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CADTH OPTIMAL USE REPORT

# Internet-Delivered Cognitive Behavioural Therapy for Major Depressive Disorder and Anxiety Disorders: A Health Technology Assessment — Project Protocol

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## Background and Rationale

Depression and anxiety (including generalized anxiety disorder, panic disorder, social anxiety disorder, and specific phobias) are leading causes of disability worldwide, with estimates suggesting that as much as 40% of the population will require some form of treatment in their lifetime.[1-3] The treatment of depression and anxiety disorders includes a wide range of options that can be broadly classified as either pharmacotherapy or psychotherapy. Although forms of pharmacotherapy (e.g., treatment with antidepressants) can be effective for some patients,[4] literature suggests that the adherence rates over time are generally poor and that only one-third of depressed patients fully respond to pharmacotherapy.[5-7] In addition, up to 75% of psychiatric patients report a preference for psychological interventions over pharmacologic treatment.[7] These factors emphasize the importance of supporting the development of effective and acceptable psychotherapies.

Cognitive behavioural therapy (CBT) is the most commonly utilized form of psychotherapy for the treatment of patients with depression or anxiety disorders.[1] Initially developed in the 1960s,[8] CBT has been the subject of numerous studies investigating its clinical effectiveness for the treatment of depression and anxiety.[9-11] By combining the principles of cognitive and behavioural therapies, CBT aims to provide patients with the coping strategies and mechanisms to solve current problems and to change dysfunctional thoughts, behaviours, beliefs, and attitudes.[12] Some of the techniques employed in CBT include graded exposure, relaxation training, challenging negative automatic thoughts, activity scheduling, social skills training, and behavioural experiments.[12,13]

Despite the clinical effectiveness of CBT,[9-11] patients suffering from depression or anxiety disorders are frequently unable to access treatment.[14,15] Traditionally delivered using face-to-face sessions involving a trained clinician and their patients, common barriers to CBT include its high cost, perceived stigma, poor access to treatment in rural areas, long wait times, privacy issues, and a lack of trained clinicians. Internet-delivered CBT (iCBT) has shown promise for the treatment of depression and anxiety, potentially offering ways for patients to overcome some of these barriers, while remaining effective as a psychotherapy.[16]

Essentially, iCBT involves the delivery of CBT through an online platform, with or without the support of a therapist, via email or telephone.[17] Currently, there is a wide variety of iCBT software available. The mode of delivery (i.e., computer or smartphone), cost of therapy, and level of therapist support can vary greatly between programs.[18] Understanding these characteristics and factors, and how they may influence the experience of iCBT, is crucial for clinicians and health care facilities looking to offer iCBT to patients suffering from depression or anxiety. Broadly speaking, there is a need to clarify current policy and the appropriate use of iCBT in the context of major depressive and anxiety disorders in Canada.

## Policy Question

Should Internet-delivered cognitive behavioural therapy be offered to people with major depressive disorder or anxiety disorders?

## Objectives

CADTH, in collaboration with Health Quality Ontario (HQO), is undertaking an Optimal Use project on the use of iCBT in patients with mild and moderate major depressive disorder (MDD) and anxiety disorders. Collaboratively, both organizations will explore relevant clinical, economic, social, and ethical evidence to inform the policy question. Analyses of the evidence will be presented in separate chapters, each with specific and different research questions and methodologies.

HQO will develop a systematic review to assess the clinical effectiveness and cost-effectiveness of iCBT, as well as an economic analysis, and will undertake direct patient engagement to explore patient preferences and values.[19] CADTH will develop reviews and analyses to assess patient perspectives and experiences, and ethical and implementation issues related to iCBT. This document outlines the research questions and methods to be used by CADTH.

## Implementation Review

Implementation of any therapy is facilitated or constrained by a set of characteristics and circumstances that are unique to the practice and to the patients for which the program is being established. For example, a psychologist who perceives the Internet as limiting his or her ability to provide patients with feedback about their interpersonal skills may be reluctant to offer iCBT.[20] Other factors, such as the level of training of the psychologist on delivering CBT through an online platform, patient referral processes, patient preferences, and the academic educational level of patients may impact the effectiveness of iCBT.[21] Issues specific to the Internet, such as concerns about patient confidentiality and liability, may also influence the implementation and uptake of iCBT.[22] Legal issues may arise if patients access iCBT programs outside the jurisdictions in which their health professionals are licensed.[23] Determining the set of factors that affect the implementation of iCBT is critical to the successful adoption of recommendations on its optimal use for adults with MDD or anxiety disorders.

The implementation issues component of this Health Technology Assessment (HTA) aims to identify existing or developing iCBT programs, explore the range of strategies that have been used to establish these programs, and identify enablers and barriers to the implementation and uptake of iCBT.

