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

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Clinical Review
Budget Impact Analysis
Perspectives and Experiences Review
Ethics Review
Stakeholder Consultations
Patient Engagement

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

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Contributors

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Reviewers

The following individuals kindly provided comments on a draft version of this report.

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Dr. Holden and Chantelle Garrity reviewed the clinical section of the protocol and draft. Dr. Shaw reviewed the ethics section of the protocol and draft. Dr. Brundisini reviewed the qualitative section of the protocol.

Conflicts of Interest

Dr. Houlden has accepted speaking engagements from Eli Lilly Canada and Novo Nordisk Canada and has received research funding from Boehringer Ingelheim, Novo Nordisk, Astra Zeneca, and Eli Lilly for diabetes.

Dr. Shaw has received funding from the Toronto Central Local Health Integration Network and VHA Home HealthCare with regard to community-based care and collaborative governance, respectively.

Abbreviations

A1C	glycated hemoglobin
BIA	budget impact analysis
BMI	body mass index
CGM	continuous glucose monitor
CI	confidence interval
DIDP	DAWN2 Impact of Diabetes Profile
DIY	do it yourself
DTSQ	Diabetes Treatment Satisfaction Questionnaire
FGM	flash glucose monitor
HCL	hybrid closed-loop insulin delivery
HTA	Health Technology Assessment
IQR	interquartile range
MDII	multiple daily insulin injections
ODB	Ontario Drug Benefit
ODSP	Ontario Disability Support Program
PAID	Problem Areas in Diabetes (questionnaire)
PLGS	predictive low-glucose suspend
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRMQ	Prospective and Retrospective Memory Questionnaire
PSQI	Pittsburgh Sleep Quality Index
RCT	randomized controlled trial
RoB 2	Cochrane Risk-of-Bias tool, version 2
RoBANS	Risk of Bias Assessment tool for Non-randomized Studies
SAP	sensor-augmented pump
SD	standard deviation
SMBG	self-monitoring of blood glucose
SR	systematic review
W-BQ28	Well-Being Questionnaire 28

Protocol Amendments

Section	Amendment	Page number in protocol	Rationale
Budget impact analysis	Added protocol on budget impact analyses	26	To address affordability considerations with the adoption of HCL systems
Literature search methods and study selection	For eligible studies that were identified after the stakeholder feedback period, the results were described in the summary of Results section as opposed to the Discussion section.	8 and 11	To help with readability and use of results, this information is better situated within the summary of results of the Clinical Review.
Selection and eligibility criteria and data extraction	Findings relating to additional clinical outcomes that were not explicitly outlined in the protocol for the Clinical Review were also extracted from the identified studies and summarized in the evidence synthesis. These outcomes included mean glucose concentration, glycemic variability, body weight, daily insulin usage, insulin-to-carbohydrate ratios, basal-insulin proportions, diabetes distress, diabetes-specific positive well-being, prospective memory, retrospective memory, and perceived sleep quality. Any additional outcomes that assessed the clinical effectiveness of HCL systems would have also been extracted, had they been identified.	9 to 10 and 12	Although these outcomes were not identified as part of the scoping process, they do provide information on the clinical effectiveness of HCL systems. These findings were extracted to ensure all available results could be considered when answering the decision problem.
Critical appraisal	An overall risk-of-bias judgment of each non-randomized study assessed with RoBANS was provided as “high risk of bias” if the study had at least 1 domain that was at “high risk of bias;” “some concerns” if the study had at least 1 domain that was “unclear” but no domain that was at “at high risk of bias;” or “low risk of bias” if the study had “low risk of bias” for all domains. This was not specified in the protocol.	13	This was done to provide an overall risk-of-bias judgment for non-randomized studies consistent with the planned approach to do this for randomized controlled trials. Because the RoBANS guidance did not provide a specific approach for making study-level judgments, this was borrowed from the RoB 2 guidance for methodological consistency.

HCL = hybrid closed-loop insulin delivery; RoB 2 = Cochrane Risk-of-Bias tool, version 2; RoBANS = Risk of Bias Assessment tool for Non-randomized Studies.

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Key Messages

- Blood glucose monitoring and insulin delivery are essential parts of the management of type 1 diabetes. Hybrid closed-loop insulin delivery (HCL) systems are a treatment option for people with type 1 diabetes and consist of an insulin pump, a continuous glucose monitor (CGM), and a computer program (algorithm) that allows the devices to communicate with each other and calculates insulin needs.
- CADTH conducted a Health Technology Assessment (HTA) of the use of HCL systems compared to other insulin delivery methods in people with type 1 diabetes to inform decisions regarding whether HCL systems have a place in the management of type 1 diabetes.
- HCL therapy generally improved the amount of time a person spent in target blood glucose ranges. Additionally, people who used HCL systems had improved average blood glucose levels (glycated hemoglobin [A1C]) over the preceding 2 or 3 months. However, the effectiveness or safety of HCL systems based on age, sex, race, glucose management, or other clinical features (e.g., those who are pregnant or planning pregnancy, or who have hypoglycemia unawareness or a history of severe hypoglycemia) is unknown. HCL systems were generally as safe as other insulin delivery methods. Additional studies with longer follow-up periods and more participants are needed to confirm the clinical effectiveness and safety of HCL systems.
- From a pan-Canadian, publicly funded health care system perspective, the cost of covering HCL systems for individuals with type 1 diabetes who are eligible for insulin pumps in their jurisdictions was estimated to be an additional $822,635,045 over 3 years compared with diabetes supplies that are currently covered. If HCL systems are covered for all individuals with type 1 diabetes, regardless of their current insulin-pump eligibility, the budget impact will be higher.
- HCL systems can help provide distance from demanding self-management and monitoring tasks for people living with type 1 diabetes; however, in order to do this, people using these systems must navigate complex relationships built on trust and collaboration. Given that type 1 diabetes self-management to date has required considerable attention to blood glucose numbers and technical tasks, developing these relationships of trust and collaboration will require a shift in understanding what it means to care for someone who has — or to self-manage — type 1 diabetes.
- It is not possible to conclude whether HCL systems will improve overall population health over the longer-term because the data for this are not available. It is also unclear which people with type 1 diabetes would benefit most from HCL systems. Eligibility criteria for the existing public insulin-pump program may be useful in making coverage decisions; trial periods may be considered to ensure HCL systems are working well for new users.
- Education and support are needed for people living with type 1 diabetes when they start to use HCL systems. Clinicians noted the need for interactions between diabetes educators and HCL system pump users. User-friendly devices and understandable reports are key to effective use.
- Eligibility for access through any publicly funded program for HCL systems should be based on evidence. The criteria for coverage should be consistent with broader public health goals and should not contribute to existing inequities in diabetes management.

Abstract

Context and Decision Problems

A hybrid closed-loop insulin delivery (HCL) system consists of an insulin pump, a continuous glucose monitor (CGM), and a computer program (algorithm) that connects the devices and calculates insulin needs. HCL systems are designed to keep blood glucose levels within a predefined range and to suspend insulin delivery if the levels are predicted to reach a predefined low-glucose threshold. They are called hybrid systems because the user must still manually account for insulin needs before eating and manually confirm the amount of any insulin bolus. A commercial HCL system became available in Canada in 2018. However, the type 1 diabetes community has built and used do-it-yourself (DIY) systems for several years longer. Since 2018, 2 additional HCL systems have been approved in Canada, and more are expected in the coming years. Given this rapidly evolving technology landscape, CADTH customers seek to understand the place in care, if any, of HCL systems compared with existing technologies. Some of the key questions are:

- If HCL systems have a place in care, are there groups of people with type 1 diabetes to whom they should not be offered?
- What are the perspectives and experiences of people with type 1 diabetes, their caregivers, and clinicians when it comes to using or implementing HCL systems?
- What factors need to be in place for the optimal use of HCL systems?
- Who (i.e., what part of the health care system) should be responsible for implementing HCL systems?
- What would be the expected costs of funding HCL systems from a public payer perspective?

Clinical Effectiveness and Safety

A systematic review (SR) of primary studies on the comparative clinical effectiveness and safety of commercialized HCL systems versus other insulin delivery methods in people of any age with type 1 diabetes was conducted.

Nine primary studies (described in 10 publications) were identified and included in the SR. These comprised 8 RCTs that were judged as being at low to moderate risk of bias and 1 matched-cohort study judged as being at high risk of bias. The investigated systems were the Tandem Control-IQ HCL system, the Diabeloop single-hormone HCL system, and the Medtronic MiniMed 670G HCL system. Control groups received open-loop sensor-augmented pump (SAP) therapy, open-loop SAP therapy with a predictive low-glucose suspend (PLGS) feature, insulin delivery with multiple daily insulin injections (MDII), or insulin-pump therapy with insulin dosing based on self-monitoring of blood glucose (SMBG). Primary studies varied in their clinical, methodological, and statistical characteristics, precluding the planned meta-analyses.

HCL therapy generally increased the proportion of time spent in euglycemic ranges and decreased time spent in hypo- and hyperglycemic ranges compared to open-loop SAP therapy (regardless of whether a PLGS feature was available) and MDII or insulin-pump therapy informed by SMBG. Additionally, across most studies, HCL therapy demonstrated a general trend in improving A1C levels, mean glucose concentrations, and glycemic

variability compared to open-loop SAP therapy (with or without a PLGS feature) or MDII or insulin-pump therapy informed by SMBG.

As for the comparative safety of HCL systems, the rates of adverse events experienced by study participants, such as hypoglycemic events and ketosis events, were generally not statistically significantly different between those who were treated with HCL therapy and those who received control interventions.

Overall, HCL therapy improved clinical outcomes and had a comparable safety profile compared to control interventions in people with type 1 diabetes; however, long-term data examining the clinical effectiveness and safety of HCLs are lacking (i.e., from studies with follow-up durations exceeding 6 months), which creates uncertainty in these findings.

Budget Impact

A budget impact analysis (BIA) was conducted to estimate the financial impact of introducing HCL systems for individuals with type 1 diabetes (i.e., a new-device scenario) compared with technologies that are currently covered by public payers (i.e., a reference scenario). An epidemiology-based approach was used to determine the size of the eligible patient population using prevalence, incidence, and population growth rate estimates from the literature. The base case considered HCL system coverage for those who are eligible for insulin pumps within their jurisdictions; broader coverage of HCL system for all individuals with type 1 diabetes, regardless of their eligibility for an insulin pump, was considered in a scenario analysis. The reference scenario was based on jurisdiction-specific public coverage of insulin delivery devices (insulin pumps, insulin-pump supplies, MDII supplies) and glucose-monitoring devices (CGMs, FGMs, and SMBG test strips), where available. In the new-device scenario, a hypothetical world where HCL systems are covered by public payers was assumed. While insulin pumps are — to an extent — covered by all Canadian jurisdictions, CGMs remain largely uncovered across public jurisdictions. In these jurisdictions, the new-device scenario assumed that CGMs would be publicly reimbursed only for use as a part of HCL systems.

The analysis was conducted over a 3-year time horizon from the perspective of the Canadian publicly funded health care system (i.e., ministries of health), excluding Quebec. As such, only costs covered by the health care payer were captured. Jurisdiction-specific prices, coverage rates, and co-pays were used to estimate the cost of each treatment approach, when possible. Reference scenario market shares and the rate of uptake of HCL systems under the new-device scenario were estimated based on input received during stakeholder consultations, with differing rates of uptake of HCL systems assumed by the approach to insulin delivery (i.e., whether the individual is currently using an insulin pump or MDII). Key base-case assumptions were tested through scenario analyses.

CADTH estimated that the budget impact of covering HCL systems for individuals with type 1 diabetes (assuming that public payers will be the first payers) who are eligible for insulin pumps to be an additional $131 million in year 1, $271 million in year 2, and $420 million in year 3, for a total budget impact over 3 years of $823 million from a pan-Canadian perspective. Should all individuals with type 1 diabetes be eligible for HCL systems, regardless of their eligibility for an insulin pump, the budget impact of covering HCL systems is estimated to be higher (an additional $916 million). The results were sensitive to the price of CGMs, meaning that a lower price for CGM devices will improve the affordability of HCL systems to public payers. An additional key source of uncertainty in the analysis was the uptake of HCL systems among those currently using MDII to deliver insulin. If current MDII

users do not switch to HCLs, the estimated budget impact of introducing HCL systems is expected to be much lower (an increase of $97 million).

Perspectives, Experiences, and Expectations

The Perspectives and Experiences Review was conducted using an adapted thematic synthesis of primary qualitative research exploring the expectations and experiences of people living (or caring for someone) with type 1 diabetes using HCL systems.

People living (or caring for someone) with type 1 diabetes hoped that HCL systems could take over enough of the work associated with type 1 diabetes self-management that they could focus on being more immersed in, and part of, the flow of life around them. While many described having some degree of success in achieving this, doing so was not without its challenges. As an example, for HCL systems to work most effectively, people need to trust the control algorithm to adjust things like basal-insulin rates and resist the trained impulse to do this themselves. This signals a shift away from previous ideals of "good" self-management that have required constant attention and ongoing device adjustments. While this could be difficult at first for people trained in other forms of self-management, others who have struggled to meet previous ideals might appreciate and benefit from this shift.

Given the difficulty of navigating these shifting notions of "good" self-management and trust that the HCL system elicits, it could be helpful to talk about and engage with HCL systems as collaborators in, rather than providers of, care. This distinction may seem inconsequential from the outside, but for people living (or caring for someone) with type 1 diabetes, the flexibility of collaboration helped them to deal with the numerous frustrations of "techno-glitches" and ongoing material needs of their particular systems.

The introduction of HCL systems also contributes to a shift in how professional care is imagined. With increased access to their patients' data, clinicians believed they could both see a more complete picture of their out-of-office experiences and reduce their own workloads as a result. However, there is concern that this could lead to mistaking the numbers associated with diabetes for the person living with diabetes, which could result in missing opportunities to provide extra support or care.

Ethical Aspects

An ethics analysis was conducted to identify the key ethics dimensions of HCL systems.

To ethically justify a decision to fund a medical device, there must be sufficient evidence that the device at least delivers a balance of benefits over harms. This includes clinical and non-clinical benefits for the device user and non-clinical effects for others. At this time, there is limited evidence to determine conclusively whether HCL systems offer long-term benefits beyond technology that is already available. There is evidence that for some users, it offers immediate clinical benefits and several non-clinical benefits without significant risks of harm.

From an autonomy perspective, HCL systems may enhance individual autonomy in the day-to-day management of diabetes; however, it is unclear whether individuals (or their care providers) are able to make meaningfully autonomous decisions to start using an HCL system due to a lack of unbiased information about the device. An HCL system may also offer the opportunity to increase a person's agency (their capacity to act) by reducing the burden of diabetes management; however, this increase in agency only occurs if users are

able to relinquish some direct control over their diabetes management and build trust in the device.

Patient selection for HCL system has important ethical dimensions, given that this process can affect the extent to which HCL system offers benefits (to individuals and to populations) and can have important equity implications regarding who is ultimately granted access to the device. Evidence suggests that health care providers are not always able to accurately assess the psychosocial factors that would indicate successful HCL system use. Therefore, relying upon these factors to select patients may result in unjustified limitations on choice, lead to failure to promote benefit for patients who may do well on HCL systems, and reinforce inequity. There is also evidence for a connection between successful continued use of HCL systems and access to support and education. Availability of this kind of support is ethically relevant, because without it, HCL systems may offer fewer benefits. The distribution of this support also has ethical implications. If comprehensive support is not widely available to those wishing to try the device, this can result in an unfair distribution of burdens and benefits.

Concerns about confidentiality and the potential for harm to users by hacking has been widely identified in the HCL system literature. If the person with diabetes clearly understands how their data may be shared and used, and consents to this sharing, then data-sharing is unproblematic. If people's data are being shared without their awareness or consent, then it is much more ethically concerning. There may be a grey zone in the case of teenagers, who may be monitored by their parents and may not have a full say in whether or how their data are shared, but are developing the capacity to be more centrally involved in these issues.

Access to diabetes supplies and devices across Canada is often determined by what is covered through public funds. Decisions about how to determine access are ethically relevant, given that they often have impacts on equity and the distribution of burdens and benefits among people living with diabetes and their families. Currently, private health insurance, which is generally available to those with higher socio-economic status, tends to offer more comprehensive coverage of diabetes supplies than public health insurance. Choosing not to cover HCL systems within public programs could reinforce inequities in access to diabetes management supplies. That said, if technologies like HCL systems continue to primarily benefit people with diabetes who already have good management and access to care, an argument could be made that using public funds to expand the coverage of more basic diabetes management supplies, rather than funding HCL systems, is more equitable. If public funds are allocated to cover HCL devices, it is important that any program criteria set to determine access to the devices is evidence-based and does not exacerbate existing health inequities.

Conclusions and Implications for Decision- or Policy-Making

The evidence suggests that HCL systems have a place in type 1 diabetes care, but provides little guidance on who may benefit most, and who may not benefit, from their use. Enrolment criteria from existing insulin-pump programs may be useful decision-making guides. Trial periods may also be considered as an option.

This review found little long-term evidence of clinical benefits of HCL therapy. Further research is needed, and information from post-market surveillance should inform ongoing decisions.

The anticipated budget impact of HCL system implementation varies across the country and depends on existing program design. Deciding to fund HCL systems would likely force conversations about reimbursement for CGMs.

As they continue to improve, HCL systems may challenge current funding programs that treat insulin pumps and diabetes supplies separately. Efforts may be needed to align and simplify programs to make these processes easier to administer and navigate.

Broader uptake of HCL systems will require additional training and education for people with type 1 diabetes, their care providers, and clinicians. Supportive care environments that allow the time and space to attend to and maintain HCL systems are also an important consideration.

An emerging market of open-source, interoperable insulin delivery systems may signal that we are entering a time of greater device choice and an end to public acceptance of programs that limit device choice.

New or updated HCL systems are anticipated to enter the market in the coming years. It is unclear how the additional evidence associated with these emerging devices could impact the conclusions of this report.

