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Internet-Delivered Cognitive Behavioural Therapy for the Management of Chronic Non-Cancer Pain: Project Protocol

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Project Protocol

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

CBT	cognitive behavioural therapy
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	health technology assessment
iCBT	internet-delivered cognitive behavioural therapy
MA	meta-analysis
PICO	population, intervention, comparator, outcome
PTSD	posttraumatic stress disorder
RCT	randomized controlled trial
RoBANS	Risk of Bias Assessment Tool for Non-randomized Studies
SR	systematic review

Introduction and Rationale

Chronic pain affects approximately 19% of adults in Canada.[1] Prevalence estimates among children and adolescents range from 11% to 38%.[2] Individuals living with chronic pain can experience substantial physical and psychological morbidity, which can contribute to reduced quality of life and increased socioeconomic difficulties.[2,3] In addition, chronic pain is associated with a significant economic impact. In Canada, on an annual basis, more than $6 billion is spent on direct health care costs to address chronic pain, while the indirect costs to the overall economy are estimated at more than $37 billion dollars.[3] Annual societal costs associated with chronic pain are estimated at between $560 and $600 billion in the US.[4]

Chronic pain is commonly defined as pain that lasts or recurs for more than 3 months and is recognized as a disease in its own right by the WHO.[5,6] The condition can be further classified as chronic primary pain and chronic secondary pain. Chronic primary pain is pain that affects 1 or more anatomic regions, persists or recurs for more than 3 months, is associated with significant emotional distress and/or significant functional disability, and its symptoms are not better accounted for by another diagnosis.[6] Conditions considered as chronic primary pain include chronic widespread pain, complex regional pain syndrome, chronic primary headache or orofacial pain, chronic primary visceral pain, and chronic primary musculoskeletal pain.[6] Chronic secondary pain is defined as pain that originates as a symptom of another condition, but the pain problem may persist and become a condition in its own right after the underlying condition has been treated.[5] Examples of chronic secondary pain syndromes include chronic cancer-related pain, chronic postsurgical or posttraumatic pain, chronic neuropathic pain, chronic secondary headache or orofacial pain, chronic secondary visceral pain, and chronic secondary musculoskeletal pain.[5] Chronic non-cancer pain, the focus of this Health Technology Assessment (HTA), is a broad category that includes chronic primary pain and chronic secondary pain conditions other than cancer-related pain. The management of cancer-related pain is commonly based on separate and different guidelines and protocols from those for non-cancer pain and is therefore beyond the scope of this HTA.

Pain is recognized as a complex, multi-dimensional condition that is characterized by an interplay of biological, psychological, and social factors.[2] People living with pain often experience comorbid mental health issues, such as depression and anxiety, which highlights the broad psychological facet of chronic pain as a disease.[7,8] Current recommendations and strategies to address pain emphasize the need for multidisciplinary care approaches to target the different dimensions of pain and improve treatment outcomes.[2,3,9] Multidisciplinary care strategies draw from a range of potential interventions such as pharmacotherapy, physical and rehabilitative therapies, psychological therapy, medical devices, manual therapy, and self-management.[2]

Cognitive behavioural therapy (CBT) is one of the most frequently used psychological interventions for the management of chronic pain.[10-12] Briefly, CBT aims to provide people with increased coping ability and self-efficacy by helping them identify and reshape their thoughts, emotions, and behaviours that can be detrimental to effective pain management or inhibit treatment progress.[12-14] In a 2019 CADTH Rapid Review Report (Summary with Critical Appraisal)[15] on the clinical effectiveness of CBT for the management of chronic non-cancer pain, 1 of the 5 identified systematic reviews (SRs) was a 2018 Cochrane SR[16] that investigated the effectiveness of in-person psychological therapies, including CBT, in the management of pediatric patients with chronic pain. Findings from this Cochrane SR[16]

suggest that psychological therapies including CBT may be associated with decreases in pain intensity, anxiety, and disability post-treatment in pediatric patients with mixed pain conditions (e.g., recurrent abdominal pain, musculoskeletal pain) compared to usual care and wait list controls. As part of scoping activities, a 2020 Cochrane SR[17] that assessed the effectiveness of in-person CBT for the management of chronic pain (excluding headache) in adults was identified. The authors of the Cochrane SR[17] concluded that there is strong evidence for CBT having very small statistically significant benefits at treatment end for pain and disability compared to active control and small statistically significant benefits for pain, disability, and distress compared to treatment as usual. The authors of the review[17] stated that they were unable to make any meaningful translation of these effect sizes into clinically interpretable changes because of variability of outcome metrics within each domain and considerable heterogeneity at baseline (i.e., the clinical significance of these results was unclear). Albeit the benefits of in-person CBT were characterized as small or very small for individuals with chronic pain, there may be a large population benefit. The authors of this Cochrane SR[17] concluded that the body of evidence was sufficient (i.e., large and of moderate quality) to support the benefits of in-person CBT and was not likely to change with additional studies. Of note, in a previous edition[18] of this Cochrane SR, the authors stated that psychologically informed subgroup analyses may be helpful in identifying which patients can benefit most from CBT, an important consideration given that the therapeutic effect of CBT is likely to vary by individual.[19-21] The authors also evaluated the risk for adverse events related to CBT; however, the evidence was of very low certainty because of inconsistency and indirectness.

While psychological interventions, such as CBT, are increasingly integrated in care approaches for pain, a notable challenge stems from the limited availability of these therapies in their traditional, in-person format. Financial costs and the ability to pay, stigma, and long-wait times are among factors that can deter those who need care from seeking and engaging in traditional psychotherapy.[22-27] Amid these various challenges, internet-based delivery of psychological treatments, such as CBT, is increasingly considered as an option that may help improve access to psychological care for chronic pain.[28-32] In this HTA, access is defined broadly, capturing not only factors related to the demand and supply sides of a health care service — such as the needs and desire for care or the availability of care — but also barriers and enablers that may impede or facilitate the utilization of, and ability to benefit from, that service — such as issues related to the affordability, physical accessibility, or acceptability of that service.[33,34]

Internet-delivered CBT (iCBT) is psychotherapy based on CBT principles delivered exclusively through the internet via an app or a website on a computer or mobile device. Available iCBT programs vary in terms of content, quality, and adherence to the principles of CBT. In the context of this HTA, the term "internet-delivered cognitive behavioural therapy" (or iCBT) is used to encompass the various forms of CBT-based therapies that are provided over the internet. The delivery of iCBT programs may be self-guided or therapist-assisted. The latter, which is also referred to as guided iCBT, includes therapeutic support provided by a trained therapist who may be a social worker, a psychologist, a psychotherapist, or other health professional. The support commonly consists of planned or ad hoc guidance and feedback to the person seeking care as they go through the internet-based treatment. Communication between the therapist and person seeking care is typically asynchronous, but iCBT programs may also include synchronous interaction that occurs on an as-needed basis or at predefined steps in the therapy process.[31,32] In this HTA, iCBT also includes CBT that is delivered through the internet in real time by a therapist (e.g., videoconference). In short, the scope of this

HTA includes guided and unguided iCBT delivered via a computer or mobile device, either synchronously or asynchronously.

To help improve health care access to psychological care for chronic pain, including at times when public health measures require physical distancing, there may be a need to virtually deliver medical and mental health care services via the internet, videoconference, or apps. The COVID-19 pandemic, particularly the unprecedented constraints that it has imposed on in-person care delivery, has highlighted the need for the comprehensive integration of virtual care options in the health care system. Early assessments of the impact of the pandemic on the delivery of health services indicate that the situation may have spurred a significant increase in interest in, acceptability of, and adoption of virtual care in Canada and globally.[35,36] In May 2021, the Canadian Pain Task Force published an action plan that includes a number of recommended actions for integrating and scaling up virtual care programs and resources in the delivery of pain care in Canada.[37] Further, according to a 2021 report[38] published by the Canadian Institutes of Health Research (CIHR), there is a need to promote the use of high-quality, evidence-based virtual care modalities for pediatric patients living with chronic pain. The CIHR report[38] also suggests that engagement with patients and their families would help facilitate the selection and implementation of virtual care for the management of chronic pain. iCBT programs for pain management are emerging in Canada and the number of providers offering such services appears to be limited at the moment.[35-37,39-41]This suggests that the current context is timely for CADTH to conduct an HTA to help inform discussions and decisions regarding the use of iCBT in the treatment of chronic pain, with a view to increasing access to CBT-based therapy.

Canadian jurisdictions have indicated that there is interest in exploring and using iCBT as an option for the management of chronic pain to improve access to psychological care. However, jurisdictions note that there is a need for reliable evidence and information to guide decisions regarding the integration of this intervention in care delivery for people living with chronic pain. The Canadian Pain Task Force Report 2020 notes that patient outcomes are improved when multiple professionals and caretakers are involved in addressing chronic pain.[42] A key question that prevails around iCBT is whether this therapy should be offered as part of a multidisciplinary (pharmacological and non-pharmacological) strategy for chronic pain management and care when CBT-based therapies are being considered. There is also interest in determining who this therapy should be offered to and if there are patients with chronic pain for whom iCBT is not appropriate; for example, because of co-occurring conditions, cognitive problems, goals, preference, readiness, and unstable housing or lack of a reliable internet connection. A related question pertains to the circumstances in which iCBT should or should not be considered in the broader context of provision of care services for chronic pain. Finally, there is an interest in understanding the factors that could impact the implementation and uptake of iCBT and what conditions could promote or hinder the achievement of the objective of improving access to psychological treatment.

Decision Problems

This HTA will inform the following decision problems:

1. With a view to increasing access to CBT-based therapy, the purpose of this HTA is to inform decisions as to whether iCBT should be offered as a treatment option, as part of a

multidisciplinary approach, in the delivery of care for chronic non-cancer pain when CBT would otherwise be provided.