### Data Acquisition

#### Survey

We will conduct a survey of stakeholders who operate at the health services delivery level across Canada. CADTH's Implementation Support and Knowledge Mobilization Officers will identify potential study participants using a purposive sampling strategy. The goal will be to obtain a sample that is representative of Canadian provinces and territories, and the range of health care professionals who may be involved in the delivery of iCBT. Potential participants include, but are not limited to, family physicians, psychologists, psychiatrists, nurses, social workers, other mental health professionals, information management professionals, online platform developers, and administrators of health care facilities across Canada. Additionally, individual consultations may take place with selected survey participants (who provide information that requires further exploration) or with other

stakeholders. The aim is to continue sampling until data saturation is obtained or no new information is emerging from subsequent participants; however, sample size will ultimately be limited by time and resource constraints.

The questions (both closed and open-ended) will elicit quantitative information, as well as the qualitative perspectives of stakeholders around the context and implementation of iCBT in Canada. A draft questionnaire will undergo a pilot test by two potential participants. Edits will be made according to feedback from the pilot test regarding the format and content of the questions before distributing the questionnaire to a wider group of potential respondents. The questionnaire will be distributed by email and administered using the Hosted in Canada Surveys online platform.

### Literature Review

In parallel with the survey, a literature review will be conducted of published information on enablers and barriers to the implementation of iCBT for adults with MDD or anxiety disorders. A targeted literature search will be performed by an information specialist using a peer-reviewed search strategy. Information related to implementation enablers and barriers will be identified by searching the following bibliographic databases: MEDLINE (1946–) with In-Process records and daily updates via Ovid; PsycINFO (1806–) via Ovid; the Cochrane Library (2018, Issue 2) via Wiley; Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1981–) via EBSCO; and PubMed. The search strategy will be comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts will be iCBT and depressive or anxiety disorders.

A methodological filter will be applied to limit retrieval to studies relevant to evaluations of previously implemented programs and general implementation issues. Retrieval will not be limited by publication year, but will be limited to the English language.

Regular alerts will be established to update the searches until the publication of the final report. Regular search updates will be performed on databases that do not provide alert services. Studies identified in the alerts and meeting the selection criteria of the review may be incorporated into the review if they are identified prior to the completion of the stakeholder feedback period of the final report and offer new analytical insight.

Grey literature (literature that is not commercially published) will be identified by searching the Grey Matters checklist (https://www.cadth.ca/grey-matters), which includes the websites of HTA agencies, clinical guideline repositories, systematic review (SR) repositories, and professional associations. Google and other Internet search engines will be used to search for additional Web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts.

Given that iCBT is relatively new and is undergoing continuous modification, it is possible that previously unanticipated implementation issues will be discovered during the early research stage. Therefore, an iterative process will be followed such that additional targeted searches may be conducted to explore any nascent topics. All modifications made to the data acquisition plan outlined in this section will be documented in the final report, along with a rationale. If changes are substantial, a protocol amendment will be published.

## Literature Selection

### Inclusion Criteria

Primary studies, reviews, and reports that provide descriptions of existing programs, that explore the range of strategies used to establish those programs, or that identify the enablers or barriers to implementing any Internet-based intervention encompassing iCBT for adult patients 16 years or older and in any country, are eligible for inclusion. Whereas the review will focus on MDD and anxiety disorders, information relevant to patients with any psychological condition will be considered. Reports on patients' or providers' preferences and experiences regarding characteristics of interest that enable or hinder implementation will be included. Characteristics of interest include accessibility, adherence, adoption, attrition, feasibility, maintenance, reach, retention, sustainability, uptake, and usability.

### Exclusion Criteria

Reports will be excluded if their focus is not on the enablers and barriers to implementing iCBT. Reports that focus on patients younger than 16 years of age will be excluded. Reports on non-traditional CBT (e.g., mindfulness CBT), CBT that is delivered via bibliotherapy, or CBT that is described as computerized (e.g., CD ROM) with no Internet component will be excluded. Case reports of individual patient experiences, abstracts, and conference papers will also be excluded.

### Screening

Two reviewers will independently screen titles and abstracts from the results of the literature searches. Reports selected by either of the reviewers will be retrieved for full-text screening. Both reviewers will then independently conduct full-text screening for inclusion and exclusion. Differences will be resolved through discussion. The list of reports labelled for inclusion will be posted online for ten business days for review by external stakeholders. Stakeholders will be asked to submit feedback and additional publications for consideration. Two reviewers will independently screen the titles and abstracts from the suggested list of additional publications and conduct full-text screening, if needed. A final list of included reports will be documented in the final report.

### Data Extraction

One reviewer will extract descriptive article characteristics (such as first author's name, year of publication, and setting) from the included articles, and findings relevant to the implementation of iCBT for psychological conditions, with a focus on MDD and anxiety disorders. A second reviewer will verify the extracted data.

## Data Analysis

One reviewer will write a narrative summary of the data relevant to the factors that may enable or constrain the implementation of iCBT, including from survey responses and the literature review. The reviewer will use the Context and Implementation of Complex Interventions framework from the INTEGRATE-HTA guidance to guide the initial categorization of the data. The Context and Implementation of Complex Interventions framework provides a structure for conceptualizing, assessing, and documenting the interacting domains of context and the implementation of complex interventions.[24] The domains of context that will guide the inquiry are setting; and geographical, epidemiological,

socio-cultural, socio-economic, legal, and political issues. Ethical issues will be analyzed in a separate section. The domains of implementation are provider, organization and structure, funding, and policy.[24] A narrative summary will be written for each domain to describe and summarize data relevant to each topic.

