usual care for severity of post-traumatic stress disorder symptoms at post-treatment (standard mean deviation [95% confidence interval] = −0.80 [−1.18 to −0.42]; participants = 391; randomized controlled trials = 6; I^2 = 65%; Figure 17). Although this analysis was not conducted as part of the Cochrane review, these results were used for scenario analyses in the economic section of this health technology assessment.

Figure 17: Comparison of Guided Internet-Delivered Cognitive Behavioural Therapy and Wait-List; Outcome: Severity of Post-Traumatic Stress Disorder Symptoms (Post-Treatment)

	Guided iCBT			Wait list				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Engel 2015	43.8	18.33	30	47.36	17.45	25	17.5%	-0.20 [-0.73, 0.34]
Ivarsson 2014	17.32	9.86	31	25.04	11.14	31	17.9%	-0.72 [-1.24, -0.21]
Knaevelsrund 2015	20.29	12.45	79	30.17	8.7	80	22.3%	-0.92 [-1.24, -0.59]
Krupnick 2017	3.58	0.3	16	3.91	0.4	15	13.2%	-0.91 [-1.66, -0.17]
Lewis 2017	17.93	12.25	21	36.53	7.1	21	13.4%	-1.82 [-2.55, -1.09]
Spence 2011	44.78	17.29	23	51.79	12.51	19	15.7%	-0.45 [-1.06, 0.17]
Total (95% CI)			**200**			**191**	**100.0%**	**-0.80 [-1.18, -0.42]**

Heterogeneity: Tau² = 0.14; Chi² = 14.39, df = 5 (P = 0.01); I² = 65%
Test for overall effect: Z = 4.15 (P < 0.0001)