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, fatigue, or diabetic ketoacidosis as blood glucose levels rise. Over time, high blood glucose levels caused by diabetes can damage organs, blood vessels, and nerves, leading to conditions such as kidney failure or blindness. High blood glucose levels also increase the risk of cardiovascular disease, including high blood pressure, heart disease, and stroke. Type 1 diabetes usually develops during childhood or adolescence, but also occurs in adults. In 2019, an estimated 2.49 million people in Canada aged 12 years and older (7.8%) were living with diabetes, about 9% of whom had type 1 diabetes. In the same year, 11,800 children in Canada were estimated to be living with type 1 diabetes.

All people with type 1 diabetes require insulin therapy to lower blood glucose levels and reduce the risk of short- and long-term complications. Treatment targets for blood glucose for people with type 1 diabetes are addressed by the Diabetes Canada 2018 *Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada* (Diabetes Canada 2018 Guidelines). Noting that blood glucose targets should be tailored to the individual to account for factors such as age, diet, and ability to self-manage, the guidelines recommend a target A1C level — a measurement of a person's average blood glucose level over the past 2 or 3 months — of less than or equal to 7% (7.5% in children and adolescents) to reduce the risk of long-term complications and the frequency and severity of hypoglycemic (low blood glucose) events.

Insulin therapy can be provided by MDII or insulin pumps (small, externally worn devices that deliver a small, user-determined amount of insulin continuously, with additional user-determined doses as needed [e.g., before meals] through a tube connected to the body). Treatment using MDII typically involves 1 or 2 injections of a long- or intermediate-acting insulin to manage blood glucose levels between meals and additional injections of short-acting insulin before meals or to correct high blood glucose. According to the Diabetes Canada 2018 Guidelines, insulin-pump therapy is an effective treatment option for people with type 1 diabetes and has been shown to improve A1C compared to MDII. Because it may also improve quality of life and treatment satisfaction compared with MDII, some people with type 1 diabetes may prefer insulin-pump therapy over MDII. The Diabetes Canada 2018 guidelines recommend insulin-pump therapy for:

- adults with type 1 diabetes: The guidelines say this therapy is "a safe and effective method of intensive insulin delivery" and that "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."[8]
- children and adolescents with type 1 diabetes. This guidelines say this therapy is "safe and effective and can be initiated at any age."[9]
- consideration in people with type 1 diabetes "with recurrent or severe hypoglycemia, or impaired awareness of hypoglycemia." The aim is to "reduce or eliminate the risk of severe hypoglycemia and to attempt to regain hypoglycemia awareness."[13]

Hypoglycemia as a result of insulin therapy is a limiting factor and major obstacle in safely achieving within-range glycemia in the management of type 1 diabetes.[8,9] Hypoglycemia can

be mild (e.g., sweating or tingling), moderate (e.g., confusion, dizziness, vision issues), or severe (e.g., loss of consciousness, coma, seizures, death).[13] While all people with type 1 diabetes are at risk of severe hypoglycemia, factors that increase the risk of severe hypoglycemia in people with type 1 diabetes include adolescence, prior severe hypoglycemic events, hypoglycemia unawareness, and the inability to self-treat hypoglycemia (e.g., in young children).[13] While mild to moderate hypoglycemia can usually be self-managed, treatment of severe hypoglycemia requires the assistance of another person.[13] Both the frequency and severity of hypoglycemia negatively impact quality of life and can create fear of future hypoglycemic events.[13] This fear is associated with reduced self-care and blood glucose levels that are not within target range, and it may make people with type 1 diabetes reluctant to intensify their insulin therapy.[13]

To achieve and maintain treatment goals that are within target range, people with type 1 diabetes must regularly monitor their blood glucose levels.[8,9,14] People with type 1 diabetes can check their blood glucose in a variety of ways.[8,9,15] These include the following:

- SMBG using a blood glucose meter (which uses a drop of blood, typically from the finger, absorbed by 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 or smartphone)
- continuous glucose monitoring (which uses a sensor inserted under the skin to measure glucose levels in the fluid surrounding the cells, transmits continuous readings to a device [e.g., a smartphone], and can alert the user to low, high, or rapidly changing glucose levels).

Blood glucose monitoring is an essential part of the management of type 1 diabetes, and frequent self-monitoring (i.e., ≥ 3 times per day) has been found to improve A1C levels.[14] More frequent monitoring, including overnight monitoring, may be needed to avoid hypoglycemic events.[14] Using continuous glucose monitoring may improve A1C levels compared to SMBG alone without increasing the risk of hypoglycemia.[8] The Diabetes Canada 2018 guidelines recommended continuous glucose monitoring be offered to people with type 1 diabetes who have not achieved their blood glucose targets.[14] Continuous glucose monitoring is also recommended for:

- adults with type 1 diabetes with hypoglycemic unawareness, provided the sensor is used the majority of the time
- consideration in people with type 1 diabetes “with recurrent or severe hypoglycemia, or impaired awareness of hypoglycemia“ to “reduce or eliminate the risk of severe hypoglycemia and to attempt to regain hypoglycemia awareness.”

For children and adolescents with type 1 diabetes, the guidelines discuss continuous glucose monitoring, but do not provide additional specific guidance for its use in these groups.

SAPs add continuous glucose monitoring to insulin-pump therapy and may provide additional improvements in A1C levels in some people with diabetes without increasing the risk of hypoglycemic events compared to CGMs or insulin pumps alone. SAPs may also include a safety feature called “low glucose suspend” that stops the delivery of insulin from the pump for a pre-specified period of time when the CGM detects blood glucose levels below a critically low threshold. This feature may help some people reduce the frequency of overnight hypoglycemic events and support those with hypoglycemic unawareness. The Diabetes Canada 2018 Guidelines recommend considering SAPs for people with type 1

diabetes “with recurrent or severe hypoglycemia, or impaired awareness of hypoglycemia“ to “reduce or eliminate the risk of severe hypoglycemia and to attempt to regain hypoglycemia awareness.”

In addition to insulin therapy and blood glucose monitoring, education, training, and support for people with type 1 diabetes are essential to achieving treatment goals and reducing the incidence of adverse events like severe hypoglycemia.[8,9,13,14,16] Type 1 diabetes is a dynamic disease that requires individuals to make daily — and as frequently as hourly — changes to their self-management.[16] Activities of daily living, such as eating, exercising, or illness, and other factors, such as age, lifestyle, and socio-economic status, may all have profound effects on the short- and long-term health of a person with type 1 diabetes.[8,9] Self-management education and self-management support programs aim to continuously engage people with type 1 diabetes in their ongoing care by providing them with the skills and knowledge needed for self-monitoring and decision-making.[16] Additional education and planning are also recommended for adolescents to reduce the risk of negative outcomes as they transition to adult care.[9]

Hybrid Closed-Loop Insulin Delivery Systems

One goal of type 1 diabetes research is to develop a system (sometimes called an artificial pancreas or closed-loop system) that can mimic the body’s ability to regulate blood glucose levels without the need for intervention (e.g., before meals) by the person with type 1 diabetes.[17,18] HCL systems are a treatment option on the path toward an artificial pancreas, which are now emerging for people with type 1 diabetes.[17,18] An HCL system consists of an insulin pump, a CGM, and a computer program (algorithm) that allows the devices to communicate with each other and calculates insulin needs.[18] HCL systems 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.[17,18] They are also designed to suspend the delivery of insulin if blood glucose levels reach or are predicted to reach a predefined low-glucose threshold.[17-21] They are called hybrid systems because the user must still manually account for insulin needs before eating and manually confirm the amount of any insulin bolus to be delivered.[18]

The potential impact of HCL systems on care may be better understood with an appreciation of the burden of diabetes management using established approaches such as SMBG, MDII, or insulin pumps described earlier. Monitoring blood glucose levels, calculating insulin needs, planning for exercise, monitoring other factors that can influence blood glucose (such as sleep and stress), and detecting and responding to hypoglycemic events are all necessary for an individual to successfully manage type 1 diabetes.[22] Caregivers, especially parents or caregivers of children, also experience the burden of type 1 diabetes and must routinely monitor blood glucose levels.[23,24] While HCL systems are not without their challenges (such as issues with alarms, technical glitches, and the visibility of the devices), users report that they offer a range of non-clinical benefits, including improved sleep, improvements in engaging with physical activity, less anxiety about food, reduced stress for family members, a greater sense of safety and peacefulness, and overall, a reduced burden of type 1 diabetes management.[25-34]

Hybrid Closed-Loop Insulin Delivery Systems in Canada

Commercially available HCL systems first became available in Canada in 2018. However, the type 1 diabetes community has been building and using DIY, or looping, systems from existing insulin pumps and CGMs connected with open-source algorithms for several years.[21] One HCL system (Medtronic's MiniMed 670G Insulin Pump System[35]) was approved by Health Canada as a class 4 medical device in 2018 "for the management of type 1 diabetes in people seven years and older."[36-39] An upgraded version HCL system, the MiniMed 770G, was approved by Health Canada as a class 4 medical device in December 2020 "for the management of type 1 diabetes mellitus in persons two years of age and older."[40-42] A third HCL system, 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[43,44] — was approved by Health Canada as a class 4 medical device in November 2020 "for the management of type 1 diabetes mellitus in persons six years of age and greater."[45,46] Additional HCL systems are anticipated to be available in Canada in the coming years.[21,47] At least 5 additional HCL systems are being developed for the US market (including Omnipod's Horizon Automated Glucose Control System[48]), and another 5 are being developed for the European market.[49]

Studies of HCL systems have included children, adolescents, and adults with type 1 diabetes.[50-59] The 2018 Diabetes Canada guidelines mention the promise of HCL systems for the management of type 1 diabetes and note a need for more research.[9] Although guidelines for the use of HCL systems have not yet been established, the role of insulin pumps and CGMs in the management of type 1 diabetes is discussed in the guidelines.[8,9]

Decision Problem

Given a rapidly evolving technology landscape for people with type 1 diabetes, what is the place in care, if any, of HCL systems compared with existing technologies?

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.[60,61] For example, while all jurisdictions in Canada provide some form of insulin-pump coverage, public coverage for CGMs is limited to Yukon, to some people with type 1 diabetes in Ontario, and to some Non-Insured Health Benefits clients.[60,62] As such, interest for CADTH work related to HCL systems varies from jurisdiction to jurisdiction.

Based on customer feedback, the purpose of a CADTH review of this topic is to inform decisions regarding whether HCL systems have a place in the management of type 1 diabetes:

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

Objective

The purpose of this HTA is to address the decision problem by assessing the clinical effectiveness and safety of HCL systems, conducting a BIA to address affordability considerations, conducting a qualitative analysis of the perspectives and experiences of users and clinicians, and reviewing ethical issues.

Research Questions

The HTA informs the decision problem by exploring the following research questions.

- Clinical Review
    1. What is the comparative clinical effectiveness of commercially available HCL systems versus other insulin delivery methods in people of any age with type 1 diabetes?
    2. What is the comparative safety of commercially available HCL systems versus other insulin delivery methods in people of any age with type 1 diabetes?
- Budget Impact Analysis
    1. What is the budget impact to Canadian publicly funded health care systems of reimbursing HCL systems for the management of type 1 diabetes compared with currently reimbursed technologies?
- Perspectives and Experiences Review
    1. How do people living with type 1 diabetes, or those involved in their care, describe their expectations of HCL systems, and how have their experiences engaging with HCL systems reflected their expectations?
    - How do people living with type 1 diabetes, or those involved in their care, envision HCL systems as contributing to type 1 diabetes management?
    - How might expectations of and experiences with HCL systems differ across various groups of people (e.g., young children, parents, elderly) engaging with these systems?
- Ethics Review
    1. What are the major ethical issues raised by the use of HCL systems for managing type 1 diabetes?
    2. How might these issues be addressed?

Methods

To inform the conduct of this HTA, a preliminary scoping review of the existing literature — including HTAs and SRs — was conducted. A protocol was written a priori, using appropriate reporting guidelines (e.g., the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) for guidance on clarity and completeness and was followed throughout the study process. Any deviations from the protocol were disclosed in this final report and updates were made to the PROSPERO submissions accordingly (Clinical Review: CRD42020193156; Perspectives and Experiences Review: CRD42020192057).[63]

For the Clinical Review, an SR of clinical primary studies was conducted (see the Clinical Review section for further details). For the Perspectives and Experiences Review, an adapted thematic synthesis of primary qualitative research inquiring into the expectations and experiences of those living with type 1 diabetes and those involved in their care was conducted (see the Perspectives and Experiences Review section for further details). A BIA using the Canadian publicly funded health care system perspective was conducted to address the financial impact of funding HCL systems as the primary method of monitoring blood glucose and delivering insulin (see the Budget Impact Analysis section for further details). For the Ethics Review, a bioethical analysis was conducted to identify and reflect upon key ethical concerns when considering HCL systems for people with type 1 diabetes (see the Ethics Review section for further details).

Opportunities for Stakeholder Feedback

Stakeholders were given the opportunity to provide feedback on the draft-included studies list and a draft report.

Clinical Review

Overview

Research Questions

The objective of this Clinical Review was to address the following research questions:

1. What is the comparative clinical effectiveness of commercially available HCL systems versus other insulin delivery methods in people of any age with type 1 diabetes?
2. What is the comparative safety of commercially available HCL systems versus other insulin delivery methods in people of any age with type 1 diabetes?

Key Messages

An SR of primary studies on the comparative clinical effectiveness and safety of commercialized HCLs versus other insulin delivery methods in people with type 1 diabetes was conducted. The SR identified 8 randomized controlled trials (RCTs) (in 9 publications[50-57,59]) and 1 matched-cohort study[58] that addressed the research questions and met the eligibility criteria. Key findings from the SR include the following:

- Of the 9 studies identified for inclusion in this review, 5 compared HCL systems versus open-loop SAP systems without PLGS features; 2 compared HCL systems versus open-loop SAP systems with PLGS features; 1 compared HCL therapy versus a control group that received open-loop SAP therapy with or without PLGS features (a mixed population); and 1 compared HCL therapy versus a control group that received insulin delivery via MDII or insulin-pump therapy (a mixed population), both of which were informed by SMBG (i.e., using a blood glucose meter without access to CGM data). The RCTs were judged to be at low to moderate risk of bias, and the cohort study was judged to be at high risk of bias during the critical appraisal process.
- HCL therapy generally increased the proportion of time spent in euglycemic ranges and decreased time spent in hypo- and hyperglycemic ranges compared to open-loop SAP therapy (regardless of whether a PLGS feature was available) and MDII or insulin-pump therapy informed by SMBG.
- HCL therapy demonstrated a general trend in improving A1C levels, mean glucose concentrations, and glycemic variability compared to open-loop SAP therapy (with or without a PLGS feature) or MDII or insulin-pump therapy informed by SMBG across most studies.
- The rates of adverse events experienced by study participants, such as hypoglycemic events and ketosis events, were generally not statistically significantly different between those who were treated with HCL therapy and those who received control interventions. While this finding is favourable, additional studies with longer follow-up periods and larger sample sizes would reduce the uncertainty surrounding the safety of HCL therapy.

Methods

To inform the conduct of this HTA, a preliminary scoping review of the existing literature, including HTAs and SRs, was conducted.[64] A protocol[63] was written a priori in consideration of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols[65] for guidance on clarity, transparency, and completeness, and was followed throughout the study process. The protocol for the Clinical Review (PROSPERO registration number: CRD42020193156) was prospectively registered in the international repository, PROSPERO. Any deviations from the prospectively registered protocol are disclosed in this

final report (see Amendment Table) and updates were made to the PROSPERO submission accordingly.

Study Design

To address the clinical research questions, a SR of primary studies of the comparative clinical effectiveness and safety of commercialized HCL systems versus other insulin delivery methods in people with type 1 diabetes, in consideration of methods outlined in the Cochrane Handbook,[66] was conducted. This study design was selected following scoping activities that included a formal scoping review[64] of existing literature and a CADTH Rapid Response report (summary of abstracts)[67] that was conducted to obtain a general understanding of the current state of the literature regarding HCLs in people with type 1 diabetes. Details on the complete methodology for the Rapid Response report — including literature search methods, detailed article selection, eligibility criteria, and the processes used for study screening, data extraction, critical appraisal, and data analysis and synthesis — are available in the Rapid Response report.[67] Scoping activities failed to identify existing SRs that directly and comprehensively addressed our research questions. Therefore, a *de novo* SR of primary studies was conducted.

A protocol for this Clinical Review (PROSPERO registration number: CRD42020193156) was written a priori and followed throughout the review process.

Literature Search Methods

The literature search for clinical studies was 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).[68] The complete search strategy is presented in Appendix 1.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid, Embase (1974–) through Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL) through Ovid. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were closed-loop systems and type 1 diabetes. Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and WHO's International Clinical Trials Registry Platform (ICTRP) search portal.

No filters were applied to limit the retrieval by study type. Retrieval was limited to English- or French-language documents published from January 1, 2003 onward. Conference abstracts were excluded from the search results.

The initial search was completed on March 24, 2020. Regular alerts updated the database literature searches until the publication of the final report. The clinical trial registries search was updated prior to the completion of the stakeholder feedback period.

Grey literature (literature that is not commercially published) was identified by searching sources listed in relevant sections of the CADTH grey literature checklist, *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters),[69] which includes the websites of regulatory agencies, HTA agencies, clinical guideline repositories, SR repositories, patient-related groups, and professional associations. Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through

contacts with experts and industry, as appropriate. The grey literature search was updated prior to the completion of the stakeholder feedback period. See Appendix 2 for more information on the grey literature search strategy.

Selection and Eligibility Criteria

Studies were included if they were published in English or French and met the selection criteria presented in Table 1. The inclusion criteria were informed by the CADTH Rapid Response report,[67] the formal scoping review of the existing literature,[64] 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 HCL systems
Comparator	Any commercially available HCL systems or existing insulin delivery methods (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]; or MDII)
Outcomes[a]	**Question 1:** • General or diabetes-specific quality of life as reported by any standardized tool (e.g., EuroQol 5-Dimensions questionnaire score, Pediatric Quality of Life Inventory score, Diabetes Quality of Life measure) • A1C levels • Glucose time-in-range metrics as measured with continuous glucose monitoring (e.g., the proportion of time glucose levels are within 3.9 mmol/L and 10.0 mmol/L)[b] • 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-randomized controlled trials • cohort studies[c] • case-control studies Exclusions: • cross-sectional studies • single-arm, before-and-after studies or single-arm, interrupted time-series studies[d] • 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[e]

A1C = glycated hemoglobin; HCL = hybrid closed-loop insulin delivery; MDII = multiple daily insulin injections; RCT = randomized controlled trial.

