

## CADTH OPTIMAL USE REPORT

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

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## Abbreviations

<b>CBT</b>	cognitive behavioural therapy
<b>DSM-5</b>	<i>Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition</i>
<b>HTA</b>	health technology assessment
<b>HTERP</b>	Health Technology Expert Review Panel
<b>iCBT</b>	internet-delivered cognitive behavioural therapy
<b>PTSD</b>	post-traumatic stress disorder
<b>QALY</b>	quality-adjusted life-year
<b>RCT</b>	randomized controlled trial

## Introduction and Rationale

Approximately 65% of the world's population experiences at least one traumatic event in their lifetime.<sup>1-3</sup> 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.<sup>4</sup> 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.<sup>5,6</sup> These conditions are associated with decreased quality of life, disability, and increased mortality.<sup>7-10</sup> 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.<sup>4</sup>

The lifetime prevalence of PTSD in the adult US population is approximately 11.7% in women and 4% in men,<sup>11</sup> and prevalence is typically greater in high-risk groups such as military personnel and first-responders.<sup>12-14</sup> 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.<sup>15</sup> In 2013, the lifetime and 12-month rates of PTSD among Canadian service members were, respectively, 11.1% and 5.3%.<sup>16</sup>

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.<sup>17</sup> 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.<sup>8,18-20</sup> 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.<sup>21</sup> 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.<sup>5,22</sup>

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.<sup>23-27</sup> 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.<sup>28,29</sup>

Insufficient access to traditional mental health treatment and services is a known challenge facing Canada's health care system.<sup>16,30</sup> In a survey conducted in 2015, around 4.9 million Canadians aged 15 years and older said they 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 1 million reporting that it was partially met.<sup>30</sup> 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.<sup>16,31,32</sup> Essentially, iCBT involves the delivery of CBT through an online platform with or without the support of a therapist (or other practitioner).<sup>22</sup> 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.<sup>5,33-35</sup> However, there may be challenges associated with iCBT programs such as the lack of 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.<sup>5,36</sup> Other potential challenges that are commonly suggested for iCBT include low adherence to the therapy; the 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.<sup>5,36</sup>

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.<sup>37,38</sup> 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<sup>5</sup> 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),<sup>39</sup> 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,<sup>37,38</sup> 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) will address the following questions that articulate the decision problems:

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

## Objective(s)

The purpose of this HTA is to inform the decision questions 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.

## Deliverables

The following deliverables are planned:

- a science report (HTA) detailing all analyses conducted to inform the decision questions
- a recommendations report detailing all considerations based on the evidence in the HTA report and specific recommendations in relation to the decision questions; the recommendations will be developed by the Health Technology Expert Review Panel (HTERP), an advisory body to CADTH, using a multicriteria [deliberative framework](#).

## Research Questions

The HTA will inform 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 of Patients, Families, and Health Care Providers

3. How do patients, their families, and their health care providers experience engaging with iCBT for the treatment of PTSD?

- a) How are varied understandings of PTSD as a diagnostic category perceived to influence both expectations toward and experiences with iCBT as a treatment option by individuals living with a diagnosis of 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?
  - a) 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?
  - b) Given existing and potential pathways of care for individuals, what resources and infrastructure would be needed to continue, expand, or optimize its delivery?
  - c) 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?

## Methods

To inform the preparation of this protocol, a preliminary scoping review of the existing literature, including HTAs and systematic reviews, was conducted. This protocol was written a priori, using appropriate reporting guidelines (e.g., the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols [PRISMA-P]) for guidance on clarity and completeness, and will be followed throughout the HTA process. Any deviations from the protocol will be disclosed in the final report and updates will be made to the PROSPERO submission accordingly (registration number: submitted; registration number not yet received).

## Clinical Review

### Study Design

The protocol for the clinical review was informed by scoping activities that included an informal scoping review of existing literature and a CADTH Rapid Response Report of the clinical effectiveness of iCBT programs for the treatment of adults diagnosed with PTSD published in November of 2018.<sup>37</sup> 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 publication.<sup>37</sup>

As part of these scoping activities, a Cochrane Review on the effectiveness of iCBT for the treatment of PTSD, published in December of 2018, was identified.<sup>40</sup> A preliminary quality assessment using A MeaSurement Tool to Assess systematic Reviews II — or AMSTAR II<sup>41</sup> — indicated that the Cochrane Review provided an accurate and comprehensive summary of the results of the available studies that address the question of interest. The Cochrane Review also extensively aligned with the objectives of the clinical review of this HTA.

There were three major differences between the selection criteria used in the Rapid Response and the Cochrane Review:

- non-randomized studies were eligible in the Rapid Response but not in the Cochrane Review
- 100% of participants were required to meet the diagnostic criteria for PTSD in the Rapid Response, compared with 70% in the Cochrane Review (i.e., broader inclusion in the Cochrane Review)
- the Rapid Response included studies that compared iCBT interventions with alternative iCBT interventions (e.g., guided versus unguided iCBT, comparison of two different guided iCBT programs, iCBT with an exposure component versus iCBT without an exposure component) in addition to all of the comparators considered in the Cochrane Review.

Although non-randomized studies were eligible for the Rapid Response, none were considered relevant following full-text screening, suggesting that their exclusion would not have a significant impact. As for the second point, although 100% of patients were required to have a diagnosis of PTSD in the Rapid Response, no restrictions for diagnostic measures were specified and clinical judgment was considered sufficient; some of the included patients may not have met objective diagnostic criteria. The broader inclusion criterion applied in the Cochrane Review therefore allowed for better alignment between the specified population of interest and those likely represented in the study samples, and also allowed for literature that was excluded in the Rapid Response to be considered. Data from these populations are likely to be relevant to clinical practice, as many individuals who may seek help for symptoms of PTSD may be at a subclinical threshold or be without a formal diagnosis. Indeed, three additional primary studies<sup>42-44</sup> were included in the Cochrane Review that were excluded from the Rapid Response. Finally, one study<sup>45</sup> identified in the Rapid Response compared iCBT with an exposure component to iCBT without an exposure component; no statistically significant differences in PTSD symptom severity were identified between these interventions. In addition to these three differences, the Cochrane Review included pooled analyses for a number of clinical outcomes. This statistical approach provides increased power and precision of effect sizes when summarizing results.

Therefore, in order to avoid duplication of work, the clinical team decided to leverage the Cochrane Review as the foundational evidence for the clinical review of this HTA. Specifically, this will involve reporting on the methods of the Cochrane Review, summarizing its findings, conducting a quality assessment, and carrying out search updates to capture any new relevant evidence.

