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CADTH OPTIMAL USE REPORT

Hybrid Closed-Loop Insulin Delivery Systems for People With Type 1 Diabetes — Project Protocol

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Abbreviations

AE	adverse event
CGM	continuous glucose monitor
HCL	hybrid closed-loop insulin delivery system
HTA	health technology assessment
MA	meta-analysis
MDII	multiple daily insulin injections
OU	optimal use
PICO	Population, Intervention, Comparator, Outcome
PO	project owner
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
RoBANS	Risk of Bias for Non-Randomized Studies
SMBG	self-monitoring of blood glucose
SR	systematic review

Introduction and Rationale

Type 1 Diabetes in Canada

Without the ability to produce insulin, people living with type 1 diabetes develop symptoms such as excessive thirst or urination, blurred vision, headache, or fatigue as blood glucose levels rise.[1-4] Over time, high blood glucose levels can damage organs, blood vessels, and nerves.[2,3] In 2017 an estimated 2.3 million Canadians 12 years and older (7.3%) were living with diabetes,[5] about 10% of whom have type 1 diabetes.[3]

All people with type 1 diabetes require insulin therapy to control blood glucose levels.[3] Insulin can be provided by multiple daily insulin injections (MDII) or by an insulin pump (a small, externally worn device that delivers a small amount of insulin continuously, with additional doses as needed. For example, before meals through a tube connected to the body).[6] People with type 1 diabetes must regularly monitor their blood glucose levels to ensure a healthy range is maintained.[4,7] People with type 1 diabetes can check their blood glucose in a variety of ways.[7] These include the following:

- self-monitoring of blood glucose (SMBG) using a blood glucose metre (which uses a drop of blood from the finger placed on a testing strip to measure blood glucose)
- flash glucose monitoring (which uses a sensor inserted under the skin to measure glucose levels in the fluid surrounding the cells and is read on-demand using a handheld reader)
- continuous glucose monitoring (which uses a sensor inserted under the skin to measure glucose levels in the fluid surrounding the cells and transmits continuous readings to a device (e.g., smartphone) and can alert the user to low and high glucose levels).

Hybrid Closed-Loop Insulin Delivery Systems

One goal of type 1 diabetes research is to develop a system that can mimic the body's ability to regulate blood glucose levels without the need for intervention by the person with type 1 diabetes.[8,9] These device systems, sometimes called artificial pancreases or closed-loop systems, are still many years from clinical use.[8,9] Hybrid closed-loop insulin delivery systems (HCLs) are an emerging treatment option for people with type 1 diabetes on the path toward an artificial pancreas.[8,9] HCLs consist of an insulin pump, a continuous glucose monitor (CGM), and a computer program (algorithm) that allows the two devices to communicate with each other and calculate insulin needs.[9] HCLs are designed to automatically keep blood glucose levels within a predefined range by using the information from the CGM to tell the insulin pump how much insulin to deliver.[8,9] They are also designed to suspend delivery of insulin if blood glucose levels have reached or are approaching a predefined low glucose threshold.[8-12] They are called hybrid systems because the user must still manually account for insulin needs before or after eating.[9]

Hybrid Closed-Loop Insulin Delivery Systems in Canada

One HCL (Medtronic's MiniMed 670G Insulin Pump System[13]) was approved by Health Canada as a Class IV medical device in 2018 "for the management of type 1 diabetes in people seven years and older."[14-18] In the US, another HCL, Tandem's Control-IQ Technology — an interoperable control algorithm that was developed using Tandem's t:slim X2 insulin pump, Dexcom's G6 CGM, and Control-IQ software from TypeZero Technologies[19,20] — was approved for marketing in the US in December 2019.[20] Both the

t:slim X2 insulin pump and Dexcom G6 CGM are currently approved for use in Canada.[21,22] The Control-IQ Technology does not appear to be approved for use in Canada and no information about its anticipated availability in Canada was identified. BCDiabetes estimates Canadians can expect additional HCLs on the market by 2021.[12] At least five additional HCLs are being developed for the US market (including Omnipod's Horizon Automated Glucose Control System[23]) and another five for the European market.[24]

Studies of HCLs have included children,[25-27] adolescents,[27,28] and adults[27,29,30] with type 1 diabetes. The 2018 Diabetes Canada guidelines for the management of type 1 diabetes mention the promise of HCLs and note a need for more research.[31] The 2018 Diabetes Canada guidelines discuss the role of insulin pumps and CGM in the management of type 1 diabetes.[31,32] According to the guidelines for adults with type 1 diabetes:

- Insulin pumps are "a safe and effective method of intensive insulin delivery" and "appropriate candidates [for insulin pump therapy] should be motivated individuals, currently on optimized basal-bolus injection therapy [i.e., MDII], who are willing to frequently monitor [blood glucose], understand sick-day management, and attend follow-up visits as required by the health care team."[32]
- Continuous glucose monitoring is recommended for "adult patients with either [hemoglobin] A1C above target or who are well-controlled (at [hemoglobin] A1C target), provided that the devices are worn nearly daily."[32]
- Continuous glucose monitoring is promising for adults with impaired hypoglycemia awareness but more research is necessary.[32]

For children and adolescents with type 1 diabetes:

- Insulin pumps are "safe and effective and can be initiated at any age."[31]
- Continuous glucose monitoring is discussed but no specific statements regarding its use in children and adolescents are made.[31]

Sensor-augmented pumps are also mentioned in the guidelines but no specific recommendations for their use are made for adults or children and adolscents.[31,32]

Decision Problem

Given a rapidly evolving technology landscape for people with type 1 diabetes, what is the place in care, if any, of HCLs compared with existing technologies with regard to clinical effectiveness, safety, and cost?

Coverage of technologies to manage type 1 diabetes varies across the country, both in the technologies reimbursed and in what part of the health care system is responsible for reimbursement.[33,34] For example, for some people with type 1 diabetes, insulin pumps are reimbursed by drug plans or special device programs in some provinces and territories, while diabetes supplies (which would include CGM components) are often paid for by provincial or territorial drug plans. Feedback from CADTH customers indicates that CGMs are rarely covered by provincial and territorial programs. As such, interest for CADTH work related to HCLs varies from jurisdiction to jurisdiction.

Based on customer feedback, the purpose of a CADTH review of this topic would be to inform if HCLs have a place in management of type 1 diabetes.

- If so, are there groups of people with type 1 diabetes for whom it should not be offered?
- What are the perspectives and experiences of using or implementing an HCL of people with type 1 diabetes, their caregivers, and clinicians?
- What factors need to be in place for the optimal use of an HCL?
- Who (i.e., what part of the health care system) should be responsible for implementing HCLs?

Objective(s)

The purpose of this health technology assessment (HTA) is to address the decision problem through an assessment of the clinical effectiveness and safety of HCLs, a qualitative analysis of the perspectives and experiences of users and clinicians, and a review of implementation considerations. Other considerations such as costs and the financial impact of implementing HCLs may be assessed if deemed relevant based on an assessment of the clinical evidence and stakeholder consultations.

Deliverables

The following deliverable is planned:

A Science Report detailing all analyses conducted to inform the decision problem including these components:

- a systematic review of the clinical effectiveness and safety of HCLs
- a qualitative analysis of the perspectives and experiences of users and clinicians
- a review of implementation considerations
- a review of ethical considerations.