2. Additionally, if evidence demonstrates that iCBT should be offered, the HTA could also inform whether there are criteria to guide decision-making regarding the suitability of iCBT for various pain conditions and people experiencing chronic pain, or other factors that should guide its implementation.

Objective(s)

The objective of this HTA is to inform the decision problems with an assessment of the clinical effectiveness and safety of iCBT, the perspectives and experiences of patients and caregivers, and operational aspects associated with the use of iCBT in the management of chronic non-cancer pain when CBT-based therapies would otherwise be provided.

Research Questions

The HTA will inform the decision problems by exploring the research questions that follow. Details on the specific interventions and outcomes are included in Table 1.

Clinical Effectiveness and Safety

1. What is the comparative clinical effectiveness of internet-delivered cognitive behavioural therapy versus in-person cognitive behavioural therapy for the management of chronic non-cancer pain?
2. What is the comparative safety of internet-delivered cognitive behavioural therapy versus in-person cognitive behavioural therapy for the management of chronic non-cancer pain?

Patients' Experiences

1. How do the experiences of people living with chronic non-cancer pain and their caregivers resonate (or not) with known experiences of iCBT for depression or anxiety and iCBT for posttraumatic stress disorder when CBT would otherwise be provided?
2. What do people living with chronic non-cancer pain and their caregivers expect to access and experience accessing (or not) with regard to iCBT for the management of chronic non-cancer pain when CBT would otherwise be provided?

Operational Aspects

1. Which iCBT programs for the management of chronic non-cancer pain are currently available or are in development in Canada and what are their characteristics?
2. What operational considerations contribute to the establishment and provision, or lack, of iCBT programs, specifically for the management of chronic non-cancer pain, at the system or site level in Canada and internationally?

Addressing the Decision Problems

Clinical Effectiveness and Safety

The clinical review will summarize available comparative evidence on the effectiveness and safety of iCBT against CBT to address Decision Problem #1. Furthermore, to help address the access element of Decision Problem #1, available contextual information (e.g., geographical, social, economic, cultural, political) regarding access to iCBT will be incorporated into the discussion. Comparative evidence on specific populations (e.g., with different underlying causes of chronic pain) and interventions (e.g., with different types or components of iCBT), if found (e.g., in subgroup analyses), could also inform Decision Problem #2. Any available data, or absence of data, regarding specific subgroups of interest (e.g., sex and/or gender, presence of comorbidities) will be considered when assessing the generalizability of the findings from the available evidence.

Patients' Experiences

To support deliberation around Decision Problem #1, we will explore what people living with chronic non-cancer pain and their caregivers expect, or hope, to be gaining access to (or not) when engaging with iCBT . We will do this by asking about and paying particular attention to the ways in which people describe things, such as:

- their understanding of what iCBT is meant to be working on and how this relates to their needs around living with chronic non-cancer pain
- their process of being referred, or introduced, to iCBT and how the potential benefits of iCBT for their lives were presented to them
- more directly, their thoughts around whether, for whom, and in what ways iCBT may improve access to CBT.

For Decision Problem #2, we will explore how people living with chronic non-cancer pain and their caregivers expect or experience iCBT to work (or not) in practice. We will do this by asking about, and paying particular attention to, the ways in which people describe things, such as:

- the types of relationships they were able to build (or not) with their care providers and how these affected their experiences of receiving care
- their particular iCBT program's modules and how the types of work involved in these modules affected their experiences of receiving care
- the material needs of engaging with iCBT (e.g., computer, cell phone, internet service, quiet space to work in) and how having access (or not) to these materials affected their experience of receiving care.

Operational Aspects

An Environmental Scan will address research questions related to the operational considerations of iCBT for chronic non-cancer pain. In relation to Decision Problem # 1, the operational considerations identified through the Environmental Scan could help inform decisions on whether iCBT should be offered. Further, the barriers and facilitators related to access to and implementation of iCBT that are identified through the Environmental Scan may be factors that should guide the implementation of iCBT and therefore could help inform Decision Problem # 2.

Methods

To inform the preparation of this protocol, a preliminary scoping review of the existing literature, including HTAs and SRs, was conducted. This protocol was written a priori in consideration of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) for guidance on clarity, transparency, and completeness, and it will be followed throughout the HTA process. The protocol for the clinical review has been prospectively registered in the international repository PROSPERO. Any deviations from the protocol and the timing of any deviations will be disclosed in the final report, and updates will be made to the PROSPERO submission (registration number: CRD42021283994) and the project protocol on the CADTH website, as appropriate.

Clinical Effectiveness and Safety

Study Design

The protocol for the clinical review was informed by detailed scoping activities that included a formal scoping review of existing literature and CADTH Rapid Review Reports regarding the clinical effectiveness of iCBT for the management of adults with chronic pain published in December 2020[43] and CBT for chronic non-cancer pain published in September 2019.[15] Details on the complete methodology for the Rapid Review Reports are available in the publications.[15,43]

A considerable body of evidence pertaining to the clinical effectiveness of iCBT for chronic pain was identified in the 2020 CADTH Rapid Review Report (Reference List).[43] Specifically, 9 SRs (6 with meta-analyses [MAs]), 28 randomized controlled trials (RCTs), and 5 non-randomized studies were identified.[43] Authors of 5[14,44-47] of the 9 identified SRs included only RCTs. However, the available evidence was characterized by a notable degree of heterogeneity arising from grouping together different forms of iCBT (e.g., traditional, acceptance-based, and exposure-based iCBT), different underlying pain conditions (e.g., mixed chronic pain, back pain, fibromyalgia, headache), and/or various comparator groups (e.g., wait list, usual care, internet-delivered education, in-person CBT). For example, although findings from 1 SR[44] suggested that iCBT was superior to controls (i.e., wait list, attention control, usual care) in improving mood and disability among patients with fibromyalgia, there were no comparisons between iCBT and in-person CBT. Authors of another SR[47] found beneficial effects in internet-delivered psychological therapies, including iCBT, for pediatric patients with chronic headache and mixed pain conditions (e.g., musculoskeletal pain, neuropathic pain) compared to controls; however, the authors did not categorize the included studies by treatment or control type (e.g., active, wait list).

Since there is a lack of up-to-date SRs assessing all the comparisons of interest for this review or matching the scope of the current research questions, it does not appear that an overview of SRs or an update of existing SRs would be an appropriate or feasible method to inform the research questions of this review. Therefore, a *de novo* SR of relevant primary studies comparing iCBT to in-person CBT would help provide Canadian decision-makers with an additional knowledge base regarding the role of iCBT in the management of chronic non-cancer pain. This approach allows for the assessment of the various population,

intervention, comparator, outcome — PICO — elements in a manner suitable in addressing the research questions.

Literature Search Methods

The literature search for clinical studies will be performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist.[48] The complete search strategy is presented in Appendix 1.

Published literature will be identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, APA PsycINFO (1806–) via Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid. All Ovid searches will be run simultaneously as a multi-file search. Duplicates will be removed using Ovid de-duplication for multi-file searches, followed by manual de-duplication in Endnote. The search strategy will comprise both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts will be iCBT and chronic pain. Clinical trials registries will be searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, and the EU Clinical Trials Register.

CADTH-developed search filters will be applied to limit retrieval to RCTs, controlled clinical trials or any other type of clinical trial, observational studies, HTAs, SRs, MAs, or network MAs. The search will also be limited to English- and French-language documents published after January 1, 2001. Conference abstracts will be excluded from the search results.

The initial search will be completed in the autumn of 2021. Regular alerts will update the database literature searches until the publication of the final report. The clinical trials registries search will be updated before the completion of the stakeholder feedback period.

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,[49] which includes the websites of regulatory agencies, HTA agencies, clinical guideline repositories, SR 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, as appropriate. The grey literature search will be updated before the completion of the stakeholder feedback period. See Appendix 1 for more information on the grey literature search strategy.

Selection and Eligibility Criteria

The study eligibility criteria for the clinical research questions can be found in Table 1.

Screening and Selecting Studies for Inclusion

- Inclusion criteria:
  - Studies meeting the eligibility criteria outlined in Table 1 will be included.
  - Chronic pain is commonly defined as pain that lasts or recurs for more than 3 months;[52] however, the explicit reporting of pain duration is not required for study inclusion. Studies that reference chronic pain and that are not related to cancer are eligible for inclusion.

Table 1: Selection Criteria for Clinical Research Questions

Criteria	Description
Population	Patients (any age) with chronic non-cancer pain[a]
Interventions	Guided and unguided[b] iCBT delivered via a computer or mobile device, either synchronously or asynchronously,[c] in combination with other interventions for the management of chronic non-cancer pain[a]
Comparators	In-person CBT, in combination with other interventions, for the management of chronic non-cancer pain[a]
Outcomes	**Question 1** • pain control (e.g., intensity, severity, frequency, duration, time to improvement) • changes in use of pharmacotherapy (e.g., cannabinoids, acetaminophen, non-steroidal anti-inflammatory drugs) • health-related quality of life or overall well-being (e.g., EuroQol 5-Dimensions score) • psychological or psychosocial function or symptoms (e.g., mood, depression, anxiety, pain-related self-efficacy, perceived injustice, pain experience [e.g., rumination, magnification, helplessness], resiliency) • sleep (e.g., quality, duration, sleep disorder) • physical function (e.g., mobility, ability to engage in activities of daily living, autonomy, disability) • patient acceptability or satisfaction with their care, as measured with any scale • patient participation (e.g., time to discontinuation) **Question 2** • Harms (e.g., proportion of patients who experienced pain and/or psychosocial symptom worsening, substance use, emergency room visits, hospitalizations, unplanned tapering/discontinuation of other therapies [e.g., pharmacotherapy, physical and rehabilitative therapies], any adverse event)
Study design	Randomized and non-randomized, comparative study designs, including: • RCTs (e.g., parallel group, crossover, cluster randomized trials) • non-randomized controlled clinical trials • cohort studies • case-control studies Exclusions • cross-sectional studies • single-arm before-and-after studies • single-arm interrupted time series studies • case reports • case series • review articles • editorials, letters, and commentaries • studies of any design published as conference abstracts, presentations, or thesis documents
Time frame	2001 to present[d]

CBT = cognitive behavioural therapy; iCBT = internet-delivered cognitive behavioural therapy; RCT = randomized controlled trial.