### Data Triangulation

Through a triangulation process, concepts that emerge from the surveys will be compared with any that emerge from consultations and the literature. Agreements and contradictions between the surveys, consultations, and the literature will be documented in the final report.

## Perspective

When analyzing data, the items coded and summaries written will be those most relevant to the research questions at the health services delivery level. We will aim to provide information to policy-makers regarding the operational requirements that should be in place or could be used to help facilitate the effective implementation and sustainability of iCBT programs.

## Outputs

The final report will contain a summary of existing and developing iCBT programs across Canada, and strategies that have been used to establish iCBT programs, including a list of enablers and barriers. Findings of this review will support the development of recommendations on implementing iCBT, as well as inform knowledge mobilization and implementation support activities.

## Protocol Amendments

Given the potential for unexpected information to be uncovered during this review, additional data collection may be required. The final report will detail the analytic methods used and, if appropriate, a protocol amendment will be published.

# Patients' Perspectives and Experiences

## Background and Rationale

Although the literature identifies Internet mediation as a modality with potentially beneficial outcomes,[25,26] relatively few studies have systematically examined how iCBT is experienced by service users.

The literature describes a range of patient (or service user) experiences[a] associated with iCBT. As an example, Bendelin et al.[27] concluded that individuals who assume self-responsibility for their treatment and credit themselves for treatment success may more readily view Internet-mediated approaches as positive. Access to human contact and real-time engagement were valued and are a consideration in iCBT. Holst et al.[28] identify varied experiences across participants, and there appears to be a range of factors and considerations that may have a bearing on how iCBT is experienced by service users.[27,29-31]

By applying technology to the therapeutic encounter, the Internet may nurture access, privacy, and potentially greater freedom and flexibility, at least for some users.[28] However, a

range of technology-related challenges are noted, which also may have a bearing on user experience. Further, differentiating between the experience of the Internet component of treatment and CBT is noted as a challenge in elucidating experience and impact.[28]

Until further analysis is conducted in iCBT, the experience of service users and the variables of experience may remain unclear. Greater understanding is needed in determining impact, including for whom iCBT may be beneficial and how it can be optimally offered. A synthesis of the qualitative literature is anticipated to increase understanding and potentially inform the potential development of guidelines supporting patient experiences relative to iCBT and, thus, how this approach can be optimally administered. Given current gaps of knowledge, this HTA will address service user experiences of iCBT for MDD and anxiety disorders.

## Synthesis Question

How do patients experience iCBT for MDD and anxiety disorders?

## Study Design

The research question will be addressed by conducting an SR and synthesis of published primary qualitative studies. The protocol was developed a priori and will be followed throughout the HTA process.

## Methods

### Literature Search Methods

The literature search will be performed by an information specialist using a peer-reviewed search strategy.

Information related to patients' perspectives and experiences will be identified by searching the following bibliographic databases: MEDLINE (1946–) with In-Process records and daily updates via Ovid; PsycINFO (1806–) via Ovid; the Cochrane Library (2018, Issue 2) via Wiley; CINAHL (1981–) via EBSCO; and PubMed. The search strategy will be comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH, and keywords. The main search concepts will be Internet-based cognitive therapy and depressive or anxiety disorders.

Methodological filters will be applied to limit retrieval to qualitative studies or studies relevant to patients' perspectives. Retrieval will not be limited by publication year, but will be limited to the English language. See Appendix A for the detailed search strategy.

Regular alerts will be established to update the searches until the publication of the final report. Regular search updates will be performed on databases that do not provide alert services. Studies identified in the alerts and meeting the selection criteria of the review may be incorporated into the review if they are identified prior to the completion of the stakeholder feedback period of the final report and offer new analytical insight.

[a]Note: The terms "patients" and "service users" are used interchangeably in this protocol to indicate the target population of individuals who have received iCBT.

*Grey literature* (literature that is not commercially published) will be identified by searching sources included in the *Grey Matters* checklist (https://www.cadth.ca/grey-matters), which include the websites of HTA agencies, clinical guideline repositories, SR repositories, and professional associations. Google and other Internet search engines will be used to search for additional Web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers.

## Iterative Search Process

Qualitative research can be difficult to locate because of the inconsistency in index terms and the potential challenges in retrieving qualitative studies using search filters.[32] Accordingly, the literature search may be modified and re-run depending on the set of studies identified that meet the inclusion criteria. The search strategy will be developed and refined as follows: initially, all qualitative research relevant to patients' experiences in iCBT for MDD or anxiety disorders will be retrieved and then screened for eligibility.