## Literature Search Methods

The proposed clinical review component of this HTA will be an update of a Cochrane Review on this topic published in 2018.<sup>40</sup> An update of the literature search for clinical studies will be performed by an information specialist using the search strategies provided in the appendices of the 2018 Cochrane Review.<sup>40</sup>

Published literature will be identified by searching the following bibliographic databases: MEDLINE All (1946– ) via Ovid, Embase (1974– ) via Ovid, PsycINFO (1806–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid, and PubMed. The search strategy will be comprised of both controlled vocabulary, such as the National Library of Medicine’s MeSH (Medical Subject Headings), and keywords. The main search concepts will be Internet-based cognitive behavioural therapies (iCBT) and PTSD. Clinical trial registries will be searched: the US National Institutes of Health’s clinicaltrials.gov and the World Health Organization’s International Clinical Trials Registry Platform (ICTRP) Search Portal.

Search filters will be applied to limit retrieval to randomized controlled trials (RCTs) and controlled clinical trials. Retrieval will be limited to documents published since January 1, 2017 but not limited by language.

In addition to this search, a supplemental search created and peer-reviewed by CADTH information specialists will be conducted on key resources including MEDLINE, PsycINFO, PubMed, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, the National Institute for Health Research Health Technology Assessment 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 will be applied to limit retrieval to HTAs, systematic reviews, meta-analyses, RCTs, clinical controlled trials, and non-randomized studies. The search will also be limited to English- or French-language documents published since January 1, 2008. The search strategy is available on request.

Regular alerts will update the searches until the publication of the final report. Studies meeting the selection criteria of the review and identified in the alerts prior to the completion of the stakeholder feedback period will be incorporated into the analysis of the final report. Any studies that are identified after the stakeholder feedback period will be described in the discussion, with a focus on comparing the results of these new studies with the results of the analysis conducted for this report.

Grey literature (literature that is not commercially published) will be 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>),<sup>46</sup> which includes the websites of regulatory agencies, HTA agencies, clinical guideline repositories, systematic review repositories, and professional associations. Google will be used to search for additional Internet-based materials. These searches will be supplemented by reviewing bibliographies of key papers.

## Study Eligibility, Literature Screening, and Selection

The inclusion criteria for the Cochrane Review (as described in the publication) will be used to assess the eligibility of studies identified in the search updates, and are reproduced in Table 1. To ensure findings for the comparison of iCBT interventions to alternative iCBT interventions are maintained, the primary study<sup>45</sup> that addressed this comparison in the Rapid Response Report, as well as any additional studies that meet the selection criteria using the Rapid Response methods but not the Cochrane Review methods, will be mentioned in the discussion of this HTA despite not being formally included.

Studies identified in the search update and alerts that meet the selection criteria in Table 1 will be included in a list of newly identified studies.

Two reviewers will independently screen titles and abstracts of all citations retrieved against eligibility criteria. Exclusion by both reviewers will be required for a record to be excluded at the title and abstract level. Full-text versions of all other articles will be retrieved for the second level of screening. Two reviewers will independently examine all full-text articles, and consensus will be required for inclusion in the review. Discrepancies between reviewers will be resolved by discussion between the reviewers or by a third reviewer, if needed.

**Table 1: Eligibility Criteria for the Clinical Research Question**

<b>Population</b>	Adults, aged 16 years or older, with traumatic stress symptoms. At least 70% of participants in any given study are required to meet diagnostic criteria for PTSD according to the DSM-III, DSM-III-R, DSM-IV, DSM-V, ICD-9, or the ICD-10, as assessed by a clinical interview or a validated questionnaire. <ul style="list-style-type: none"> <li>• There are no restrictions placed on sex or gender, ethnicity, comorbidities, setting, type of traumatic event, severity of symptoms, or length of time since trauma.</li> </ul>
<b>Intervention</b>	Guided and unguided iCBTs delivered via a computer or mobile device <ul style="list-style-type: none"> <li>• Excluding: Interventions based on EMDR or online psychoeducation alone, and interventions using mindfulness-based approaches, apart from mindfulness-based iCBT</li> </ul>
<b>Comparator</b>	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)
<b>Outcomes</b>	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): <ul style="list-style-type: none"> <li>• Studies that met the aforementioned inclusion criteria were included regardless of whether they reported on these outcomes.</li> </ul>
<b>Study Designs</b>	RCTs, randomized crossover trials, and cluster-randomized trials

Source: Lewis et al., 2018<sup>40</sup>

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CAPS = Clinician-Administered PTSD 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 = PTSD Checklist; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial.

## Data Extraction

Data extraction will be performed by one reviewer and independently checked for accuracy by a second reviewer. Disagreements will be resolved through discussion until consensus is reached or through adjudication by a third reviewer, if necessary. Relevant information will be extracted, including study characteristics, methodology, population, intervention, comparator, and results and conclusions regarding the outcomes and subgroups of interest.

## Quality Assessment

Critical appraisal of the Cochrane Review will be conducted by two independent reviewers using A Measurement Tool to Assess systematic Reviews II<sup>41</sup> — the AMSTAR — to confirm its methodological quality. Any disagreements will be resolved by discussion with a third reviewer, if required. Results of this assessment will be summarized in tabular form and reported narratively, including a description of the strengths and weaknesses. The risk of bias in primary studies included in the systematic review will be summarized, as assessed by the authors of the Cochrane Review.

Quality assessment of primary studies identified in the search update will be evaluated by two independent reviewers using the revised Cochrane risk-of-bias tool for randomized trials, the RoB 2,<sup>47</sup> with any disagreements resolved by discussion with a third reviewer, if required. The critical appraisal of the individual studies will be reported narratively, including a description of the strengths and weaknesses of each study. The results of the critical appraisal will be used to assess confidence in the results.

## Data Analysis and Reporting of Findings

Narrative syntheses will be 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. The direction and size of any observed effects will be 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). The narrative synthesis will emphasize studies that fill an evidence gap (e.g., report a new comparison or new subgroup) or would alter the overall findings (e.g., by changing the magnitude or precision of an effect) of the Cochrane Review.<sup>40</sup> Studies that compare iCBT interventions to alternative iCBT interventions, or that meet the eligibility criteria for the Rapid Response but not the Cochrane Review (and therefore the update) for any reason, will be mentioned in the discussion of the HTA.