[a]Chronic non-cancer pain associated with health conditions such as (but not limited to) fibromyalgia, headache, migraine, rheumatoid arthritis, osteoarthritis, multiple sclerosis, surgical procedures, idiopathic chronic non-cancer pain, or injuries to muscle, nerve, or ligament.

[b]Guided iCBT programs involve support from a clinician or technician (e.g., via emails or phone calls), whereas unguided iCBT programs are delivered entirely by computer and driven by patients.[50]

[c]Asynchronous counselling refers to a delayed exchange of therapeutic communication between a licensed mental health care professional and the client.[51]

[d]As part of the detailed scoping process, a 2020 Rapid Review Report (Reference List) identified systematic reviews, which included primary studies dating back to the early 2000s. Therefore, studies published in or after the year 2001 are eligible.

- There are no restrictions placed on age, sex or gender, ethnicity, comorbidities, setting, cause of chronic non-cancer pain, or severity of symptoms.
- Participants may receive CBT or iCBT in conjunction with usual care (e.g., pharmacological and non-pharmacological options) as part of a multidisciplinary approach. Usual care may vary between the CBT and iCBT arms within each study. Explicit reporting and a description of the multidisciplinary approach is not required for study inclusion.
- Traditional iCBT/CBT or psychotherapies firmly grounded in CBT approaches or based on "third wave" CBTs[53-56] are eligible for inclusion (e.g., acceptance and commitment therapy,[57] compassionate mind training, dialectical behavioural therapy, behavioural activation, metacognitive therapy, exposure-based CBT, mindfulness-based cognitive therapy, mindfulness-based stress reduction, or mindfulness-based CBT).[58]
- For the outcomes, all instruments and all time points are eligible for inclusion.

- Exclusion criteria:
  - Studies not meeting the eligibility criteria outlined in Table 1, are duplicate publications, or were published before year 2001 will be excluded.
  - Participants using iCBT/CBT primarily for indications other than chronic non-cancer pain (e.g., primary diagnosis of major depressive disorder, anxiety disorder, posttraumatic stress disorder) will not be included.
  - Any psychological interventions not based on CBT will be excluded (e.g., interventions based on online psychoeducation or exposure alone, psychodynamic therapy, humanistic approaches [e.g., emotion-focused therapy, internal family systems-based interventions]).
  - Comparisons between interventions that differ in treatment protocols (e.g., dialectical behavioural therapy versus CBT) in addition to delivery method (i.e., in-person versus internet-delivered) will be excluded.

Chronic pain has been reported in children as young as 2.5 years old.[59] Furthermore, 1 Cochrane SR[47] and 1 SR with MAs[60] evaluating the use of iCBT for chronic pain included pediatric patients aged 0 to 18 years. Therefore, patients of any age will be included in this review.

All types of iCBT or CBT, including CBT delivered through the internet in real time by a therapist (e.g., videoconference), in all settings (e.g., guided or unguided, synchronous or asynchronous, individual or group) will be in scope. Since the multidisciplinary approach for managing chronic non-cancer pain that embeds iCBT may be different from one that embeds CBT, usual care provided in conjunction with CBT or iCBT may vary between the CBT and iCBT arms within each study.

This review will be limited to RCTs, randomized crossover trials, cluster randomized trials, and non-randomized comparative studies. Furthermore, comparative studies with real-world data will be included if they meet the PICO criteria. The inclusion of non-randomized comparative studies could help capture populations that may not have been included in RCTs and provide additional context (e.g., geographical, social, economic, cultural, political) pertaining to patient access to iCBT. During detailed scoping, the CADTH Rapid Review Report (Reference List) published in December 2020[43] identified 28 RCTs and 5 non-randomized studies regarding the clinical effectiveness of iCBT compared to various comparators (e.g., in-person CBT, usual care, wait list) for patients of any age with chronic pain, suggesting there is comparative evidence. As this current review is intended to inform decisions as to whether iCBT should

be offered as a management option, as part of a multidisciplinary approach in the delivery of care for chronic pain when CBT would otherwise be provided, it is suitable to exclude non-comparative studies.

The review will be limited to studies published in English and French. While there is evidence[61,62] that suggests that excluding non-English publications from evidence synthesis does not bias conclusions, publications in French will also be included, as CADTH has the capacity for reviewing in both languages. In the event that multiple publications are identified for the same study, they will all be included and cited; however, only unique data will be extracted without duplication and the publications will be discussed as a single study.

Study Selection

The SR management software DistillerSR (from Evidence Partners in Ottawa, Canada) will be used for study selection. Two reviewers will independently screen titles and abstracts of all retrieved citations for relevance to the clinical research questions. Full texts of articles that are judged to be potentially relevant by at least 1 reviewer will be retrieved and independently assessed for possible inclusion based on the pre-determined selection criteria outlined in Table 1 (i.e., if 1 reviewer believes the citation should be screened at the full-text level, it will move forward to the next level of screening; no conflict resolution will be performed). Two reviewers will then independently examine all full-text articles and consensus will be required for inclusion in the review. Discrepancies between reviewers will be discussed until consensus is reached, involving a third reviewer for adjudication, if required. The study selection process will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart. A list of studies selected for inclusion in the clinical review will be posted to the CADTH website for stakeholder review for 10 business days and feedback and any additional studies identified for potential inclusion will be reviewed following the aforementioned process. Studies meeting the selection criteria for the review that are identified through alerts before the completion of the stakeholder feedback of the draft report will be incorporated into the analysis. Relevant publications identified after the stakeholder feedback period will be described in the discussion, with a focus on comparing their results with those obtained from the synthesis of earlier reports included in the review.

Data Extraction

Data extraction will be performed by 1 reviewer and independently checked for accuracy and completeness by a second reviewer. Disagreements will be resolved through discussion until consensus is reached or through adjudication by a third reviewer, if required. Data will be extracted directly into tables created in Microsoft Word, which will be developed, piloted, and modified, as necessary. Relevant information to be extracted will include study characteristics, methodology (e.g., study design), population, intervention, comparator, results, and conclusions regarding the outcomes and the subgroups of interest that follow.

Subgroups of Interest:

- underlying causes of chronic non-cancer pain (as defined by the International Association for the Study of Pain classification of chronic pain system)
- severity of chronic non-cancer pain
- population age (e.g., children, adolescents, adults, older adults)
- sex and/or gender

- race and/or ethnicity
- type of iCBT (e.g., self-guided or therapist-assisted, synchronous or asynchronous, face-to-face traditional CBT via videoconference versus online modules and without face-to-face contact, individual or group)
- components of iCBT (e.g., number of sessions, type of modules)
- length of follow-up after completion of iCBT
- presence and type of concurrent interventions
- presence of comorbidities (e.g., depression, anxiety)
- place of residence.

Attempts will be made to contact corresponding authors to obtain missing relevant data, if those data are needed for data synthesis or an MA, or to clarify conflicting relevant data in the included studies. Relevant data will be deemed missing if numerical data supporting qualitative statements or findings presented in figures are absent. If the authors do not provide the requested numerical data related to findings presented in a figure, the best numerical estimates based on the figure will be used in the MA. Furthermore, if data are not reported for an outcome, no assumptions will be made about its presence or absence. Relevant data will be deemed conflicting if there are discrepancies within the study (e.g., between the abstract and the main text of a publication) or between different publications of the same study. If the authors do not provide clarifications for the conflicting information, all data will be reported and the most conservative data available will be incorporated into a data synthesis or an MA, if performed.

Critical Appraisal

Risk of bias assessment of relevant RCTs identified in the literature search will be evaluated by 2 independent reviewers using the revised Cochrane risk-of-bias tool for randomized trials, the RoB 2.[63] The RoB 2 assessment tool is structured into 5 domains to evaluate biases arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Signalling questions in each domain help the user make domain-level judgments about the risk of bias by answering "Yes," "Probably Yes," "Probably No," "No," and "No Information." A judgment of low risk of bias, high risk of bias, or some concerns will be assigned for each domain. The overall risk of bias of each trial will be rated and designated as low risk of bias, some concerns, or high risk of bias based on the domain-level determinations. A rationale will be provided for decisions about the risk of bias for both the domain-level and overall assessments.

The risk of bias in non-randomized studies will be assessed using the Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS).[64] RoBANS contains 8 domains evaluating the risk of biases in a study based on the possibility of the target group comparisons, target group selection, confounders, exposure measurement, blinding of assessors, outcomes assessment, incomplete outcomes data, and selective outcomes reporting. The tool was selected for its reliability, validity, and user-friendly design.[64] A judgment of low risk of bias, high risk of bias, or unclear risk of bias will be assigned for each domain using the criteria provided in the instrument.[64] The overall risk of bias for each study will be classified as low, some, or high, based on the domain-level judgments about the risk of bias, following the RoB 2 guidance,[65] as RoBANS did not provide a specific approach for

making study-level judgments. A rationale will be provided for decisions about the risk of bias for both the domain-level and overall assessments.

For sources of bias that may differ across outcomes within a single primary study (e.g., blinding, bias related to missing outcomes data or the method of outcomes measurement in RCTs, outcomes assessment and incomplete outcomes data in non-randomized studies), the risk of bias will be assessed for individual outcomes within the individual studies.