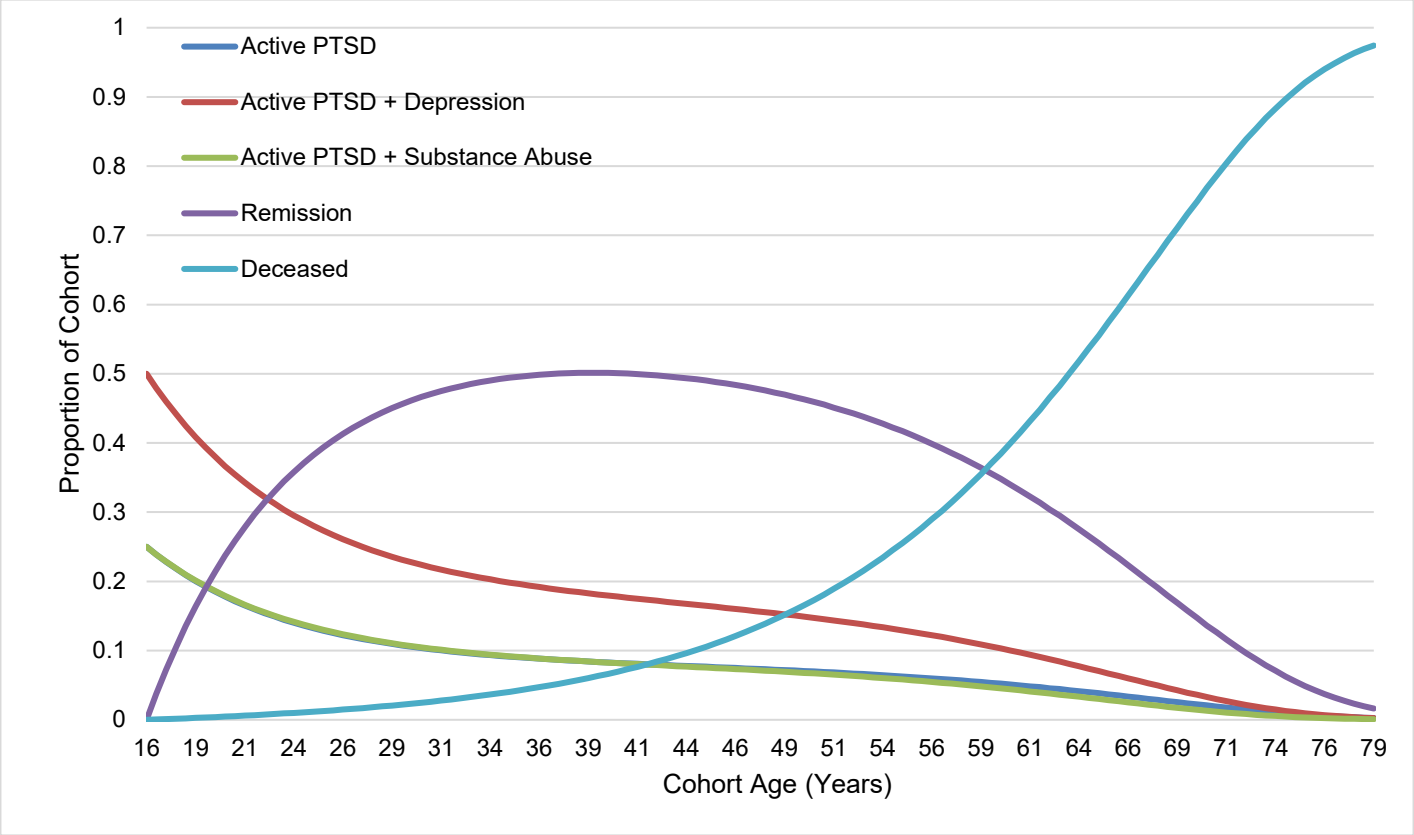


CI = confidence interval; iCBT = internet-delivered cognitive behavioural therapy; IV = inverse variance; SD = standard deviation; Std. = standard; WL = wait-list.

Source: Lewis et al. (2018).[40]

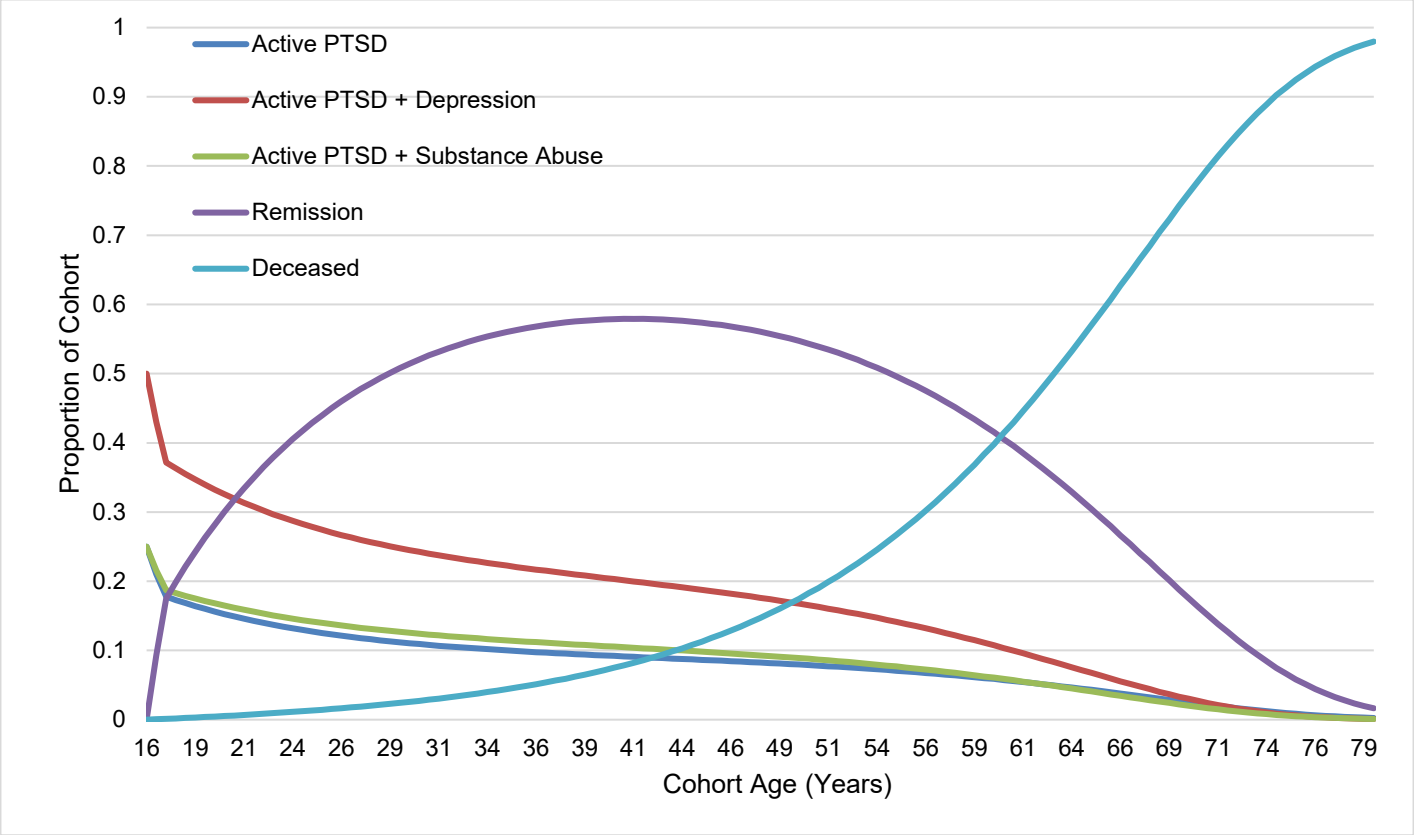
Appendix 10: Proportion of Patients by Health State Over Time — Economic Evaluation