In addition to the Science Report, CADTH will produce a Recommendations Report detailing all recommendations and considerations to answer the decision problem. Depending on the availability of information in the Science Report, CADTH may also produce a budget impact analysis to inform the decision problem.

Research Questions

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

- Clinical Review
  1. What is the comparative clinical effectiveness of HCLs versus other insulin delivery methods in people, of any age, with type 1 diabetes?
  2. What is the comparative safety of HCLs versus other insulin delivery methods in people, of any age, with type 1 diabetes?
- Perspectives and Experiences Review
  3. How do people living with type 1 diabetes, or those involved in their care, describe their expectations of HCLs; and how have their experiences engaging with HCLs been reflective of their expectations?
     - How do people living with type 1 diabetes, or those involved in their care, envision HCLs as contributing to type 1 diabetes management?

- How might expectations of and experiences with HCLs differ across various people (e.g., young children, parents, elderly) engaging with these systems?
- For people living with type 1 diabetes who have built their own HCLs (or do-it-yourself [DIY] artificial pancreas systems) by "hacking" an insulin pump to communicate with their CGM via a computer program, what motivated them to begin and how does the emergence of commercial HCLs influence their motivations?

- Ethical Issues Analysis
  4. What are the major ethical issues raised by the use of HCLs compared with existing technologies for managing type 1 diabetes?
  5. How might these issues be addressed?

Methods

To inform the preparation of this protocol, a preliminary scoping review of the existing literature, including HTAs and systematic reviews, was conducted. This protocol was written a priori in consideration of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guideline for clarity, transparency, and completeness. The protocols for the clinical review (PROSPERO registration number: CRD42020193156) and the perspectives and experiences review (PROSPERO registration number: CRD42020192057) have been prospectively registered in the international repository, PROSPERO, and any deviations from the protocols will be disclosed in the final report. Updates to the PROSPERO submissions will be made accordingly.

Clinical Review

Scoping

The protocol for the clinical review was informed by scoping activities that included a formal scoping review[35] of existing literature and a CADTH Rapid Response report (summary of abstracts)[36] that was conducted to obtain an understanding of the clinical effectiveness of HCLs in people with type 1 diabetes published in September of 2019. Details on the complete methodology for the Rapid Response report — including literature search methods, detailed article selection, and eligibility criteria — are available in the publication.[36]

Study Design

The two research questions for the clinical review will be addressed by conducting a systematic review (SR) of primary studies. This review will identify relevant literature, narratively and, if possible, quantitatively summarize the findings and conduct a quality assessment of included studies. The protocol was developed a priori and will be followed throughout the HTA process.

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 (https://www.cadth.ca/resources/finding-evidence/press).[37] The preliminary search strategy is presented in Appendix 2.

Published literature will be identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid. 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 closed-loop systems and type 1 diabetes. Clinical trial registries will be searched: the US National Institutes of Health's ClinicalTrials.gov and the World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal. The initial search will be completed in March 2020. No filters will be applied to limit the retrieval by study type. Retrieval will be limited to English- or French-language documents published since January 1, 2003. Conference abstracts will be excluded from the search results. Regular alerts will update the database literature searches until the publication of the final report. The clinical trial registries search will be updated before the completion of the stakeholder feedback period. Studies meeting the selection criteria of the review and identified in the alerts before the completion of the stakeholder feedback period will be incorporated into the analysis of the final report. Any studies that are identified after the stakeholder feedback period will be described in the discussion, with a focus on comparing the results of these new studies with the results of the analysis conducted for this report.

Grey literature (literature that is not commercially published) will be identified by searching sources listed in relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters),[38] 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. The grey literature search will be updated before the completion of the stakeholder feedback period. These searches will be supplemented by reviewing bibliographies of key papers and through contacts with experts and industry, as appropriate.

Selection and Eligibility Criteria

The review's eligibility criteria, including the specific Population, Intervention, Comparators, Outcomes (PICO) for the clinical research questions can be found in Table 1. The inclusion criteria were informed by the CADTH Rapid Response report,[36] the formal scoping review of the existing literature,[35] and stakeholder engagement.

Table 1: Selection Criteria for Clinical Research Questions

Population	Individuals (of any age and with any associated clinical feature [e.g., those who are pregnant or planning for pregnancy, those with a history of severe hypoglycemia, those with hypoglycemia unawareness]) with type 1 diabetes
Intervention	Medtronic MiniMed 670G, Medtronic MiniMed 780G, Tandem Control-IQ, Omnipod Horizon, or any other commercially available HCLs
Comparator	Any other commercially available HCL(s) or existing insulin delivery method(s) (e.g., sensor-augmented pumps; closed loops [i.e., an artificial pancreas that requires little to no user input for basal or prandial insulin dosing]; open loops [i.e., an insulin pump, with or without continuous glucose monitoring, that requires substantial user input for basal and prandial insulin dosing]; MDII)
Outcomes	**Question 1** • quality of life, general or diabetes-specific, as reported by any standardized tool (e.g., EuroQol 5-Dimensions score, Pediatric Quality of Life Inventory score, Diabetes Quality of Life measure)

	• hemoglobin A1C
	• glucose time-in-range metrics, as measured with continuous glucose monitoring (e.g., proportion of time glucose levels are within 70 mg/dL to 180 mg/dL)[a] • fear of hypoglycemia, as reported by any standardized tool (e.g., Hypoglycemia Fear Survey score) • patient satisfaction, as reported by any standardized tool (e.g., Diabetes Treatment Satisfaction Questionnaire score) • discontinuation rates (e.g., proportion of individuals who discontinue use of the device) **Question 2** Adverse events and complications (e.g., episodes of severe hypoglycemia, diabetic ketoacidosis, number of hypoglycemic events requiring assistance, device-related adverse events, management of hypoglycemic events [e.g., emergency room visits, hospitalizations])
Study designs	Comparative study designs, including: • RCTs • non-RCTs • cohort studies[b] • case-control studies Exclusions: • cross-sectional studies • single-arm before-and-after studies or single-arm interrupted time series studiesc • case reports • case series • review articles • qualitative studies • animal and in vitro studies • guidelines • editorials, letters, and commentaries • studies of any design published as conference abstracts, presentations, or dissertations
Study setting	Any setting
Time frame	2003 to present[d]

HCL = hybrid closed-loop insulin delivery system; MDII = multiple daily insulin injections; RCT = randomized controlled trial, SMBG = self-monitoring of blood glucose.

[a] Time-in-range denotes the proportion of time that an individual's glucose level is within a desired target range. Target ranges are expected to vary between primary studies; all target ranges will be considered relevant for the clinical review.

[b] Cohort studies are defined as studies in which participants are sampled on the basis of exposure and in which outcomes are assessed in a follow-up.[39] This is distinct from case series studies, in which participants are sampled on the basis of the presence of an outcome, or of both an exposure and outcome, where absolute or relative risk cannot be calculated.[39] Only study designs providing comparative evidence are eligible for inclusion.

[c] Single-arm before-and-after studies and single-arm interrupted time series studies will be excluded as they are not controlled with a separate group of patients and therefore are prone to many sources of bias that threaten both internal and external validity.[40]

[d] The year 2003 was selected as it corresponded with a significant change in the clinical guidelines on the diagnosis and management of type 1 diabetes.