Any disagreements in the risk of bias for the domain-level and overall assessments will be resolved through discussion, with involvement of a third reviewer if consensus cannot be reached. In evaluating the risk of bias in the included studies, the critical appraisal tools will be considered as guides and additional insight beyond the instruments' signalling items will be applied when necessary. The results of the risk-of-bias assessment will be reported by describing each study's strengths and limitations narratively. Studies will not be excluded from the review based on the results of the critical appraisal. However, the critical appraisal results and how they affect study findings will be used to assess certainty in the evidence from the individual studies and/or across the body of evidence.

Data Analysis and Synthesis

Narrative Synthesis

A narrative synthesis of the results reported in the primary studies will be performed. This will include the presentation of study characteristics and findings by outcome within summary tables, together with descriptions in the main text for details and clarity. The study and patient characteristics will be considered in the analysis of the effectiveness and safety measures across the studies to determine the likelihood of clinical benefits (i.e., clinical effectiveness) or harms (i.e., safety, including worsening of chronic pain). Data from different populations or different time points will not be combined but rather described separately and compared, if appropriate.

Existing guidance on the conduct of narrative synthesis will be consulted, as appropriate.[66] The within- and between-study relationships will be evaluated and the findings about the direction and magnitude of any observed effects, trends, and deviations will be summarized and discussed by research question and by outcome. Outcomes will be reported in the measurement units used by the study authors and results will be interpreted with due consideration for the differences in the instruments of assessment across the studies. Where possible, study results for different types of iCBT (e.g., face-to-face traditional CBT via videoconference versus online modules without face-to-face contact) will be reported separately. The term "iCBT" will refer to both guided and unguided iCBT unless otherwise specified. Data on specific subgroups of interest reported in studies will be narratively described and compared, if appropriate.

A narrative summary of the results of the methodological assessments for each included study will be provided. Specifically, tables will be developed to present the answers to the questions within the critical appraisal tools and a narrative description of the strengths and limitations of the included studies and body of evidence will be provided within the main text of the report to give the reader an overview of the methodological quality of the literature. Although studies will not be excluded from this review based on the critical appraisal results, the discussions and conclusions of the final report will emphasize the findings from higher-quality studies.

Quantitative Synthesis

In addition to the narrative synthesis, the results of the included studies will be pooled in MAs if data are sufficiently homogeneous in their clinical, methodological, and statistical characteristics. Clinical, methodological, and statistical heterogeneity and whether studies are sufficiently homogeneous for pooling will be assessed in consultation with clinical and methods experts.

MAs will be considered for each outcome of interest for each research question on clinical effectiveness and safety. If the included studies are deemed too heterogeneous to combine (e.g., with respect to participant characteristics, types or timing of outcome measurements, and intervention characteristics), a quantitative pooling of results from individual studies will be deemed inappropriate. In that case, the affected studies will be summarized narratively only, and the rationale for not pooling will be provided. If deemed appropriate, MAs will be conducted for each outcome of interest (e.g., level of pain control, health-related quality of life, the risk for adverse events and complications) reported across multiple studies showing sufficient homogeneity. If data from certain studies cannot fit into the MA (e.g., the right data are not reported), they will be presented alongside the MA and compared. Results from randomized and non-randomized studies will not be pooled in the analysis. Instead, separate MAs will be conducted for these 2 types of study designs. It is expected that random effects models will be used, based on expected clinical and methodological heterogeneity across studies, although a fixed-effects model could be considered if the studies being pooled are highly homogeneous.

As aggregate data will be used, the unit of analysis will be the primary study. Dichotomous data will be analyzed as risk ratios or odds ratios, with 95% confidence intervals (CIs) to allow for comparisons across studies. Continuous data will be analyzed using either mean differences or standardized mean differences, with 95% CIs. Mean differences will be used when pooling studies that used the same outcomes measure. Standardized mean differences will be applied when pooling studies with different measures of assessment of the same outcome. If both unadjusted and adjusted effects are reported, the unadjusted effects will be used in MAs of RCTs and adjusted effects in MAs of non-randomized studies. If multiple adjusted estimates of effects are reported, the one that is judged to minimize the risk of bias due to confounding will be used in MAs.

Statistical heterogeneity will be assessed using graphical presentations (e.g., forest plots) and calculations of the Chi^2 statistic and the I^2 statistic, which quantifies the variability in effect estimates because of heterogeneity rather than chance (i.e., sampling error).[67] Statistical heterogeneity will be interpreted with guidance from Higgins and colleagues,[68] who define low, moderate, and high I^2 values as 25%, 50%, and 75%, respectively. Heterogeneity will be interpreted with P values.

If sufficient evidence is available for any outcome of interest (i.e., data from at least 10 studies), meta-regression analyses will be considered to investigate the association between studies' effect estimates and potential effect modifiers, such as patient characteristics (e.g., age), intervention characteristics (e.g., length of iCBT treatment), and study characteristics (e.g., length of follow-up). If there are 10 or more included studies of a given study design and a particular outcome, publication bias will be assessed visually using funnel plots and objectively using Egger's regression test and Begg's rank correlation test.[69,70]

MAs will be carried out using the Cochrane Review Manager, or RevMan, software (version 5.3, or the most up-to-date version available at the time of the analysis).

Certainty of the Evidence

The overall certainty of the evidence for each outcome-comparison will be assessed by 2 independent reviewers using the methods of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[71,72] Discrepancies between reviewers will be discussed until consensus is reached, involving a third reviewer for adjudication, if required.

In the GRADE approach, RCTs start as high certainty evidence and non-randomized studies as low certainty evidence, but certainty in treatment effect estimates can be rated up or down depending on several factors related to internal validity and to external validity.[72,73] The certainty of the evidence may be rated down for concerns related to risk of bias, inconsistency across studies, indirectness, imprecision of evidence, and publication bias. Rarely, and if no other serious concerns are identified, the certainty of the evidence may be rated up (i.e., large effect size, dose-response gradient, and plausible confounding effect).[72,73] GRADE assessments for the findings from RCTs and from non-randomized studies will be conducted separately and any differences in the assessments for these 2 types of study designs will be described. Ultimately, the GRADE approach results in an assessment of the certainty of a body of evidence in 1 of 4 grades:[74]

- 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.

If MAs are not conducted for any particular outcome, the certainty of evidence will be assessed using published guidance on the use of GRADE in the absence of a single estimate of effect.[75] The results of GRADE assessments will be reported in summary of findings tables, which will include footnotes to justify all decisions to rate up or rate down the certainty of the evidence for any given outcome-comparison. When providing summaries of the evidence in the text, we will use the word "may" for low certainty evidence, "probably" or "likely" for moderate certainty evidence, and simply describe very low certainty evidence as "very uncertain."[76]

Reporting of Findings

The SR will be prepared in consideration of relevant reporting guidelines (e.g., PRISMA statement,[77] PRISMA harms,[78] Meta-analysis of Observational Studies in Epidemiology [or MOOSE] reporting checklist,[79] Synthesis Without Meta-analysis [or SWiM] guideline)[80] and will meet the criteria outlined in A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) checklist.[81]

Patient Engagement

CADTH involves patients, families, and patient groups to improve the quality and relevance of its assessments, ensuring that those affected by the assessments have an opportunity to contribute to them. CADTH has developed a CADTH Framework for Patient Engagement in Health Technology Assessment.[82] The *Framework* includes standards for patient involvement in individual HTAs and is used to support and guide CADTH activities involving patients. For this HTA on chronic pain and iCBT, the belief that patients have knowledge, perspectives, and experiences that are unique and contribute to essential evidence for HTA will guide the patient engagement activities.

Objectives

The purpose of patient engagement for this project is twofold. First, the people CADTH engages with will serve as collaborators with the project team by providing critical insight into things such as outcomes of interest and the material and procedural realities of iCBT programming. Second, the people CADTH engages with will also support the validation (or not) of people's experiences with iCBT from 2 previous CADTH reports centred on iCBT for depression or anxiety,[83] and iCBT for posttraumatic stress disorder (PTSD),[84] through an interview study.

Engagement Plan and Approach

There will be 3 overarching stages of our engagement activities: before protocol finalization, during the drafting of the initial reviews, and upon completion of the final report.

During protocol development and finalization, perspectives gained through engagement processes have been used for things like ensuring the relevance of outcomes of interest for the clinical review. At this stage, patient engagement has enabled the research team to prepare themselves to consider the evidence found in the literature alongside an understanding of the wider experiences of patients and caregivers.

During the research and drafting of initial review stages, we will be facilitating the involvement of people we have already engaged during protocol development and at least 3 new participants to comment on the relevance of key findings identified through previous CADTH reviews on the use of iCBT in depression and anxiety[83] and PTSD.[84] Further details on the interview study process are noted in the subsequent section.

Upon completion of the final report, the same participants who have been engaged at the 2 prior stages will be invited to provide feedback on the clarity of writing and comment on the relevance of the findings to Canadian patients and families. At this point, they will also be asked if they feel their contributions to the project are reflected in the final report.

CADTH will share the key results of the full assessment and describe how engagement activities were used.

Invitation to Participate and Consent

Two people with lived experience of chronic pain treatment have been involved as patient contributors during protocol development and finalization and will be involved through the remainder the project.

CADTH will engage at least 5 people (including the 2 patient contributors already engaged during protocol development) living with chronic pain who have experience with (or have been offered) either CBT or iCBT as part of their pain management strategy in the interview study. The people with lived experience are not meant to be representative of all people with chronic pain; rather, we are interested in working with people from a diversity of lived experiences in an effort to be attentive to as much breadth as possible. Given the emphasis on gendered, racialized, sociocultural, and socioeconomic dynamics of both the presence of chronic pain and care for people living with chronic pain in the literature,[37] we plan to engage people living (or caring for someone) with chronic pain (of any age) who are reflective of the diversity of these dynamics.