Figure 18: Proportion of Patients by Health State Over Time — Reference Case, No Additional Treatment



PTSD = post-traumatic stress disorder.

Figure 19: Proportion of Patients by Health State Over Time — Reference Case, Internet-Delivered Cognitive Behavioural Therapy



PTSD = post-traumatic stress disorder.

Appendix 11: Additional Scenario and Sensitivity Analysis Results — Economic Evaluation

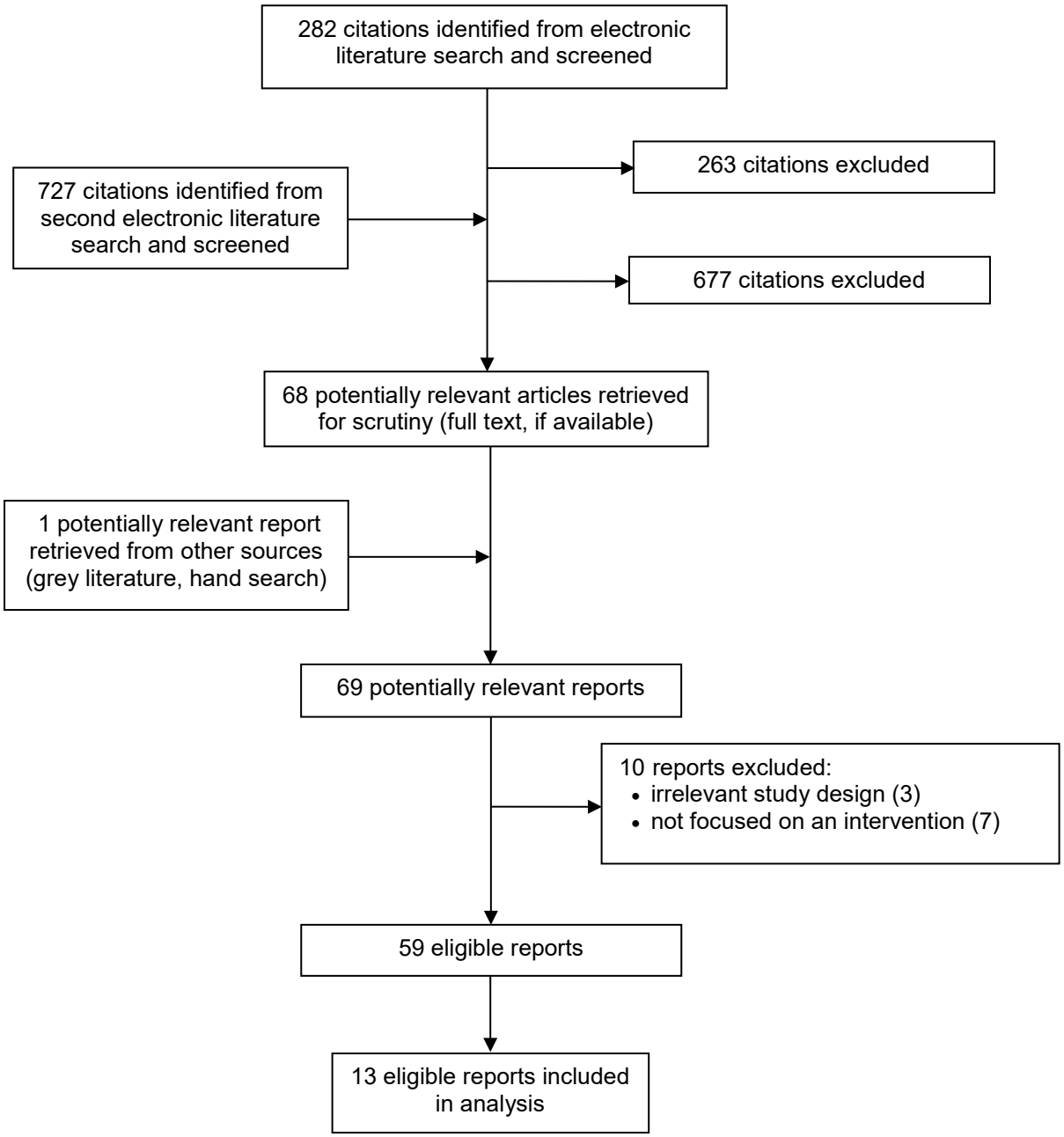
Table 19: Additional Scenario and Sensitivity Analysis Results