[a] These outcomes were identified during scoping. However, findings relating to additional clinical outcomes that were not explicitly outlined here were still considered for inclusion for comprehensiveness. From the studies identified for inclusion in this review, these additional outcomes included mean glucose concentration, glycemic variability, body weight, daily insulin usage, insulin-to-carbohydrate ratios, basal-insulin proportions, diabetes distress, diabetes-specific positive well-being, prospective memory, retrospective memory, and perceived sleep quality.

[b] Time in range denotes the proportion of time that an individual's glucose level is within a desired target range. Given that target ranges were expected to vary among primary studies, all target ranges were considered relevant for this Clinical Review.

[c] 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.[70] 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.[70] Only study designs providing comparative evidence were eligible for inclusion.

[d] Single-arm, before-and-after studies and single-arm, interrupted time-series studies were excluded because they are not controlled with a separate group of patients; therefore, they are prone to many sources of bias that threaten both internal and external validity.[71]

[e] The year 2003 was selected because 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 was HCL systems in their commercially available (or expected to be commercially available) form. Studies that specifically referred to HCL systems by their commercial names or that provided clear descriptions of the HCL components (i.e., the control algorithm, insulin pump, and CGM) as being identical to those of commercially available systems were considered relevant for inclusion. Studies investigating HCL systems that were only available in experimental settings and were not on a path to commercialization were excluded. Studies that investigated an HCL system but did not include an explicit description of the device (e.g., if it was unclear whether the device was the same as the commercially available version) were excluded. Eligible study populations were not restricted by sex, gender, ethnicity, or comorbidities.

For the outcomes, all instruments and all time points were eligible for inclusion. For the safety outcomes for research question 2, data that allowed for comparisons between the intervention and comparator groups were of interest and included. (For example, the frequencies or prevalence of adverse events reported for each group were in scope, but non-quantifiable and non-comparable lists of adverse events for both groups were not in scope.)

Articles were excluded if they did not meet the selection criteria outlined in Table 1 or if they were duplicate publications. The protocol[63] had stated that if there were multiple publications fulfilling the inclusion criteria from the same study (i.e., same population), they would all be included, and data would be extracted and discussed as a single study. However, no such situation was encountered. Lists of included and excluded studies, with reasons for exclusion after full-text review, are provided in the Results section of this Clinical Review section.

Study Selection

The SR management software DistillerSR (Evidence Partners, Ottawa, Canada) was used for study selection. Two reviewers independently screened titles and abstracts of all the citations retrieved from the literature search (i.e., academic database and grey literature searches). Full texts that were judged to be potentially relevant by at least 1 reviewer were

retrieved and independently assessed for possible inclusion based on the selection criteria outlined in Table 1 (i.e., if 1 reviewer believed the citation should be screened at the full-text level, it was moved forward to the next level of screening; no conflict resolution was performed). Two reviewers independently examined all full-text articles; consensus was required for inclusion in the review. Discrepancies between reviewers were resolved by discussion between the reviewers or by consultation with a third reviewer, if necessary. A list of studies selected for inclusion was posted on the CADTH website for stakeholder review for 10 business days for feedback, and any additional studies identified for potential inclusion were reviewed following the process discussed previously.

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

The study selection process was presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart,[72] which is provided in the Results section of this Clinical Review section.

Data Extraction

Data extraction was performed by 1 reviewer in structured tables in Microsoft Word, and independently checked by a second reviewer for accuracy and for any relevant data that might have been missed by the first reviewer. Disagreements were resolved through discussion until consensus was reached, or through adjudication by a third reviewer, if necessary. Relevant information on the following was extracted, where available:

- 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, pregnancy or plans for pregnancy, history of severe hypoglycemia, hypoglycemia unawareness])
- intervention (e.g., type of HCL system, a description of any pertinent device settings or options)
- comparators (e.g., type of insulin delivery system or method)
- description of outcomes (e.g., measurement method, unit of measurement, length of follow-up) and results and conclusions regarding the outcomes and subgroups of interest.

Data were extracted for all relevant outcomes for this study at any duration of follow-up. Data on outcomes not identified during scoping — and, consequently, not explicitly outlined as being of interest in the protocol for the Clinical Review but that addressed the clinical effectiveness and safety of HCL systems — were also extracted from the included studies. Although the decision to include these findings required a protocol amendment (Amendment Table), it was agreed that it was necessary to ensure all relevant results could be considered when addressing the decision problem. 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 were extracted.

The protocol had stated that if relevant data were missing from or conflicting in the included studies, attempts would be made to contact the corresponding authors of these studies to obtain missing information or clarify conflicting information. While no such situation was encountered, in 2 studies, it was unclear whether participants in the control group received open-loop SAP therapy with or without PLGS features. Attempts were made to contact the authors of these studies to clarify this information. Responses were received from the authors of both studies and the information was included in the extracted data.

Critical Appraisal

The risk of bias for included studies was evaluated using the Cochrane Risk-of-Bias tool, version 2 (RoB 2)[73] for RCTs and the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS)[74,75] for non-randomized studies.[76] RoB 2[73] allows for the assessment of 5 sources of bias or "domains": bias arising from the randomization process; bias due to deviations from intended interventions; bias due to missing outcomes data; bias in measurement of the outcome; and bias in selection of the reported result. Each question was answered with 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 was assigned, with rationale for each decision included in the comments box field. Based on judgments across the 5 domains, an overall risk of bias was assigned to each study (low, high, or some concerns).[73] RoBANS, which was selected for its reliability, validity, and user-friendly design,[74,75] also allows for the assessment of risk of bias across 8 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 was assigned, with a rationale for each decision included in the comments box field. An overall risk-of-bias judgment for each study was provided: "high risk of bias" if the study had at least 1 domain that was at "high risk of bias;" "some concerns" if the study had at least 1 domain that was "unclear" but no domain that was at "at high risk of bias;" or "low risk of bias" if the study had "low risk of bias" for all domains. Because the RoBANS guidance did not provide a specific approach for making study-level judgments, this was borrowed from the RoB 2 guidance for methodological consistency.

The risk-of-bias assessments of the included studies was performed by 1 reviewer and independently checked for accuracy by a second. Disagreements were resolved through discussion, and could involve a third reviewer if necessary. The tools were used as a guide to evaluate the risk of bias in the included studies; additional insight beyond the items on the instruments was provided when applicable. Summary scores were not calculated; rather, reviews of the strengths and limitations of each included study and how they affect the study findings were described narratively. The results of the critical appraisal were used to assess confidence in the results, not to exclude studies from this review.

Data Analysis and Synthesis

Narrative Synthesis

Narrative syntheses were performed, including the presentation of study characteristics and findings within summary tables and in the main text. Findings were 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 were not combined, but rather described separately.

A narrative summary of the results of the methodological assessments for each included study was provided. Specifically, tables were 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 were considered, where the results of eligible studies would be pooled, if data were deemed sufficiently homogeneous in terms of clinical, methodological, and statistical characteristics. A meta-analysis was to be conducted for each outcome of interest (e.g., quality of life, risk for hypoglycemic events, risk for other adverse events, fear of hypoglycemia, patient satisfaction) and separately between randomized and non-randomized studies (i.e., results from randomized and non-randomized studies would not be pooled). However, there were no instances where multiple studies were considered sufficiently homogeneous to conduct a meta-analysis. A detailed description of the sources of clinical, methodological, and statistical heterogeneity and reasons for not conducting meta-analyses was documented and is provided in the Results section of this Clinical Review section.

Subgroup Analyses

Based on the results of preliminary scoping, the protocol identified the following as potential subgroups of interest to explore in narrative syntheses and meta-analyses:

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

Any relevant data on these subgroups of interest were extracted and are described in narrative syntheses.

Reporting of Findings

The SR was prepared in consideration of relevant reporting guidelines (i.e., the PRISMA statement, PRISMA harms, and Synthesis Without Meta-analysis guideline) and the criteria outlined in the checklist A Measurement Tool to Assess Systematic Reviews 2.

Results

Quantity of Research Available

A total of 1,875 unique citations were identified in the electronic literature search. After titles and abstracts were screened, 1,532 citations were excluded, and 343 potentially relevant reports were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full-text review. In addition, 26 potentially relevant reports were retrieved from the search alerts. Of these 371 potentially relevant

articles, 361 publications were excluded for various reasons, while 9 unique studies (8 RCTs and 1 non-randomized study) in 10 publications met the inclusion criteria and were included in this Clinical Review. No new studies were identified during the stakeholder review of the included studies. The study selection process is outlined in Appendix 2 using a PRISMA[72] diagram (Figure 4). Lists of included and excluded citations, with details describing the rationale for those excluded, are presented in Appendix 3 and Appendix 4, respectively.

Study Characteristics

The characteristics of the 8 RCTs (in 9 publications[50-57,59]) and 1 non-randomized study[58] that were identified for inclusion in this Clinical Review are described here. Additional details regarding the characteristics of the included studies are available in Table 38 inAppendix 2.

Study Design, Year of Publication, Setting, and Source of Funding

Eight RCTs (in 9 publications) were included in this Clinical Review. Six of these RCTs were conducted using a parallel-group design, while the other 2 RCTs used a randomized crossover design. All 8 RCTs were multi-centre and open-label (i.e., participants, care providers, and outcome assessors were aware of the intervention that participants received). Brown et al. (2020) and Forlenza et al. (2019) were extension studies of Brown et al. (2019) and Ekhlaspour et al. (2019), respectively, both of which were also included in this Clinical Review. Isganaitis et al. (2020) reported on a subgroup analysis from the RCT by Brown et al. (2019) and is reported together with Brown et al. (2019) throughout this Clinical Review. In addition to the RCTs, 1 non-randomized study was included in this Clinical Review. This study was a single-centre, open-label, retrospective, matched-cohort study.

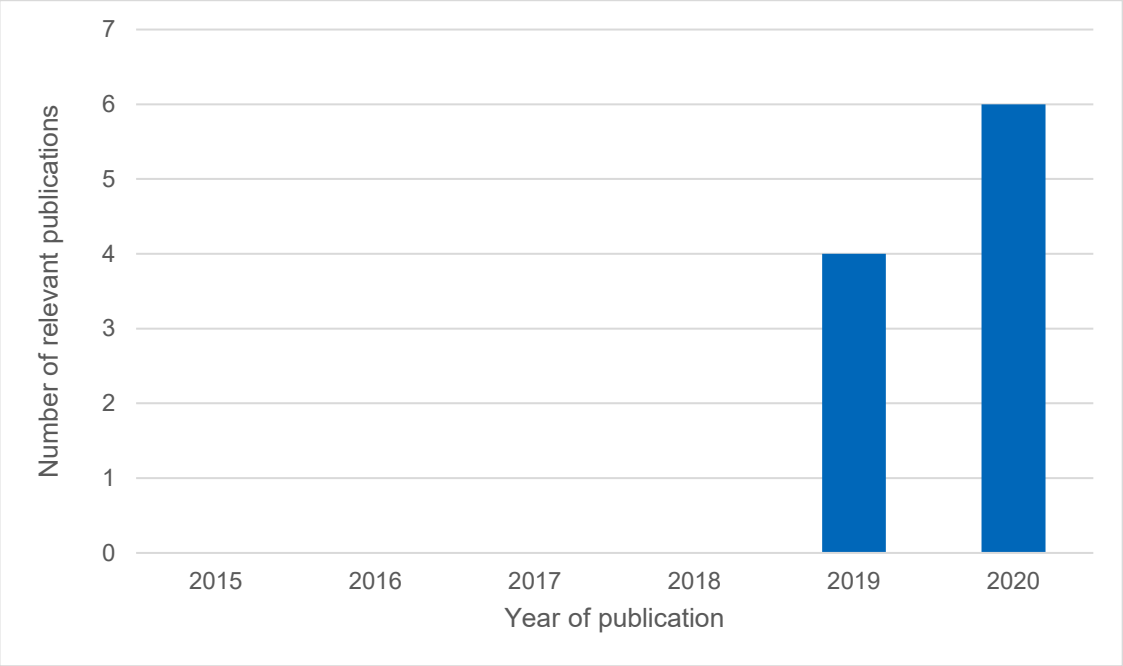
The 10 publications identified for inclusion in this Clinical Review were published in 2019 and 2020 (Figure 1).

Three RCTs were conducted in relatively controlled environments, while 6 studies (5 RCTs in 6 publications and 1 non-randomized study) were conducted under free-living conditions. Participants in the Hanaire et al. (2020) study were largely restricted to hospital settings throughout the 3-day testing period. They were divided into 3 groups: 1 was tested under rest conditions (i.e., minimal physical activity); 1 was provided restaurant dinners over 3 consecutive nights; and 1 was asked to participate in sustained and repeated bouts of physical exercise followed by uncontrolled food and carbohydrate intake. The Ekhlaspour et al. (2020) study was conducted at 3 ski camp environments over the course of 48 hours, and all participants had their CGM data remotely monitored by study staff throughout the study period. Participants of the Forlenza et al. (2019) study were provided study devices for 3 days of at-home use; however, all participants were remotely monitored through alerts by a study physician 24 hours per day. The 6 remaining studies monitored participants using study devices under “real-world” environments.

The authors of 5 studies received study funding directly from industry, either from Diabeloop[50,56] or Tandem Diabetes Care.[51,54,55] Three studies[52,53,57,59] received HCL systems, supplies, and technical expertise (to deal with device issues) from industry (i.e., Tandem Diabetes Care, Roche Diabetes Care, or Medtronic), but stated explicitly that these companies were not involved in the trial design or data analysis. Additional sources of funding included the National Institute of Diabetes and Digestive and Kidney Diseases,[51-53,57] the University of Virginia Strategic Investment Fund,[52-55,57] bpiFrance,[56] the Center for Studies and Research for the Intensification of the Treatment of Diabetes,[56] the Australian Type 1 Diabetes Clinical Research Network,[59] the National Health and Medical Research

Council of Australia,[59] and the French Innovation Fund. The authors of the cohort study[58] stated that no specific funding was received for their study.

Figure 1: Number of Included Publications by Publication Year



Note: Two publications reported on the same study.

Alt text: 10 publications were included in the Clinical Review. Of these, 4 were published in 2019, and 6 were published in 2020.

Country of Origin

Five RCTs were conducted in the US, 2 RCTs were conducted in France, and 1 RCT was conducted in Australia. The cohort study was conducted in Italy.

Patient Population

Consistent with the inclusion criteria, all participants in the included studies had type 1 diabetes. Four studies[50,56,58,59] (3 RCTs and 1 cohort study) were specific to adult populations; 3 RCTs[51,54,55] were specific to children and adolescents; and 2 RCTs (in 3 publications) recruited a diverse population that included both adults and adolescents. Hanaire et al. (2020)[56] enrolled 38 adults (18 years of age or older; mean age: 49.9 years) who had used insulin-pump therapy continuously over the last 6 months, had experience with carbohydrate counting, and had A1C values from 6.0% to 9.5% (42 mmol/mol to 80 mmol/mol). Lepore et al. (2020)[58] included data from 40 adults (mean age: 44 years) who had been using SAP therapy for at least 12 months before the study. McAuley et al. (2020)[59] included 120 adults (ages 25 years to 75 years; mean age: 44.2 years) who had had a clinical diagnosis of type 1 diabetes for at least 1 year, had A1C values of less than 10.5% at the time of enrolment, and had been receiving treatment using MDII or insulin-pump therapy. Benhamou et al. (2019) recruited 63 adults (18 years of age or older; mean age: 48.2 years) who had used insulin-pump therapy continuously over the preceding 6 months, had A1C values of less than 10.0% (86 mmol/mol), and had preserved hypoglycemia awareness. Breton et al. (2020)[51] enrolled 101 children between the ages of 6 years and 13 years (mean

age: 11.2 years) who had been diagnosed with type 1 diabetes at least 1 year prior to the study, had received treatment with insulin for at least the preceding 6 months (with a minimum dose of 10 units per day), and were familiar with carbohydrate ratios for meal boluses. Ekhlaspour and colleagues[54] enrolled 24 children and adolescents (between the ages of 6 years and 18 years; mean age: 12.3 years) who had been on insulin-pump therapy for at least 3 months and insulin-treated for a total of at least 6 months. The Forlenza et al. (2019)[55] study, which was an extension of the Ekhlaspour et al. (2019)[54] study, included 24 children between the ages of 6 years and 12 years with a mean age of 9.6 years. Brown et al. (2019)[53] included 168 individuals (14 years of age or older; mean age: 33 years) who had been treated using insulin delivered by a pump or MDII for at least 1 year, were familiar with using carbohydrate ratios for meal boluses, and had a total daily insulin dose of at least 10 units per day. Isganaitis et al. (2020)[57] reported on a subgroup of 63 participants (between the ages of 14 years and 25 years; mean age: 17 years) from the RCT by Brown et al. (2019).[53] Brown et al. (2020)[52] was an extension to Brown et al. (2019);[53] thus, it had similar inclusion criteria. It enrolled a subset of the participants included in the original study (N = 109; mean age: 33 years).

