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CADTH SCOPING BRIEF

Hybrid Closed-Loop Insulin Delivery Systems for People with Type 1 Diabetes

CADTH

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

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Current Considerations

Hybrid closed-loop insulin delivery systems (HCLs) are an emerging technology for the management of people living with type 1 diabetes. One HCL was approved by Health Canada for people with type 1 diabetes in 2018.[1] A second HCL[2] (which is compatible with components already approved by Health Canada[3,4]) was approved by the US FDA in December 2019.[5] The expected availability of this second HCL in Canada is currently unknown. Additional HCLs are anticipated to be available in Canada by 2021.[6] As a new and emerging technology, HCLs are addressed briefly in the most recent guidance from Diabetes Canada.[7,8] The guidelines address the role of HCLs' components — insulin pumps and continuous glucose monitoring (CGM) — in the care of people with type 1 diabetes.[7,9,10]

This topic originated as a request from two jurisdictions for information to support decision-making about extending funding of insulin pumps to people older than 25 with type 1 diabetes. Citing a rapidly evolving field, the requestors indicated that work to support decision-making about new and emerging technologies, such as an HCL, to manage diabetes would be of interest. Feedback on the topic was gathered from CADTH customers, and an additional five jurisdictions expressed interest in CADTH work in this space. Two jurisdictions flagged a potential for duplication of effort with ongoing health technology assessment work[11] evaluating CGM, and any work undertaken by CADTH will need to be conducted with attention to this project. One customer also emphasized the need for recommendations from CADTH being a part of any work produced.

For the purposes of this Scoping Brief, "user" refers to any person who uses an HCL and the people (e.g., parents, caregivers) who support those wearing the device who are unable to operate it independently.

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 appears to vary across the country, both in the technologies reimbursed and in what part of the health care system is responsible for reimbursement.[12,13] 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 CGM devices are rarely covered by provincial and territorial programs. As such, interest for CADTH work related to HCLs varies from jurisdiction to jurisdiction.

Customer needs include identifying the following:

- which people with type 1 diabetes are best suited for HCLs (to help prioritize access)
- information about how clinical trial end points, such as time-in-range and glycated hemoglobin (A1C) impact long-term outcomes
- the clinical effectiveness and safety of HCLs compared with existing, reimbursed and non-reimbursed technologies
- which area of the health sector is best able to fund HCLs
- the costs of an HCL compared with currently covered technologies

- trends and availability of private insurance coverage for HCLs
- implementation issues (e.g., training required for users or health care providers)

Based on customer feedback, the purpose of a CADTH review of this topic would be to inform if HCL has 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?

Proposed Products

Based on customer needs and the considerations discussed in this Scoping Brief, the following tailored approach to CADTH work is proposed:

- A rapid review of the clinical effectiveness and safety of HCLs.
- A qualitative analysis of the perspectives and experiences of users and clinicians.
  - Supplemented with interviews with users and health care providers, particularly if there is a need to understand the place of hacking existing devices to create HCLs (i.e., “looping”), if needed.
- A review of implementation considerations informed by data inputs from other components including published literature, patient and clinician groups, and the perspectives and experiences qualitative analysis.
- A review of the ethical considerations of HCL implementation informed by other components.

Other potential CADTH work could include a budget impact analysis and a recommendations report. An assessment or scan of private insurance coverage for HCLs is beyond the scope of CADTH’s role.

Methods of Information Gathering

Scoping Briefs are based on a limited literature search; they are not extensive, systematic reviews of the literature. They are provided as a summary of important, current assessment information on this topic to inform CADTH work and have not been externally peer reviewed. More details regarding methods is available in Appendix 1.

The Technology

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.[14-17] Over time, high blood glucose levels can damage organs, blood vessels, and nerves.[15,16]

All people with type 1 diabetes require insulin therapy to control blood glucose levels.[16] 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 [e.g., before meals] through a tube connected to the body).[18] People with type 1 diabetes must regularly monitor their blood glucose levels to ensure a

healthy range is maintained.[17,19] People with type 1 diabetes can check their blood glucose in a variety of ways.[19] 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)
- CGM (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).