People will be identified through CADTH's connections to patient groups and to people who contributed to previous projects related to chronic pain. A CADTH Patient Engagement Officer will contact potential participants by email and phone to explore their interest in becoming involved. The preliminary request will include the purpose and scope of this HTA, the purpose of engagement, and the nature of engagement activities. We will seek to minimize risks by ensuring the complete confidentiality of their engagement and by providing them with assurances that they may withdraw at any time from this project. The Patient Engagement Officer will obtain the person's informed consent to share their information and comments with CADTH staff.

Reporting

The reporting of this section will follow the GRIPP2 Short Form[85] reporting checklist and include the outcomes, discussion, and reflection items as suggested by that guidance. This is to outline, in a final report, the process of engagement and where and how participants' contributions were used in the assessment. The Patient Engagement Officer will keep track of patient engagement activities and interactions in detailed notes and communications.

Finally, CADTH will provide reflections and critical perspectives on the experience of the involvement for the patient, other members of the chronic pain community, and the research team in the final report. A link to the final assessment will be shared.

Patient Experiences

We will conduct an interview study that is guided by the following research questions:

1. How do the experiences of people living with chronic non-cancer pain and their caregivers resonate (or not) with known experiences of iCBT for depression or anxiety, and iCBT for PTSD when CBT would otherwise be provided?
2. What do people living with chronic non-cancer pain and their caregivers expect to access and experience accessing (or not) with regard to iCBT for the management of chronic non-cancer pain when CBT would otherwise be provided?

Study Design

Based on a high-level scoping review of 5 primary qualitative or mixed-methods studies' abstracts, we expect the literature exploring the perspectives and experiences of people

engaging with iCBT for the management of chronic non-cancer pain to be largely reflective of the findings from the 2 previous CADTH Optimal Use projects on iCBT for major depressive disorder and anxiety,[83] and PTSD.[84]

To examine the potential nuances of these expected findings for the management of chronic pain, this interview study will interview and probe participants' responses for further detail, clarity, or insight. These interviews 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, or inform the processes underlying iCBT for chronic pain.

With the support of CADTH's patient engagement team, we have identified 2 patient contributors who have assisted in drafting the protocol and will be providing support as we identify patients interested in providing input and develop and test the interview guide. These patient contributors will also be providing feedback on the analysis and final draft. These 2 patient contributors will help guide our work conceptually and methodologically, and ensure that we capture constructs that are relevant to patients and to the context-dependent interactions that shape patients' experiences.

Participants

We will invite at least 5 adults (including the 2 patient contributors we have already engaged during protocol development) living with chronic non-cancer pain or involved in the care of a person living with chronic non-cancer pain who have experience with (or have been offered) either CBT or iCBT as part of the pain management strategy in Canada. While we are also interested in the experiences of pediatric populations, we will not be interviewing anyone younger than the age of 18 for this study. Instead, we will rely on the experiences and perspectives of parents or legal guardians, given the ethical challenges of interviewing pediatric populations. How many interviews we conduct will ultimately be determined by project timelines. The people with lived experience are not meant to be representative of all people with chronic pain. Rather, we are interested in working with people from a diversity of lived experiences in an effort to be attentive to the breadth of chronic pain, as much as is possible.

To attend to this diversity of perspectives and experiences, we will seek to invite people using the following rationale:

- Given the emphasis on gendered, racialized, sociocultural and socioeconomic dynamics of both the presence of chronic pain and care for people living with chronic pain in the literature,[37] we plan to engage people living (or caring for someone) with chronic pain (of any age) who are reflective of the diversity of these dynamics.
- In light of iCBT's potential to offer treatment for the management of chronic non-cancer pain from anywhere, we will also hope to engage with people who live in geographically and demographically diverse areas (i.e., urban and rural and remote areas).
- We will also iteratively look for people with chronic pain characteristics as identified by the Clinical Effectiveness and Safety review of this Optimal Use project.

Interviews

People living with chronic pain or their caregivers will be invited to share their experiences and perspectives on their condition and treatment, and provide insights on the relevance of key findings identified through previous CADTH reviews on the use of iCBT in depression and

anxiety,[83] and PTSD.[84] Given the small number of interviewees, we will strive for a richness and diversity of perspectives. We will use semi-structured interviews to ask questions guided by the research questions and by the thematic categories identified in CADTH's previous 2 iCBT reviews.[83,84]

Interviews will be conducted by CADTH staff with expertise in qualitative research, over the phone or through videoconference call. These interviews will be recorded and notes with the consent of the people involved in the consultation. Audio files, transcripts, and summaries of these conversations will be available to project team members.

Invitation to Participate and Consent

As described within the Patient Engagement section of this protocol, a Patient Engagement Officer will identify people through CADTH's connections to patient groups and to people who contributed to previous projects related to chronic pain.

The Patient Engagement Officer will obtain participants' informed consent to both share their information and comments with CADTH staff and use these interviews as part of the analysis for this interview study, which will be publicly available. At the beginning of each interview, we will inform participants that they may be sharing personal and sensitive information, and that they can raise concerns at any time. If participants would like to withdraw at any point or for any reason, and would like to withdraw information, we will work with them to remove the material or information they have shared, including places in our report reflective of their input. However, it may not be possible to remove individual contributions from the final synthesized findings. In this circumstance, we will discuss with them whether some of the information could be used; for example, by ensuring the complete anonymity of all the information and ensuring that we do not report the individual's identifiable concepts and ideas, and illustrative quotes, from their interviews.

Approach

A modified framework analysis approach[86] will be used to describe and summarize people living with chronic pain inputs on iCBT and reflect on how they resonate and clarify findings identified in 2 earlier iCBT reviews.[83,84]

This study will use an iterative deductive and inductive approach to identify common and different expectations, views, and experiences on iCBT across people living with chronic non-cancer pain, while drawing descriptive conclusions clustered around major themes.

A foundational framework will be developed during the initial deductive analysis informed by the research questions and thematic categories identified within the Patients' Perspectives and Experiences sections of CADTH's Optimal Use projects on iCBT for major depressive disorder and anxiety,[83] and on iCBT for PTSD.[84] These thematic categories include experiences related to iCBT therapist guidance and the opportunity to develop a relationship with their therapist, iCBT as not a one-size-fits-all solution and the opportunity to tailor the intervention to specific care needs, contextual constraints, belief systems and learning styles, and ambivalence about issues around technological literacy, utility of homework, and ability to remain motivated. Additionally, given the focus of this analysis on iCBT when CBT would otherwise be offered, any aspect that may not be specifically related to iCBT will be carefully considered and its relationship to iCBT for the management of chronic non-cancer pain will be explored.

The qualitative researcher will first read and familiarize himself with 2 interview transcripts and contextual and reflective interview notes, taking note of analytical thoughts and impressions defined by the thematic categories identified in the earlier CADTH reviews on iCBT for major depressive disorder and anxiety,[83] and on iCBT for PTSD.[84] A second researcher will concurrently read the 2 transcripts and independently list key ideas informed by the same predefined categories. Both researchers will then meet to critically reflect and discuss the emergent ideas, and define the foundational framework to apply to subsequent transcripts.

The qualitative researcher will then read and apply the foundational framework to all the transcripts, continuing to take notes and beginning to summarize the identified characteristics of and differences within and across ideas and thematic categories, interrogating predefined concepts and drawing out connections to explore their relationships. If new concepts and thematic categories that may highlight differences in experiences in relation to chronic pain emerge, the initial foundational framework will be adapted to accommodate these new emergent ideas through written analytical memos and team discussions. Of note, interviews and analysis will occur concurrently. If new insights emerge, the analysis might also inform the subsequent interview guide to attend to these new developing areas of interest.

Gradually, the qualitative researcher will revise and refine the framework and concepts through critical reflection, memoing, and regular discussions with the study team. Memoing and the team-based approach will ensure that the primary researcher will engage with the material in a reflexive mode of inquiry. Finally, the qualitative researcher will share with the patient contributors and other consulted patients the final synthesized summary to ensure that CADTH accurately represents people living with chronic non-cancer pain experiences and their views.

Summarizing and Presenting Findings

We will report the key findings from previous iCBT reviews[83,84] and summarize how people we consulted reflected on the relevance of these findings to their own lives with chronic pain in a publicly available report. We will present findings of "practical import;"[87] that is, we will aim to show where, how, and why these findings help respond to the decision problem and inform the deliberative discussions on iCBT for the management of chronic non-cancer pain.

If interview participants have raised relevant considerations not identified in the 2 previous iCBT reviews, we will also summarize and highlight these. In the final report, quotes from participants will be used for illustrative purposes.

Operational Aspects

To help inform the decision problems, the following questions related to identifying operational aspects of iCBT implementation and delivery will be addressed.

Research Questions:

1. Which iCBT programs for the management of chronic non-cancer pain are currently available or are in development in Canada and what are their characteristics?

2. What operational considerations contribute to the establishment and provision, or lack, of iCBT programs, specifically for the management of chronic non-cancer pain, at the system or site level in Canada?

Study Design

An Environmental Scan will be conducted to identify established iCBT programs in Canada, their characteristics, and related operational aspects associated with iCBT programs for the management of chronic non-cancer pain. The findings of this Environmental Scan will be based on a limited literature search and online survey.

Literature Search

Literature Search Methods

A literature search of key bibliographic databases and grey literature (based on the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist)[49] will be conducted by an information specialist, based on a peer-reviewed search strategy developed with input from the relevant project team. The primary purpose of the literature search will be to identify existing iCBT programs for the management of chronic non-cancer pain that are currently available or in development in Canada and their characteristics. The literature search will also seek to gather information on operational aspects related to the provision of iCBT programs, specifically in the management of chronic non-cancer pain.