In addition to the narrative syntheses, the results of any additional eligible studies will be pooled, using random effects meta-analyses (because of the expected heterogeneity between trials) if data are sufficiently homogeneous in terms of clinical, methodological, and statistical characteristics. Any studies that are deemed inappropriate for pooling because of heterogeneity will be summarized narratively. An analysis will be conducted for each outcome pooled in the Cochrane Review<sup>48</sup> for which new data have been identified within the update. All subgroup analyses conducted in the Cochrane Review<sup>40</sup> will be retained and updated as part of the analyses (if new data are available). In order to remain consistent with the previous work, the methodology used in an updated meta-analysis will follow the procedures used in the Cochrane Review.<sup>40</sup> Dichotomous data will be analyzed as risk ratios to allow for comparisons across studies. Continuous data will be analyzed using either mean differences or standardized mean differences. Mean differences will be used for outcomes where all studies used the same outcome measure; standardized mean differences will be applied in instances where different outcome measures were used to assess the same outcome. Statistical heterogeneity will be assessed using graphical presentations (e.g., forest plots) and calculations of Cochrane's  $\text{Chi}^2$  test and the  $I^2$  statistic, which quantifies the variability in the effect estimates because of heterogeneity rather than chance (i.e., sampling error). Heterogeneity will be interpreted according to the guidance in the Cochrane handbook,<sup>49</sup> as follows:  $I^2$  values of less than 40% might not be important, values of 30% to 60% may represent moderate heterogeneity, values of 50% to 90% may represent substantial heterogeneity, and values of 75% or greater will be interpreted as considerable heterogeneity. Any updated meta-analyses will only include study designs that were eligible for the Cochrane Review (i.e., RCTs, randomized crossover trials, and cluster-randomized trials). Adjustments of sample sizes for cluster-randomized trials will be conducted using the methods described in the Cochrane handbook to remain consistent.<sup>49</sup> Additional detail on specific methods for meta-analyses is provided in the Cochrane Review.<sup>40</sup> Updated meta-analyses will be carried out using the Cochrane Review Manager software (version 5.3, or the most up-to-date version available at the time of analysis).

## Economic Evaluation

A primary economic analysis to evaluate 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 will be conducted.

### Primary Economic Analysis

A *de novo* decision analytic model will be developed to assess the costs and health outcomes associated with interventions for the treatment of PTSD in the population previously described. The interventions considered will mirror those in the clinical review, should data be available, and will include guided iCBT, unguided iCBT, individual face-to-face CBT, group face-to-face CBT, alternative psychotherapy intervention, treatment as usual, and no treatment (Table 1). The optimal sequence of therapy to treat PTSD may be of interest, as outlined in the Implementation Issues Analysis section. An exploratory analysis comparing treatment sequences in a stepped-care approach may be conducted in support of this.

The patient cohort will be described by specific risk factors and clinical characteristics that will be identified from the clinical review. Separate patient subgroups may be assessed based on feedback from clinical experts consulted for this project and the availability of subgroup data. This may include number of exposures (single or repeated trauma) and type of exposure.

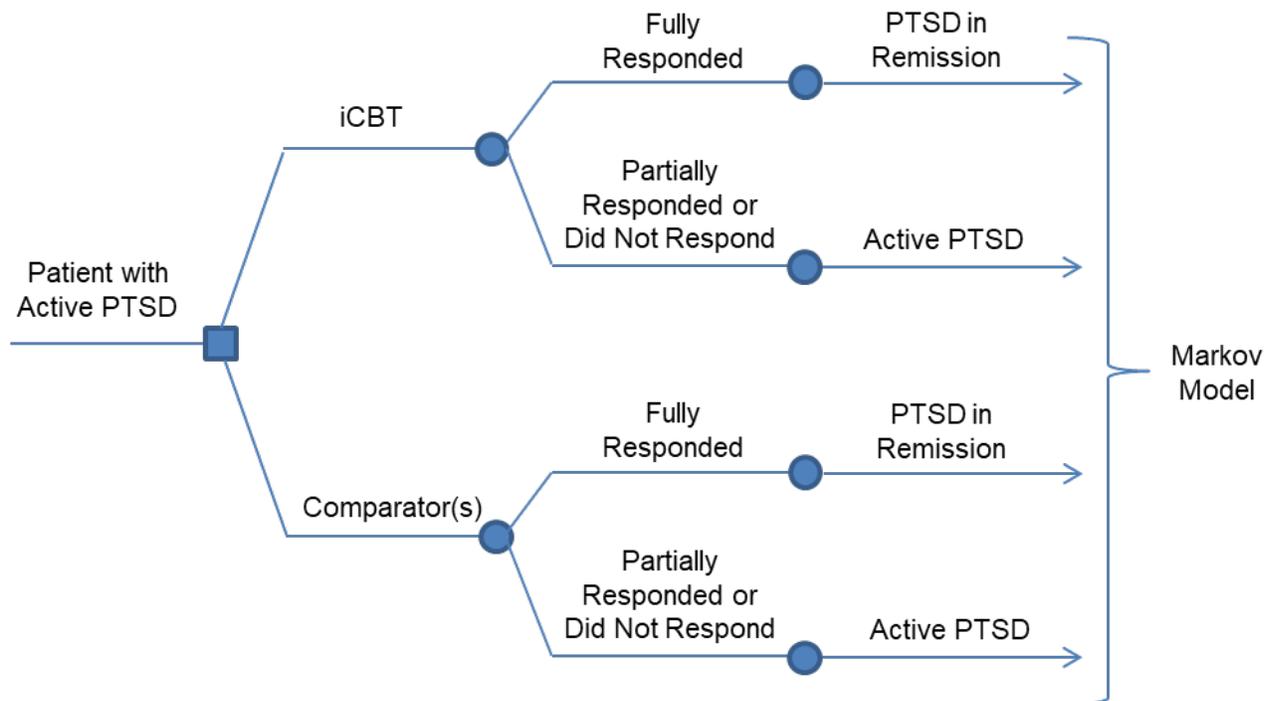
### Model Design

An economic model will be developed to describe the movement of patients between health states reflective of the typical clinical progression of PTSD. Over the course of the patients' lifetime, their PTSD and/or related comorbidities may improve or deteriorate, depending on the effectiveness of the treatment for PTSD, which may impact the natural disease progression. The model will be used to evaluate, for each identified patient population (or subpopulation, if applicable), the cost-effectiveness of iCBT compared with other interventions currently used in clinical practice (Table 1).

A hybrid decision tree and cohort-level state transition model will be developed. Patients with PTSD would first begin in the decision tree, where they would be assigned to one of the interventions under consideration. Patients would then have a probability of either fully responding or not responding (including partial response) to the intervention of interest based on the results of the clinical review. A hypothetical model structure for the decision tree can be found in Figure 1.