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.[20,21] These device systems, sometimes called artificial pancreases or closed-loop systems, are still many years from clinical use.[20,21] HCL is an emerging treatment option for people with type 1 diabetes on the path toward an artificial pancreas.[20,21] HCLs consist of an insulin pump, a CGM, and a computer program (algorithm) that allows the two devices to communicate with each other and calculate insulin needs.[21] 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.[20,21] They are also designed to suspend delivery of insulin if blood glucose levels have reached or are approaching a predefined low glucose threshold.[1,6,20-22] They are called hybrid systems because the user must still manually account for insulin needs before or after eating.[21]

One HCL (Medtronic's MiniMed 670G Insulin Pump System[23]) 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."[24-28] In the US, another HCL, the Tandem 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[5,29] — was approved for marketing in the US in December 2019.[5] Both the t:slim X2 insulin pump and Dexcom G6 CGM are currently approved for use in Canada.[3,4] 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.[6] At least five additional HCL systems are being developed for the US market (including Omnipod's Horizon Automated Glucose Control System[30]) and another five for the European market.[31]

Who Might Benefit?

The MiniMed 670G is approved for use in Canada for people with type 1 diabetes who are seven years and older.[1]

In 2017 an estimated 2.3 million Canadians 12 years and older (7.3%) were living with diabetes,[32] about 10% of whom have type 1 diabetes.[16] Studies of HCL have included children,[33-35] adolescents,[35,36] and adults[35,37,38] with type 1 diabetes. The 2018 Canadian guidelines for the management of type 1 diabetes mention the promise of HCL and note a need for more research.[7] The 2018 Canadian guidelines do discuss the role of insulin pumps and CGM in the management of type 1 diabetes.[7,9] 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.”[9]
- CGM is recommended for “adult patients with either A1C above target or who are well-controlled (at A1C target), provided that the devices are worn nearly daily.”[9]
- CGM is promising for adults with impaired hypoglycemia awareness but more research is necessary.[9]

For children and adolescents with type 1 diabetes:

- Insulin pumps are “safe and effective and can be initiated at any age.”[7]
- CGM is discussed but no specific statements regarding its use in children and adolescents are made.[7]

Sensor-augmented pumps are also mentioned in the guidelines but no specific recommendations for their use are made for adults or children and adolscents.[7,9]

Clinical Considerations

As part of the scoping process, four randomized controlled trials (RCTs)[34,39-41] regarding the clinical effectiveness of HCLs compared with alternative methods of insulin delivery for the management of individuals with type 1 diabetes were identified. No relevant health technology assessments or systematic reviews were identified.

Three RCTs[34,39,40] compared the Tandem Control-IQ system with a sensor-augmented pump in adolescents or adults with type 1 diabetes. The findings of these studies[34,39,40] indicated that participants randomized to the Tandem Control-IQ system had significantly better time-in-range compared with those randomized to a sensor-augmented pump. The fourth RCT[41] compared the Medtronic MiniMed 670G system versus the Medtronic MiniMed 530G system with threshold suspend in people (both children and adults) with type 1 diabetes over the course of six days. The authors of this study[41] reported similar outcomes for patients in either treatment group.

In addition to the RCTs, six single-arm, non-randomized, before-and-after studies[42-47] were identified regarding the clinical effectiveness of HCLs. All six of the studies compared the Medtronic MiniMed 670G system in HCL mode versus the same system in manual mode (i.e., the open loop mode).

None of the included studies[34,39,41] compared HCL versus MDII using a syringe, CGM alone, flash glucose monitor, open loops, SMBG, or continuous insulin infusion without sensor augmentation (i.e., insulin pump alone).

Based on the literature identified as part of the scoping process, there appears to be a paucity of comparative clinical evidence for HCL systems. The retrieved clinical studies[34,39-41] compared HCLs versus sensor-augmented pumps, recruited a limited number of participants (maximum of 168 individuals), and generally had short follow-up durations (maximum of six months). Further assessment (critical appraisal) into the quality of the literature is therefore needed to understand if there is a place for HCLs in therapy.