Selection Criteria

Publications will be included that describe iCBT programs and/or provide insights on the operational aspects associated with iCBT programs for the management of chronic non-cancer pain from the perspectives of Canadian patients, health professionals, and decision-makers. Identified publications will be screened for selection, and those that meet the inclusion criteria (Table 2) will be synthesized and summarized within the report.

Table 2: Inclusion Criteria for Information Screening

Criteria	Description
Population	Patients (any age) with chronic non-cancer pain, regulated health professionals, and decision-makers
Intervention	Guided and unguided iCBT delivered via a computer or mobile device, either synchronously or asynchronously, in combination with other interventions for the management of chronic non-cancer pain
Settings	Settings of care (e.g., primary, home, tertiary, community, long-term care) in rural, remote, and urban areas in Canada
Outcomes	• Descriptions of iCBT programs including but not limited to type of pain treated, how patients are referred, age of participants, number of modules and information covered, length of modules, and whether the program is self-guided or therapist-assisted • Operational aspects of iCBT programs, including but not limited to, technical requirements, resource needs, logistical considerations, and operational constraints; staffing, training, and accreditation issues (e.g., clinical specialties); referral pathways and multidisciplinary patient management schemes; design of public funding programs and models, including eligibility and prioritization criteria

iCBT = internet-delivered cognitive behavioural therapy.

Programs of interest for this Environmental Scan will be those that include a guided or unguided iCBT intervention, delivered either synchronously or asynchronously, and embedded within a multidisciplinary approach. Programs that include patients with concurrent pharmacotherapy use will be included.

For Research Question 1, programs that include patients using iCBT primarily for indications other than chronic non-cancer pain (e.g., primary diagnosis of major depressive disorder, anxiety disorder, PTSD) and programs outside of Canada will be excluded. For Research Question 2, publications that identify operational aspects of iCBT programs in Canada will be eligible for inclusion. Publications that describe experimental studies (e.g., RCTs) and those that do not provide a summary or describe Canadian iCBT programs for the management of pain will be excluded.

Screening and Selecting Publications for Inclusion

Publications will be screened and selected for inclusion based on the described eligibility criteria by 1 reviewer. First, titles and abstracts will be reviewed to identify potential papers; then, the full text of all potentially relevant reports will be retrieved for definitive determination of eligibility.

Data Extraction

Data extraction will be performed by 1 reviewer. The data will be extracted to a Microsoft Word or Excel spreadsheet and will include bibliographic details (i.e., authors, year of publication, and country of origin) of included papers, descriptions of iCBT programs (e.g., program name, complement of staff, information technology requirements; referral pathways; eligibility criteria), reported implementation challenges and enablers, and other key findings related to implementation and operational aspects.

Survey Methods

A survey will be conducted to address the research questions of the Environmental Scan. A questionnaire will be distributed by email and administered electronically using Survey Monkey to key jurisdictional informants and stakeholders involved in research, planning, management, and service provision related to iCBT programs for the management of chronic non-cancer pain in Canada. Attempts will be made to capture information relevant to each province or territory, as well as rural, remote, and urban settings. Ideally, multiple respondents from each jurisdiction and geographical setting representing different perspectives will be engaged. Survey respondents will be asked to consent to the aggregate reporting of the information they provide electronically. Respondents will be identified through CADTH's Implementation Support and Knowledge Mobilization team networks and other available networks via stakeholder and expert suggestions. Respondents may also be identified through the literature search.

Identified potential participants will receive email invitations to participate and the survey will be promoted through other platforms (e.g., social media, newsletters). Participants will have 10 business days to respond to the survey.

The survey will target a variety of stakeholders involved in internet-delivered therapy, specifically for the management of chronic non-cancer pain including:

- regulated health professionals (e.g., physicians, nurses, psychotherapists, psychologists, occupational therapists, social workers, other mental health professionals, program managers) in primary, home, tertiary, community, or long-term care, in rural, remote, or urban areas
- policy-makers
- decision-makers involved in program or practice development
- information management professionals
- employee assistance program providers
- online CBT platform developers
- staff at community organizations that support people living with chronic non-cancer pain.

Patients' perspectives on iCBT for the management of chronic non-cancer pain will be captured in the Patient Engagement and Interview Study sections of this report.

For Research Question 1, the survey questions will seek to identify existing or developing iCBT programs for chronic non-cancer pain and their characteristics. For Research Question 2, survey questions will explore aspects related to the organization and delivery of iCBT programs for chronic non-cancer pain, including referral pathways, eligibility criteria, therapist credentials and training, information technology requirements, funding and reimbursement models, access considerations, and utilization patterns.

Data Analysis

The analysis of data collected from each of the data sources (i.e., literature review, survey) will be performed by 1 reviewer. A descriptive analysis will be conducted to respond directly to the research questions and produce a narrative summary that reflects responses received. A description of the literature search results, including the number of relevant publications and their sources, will be provided. Literature search findings will be used to supplement survey data. For the survey data, first, respondents will be described according to information provided using descriptive statistics (e.g., number and proportion of respondents who are associated with programs in remote, rural, and urban areas, etc.). Next, and to respond to the first research question, a list of iCBT programs that support people living with chronic non-cancer pain will be developed, and their characteristics will be summarized using descriptive statistics for closed-ended questions and narrative summaries for open-ended questions. To respond to the second research question, a list and description of factors that have the potential to enable or create challenges to successful implementation will be developed, as well as a summary of potential strategies that could be used to implement or increase the uptake of iCBT programs, if the decision is made to do so. Additionally, a summary of how each factor influences implementation will be provided and, where possible, strategies will be identified that could be used to ensure these factors are taken into consideration or mitigated. As with the first research question, descriptive statistics and narrative summaries will be used, as appropriate, depending on the data available.

Throughout data analysis, the focus will remain on those issues most relevant at the health services delivery level, with the aim of providing information to decision-makers regarding relevant to operational aspects related to the provision and use of iCBT programs for the management of chronic non-cancer pain.

Opportunities for Stakeholder Feedback

All stakeholders will be given the opportunity to provide feedback on the draft report, the draft included studies list, and the recommendations, if applicable. Unpublished data identified as part of the feedback process may only be included if the source of the data is in the public domain.

Protocol Amendments

If amendments are required at any time during the study, reasons for changes will be recorded in a study file and subsequently reported within the final study report. If necessary, a rescreening of the previous literature search or an updated literature search will be performed to capture additional data, according to the amendments. Any deviations from the protocol and the timing of any deviations will be disclosed in the final report, and updates will be made to the PROSPERO submission (registration number: CRD42021283994) and the project protocol on the CADTH website, as appropriate.

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Appendix 1: Literature Search Strategy

Clinical Literature Search

Overview

Interface: Ovid

Databases

- MEDLINE All (1946 to present)
- Embase (1974 to present)
- Cochrane Central Register of Controlled Trials (CCTR)
- APA PsycINFO (1806 to present)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: Autumn 2021

Alerts: Monthly search updates until project completion

Search filters applied: Systematic reviews; meta-analyses; network meta-analyses; health technology assessments; randomized controlled trials; controlled clinical trials; and observational studies

Limits

- Publication date limit: 2001 to present
- Humans
- Language limit: English- and French-language
- Conference abstracts: excluded

Table 3: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical 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
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase); keyword (CCTR)
.dq	Candidate term word (Embase)

Syntax	Description
.id	Key concept (PsycINFO)
.yr	Publication year
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; APA PsycINFO, 1806 to present, updated weekly

Multi-Database Strategy

1. exp Cognitive Behavioral Therapy/ or Psychotherapy/ or Desensitization, Psychologic/ or Implosive Therapy/ or Dialectical Behavior Therapy/
2. (((cognitive or behavio* or facilitate* or guided or saturat* or unguided or dialectical* or acceptance* or commitment* or metacognitive or meta cognitive or exposure*) adj2 (therap* or psychotherap* or psycho-therap*)) or cognitive behavio* or cognition therap* or CBT* or mindfullness* or behavioural activation* or behavioral activation*).ti,ab,kf,kw.
3. (self-manag* or selfmanag* or self-help* or selfhelp*).ti,ab,kf,kw.
4. ((psycholog* adj3 desensiti*) or imaginal flooding* or (imager* adj3 exposure*)).ti,ab,kf,kw.
5. ((exposure or flooding* or implosive or saturation) adj3 therap*).ti,ab,kf,kw.
6. or/1-5
7. Internet/ or internet-based intervention/ or exp Computers/ or Therapy, Computer-Assisted/ or Computer-Assisted Instruction/ or Distance Counseling/ or exp Cell Phone/ or Mobile Applications/ or telemedicine/ or remote consultation/ or exp Videoconferencing/ or Medical Informatics Applications/
8. (internet* or digital* 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 phone* or online* or telephone* or tele phone* or cell phone* or cellphone* or smartphone* or smart phone* or smart watch* or smartwatch* 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 m health* or mhealth* or virtual or virtualist? or webbased or web based or web deliver* or webdeliver*).ti,ab,kf,kw.
9. or/7-8
10. (iCBT* or cCBT* or eCBT* or dCBT*).ti,ab,kf,kw.
11. ((internet* or computer* or cyber* or digital* or digital* or web*) adj6 (CBT* or CPT*)).ti,ab,kf,kw.
12. ((internet* or computer* or cyber* or digital* or digital* or web* or technolog*) adj6 (cognitive behavior* or cognitive behaviour* or cognitive process*) adj6 (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.
13. (MoodGym* or Mood Gym* or Big White Wall* or Togetherall* or Together All* or "Beating the Blues*" or Fear Fighter* or FearFighter* or E compass* or Ecompass* or mycompass* or my compass* or Deprexis* or Moodkit* or Mood kit* or "Living Life to the Full*" or Woebot* or AbilitiCBT* or ALAViDA* or TruReach* or Tru Reach* or Beacon* or MindBeacon* or Mind Beacon* or i-Volve* or iVolve* or Interapy* or CBT-I Coach* or CBTi Coach* or CPT Coach* or Life Armor* or "T2 Mood Tracker*" or SilverCloud* or Silver Cloud* or "What's Up*" or MindShift* or Mind Shift* or MoodMission* or Mood Mission* or Depression CBT* or Brave Online* or "Camp Code A Lot*" or BounceBack* or Bounce Back* or Pacifica* or iCANCOPE* or "i can cope*" or WebMap* or

ManageMyPain or "Manage My Pain*" or ABC-Schema* or ABCSchema* or Aventurine Mood Improver* or "Catch It*" or CBT Diary* or CBT Journal* or CBT Thought Record* or Cgoni or Cognitive Diary or Cognitive Styles* or End Anxiety Hypnosis or Good Blocks* or Happify* or Happy Habits* or Jitters CBT* or Joyable* or Lantern* or Merrier* or Mindbliss* or Moodpath* or MoodTools* or See Betty* or TF-CBT* OT TFCBT* or Wysa* or Youper*).ti,ab,kf,kw.