A total of 578 unique participants were included in the 9 primary studies reported in 10 publications[50-59] (when those who also participated in the extension studies[52,55] were only counted once). The proportion of female participants in studies ranged from 45%[58] to 62%. The mean body mass index (BMI) of study populations ranged from 18.5 kg/m[55] to 26.4 kg/m (1 study did not report the mean BMI of study participants[51]);[59] mean baseline A1C values ranged from 7.0% (53.5 mmol/mol)[52] to 7.8% (62 mmol/mol).[56]

Interventions and Comparators

This review included studies that compared HCL systems in their commercially available (or expected to be commercially available) forms with existing insulin delivery methods (i.e., MDII, open-loop SAP therapies with or without PLGS features, or insulin-pump therapy informed by SMBG). No studies comparing HCL system to each other were found. Within the included literature, 5 studies (in 6 publications[51-55,57]) examined the Tandem Control-IQ HCL system; 2 studies[50,56] examined the Diabeloop single-hormone HCL system; and 2 studies[58,59] examined the Medtronic MiniMed 670G system. The Control-IQ system was composed of a t:slim X2 insulin pump, a Dexcom G6 CGM, and the Control-IQ software.[51-55,57] The Diabeloop HCL included a Cellnovo insulin pump and a Dexcom G5 CGM that were managed by the Diabeloop algorithm installed on an Android smartphone. The MiniMed 670G system consisted of a MiniMed 670G insulin pump and a Guardian Sensor 3 or Enlite 3 CGM managed by the MiniMed 670G software.[58,59]

As for comparators, 5 studies (in 6 publications[50,53-57]) included control groups that received open-loop SAP therapy; 2 studies[52,58] included control groups that received open-loop SAP therapies with PLGS features; 1 study[51] compared HCL therapy to a control group that included participants with either an open-loop SAP system or an open-loop SAP system with a PLGS feature; and 1 study[59] included a control group that received insulin delivery with MDII or insulin-pump therapy with insulin dosing based on SMBG. Specifically, participants in the control groups of 4 studies[50,54-56] used open-loop SAP therapies that included their existing insulin pumps and a Dexcom G5 CGM. The RCT described in Brown et al. (2019)[53] and Isganaitis et al. (2020)[57] provided control group participants with open-loop SAP therapy that included the participants' existing insulin pump or a study-provided t:slim X2 pump (without the Control-IQ software) and a Dexcom G6 CGM. The authors of the Brown et al. (2020)[52] study provided participants in their control group with an open-loop PLGS system

that included a t:slim X2 insulin pump and a Dexcom G6 CGM that were managed by the Basal-IQ software. The control group in the study by Lepore and colleagues[58] used a MiniMed 640G insulin pump with a PLGS feature and a Guardian Sensor 3 CGM. Participants allocated to the control group of the 2020 RCT by Breton et al.[51] who were already on open-loop SAP therapy continued to use their personal systems (with Dexcom G6 CGMs); those who were receiving MDII were provided with a t:slim X2 insulin pump with a PLGS feature and a Dexcom G6 CGM. Therefore, the control group included a mix of patients who used an open-loop SAP system with (N = 15) or without a PLGS feature (N = 8).Finally, participants allocated to the control group in the 2020 RCT by McAuley et al.[59] continued the use of their own personal insulin delivery devices, which were either MDII or insulin pumps that did not include automated insulin delivery features but were informed by SMBG using blood glucose meters. These participants wore Guardian Sensor 3 CGMs to collect study outcome measurements, but did not have access to the glucose levels recorded by the CGM devices to inform their insulin dosing. Of the 59 participants in this control group, 31 used MDII, while 28 used an insulin pump.

Outcome Measures

Measures of Clinical Effectiveness (Research Question #1)

All included studies reported on outcomes relating to the clinical effectiveness of HCL systems. Nine studies examined various glucose time-in-range metrics; 6 studies reported on A1C measures; 3 studies examined patient satisfaction; 1 study reported on quality of life measures; and 9 studies reported on additional clinical outcomes that were not explicitly outlined in the protocol for this Clinical Review, but were related to clinical effectiveness, including mean glucose concentration (9 studies), glycemic variability (9 studies), body weight (9 studies), daily insulin usage (8 studies), insulin-to-carbohydrate ratios (1 study), basal-insulin proportions (1 study), diabetes distress (1 study), diabetes-specific positive well-being (1 study), prospective memory (1 study), retrospective memory (1 study), and perceived sleep quality (1 study). Findings for all outcomes that were reported in the identified studies and that addressed the research question, regardless of whether they were outlined in the protocol, were considered relevant for this Clinical Review.

Glucose time-in-range metrics refer to the proportion of time that an individual's glucose level is within a specified glucose range, as measured with a CGM. These included ranges or thresholds indicating euglycemia (e.g., glucose levels from 3.9 mmol/L to 10.0 mmol/L or 3.9 mmol/L to 7.8 mmol/L), hypoglycemia (e.g., glucose levels < 2.8 mmol/L, < 3.0 mmol/L, < 3.3 mmol/L, or < 3.9 mmol/L), and hyperglycemia (e.g., glucose levels > 10.0 mmol/L, > 11.1 mmol/L, > 13.9 mmol/L, > 16.7 mmol/L). The ranges were not standardized across primary studies; however, there were common ranges or thresholds reported across multiple studies. These percentages were reported as a mean value with a standard deviation (SD) or as a median value with an interquartile range (IQR) or a 75% confidence interval (CI). Although 2 studies[50,56] expressed glucose time-in-range thresholds in mmol/L, most studies[51-55,57-59] provided values in mg/dL. Values in mg/dL were converted to mmol/L by multiplying them by 0.05551 to permit consistency in the reporting of the results.

Measures of A1C included mean values at the end of study period,[51-53,57,59] mean percentage changes in A1C levels from baseline,[50,58] the proportion of participants with A1C levels at specific thresholds post-treatment (e.g., < 7.0%, < 7.5%),[51-53,57] and the proportion of participants whose A1C levels improved by a specific amount throughout the study period (e.g., an absolute reduction of > 0.5% from baseline, an absolute reduction of > 1.0% from baseline, or a relative reduction of > 10% from baseline).[51-53,57] A1C levels were expressed

as a percentage (National Glycohemoglobin Standardization Program unit) or as a value in mmol/mol (the International Federation of Clinical Chemistry and Laboratory Medicine unit).[81,82]

Patient satisfaction was measured using the Diabetes Treatment Satisfaction Questionnaire (DTSQ),[83] which is composed of 8 questions that patients score on a scale ranging from 0 (e.g., "very dissatisfied," "very inconvenient") to 6 (e.g., "very satisfied," "very convenient"). Six questions assess patient satisfaction, while 2 questions assess the burden of hyperglycemia and hypoglycemia. Total satisfaction scores range between 0 and 36 (based on the answer to the 6 satisfaction questions), where higher scores indicate higher treatment satisfaction. The DTSQ is a standardized and validated tool.[84] None of the studies[50,56,59] that administered the DTSQ to participants reported on the results of the 2 questions that assessed the burden of hyperglycemia and hypoglycemia.

Diabetes-specific quality of life was measured using the DAWN2 Impact of Diabetes Profile (DIDP). The RCT[59] that assessed this outcome did not provide any information on how the DIDP is scored.

Several additional psychosocial, cognitive, and sleep quality outcomes were measured in 1 study.[59] Diabetes distress was measured with the Problem Areas in Diabetes (PAID) scores. The PAID questionnaire includes 20 items, each of which asks the person about problems that are commonly experienced by patients with diabetes. Each item is ranked on a scale of 0 (not a problem) to 4 (serious problem). Total scores can be standardized to a score out of 100 by multiplying the total or each item by 1.25. Higher total scores indicate higher levels of diabetes-related distress.[85] Diabetes-specific positive well-being was measured with the 4-item subscale of Well-Being Questionnaire 28 (W-BQ28) scores. No information about the scoring of the W-BQ28 was available in the study.[59] Prospective memory and retrospective memory were measured with the Prospective and Retrospective Memory Questionnaire (PRMQ).[86] The PRMQ consists of 16 items that gauge prospective and retrospective memory. Items are rated on a 5-point scale between 1 (never) and 5 (very often). Higher scores represent greater frequency of memory failures. Perceived sleep quality was measured with the Pittsburgh Sleep Quality Index (PSQI), which contains a total of 19 self-rated questions. The 19 self-rated questions are combined to form 7 component scores, each of which is scored between 0 (no difficulty) and 3 (severe difficulty). Total scores range between 0 and 21, with higher scores indicating increased difficulty with sleeping.[87]

Mean glucose concentration was measured using CGM devices and was typically reported as a mean value throughout the entire study period. Similar to glucose time-in-range metrics, mean glucose values that were expressed by primary study authors in mg/dL were converted to mmol/L for the evidence synthesis. Glycemic variability was assessed by the coefficient of variation of sensor glucose in 8 studies[50-55,57-59] and was assessed by the standard deviations of the mean percentage of time spent in the glucose range of 4.4 mmol/L to 7.8 mmol/L overnight in 1 study.[56] Body weight was reported in kg, while daily insulin usage was expressed in units per day or units per kg of body weight per day.

Durations of follow-up periods were 2 days,[54] 3 days,[55,56] 12 weeks, 13 weeks,[52] 16 weeks,[51] and 26 weeks.[53,57-59] Outcome data obtained using CGMs were measured continuously throughout the study periods. For other outcomes, measurements occurred at baseline and follow-up visits.

No studies reporting on fear of hypoglycemia or discontinuation rates were identified.

Measures of Safety (Research Question #2)

Nine studies (in 10 publications[50-59]) reported on safety data that allowed for comparisons between the intervention and comparator groups (e.g., frequencies or prevalence of adverse events). These outcomes included the number of hypoglycemic events (9 studies[50-59]), hyperglycemic events (4 studies[50-53,57]), adverse events (5 studies[51-53,56,59]), diabetic ketoacidosis events (6 studies[50-53,57-59]), ketosis events (3 studies[51-53]), and the proportion of participants who had a worsening in their A1C levels of 0.5% or greater (3 studies[51-53]). The definitions of these events were not uniform across all studies.

Hypoglycemic events were defined as at least 15 consecutive minutes with a CGM-measured glucose level of less than 3.9 mmol/L by Breton and colleagues[51] and Brown and colleagues,[52] as a CGM-measured glucose level of less than 3.9 mmol/L by Hanaire and colleagues[56] (without specifying a time window), as at least 15 consecutive minutes with a CGM-measured glucose level of less than 3.0 mmol/L in Brown et al. (2019),[53] and as hypoglycemia requiring third-party intervention in Lepore et al. (2020),[58] McAuley et al. (2020),[59] and Benhamou et al. (2019). Ekhlaspour and colleagues[54] and Forlenza and colleagues[55] reported on the total amount of carbohydrate used in carbohydrate treatments, in grams, and the total number of carbohydrate treatments for hypoglycemia required by participants in their studies. These definitions of hypoglycemic events were selected by the authors of the primary studies, and may indicate more severe occurrences of hypoglycemic events than those described in the Diabetes Canada Clinical Practice Guidelines,[88] which define hypoglycemia as the development of autonomic or neuroglycopenic symptoms; a plasma glucose level of less than 4.0 mmol/L; or symptoms responding to the administration of carbohydrate.

Four RCTs[50,51,53,59] reported on the number of hyperglycemic events experienced by participants. A hyperglycemic event was defined as at least 15 consecutive minutes with a glucose level greater than 16.7 mmol/L by 2 studies,[51,53] and as a capillary blood glucose level greater than 20.0 mmol/L by the Benhamou et al. (2019) study. It was undefined in McAuley et al. (2020).[59]

Three studies[51-53] reported on the proportion of participants who experienced any adverse event. Adverse events included diabetic ketoacidosis, hyperglycemia, hypoglycemia, and hospitalizations for various reasons (e.g., concussion, otitis, cardiac bypass surgery, and gastroenteritis leading to ketosis).

Three studies[51-53] reported on the mean number of days where patients had 1 or more blood ketone measurements indicating a level greater than > 1.0 mmol/L (i.e., a ketosis event).

Critical Appraisal

A summary of the risk of bias assessment can be found inAppendix 2, Table 39 for the 8 RCTs and in Table 40 for the non-randomized study. Overall, each of the included studies exhibited some risk of bias, described in the sections that follow.

Risk of Bias in Randomized Controlled Trials

The risk of bias in 8 RCTs (in 9 publications) was assessed using the RoB 2 tool.

There were some concerns with the risk of bias arising from the randomization process in 5 RCTs.[50-53,56,57] The authors of 2 RCTs[52,56] provided no information on their methods of randomization, their allocation sequences, or whether their allocation sequences were concealed until participants were enrolled and assigned to an intervention. Three

RCTs[50,51,53,57] used computerized random allocation sequences; however, no information was provided about whether the allocation sequence was concealed until participants were enrolled and assigned to the intervention in any of these 3 RCTs.[50,51,53] Three RCTs[54,55,59] were judged as being at low risk of bias arising from the randomization process because participants were enrolled and matched based on various baseline characteristics (e.g., their age, baseline A1C values, trial site, and previous mode of insulin delivery) prior to randomization, precluding recruiters from selectively enrolling participants into permutated blocks of known size. As a result, the allocation sequence was concealed until participants were enrolled and assigned to interventions in all 3 studies. In all 8 RCTs,[50-57,59] there were no baseline differences between intervention groups that suggested a problem with the randomization process, given that all intervention groups within the RCTs were well-balanced for characteristics such as age, sex, BMI, and baseline A1C values.

The risk of bias due to deviation from the intended interventions was judged to be low in all 8 RCTs.[50-57,59] Because HCL systems and the comparator interventions investigated in these studies (i.e., open-loop SAP therapies with or without PLGS features, MDII, and insulin-pump therapy informed by SMBG) required significant user input, it would not have been possible to blind the participants or the individuals delivering care to the intervention assignment during the trial. Although these RCTs[50-57,59] were open-label, there were no reported deviations from the intended interventions that arose because of the trial context. Appropriate analyses were used to estimate the effects of assignment to intervention. Although it is expected that participants assigned to HCL therapy or to open-loop SAP systems with PLGS features may have disabled key automation features for various lengths of time throughout the trials, this was not considered a deviation from the intended intervention, given that users of HCL therapy in the real world are expected to similarly enable and disable features as they desire. For example, an individual assigned to the HCL therapy group in a clinical trial could have disabled auto mode on the device, effectively changing the device to function as an open-loop SAP system. Similarly, participants in the Ekhlaspour et al. (2019)[54] study who were assigned to the control group and asked to deactivate automated insulin modes (e.g., PLGS features) could have reactivated these features during the study period. The proportion of participants using their devices as prescribed was typically high when reported. HCL modes were enabled for a median of 93% (IQR, 91% to 95%) of the time in the Breton et al. (2020)[51] study, 83.8% (IQR, 72.3% to 89.3%) of the time in the Benhamou et al. (2019) study, 90% (IQR, 86% to 94%) of the time in the Brown et al. (2019)[53] study, and mean proportions of time of 82.9%, 94%, and 94.4% in the RCTs by Hanaire and colleagues,[56] Ekhlaspour and colleagues,[54] and Forlenza and colleagues,[55] respectively. Brown et al. (2020)[52] reported that the median proportion of time spent in auto mode for participants assigned to the HCL group was 67% (IQR, 60% to 79%). This lower value was attributed to a 4-week period where a temporary suspension of HCL systems was implemented as a precaution after a software error was found. McAuley et al. (2020)[59] reported on the median proportion of time participants in their HCL group had the closed-loop system enabled during each month of their 6-month trial. These values ranged from 84% during month 6 (IQR, 78% to 89%) to 88% during month 1 (IQR, 82% to 92%). Statistical analyses were performed on an intention-to-treat basis in 4 RCTs,[51-53,57,59] while modified intention-to-treat analyses were conducted in the 4 RCTs[50,54-56] that had participants with missing outcome data. In all 4 studies[50,54-56] that used modified intention-to-treat analyses, participants' data were analyzed according to the treatment group to which they were originally assigned, regardless of the treatment received; however, participants who withdrew from the study for any reason (e.g., those who withdrew consent) were excluded from the analysis.

Data for all outcomes of interest, including glucose time-in-range metrics, A1C values, participant satisfaction, quality of life, other clinical outcomes, and safety outcomes were available from all or nearly all participants randomized in the included RCTs.[50-57,59] For example, 3 RCTs[52,53,55,57] had outcome data for all participants randomized, while the remaining 5 RCTs[50,51,54,56,59] appeared to have data from at least 90% of the randomized participants. Thus, the included RCTs[50,52-56,59] were judged to be at low risk of bias due to missing outcome data. Nevertheless, McAuley et al. (2020)[59] replaced missing data under a "missing at random" assumption, where data were multiply imputed using a multivariate normal regression imputation method. Additionally, McAuley et al. (2020)[59] conducted sensitivity analyses of the primary outcome by changing the missing data replacement assumption to "missing completely at random" and "missing not at random" as well as to the per-protocol population. Data imputation strategies were not used for those with missing outcome data in the other 7 RCTs.[50-57]

The risk of bias in the measurement of outcomes was assessed across all 8 RCTs[50-57,59] for each outcome of interest. Overall, the method of measurement for all included outcomes was deemed to be likely appropriate (e.g., CGM devices were used to measure glucose time-in-range metrics and mean glucose values; A1C values were measured using appropriate laboratory or point-of-care techniques; the DTSQ was used to measure patient satisfaction; the DIDP was used to measure diabetes-specific quality of life; and safety events were patient-reported or measured using predefined CGM thresholds). Four RCTs[51-53,57,59] reported an increased number of follow-up visits or phone contacts with care providers in 1 of their intervention groups. Breton et al. (2020)[51] and the RCT described in Brown et al. (2019)[53] and Isganaitis et al. (2020)[57] reported an increased number of unscheduled follow-up visits by those who received HCL therapy, mostly to retrieve HCL system updates or supplies related to the trial. The Brown et al. (2020)[52] study provided 2 additional scheduled phone contacts to participants who received open-loop SAP therapy with a PLGS feature in order to review device data and make changes to their diabetes management as indicated. McAuley et al. (2020)[59] noted that participants in their HCL group had a higher total number of visits and contacts (in person or by email or phone) and more time spent with study staff for study activities, education, and time to review pump settings than those in their control group. In all 4 studies, these additional follow-up visits or phone contacts were considered insignificant because the reasons for them were well-reported and likely did not affect the outcome assessment. The studies by Hanaire et al. (2020)[56] and Benhamou et al. (2019) were conducted using crossover designs; however, in both cases, an appropriate washout period was provided that would have minimized any potential carry-over effects from one intervention period to the next. Benhamou et al. (2019) conducted a sensitivity analysis of the primary end point that indicated there was no carry-over effect present. It was not likely that the measurement or ascertainment of the reported outcomes would have differed between intervention groups in all 8 RCTs.[50-57,59] Outcome assessors were aware of the interventions received by study participants in all 8 RCTs.[50-57,59] In general, open-label trials are regarded as being more susceptible to bias than blinded trials, given that knowledge of treatment allocation may have an effect on the reporting of outcomes; however, it was unlikely that the assessment of most outcomes was influenced by knowledge of the intervention received, given that the reported outcomes were largely objectively measured (e.g., CGM data and A1C values cannot be influenced by the assessor). For outcomes that relied on patient reporting — such as adverse events that were not measured using CGM devices, patient satisfaction, and diabetes-specific quality of life — it is possible that their assessment could have been influenced by the knowledge of the intervention received. Overall, there were some concerns with the risk of bias in the

measurement of outcomes in 5 RCTs.[50,51,53,56,57,59] The risk of bias in the measurement of outcomes was deemed to be low in 3 RCTs.[52,54,55]

The risk of bias in the selection of the reported results was judged to be low for the included RCTs.[50-57,59] The data that produced the reported results were likely analyzed in accordance with pre-specified analysis plans that were finalized before outcome data were made available. Published protocols were made available prior to participant enrolment in all 8 RCTs.[50-57,59] In 4 studies,[50,51,53,57,59] authors explicitly stated that their analyses followed a pre-specified statistical analysis plan. For the remaining 4 RCTs, it was not likely that the numeric results being assessed were selected on the basis of results from multiple eligible outcome measurements within the outcome domains or multiple eligible analyses of the data, based on a review of the published a priori protocols where the pre-specified outcomes were compared with those that were reported in the final publication. Additionally, the 2 extension studies[52,55] were both outlined in the protocols for their preceding studies,[53,54] decreasing the risk that they were conducted to select for favourable results.