Cost and Economic Considerations

The current cost of the intervention in Canada is unclear based on our literature search.

No economic evaluations or budget impact analyses in a Canadian context were identified. One economic evaluation comparing the MiniMed 670G system to insulin pump therapy alone in people with type 1 diabetes in Sweden was identified.[48] The analysis was performed using the IQVIA CORE Diabetes Model from the societal perspective over a lifetime time-horizon. Treatment with the MiniMed 670G system was associated with quality-adjusted life-year gains, as well as higher costs, and was considered cost-effective at conventional Swedish willingness-to-pay thresholds.[48] It was considered most cost-effective in a population with poorly controlled type 1 diabetes (A1C ≥ 7.5%).

Based on the scoping search, there is a lack of evidence on the value for money and affordability of HCL for people with type 1 diabetes specific to a Canadian setting. As such, there are knowledge gaps in the current available economic information to inform the decision problem. The approaches that CADTH could take to address these knowledge gaps would depend on the availability of clinical, resource use and other health economic data used to conduct the respective types of analyses.

Perspectives and Experiences Considerations

HCL, as technology, involves multiple devices attached to and implanted in users' bodies, and as such it has daily presence in users' lives. Through the process of device development, the experiences of young children, adolescents with type 1 diabetes and their parents,[49-55] adults with type 1 diabetes, [50,52,55-60] and pregnant people[61,62] have been studied using qualitative methods. Reports from these studies described issues around adopting and learning how to use HCL devices,[50,53,57] trust in the devices,[59,60] and how using HCL affects users' self-management and daily life including food choices, sleep, and intimacy.[54,55,58,63] The experiences of children and their parents who use HCLs are likely to differ from those of adults in meaningful ways, such as the need for additional support and device modifications in young children.[51]

Studies that included physicians and health care providers described how they experienced HCL as a shift in their relationship and patterns of providing for patients with type 1 diabetes who use HCL.[58,64]

One systematic review of qualitative and quantitative studies on the patients' values and preferences relating to insulin pumps and artificial pancreases was identified.[63] The findings point to glycemic control as a preferred treatment outcome, with glycemic variability and decreased incidence of hypoglycemia being ranked as the intermediate importance to patients.

A CADTH Perspectives and Experiences review would contribute to addressing questions about patient-specific implementation considerations (e.g., learning and adjusting to the technology, impact of the technology on relationships) and potential factors that may affect clinical effectiveness and safety (e.g., continued self-management through diet, the need to calibrate the device).

Equity and Ethical Considerations

An initial scoping search retrieved twenty articles[56,61,65-82] that identified ethical issues relevant to HCL for type 1 diabetes. Of note, one article was a recent critical review and analysis of ethical issues related to the "artificial pancreas," conducted by a Canadian research team.[67] The critical review identified five main domains of ethical issues.

Confidentiality and safety: patient confidentiality and safety can be jeopardized by the technology's vulnerability to security breaches or unauthorized data sharing.

Coverage: public and private coverage could be cost-effective and warranted. The technology presents additional out-of-pocket expenditures for patients who already face significant socioeconomic burdens. In addition, coverage could be discontinued through a change in insurability, forcing the patient to resort to simpler and less effective treatment modalities.

Patient selection: patient selection criteria need to ensure equitable access and sensitivity to patient-reported outcomes; e.g., by not allocating the technology simply according to age and technological ability, or strength of social support.

Patient coaching and support: patient coaching and support by health care professionals or industry representatives could help foster realistic expectations in patients. Patients should be provided with a balanced account of the technology's advantages, drawbacks, and capabilities.

Personal identity and agency: the technology increases the visibility of diabetes and could generate issues related to personal identity and autonomy. Visibility may limit adherence, elicit stigmatization, or negatively impact relationships. Patients may become dependent on the technology and forget how to resort to conventional management strategies if a technical problem arises.

An additional ethics review by CADTH would likely represent a duplication of effort; however, a supplemental analysis by an ethicist might be beneficial to integrate the findings of this recent review with other health technology assessment components.