14. or/10-13
15. Chronic Pain/ or exp Neuralgia/ or Nociceptive Pain/ or Pain, Intractable/ or Pain, Referred/ or exp Myofascial Pain Syndromes/ or exp Pain, Postoperative/ or Fibromyalgia/ or exp Arthritis/ or exp Inflammatory Bowel Diseases/ or Endometriosis/
16. exp Chronic Disease/ and (Back Pain/ or Musculoskeletal Pain/ or exp Headache Disorders/ or exp Headache/ or exp Cumulative Trauma Disorders/)
17. ((pain or pains or paining or painful or ache or aches or aching) adj5 (chronic* or subacute* or sub-acute* or recurr* or re-curr* or unresolv* or persist* or intractable or refract* or severe* or debilitat* or nociceptive* or neuropathic* or superficial* or visceral or burning or crushing or migratory or radiat* or splitting or somatic* or constant* or continu* or widespread or non malignant* or nonmalignan* or non-cancer* or noncancer* or myofascial* or prolong* or sustain*)).ti,ab,kf,kw.
18. ((chronic* or recurr* or re-curr* or unresolv* or persist*) adj5 (headache* or head ache* or back* or carpal tunnel* or cubital tunnel* or cephalalgia* or hemicrania* or cephalodynia* or cephalgia*)).ti,ab,kf,kw.
19. ((pain or pains or paining or painful or ache or aches or aching) adj5 (migraine* or arthriti* or osteoarthriti* or polyarthriti* or endometrioma* or endometrioses or endometriosis or colitis* or crohn* or fibromyalgia* or post operat* or postoperat* or post surg* or postsurg* or phantom*)).ti,ab,kf,kw.
20. ((repetitive stress* or repetitive strain* or repetition stress* or repetition strain* or overuse cumulativ*) adj5 (injur* or syndrome* or trauma*)).ti,ab,kf,kw.
21. ((pain or pains or paining or painful or ache or aches or aching or compress* or entrap*) adj5 nerve*).ti,ab,kf,kw.
22. or/15-21
23. 6 and 9 and 22
24. 14 and 22
25. or/23-24
26. 25 use medall
27. 25 use cctr
28. limit 27 to yr=2001-current
29. exp Cognitive Behavior Therapy/ or Cognitive Therapy/ or psychotherapy/ or implosive therapy/ or exp exposure therapy/ or Dialectical Behavior Therapy/ or Mindfulness/ or Mindfulness-Based Interventions/
30. (((cognitive or behavio* or facilitate* or guided or saturat* or unguided or dialectical* or acceptance* or commitment* or metacognitive or meta cognitive or exposure*) adj2 (therap* or psychotherap* or psycho-therap*)) or cognitive behavio* or cognition therap* or CBT* or mindfullness* or behavioural activation* or behavioral activation*).ti,ab,id.
31. (self-manag* or selfmanag* or self-help* or selfhelp*).ti,ab,id.
32. ((psycholog* adj3 desensiti*) or imaginal flooding* or (imager* adj3 exposure*)).ti,ab,id.
33. ((exposure or flooding* or implosive or saturation) adj3 therap*).ti,ab,id.
34. or/29-33
35. exp internet/ or digital interventions/ or exp computers/ or exp Computer Assisted Therapy/ or exp Computer Assisted Instruction/ or Computer Assisted Instruction/ or exp Mobile Phones/ or exp mobile phones/ or mobile applications/ or exp Telemedicine/

36. (internet* or digital* 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 phone* or online* or telephone* or tele phone* or cell phone* or cellphone* or smartphone* or smart phone* or smart watch* or smartwatch* 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 m health* or mhealth* or virtual or virtualist? or webbased or web based or web deliver* or webdeliver*).ti,ab,id.
37. or/35-36
38. (iCBT* or cCBT* or eCBT* or dCBT*).ti,ab,id.
39. ((internet* or computer* or cyber* or digital* or digital* or web*) adj6 (CBT* or CPT*)).ti,ab,id.
40. ((internet* or computer* or cyber* or digital* or digital* or web* or technolog*) adj6 (cognitive behavior* or cognitive behaviour* or cognitive process*) adj6 (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,id.
41. (MoodGym* or Mood Gym* or Big White Wall* or Togetherall* or Together All* or "Beating the Blues*" or Fear Fighter* or FearFighter* or E compass* or Ecompass* or mycompass* or my compass* or Deprexis* or Moodkit* or Mood kit* or "Living Life to the Full*" or Woebot* or AbilitiCBT* or ALAViDA* or TruReach* or Tru Reach* or Beacon* or MindBeacon* or Mind Beacon* or i-Volve* or iVolve* or Interapy* or CBT-I Coach* or CBTi Coach* or CPT Coach* or Life Armor* or "T2 Mood Tracker*" or SilverCloud* or Silver Cloud* or "What's Up*" or MindShift* or Mind Shift* or MoodMission* or Mood Mission* or Depression CBT* or Brave Online* or "Camp Code A Lot*" or BounceBack* or Bounce Back* or Pacifica* or iCANCOPE* or "i can cope*" or WebMap* or ManageMyPain or "Manage My Pain*" or ABC-Schema* or ABCSchema* or Aventurine Mood Improver* or "Catch It*" or CBT Diary* or CBT Journal* or CBT Thought Record* or Cgoni or Cognitive Diary or Cognitive Styles* or End Anxiety Hypnosis or Good Blocks* or Happify* or Happy Habits* or Jitters CBT* or Joyable* or Lantern* or Merrier* or Mindbliss* or Moodpath* or MoodTools* or See Betty* or TF-CBT* OT TFCBT* or Wysa* or Youper*).ti,ab,id.
42. or/38-41
43. chronic pain/ or exp neuralgia/ or exp Neuropathic Pain/ or exp Myofascial Pain/ or exp Fibromyalgia/ or exp arthritis/ or exp colitis/ or irritable bowel syndrome/
44. chronic illness/ and (back pain/ or exp headache/ or somatoform pain disorder/ or exp musculoskeletal disorders/)
45. ((pain or pains or paining or painful or ache or aches or aching) adj5 (chronic* or subacute* or sub-acute* or recurr* or re-curr* or unresolv* or persist* or intractable or refract* or severe* or debilitat* or nociceptive* or neuropathic* or superficial* or visceral or burning or crushing or migratory or radiat* or splitting or somatic* or constant* or continu* or widespread or non malignant* or nonmalignan* or non-cancer* or noncancer* or myofascial* or prolong* or sustain*)).ti,ab,id.
46. ((chronic* or recurr* or re-curr* or unresolv* or persist*) adj5 (headache* or head ache* or back* or carpal tunnel* or cubital tunnel* or cephalalgia* or hemicrania* or cephalodynia* or cephalgia*)).ti,ab,id.
47. ((pain or pains or paining or painful or ache or aches or aching) adj5 (migraine* or arthriti* or osteoarthriti* or polyarthriti* or endometrioma* or endometrioses or endometriosis or colitis* or crohn* or fibromyalgia* or post operat* or postoperat* or post surg* or postsurg* or phantom*)).ti,ab,id.
48. ((repetitive stress* or repetitive strain* or repetition stress* or repetition strain* or overuse cumulativ*) adj5 (injur* or syndrome* or trauma*)).ti,ab,id.
49. ((pain or pains or paining or painful or ache or aches or aching or compress* or entrap*) adj5 nerve*).ti,ab,id.
50. or/43-49
51. 34 and 37 and 50