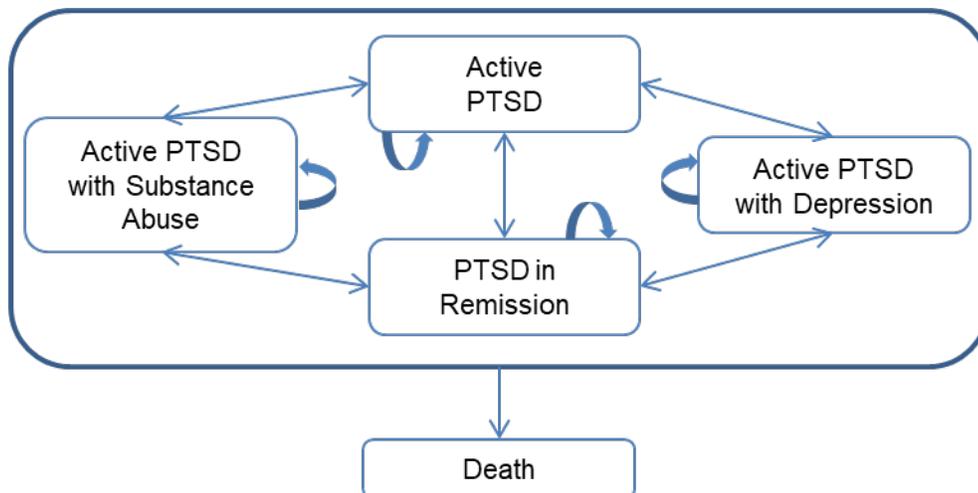
The Markov model describes health states relevant to the natural history of PTSD and long-term effects of treatment. Health states will include remission, active PTSD with or without comorbidities (i.e., depression and substance abuse), and death. Patients will enter the Markov model based on their response to treatment according to the decision tree. Patients can enter the Markov model in one of four states, depending on initial comorbidity status. Patients who fully responded to the initial treatment will begin in a "PTSD in remission" health state, while patients not responding to the intervention will enter the model in an "active PTSD" health state or its equivalent combined comorbid health state should a comorbidity be present at baseline. Throughout each cycle, patients can then transition between model health states based on the natural history of disease and the treatment effectiveness. A hypothetical model structure for the Markov model can be found in Figure 2.

**Figure 1: Proposed Structure of PTSD Model — Decision Tree to Capture Initial Treatment Effect**



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

**Figure 2: Proposed Structure of PTSD Model — Markov Model to Capture Natural History and Long-term Treatment Effects**



PTSD = post-traumatic stress disorder.

The details of the model will be developed based on feedback from the CADTH clinical review team and the clinical co-authors, as well as clinical experts and HTERP members to ensure that it reflects the current clinical literature and clinical practice. Both the internal and external validity of the model will be assessed for any logical discrepancies. The model will be constructed in Microsoft Excel.

### *Perspective*

The primary perspective in the model will be that of a publicly funded health care system (i.e., provincial Ministry of Health) focusing only on direct medical costs. Other perspectives may be considered (e.g., societal perspective) if deemed suitable based on findings from the other sections of this HTA and feedback from clinical experts consulted for this report or other stakeholders.

### *Resource Use and Cost Data*

The costs captured in the model will reflect the scope of the project and the perspective of the economic analysis. Costs will include those related to the interventions, resource use related to patient health states, and event-related costs, as well as any additional relevant costs identified in consultation with clinical experts and the literature.

Canadian specific costs will be used, when available. If unavailable, costs will be estimated from the medical literature and, ideally, from comparable health systems. If necessary, costs will be adjusted to 2019 Canadian dollars, using the consumer price index.

### *Utilities*

Utilities associated with each health state will be obtained from the literature from Canadian sources, where possible. A literature search of economic studies will provide the basis to identify suitable utility values.

### *Clinical Parameters*

Parameters describing the natural history of patients with PTSD will be identified from peer-reviewed medical literature and medical registries to generate health state transition probabilities.

The clinical review will be primarily used to identify treatment effects describing the comparative clinical effectiveness of interventions for PTSD. These values will be applied to the relevant natural history inputs in the form of relative treatment effects. Additional information from the clinical review that is of interest to the economic model includes data on dropout rates, proportion of patients with comorbidities of interest, and baseline medication use. In cases where no data are available to describe the impact of treatments to certain clinical outcomes, a clinical expert will be consulted.

### *Outcomes*

The model will estimate the expected lifetime costs and quality-adjusted life-years (QALYs) for each of the included treatment strategies. The generic QALY outcome was selected as the measure of treatment benefit, given the nature of PTSD and the potential impact of treatment. The primary outcome will be the incremental cost-utility ratios, measured in terms of the incremental costs per QALY gained, of the treatment strategies on the efficiency frontier.

Costs, disaggregated by type, will also be reported. Additional outcomes, such as the reduction in comorbid depression, may also be reported and will reflect the feedback received of patient important outcomes during patient engagement or the qualitative synthesis of perspectives and experiences of patients, families, and caregivers, or clinically important outcomes from clinical expert feedback.

### *Time Horizon and Discounting*

A lifetime time horizon is proposed, given that PTSD is potentially lifelong and that interventions to treat PTSD may have different impacts on both short- and long-term morbidity and mortality, resulting in differences in lifetime costs and benefits. Discounting will be set at 1.5% per year as per the CADTH *Guidelines for the Economic Evaluation of Health Technologies: Canada*.<sup>50</sup>

### *Sensitivity Analysis*

The base-case analysis will represent the probabilistic findings, capturing the extent to which parameter uncertainty may impact the incremental cost-effectiveness findings. Results of the probabilistic analysis will be presented on a cost-effectiveness acceptability curve, whereby the probability each intervention is most likely cost-effective will be highlighted across different willingness-to-pay thresholds.

Probabilistic scenario analyses will be performed to evaluate key model assumptions and potential scenarios of interest, which may include:

- types of iCBT programs (cost or efficacy differences)
- removal of comorbidities
- time horizon.

Uncertainty in the model will be further evaluated in a number of ways. Other analyses to address parameter uncertainty will include varying sets of related inputs (e.g., dropout rates and treatment effect) or extreme scenarios (e.g., best- and worst-case analysis, threshold scenarios). This may help identify key inputs driving the results of the cost-effectiveness analysis.

### *Assumptions*

During the course of the model development, assumptions and limitations will be identified and acknowledged in the report. Assumptions will be tested through the conduct of sensitivity analyses, where possible.

## **Perspectives and Experiences of Patients, Families, and Health Care Providers**

### **Research Question**

The review of perspectives and experiences of patients, families, and health care providers will be guided by the following research question:

How do patients, their families, and their health care providers experience engaging with iCBT for the treatment of PTSD?

Exploration of this question will be guided by the following subquestion:

How are varied understandings of PTSD as a diagnostic category perceived to influence both expectations toward and experiences with iCBT as a treatment option by individuals living with a diagnosis of PTSD?

## Study Design

A rapid qualitative review will be conducted. The primary goal is to invite reflection on the ways in which people living with PTSD understand their condition and subsequently navigate the health care spaces afforded them. Particular attention will be paid to interactions with iCBT as the focus of this HTA.

This protocol provides a general overview of methods to be used at each stage of the review. In line with the iterative nature of qualitative research, protocol refinement and amendment will be actively engaged at several stages as the review team responds to the set of eligible studies and available data for analysis. The potential for refinements and amendments are identified in each of the sections that follow. This iterative approach to protocol development and execution is not only consistent with the inductive principles of qualitative research but also allows further reflection on the relationship between the available qualitative studies and the decisions being made on study selection, data extraction, and analysis. Any subsequent refinements or amendments will be documented in a final report, together with their rationale.