For this HTA, the intervention of interest is HCLs in their commercially available (or expected to be commercially available) form. Studies investigating HCLs that are only available in experimental settings and are not on a path to commercialization will not be eligible for inclusion. Eligible study populations will not be restricted by participant sex, gender, ethnicity, or comorbidities.

For the outcomes, all instruments and all time points will be eligible for inclusion. For the safety outcomes for research question 2, data that allow for comparisons between the intervention and comparator groups will be of interest and included (e.g., frequencies or prevalence of adverse events [AEs] reported for each group are in scope, but non-quantifiable and non-comparable lists of AEs for both groups are not in scope).

The review will be limited to studies published in English and French. While there is evidence that suggests excluding non-English publications from evidence synthesis does not change conclusions,[41,42] publications in French will also be included, as CADTH has the capacity for reviewing in both languages.

Exclusion Criteria

Articles will be excluded if they do not meet the selection criteria outlined in Table 1, they are duplicate publications, or are published before 2003. If there are multiple publications fulfilling the inclusion criteria from the same study (i.e., same population), they will all be included, and data will be extracted and discussed as one single study. Studies that investigate an HCL delivery system but do not include an explicit description of the device (e.g., if it is unclear whether the device is the same as the commercially available version) will be excluded. A list of excluded studies, with reasons for exclusion after full-text review, will be provided.

Study Selection

The SR management software DistillerSR (Evidence Partners, Ottawa, Canada) will be used for study selection. Two reviewers will independently screen titles and abstracts of all citations retrieved from the literature search (i.e., academic database and grey literature searches). Full texts articles that are judged to be potentially relevant by at least one reviewer will be retrieved and independently assessed for possible inclusion based on the pre-determined selection outlined in Table 1 (i.e., if one 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 independently examine all full-text articles, and consensus will be required for inclusion in the review. Discrepancies between reviewers will be resolved by discussion between the reviewers or by a third reviewer, if needed. 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 above process.

Studies identified via search alerts meeting the selection criteria of the review will be incorporated into the analysis if they are identified before the end of the stakeholder feedback period of the review. Any studies that are identified after the stakeholder feedback period will be described in the discussion, with a focus on comparing the results of these new studies with the results of the analysis conducted for this report. While single-arm before-and-after studies and single-arm interrupted time series studies will not be eligible for inclusion in this SR of comparative evidence, any unique evidence provided by such studies will be described in the discussion.

The study selection process will be presented in a PRISMA[43] flow chart.

Data Extraction

Data extraction will be performed by one reviewer and independently checked for accuracy by a second reviewer. The second reviewer will also check for any relevant data that might have been missed by the first reviewer to ensure all relevant data from each included study are extracted. Disagreements will be resolved through discussion until consensus is reached or through adjudication by a third reviewer, if necessary. Data will be extracted directly into tables created in Microsoft Word, which will be developed, piloted, and modified, as necessary. Relevant information will be extracted, including the following:

- study characteristics (e.g., first author's name, publication year, country where the study was conducted, funding sources) and methodology (e.g., study design and objectives, inclusion and exclusion criteria, recruitment method, setting)
- population (e.g., number of participants, age, sex, gender, baseline characteristics [e.g., body mass index, diabetes duration, pregnant or planning for pregnancy, history of severe hypoglycemia, hypoglycemia unawareness])
- intervention (e.g., type of HCL, a description of any pertinent device settings or modifications)
- comparator (e.g., type of insulin delivery system or method)
- outcome (e.g., measurement method, unit of measurement, length of follow-up) and results and conclusions regarding the outcomes and subgroups of interest

Data will be extracted for all relevant outcomes for this study at any duration of follow-up. Measures of treatment effects (e.g., risk ratios, odds ratios, or risk differences for dichotomous outcomes, mean differences or standardized mean differences for continuous outcomes, and hazard ratios for survival outcomes), any results of statistical tests reported on those measures, and whether fixed-effects or random-effects models were used will be extracted.

If relevant data are missing from or conflicting in the included studies, attempts will be made to contact the corresponding authors of these studies to obtain missing information or to clarify conflicting information. Relevant data will be deemed missing if numerical data supporting qualitative statements or findings presented in figures are absent, and authors will be contacted if those data are needed for a meta-analysis (MA). 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, and authors will be contacted. If no response is received from study authors to a request for clarification of discrepant data reporting, all results will be reported in the HTA; for numerical data, the most conservative value will be used for conflicting data, if needed (e.g., in an MA). If no response is received from study authors to a request for numerical data related to findings presented in a figure, the best numerical estimate based on the figure will be used, if needed.

Critical Appraisal

The risk of bias for included studies will be systematically evaluated using Version 2 of the Cochrane Risk of Bias tool (RoB 2)[44] for RCTs and the Risk of Bias for Non-randomized Studies (RoBANS)[45] for non-randomized studies.[46] The RoB 2 tool[44] allows for the assessment of five sources of bias or "domains" (bias arising from the randomization process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result). Each question will be answered with a yes, probably yes, probably no, no, or no information. For each domain, a judgment of low risk of bias, high risk of bias, or some concerns will be assigned, with rationale for each decision included in the comments box field. Based on judgments across the five domains, an overall risk of bias will be assigned to each study (low, high, or some concerns).[44] The RoBANS tool, which was selected for its reliability, validity, and user-friendly design,[45] also allows for the assessment of risk of bias across eight domains (the possibility of the target group comparisons, target group selection, confounder, exposure measurement, blinding of assessors, outcome assessment, incomplete outcome data, and selective outcome reporting). For each item, a judgment of low, high, or unclear will be assigned with rationale for each decision included in the comments box field.

The risk of bias assessments of the included studies will be performed by one reviewer and independently checked for accuracy by a second reviewer. Disagreements will be resolved through discussion, involving a third reviewer if necessary. The tools will be used as a guide to evaluate the risk of bias in the included studies, and additional insight beyond the items on the instruments will be provided, when applicable. Summary scores will not be calculated; rather, a review of the strengths and limitations of each included study and how they affect the study findings will be described narratively. The results of the critical appraisal will be used to assess confidence in the results. Results of the quality assessment will not be used to exclude studies from this review.

Data Analysis and Synthesis

Narrative Synthesis

Narrative syntheses will be performed, including the presentation of study characteristics and findings within summary tables and in the main text. Findings will be summarized within and across studies (by comparator), including the direction and magnitude of any observed effects, trends, and deviations, and an assessment of the likelihood of clinical benefit (i.e., clinical effectiveness) or harm (i.e., safety). Data from different populations or different time points will not be combined but rather described separately.

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, along with a narrative description of the strengths and limitations of the included studies within the main text of the report to provide the reader with an overview of the quality of the literature.

Quantitative Synthesis

In addition to narrative syntheses, meta-analyses will be conducted, where the results of eligible studies will be pooled, if data are sufficiently homogeneous in terms of clinical, methodological, and statistical characteristics. Because heterogeneity is expected between trials, any MA conducted will use a random-effects model. Any studies that are deemed inappropriate for pooling because of heterogeneity will be summarized narratively only.