Judgments made across the 5 RoB 2 domains were combined to provide an overall risk-of-bias judgment for each of the included RCTs.[50-57,59] The Ekhlaspour et al. (2019)[54] and Forlenza et al. (2019)[55] studies were given an overall risk-of-bias score of low risk, while the remaining 6 RCTs[50-53,56,57,59] were judged as having some concerns with their risk of bias. This distinction is due to the differences in the risk for bias arising from the randomization process and in the measurement of outcomes. A summary of the results of the risk-of-bias assessments of the identified RCTs is provided in Table 2.

Table 2: Summary of Risk of Bias in the Randomized Controlled Trials Assessed Using the RoB 2

Study citation	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	Bias in selection of the reported result	Overall risk of bias
Breton et al. (2020)[51]	Some concerns	Low risk	Low risk (for all outcomes)	Glucose TIR metrics: Low risk A1C: Low risk AEs: Some concerns	Low risk	Some concerns
Brown et al. (2020)[52]	Some concerns	Low risk	Low risk (for all outcomes)	Low risk (for all outcomes)	Low risk	Some concerns
Hanaire et al. (2020)[56]	Some concerns	Low risk	Low risk (for all outcomes)	Glucose TIR metrics: Low risk Patient satisfaction: Some concerns AEs: Low risk	Low risk	Some concerns
McAuley et al. (2020)[59]	Low risk	Low risk	Low risk (for all outcomes)	Glucose TIR metrics: Low risk A1C: Low risk Patient satisfaction: Some concerns Psychosocial, cognitive, and sleep quality outcomes: Some concerns[a]	Low risk	Some concerns
Benhamou et al. (2019)[50]	Some concerns	Low risk	Low risk (for all outcomes)	Glucose TIR metrics: Low risk A1C: Low risk Patient satisfaction: Some concerns	Low risk	Some concerns
Brown et al. (2019)[53] and	Some concerns	Low risk	Low risk (for all outcomes)	Glucose TIR metrics: Low risk	Low risk	Some concerns

Study citation	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	Bias in selection of the reported result	Overall risk of bias
Isganaitis et al. (2020)[57]				A1C: Low risk AEs: Some concerns		
Ekhlaspour et al. (2019)[54]	Low risk	Low risk	Low risk (for all outcomes)	Low risk (for all outcomes)	Low risk	Low risk
Forlenza et al. (2019)[55]	Low risk	Low risk	Low risk (for all outcomes)	Low risk (for all outcomes)	Low risk	Low risk

A1C = glycated hemoglobin; AE = adverse event; RoB 2 = Cochrane Risk-of-Bias tool, version 2; TIR = time in range.

[a] Psychosocial, cognitive, and sleep quality outcomes included diabetes-specific quality of life, diabetes distress, diabetes-specific positive well-being, prospective memory, retrospective memory, and perceived sleep quality.

Risk of Bias in Non-Randomized Studies

The risk of bias in 1 non-randomized study was assessed using the RoBANS tool.

The risk of selection bias due to the selection of an inappropriate comparison target group was judged to be low, given that the intervention (HCL therapy) and control groups (open-loop SAP therapy with a PLGS feature) were selected from comparable populations from the same centre and that there were no statistically significant differences between groups in demographic and baseline characteristics (e.g., age, sex, duration of diabetes, BMI, A1C levels).

Although a standardized list of inclusion and exclusion criteria were applied to both study groups, the target group selection domain was at high risk of bias because the study authors were responsible for deciding which participants should be suggested for switching to HCL therapy. It is possible that participants' and the authors' perceptions and expectations of the effectiveness of HCL therapy may have influenced who received HCL treatment in a biased manner. Additionally, participants who volunteered to switch to HCL therapy may have had a stronger motivation to improve glucose control than those who remained on the open-loop system with a PLGS feature.

The study was considered at low risk of bias due to confounding, given that the major confounding variables were adequately confirmed and considered during the planning and analysis stages of the study. For example, confounding characteristics — such as age, baseline A1C values, and familiarity with CGM devices, carbohydrate counting, and insulin bolus calculators — were measured across the study groups, and were described as being similar.

There was a low risk of performance bias due to inappropriate exposure measurement, given that the data were obtained from insulin pump data logs directly or from medical records.

Although outcome assessors were aware of the interventions received by participants, the reported outcomes were measured objectively using appropriate methods (e.g., glucose time-in-range metrics and mean glucose values were measured using CGM data). It was considered unlikely that the findings could be influenced by knowledge of the interventions received. As a result, the risk of confirmation bias due to inappropriate blinding of assessors or inappropriate outcome assessment methods was considered low.

The risk of attrition bias resulting from inappropriate handling of incomplete data was low, given that all 40 people included in the analysis provided complete outcome data (i.e., there do not appear to be any data missing from participants in either group).

Finally, the Lepore et al. (2020) study did not make reference to a published a priori protocol; therefore, the risk for reporting bias due to selective outcome reporting was unclear, although the authors reported on outcomes that are typical for clinical trials investigating insulin delivery systems for people with type 1 diabetes.

The overall risk of bias in this study was judged to be high as a result of the high risk of bias in the target group selection domain.

A summary of the results of the risk-of-bias assessments of the identified non-randomized study is provided in Table 3.

Table 3: Summary of Risk of Bias in the Non-Randomized Study Assessed Using RoBANS

Study citation	Lepore et al. (2020)[58]
The possibility of the target group comparisons	High
Target group selection	Low
Cofounder	Low
Exposure measurement	Low
Blinding of assessors	Low
Outcome assessment	Low (for all outcomes)
Incomplete outcome data	Low (for all outcomes)
Selective outcome reporting	Unclear

RoBANS = Risk of Bias Assessment tool for Non-randomized Studies.

Additional Limitations

Several methodological limitations were outlined using the RoB 2 and RoBANS tools; however, the literature included in the Clinical Review had some additional limitations to consider.

While all 9 studies[50-59] were sufficiently powered to detect statistically significant differences between treatment groups for their primary outcomes, studies may not have been sufficiently powered to detect significant differences for all secondary and exploratory outcomes. This is particularly concerning for studies with smaller samples sizes, such as Forlenza et al. (2019),[55] Hanaire et al. (2020),[56] Lepore et al. (2020),[58] and Ekhlaspour et al. (2019),[54] where totals of 24, 38, 40, and 48 participants were included, respectively.

Apart from the Breton et al. (2020)[51] study and the RCT described in Brown et al. (2019)[53] and Isganaitis et al. (2020),[57] none of the included studies adjusted for multiplicity, even though they all conducted multiple statistical tests. As a result, there may be potential inflation of the type I error rate in these 7 studies.[50,52,54-56,58,59]

Data Analysis and Synthesis

This discussion synthesizes the findings of the included clinical studies. The synthesis was conducted narratively, with the findings summarized within and across studies by outcome and comparator. Based on the available clinical literature, 4 intervention and comparator pairings were used to classify the 9 primary studies (reported in 10 publications) for data synthesis: HCL therapy versus open-loop SAP therapy without a PLGS feature; HCL therapy versus open-loop SAP therapy with a PLGS feature; HCL therapy versus open-loop SAP therapy that had systems both with and without PLGS features; and HCL therapy versus MDII or insulin-pump therapy informed by SMBG. Studies that provided control group participants with systems that had PLGS features enabled were analyzed separately because the literature suggests these features may impact clinical and safety outcomes.[89-91] The authors of 8 studies[50,52-59] made it clear whether control group participants were provided systems with PLGS features activated[52,58] or did not have access to such a feature;[50,53-57,59] however, the Breton et al. (2020) RCT[51] included both participants with an open-loop SAP system and with an open-loop SAP system with a PLGS feature in its control group. Because this study could not be grouped into the first 2 subcategories, a third category was created to capture studies that used a mixed comparator group (i.e., with or without PLGS features). The fourth category included both patients who were receiving MDII

and patients on insulin-pump therapy because the primary study[59] that examined this comparison conducted all analyses with these patients combined as their control group.

Although meta-analyses were planned to quantitatively synthesize the findings of the included literature if appropriate, there were no instances where multiple studies of a given design (i.e., RCT or non-randomized studies) reporting on the same outcome and intervention and comparator pair were deemed sufficiently homogeneous in terms of their clinical, methodological, and statistical characteristics to justify pooling. Sources of heterogeneity across the 5 RCTs[50,53-56] that compared HCL versus open-loop SAP therapy included:

- interventions and comparators (e.g., 3 different HCL systems were examined [the MiniMed 670G, the Diabeloop HCL system, and the Control-IQ HCL system], and the components used in the open-loop SAP comparator groups varied significantly)
- methods of defining and measuring outcomes (particularly for safety outcomes; e.g., hypoglycemic events were defined differently in the 9 studies[50-56,58,59] that monitored them as an outcome of interest)
- methods of reporting outcome data (e.g., time-in-range metrics were expressed either as means with standard deviations or medians with IQRs, depending on the distribution of data).

Most importantly, the 5 RCTs[50,53-57] had substantial variations in their lengths of follow-up. Ekhlaspour et al. (2019)[54] had a 2-day follow-up duration; Hanaire et al. (2020)[56] and Forlenza et al. (2019)[55] had a 3-day follow-up duration; Benhamou et al. (2019) had a 12-week follow-up duration; and the RCT described in Brown et al. (2019)[53] and Isganaitis et al. (2020)[57] had a 26-week (6-month) follow-up duration. Pooling data across these studies would ignore the time-dependent effects of an intervention, which could potentially lead to biased estimates.[92] This is especially concerning for outcomes such as A1C values, patient satisfaction, and all safety outcomes, given that the length of therapy is expected to have significant effects on these outcomes. Two studies[52,58] were identified within the comparison of HCL therapy versus open-loop SAP therapy with a PLGS feature; however, 1 of these studies was an RCT[52] and the other was a non-randomized study.[58] Thus, pooling the 2 studies under this comparison was not possible, given that our protocol stated that RCTs and non-randomized studies would be analyzed separately. For the comparison of HCL therapy versus open-loop SAP therapy with or without a PLGS feature and of HCL therapy versus MDII or insulin-pump therapy informed by SMBG, no pooling was possible because there was only 1 study for either comparison.[51,59]

Detailed summaries of the main findings of each of the primary studies, as well as data from relevant subgroup analyses, are available in Appendix 2, Table 41.

Research question 1: What is the comparative clinical effectiveness of commercialized HCL systems versus other insulin delivery methods in people of any age with type 1 diabetes?

Glucose Time-in-Range Metrics

A high-level summary of findings related to glucose time-in-range metrics from the included studies is presented in Table 4, grouped into 4 comparisons: HCL therapy versus open-loop SAP therapy without a PLGS feature; HCL therapy versus open-loop SAP therapy with a PLGS feature; HCL therapy versus open-loop SAP therapy with or without a PLGS feature (mixed); and HCL therapy versus MDII or insulin-pump therapy informed by SMBG (mixed).

Table 4: High-Level Summary of Glucose Time-in-Range Findings by Comparison in the Included Primary Clinical Studies

Outcome		Direction of effect				
HCL therapy vs. open-loop SAP therapy without a PLGS feature						
		RCTs				
		Hanaire et al. (2020)[56]	**Benhamou et al. (2019)[50]**	**Brown et al. (2019)[53]**	**Ekhlaspour et al. (2019)[54]**	**Forlenza et al. (2019)[55]**
Proportion of time spent with a glucose value of:	3.9 mmol/L to 10.0 mmol/L	+	+	+	+	+
	3.9 mmol/L to 7.8 mmol/L	NR	NR	+	NR	+
	4.4 mmol/L to 7.8 mmol/L	+	+	NR	NR	NR
	< 2.8 mmol/L	NR	+	NR	NS	NS
	< 3.0 mmol/L	NR	NR	+	NS	NS
	< 3.3 mmol/L	NR	+	+	NS	NS
	< 3.9 mmol/L	NS	+	+	NS	NS
	> 10.0 mmol/L	+	+	+	+	+
	> 13.9 mmol/L	NR	+	+	NS	+
	> 16.7 mmol/L	NR	+	+	+	NS
HCL therapy vs. open-loop SAP therapy with a PLGS feature						
		RCTs			**Non-RCTs**	
		Brown et al. (2020)[52]			**Lepore et al. (2020)[58]**	
Proportion of time spent with a glucose value of:	3.9 mmol/L to 10.0 mmol/L	+			+	
	3.9 mmol/L to 7.8 mmol/L	+			NR	
	3.0 mmol/L to 3.8 mmol/L	NR			NS	
	10.0 mmol/L to 13.9 mmol/L	NR			+	
	< 3.0 mmol/L	NS			NS	
	< 3.3 mmol/L	NS			NR	
	< 3.9 mmol/L	NS			NR	
	> 10.0 mmol/L	+			NR	
	> 13.9 mmol/L	+			+	
	> 16.7 mmol/L	+			NR	
HCL therapy vs. open-loop SAP therapy with or without a PLGS feature (mixed)						
		RCTs				
		Breton et al. (2020)[51]				
Proportion of time spent with a glucose value of:	3.9 mmol/L to 10.0 mmol/L	+				
	3.9 mmol/L to 7.8 mmol/L	?				
	< 3.0 mmol/L	?				

Outcome		Direction of effect
	< 3.3 mmol/L	?
	< 3.9 mmol/L	?
	> 10.0 mmol/L	+
	> 13.9 mmol/L	?
	> 16.7 mmol/L	?
HCL therapy vs. MDII or insulin-pump therapy informed by SMBG (mixed)		
		RCTs
		McAuley et al. (2020)[59]
Proportion of time spent with a glucose value of:	3.9 mmol/L to 10.0 mmol/L	+
	3.9 mmol/L to 7.8 mmol/L	+
	< 2.8 mmol/L	+
	< 3.0 mmol/L	+
	< 3.3 mmol/L	+
	< 3.9 mmol/L	+
	> 10.0 mmol/L	+
	> 11.1 mmol/L	+
	> 13.9 mmol/L	+

HCL = hybrid closed-loop insulin delivery system; MDII = multiple daily insulin injections; NR = not reported; NS = not statistically significant; PLGS = predictive low-glucose suspend; RCT = randomized controlled trial; SAP = sensor-augmented pump; SMBG = self-monitoring of blood glucose; vs. = versus.

Note: [+] suggests intervention more favourable than comparator; [?] suggests not compared statistically.

HCL Therapy Versus Open-Loop SAP Therapy Without a PLGS Feature

Glucose time-in-range metrics were monitored in 5 RCTs[50,53-56] comparing HCL therapy versus open-loop SAP therapy without a PLGS feature that were either at low risk of bias or that had some concerns of bias overall HCL.

Across all 5 of these studies,[50,53-56] participants who received HCL therapy had increased time in euglycemic ranges (e.g., glucose levels from 3.9 mmol/L to 10.0 mmol/L, 3.9 mmol/L to 7.8 mmol/L, or 4.4 mmol/L to 7.8 mmol/L) compared to those who received open-loop SAP therapy without a PLGS feature . All 5 studies[50,53-56] provided data on the glucose range of 3.9 mmol/L to 10.0 mmol/L. In all cases, treatment with HCL therapy improved the proportion of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L compared to open-loop SAP therapy without a PLGS feature. Two studies[50,56] reported data for the glucose range of 4.4 mmol/L to 7.8 mmol/L, and both demonstrated increased time spent in this range during HCL therapy compared to open-loop SAP therapy without a PLGS feature. Similarly, Brown et al. (2019)[53] indicated that participants in their trial who were assigned to HCL therapy spent an increased proportion of time with a glucose value from 3.9 mmol/L to 7.8 mmol/L compared to those who received open-loop SAP therapy without a PLGS feature.