52. 42 and 50
53. or/51-52
54. 53 use psyh
55. exp cognitive behavioral therapy/ or "acceptance and commitment therapy"/ or exp mindfulness/ or psychotherapy/ or exp exposure therapy/
56. behavior therapy/ and cognitive therapy/
57. (((cognitive or behavio* or facilitate* or guided or saturat* or unguided or dialectical* or acceptance* or commitment* or metacognitive or meta cognitive or exposure*) adj2 (therap* or psychotherap* or psycho-therap*)) or cognitive behavio* or cognition therap* or CBT* or mindfullness* or behavioural activation* or behavioral activation*).ti,ab,kw,dq.
58. (self-manag* or selfmanag* or self-help* or selfhelp*).ti,ab,kw,dq.
59. ((psycholog* adj3 desensiti*) or imaginal flooding* or (imager* adj3 exposure*)).ti,ab,kw,dq.
60. ((exposure or flooding* or implosive or saturation) adj3 therap*).ti,ab,kw,dq.
61. or/55-60
62. internet/ or web-based intervention/ or exp computer/ or computer assisted therapy/ or e-counseling/ or exp mobile phone/ or exp mobile application/ or telemedicine/ or teleconsultation/ or telediagnosis/ or telemonitoring/ or telepsychiatry/ or teletherapy/ or videoconferencing/ or webcast/
63. (internet* or digital* 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 phone* or online* or telephone* or tele phone* or cell phone* or cellphone* or smartphone* or smart phone* or smart watch* or smartwatch* 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 m health* or mhealth* or virtual or virtualist? or webbased or web based or web deliver* or webdeliver*).ti,ab,kw,dq.
64. or/62-63
65. (iCBT* or cCBT* or eCBT* or dCBT*).ti,ab,kw,dq.
66. ((internet* or computer* or cyber* or digital* or digital* or web*) adj6 (CBT* or CPT*)).ti,ab,kw,dq.
67. ((internet* or computer* or cyber* or digital* or digital* or web* or technolog*) adj6 (cognitive behavior* or cognitive behaviour* or cognitive process*) adj6 (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,kw,dq.
68. (MoodGym* or Mood Gym* or Big White Wall* or Togetherall* or Together All* or "Beating the Blues*" or Fear Fighter* or FearFighter* or E compass* or Ecompass* or mycompass* or my compass* or Deprexis* or Moodkit* or Mood kit* or "Living Life to the Full*" or Woebot* or AbilitiCBT* or ALAViDA* or TruReach* or Tru Reach* or Beacon* or MindBeacon* or Mind Beacon* or i-Volve* or iVolve* or Interapy* or CBT-I Coach* or CBTi Coach* or CPT Coach* or Life Armor* or "T2 Mood Tracker*" or SilverCloud* or Silver Cloud* or "What's Up*" or MindShift* or Mind Shift* or MoodMission* or Mood Mission* or Depression CBT* or Brave Online* or "Camp Code A Lot*" or BounceBack* or Bounce Back* or Pacifica* or iCANCOPE* or "i can cope*" or WebMap* or ManageMyPain or "Manage My Pain*" or ABC-Schema* or ABCSchema* or Aventurine Mood Improver* or "Catch It*" or CBT Diary* or CBT Journal* or CBT Thought Record* or Cgoni or Cognitive Diary or Cognitive Styles* or End Anxiety Hypnosis or Good Blocks* or Happify* or Happy Habits* or Jitters CBT* or Joyable* or Lantern* or Merrier* or Mindbliss* or Moodpath* or MoodTools* or See Betty* or TF-CBT* OT TFCBT* or Wysa* or Youper*).ti,ab,kw,dq.
69. or/65-68

70. chronic pain/ or exp neuralgia/ or nociceptive pain/ or intractable pain/ or referred pain/ or myofascial pain/ or postoperative pain/ or fibromyalgia/ or exp arthritis/ or exp colitis/ or exp inflammatory bowel disease/ or endometriosis/
71. chronic disease/ and (exp backache/ or musculoskeletal pain/ or exp "headache and facial pain"/ or exp cumulative trauma disorder/)
72. ((pain or pains or paining or painful or ache or aches or aching) adj5 (chronic* or subacute* or sub-acute* or recurr* or re-curr* or unresolv* or persist* or intractable or refract* or severe* or debilitat* or nociceptive* or neuropathic* or superficial* or visceral or burning or crushing or migratory or radiat* or splitting or somatic* or constant* or continu* or widespread or non malignant* or nonmalignan* or non-cancer* or noncancer* or myofascial* or prolong* or sustain*)).ti,ab,kw,dq.
73. ((chronic* or recurr* or re-curr* or unresolv* or persist*) adj5 (headache* or head ache* or back* or carpal tunnel* or cubital tunnel* or cephalalgia* or hemicrania* or cephalodynia* or cephalgia*)).ti,ab,kw,dq.
74. ((pain or pains or paining or painful or ache or aches or aching) adj5 (migraine* or arthriti* or osteoarthriti* or polyarthriti* or endometrioma* or endometrioses or endometriosis or colitis* or crohn* or fibromyalgia* or post operat* or postoperat* or post surg* or postsurg* or phantom*)).ti,ab,kw,dq.
75. ((repetitive stress* or repetitive strain* or repetition stress* or repetition strain* or overuse cumulativ*) adj5 (injur* or syndrome* or trauma*)).ti,ab,kw,dq.
76. ((pain or pains or paining or painful or ache or aches or aching or compress* or entrap*) adj5 nerve*).ti,ab,kw,dq.
77. or/70-76
78. 61 and 64 and 77
79. 69 and 77
80. or/78-79
81. 80 use oemezd
82. 81 not conference abstract.pt.
83. 26 or 54 or 82
84. (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study or Adaptive Clinical Trial or Equivalence Trial).pt.
85. (Clinical Trial or Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV or Clinical Trial Protocol).pt.
86. Multicenter Study.pt.
87. Clinical Studies as Topic/
88. exp Clinical Trial/ or exp Clinical Trials as Topic/ or Clinical Trial Protocol/ or Clinical Trial Protocols as Topic/ or exp "Clinical Trial (topic)"/
89. Multicenter Study/ or Multicenter Studies as Topic/ or "Multicenter Study (topic)"/
90. Randomization/
91. Random Allocation/
92. Double-Blind Method/
93. Double Blind Procedure/
94. Double-Blind Studies/
95. Single-Blind Method/

96. Single Blind Procedure/
97. Single-Blind Studies/
98. Placebos/
99. Placebo/
100. Control Groups/
101. Control Group/
102. Cross-Over Studies/ or Crossover Procedure/
103. (random* or sham or placebo*).ti,ab,hw,kf,kw.
104. ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
105. ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
106. (control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf,kw.
107. (clinical adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
108. (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.
109. (phase adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
110. ((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
111. ((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
112. allocated.ti,ab,hw.
113. ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
114. ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
115. (pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.
116. ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.
117. ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
118. trial.ti,kf,kw.
119. or/84-118
120. exp animals/
121. exp animal experimentation/
122. exp models animal/
123. exp animal experiment/
124. nonhuman/
125. exp vertebrate/
126. animal.po.
127. or/120-126
128. exp humans/
129. exp human experiment/

130. human.po.
131. or/128-130
132. 127 not 131
133. 119 not 132
134. epidemiologic methods.sh.
135. epidemiologic studies.sh.
136. observational study/
137. observational studies as topic/
138. clinical studies as topic/
139. controlled before-after studies/
140. cross-sectional studies/
141. historically controlled study/
142. interrupted time series analysis/
143. exp seroepidemiologic studies/
144. national longitudinal study of adolescent health/
145. cohort studies/
146. cohort analysis/
147. longitudinal studies/
148. longitudinal study/
149. prospective studies/
150. prospective study/
151. follow-up studies/
152. follow up/
153. followup studies/
154. retrospective studies/
155. retrospective study/
156. case-control studies/
157. exp case control study/
158. cross-sectional study/
159. observational study/
160. quasi experimental methods/
161. quasi experimental study/
162. single-case studies as topic/
163. (observational study or validation studies or clinical study).pt.

164. (observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw.
165. cohort*.ti,ab,kf,kw.
166. (prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf,kw.
167. ((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf,kw.
168. ((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf,kw.
169. (retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf,kw.
170. ((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf,kw.
171. (case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw.
172. (population adj3 (study or studies or analysis or analyses)).ti,ab,kf,kw.
173. (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw.
174. ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw.
175. (cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf,kw.
176. ((natural adj experiment) or (natural adj experiments)).ti,ab,kf,kw.
177. (quasi adj (experiment or experiments or experimental)).ti,ab,kf,kw.
178. ((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw.
179. (prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kf,kw.
180. case series.ti,ab,kf,kw.
181. case reports.pt.
182. case report/
183. case study/
184. (case adj3 (report or reports or study or studies or histories)).ti,ab,kf,kw.
185. organizational case studies.sh.
186. or/134-185
187. (systematic review or meta-analysis).pt.
188. meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/
189. ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.
190. ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.
191. ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.
192. (data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.
193. (handsearch* or hand search*).ti,ab,kf,kw.
194. (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.
195. (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw.

196. (meta regression* or metaregression*).ti,ab,kf,kw.

197. (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.

198. (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.

199. (cochrane or (health adj2 technology assessment) or evidence report).jw.

200. (comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.

201. (outcomes research or relative effectiveness).ti,ab,kf,kw.

202. ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf,kw.

203. (meta-analysis or systematic review).md.

204. (multi* adj3 treatment adj3 comparison*).ti,ab,kf,kw.

205. (mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf,kw.

206. umbrella review*.ti,ab,kf,kw.

207. (multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.

208. (multiparamet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.

209. (multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.

210. or/187-209

211. 83 and 133

212. 83 and 186

213. 83 and 210

214. or/211-213

215. limit 214 to (english or french)

216. limit 215 to yr=2001-current

217. 28 or 216

218. remove duplicates from 217

Clinical Trials Registries

ClinicalTrials.gov

Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search -- Studies with results | iCBT AND chronic pain]

WHO ICTRP

International Clinical Trials Registry Platform, produced by WHO. Targeted search used to capture registered clinical trials.

[Search terms -- iCBT AND chronic pain]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms -- iCBT AND chronic pain]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- iCBT AND chronic pain]

Grey Literature

Search dates: Autumn 2021

Keywords: [iCBT AND chronic pain]

Limits: Publication years: 1996 to present

Updated: Search updated prior to the completion of stakeholder feedback period.

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool for Searching Health-Related Grey Literature were searched:

- Health Technology Assessment Agencies
- Clinical Practice Guidelines
- Clinical Trials Registries
- Databases (free)
- Health Statistics
- Internet Search
- Patient Involvement
- Open Access Journals