## Literature Search Methods

The search for literature exploring perspectives and experiences of persons living with a diagnosis of PTSD, their families, and health care providers will be performed by an information specialist using a peer-reviewed search strategy according to the PRESS (Peer Review of Electronic Search Strategies) checklist (<https://www.cadth.ca/resources/finding-evidence/press>).<sup>51</sup> The complete search strategy is presented in Appendix 1.

Published literature will be 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 will be comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH, and keywords. The main search concepts will be Internet-based cognitive behavioural therapies and PTSD.

Search filters will be applied to limit retrieval to qualitative studies. Retrieval will also be limited to English- or French-language documents published between January 1, 2008 and the date the search is run.

The initial search will be completed in May 2019. Regular alerts will update the search until the publication of the final report.

Grey literature (literature that is not commercially published) will be 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>),<sup>46</sup> which includes the websites of regulatory agencies, HTA agencies, clinical guideline repositories, systematic review repositories, patient-related groups, and professional associations. Google will be used to search for additional Internet-based materials. These searches will be supplemented by reviewing bibliographies of key papers and through contacts with experts and industry, as appropriate.

Appendix 2 provides more information on the grey literature search strategy.

## Selection and Eligibility Criteria

Studies published in English or French that used qualitative data collection (e.g., interviews, participant-observation) and analysis methods will be eligible for this review. Studies must be about the personal experiences of people living with a diagnosis of PTSD, or their families or health care providers, or about engaging with iCBT for the treatment of PTSD. While iCBT will be the focus of this review, related interventions, particularly those that may play a part in a stepped-care approach to PTSD (e.g., face-to-face CBT) will be included. The following types of publications will be excluded: theses and dissertations, data presented in abstract form only, commentaries, case reports, and editorials. In addition, the following elements will render a study ineligible for inclusion: focused primarily on comorbidities (e.g., depression, substance use, anxiety) rather than PTSD, and other exclusions as they become apparent.

**Table 2: Eligibility Criteria**

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

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

## Screening and Selecting Studies for Inclusion

Titles and abstracts of retrieved citations from the literature search will be screened by one reviewer in DistillerSR<sup>52</sup> according to the predefined eligibility criteria (Table 2). The full texts of all potentially eligible citations will be retrieved and subsequently screened by a single reviewer, with a second reviewer screening a small sample and engaging in discussion with the primary reviewer in the final determination of inclusion. The size of the small sample will depend on the number and characteristics of studies that the primary researcher is uncomfortable either excluding or including. Either all such studies will be chosen to create the sample for discussion, or one of each “type” if the studies can be categorized based on issues raised or methods used. Disagreements regarding eligibility will be resolved through discussion until consensus is reached.

Once the eligibility of all citations has been determined, an assessment will be made about whether the research questions are answerable with this data set and whether the data set is manageable. If the data set is deemed too large, the research questions may be refined to focus on areas of particular relevance and a purposive sampling strategy may be developed.<sup>53</sup> If the data set is deemed too small, the search may be refined to capture additional experiences or constructs of interest. As appropriate, an iterative approach will accordingly be adopted to refine the research questions.<sup>54</sup> This iterative refinement is

common in qualitative approaches and requires familiarity with the data set.<sup>54,55</sup> Decisions will be documented in a final report, along with a rationale.

## Data Extraction

Bibliographic details including the country and funding of the research team, the description of participants, the research methods used, and the research question(s) will be extracted into structured forms. Data extraction forms will be piloted by two reviewers until both reviewers agree that consistency is reached. The remaining descriptive data extraction will be completed by a single reviewer and will be presented in tabular form in the final report, accompanied by a narrative summary.

## Critical Appraisal

A streamlined approach to critical appraisal will be used as a way of remaining attuned to both the rigour and relevance of included studies, as well as the abbreviated timelines of rapid qualitative evidence syntheses. As critique and analysis are often co-constitutive in qualitative research, this streamlined appraisal is consistent with disciplinary norms in which understanding things like how data are collected or where data sources are situated in relation to the researcher represent more than methodological considerations. In this review, critical appraisal will follow Krefting's<sup>48</sup> interpretation of Lincoln and Guba's<sup>56</sup> model for assessing trustworthiness in qualitative research. Krefting's emphasis on and mode of exploring trustworthiness<sup>48</sup> asks the reviewer to consider the interactions between research methods and results as a way of evaluating the process involved in arriving at a certain result or conclusion. This is done with a particular focus on three guiding questions: Is it credible? Is it trustworthy? Are the results transferable?<sup>48</sup>

The primary reviewer will conduct the appraisal, engaging with a second reviewer as a devil's advocate regarding key issues around credibility, trustworthiness and dependability, and transferability. Disagreements on the appraisal will be resolved through conversation. Results of the critical appraisal will not be used to exclude studies from this review; rather, they will be used to understand the methodological and conceptual limitations of the included publications in specific relation to the decision problems and research questions. A narrative summary of the credibility, trustworthiness, and transferability of the included studies will be presented in the final review.

## Data Analysis and Synthesis

A "best fit" framework approach to data analysis will be 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 clinical and non-clinical caregivers.<sup>57,58</sup> 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.<sup>37</sup> As iCBT is the intervention of interest in both reviews, these categories were perceived as a suitable framework without the need to undergo an extra systematic search under abbreviated timelines. These categories include experiences related to:

- 1) 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.

- 2) 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.
- 3) Relationality: This involves perceptions of and experiences with a therapist or supporter throughout the use of iCBT.
- 4) 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 engagements with iCBT.

Articles will be imported into NVivo 11<sup>59</sup> for data analysis. The primary reviewer will begin 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 will be developed to accommodate findings emerging from the included literature not accommodated within the initial framework. An initial set of articles (n = 3) will be coded and a second reviewer will be engaged for a preliminary discussion of emergent findings. If agreement is not reached on the fit of findings to the predefined framework or relevance of newly emergent findings, a second set of three articles will be coded with a subsequent meeting to discuss the process. As appropriate, codes will be refined and organized into concepts and findings through ongoing and frequent discussions between the reviewers, supported by the use of diagramming and memoing. This iterative and conversational approach will aid in ensuring the reviewer is engaging with the material in an appropriately reflexive mode of inquiry.

As the goal of this review is to understand how iCBT is experienced as a treatment modality for PTSD and is broadly incorporated (or not) into people's lives, perspectives and experiences articulated within the included literature will not be considered as universally representative of a particular speaker's group (e.g., people living with a diagnosis of PTSD, families, care providers). Therefore, the varied thoughts, experiences, and perspectives articulated within included studies will be analyzed relationally to understanding how varied speakers' perspectives and experiences may be co-constitutive of each other, as opposed to being analyzed within distinct sets.