Scenario or Sensitivity Analysis	Strategies	Expected Costs, $	Expected QALYs	Incremental Costs, $	Incremental QALYs	Sequential ICUR, $/QALY Gained	Probability of Being Cost-Effective at a Willingness-to-Pay of $50,000/QALY
Scenarios							
Societal Perspective	No additional treatment	36,327	22.80				100%
	iCBT	34,768	23.12	–1,559	0.32	Dominant	
Therapist Support Provided by a Registered Non-Physician Therapist	No additional treatment	16,174	22.81				100%
	iCBT	16,098	23.13	–77	0.32	Dominant	
All Patients Receive Referral to iCBT	No additional treatment	16,179	22.79				100%
	iCBT	16,009	23.11	–170	0.32	Dominant	
Comorbidities Develop After Entry Into Model Over Course of One Year	No additional treatment	16,234	23.30				100%
	iCBT	16,051	23.55	–183	0.25	Dominant	
Sensitivity Analyses							
Additional Costs for Comorbid Conditions Applied	No additional treatment	21,570	22.78				100%
	iCBT	21,027	23.09	–542	0.32	Dominant	
No Change in Recovery for Patients With Comorbidities Compared With Patients Without Comorbidities	No additional treatment	15,452	23.81				100%
	iCBT	15,213	23.52	-240	0.33	Dominant	
One-Year Time Horizon	No additional treatment	511	0.60				91%

Scenario or Sensitivity Analysis	Strategies	Expected Costs, $	Expected QALYs	Incremental Costs, $	Incremental QALYs	Sequential ICUR, $/QALY Gained	Probability of Being Cost-Effective at a Willingness-to-Pay of $50,000/QALY
	iCBT	999	0.62	487	0.028	17,435	
Assumed Any Recurrence Was Not Related to Initial Trauma	No additional treatment	9,451	24.56				100%
	iCBT	8,690	25.01	–762	0.46	Dominant	

ICUR = incremental cost-utility ratio; iCBT = internet-delivered cognitive behavioural therapy; QALY = quality-adjusted life-year.