Five studies[50,53-56] that compared treatment with HCL therapy versus open-loop SAP therapy without a PLGS feature reported on time spent in hypoglycemic ranges (e.g., < 2.8 mmol/L, < 3.0 mmol/L, < 3.3 mmol/L, and < 3.9 mmol/L). The findings for hypoglycemic ranges were not consistent across all 5 studies:[50,53-56] 2 studies[50,53] reported a statistically significant improvement for those on HCL therapy, while 3 studies[54-56] did not report statistically

significant differences between treatment with HCL and open-loop SAP therapy. Three studies[50,54,55] reported on the glucose range of less than 2.8 mmol/L, with 1 study finding a statistically significant difference between groups, favouring treatment with HCL therapy, while 2 studies[54,55] did not observe statistically significant differences in the median time spent with a glucose level of less than 2.8 mmol/L between pediatric participants in their HCL groups and those in their open-loop SAP groups. Three studies[53-55] reported on the glucose range of less than 3.0 mmol/L. Brown et al. (2019)[53] concluded that HCL therapy improved the mean time spent with a glucose level of less than 3.0 mmol/L compared to open-loop SAP therapy, while Ekhlaspour and collegagues[54] and Forlenza and colleagues[55] noted that there were no statistically significant differences with respect to the time spent with a glucose value of less than 3.0 mmol/L between participants who received HCL therapy and those who received open-loop SAP therapy. Four studies[50,53-55] reported on the glucose range of less than 3.3 mmol/L: Benhamou et al. (2019) and Brown et al. (2019) reported statistically significant improvements in the mean time spent with a glucose value of less than 3.3 mmol/L for those who received HCL therapy compared to those who received open-loop SAP therapy without a PLGS feature , while pediatric participants in the Ekhlaspour et al. (2019)[54] and Forlenza et al. (2019)[55] studies did not demonstrate any statistically significant differences in the median percentages of time spent with glucose values of less than 3.3 mmol/L. The final hypoglycemic threshold reported in these studies was less than 3.9 mmol/L, which was measured in 5 studies.[50,53-56] Of these studies, 2 studies[50,53] suggested that HCL therapy improved the amount of time spent with a glucose value of less than 3.9 mmol/L, while 3 studies[54-56] did not detect any statistically significant differences in the percentage of time in which glucose values were less than 3.9 mmol/L between the HCL groups and those using open-loop SAP therapy without a PLGS feature.

Five studies[50,53-56] that compared treatment with HCL therapy versus open-loop SAP therapy without a PLGS feature reported on time spent in hyperglycemic ranges (e.g., > 10.0 mmol/L, > 13.9 mmol/L, and > 16.7 mmol/L). Similar to the results for hypoglycemic ranges, there was variability in the statistical significance of the results across studies. With respect to the time spent with glucose values greater than 10.0 mmol/L, all 5 studies[50,53-56] reported results favourable to treatment with HCL therapy compared to treatment with open-loop SAP therapy without a PLGS feature. Four studies[50,53-55] reported on the glucose range of greater than 13.9 mmol/L; 3 studies[50,53,55] concluded that HCLs improved time spent in this hyperglycemic range, while 1 study[54] did not find any statistically significant differences between HCL and open-loop SAP therapy. The final hyperglycemic range reported in these studies was greater than 16.7 mmol/L. Three studies[50,53,54] noted that treatment with HCL therapy improved the amount of time spent with glucose values greater than 16.7 mmol/L compared to open-loop SAP therapy without a PLGS feature, while 1 study[55] did not observe any statistically significant differences.

In addition to these findings, the authors of 1 study (reported in 2 publications[53,57]) conducted exploratory subgroup analyses to examine the impact of several baseline variables on the percentage of time with a glucose value between 3.9 mmol/L and 10.0 mmol/L and on the percentage of time with a glucose value below 3.9 mmol/L. The relevant baseline characteristics included age (14 years to 24 years versus 25 years to 71 years), sex (female versus male), and measures of glycemic control (A1C values ≤ 7.5% versus > 7.5%; percentage of time spent with a glucose value below 3.9 mmol/L [≤ 4% versus > 4%]; percentage of time spent with a glucose value higher than 10.0 mmol/L [≤ 40% versus 40%]; and percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L [≤ 60% versus > 60%]). The authors concluded that the findings related to percentage of time spent with a glucose value in the target range (i.e., between 3.9 mmol/L

and 10.0 mmol/L) and the percentage of time spent with a glucose value lower than 3.9 mmol/L consistently favoured the HCL group across a broad range of baseline characteristics, including age, sex, and A1C level.[53,57] Numerical data from these subgroup analyses are detailed in Appendix 2, Table 41.

Detailed findings from studies that compared HCL therapy versus open-loop SAP therapy without a PLGS feature related to glucose time-in-range metrics — including numerical data, risk-adjusted or paired differences, and P values — are presented in Table 5.

Table 5: Detailed Findings Related to Glucose Time-in-Range Metrics for Studies That Compared HCL Therapy With Open-Loop SAP Therapy Without a PLGS Feature

Outcome	Detailed findings			
Primary study citation	Proportion of time spent in the range during the study period		Risk-adjusted or paired difference (HCL less open-loop SAP without a PLGS feature; 95% CI)	P value
	Groups using HCLs	Groups using open-loop SAPs without a PLGS feature		
Euglycemic ranges				
3.9 mmol/L to 10.0 mmol/L				
Hanaire et al. (2020)[56]	79.4% (SD = 9.6%)	64.1% (SD = 15.9%)	NR	< 0.0001[a]
Benhamou et al. (2019)[50]	68.5% (SD = 9.4%)	59.4% (SD = 10.2%)	9.2% (6.4% to 11.9%)	< 0.0001[a]
Brown et al. (2019)[53]	71% (SD = 12%)	59% (SD = 14%)	11% (9% to 14%)	< 0.001[a]
Ekhlaspour et al. (2019)[54]	66.4% (SD = 16.4%)	53.9% (SD = 24.8%)	NR	0.01[a]
Forlenza et al. (2019)[55]	71.2% (SD = 6.3%)	52.8% (SD = 13.5%)	NR	< 0.00 [a]
3.9 mmol/L to 7.8 mmol/L				
Brown et al. (2019)[53]	46% (SD = 12%)	36% (SD = 12%)	8% (6% to 11%)	< 0.001[a]
Forlenza et al. (2019)[55]	48.5% (SD = 9.5%)	28.7% (SD = 11.7%)	NR	< 0.001[a]
4.4 mmol/L to 7.8 mmol/L				
Hanaire et al. (2020)[56]	63.2% (SD = 15.3%)	40.9% (SD = 24.7%)	NR	< 0.0001[a]
Benhamou et al. (2019)[50]	39.3% (SD = 7.9%)	33.5% (SD = 7.9%)	5.8% (3.7% to 7.9%)	< 0.0001[a]
Hypoglycemic ranges				
< 2.8 mmol/L				
Benhamou et al. (2019)[50]	0.2% (SD = 0.8%)	0.7% (SD = 0.8%)	–0.5% (–0.7% to –0.3%)	< 0.0001[a]
Ekhlaspour et al. (2019)[54]	0% (IQR, 0% to 0%)	0% (IQR, 0% to 0%)	NR	NS
Forlenza et al. (2019)[55]	0% (75% CI, 0% to 0.2%)	0% (75% CI, 0% to 0.4%)	NR	NS
< 3.0 mmol/L				
Brown et al. (2019)[53]	0.29% (SD = 0.29%)	0.35% (SD = 0.32%)	–0.10% (–0.19% to –0.02%)	0.02[a]
Ekhlaspour et al. (2019)[54]	0% (IQR, 0% to 0%)	0% (IQR, 0% to 0.1%)	NR	NS

Outcome	Detailed findings			
Primary study citation	**Proportion of time spent in the range during the study period**		**Risk-adjusted or paired difference (HCL less open-loop SAP without a PLGS feature; 95% CI)**	**P value**
	Groups using HCLs	**Groups using open-loop SAPs without a PLGS feature**		
Forlenza et al. (2019)[55]	0.3% (75% CI, 0% to 0.5%)	0.2% (75% CI, 0% to 0.6%)	NR	NS
< 3.3 mmol/L				
Benhamou et al. (2019)[50]	0.8% (SD = 0.8%)	2.0% (SD = 1.6%)	–1.3% (–1.6% to −0.9%)	< 0.0001[a]
Brown et al. (2019)[53]	0.58% (SD = 0.52%)	0.75% (SD = 0.61%)	–0.26% (–0.40% to −0.11%)	< 0.001[a]
Ekhlaspour et al. (2019)[54]	0% (IQR, 0% to 0.8%)	0.0% (IQR, 0% to 0.6%)	NR	NS
Forlenza et al. (2019)[55]	0.7% (75% CI, 0.2% to 1.2%)	0.5% (75% CI, 0% to 0.9%)	NR	NS
< 3.9 mmol/L				
Hanaire et al. (2020)[56]	2.7% (SD = 2.6%)	4.0% (SD = 4.1%)	NR	NS
Benhamou et al. (2019)[50]	2.0% (SD = 2.4%)	4.3% (SD = 2.4%)	–2.4% (–3.0% to –1.7%)	< 0.0001[a]
Brown et al. (2019)[53]	1.58% (SD = 1.15%)	2.25% (SD = 1.46%)	–0.88% (–1.19% to –0.57%)	< 0.001
Ekhlaspour et al. (2019)[54]	2% (IQR, 0.5% to 3.8%)	0.8% (IQR, 0% to 3.7%)	NR	NS
Forlenza et al. (2019)[55]	2.1% (SD = 1.5%)	2.1% (SD = 2.9%)	NR	NS
Hyperglycemic ranges				
> 10.0 mmol/L				
Hanaire et al. (2020)[56]	17.9% (SD = 9.3%)	31.9% (SD = 17.5%)	NR	< 0.0001[a]
Benhamou et al. (2019)[50]	29.5% (SD = 10.2%)	36.3% (SD = 10.2%)	–6.8% (–9.7% to –3.9%)	< 0.0001[a]
Brown et al. (2019)[53]	27% (SD = 12%)	38% (SD = 15%)	–10.0% (–13.0% to –8.0%)	< 0.001[a]
Ekhlaspour et al. (2019)[54]	31.4% (SD = 17.6%)	43.0% (SD = 24.5%)	NR	0.015[a]
Forlenza et al. (2019)[55]	26.2% (SD = 7.1%)	44.7% (SD = 13.8%)	NR	< 0.001[a]
> 13.9 mmol/L				
Benhamou et al. (2019)[50]	7.4% (SD = 6.3%)	11.7% (SD = 6.3%)	–4.3% (–6.2% to –2.4%)	< 0.0001[a]
Brown et al. (2019)[53]	7.0% (SD = 6.7%)	12.3% (SD = 10.2%)	–5.3% (–7.1% to –3.6%)	< 0.001[a]
Ekhlaspour et al. (2019)[54]	10.4% (SD = 11.4%)	16.0% (SD = 13.6%)	NR	NS
Forlenza et al. (2019)[55]	6.8% (SD = 4.5%)	16.1% (SD = 10.3%)	NR	0.009[a]

Outcome	Detailed findings			
Primary study citation	Proportion of time spent in the range during the study period		Risk-adjusted or paired difference (HCL less open-loop SAP without a PLGS feature; 95% CI)	P value
	Groups using HCLs	Groups using open-loop SAPs without a PLGS feature		
> 16.7 mmol/L				
Benhamou et al. (2019)[50]	2.4% (SD = 3.1%)	4.3% (SD = 3.1%)	–2.0% (–3.0% to –1.0%)	0.0002[a]
Brown et al. (2019)[53]	2.4% (SD = 3.4%)	4.6% (SD = 6.0%)	–2.4% (–3.5% to –1.3%)	< 0.001[a]
Ekhlaspour et al. (2019)[54]	3.9% (SD = 5.9%)	6.9% (SD = 6.7%)	NR	0.034[a]
Forlenza et al. (2019)[55]	2.7% (SD = 2.7%)	5.3% (SD = 3.9%)	NR	NS

CI = confidence interval; HCL = hybrid closed-loop insulin delivery; IQR = interquartile range; NR = not reported; NS = non-significant; PLGS = predictive low-glucose suspend; SAP = sensor-augmented pump; SD = standard deviation.

Note: Data are expressed as means with SDs or medians with IQRs or 75% CIs, depending on the distribution of data.

[a] Statistically significant.

HCL Therapy Versus Open-Loop SAP Therapy With or Without a PLGS feature (Mixed)

The Breton et al. (2020)[51] RCT, which had some concerns about bias overall, compared HCL therapy with the Control-IQ system versus a control group that received open-loop SAP therapy with or without a PLGS feature (15 participants used a PLGS feature and 8 participants did not). This study reported data for the euglycemic ranges of 3.9 mmol/L to 10.0 mmol/L and 3.9 mmol/L to 7.8 mmol/L, the hyperglycemic ranges of less than 3.0 mmol/L, less than 3.3 mmol/L, and less than 3.9 mmol/L, and the hyperglycemic ranges of greater than 10.0 mmol/L, greater than 13.9 mmol/L, and greater than 16.7 mmol/L.

Starting with euglycemic ranges, treatment with HCL therapy improved mean time in the glucose range of 3.9 mmol/L to 10.0 mmol/L compared to open-loop SAP therapy with or without a PLGS feature. For the glucose range of 3.9 mmol/L to 7.8 mmol/L, the observed mean time-in-range values were 44% (SD = 10%) and 35% (SD = 11%) for the HCL group and the group on open-loop therapy with or without a PLGS feature, respectively; however, the statistical significance of this result was not reported by the study authors because this outcome was considered exploratory and not included in their hierarchical analysis.

For hypoglycemic ranges, Breton and colleagues[51] reported median time spent with a glucose value of less than 3.0 mmol/L, less than 3.3 mmol/L, and less than 3.9 mmol/L; however, the statistical significance of these findings was not calculated because a P value of more than 0.05 was observed for an outcome ranked higher than these in the hierarchical analysis.

Compared to open-loop SAP therapy with or without a PLGS feature, treatment with HCL therapy improved the mean time spent with a glucose value greater than 10.0 mmol/L. Median glucose time-in-range values were also reported for time spent with a glucose value greater than 13.9 mmol/L and greater than 16.7 mmol/L; however, once again, the statistical significance of these findings was not reported by the study authors because these outcomes were considered exploratory and not included in their hierarchical analysis.

In addition to these findings, Breton et al. (2020)[51] included exploratory subgroup analyses to examine the impact of several baseline variables on the change in the percentage of time with a glucose value between 3.9 mmol/L and 10.0 mmol/L and in the percentage of time with a glucose value lower than 3.9 mmol/L from baseline. Relevant baseline variables included age (6 years to 9 years versus 10 years to 14 years), sex (female versus male), and measures of glycemic control (A1C values < 8.0% versus ≥ 8.0%, percentage of time spent with a glucose value below 3.9 mmol/L [< 1.5% versus ≥1.5%], percentage of time spent with a glucose value higher than 10.0 mmol/L [< 50% versus 50%], percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L [< 50% versus ≥ 50%]). The authors did not provide any conclusions regarding these exploratory subgroup analyses, although it appeared that the findings related to the percentage of time spent with a glucose value in the target range (i.e., from 3.9 mmol/L to 10.0 mmol/L) and the findings related to the percentage of time with a glucose value lower than 3.9 mmol/L generally favoured the HCL group across a broad range of baseline characteristics (i.e., age, sex, and measures of glycemic control). Numerical data from these subgroup analyses are detailed in Appendix 2, Table 41.

Detailed findings from the Breton et al. (2020)[51] RCT related to glucose time-in-range metrics, including numerical data, risk-adjusted differences, and P values, are presented in Table 6.

Table 6: Detailed Findings Related to Glucose Time-in-Range Metrics for Studies That Compared HCL Therapy With Open-Loop SAP Therapy With or Without a PLGS feature

Outcome	Detailed findings			
Primary study citation	Proportion of time spent in the range during the study period		Risk-adjusted difference (HCL less open-loop SAP ± PLGS feature; 95% CI)	P value
	Group using HCLs	Group using open-loop SAPs with or without a PLGS feature		
Euglycemic ranges				
3.9 mmol/L to 10.0 mmol/L				
Breton et al. (2020)[51]	67% (SD = 10%)	55% (SD = 13%)	11% (7% to 14%)	< 0.001[a]
3.9 mmol/L to 7.8 mmol/L				
Breton et al. (2020)[51]	44% (SD = 10%)	35% (SD = 11%)	8.1% (4.3% to 12%)	Not calculated[b]
Hypoglycemic ranges				
< 3.0 mmol/L				
Breton et al. (2020)[51]	0.2% (IQR, 0.1% to 0.4%)	0.3% (IQR, 0.1% to 0.6%)	–0.07% (–0.19% to 0.02%)	Not calculated[b]
< 3.3 mmol/L				
Breton et al. (2020)[51]	0.48% (IQR, 0.22% to 0.93%)	0.60% (IQR, 0.32% to 1.19%)	–0.15% (−0.36% to 0.01%)	Not calculated[b]
< 3.9 mmol/L				
Breton et al. (2020)[51]	1.6% (IQR, 0.8% to 2.4%)	1.8% (IQR, 1.1% to 3.0%)	−0.40% (–0.83% to –0.02%)	Not calculated[b]
Hyperglycemic ranges				
> 10.0 mmol/L				
Breton et al. (2020)[51]	31.0% (SD = 10%)	43.0% (SD = 14%)	–10.0% (–14.0% to –6.0%)	< 0.001*
> 13.9 mmol/L				
Breton et al. (2020)[51]	7.8% (IQR, 5.1% to 14.3%)	18.4% (IQR, 9.4% to 24.6%)	–5.8% (–8.7% to –3.0%)	Not calculated[b]
> 16.7 mmol/L				
Breton et al. (2020)[51]	2.6% (IQR, 1.5% to 5.5%)	6.8% (IQR, 2.9% to 11.2%)	–1.8% (–3.8% to –0.4%)	Not calculated[b]

CI = confidence interval; HCL = hybrid closed-loop insulin delivery system; IQR = interquartile range; PLGS = predictive low-glucose suspend; SAP = sensor-augmented pump; SD = standard deviation.

Note: Data are expressed as means with SDs or medians with IQRs, depending on the distribution of data.

[a] Statistically significant.

[b] The statistical significance of these findings was not calculated, either because these outcomes were considered exploratory and not included in the hierarchical analysis, or because an outcome that was specified before this one in the hierarchical analysis did not reach statistical significance.