The titles and abstracts of included articles will be reviewed to identify potentially relevant articles for full-text review. As articles are reviewed, memos on the topics, populations, and outcomes within articles will be identified to develop an understanding of what type of information is present in this literature. At this point, an assessment will be made about whether the initial research question is answerable with this data set. If not, the search may be refined to either broaden it or to capture additional experiences or constructs of interest. After judging the sufficiency of the research data, an iterative approach will be adopted to refine the question, if necessary, and appraise the available evidence.[33] This iterative refinement is common in some qualitative approaches and requires familiarity with the data set.[33,34]

The refinement of the research question will remain an open question as analysis continues. As data are extracted from relevant studies and analyzed, the breadth and depth of these data will be discussed to consider whether they answer the proposed question. The evolution of the question and search strategy will be documented to maximize the authenticity of the final account.[35]

## Literature Selection Criteria

### *Inclusion Criteria*

Eligible studies will be primary English language qualitative studies or mixed-methods studies, with separate reporting of the qualitative component. For the purpose of this review, qualitative studies are defined as studies that produce data from qualitative data collection methods (e.g., interviews, participant observation) and utilize qualitative data analysis methods (e.g., constant comparative method, content analysis, thematic analysis, etc.). The qualitative component of mixed-method studies will be included, if qualitative processes have been implemented and qualitative data are produced in those studies. Studies that have multiple publications using the same data set will be included only if they report on distinct research questions. Accordingly, in cases of duplicate publications using the same data with the same findings, duplicate documents will be excluded.

No limits are being placed regarding countries studied, and as noted previously, studies that report patients' experiences with iCBT for MDD or anxiety disorders will be included. To be eligible, studies must explore participants' own perspectives directly, not indirectly (i.e., through another person). There is no standard approach to including primary studies *and* syntheses in a qualitative synthesis. Typically in quantitative syntheses, only primary studies

are included to avoid the issue of "double counting" or giving undue weight to one set of study findings. Following these principles, qualitative syntheses will be excluded.

Table 1 describes the eligibility criteria to be used.

## Table 1: Eligibility Criteria

| | |
|---|---|
| **Definition of Patient Perspective or Experience** | • Experience, view, or reflection of individuals participating in an Internet-delivered cognitive behavioural therapy intervention for mild or moderate major depressive disorder and/or anxiety |
| **Target Population Age** | • 16 years of age or older (adult-based studies) |
| **Time Frame** | • Unlimited |
| **Study Designs** | • Qualitative studies<br>• Mixed-method studies (with a focus only on qualitative data) |
| **Countries to Be Included** | • No limits |

### *Exclusion Criteria*

The following elements will render a study ineligible for inclusion in this synthesis review:

- studies not focused on iCBT for MDD or anxiety disorders
- studies addressing topics other than patients' experiences of iCBT
- commentaries, case reports, or editorials
- non–full-text publications (e.g., abstracts)
- work that has not been peer-reviewed or is not published (e.g., theses, editorials, letters to the editor, reports)
- book chapters
- studies labelled "qualitative" but that did not use a qualitative descriptive or interpretive methodology (e.g., case studies, experiments, surveys, or observational analyses not using qualitative approaches)
- studies not involving the first-person perspectives of patients receiving iCBT.

### Literature Screening and Selection

Two reviewers will independently assess titles and abstracts of potentially eligible studies in DistillerSR.[36] Disagreements about eligibility at the title and abstract level will be resolved through discussion, with a third reviewer, if required. The full text of all potentially relevant studies will be retrieved, and the screening and assessment of these studies for inclusion will be conducted independently by two reviewers. Again, differing judgments about study inclusion will be resolved through discussion. Study selection will be documented and reported using a PRISMA flow diagram in a final report.[37]

After the completion of full-text screening, two researchers will review the set of included studies and discuss whether the final set of included studies is judged to include sufficient data for analysis or if there is a need to modify the literature search and selection criteria. Reflection on the potential need to refine the research question will occur should modifications to the literature search and selection criteria be necessary.

The draft list of included studies will be posted online for stakeholder review for ten business days, during which stakeholders may submit feedback or additional publications for potential inclusion. Any additional publications identified will be screened using the same two-stage

process as previously described. The final list of included studies will be included in the final report.

## Descriptive Study Data

Descriptive data extraction for the included studies will be conducted using standardized data extraction forms in a spreadsheet, which have been designed to extract relevant information from the studies, including but not limited to:

- first author's name, publication year, country, funding sources, and reported conflicts of interest
- study objectives
- study design
- participant eligibility criteria
- participant characteristics including number of participants, age, sex, diagnosis, and comorbidities
- description of iCBT including length of treatment, guided or unguided, lower intensity or higher intensity
- description of subgroups of interest.

Two reviewers will pilot the data extraction form, in duplicate, on a representative sample of included studies until consistency is reached; i.e., the reviewers are in agreement on all extracted information. After calibration, one reviewer will extract the data and the second reviewer will verify of the extraction for accuracy. Disagreements will be resolved through consensus, involving a third reviewer, as necessary. Only information from the selected published studies will be reviewed.