An MA will be conducted for each outcome of interest (e.g., quality of life, risk for hypoglycemic events, risk for other AEs, fear of hypoglycemia, patient satisfaction) that is examined across multiple sufficiently homogenous studies. Separate MAs will be conducted between randomized and non-randomized studies (i.e., results from randomized and non-randomized studies will not be pooled).

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 to allow for comparisons across studies. Continuous data will be analyzed using either mean differences or standardized mean differences. Mean differences will be used for outcomes where all studies used the same outcome measure; standardized mean differences will be applied in instances where different outcome measures were used to assess the same outcome. If adjusted effects measures are reported, the adjusted results will be used in the primary analysis, and differences between unadjusted and adjusted results will be discussed.

Statistical heterogeneity will be assessed using graphical presentations (e.g., forest plots) and calculations of Cochrane's Chi^2 test and the I^2 statistic, which quantifies the variability in the effect estimates because of heterogeneity rather than chance (i.e., sampling error). Heterogeneity will be interpreted with the guidance from Higgins and colleagues,[47] which assigns adjectives of low, moderate, and high to I^2 values of 25%, 50%, and 75%, respectively. Heterogeneity will be interpreted with true P values.

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.[48]

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

Subgroup Analyses

Based on the results of preliminary scoping, the benefit or harm of HCLs is likely to depend upon user characteristics. We have identified the following potential subgroups to explore in narrative syntheses and meta-analyses, as the data permit:

- age (e.g., children, adolescents, adults, elderly)
- sex and gender (e.g., female versus male, woman versus men)
- glycemic control (e.g., hemoglobin A1C of ≤ 7% versus > 7 %)
- associated clinical features (e.g., pregnant or planning for pregnancy, history of severe hypoglycemia, hypoglycemia unawareness).

Reporting of Findings

The SR will be prepared in consideration of relevant reporting guidelines (e.g., PRISMA statement,[49] PRISMA harms,[50] Meta-analysis of Observational Studies in Epidemiology [MOOSE] reporting checklist,[51] Synthesis Without Meta-analysis [SWiM] guideline,[52] and will meet the criteria outlined in A Measurement Tool to Assess Systematic Reviews 2 [AMSTAR 2] checklist).[53]

Perspectives and Experiences Review

This portion of the HTA will review the perspectives and experiences of people living with type 1 diabetes and those involved in their care (e.g., health care providers, family members, and friends). This review will be guided by the following research question:

- How do people living with type 1 diabetes, or those involved in their care, describe their expectations of HCLs and how have their experiences engaging with HCLs been reflective of their expectations?

This question will be further supported through an exploration of the following topics:

- How do people living with type 1 diabetes, or those involved in their care, envision HCLs as contributing to type 1 diabetes management?
- How might expectations of and experiences with HCLs differ across various people (e.g., young children, parents, elderly) engaging with these systems?
- For people living with type 1 diabetes who have built their own HCLs (or DIY artificial pancreas) by "hacking" an insulin pump to communicate with their CGM via a computer program, what motivated them to begin and how does the emergence of commercial HCL influence their motivations?

Study Design

An adapted thematic synthesis[54] of primary qualitative research inquiring into the expectations and experiences of those interacting with HCLs will be conducted. The primary goal of this analysis is to describe and examine the ways in which people living with a diagnosis of type 1 diabetes engage with their condition and subsequently navigate the health care spaces in which they are situated. While particular attention will be paid to interactions with commercially produced HCLs as the focus of this HTA, given the growth and development of DIY systems among type 1 diabetes communities, interactions with DIY systems will also be included. Other interventions relevant to the inquiry may be included as a means of providing more depth to the analysis (e.g., insulin pumps, CGMs, flash glucose monitors).

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

Literature Search Methods

The search for literature exploring perspectives and experiences will be performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[37] The preliminary search strategy is presented in Appendix 2.

Published literature will be identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO, and Scopus. 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 closed-loop systems and diabetes.
Search filters will be applied to limit retrieval to qualitative studies. Retrieval will not be limited by publication date but will be limited to the English language.

The initial search will be completed in March 2020. Regular alerts will update the search until the publication of the final report.

Grey literature (literature that is not commercially published) will be identified by searching sources listed in relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters),[38] 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. The grey literature search will be updated before the completion of the stakeholder feedback period. These searches will be supplemented by reviewing bibliographies of key papers and through contacts with experts and industry, as appropriate.

Selection and Eligibility Criteria

Eligible studies will be primary English-language qualitative studies. For the purpose of this review, qualitative studies are studies that use qualitative data collection methods (e.g., document analysis, interviews, or participant observation) and qualitative data analysis methods (e.g., constant comparative method, content analysis). Studies that have multiple publications using the same data set will be included if they report on distinct research questions. Duplicate publications using the same data with the same findings will be excluded and detailed in an additional reference list as an Appendix to the HTA. Table 2 describes the eligibility criteria to be used, built using the Sample, Phenomenon of Interest, Design, Evaluation, Research (SPIDER) criteria for framing qualitative evidence synthesis research questions.[55]

Qualitative research can be difficult to find due to inconsistency in indexing terms and the challenges in retrieving qualitative studies using validated search filters.[56] In addition to the methods described above, the literature search may be modified and re-run depending on the set of studies that meet the inclusion criteria. During the completion of full-text review of eligible studies, the review team may conclude that the initial search did not include a term or concept seen in the literature that is relevant for inclusion, or that the number of included studies is likely to be small (e.g., < 20 studies). While it is possible to describe the results from a small set of studies, it is difficult to reorder and reimagine the perceptions, experiences, expectations, and themes reported to produce de novo analyses. In this case, the search may be redefined to either broaden it (e.g., include insulin pumps, CGMs, and flash glucose monitors) or capture additional experiences or constructs of interest (e.g.,

living with type 1 diabetes generally). Should the team determine that it is necessary to expand the literature search to capture an additional set of studies this decision will be made by consensus by the qualitative review team and will be documented.

Table 2: Eligibility Criteria

Sample	People of any age who are living with type 1 diabetes; people involved in the care of those living with type 1 diabetes (e.g., family, friends, health care providers).
Phenomena of interest	From initial search: How living with a diagnosis of type 1 diabetes is understood and experienced; experiences with and expectations of engaging with HCLs (commercial or DIY) for people living with type 1 diabetes; how HCLs are imagined as fitting with the potentially diverse conceptualizations of appropriately managed type 1 diabetes and type 1 diabetes care; experiences providing care through HCLs to persons living with type 1 diabetes or engaging with patients use of DIY systems. Should we need to broaden our search: experiences with and expectations of other type 1 diabetes technologies (e.g., insulin pumps, CGMs, flash glucose monitors) for persons living with type 1 diabetes; how these technologies (e.g., HCLs, CGMs, insulin pumps, flash glucose monitors) are imagined as fitting with the potentially diverse conceptualizations of appropriately managed type 1 diabetes and type 1 diabetes care.
Design	Qualitative studies of any design (e.g., phenomenology, grounded theory, qualitative description)
Evaluation	Expectations, experiences, understandings, social relations, and perspectives of people living with type 1 diabetes and of those involved in their care.
Research type	Primary qualitative studies using qualitative methods for both data collection (e.g., interviews, focus groups, participant observation) and data analysis (e.g., thematic analysis, discourse analysis, framework analysis).