HCL Therapy Versus MDII or Insulin-Pump Therapy Informed by SMBG (Mixed)

The McAuley et al. (2020)[59] RCT, which had some concerns about bias overall, compared HCL therapy using the Medtronic MiniMed 670G system with a control group that received insulin delivery through MDII or insulin-pump therapy informed by SMBG (31 control participants used MDII, and 28 control participants used an insulin-pump). This study reported data for the euglycemic ranges of 3.9 mmol/L to 10.0 mmol/L and 3.9 mmol/L to 7.8 mmol/L, the hypoglycemic ranges of less than 2.8 mmol/L, less than 3.0 mmol/L, less than 3.3 mmol/L, and less than 3.9 mmol/L, and the hyperglycemic ranges of greater than 10.0 mmol/L, greater than 11.1 mmol/L, and greater than 13.9 mmol/L.

Compared to those on MDII or insulin-pump therapy informed by SMBG, participants allocated to treatment with HCL therapy demonstrated statistically significantly increased mean time spent in both of the reported euglycemic ranges (i.e., 3.9 mmol/L to 10.0 mmol/L and 3.9 mmol/L to 7.8 mmol/L). Similarly, treatment with HCL therapy led to statistically significant improvements in the proportion of time spent in all reported hypoglycemic (i.e., < 2.8 mmol/L, < 3.0 mmol/L, < 3.3 mmol/L, and < 3.9 mmol/L) and hyperglycemic ranges (i.e., > 10.0 mmol/L, > 11.1 mmol/L, and > 13.9 mmol/L) compared to treatment with MDII or insulin-pump therapy informed by SMBG.

Detailed findings from the McAuley et al. (2020) RCT[59] related to glucose time-in-range metrics, including numerical data, adjusted differences, and P values, are presented in Table 7.

Table 7: Detailed Findings Related to Glucose Time-in-Range Metrics for Studies That Compared HCL Therapy With MDII or Insulin-Pump Therapy Informed by SMBG

Outcome	Detailed findings			
Primary study citation	Proportion of time spent in the range during the study period		Adjusted difference (HCL less MDII or pump with SMBG; 95% CI)	P value[a]
	Group using HCL	Group using MDII or insulin-pump therapy with SMBG		
Euglycemic ranges				
3.9 mmol/L to 10.0 mmol/L				
McAuley et al. (2020)[59]	69.9% (SD = 9.5%)	54.7% (SD = 12.7%)	14.8% (11.0% to 18.5%)	< 0.0001
3.9 mmol/L to 7.8 mmol/L				
McAuley et al. (2020)[59]	44.1% (SD = 8.5%)	33.6% (SD = 12.0%)	9.7% (6.3% to 13.2%)	< 0.000
Hypoglycemic ranges				
< 2.8 mmol/L				
McAuley et al. (2020)[59]	0.1% (IQR, 0.1% to 0.5%)	0.6% (IQR, 0.2% to 1.3%)	–0.4% (–0.6% to –0.2%)	< 0.0001
< 3.0 mmol/L				
McAuley et al. (2020)[59]	0.2% (IQR, 0.1% to 0.8%)	0.9% (IQR, 0.4% to 1.5%)	–0.6% (–0.8% to –0.3%)	< 0.0001
< 3.3 mmol/L				
McAuley et al. (2020)[59]	0.6% (IQR, 0.3% to 1.3%)	1.4% (IQR, 1.0% to 2.3%)	–0.8% (–1.1% to –0.6%)	< 0.0001
< 3.9 mmol/L				
McAuley et al. (2020)[59]	1.8% (IQR, 1.1% to 3.4%)	3.8% (IQR, 2.9% to 5.2%)	–2.0% (–2.5% to –1.3%)	< 0.0001
Hyperglycemic ranges				
> 10.0 mmol/L				
McAuley et al. (2020)[59]	27.6% (SD = 9.5%)	40.3% (SD = 14.4%)	–12.0% (–16.1% to –7.9%)	< 0.0001
> 11.1 mmol/L				
McAuley et al. (2020)[59]	5.7% (IQR, 3.5% to 8.3%)	13.3% (IQR, 9.8% to 17.7%)	–7.5% (–5.6% to –9.4%)	< 0.0001
> 13.9 mmol/L				
McAuley et al. (2020)[59]	1.3% (IQR, 0.5% to 2.8%)	4.3% (IQR, 2.8% to 6.8%)	–2.9% (–2.1% to –3.5%)	< 0.0001

CI = confidence interval; HCL = hybrid closed-loop insulin delivery; IQR = interquartile range; MDII = multiple daily insulin injections; SD = standard deviation; SMBG = self-monitoring of blood glucose.

Note: Data are expressed as means with SDs or medians with IQRs, depending on the distribution of data.

[a] All P values were statistically significant.

Measures of A1C

A high-level summary of findings related to measures of A1C from the included studies is presented in Table 8 and grouped into 4 comparisons: HCL therapy versus open-loop SAP therapy without a PLGS feature; HCL therapy versus open-loop SAP therapy with a PLGS feature; HCL therapy versus open-loop SAP therapy with or without a PLGS feature (mixed); and HCL therapy versus MDII or insulin-pump therapy informed by SMBG (mixed).

Table 8: High-Level Summary of Findings Related to A1C by Comparison in the Included Primary Clinical Studies

Outcome	Direction of effect				
HCL therapy versus open-loop SAP therapy without a PLGS feature					
	RCTs				
	Hanaire et al. (2020)[56]	**Benhamou et al. (2019)[50]**	**Brown et al. (2019)[53]**	**Ekhlaspour et al. (2019)[54]**	**Forlenza et al. (2019)[55]**
A1C values post-treatment	NR	NS	+	NR	NR
Proportion of participants with A1C < 7.0% post-treatment	NR	NR	+	NR	NR
Proportion of participants with A1C < 7.5% post-treatment	NR	NR	NS	NR	NR
Proportion of participants with an absolute reduction in A1C of ≥ 0.5%	NR	NR	+	NR	NR
Proportion of participants with an absolute reduction in A1C of ≥ 1.0%	NR	NR	+	NR	NR
Proportion of participants with a relative reduction in A1C of ≥ 10%	NR	NR	+	NR	NR
Proportion of participants with an absolute reduction in A1C of ≥ 1.0% from baseline or an A1C value of < 7.0%	NR	NR	+	NR	NR
HCL therapy versus open-loop SAP therapy with a PLGS feature					
	RCTs	**Non-RCTs**			
	Brown et al. (2020)[52]	**Lepore et al. (2020)[58]**			
A1C values post-treatment	+	+			
Proportion of participants with A1C < 7.0% post-treatment	+	NR			
Proportion of participants with A1C < 7.5% post-treatment	NS	NR			
HCL therapy versus open-loop SAP therapy with or without a PLGS feature (mixed)					
	RCTs				
	Breton et al. (2020)[51]				
A1C values post-treatment	NS				
Proportion of participants with A1C < 7.0% post-treatment	?				
Proportion of participants with A1C < 7.5% post-treatment	?				
Proportion of participants with an absolute reduction in A1C of ≥ 0.5%	?				

Outcome	Direction of effect
Proportion of participants with an absolute reduction in A1C of ≥ 1.0%	?
Proportion of participants with a relative reduction in A1C of ≥ 10%	?
Proportion of participants with an absolute reduction in A1C by ≥ 1.0% from baseline or an A1C value of < 7.0% at 26 weeks	?
HCL therapy versus MDII or insulin-pump therapy informed by SMBG (mixed)	
	RCTs
	McAuley et al. (2020)[59]
A1C values post-treatment	+

A1C = glycated hemoglobin; HCL = hybrid closed-loop insulin delivery; MDII = multiple daily insulin injections; NR = not measured or not reported; NS = not statistically significant; PLGS = predictive low-glucose suspend; RCT = randomized controlled trial; SAP = sensor-augmented pump; SMBG = self-monitoring of blood glucose.

Note: [+] suggests intervention more favourable than comparator; [?] suggests not compared statistically.

HCL Therapy Versus Open-Loop SAP Therapy Without a PLGS Feature

Two RCTs[50,53] that had some concerns of bias overall that compared treatment with HCL therapy versus open-loop SAP therapy without a PLGS feature reported on A1C measures.

In their 2019 RCT,[53] for the outcome of mean A1C values post-treatment, Brown et al. reported improvements with HCL therapy compared to open-loop SAP therapy. Conversely, Benhamou and colleagues did not observe any statistically significant differences in participants' mean change in A1C values post-treatment compared to baseline.

Additional measures related to A1C were reported in the Brown et al. (2019)[53,57] RCT. The authors observed statistically significant improvements in those treated with HCL therapy compared to open-loop therapy with respect to the proportion of participants with A1C values of less than 7.0% post-treatment, the proportion of participants with an absolute reduction in A1C values of greater than or equal to 0.5%, the proportion of participants with an absolute reduction in A1C values of greater than or equal to 1.0%, the proportion of participants with a relative reduction in A1C values of greater than or equal to 10%, and the proportion of participants with an absolute reduction in A1C values of greater than or equal to 1.0% from baseline or an A1C value of less than 7.0% at 26 weeks. There were no statistically significant differences between treatment with HCL therapy and open-loop SAP therapy with respect to the proportion of participants with A1C values of less than 7.5% post-treatment. Similar trends were observed with respect to mean A1C values post-treatment, the proportion of participants with A1C values of less than 7.0% post-treatment, and the proportion of participants with an absolute reduction in A1C values of greater than or equal to 0.5% in the exploratory subgroup analysis of children and adolescents (between the ages of 14 years and 24 years) in the Brown et al. (2019)[53] study population.[57] Numerical data from this subgroup analysis are shown in Appendix 2, Table 41.

Detailed numerical results related to A1C measures from these 2 RCTs[50,53] are presented in Table 9.

Table 9: Detailed Findings Related to A1C Measures for Studies That Compared HCL Therapy With Open-Loop SAP Therapy Without a PLGS Feature

Outcome	Detailed findings			
Primary study citation	**HCL group**	**Group using open-loop SAPs without PLGS feature**	**Risk-adjusted or paired difference (HCL less open-loop SAP without PLGS feature; 95% CI)**	**P value**
A1C post-treatment				
Brown et al. (2019)[53]	7.06% (SD = 0.79%)	7.39% (SD = 0.92%)	–0.33% (–0.53% to –0.13%)	0.001[a]
Change in A1C				
Benhamou et al. (2019)[50]	–0.29% (SD = 0.6%)	–0.14% (SD = 0.6%)	–0.15% (–0.33% to 0.03%)	0.098
Proportion of participants with A1C values < 7.0% post-treatment				
Brown et al. (2019)[53]	47.0%	31.0%	14.0% (3.0% to 23.0%)	0.02[a]
Proportion of participants with A1C values < 7.5% post-treatment				
Brown et al. (2019)[53]	71.0%	60.0%	14.0% (−5.0% to 20.0%)	0.11
Proportion of participants with an absolute reduction in A1C values of ≥ 0.5% post-treatment				
Brown et al. (2019)[53]	32.0%	11.0%	19.0% (11.0% to 27.0%)	0.005[a]
Proportion of participants with an absolute reduction in A1C values of ≥ 1.0% post-treatment				
Brown et al. (2019)[53]	11%	0%	11% (6% to 18%)	0.009[a]
Proportion of participants with a relative reduction in A1C values of ≥ 10% post-treatment				
Brown et al. (2019)[53]	19%	4%	14% (8% to 20%)	0.02[a]
Proportion of participants with an absolute reduction in A1C values of ≥ 1.0% or A1C values of < 7.0% post-treatment				
Brown et al. (2019)[53]	53%	31%	21% (10% to 31%)	0.004[a]

A1C = glycated hemoglobin; CI = confidence interval; HCL = hybrid closed-loop insulin delivery; PLGS = predictive low-glucose suspend; SAP = sensor-augmented pump; SD = standard deviation.

Note: Data are expressed as means with SDs or as proportions of the participants allocated to the study group.

[a] Statistically significant.

HCL Therapy Versus Open-Loop SAP Therapy With a PLGS Feature

A1C measures were reported in 1 RCT[52] with some concerns of bias overall and in 1 cohort study[58] at high risk of bias that compared HCL therapy versus open-loop SAP therapy with PLGS feature.

The authors of both studies[52,58] reported that participants who were treated with HCL therapy had improved A1C values post-treatment compared to those who received open-loop SAP therapy with a PLGS feature. Brown and colleagues[52] noted that participants who were treated with 13 weeks of HCL therapy had lower mean A1C values compared to those who received open-loop therapy with a PLGS feature. Participants in the 2020 cohort study by Lepore and colleagues[58] who received HCL therapy had a statistically significantly greater decrease in median A1C values from the start of the study to the end of the 6-month study period than those who received open-loop therapy with a PLGS feature.

Brown and colleagues[53] also observed a statistically significant improvement in those treated with HCL therapy compared to open-loop SAP therapy with a PLGS feature with respect to the proportion of participants with A1C values of less than 7.0% at 13 weeks. There were no statistically significant differences between treatment with HCL therapy and

open-loop SAP therapy with respect to the proportion of participants with A1C of less than 7.5% at 13 weeks.

The findings related to A1C measures from both studies[52,58] are detailed in Table 10.

Table 10: Detailed Findings Related to A1C Measures for Studies That Compared HCL Therapy With Open-Loop SAP Therapy and a PLGS Feature

Outcome	Detailed findings			
Primary study citation	**Group using HCLs**	**Group using open-loop SAPs with PLGS feature**	**Risk-adjusted difference (HCL less open-loop SAP with PLGS feature; 95% CI)**	**P value**
A1C post-treatment				
Brown et al. (2020)[52]	7.18% (SD = 0.80%)	7.53% (SD = 1.14%)	–0.34% (–0.57% to –0.11%)	0.0035[a]
Change in A1C				
Lepore et al. (2020)[58]	–0.4% (SD = 0.6%)	0.1% (SD = 0.4%)	NR	< 0.01[a]
Proportion of participants with A1C < 7.0% post-treatment				
Brown et al. (2020)[52]	43.0%	27.0%	13.0% (–6.0% to 32.0%)	0.05[a]
Proportion of participants with A1C < 7.5% post-treatment				
Brown et al. (2020)[52]	65.0%	58.0%	9.0% (–14.0% to 31.0%)	0.20

A1C = glycated hemoglobin; CI = confidence interval; HCL = hybrid closed-loop insulin delivery; NR = not reported; PLGS = predictive low-glucose suspend; SAP = sensor-augmented pump; SD = standard deviation.

Note: Data are expressed as means with SDs or as proportions of the participants allocated to the study group.

[a] Statistically significant.

HCL Therapy Versus Open-Loop SAP Therapy With or Without a PLGS Feature (Mixed)

One RCT[51] with some concerns of bias overall that compared HCL therapy with the Control-IQ system versus a control group of participants who received open-loop SAP therapy with or without a PLGS feature reported data for various measures of A1C.

Breton and colleagues[51] did not observe any statistically significant differences in mean A1C values following 16 weeks of treatment with HCL therapy or treatment with open-loop SAP therapy with or without a PLGS feature.

Breton and colleagues reported additional outcomes related to A1C, including: the proportion of participants with A1C values of less than 7.0% post-treatment, the proportion of participants with A1C values of less than 7.5% post-treatment, the proportion of participants with an absolute reduction in A1C value of greater than 0.5% from baseline, the proportion of participants with an absolute reduction in A1C value of greater than 1.0% from baseline, the proportion of participants with a relative reduction in A1C value of greater than 10% from baseline, and the proportion of participants with an absolute reduction in A1C of greater than 1.0% from baseline or an A1C value of less than 7.0% post-treatment;[51] however, the statistical significance of these findings was not calculated because these outcomes were considered exploratory and not included in their hierarchical analysis.

Breton et al. (2020)[51] conducted exploratory subgroup analyses to examine the impact of several baseline variables on change in A1C from baseline. Relevant baseline variables included: age (6 years to 9 years versus 10 years to 14 years), sex (female versus male), and measures of glycemic control (A1C values < 8.0% versus ≥ 8.0%, percentage of time spent with a glucose value below 3.9 mmol/L [< 1.5% versus ≥ 1.5%], percentage of time spent with a glucose value higher than 10.0 mmol/L [< 50% versus ≥ 50%], and percentage

of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L [< 50% versus ≥50%]). The authors did not provide any conclusions regarding these exploratory subgroup analyses, although it appeared that the findings related to change in A1C from baseline generally favoured the HCL group across a broad range of baseline characteristics (i.e., age, sex, and measures of glycemic control). The numerical data from these subgroup analyses were extracted and are detailed in Appendix 2, Table 41.

The results of measures of A1C from the 2020 RCT by Breton and colleagues[51] are presented in Table 11.

Table 11: Detailed Findings Related to A1C Measures for Studies That Compared HCL Therapy With Open-Loop SAP Therapy With or Without a PLGS Feature

Outcome	Detailed findings			
Primary study citation	**HCL group**	**Group using open-loop SAPs with or without PLGS feature**	**Risk-adjusted difference (HCL less open-loop SAP ± PLGS feature; 95% CI)**	**P value**
A1C post-treatment				
Breton et al. (2020)[51]	7.0% (SD = 0.8%)	7.6% (SD = 0.9%)	−0.4% (−0.9% to 0.1%)	0.08
Proportion of participants with A1C values < 7.0% post-treatment				
Breton et al. (2020)[51]	51%	15%	28.0% (10.0% to 45.0%)	Not calculated[a]
Proportion of participants with A1C values < 7.5% post-treatment				
Breton et al. (2020)[51]	74%	45%	22.0% (2.0% to 42.0%)	Not calculated[a]
Proportion of participants with an absolute reduction in A1C values of ≥ 0.5% post-treatment				
Breton et al. (2020)[51]	52%	50%	12.0% (−13.0% to 30.0%)	Not calculated[a]
Proportion of participants with an absolute reduction in A1C values of ≥ 1.0% post-treatment				
Breton et al. (2020)[51]	25%	9%	19.0% (4.0% to 31.0%)	Not calculated[a]
Proportion of participants with a relative reduction in A1C values of ≥ 10% post-treatment				
Breton et al. (2020)[51]	36%	18%	23.0% (4.0% to 38.0%)	Not calculated[a]
Proportion of participants with an absolute reduction in A1C values of ≥ 1.0% or an A1C value of < 7.0% post-treatment				
Breton et al. (2020)[51]	61%	27%	35% (11% to 56%)	Not calculated[a]

A1C = glycated hemoglobin; CI = confidence interval; HCL = hybrid closed-loop insulin delivery system; PLGS = predictive low-glucose suspend; SAP = sensor-augmented pump; SD = standard deviation.