## Technique to Strengthen Methodological Rigour

In addition to the methods previously described, the credibility of the analysis will be strengthened by engaging individuals living with a diagnosis of PTSD (or their families) who are willing to share their experiences and perspectives on the use of iCBT and related interventions (e.g., face-to-face CBT) throughout their treatment pathways. This will be done at several stages of the review and is detailed in the following Patient Engagement section.

## Patient Engagement

This protocol outlines how CADTH has, and will continue to, engage individuals living with a diagnosis of PTSD (or their families) with or without the experience of iCBT in their discussions to inform the development of the HTA protocol and research questions. It will also help in the interpretation of findings of the patients' perspectives and experiences analysis, and the reporting of HTA results. We describe how patient engagement has been and will be used in the assessment so as to be accountable to the people we engage.

## Methods of Engagement

### *Invitation to Participate*

Prior to protocol completion, we engaged with three adults (18 or older) who are currently living with a diagnosis of clinical or subclinical PTSD. Two indicated developing PTSD during their encounters with the Canadian health care system and the third through military service. None of the three indicated having any experience with iCBT for the treatment of their PTSD diagnosis. We will engage at least three more adults (18 or older) with a diagnosis of PTSD, with or without experience of iCBT. Potential participants have and will continue to be identified through multiple sources including but not limited to patient organizations including the PTSD Association of Canada, clinical experts involved in the project, CADTH Liaison Officers, and other CADTH networks across Canada. A CADTH Patient Engagement Officer has and will continue to contact potential participants by phone or email to explore their interest in becoming involved. The preliminary request describes CADTH and the purpose and scope of this Optimal Use project, the purpose of engagement and the nature of engagement activities, and invites the individual to participate in the project. Should they be interested in participating, we will continue to obtain their informed consent.

### *Engagement Activities*

Engagement activities will involve participants at several points during the assessment including:

- prior to protocol finalization
- during drafting of the final report
- upon project completion.

When consent is obtained (if participants remain interested), individual participants will continue to be led in conversation about their health condition and their treatment experiences and perspectives on those experiences. Notes from the conversation will continue to be summarized, with any personal identifiers removed, and provided to individual participants for their review and edits to ensure clarity and accuracy in representation of their experiences and perceptions. It is important to note that the individuals engaged throughout the course of this HTA are not considered research participants but rather as expert informants. They will comment on and direct investigations of what it might be like to be living with a diagnosis of PTSD and subsequently engaging within interventions like iCBT.

While no direct outcome on the protocol has developed from the three conversations already held, each of these participants have directed our attention to elements of stigma around a diagnosis of PTSD, difficulties accessing both a diagnosis and subsequent care for PTSD, and elements of PTSD care that have been either helpful or detrimental in their own experiences with PTSD care. These elements are helping to orient early planning and progress through the rapid qualitative synthesis and analysis process.

The next stage of engagement will occur once preliminary findings from the qualitative synthesis of patients' perspectives and experiences are available. At this time, individual participants will again be invited to participate in discussion. The conversations will explore participants' perceptions of key findings, including if the findings are understandable and if they reflect their experiences or understandings. These conversations will be used to consider the possible need to explore avenues of analysis that have been missed or underdeveloped, add additional concepts or experiences that relate to identified categories

in the qualitative synthesis, or inform the processes underlying PTSD treatment and the context of analysis.

Final conversations will be had with participants upon completion of the assessment and following HTERP deliberation and recommendation development. Through conversation, we will share the key results of the full assessment, including the HTERP recommendation document, and describe how engagement activities were used.

### *Reporting*

Throughout the assessment process and during team meetings, we will take detailed notes so as to outline in a final report the process of engagement and where and how participants' contributions were used in the assessment.

## Ethical Issues Analysis

The purpose of this analysis is 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 is to make such issues explicit and to identify others that may be relevant to any decisions in this regard. The issues raised in this section can go beyond narrowly defined ethical concerns to encompass broader legal, social, and cultural considerations, as well. Nevertheless, the primary emphasis here will be on ethical considerations rather than on legal and social issues. There are two questions to consider about the provision, development, and use of iCBT for PTSD in Canada:

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. This may require further yet 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. By this approach, we identify and assess the relative importance and strength of the identified concerns and proposed solutions, identify and assess ethics issues that have not yet been identified in the iCBT literature, and delineate ethical desiderata for possible solutions to the issues where such solutions have not yet been proposed. Insofar as this process involves ethical concerns in applied ethics, typically the analysis will reflect on the specific details of community and patients' perspectives, clinical utility, economic analysis, and implementation considerations. As such, the Ethical Issues Analysis section and approach involves an iterative process whereby the analysis is responsive to results emerging from the other sections of this HTA.

### Review of the Bioethics Literature

A review of the empirical and normative bioethics literature will be conducted to identify literature relevant to the identification and analysis of the potential ethical issues related to the provision, development, and use of iCBT for PTSD. We will search for articles, studies, and reports that explicitly and specifically raise ethical issues related to the central

question(s) of this HTA, as well as literature not explicitly about ethical issues (for example, an empirical investigation of patient attitudes about iCBT for PTSD) but which point to potential ethical issues even if the participants and researchers did not formulate them as such.

## Literature Search Methods

The search for literature identifying explicit ethical considerations will be performed by an information specialist using a peer-reviewed search strategy according to the PRESS checklist (<https://www.cadth.ca/resources/finding-evidence/press>).<sup>51</sup> The search strategy is available on request.

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

Search filters will be applied to limit retrieval to citations related to empirical and normative ethical considerations. Retrieval will also be limited to English- or French-language documents published between January 1, 2008 and the date the search is run. The initial search will be completed in June 2019. Regular alerts will update the search until the publication of the final report.

Grey literature (literature that is not commercially published) will be 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/resources/finding-evidence/grey-matters>),<sup>46</sup> which includes the websites of regulatory agencies, HTA agencies, clinical guideline repositories, systematic review repositories, patient-related groups, and professional associations. Google will be used to search for additional Internet-based materials. These searches will be supplemented by reviewing bibliographies of key papers and through contacts with experts and industry, as appropriate.

Appendix 2 provides more information on the grey literature search strategy.

Additionally, literature identified as relevant in a recent review on a similar topic<sup>60</sup> will be included where overlapping themes are found.

## Literature Screening and Selection

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

- provide normative analysis of an ethical issue arising in the provision, development, and use of iCBT, whether for the treatment of PTSD or more generally
- present 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 does not figure in the article selection criteria: any identification of an issue by the public, patients, health care providers, researchers, or policy-makers is 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 are 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 will be reviewed by a single reviewer with ethics expertise. Reports meeting the abovementioned criteria will be included in the analysis and reports that do not meet these criteria will be excluded from analysis.