HCL = hybrid closed-loop system; CGM = continuous glucose monitor; DIY = do-it-yourself.

Screening and Selecting Studies for Inclusion

Title and abstract screening will be conducted independently by two reviewers (both Qualitative Research Officers) in DistillerSR,[57] according to the predefined eligibility criteria (Table 2). The tags function in DistillerSR will be used to help screen references and sort them into categories (e.g., technology being used, types of participants included). In addition, as titles and abstracts are reviewed, notes on the topics, emphases, and populations of the articles will be kept to develop an understanding of the types of information present in the data set.

The full texts of all citations that appear eligible for inclusion and for which it is difficult to determine eligibility on the basis of title and abstract alone will be retrieved and assessed by each reviewer before determining eligibility. Disagreements regarding eligibility will be resolved through discussion until consensus is reached.

At this stage, the two reviewers will review the set of included studies and discuss whether the final set includes sufficient data to answer the initial research question or if there is a need to modify the literature search and selection criteria. Relatedly, reflection on the potential need to refine the primary and secondary research questions will occur to determine whether they are the most appropriate to address the decision problem. This iterative refinement is typical of many qualitative approaches, and requires familiarity with the data set obtained through screening and selecting studies.[58] Building on the categories created and notes taken during screening, the reviewers will reflect and consider whether the research question could be refined to optimize the strengths of the available data. Throughout the process, the decision problem will remain the primary driver of the research question. The primary author will document the evolution of the research question and search strategy. Study selection will be documented using a PRISMA flow chart.[43]

Study Detail and Participant Data Extraction

Descriptive characteristics about the studies, including the country and funding of the research team, the description of participants, the research methods used, and the research question(s) will be extracted into structured forms in Word by one reviewer. Extracted data will be verified by a second reviewer.

Critical Appraisal

Critical appraisal will be used as a way of remaining attuned to both the rigour and relevance of included studies. As critique and analysis are often co-constitutive in qualitative research, this streamlined appraisal is consistent with disciplinary norms in which understanding aspects such as how data are collected or where data sources are situated in relation to the researcher represent more than methodological considerations. In this review, critical appraisal will follow Krefting's[59] interpretation of Lincoln and Guba's[60] model for assessing trustworthiness in qualitative research. Krefting's emphasis on and mode of exploring trustworthiness[59] asks the reviewer to consider the interactions between research methods and results as a way of evaluating the process involved in arriving at a certain result or conclusion. This is done with a particular focus on three guiding questions: Is it credible? Is it trustworthy? Are the results transferable?[59] The 10 items of the Critical Appraisal Skills Program Qualitative Checklist[61] will be used as prompts to engage with questions of credibility, trustworthiness, and transferability.

The primary reviewer will conduct the appraisal. The second reviewer will probe the primary reviewer's assessment of the literature on key issues around credibility, trustworthiness and dependability, and transferability through conversation and a review of the Table of Quality Appraisal. Disagreements on the appraisal will be resolved through discussion. Results of the critical appraisal will not be used to exclude studies from this review; rather, they will be used to understand the methodological and conceptual limitations of the included publications in specific relation to the decision problems and research questions. A narrative summary of the credibility, trustworthiness, and transferability of the included studies will be presented in the final review and accompanied by a Table of Quality Appraisal.

Data Analysis and Synthesis

To begin, a descriptive analysis of study characteristics will be conducted. These will be presented in tabular form in the final report accompanied by a narrative summary. The purpose of this analysis is to describe the set of included studies and understand the range of study designs and methods that will inform the resulting synthesis.

Drawing on the tenants of thematic synthesis[54] and grounded theory,[62] the synthesis will follow an iteratively staged process that includes several close readings of eligible studies, note making, descriptive and analytic memoing, and the construction of a synthetic analysis. The intent of the synthetic analysis will be to elucidate how some people living with type 1 diabetes, or those involved in their care, experience engaging with HCLs, and how their experiences align with their expectations. The constant comparison method will be adapted to include comparing notes or memos within and across studies. The synthesis will be conducted by one primary reviewer who is supported by a secondary reviewer.

The primary reviewer will begin by reading and rereading eligible studies multiple times while making marginal notes and memos (in Word) to reflect preliminary thoughts, impressions, and insights. While many of the notes will be descriptive and refer directly to the content of a single line or paragraph, others may act as critique and draw upon various

study components (e.g., design or method, positioning of study authors, commentary in the discussion section) to be used as part of critical appraisal. The reviewer will code the data by underlining and bracketing lines or sections that seem particularly salient. Similar to the inductive logics of line-by-line and descriptive coding, this process will allow the reviewer to begin making connections throughout the empirical data found across the body of eligible studies.

These connections will form the basis of an outline of descriptive themes in Word and brought to the second reviewer for discussion. The purpose of this discussion is threefold in that it will provide reviewers the opportunity to:

- determine where multiple themes may be pointing toward similar, broader constructs or themes
- reflect on the intent of this review and how emergent themes may respond to both this section's research question as well as the broader HTA's decision problem
- explicitly engage in the methodological practice of reflexivity as they turn their focus toward navigating how emergent themes articulate notions of what is at stake for people who are living with, or caring for others living with, type 1 diabetes when engaging with HCLs (e.g., expectations regarding things like management and care).

The outcome of this discussion will be a refined outline of descriptive findings and their connections that will serve as a skeleton for orienting and framing the synthetic analysis. Memos of this discussion will also be produced and used by the primary reviewer as a tool for future reflection. These outcomes will also be shared with the Patient Engagement Officer as well as authors of the ethics and implementation portions of this HTA to spur discussion and invite reflection regarding potential overlap across sections.

At this stage the primary reviewer will formally turn toward the construction of a synthetic analysis, though it is still possible that new descriptive themes may emerge from the literature. If so, the second reviewer will be consulted and both will co-determine how best to work in this new theme to the outline. Nonetheless, drawing on the primary reviewer's growing familiarity with the data set as built through (ongoing) iterative readings, successive layers of marginal notes, outline development, and the discussions detailed above, the descriptive and analytic practice of memoing will be used as a way of identifying links across descriptive themes and this section's questions. As alluded to in point three above, the goal of this practice will be to describe how these relations articulate notions of what is at stake for people who are living with, or caring for people living with, type 1 diabetes when engaging with HCLs. The second reviewer will be engaged throughout this process by reading written memos and will remain in regular conversation with the primary reviewer. Their role will be to probe for gaps in the primary reviewer's thoughts (as represented in memos and discussion) and to remain attuned to the purpose of the review and direction of the research questions. These memos will form the basis of the synthetic analysis and will be incorporated with the descriptive themes at the time of writing.

Reflexivity

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 means to seek greater transparency in how researchers make observations and interpretations from the data. To this end, reflexive practices of memoing and frequent dialogue among team members will be done to probe and position the reviewer in relation to the analysis.

Ethics Review

The purpose of this analysis is to identify and reflect upon key ethical concerns when considering HCLs for people with type 1 diabetes. Though other sections of this HTA will 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 sets of questions to consider when employing HCLs for managing type 1 diabetes:

- What are the major ethical issues raised by the use of HCLs compared with existing technologies for managing type 1 diabetes?
- How might these issues be addressed?