## Quality Assessment

Two reviewers will independently critically appraise all included studies concurrently with data extraction and checking. The items of the Critical Appraisal Skills Program (CASP) Qualitative Checklist will be used to guide the critical appraisal. Disagreements in assessments will be resolved through discussion, involving a third reviewer, if required. Quality appraisal in qualitative evidence synthesis supports the evaluation of the credibility of the conclusions and aims in seeking to ensure that findings represent the relevant literature; however, studies will not be excluded from the review on the basis of the quality appraisal.

## Data Analysis

NVivo 11[38] will be used to extract and manage qualitative data from included studies. Sections of the publications reporting findings will be coded (i.e., not background and discussion sections) to ensure the capture of qualitative data and findings (and not findings in, or interpretations of, background literature, or authors' conclusions).

The analysis will follow a staged coding process similar to grounded theory via three stages: open or line-by-line coding, descriptive coding, and developing analytic themes and constructs.[39] The constant comparison method will be adapted to include comparing codes within and across studies. The synthesis will be conducted by one reviewer who has experience in undertaking primary qualitative research.

The reviewer will conduct line-by-line coding of an initial set of four to six studies. Line-by-line coding encourages "staying close to the data," a process that encourages the inductive

development of codes. Upon completing this initial set and reflecting on the coding process, a decision will be made to either continue line-by-line coding or move toward developing descriptive codes. Further line-by-line coding will be warranted if there are no patterns appearing in the open codes used and if each passage being coded continues to give rise to a new set of codes (i.e., there is no stability in the codes being used). In this case, the process of line-by-line coding will continue for a subset of additional studies (approximately four), again with subsequent reflection on the coding process as previously noted.

Once it is determined that line-by-line coding is sufficient (i.e., that patterns have emerged in the codes used), the reviewer will begin descriptive coding, which will advance the synthesis process. The reviewer will use the research question as a guide in developing and refining a set of descriptive codes. During descriptive coding, the reviewer will use text passages, as relevant, to group and cluster codes using descriptive concepts that remain close to the data. Upon completing this subset, the reviewer will reflect on the breadth and meaning of descriptive codes and their related concepts as part of refining the coding set. Once codes are outlined that describe the dimensions of the data relevant to the research question, the reviewer will code the remaining studies using the set of descriptive codes.

The reviewer will continue to verify descriptive codes through a review of these codes and their structure — through the ongoing coding of data. The reviewer will compare and contrast codes within and across the reviewed studies. As the codes become solidified and thickened, it is anticipated that higher-order constructs or categories (for which other codes are dimensions or facets) will emerge via relationships between codes. Through this process, it is expected that the analysis will evolve from coding to analytic synthesis.

Analytic synthesis is the development of themes or abstracted constructs that are interpretations of the data. To develop analytic themes, memoing and diagramming will be used to assemble and sort the previously established descriptive codes, going back to the data to further develop the relationship between themes and codes. In keeping with the iterative nature of qualitative analysis, the reviewer may revert to descriptive coding to additionally describe dimensions or facets of particular codes or themes, to develop themes that are conceptually rich (i.e., described in rich detail and supported by data). This analytic approach ensures that the review is more than a summary of findings of qualitative studies in that a new synthesis or interpretation of the reviewed data is anticipated to emerge in response to the research question. Data that are relevant to the research question of this review but that do not feature prominently in the data set will be coded and analyzed even if there is an absence of theoretical saturation around those codes and they remain descriptive versus analytic.

Reflexivity is an epistemological principle and methodological approach in qualitative research that recognizes the role of the researcher as a key instrument in the research. Reflexive practices and techniques allow for and offer the means to seek greater transparency in how researchers make observations and interpretations from the data. To this end, reflexive practices of memoing and frequent dialoguing among team members will be done to probe and position the reviewer in relation to the analysis.

# Ethical Issues

The purpose of this analysis is to identify and reflect upon key ethical issues that should be contemplated when considering the public provision of iCBT adults with MDD or anxiety disorders in Canada. Although other sections of this HTA implicitly touch upon broadly ethical concerns, the aim of this analysis is to make such issues explicit and to identify others that may be relevant to any decisions in this regard.

The issues raised in this section can go beyond narrowly defined ethical concerns to encompass broader legal, social, and cultural considerations, as well. Nevertheless, the primary emphasis here will be on ethical considerations rather than on legal and social issues.

There are two questions to consider about the provision, development, and use of iCBT:

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

## Inquiry

Bioethical analysis requires a two-step approach to identify potential issues. The first is a review of the ethics, clinical, and public health literatures to identify existing ethical analyses of the technology. The second is a novel ethical analysis based on gaps identified in the ethics literature and the results of concurrent reviews. This may require selective searches to provide the basis in theoretical ethics, in applied ethical analyses of similar technologies, and in evidence for the ethical analysis of emerging issues specific to iCBT for MDD and anxiety disorders. By this approach, we identify and assess the relative importance and strength of the identified concerns and proposed solutions, identify and assess ethics issues that have not yet been identified in the iCBT literature, and delineate ethical desiderata for possible solutions to the issues where such solutions have not yet been proposed.