Appendix 12: Selection of Included Studies — Perspectives and Experiences Review



Appendix 13: Characteristics of Included Primary Studies — Perspectives and Experiences

Table 20: Characteristics of Included Studies

First Author (Publication Year), Country	Study Design (Data Analysis)	Study Objectives	Participant Characteristics, Sample Size (n)	Inclusion Criteria	Intervention Type	Data Collection
Hundt (2018), US[99]	NS (grounded theory)	To understand the attitudes, experiences, and barriers and facilitators to treatment for veterans who enrolled in a VA PTSD specialty clinic and were offered either PE or CPT	24 veterans	Veterans with a primary psychiatric diagnosis of PTSD who were admitted to the PTSD clinic and judged to be appropriate to for PE or CPT, offered PE or CPT, but not starting PE or CPT within 12 months	PE and CPT	Interviews
Cook (2017), US[100]	NS (grounded theory)	To assess how residential treatment providers within the VA conceptualize and address patient readiness for trauma-focused EBTs for PTSD	99 psychologists, 62 social workers, 4 psychiatrists, 3 nurses, 4 “other”	NS	PE and CPT	Semi-structured telephone interview
Hundt (2017), US[101]	NS (grounded theory)	To explore how veterans living with PTSD experience the use of EBT in their treatment	23 veterans	Veterans who had completed at least 8 sessions of PE or CPT in a VA PTSD clinic	PE and CPT	Interviews
Stige (2017), Norway[102]	NS (hermeneutic phenomenological approach)	To explore how former trauma clients experienced the inclusion of skill training in their treatment, their ways of relating	13 patients	NS	Skills training components of a trauma specific stabilization group	Semi-structured interviews conducted over two time points

First Author (Publication Year), Country	Study Design (Data Analysis)	Study Objectives	Participant Characteristics, Sample Size (n)	Inclusion Criteria	Intervention Type	Data Collection
		to and using these skills, and how this changed over time				
Tong (2017), Australia[103]	NS (interpretive phenomenological approach)	To explore young people's reactions to a trauma-focused treatment for PTSD in FEP	8 participants	Individuals aged 15 to 25 years with a *DSM-IV* psychotic disorder or mood disorder with psychotic features and having current trauma symptoms that meet the full criteria for PTSD using CAPS	Intervention drawing on principles of CBT	Semi-structured interviews
Whealin (2016), US[111]	Mixed-methods (content analysis)	To identify the types of eHealth tools that veterans with PTSD and comorbid CMCs use, understand how they currently use eHealth technology to self-manage their unique health care needs, and identify new e-health resources that veterans feel would empower them to better manage their health	10 veterans	Veterans with three or more chronic conditions and experience using technology to help them care for their health or manage their health care, and having received care at the VA facility	NS	Focus groups
Hamblen (2015), US[104]	NS (NS)	To examine VA PTSD clinic director perspectives on the implementation of PE and CPT in PTSD	31 psychologists, 5 social workers, 2 psychiatrists	NS	PE and CPT	Semi-structured interviews

First Author (Publication Year), Country	Study Design (Data Analysis)	Study Objectives	Participant Characteristics, Sample Size (n)	Inclusion Criteria	Intervention Type	Data Collection
		outpatient programs to better understand the local challenges be faced				
Hundt (2015), US[105]	NS (grounded theory)	To enhance knowledge of facilitators to EBP initiation by examining veterans' real-world experiences initiating EBP for PTSD and how they overcame barriers to EBP in their own lives	23 veterans	Veterans who had completed at least 8 sessions of EBP in a VA PTSD clinic	PE and CPT	Interviews
McCormack (2015), Australia[106]	NS (interpretive phenomenological analysis)	To explore the "lived" experience of trauma-focused therapists working with mental health in-patients with complex trauma histories	2 psychiatric consultants, 1 clinical psychologist, 1 psychologist/clinical manager	NS	NS	Interviews
Cook (2014), US[107]	NS (NS)	To present VA residential PTSD treatment provider perceptions of dissuading factors to the use of PE and CPT	110 psychologist, 66 social workers, 11 nurses, 5 psychiatrists, 6 "other"	NS	PE and CPT	Semi-structured telephone interviews
Lawrence (2014), UK[108]	NS (interpretive phenomenological analysis)	To produce an in-depth understanding of the experience of completing a course of compassion-focused therapy for PTSD and the process of	9 patients	People who had completed two CFT groups for PTSD	CFT	Interviews