These questions can be considered as matters of systems-level (or population-level) ethics, which examines decisions that will affect large numbers of people, and in which outcomes and interests are considered in aggregate (organizational ethics, policy ethics, and public health ethics are all domains of systems-level ethics). For systems-level ethics, instead of asking “Does this technology benefit the patient?” or “Does this technology disadvantage a vulnerable individual?” we ask, Does this technology create overall benefit with minimized and proportional harms for the population?” and “Does this technology disadvantage marginalized groups?”

These questions can also be considered at the individual level, invoking individualist considerations that are typically concerns of clinical ethics (rather than systems-level ethics). Within a clinical ethics paradigm, the ethics analysis considers matters of respect for persons, autonomy, dignity, harms/benefits, and fairness, from an individual perspective. These considerations inform recommendations for whether and how a technology can be implemented and delivered in a way that aligns with these key values and principles.

Inquiry

Bioethical analysis requires a two-step approach to identifying 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 technologies for

managing type 1 diabetes. By this approach, we identify and assess the relative importance and strength of the identified concerns and proposed solutions, identify and assess issues that have not yet come to the attention of the ethics researchers, 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 patient perspectives, clinical utilities, economic analyses, environmental impacts, and implementation considerations. As such, the ethical review involves an iterative process whereby the analysis is responsive to results emerging from the clinical review and the Perspectives and Experiences Review.

Based on what is already known about HCLs for treating type 1 diabetes, it is anticipated that the ethics inquiry will at least explore the extent to which the technology may:

- pose risks to, or incursions on patients' privacy and confidentiality, specifically to do with how health data gathered by the technology will be owned, stored, transmitted, and accessed
- limit or affect a patient's capacity to exercise their autonomy, particularly if the technology includes ongoing monitoring and surveillance
- provide meaningful benefit, including measurable improvements in health outcomes (e.g., reduced hospitalizations/ complications, improvements in physical function) as assessed by primary care providers or medical specialists; and improvements to the quality of life of those using HCLs, as assessed by those users
- raise concerns regarding justice in the health care systems, particularly to do with how HCLs may be accessed and funded, and whether funding HCLs would result in disinvestment in other technologies to treat type 1 diabetes
- pose particular risks to more vulnerable populations including children and those in marginalized or underserved communities
- elicit tensions or inconsistencies between the interests of industry and those of the health system, particularly if the technology is being heavily marketed directly to patients and physicians.

Perspectives

The relevant perspectives that need to be considered in identifying and addressing the ethical issues associated with HCLs for treatment of type 1 diabetes include patients, family members, or informal caregivers, patient organizations, health care providers, and health care insurers.

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 HCLs. We will search primarily for articles, studies, reports that explicitly and specifically raise ethical issues related to the use of technologies for type 1 diabetes management. This search will focus on the use of HCLs but may also include literature on the ethics dimensions of other diabetes management technologies (e.g., CGMs). If this initial search fails to yield sufficiently detailed or comprehensive resources, literature which implicitly points to ethical issues may also be included.

Literature Search Methods

The search for literature identifying explicit ethical considerations will be performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[37] The search strategy is available on request.

Published literature will be identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid and the CINAHL via EBSCO. 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 closed-loop systems and type 1 diabetes.

Search filters will be applied to limit retrieval to citations related to empirical and normative ethical considerations. Retrieval will not be limited by publication date, but will be limited to the English language. The initial search will be completed in March 2020. Regular alerts will update the search until the publication of the final report.

Grey literature (literature that is not commercially published) will be identified by searching sources listed in relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters),[38] 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. The grey literature search will be updated before the completion of the stakeholder feedback period. These searches will be supplemented by reviewing bibliographies of key papers and through contacts with experts and industry, as appropriate. See Appendix 2 for more information on the grey literature search strategy.

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 independently by a single reviewer. Articles will be categorized as "retrieve" or "do not retrieve," according to whether the article provides normative analysis of an ethical issue arising in the use of HCLs or related technology for type 1 diabetes management.

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, while 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. Despite the different standards of normative argumentation for each kind of report, the importance of the issues raised cannot be assessed solely by these standards and so literature cannot be excluded based on methodological standards.

In the second stage, the full-text reports will be reviewed by a single reviewer with ethics expertise. Reports meeting the above 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 attending to the possibility of the neglect of marginalized and vulnerable populations. The specific values of health care and health care policy used in this analysis will be drawn from the literature and may be supplemented by current knowledge of the health system.

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 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 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.

Summarizing and Presenting Results

The reporting of ethical issues will be organized according to the five domains outlined in Quintal et al.'s (2018)[63] review and analysis of ethical issues associated with HCLs. These are Confidentiality and Safety; Coverage; Patient Selection; Patient Coaching and Support; and Personal Identity and Agency. Each domain is comprised of subdomains that examine core ethical issues more closely. These domains may be modified or supplemented, depending on the results of the ethics analysis. Where the report undertakes an analysis that is not derived from the peer-reviewed literature, this will be noted.

Ethical analysis assists in social and policy decision-making but is not itself the site of legitimate social decision-making, which requires the 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.

Stakeholder Consultations

To gain a better understanding of the context and relevant issues of implementing HCLs in Canada, and to help inform the decision problem, we will consult with stakeholders representing various levels of decision-making and health care delivery in type 1 diabetes care.

In conjunction with the research team (a policy and program analyst and qualitative research officer), CADTH's Implementation Support and Knowledge Mobilization team will identify potential stakeholders through existing CADTH networks and other relevant national or provincial stakeholder groups using an operational construct, a purposive sampling strategy emerging in relation to the findings of this HTA's varied sections. Potential participants will include, but will not be limited to, policy-makers (e.g., those at the ministry level), clinicians (e.g., endocrinologists, primary care providers, and diabetes educators), researchers, private insurance providers, and health systems managers. The aim is to continue with stakeholder consultations until no new information is emerging (data saturation); however, sample size may also be limited because of time and resource constraints.

The consultations will be facilitated by two CADTH staff members (a knowledge mobilization officer and a policy and program analyst) and a semi-structured interview questionnaire will be used to guide the discussions with the stakeholders on the context and implementation of HCLs for type 1 diabetes in Canada. Depending on which stakeholder we are speaking with, questions will touch on areas such as, but not limited to, how insulin pumps are currently used in the stakeholder's jurisdiction, what sort of conversations are currently surrounding the use of HCLs (e.g., expected uptake, populations of interest, differences from insulin pump programs), and, what are the considerations if HCLs are to be publicly funded under existing public insulin pump programs (e.g., costs, educational, or resourcing needs)? The consultation sessions will be recorded, with consent.

Stakeholder consultations will be used as a tool for reflecting on connections across the HTA and how these might be pieced together to inform decisions regarding the implementation of HCLs for type 1 diabetes. Put otherwise, consultations will help to provide insight regarding the ways in which our HTA findings could be taken up across jurisdictions and the kinds of questions stakeholders may be navigating when deliberating how HCLs fit within their current models of care for type 1 diabetes. While there will be no independent summary of these consultations, they will be informative as we write the Discussion and Considerations section for this HTA.