Insofar as this process involves ethical concerns in applied ethics, typically the analysis will reflect on the specific details of community and patients' perspectives, clinical utility, economic analysis, and implementation considerations. As such, the ethical review involves an iterative process whereby the analysis is responsive to results emerging from clinical, implementation, patients' perspective, and economic reviews.

## Review of the Bioethics Literature

A review of the empirical and normative bioethics literature will be conducted to identify literature relevant to the identification and analysis of the potential ethical issues related to the use of iCBT. We will search for articles, studies, and reports that explicitly and specifically raise ethical issues related to the central question of this HTA, as well as literature not explicitly about ethical issues (for example, an empirical investigation of patient attitudes about iCBT) but which may point to potential ethical issues even if the participants and researchers did not formulate them as such.

## Literature Search Methods

The literature search will be performed by an information specialist using a peer-reviewed search strategy.

Information related to ethical issues will be identified by searching the following bibliographic databases: MEDLINE ALL (1946– ) via Ovid; PsycINFO (1806– ) via Ovid; the Cochrane Library (2018, Issue 2) via Wiley; Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1981–) via EBSCO; and PubMed. The search strategy will be comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH, and keywords. The main search concepts will be Internet-based cognitive therapy and depressive or anxiety disorders.

Methodological filters will be applied to limit retrieval to studies relevant to ethical issues. Retrieval will not be limited by publication year but will be limited to the English language.

Regular alerts will be established to update the searches until the publication of the final report. Studies identified in the alerts and meeting the selection criteria of the review may be incorporated into the review if they are identified prior to the completion of the stakeholder feedback period of the final report and offer new analytical insight.

Grey literature (literature that is not commercially published) will be identified by searching the *Grey Matters* checklist (https://www.cadth.ca/grey-matters), which includes the websites of HTA agencies, clinical guideline repositories, SR repositories, and professional associations. Google and other Internet search engines will be used to search for additional Web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts.

## Literature Screening and Selection

The selection of relevant literature will proceed in two stages. In the first stage, the title and abstracts of citations will be screened for relevance by a single reviewer. Articles will be categorized as "retrieve" or "do not retrieve," according to the following criteria:

- provides normative analysis of an ethical issue arising in the use of iCBT, whether for the treatment of the two conditions of interest or more generally
- presents empirical research directly addressing an ethical issue arising in the use of iCBT.

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

In the second stage, the full-text reports will be reviewed by a single reviewer with ethics expertise. Reports meeting the abovementioned criteria will be included in the analysis, and reports that do not meet these criteria will be excluded from analysis.

## Analysis

The ethical issues identified, values described, and solutions proposed in the literature will at this stage be evaluated using the methods of ethical (applied philosophical) analysis, which includes applying standards of logical consistency and rigour in argumentation, particularly where specific implications are identified and specific solutions advocated; responsiveness to important values of health care and health care policy in the field in which the technology is proposed for implementation; adequacy to the context for which the technology is being considered; and the representation of perspectives from diverse relevant communities, particularly marginalized and vulnerable populations.

The proposed analysis will draw most directly on two classic perspectives that are well-established in the health ethics literature, namely the utilitarian/consequentialist approach and the deontological/duty-based approach. The former focuses more directly on the overall consequences of a particular course of action and deals with questions of individual rights and duties, and considerations of social justice, only indirectly. Conversely, the deontological/duty-based approach gives priority to considerations of individual rights and concomitant duties while treating overall utility (i.e., the greatest good for the greatest number) as of only secondary importance. While these two theoretical approaches are often treated as opposed, there is a well-established tradition within contemporary health care ethics that treats them as complementary. Depending on the nature of the issue and the context in which it arises, it is possible that other normative ethical perspectives may be invoked in the analysis (e.g., virtue theory may be particularly relevant to issues regarding the professional conduct of psychiatrists or other therapists).

## Summarizing and Presenting Results

The reporting of ethical issues will follow the key values identified or issues being explored and will be determined by the values and issues that are identified. For example, the results may be summarized according to a principlist framework (issues concerned with autonomy, beneficence, non-maleficence, and justice) or by categorizing moral concerns as micro-, meso-, and macro-level issues. Regardless of the framework selected, the implications of the choice of framework on how the findings are presented and interpreted will be described. In addition, where the report undertakes analysis that is not derived from the peer-reviewed literature, this will be noted. It may also be appropriate to summarize the bibliographic details for each report (e.g., author, publication date, journal), the potential ethical issues raised, and the report's conclusions, as well as other information. The relevance and appropriateness of providing this summary will be determined after the analysis is complete.

Ethical analysis assists in policy decision-making but is not itself the site of legitimate decision-making, which requires consultation and deliberation on the part of relevant stakeholders in a given context. Decisions will also be sensitive to emerging empirical evidence. Furthermore, the ethical implications of a health technology are often determined by the nature of the local context. The implications of values of fair access and consistency of service within the population, for example, are determined by facts about how health care services are arranged and provided.

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

## Protocol Amendments

If amendments to the protocol are required at any time during the study, reasons for changes will be recorded and reported in the final report.