## Analysis

The ethical issues identified, values described, and solutions proposed in the literature will at this stage be evaluated using the methods of ethical (applied philosophical) analysis, which includes applying standards of logical consistency and rigour in argumentation. This is particularly true where specific implications are identified and specific solutions advocated; there is responsiveness to important values of health care and health care policy in the field in which the technology is proposed for implementation; there is adequacy to the context for which the technology is being considered; and there is representation of perspectives from diverse relevant communities, particularly marginalized and vulnerable populations. The proposed analysis will draw most directly on two classic perspectives that are well-established in the health ethics literature, namely the utilitarian/consequentialist approach and the deontological/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/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. Whereas 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 arises, it is possible that other normative ethical perspectives may be invoked in the analysis (e.g., virtue theory may be particularly relevant to issues regarding the professional conduct of psychiatrists or other therapists).

## Summarizing and Presenting Results

The reporting of ethical issues will follow the key values identified or issues being explored and will be determined by the values and issues that are identified. For example, the results may be summarized according to a principlist framework (issues concerned with autonomy, beneficence, non-maleficence, and justice) or by categorizing moral concerns as micro-, meso-, and macro-level issues. Regardless of the framework selected, the implications of the choice of framework on how the findings are presented and interpreted will be described. In addition, where the report undertakes analysis that is not derived from the peer-reviewed literature, this will be noted. It may also be appropriate to summarize the bibliographic details for each report (e.g., author, publication date, and journal), the potential ethical issues raised, and the report's conclusions, as well as other information. The relevance and appropriateness of providing this summary will be determined after the analysis is complete. Ethical analysis assists in policy decision-making but is not itself the site of legitimate decision-making, which requires consultation and deliberation on the part of relevant stakeholders in a given context. Decisions will also be sensitive to emerging empirical evidence. Furthermore, the ethical implications of a health technology are often determined by the nature of the local context. The implications of values of fair access and consistency of service within the population, for example, are determined by facts about how health care services are arranged and provided.

Given these features of ethical decision-making, results of the Ethical Issues Analysis will be presented in a way that helps decision-makers better understand the ethical implications of the decisions and recommendations they come to. For example, a number of contextualizing questions may be developed based on the identified issues so that decision-makers can assess localized impact, and proposed solutions will be analyzed to indicate the relevant ethical trade-offs at stake and mitigation strategies that could be employed to manage these trade-offs.

## Implementation Issues Analysis

### Research Question

The Implementation Issues Analysis will be 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., an individual living with the diagnosis of PTSD and a 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 will be 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 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 will be conducted to explore implementation issues associated with the use of iCBT in the treatment of PTSD.

### Literature Search Methods

The search for literature describing implementation considerations will be performed by an information specialist using a peer-reviewed search strategy according to the PRESS checklist (<https://www.cadth.ca/resources/finding-evidence/press>).<sup>51</sup> The search strategy is available on request.

Published literature will be 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 (DARE), the National Institute for Health Research Health Technology Assessment database, CINAHL via EBSCO, and PubMed. The search strategy will be comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH, and keywords. The main search concepts will be Internet-based cognitive behavioural therapies (iCBT) and PTSD.

No search filters will be applied. Retrieval will also be limited to English- or French-language documents published between January 1, 2008 and the date the search is run. The initial search will be completed in May 2019. Regular alerts will update the search until the publication of the final report.

Grey literature (literature that is not commercially published) will be 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/resources/finding-evidence/grey-matters>),<sup>46</sup> which includes the websites of regulatory agencies, HTA agencies, clinical guideline repositories, systematic review repositories, patient-related groups, and professional associations. Google will be used to search for additional Internet-based materials. These searches will be supplemented by reviewing bibliographies of key papers and through contacts with experts and industry, as appropriate.

Appendix 2 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, will be eligible for this review. The categories included in the INTEGRATE-HTA Context and Implementation of Complex Interventions Framework,<sup>61</sup> as well as stakeholder consultation, will be used to sensitize the reviewer to particular points of concern. For example, the issues may include, but won't be 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 eligibility criteria previously noted will be considered for inclusion in this review regardless of publication type, although conference abstracts will be excluded. In alignment with iterative search standards in qualitative research, eligibility criteria may be refined, as necessary, to ensure a data-rich and relevant set of included documents; finalized inclusion criteria will be documented in the final report.

Titles and abstracts of retrieved citations will be screened by a single reviewer in DistillerSR.<sup>52</sup> First-level screening will exclude all citations that are not primarily about or include substantive discussion about iCBT, particularly in relation to the treatment of PTSD. The full text of all remaining potentially eligible citations will then be screened by one reviewer, using the eligibility criteria.

## Data Extraction

Data extraction will include bibliographic details of included documents including country and funding of authors, research question or aim, and document type (e.g., editorial, HTA document). Data extraction forms will be piloted by two reviewers until both reviewers agree that consistency is reached. The remaining data extraction will be completed by a single reviewer.

## Stakeholder Consultations

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

CADTH's Implementation Support and Knowledge Mobilization team will identify potential stakeholders through existing CADTH networks and other relevant national or provincial stakeholder groups using a purposive sampling strategy. The goal will be 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 will include, but will not be limited to, policy-makers (e.g., at the Ministry level), clinicians (e.g., psychologists, psychiatrists, 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 will be approached. The aim is to continue with stakeholder consultations until no new information is emerging (data saturation); however, sample size may also be limited because of time and resource constraints.

The consultations will be facilitated by two CADTH staff members (a Knowledge Mobilization Officer and a Research Officer) and a semi-structured interview questionnaire will be used to guide the discussions with the stakeholders on the context and implementation of iCBT for PTSD in Canada. Depending on which stakeholder we are speaking with, questions will touch on areas such as, but not limited to, how PTSD is currently cared for in the stakeholder's jurisdiction, what sort of conversations are currently surrounding the use of iCBT for PTSD, has iCBT for PTSD been used in their jurisdiction already, how will or does funding for iCBT currently happen? The consultation sessions will be recorded, with consent.

Stakeholders will be asked to provide informed consent on the purpose and process of the consultations, as well as permission to use any relevant information they may provide as part of the final HTA report results.

## Data Analysis

The findings of the literature review, stakeholder consultations, as well as information from the analyses of other sections of this HTA, will be synthesized using a framework approach.<sup>62</sup>

A framework approach involves a five-stage process of data analysis: familiarization, indexing, charting, mapping, and interpretation. Whereas analysis will be led by the primary reviewer, conversations with a second reviewer, as well as the project's Knowledge Mobilization and Patient Engagement Officers, will provide clarity and depth to the analysis.

### Stage 1: Familiarization

Familiarization involves 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 will be done through team discussion, review of the retrieved literature and draft reports from other sections, and stakeholder consultations. During the process of familiarization, researchers will aim to draw out initial ideas and concepts through diagramming, memoing, and discussion. Categories included in the Context and Implementation of Complex Interventions Framework<sup>61</sup> will also be used to aid

in the development of these ideas and concepts, although not strictly followed as the primary categories of import.