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

Knowledge Mobilization

Knowledge mobilization activities will include relevant educational outreach and related activities to increase the demand and use of the HTA. This includes supporting the implementation of any resulting decisions or changes to the health care system or health service delivery. Efforts will also be made to ensure CADTH activities and products meet the needs of key stakeholders, such as jurisdictional bodies, health care providers, HCL users, and other users of health evidence. Implementation issues identified in the report will help guide some of the knowledge mobilization activities.

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 data is in the public domain.

Patient Engagement

CADTH involves patients, families, and patient groups to improve the quality and relevance of our assessments, ensuring that those affected by the assessments have an opportunity to contribute to them. CADTH has adopted a Framework for Patient Engagement in HTA. The framework includes Standards for Patient Involvement in Individual HTAs and is used to support and guide our activities involving patients. For this HTA, the value of relevance and the belief that patients have knowledge, perspectives, and experiences that are unique and contribute to essential evidence for HTA will guide our patient engagement activities. CADTH will engage up to three adults with experience of using an HCL for their type 1 diabetes.

Invitation to Participate and Consent

Potential participants will be identified through Diabetes Canada. A CADTH Patient Engagement Officer will contact potential participants by phone to explore their interest to become involved. The preliminary request will include the purpose and scope of this HTA, the purpose of engagement, and the nature of engagement activities. The Patient Engagement Officer will obtain the person's informed consent to share their information and comments with CADTH staff.

Engagement Activities

Patients will be asked to reflect on their own personal experiences at several time points during assessment including:

- before protocol finalization
- during drafting of the initial reviews
- upon completion of final report.

Patients' perspectives gained through engagement processes will be used in several ways, including ensuring relevance of outcomes of interest for the clinical assessment, commenting on themes emerging from the patients' experiences and perspectives and implementation reviews and commenting on other key concepts that were initially identified through prior scoping activities. The involvement of patients will enable the research team to consider the evidence alongside an understanding of the wider experiences of patients and caregivers. Patients may provide valuable feedback on the clarity of writing and comment on the relevance of the findings to Canadian patients and families.

Once preliminary findings are available, the participant will be invited to a discussion with the researchers. The conversation will explore the participant's perceptions of key findings, including if the findings are understandable, and if they reflect personal experiences or understandings. This conversation 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 the use of HCLs and the context of analysis.

Final conversations will be had with the participant upon completion of the final report. Through conversation, CADTH will share the key results of the full assessment and describe how engagement activities were used.

Reporting

The reporting of this section will follow the GRIPP2 Short Form reporting checklist,[64] and include the outcomes, discussion and reflection items as suggested by that guidance 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. CADTH will provide reflections and critical perspectives on the experience of the involvement for the patient and the research team in the final report.

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.

Protocol addendum reporting the methods to an additional budget impact analysis may also be completed at a later time after consideration of preliminary clinical results and stakeholder consultation. Updates to the PROSPERO submissions will be made accordingly (PROSPERO registration number CRD42020193156 [Clinical Review] and CRD42020192057 [Perspectives and Experiences Review]).

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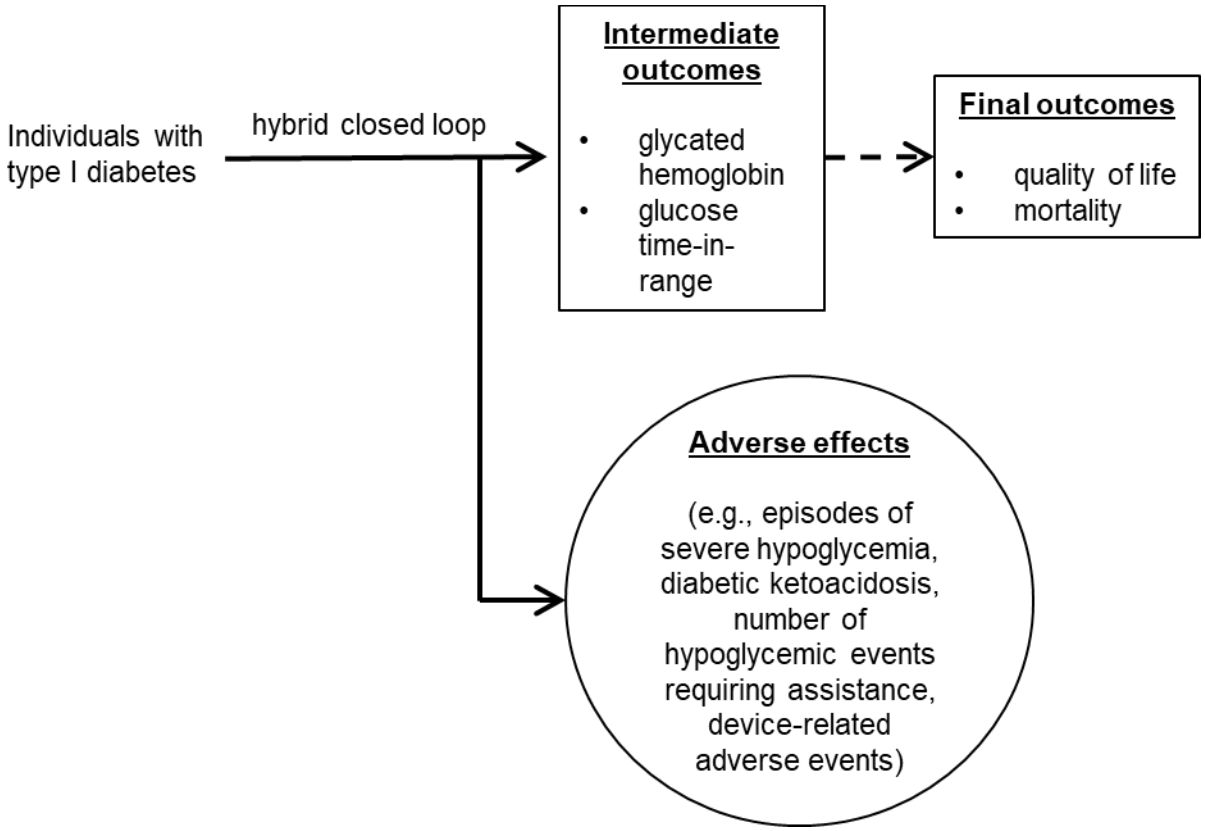
Appendix 1: Analytic Framework



Appendix 2: 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) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 2020
Alerts:	Monthly search updates until project completion
Study Types:	No filters applied to limit by study type
Limits:	Publication date limit: 2003 to present Language limit: English- and French-language Conference abstracts: Excluded

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; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.dq	Candidate term word (Embase)
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase); keyword (CENTRAL)
.dv	Device trade name (Embase)
.dm	Device manufacturer (Embase)
.pt	Publication type
.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