First Author (Publication Year), Country	Study Design (Data Analysis)	Study Objectives	Participant Characteristics, Sample Size (n)	Inclusion Criteria	Intervention Type	Data Collection
		developing self-compassion				
Lowe (2014), UK[109]	Phenomenological and idiographic (interpretive phenomenological analysis)	To gain an understanding of the aspects of trauma-focused CBT for PTSD that service users find important in contributing to their improvement	9 patients	NS	Trauma-focused CBT	Interviews
Reeves (2014), Canada[110]	Naturalistic paradigm informed by Indigenous inquiry(grounded theory)	Investigate the use of traditional Indigenous healing alongside Western mental health services to address issues related to recovery from sexual trauma at a culture-based multiservice health centre	3 traditional healers/medicine people, 5 traditional counsellors, 1 traditional counsellor/traditional teacher, 1 Elder	NS	NS	Two sets of interviews

CAPS = clinician-administered PTSD scale; CBT = cognitive behavioural therapy; CFT = compassion-focused therapy; CMC = chronic medical conditions; CPT = cognitive processing therapy; *DSM* = *Diagnostic and Statistical Manual of Mental Disorders*; EBP = evidence-based psychotherapies; EBT = evidence-based therapies; FEP = first-episode psychosis; NS = not specified; PE = prolonged exposure; PTSD = post-traumatic stress disorder; VA = Department of Veterans Affairs (US).

Appendix 14: Critical Appraisal of Included Publications — Perspectives and Experiences Review

Qualitative Studies Assessed Using CASP Qualitative Checklist[228]										
First Author (Year), Country	Clear statement of the aims of the research?	Qualitative methodology appropriate?	Research design appropriate to address the aims of the research?	Recruitment strategy appropriate to the aims of the research?	Data collected in a way that addressed the research issue?	Relationship between researcher and participants been adequately considered?	Ethical issues been taken into consideration?	Data analysis sufficiently rigorous?	Clear statement of findings?	Relevant to the current review?
Hundt (2018), US[99]	+	+	+	+	+	–	+	+	+	–
Cook (2017), US[100]	+	+	+	+	+	–	+	+	+	–
Hundt (2017), US[101]	+	+	+	+	+	–	+	+	+	–
Stige (2017), Norway[102]	+	+	+	+	+	+	+	+	+	–
Tong (2017)[103]	+	+	+	+	+	+	+	–	+	–
Whealin (2016)[111]	+	+	+	+	+	+	+	–	+	–
Hamblen (2015), US[104]	+	+	+	+	+	–	–	–	+	–

Qualitative Studies Assessed Using CASP Qualitative Checklist[228]										
First Author (Year), Country	Clear statement of the aims of the research?	Qualitative methodology appropriate?	Research design appropriate to address the aims of the research?	Recruitment strategy appropriate to the aims of the research?	Data collected in a way that addressed the research issue?	Relationship between researcher and participants been adequately considered?	Ethical issues been taken into consideration?	Data analysis sufficiently rigorous?	Clear statement of findings?	Relevant to the current review?
Hundt (2015), US[105]	+	+	+	+	+	–	+	+	+	–
McCormack (2015)[106]	+	+	+	+	+	+	+	+	+	–
Cook (2014), US[107]	+	+	+	+	+	–	–	+	+	–
Lawrence (2014)[108]	+	+	+	+	+	+	+	+	+	–
Lowe (2014), UK[109]	+	+	+	+	+	–	+	+	+	–
Reeves (2014), Canada[110]	+	+	+	+	+	+	+	+	+	–

+ = yes; – = no; CASP = Critical Appraisal Skills Programme.