Implementation Considerations

To our knowledge, the MiniMed 670G system is only being funded by one publicly funded health plan in Canada for some people with type 1 diabetes.

In Canada, insulin pumps are a recommended management option for some people with type 1 diabetes and reimbursed for eligible patients in all provinces and territories.[12] CADTH customers have indicated that CGM is rarely covered. Instead, test strips (up to a maximum number per year) are reimbursed for eligible people with type 1 diabetes.[13] In an environment where CGM is rarely reimbursed, implementation of HCL — in which the system depends on CGM — would represent a departure from existing practices, an issue that led one CADTH customer to ask what part of the health care system should be responsible for paying for HCL. However, the transition to HCL may be akin to the shift from MDII to insulin pumps,[83] and the experience implementing insulin pumps and related technologies, like CGM, could help inform the implementation of HCL in Canada.

The implementation analysis in a recently completed Canadian CGM health technology assessment presented considerations that included: income, blood glucose control, limiting access to a specific device, and limiting access to people who need extra help managing diabetes.[11]These considerations may be relevant to the implementation of HCL.

Based on our literature search, research about the implementation of available HCL systems appears limited.[42,57,83-85] Because of this, CADTH work may need to consider knowledge about the implementation of related type 1 diabetes technologies (e.g., CGM) or closed-loop or artificial pancreas technologies more generally.[86-93] Factors that may influence the uptake of HCLs identified in our search include the following:

- population selection[89 90 93]
- education and training programs for users, caregivers, and health care providers [42,84,85 57,83,89,90]
- use of HCL during exercise or illness[86,87]
- differences in features and function between systems[85 57,83,88]
- supports for adolescents and young adult users.[91,92]

CADTH implementation work on HCL could help customers understand the barriers and facilitators to successful implementation and support decisions regarding:

- The populations best suited to use an HCL.
- Which part of the public health care system should be responsible for reimbursement.
- The design of education and training programs for users, caregivers, and care providers.
- The features and functions of devices that are important for uptake.

Manufacturer Information

Table 1: Available or Emerging Hybrid Closed-Loop Insulin Delivery Systems

Manufacturer	Name	Constituent Devices	Regulatory Status
Medtronic of Canada Ltd.	MiniMed 670G Insulin Pump System[23]	• MiniMed 670G insulin pump • Guardian Link (3) transmitter • Guardian Sensor • Contour Next Link 2.4 Meter	Approved in Canada[1]
Tandem Diabetes Care, Inc.	Tandem Control-IQ system[2]	• Tandem t :slim X2 insulin pump • Dexcom G6 CGM • Control-IQ algorithm by TypeZero Technologies	Approved in the US[5] CGM and insulin pump approved in Canada[3,4]

CGM = continuous glucose monitor.

Summary of Key Considerations

The CADTH scoping team met to discuss the information summarized in the previous sections of this Scoping Brief. The purpose of this meeting was to reflect on the information gathered and to consider how CADTH work could address the decision problems and potential policy issues expressed by its customers. Key considerations from this group discussion are as follows:

- Overall the current published literature about HCL appears limited. Therefore, CADTH work in this space would be early and, in some cases, may need to apply lessons learned from the implementation of related technologies (e.g., CGM, insulin pumps) when considering how HCL could be implemented in Canada.
- Customer questions related to the clinical effectiveness and safety of HCLs could be addressed through a rapid review of available clinical trials.
- A rapid review of clinical effectiveness and safety would help support other components of potential CADTH work (e.g., economic, perspectives and experiences) by elucidating relevant subpopulations and outcomes.
- Without existing Canadian economic studies of HCLs, CADTH work in this space requires additional input and validation from CADTH customers.
- A qualitative analysis of user and health care provider perspectives and experiences could help answer customer questions about appropriate user populations, and barriers and facilitators to use.
- Questions remain about customer interest in users of existing technology who are hacking their current devices to create off-label HCLs. Referred to in the literature as “loopers” this group may have important perspectives and experiences to consider.
- There are ethical issues involved in the implementation of HCLs. Therefore, it is important that an ethical lens be applied to CADTH work on HCLs. The existing Canadian ethics review[67] could be used to support such a review when making conclusions and/or recommendations about HCLs in Canada. This work could take the form of a separate ethical review.
- Customers have questions about how to implement HCLs. A review of implementation considerations could make use of clinical, economic, and perspectives and experiences inputs in conjunction with published literature gathered through an expanded literature search.
- CADTH may not be able to answer customers’ questions regarding which part(s) of the public health care system should be responsible for paying for HCL. However, this could be made clear through additional stakeholder consultations.