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# Appendix A: Literature Search Strategy

## Patients' Perspectives and Experiences Database Search

| OVERVIEW | |
|---|---|
| Interface: | Ovid |
| Databases: | Ovid MEDLINE(R) ALL 1946 to present<br>Ovid PsycINFO 1806 to present<br>**Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid. |
| Date of Search: | 2018 Apr 17 |
| Alerts: | Bi-weekly search updates until project completion |
| Study Types: | Qualitative and patient perspectives filters |
| Limits: | No date limit<br>English language |
| **SYNTAX GUIDE** | |
| / | 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;<br>or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings |
| ? | |
| adj# | Adjacency within # number of words (in any order) |
| .ti | Title |
| .ab | Abstract |
| .kf | Author keyword heading word (MEDLINE) |
| .id | Keyword concepts (PsycINFO) |
| /freq=n | Frequency threshold of occurrence of a term |

| MULTI-DATABASE STRATEGY | |
|---|---|
| **Line #** | **Search Strategy** |
| 1 | Cognitive Therapy/ |
| 2 | Cognitive Behavior Therapy/ |
| 3 | (((cognitive or behavio*) adj2 (therap* or psychotherap*)) or cognitive behavio* or cognition therap* or CBT*).ti,ab,kf,id. |
| 4 | or/1-3 |
| 5 | Internet/ |
| 6 | Therapy, Computer-Assisted/ |
| 7 | Computer-Assisted Instruction/ |
| 8 | Mobile Applications/ |
| 9 | Remote Consultation/ |
| 10 | Computer Assisted Therapy/ |
| 11 | Computer Mediated Communication/ |
| 12 | Computer Software/ |
| 13 | Computer Applications/ |
| 14 | Mobile Devices/ |
| 15 | Electronic Communication/ |

| MULTI-DATABASE STRATEGY | |
|---|---|
| **Line #** | **Search Strategy** |
| 16 | Human Computer interaction/ |
| 17 | Information Technology/ |
| 18 | Electronic Learning/ |
| 19 | Online Therapy/ |
| 20 | (internet* or Beacon or app or apps or computer based or computerbased or (mobile adj2 application*) or smartphone* or smart phone* or mobile based 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 online or media delivered or webbased or web based or web delivered or webdelivered).ti,ab,kf,id. |
| 21 | ((technolog* or computer* or digital*) adj6 (therap* or psychotherap* or CBT or intervention* or treatment* or deliver* or technique* or training)).ti,ab,kf,id. |
| 22 | or/5-21 |
| 23 | Depression/ |
| 24 | Depressive Disorder/ |
| 25 | Depressive Disorder, Major/ |
| 26 | Depressive Disorder, Treatment-Resistant/ |
| 27 | exp Anxiety/ |
| 28 | exp Anxiety Disorders/ |
| 29 | Mutism/ |
| 30 | *Mental Health/ |
| 31 | "Depression (emotion)"/ |
| 32 | Major Depression/ |
| 33 | Recurrent Depression/ |
| 34 | Treatment Resistant Depression/ |
| 35 | Anxiety/ |
| 36 | exp Anxiety Disorders/ |
| 37 | Generalized Anxiety Disorder/ |
| 38 | Panic Disorder/ |
| 39 | Panic Attack/ |
| 40 | Social Anxiety/ |
| 41 | exp Phobias/ |
| 42 | Separation Anxiety Disorder/ |
| 43 | *Mental Health Programs/ |
| 44 | *Mental Health Services/ |
| 45 | *Primary Mental Health Prevention/ |
| 46 | *Well Being/ |
| 47 | (depress* or MDD).ti,ab,kf,id. |
| 48 | (anxiet* or anxious* or panic* or phobi* or agoraphobi* or GAD or mute or mutism).ti,ab,kf,id. |
| 49 | mental health.ti. |
| 50 | or/23-49 |
| 51 | (cCBT* or iCBT* or eCBT*).ti,ab,kf,id. |
| 52 | (MoodGym or Big White Wall or Beating the Blues or Fear Fighter or E compass or Ecompass or Deprexis or Moodkit or Living Life to the Full).ti,ab,kf,id. |
| 53 | (e-mental health or emental health).ti,ab,kf,id. |
| 54 | or/51-53 |
| 55 | 4 and 22 and 50 |