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
1	Diabetes Mellitus, Type 1/
2	(T1D or T1DM or type 1 DM or DM 1 or DM1 or IDDM).ti,ab,kf,kw.
3	(Diabet* and (type 1 or type one or type I or juvenile)).ti,ab,kf,kw.
4	(Diabet* adj2 (insulin dependent or insulin requiring or autoimmune or auto immune or brittle or labile)).ti,ab,kf,kw.
5	1 or 2 or 3 or 4
6	(closedloop* or closed loop*).ti,ab,kf,kw.
7	(670G* or 670 G* or ControlIQ or Control IQ or BasalIQ or Basal IQ or tslim* or t slim* or (omnipod* and horizon*) or (ilet* and pancreas*)).ti,ab,kf,kw.
8	((hybrid or smart or automat*) adj5 insulin adj5 (system* or delivery or dosing or device* or infusion*)).ti,ab,kf,kw.
9	(predictive adj2 low glucose adj2 suspen*).ti,ab,kf,kw.
10	Pancreas, Artificial/
11	((artificial or robotic or bionic) adj2 pancreas*).ti,ab,kf,kw.
12	(looping or looper* or OpenAPS* or Tidepool* or DIYpancreas or wearenotwaiting or Nightscout).ti,ab,kf,kw.
13	(loop* adj3 (DIY or do it yourself or hack*)).ti,ab,kf,kw.
14	or/6-13
15	5 and 14
16	15 use cctr
17	limit 15 to (english or french)
18	17 use medal
19	16 or 18
20	exp insulin dependent diabetes mellitus/
21	(T1D or T1DM or type 1 DM or DM 1 or DM1 or IDDM).ti,ab,dq,kw.
22	(Diabet* and (type 1 or type one or type I or juvenile)).ti,ab,dq,kw.
23	(Diabet* adj2 (insulin dependent or insulin requiring or autoimmune or auto immune or brittle or labile)).ti,ab,dq,kw.
24	20 or 21 or 22 or 23
25	(closedloop* or closed loop*).ti,ab,dq,kw,dv,dm.
26	(670G* or 670 G* or ControlIQ or Control IQ or BasalIQ or Basal IQ or tslim* or t slim* or (omnipod* and horizon*) or (ilet* and pancreas*)).ti,ab,dq,kw,dv,dm.
27	((hybrid or smart or automat*) adj5 insulin adj5 (system* or delivery or dosing or device* or infusion*)).ti,ab,dq,kw.
28	(predictive adj2 low glucose adj2 suspen*).ti,ab,dq,kw.
29	artificial pancreas/
30	((artificial or robotic or bionic) adj2 pancreas*).ti,ab,dq,kw.
31	(looping or looper* or OpenAPS* or Tidepool* or DIYpancreas or wearenotwaiting or Nightscout).ti,ab,dq,kw.

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
32	(loop* adj3 (DIY or do it yourself or hack*)).ti,ab,dq,kw.
33	or/25-32
34	24 and 33
35	34 not conference abstract.pt.
36	limit 35 to (english or french)
37	36 use oemezd
38	19 or 37
39	limit 38 to yr="2003 -Current"
40	remove duplicates from 39

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials. [Search terms — closed-loop systems, type 1 diabetes]	
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. [Search terms -- closed-loop systems, type 1 diabetes]	

Patients' Preferences and Experiences Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946 to present)
Date of Search:	March 2020
Alerts:	Monthly search updates until project completion
Study Types:	Qualitative studies
Limits:	Language limit: 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; 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
.jw	Journal word title

DATABASE STRATEGY

Line #	Search Strategy
1	exp Diabetes Mellitus/
2	(T1D or T1DM or type 1 DM or DM 1 or DM1 or IDDM).ti,ab,kf.
3	diabet*.ti,ab,kf,jw.
4	insulin.ti,kf.
5	1 or 2 or 3 or 4
6	(closedloop* or closed loop*).ti,ab,kf.
7	(670G* or 670 G* or ControlIQ or Control IQ or BasalIQ or Basal IQ or tslim* or t slim* or (omnipod* and horizon*) or (ilet* and pancreas*)).ti,ab,kf.
8	((hybrid or smart or automat*) adj5 insulin adj5 (system* or delivery or dosing or device* or infusion*)).ti,ab,kf.
9	(predictive adj2 low glucose adj2 suspen*).ti,ab,kf.
10	Pancreas, Artificial/
11	((artificial or robotic or bionic) adj2 pancreas*).ti,ab,kf.
12	(looping or looper* or OpenAPS* or Tidepool* or DIYpancreas or wearenotwaiting or Nightscout).ti,ab,kf.
13	(loop* adj3 (DIY or do it yourself or hack*)).ti,ab,kf.
14	or/6-13

DATABASE STRATEGY	
Line #	**Search Strategy**
15	5 and 14
16	exp Empirical Research/ or Interview/ or Interviews as Topic/ or Personal Narratives/ or Focus Groups/ or exp Narration/ or Nursing Methodology Research/ or Narrative Medicine/
17	Interview/
18	interview*.ti,ab,kf.
19	qualitative.ti,ab,kf,jw.
20	(theme* or thematic).ti,ab,kf.
21	ethnological research.ti,ab,kf.
22	ethnograph*.ti,ab,kf.
23	ethnomedicine.ti,ab,kf.
24	ethnonursing.ti,ab,kf.
25	phenomenol*.ti,ab,kf.
26	(grounded adj (theor* or study or studies or research or analys?s)).ti,ab,kf.
27	life stor*.ti,ab,kf.
28	(emic or etic or hermeneutic* or heuristic* or semiotic*).ti,ab,kf.
29	(data adj1 saturat$).ti,ab,kf.
30	participant observ*.ti,ab,kf.
31	(social construct* or postmodern* or post-structural* or post structural* or poststructural* or post modern* or post-modern*).ti,ab,kf.
32	(action research or cooperative inquir* or co operative inquir* or co-operative inquir*).ti,ab,kf.
33	(humanistic or existential or experiential or paradigm*).ti,ab,kf.
34	(field adj (study or studies or research or work)).ti,ab,kf.
35	(human science or social science).ti,ab,kf.
36	biographical method.ti,ab,kf.
37	theoretical sampl*.ti,ab,kf.
38	((purpos* adj4 sampl*) or (focus adj group*)).ti,ab,kf.
39	(open-ended or narrative* or textual or texts or semi-structured).ti,ab,kf.
40	(life world* or life-world* or conversation analys?s or personal experience* or theoretical saturation).ti,ab,kf.
41	((lived or life) adj experience*).ti,ab,kf.
42	cluster sampl*.ti,ab,kf.
43	observational method*.ti,ab,kf.
44	content analysis.ti,ab,kf.
45	(constant adj (comparative or comparison)).ti,ab,kf.
46	((discourse* or discurs*) adj3 analys?s).ti,ab,kf.
47	(heidegger* or colaizzi* or spiegelberg* or merleau* or husserl* or foucault* or ricoeur or glaser*).ti,ab,kf.
48	(van adj manen*).ti,ab,kf.

DATABASE STRATEGY	
Line #	**Search Strategy**
49	(van adj kaam*).ti,ab,kf.
50	(corbin* adj2 strauss*).ti,ab,kf.
51	or/16-50
52	15 and 51

OTHER DATABASES		
Scopus	Same keywords and limits used as per MEDLINE search. Syntax adjusted for Scopus platform.	
CINAHL	Same MeSH, keywords, and limits used as per MEDLINE search. Syntax adjusted for EBSCO platform, including the addition of CINAHL headings.	

Grey Literature

Dates for Search:	March 2020
Keywords:	[closed-loop systems, type 1 diabetes]
Limits:	Publication years: 2003 to present

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) will be searched:

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