Summary of Customer Validation

A draft version of this Scoping Brief was circulated to CADTH customers who indicated interest in the topic so they may validate the content of the document and the proposed scope of CADTH's work. The CADTH customers consulted agreed that the content of this Scoping Brief addressed the concerns of their jurisdictions correctly. When asked if any important information was missing from the Scoping Brief, one customer asked whether CADTH would consider using real-world evidence where there are data gaps or to supplement information from published studies. Another jurisdiction stated that knowledge of confidential pricing that was potentially negotiated by some jurisdictions could help support economic modelling. CADTH customers consulted generally felt the proposed products would meet their decision-making needs. One customer asked that CADTH consider how the project could address how HCL might affect the use of blood glucose testing strips that are currently reimbursed by jurisdictions.

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Appendix 1: Methods of Information Gathering

Scoping Briefs are based on a limited literature search; they are not extensive, systematic reviews of the literature. They are provided here as a summary of important, current assessment information on this topic. Additionally, they have not been externally peer reviewed.

A CADTH Rapid Response Report (summary of abstracts)[94] regarding the clinical effectiveness of hybrid closed-loop insulin delivery systems (e.g., Medtronic MiniMed 670G, Tandem "Control-IQ") was conducted to identify and summarize the available clinical literature. This report used a limited literature search on key resources including MEDLINE, the Cochrane Library, the University of York Centre for Reviews and Dissemination databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search, to identify studies that compared hybrid closed-loop insulin delivery systems with alternative methods of insulin delivery with respect to a variety of clinical outcomes. The search was restricted to articles published between January 1, 2003 and August 29, 2019. Additional details on the complete methodology — including literature search methods, detailed article selection, and eligibility criteria, and the processes used for study selection — are available in the publication.[94] In addition to the limited literature search, a supplemental grey literature search was conducted following the completion of the Rapid Response Report.[94] This supplemental search identified one additional RCT[40] for consideration in the Scoping Brief.

Additional information to support the Implementation Considerations section was gathered through consultation with CADTH customers and input from CADTH committees.

Appendix 2: Proposed PICO

	Proposed PICO

Population	• People with type 1 diabetes
	  ○ Children
	  ○ Adolescents
	  ○ Adults
	  ○ Degree of glycemic control

Intervention	• Hybrid closed-loop insulin delivery systems
	  ○ Medtronic Minimed 670G
	  ○ Tandem t:slim X2 / Dexcom G6 / Tandem Control-IQ

Comparator(s)	• SMBG with or without insulin pump • CGM with or without insulin pump • Sensor-augmented insulin pumps • Flash glucose monitoring with or without insulin pump

Outcome(s)	• Clinical effectiveness:
	  ○ time-in-range
	  ○ A1C
	  ○ number of hypoglycemic events requiring assistance
	  ○ diabetic ketoacidosis
	  ○ EQ-5D
	  ○ hypoglycemia fear survey overall score
	  ○ diabetes treatment satisfaction questionnaire overall score
	• Economic
	  ○ Cost-effectiveness
	  ○ Budget impact
	• Perspectives and Experiences
	  ○ Patients
	  ○ Care providers
	  ○ Clinicians

A1C = glycated hemoglobin; CGM = continuous glucose monitoring; EQ-5D = EuroQol 5-Dimensions questionnaire; PICO = population, intervention, comparator(s), outcome(s); SMBG = self-monitoring of blood glucose.