| MULTI-DATABASE STRATEGY | |
|---|---|
| **Line #** | **Search Strategy** |
| 56 | 54 or 55 |
| 57 | exp Empirical Research/ |
| 58 | Interview/ |
| 59 | Interviews as Topic/ |
| 60 | Personal Narratives/ |
| 61 | Focus Groups/ |
| 62 | exp Narration/ |
| 63 | Nursing Methodology Research/ |
| 64 | Narrative Medicine/ |
| 65 | Qualitative Research/ |
| 66 | exp Empirical Methods/ |
| 67 | exp Interviews/ |
| 68 | Interviewing/ |
| 69 | Grounded Theory/ |
| 70 | Narratives/ |
| 71 | Storytelling/ |
| 72 | interview*.ti,ab,kf,id. |
| 73 | qualitative*.ti,ab,kf,jw,id. |
| 74 | (theme* or thematic).ti,ab,kf,id. |
| 75 | ethnological research.ti,ab,kf,id. |
| 76 | ethnograph*.ti,ab,kf,id. |
| 77 | ethnomedicine.ti,ab,kf,id. |
| 78 | ethnonursing.ti,ab,kf,id. |
| 79 | phenomenol*.ti,ab,kf,id. |
| 80 | (grounded adj (theor* or study or studies or research or analys?s)).ti,ab,kf,id. |
| 81 | (life stor* or women* stor*).ti,ab,kf,id. |
| 82 | (emic or etic or hermeneutic* or heuristic* or semiotic*).ti,ab,kf,id. |
| 83 | (data adj1 saturat*).ti,ab,kf,id. |
| 84 | participant observ*.ti,ab,kf,id. |
| 85 | (social construct* or postmodern* or post-structural* or post structural* or poststructural* or post modern* or post-modern* or feminis*).ti,ab,kf,id. |
| 86 | (action research or cooperative inquir* or co operative inquir* or co-operative inquir*).ti,ab,kf,id. |
| 87 | (humanistic or existential or experiential or paradigm*).ti,ab,kf,id. |
| 88 | (field adj (study or studies or research or work)).ti,ab,kf,id. |
| 89 | (human science or social science).ti,ab,kf,id. |
| 90 | biographical method.ti,ab,kf,id. |
| 91 | theoretical sampl*.ti,ab,kf,id. |
| 92 | ((purpos* adj4 sampl*) or (focus adj group*)).ti,ab,kf,id. |
| 93 | (open-ended or narrative* or textual or texts or semi-structured).ti,ab,kf,id. |
| 94 | (life world* or life-world* or conversation analys?s or personal experience* or theoretical saturation).ti,ab,kf,id. |
| 95 | ((lived or life) adj experience*).ti,ab,kf,id. |
| 96 | cluster sampl*.ti,ab,kf,id. |
| 97 | observational method*.ti,ab,kf,id. |
| 98 | content analysis.ti,ab,kf,id. |
| 99 | (constant adj (comparative or comparison)).ti,ab,kf,id. |

| MULTI-DATABASE STRATEGY | |
|---|---|
| **Line #** | **Search Strategy** |
| 100 | ((discourse* or discurs*) adj3 analys?s).ti,ab,kf,id. |
| 101 | (heidegger* or colaizzi* or spiegelberg* or merleau* or husserl* or foucault* or ricoeur or glaser*).ti,ab,kf,id. |
| 102 | (van adj manen*).ti,ab,kf,id. |
| 103 | (van adj kaam*).ti,ab,kf,id. |
| 104 | (corbin* adj2 strauss*).ti,ab,kf,id. |
| 105 | or/57-104 |
| 106 | exp Patient Acceptance of Health Care/ |
| 107 | Caregivers/ |
| 108 | exp Client Attitudes/ |
| 109 | Health Care Seeking Behavior/ |
| 110 | ((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers or personal or spous* or partner or partners or couples or users or participant* or people or child* or teenager* or adolescent* or youth or girls or boys or adults or elderly or females or males or women* or men or men's or mother* or father* or parents or parent or parental or maternal or paternal) and (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concerns or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or barrier* or facilitator* or survey* or questionnaire* or Likert)).ti. |
| 111 | ((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) adj2 (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concerns or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or barrier* or facilitator* or survey* or questionnaire* or Likert)).ab,kf,id. |
| 112 | ((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) adj7 (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concern or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or barrier* or facilitator* or survey* or questionnaire* or Likert)).ab. /freq=2 |
| 113 | ((personal or spous* or partner or partners or couples or users or participant* or people or child* or teenager* or adolescent* or youth or girls or boys or adults or elderly or females or males or women* or men or men's or mother* or father* or parents or parent or parental or maternal or paternal) adj2 (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concerns or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or barrier* or facilitator* or survey* or questionnaire* or Likert)).ab. /freq=2 |
| 114 | (patient adj (reported or centered* or centred* or focused)).ti,ab,kf,id. |

| MULTI-DATABASE STRATEGY | |
|---|---|
| **Line #** | **Search Strategy** |
| 115 | (treatment* adj2 (satisf* or refus*)).ti,ab,kf,id. |
| 116 | or/106-115 |
| 117 | 56 and (105 or 116) |
| 118 | limit 117 to english language |
| 119 | remove duplicates from 118 |

| OTHER DATABASES | | |
|---|---|---|
| Cochrane Library Issue 2, 2018 | Same MeSH and keywords used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases. | |
| PubMed | A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax. | |
| CINAHL (EBSCO interface) | Same keywords and study types used as per MEDLINE search. Syntax adjusted for EBSCO platform. | |

### Grey Literature

| | |
|---|---|
| Dates for Search: | April to May 2018 |
| Keywords: | Internet-based cognitive therapy and depressive or anxiety disorders |
| Limits: | English language |

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Databases (free)
- Internet Search
- Open Access Journals