### **Stage 2: Identifying a thematic framework**

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

### **Stage 3: Indexing**

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

More than one concept or idea can be 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 research judgment to explore the meaning and significance of the data, indexing provides transparency to this process. During indexing, changes may be made to the framework to improve its clarity and relevance to research objectives.

### **Stage 4: Charting**

The process of charting involves 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)<sup>62</sup>

Charting will help to visualize the data across cases or themes; data will be sorted into charts based on key ideas or concepts, or will be sorted based on the type of source data. This process will aid 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 and stakeholder consultations, and information from other sections of the HTA, will be mapped onto this framework, progressing through the steps of indexing and charting using memoing and diagramming.

### **Stage 5: Mapping and interpretation**

This stage involves 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 will be supported by frequent discussion among researchers involved in all components of the implementation analysis and through larger team discussion.

## **Reporting**

Results of the implementation analysis will be presented using tables and diagrams, where appropriate. The full analysis will be reported narratively and will incorporate feedback provided from stakeholders and CADTH expert committees.

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## Appendix 1: Literature Search Strategy

### Literature Search for Perspectives and Experiences of Patients, Families, and Health Care Providers

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946 to present) PsycINFO (1806 to present) <b>Note:</b> Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 2019
Alerts:	Monthly search updates until project completion
Study Types:	Qualitative studies
Limits:	Publication date limit: 2008 to present Language limit: English- or French-language
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
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 or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.id	Key concepts (PsycINFO); summarizes a document's subject content
.kf	Author keyword heading word (MEDLINE)
.jw	Journal word title
MULTI-DATABASE STRATEGY	
CBT Concept	
1	Cognitive Behavioral Therapy/ or "Acceptance and Commitment Therapy"/ or Psychotherapy/ or Desensitization, Psychologic/ or Implosive Therapy/
2	exp Cognitive Behavior Therapy/ or Cognitive Therapy/
3	(((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.
4	(self-manag* or selfmanag* or self-help* or selfhelp*).ti,ab,kf,kw,id.
5	((psycholog* adj3 desensiti*) or imaginal flooding* or (imager* adj3 exposure*).ti,ab,kf,kw,id.
6	((exposure or flooding* or implosive or saturation) adj3 therap*).ti,ab,kf,kw,id.
7	or/1-6
Internet Concept	
8	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/

MULTI-DATABASE STRATEGY	
9	Telemedicine/ or Computer-Assisted therapy/ or Computer-Assisted Instruction/ or Internet/ or exp Mobile Devices/ or Online Therapy/
10	(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.
11	or/8-10
<b>PTSD Concept</b>	
12	exp Stress Disorders, Traumatic/
13	exp Posttraumatic Stress Disorder/ or Combat Experience/ or Emotional Trauma/ or Post-Traumatic Stress/ or Traumatic Neurosis/
14	(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 PTSD or complex trauma* or traumatic stress or moral injur* or trauma-base* or trauma-focus*).ti,ab,kf,kw,id.
15	(combat* adj3 (neuroses* or neurosis* or stress* or fatigue* or disorder*).ti,ab,kf,kw,id.
16	or/12-15
<b>iCBT Concept</b>	
17	(cCBT* or iCBT* or eCBT*).ti,ab,kf,kw,id.
18	((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.
19	(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.
20	(e-mental health or emental health).ti,ab,kf,kw,id.
21	(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.
22	or/17-21
23	7 and 11 and 16
24	16 and 22
25	23 or 24
26	limit 25 to (english or french)
27	limit 26 to yr="2008 -Current"
<b>Qualitative Filter</b>	
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	Qualitative Research/ or Grounded Theory/ or Narratives/ or Storytelling/ or exp Life Experiences/ or exp Interviews/
30	interview*.ti,ab,kf,id.

MULTI-DATABASE STRATEGY	
31	qualitative*.ti,ab,kf,jw,id.
32	(theme* or thematic).ti,ab,kf,id.
33	ethnological research.ti,ab,kf,id.
34	ethnograph*.ti,ab,kf,id.
35	ethnomedicine.ti,ab,kf,id.
36	ethnonursing.ti,ab,kf,id.
37	phenomenol*.ti,ab,kf,id.
38	(grounded adj (theor* or study or studies or research or analys?s)).ti,ab,kf,id.
39	(life stor* or women* stor*).ti,ab,kf,id.
40	(emic or etic or hermeneutic* or heuristic* or semiotic*).ti,ab,kf,id.
41	(data adj1 saturat\$).ti,ab,kf,id.
42	participant observ*.ti,ab,kf,id.
43	(social construct* or postmodern* or post-structural* or post structural* or poststructural* or post modern* or post-modern* or feminis*).ti,ab,kf,id.
44	(action research or cooperative inquir* or co operative inquir* or co-operative inquir*).ti,ab,kf,id.
45	(humanistic or existential or experiential or paradigm*).ti,ab,kf,id.
46	(field adj (study or studies or research or work)).ti,ab,kf,id.
47	(human science or social science).ti,ab,kf,id.
48	biographical method.ti,ab,kf,id.
49	theoretical sampl*.ti,ab,kf,id.
50	((purpos* adj4 sampl*) or focus group*).ti,ab,kf,id.
51	(open-ended or narrative* or textual or texts or semi-structured).ti,ab,kf,id.
52	(life world* or life-world* or conversation analys?s or personal experience* or theoretical saturation).ti,ab,kf,id.
53	((lived or life) adj experience*).ti,ab,kf,id.
54	cluster sampl*.ti,ab,kf,id.
55	observational method*.ti,ab,kf,id.
56	content analysis.ti,ab,kf,id.
57	(constant adj (comparative or comparison)).ti,ab,kf,id.
58	((discourse* or discours*) adj3 analys?s).ti,ab,kf,id.
59	(heidegger* or colaizzi* or spiegelberg* or merleau* or husserl* or foucault* or ricoeur or glaser*).ti,ab,kf,id.
60	van manen*.ti,ab,kf,id.
61	van kaam*.ti,ab,kf,id.
62	(corbin* adj2 strauss*).ti,ab,kf,id.
63	or/28-62
64	27 and 63
65	remove duplicates from 64

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials. [Search terms – PTSD and iCBT]	
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. [Search terms – PTSD and iCBT]	

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. Syntax adjusted for EBSCO platform, including the addition of CINAHL headings.	

## Appendix 2: Grey Literature

Dates for Search:	June 2019
Keywords:	[PTSD and iCBT]
Limits:	Publication years: 2008 to 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/resources/finding-evidence/grey-matters>) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Clinical Trial Registries
- Databases (free)
- Internet Search
- Open Access Journals