Note: Data are expressed as means with SDs or as proportions of the participants allocated to the study group.

[a] The statistical significance of these findings was not calculated because these outcomes were considered exploratory and not included in the hierarchical analysis.

HCL Therapy Versus MDII or Insulin-Pump Therapy Informed by SMBG (Mixed)

One RCT[59] with some concerns of bias overall that compared HCL therapy with the Medtronic MiniMed 670G system versus a control group that received insulin delivery via MDII or insulin-pump therapy informed by SMBG reported findings related to A1C.

Treatment with 26 weeks of HCL therapy led to statistically significant improvements in mean A1C values post-treatment compared to treatment with MDII or insulin-pump therapy informed by SMBG. These findings are presented in Table 12.

Table 12: Detailed Findings Related to A1C Measures for Studies That Compared HCL Therapy With MDII or Insulin-Pump Therapy Informed by SMBG

Outcome	Detailed findings			
Primary study citation	**HCL group**	**Group using MDII or insulin-pump therapy with SMBG**	**Adjusted difference (HCL less MDII or pump with SMBG; 95% CI)**	**P value**
A1C values post-treatment				
McAuley et al. (2020)[59]	7.0% (SD = 0.6%)	7.4% (SD = 0.8%)	−0.4% (−0.6% to −0.2%)	< 0.0001[a]

A1C = glycated hemoglobin; CI = confidence interval; HCL = hybrid closed-loop insulin delivery system; MDII = multiple daily insulin injections; SD = standard deviation; SMBG = self-monitoring of blood glucose.

Note: Data are expressed as means with SDs.

[a] Statistically significant.

Patient Satisfaction

A high-level summary of findings related to measures of patient satisfaction from the included studies is presented in Table 13, which was grouped into 2 comparisons: HCL therapy versus open-loop SAP therapy without a PLGS feature and HCL therapy versus MDII or insulin-pump therapy informed by SMBG (mixed). None of the studies that compared HCL therapy versus open-loop SAP therapy with a PLGS feature or HCL therapy versus open-loop SAP therapy with or without a PLGS feature (mixed) reported on patient satisfaction.

Table 13: High-Level Summary of Findings Related to Patient Satisfaction by Comparison in the Included Primary Clinical Studies

Outcome	Direction of effect				
HCL therapy vs. open-loop SAP therapy without a PLGS feature					
	RCTs				
	Hanaire et al. (2020)[56]	**Benhamou et al. (2019)[50]**	**Brown et al. (2019)[53]**	**Ekhlaspour et al. (2019)[54]**	**Forlenza et al. (2019)[55]**
DTSQ scores post-treatment	+	NS	NR	NR	NR
HCL therapy vs. MDII or insulin-pump therapy informed by SMBG (mixed)					
	RCTs				
	McAuley et al. (2020)[59]				
DTSQ scores post-treatment	NS				

DTSQ = Diabetes Treatment Satisfaction Questionnaire; HCL = hybrid closed-loop insulin delivery system; MDII = multiple daily insulin injections; NR = not measured or reported; NS = not statistically significant; PLGS = predictive low-glucose suspend; RCT = randomized controlled trial; SAP = sensor-augmented pump; SMBG = self-monitoring of blood glucose; vs. = versus.

Note: [+] suggests intervention more favourable than comparator.

HCL Therapy Versus Open-Loop SAP Therapy Without a PLGS Feature

Two RCTs[50,56] with some concerns of bias overall involving a total of 101 participants assessed patient satisfaction using the DTSQ following treatment with HCL therapy compared with open-loop SAP therapy. Hanaire and colleagues[56] reported statistically significantly higher mean values of the satisfaction index following 3 days of HCL therapy with the Diabeloop system (N = 36) compared with 3 days of open-loop SAP therapy (N = 36). Conversely, Benhamou et al. (2019) did not detect any statistically significant differences in mean DTSQ scores following 12 weeks of HCL therapy with the Diabeloop system or 12 weeks of open-loop SAP therapy. These findings are detailed in Table 14.

Table 14: Detailed Findings Related to Patient Satisfaction for Studies That Compared HCL Therapy With Open-Loop SAP Therapy Without a PLGS Feature

Outcome	Detailed findings			
Primary study citation	**HCL groups**	**Groups using open-loop SAPs without PLGS feature**	**Risk-adjusted or paired difference (HCL less open-loop SAP without PLGS feature; 95% CI)**	**P value**
DTSQ scores post-treatment				
Hanaire et al. (2020)[56]	31.0 (SD = 5.5)	26.0 (SD = 5.5)	NR	< 0.001[a]
Benhamou et al. (2019)[50]	27.2 (SD = 7.4)	27.9 (SD = 5.0)	NR	NR

CI = confidence interval; DTSQ = Diabetes Treatment Satisfaction Questionnaire; HCL = hybrid closed-loop insulin delivery system; NR = not reported; PLGS = predictive low-glucose suspend; SAP = sensor-augmented pump; SD = standard deviation.

Note: Data are expressed as means with SDs.

[a] Statistically significant.

HCL Therapy Versus MDII or Insulin-Pump Therapy Informed by SMBG (Mixed)

The 2020 RCT by McAuley et al., which had some concerns of bias overall, measured patient satisfaction with DTSQ scores following 26 weeks of therapy with either an HCL (N = 61) or with MDII or an insulin-pump informed by SMBG (N = 59). There were no statistically significant differences in DTSQ scores post-treatment between the 2 groups. These findings are detailed in Table 15.

Table 15: Detailed Findings Related to Patient Satisfaction for Studies That Compared HCL Therapy With MDII or Insulin-Pump Therapy Informed by SMBG

Outcome	Detailed findings			
Primary study citation	**HCL group**	**Group using MDII or insulin-pump therapy with SMBG**	**Adjusted difference (HCL less MDII or pump with SMBG; 95% CI)**	**P value**
DTSQ scores post-treatment				
McAuley et al. (2020)[59]	28.2 (SD = 5.9)	27.3 (SD = 5.1)	1.0 (−0.8 to 2.7)	0.29

CI = confidence interval; DTSQ = Diabetes Treatment Satisfaction Questionnaire; HCL = hybrid closed-loop insulin delivery system; MDII = multiple daily insulin injections; SD = standard deviation; SMBG = self-monitoring of blood glucose.

Note: Data are expressed as means with SDs.

Quality of Life

HCL Therapy Versus MDII or Insulin-Pump Therapy Informed by SMBG (Mixed)

One RCT with some concerns of bias overall measured the impact of diabetes on quality of life using the DIDP in 120 adult participants who were randomized to receive treatment with the MiniMed 670G (N = 61) or with MDII or insulin-pump therapy informed by SMBG (N = 59). After 26 weeks of therapy, participants assigned to the HCL group had statistically significantly improved diabetes-specific quality of life compared to those in the group using MDII or insulin-pump informed by SMBG. These findings are detailed in Table 16.

Table 16: Detailed Findings Related to Quality of Life for Studies That Compared HCL Therapy With MDII or Insulin-Pump Therapy Informed by SMBG

Outcome	Detailed findings			
Primary study citation	**HCL group**	**Group using MDII or insulin-pump therapy with SMBG**	**Adjusted difference (HCL less MDII or pump with SMBG; 95% CI)**	**P value**
DIDP scores post-treatment				
McAuley et al. (2020)[59]	4.5 (SD = 0.9)	4.8 (SD = 0.7)	−0.3 (SD = −0.6 to 0.0)	0.023

CI = confidence interval; DIDP = DAWN2 Impact of Diabetes Profile; HCL = hybrid closed-loop insulin delivery system; MDII = multiple daily insulin injections; SD = standard deviation; SMBG = self-monitoring of blood glucose.

Note: Data are expressed as means with SDs.

Additional Clinical Outcomes

There were several clinical outcomes that were not explicitly outlined as being of interest in the protocol for this Clinical Review, but were reported in the identified clinical literature. Data from these outcomes were extracted and summarized, when available. A high-level summary of findings related to additional clinical outcomes from the included studies is presented in Table 17, grouped into 4 comparisons: HCL therapy versus open-loop SAP therapy without a PLGS feature; HCL therapy versus open-loop SAP therapy with a PLGS feature; HCL therapy versus open-loop SAP therapy with or without a PLGS feature (mixed); and HCL therapy versus MDII or insulin-pump therapy informed by SMBG (mixed).

Table 17: High-Level Summary of Findings Related to Additional Clinical Outcomes by Comparison in the Included Primary Clinical Studies

Outcome	Direction of effect				
HCL therapy vs. open-loop SAP therapy without a PLGS feature					
	RCTs				
	Hanaire et al. (2020)[56]	**Benhamou et al. (2019)[50]**	**Brown et al. (2019)[53]**	**Ekhlaspour et al. (2019)[54]**	**Forlenza et al. (2019)[55]**
Glucose concentration	+	+	+	+	+
Glycemic variability	+	+	+	NS	NS
Body weight	NR	NR	NS	NR	NR
Total daily insulin amount	+	NR	NS	NS	NS
HCL therapy vs. open-loop SAP therapy with a PLGS feature					
	RCTs			**Non-RCTs**	
	Brown et al. (2020)[52]			**Lepore et al. (2020)[58]**	
Glucose concentration	+			+	
Glycemic variability	NS			+	
Body weight	NS			NR	
Total daily insulin amount	NS			NS	
HCL therapy vs. open-loop SAP therapy with or without a PLGS feature (mixed)					
	RCTs				
	Breton et al. (2020)[51]				
Glucose concentration	+				
Glycemic variability	?				

Outcome	Direction of effect
Body weight	?
Total daily insulin amount	?
HCL therapy vs. MDII or insulin-pump therapy informed by SMBG (mixed)	
	RCTs
	McAuley et al. (2020)[59]
Glucose concentration	+
Glycemic variability	+
Fasting capillary blood glucose	+
1,5-Anhydroglucitol levels	+
Body weight	NS
Total daily insulin amount	NS
Insulin-to-carbohydrate ratio	+
Basal-insulin proportion	+
Diabetes distress	NS
Diabetes-specific well-being	+
Prospective memory	NS
Retrospective memory	NS
Sleep quality	NS

HCL = hybrid closed-loop insulin delivery system; MDII = multiple daily insulin injections; NR = not measured or reported; NS = not statistically significant; PLGS = predictive low-glucose suspend; RCT = randomized controlled trial; SAP = sensor-augmented pump; SMBG = self-monitoring of blood glucose; vs. = versus.

Note: [+] suggests intervention more favourable than comparator; [?] suggests not compared statistically.

HCL Therapy Versus Open-Loop SAP Therapy Without a PLGS Feature

Mean glucose concentrations, as measured with study CGM devices, were reported in 5 RCTs[50,53-56] at either low risk of bias or with some concerns of bias overall that compared HCL therapy versus open-loop SAP therapy. All 5 of these RCTs[50,53-56] reported that participants who were receiving HCL therapy had statistically significantly improved mean glucose values (i.e., lower mean glucose values) compared to those who were on open-loop SAP therapy. Isganaitis et al. (2020)[57] observed similar trends in findings related to mean glucose values in their exploratory subgroup analysis of the children and adolescents (between the ages of 14 years and 24 years) in the Brown et al. (2019)[53] study. Numerical data from this subgroup analysis were extracted and are shown inAppendix 2, Table 41.

All 5 of these RCTs[50,53-56] (at either low risk of bias or with some methodological concerns) reported on glycemic variability. The authors of 3 studies[50,53,56] concluded that treatment with HCL therapy improved glycemic variability compared to treatment with open-loop SAP therapy, while the findings of 2 studies[54,55] did not indicate statistically significant differences between HCL and open-loop SAP therapy. Hanaire and colleagues[56] assessed glycemic variability by the standard deviations of the mean percentage of time spent in the glucose range of 4.4 mmol/L to 7.8 mmol/L overnight, which favoured treatment with HCL therapy. The 4 remaining studies[50,53-55] assessed glycemic variability using the coefficient of variation of sensor glucose. Isganaitis and colleagues[57] concluded that treatment with HCL therapy improved glycemic variability compared to treatment with open-loop SAP therapy in their exploratory subgroup analysis of children and adolescents (between the ages of 14 years and 24 years) in the Brown et al. (2019)[53] RCT. Numerical data from this subgroup analysis were extracted and are shown in Appendix 2, Table 41.

One study[53] with some concerns of bias overall reported on body weight post-treatment as an outcome of interest. The authors of the Brown et al. (2020) RCT[53] did not observe a statistically significant difference in mean body weight following 26 weeks of treatment with HCL therapy.

Four studies[53-56] at either low risk of bias or with some concerns of bias overall that compared treatment with HCL therapy versus open-loop SAP therapy (without a PLGS feature) reported on daily insulin utilization. Hanaire and colleagues[56] reported a statistically significant decrease in the mean daily insulin amount for participants during HCL therapy compared to open-loop SAP therapy. The 3 other studies[53-55] did not observe statistically significant differences in daily insulin usage between treatment with HCL therapy and open-loop SAP therapy.

Detailed results for the outcomes of glucose concentration, glycemic variability, body weight, and total daily insulin from the 5 RCTs[50,53-56] that compared HCL therapy versus open-loop SAP therapy without SAP are presented in Table 18.

Table 18: Detailed Findings Related to Additional Clinical Outcomes for Studies That Compared HCL Therapy With Open-loop SAP Therapy Without a PLGS Feature

Outcome	Detailed findings			
Primary study citation	**HCL groups**	**Groups using open-loop SAPs without PLGS feature**	**Risk-adjusted or paired difference (HCL less open-loop SAP without PLGS feature; 95% CI)**	**P value**
Glucose concentration (mmol/L)				
Hanaire et al. (2020)[56]	7.7 (SD = 0.8)	8.7 (SD = 1.5)	NR	< 0.0001[a]
Benhamou et al. (2019)[50]	8.7 (SD = 0.8)	9.1 (SD = 0.8)	−0.4 (−0.6 to −0.1)	0.012[a]
Brown et al. (2019)[53]	8.66 (SD = 1.05)	9.44 (SD = 1.39)	−0.72 (−0.94 to −0.44)	< 0.001[a]
Ekhlaspour et al. 2019)[54]	8.94 (SD = 1.66)	9.81 (SD = 2.03)	NR	0.023[a]
Forlenza et al. (2019)[55]	8.45 (SD = 0.77)	10.00 (SD = 1.28)	NR	0.002[a]
Glycemic variability (coefficient of variation of sensor glucose)				
Benhamou et al. (2019)[50]	31.0% (SD = 3.9%)	33.3% (SD = 3.9%)	−2.3% (−3.1% to −1.5%)	< 0.0001[a]
Brown et al. (2019)[53]	34% (SD = 5%)	36% (SD = 5%)	−3.0% (−4.0% to −2.0%)	< 0.001[a]
Ekhlaspour et al. 2019)[54]	34.2% (SD = 6.1%)	33.9% (SD = 8.4%)	NR	NS
Forlenza et al. (2019)[55]	32.6% (SD = 4.1%)	33.3% (SD = 5.4%)	NR	NS
Glycemic variability (SD of the time spent in the glucose range of 4.4 mmol/L to 7.8 mmol/L)				
Hanaire et al. (2020)[56]	0.8 mmol/L	1.5 mmol/L	NR	0.0014[a]
Body weight (kg)				
Brown et al. (2019)[53]	78.7 (SD = 17.0)	76.0 (SD = 18.9)	−0.2 (−1.8 to 1.4)	0.83
Total daily insulin amount (U/day)				
Hanaire et al. (2020)[56]	37.7 (SD = 13.9)	43.9 (SD = 12.9)	NR	< 0.0001[a]
Brown et al. (2019)[53]	55.0 (SD = 27)	51.0 (SD = 20)	3.0 (−7.0 to 13.0)	0.83
Ekhlaspour et al. 2019)[54]	40.5 (SD = 16.7)	43.9 (SD = 28.4)	NR	NS
Forlenza et al. (2019)[55]	33.1 (SD = 14.8)	27.8 (SD = 12.3)	NR	NS

CI = confidence interval; HCL = hybrid closed-loop insulin delivery system; NR = not reported; NS = non-significant; PLGS = predictive low-glucose suspend; SAP = sensor-augmented pump; SD = standard deviation.

Note: Data are expressed as means with SDs.

[a] Statistically significant.

HCL Therapy Versus Open-Loop SAP Therapy With a PLGS Feature

One RCT[52] with some concerns of bias overall and 1 cohort study[58] at high risk of bias that compared HCL therapy versus open-loop SAP therapy with a PLGS feature reported on mean CGM-measured glucose concentrations. The authors of the Brown et al. (2020)[52] RCT observed statistically significantly lower mean glucose levels in their HCL therapy group compared to the group using open-loop SAPs with a PLGS feature over the course of 13 weeks of treatment. Similarly, Lepore and colleagues[58] reported that participants who received HCL therapy had a greater decrease in their mean glucose concentrations from the start of the trial to the end of the 6-month study period compared to those who received open-loop SAP therapy with a PLGS feature.

Mean glycemic variability was assessed in both studies using the coefficient of variation of sensor glucose. Lepore and colleagues[58] noted that participants in the cohort study who received HCL therapy had a statistically significantly greater decrease in median change in the coefficient of variation of sensor glucose from the start of the study to the end of the 6-month study period than those who received open-loop therapy with a PLGS feature. Conversely, Brown et al. (2020)[52] did not observe any statistically significant differences in participants' coefficient of variation of sensor glucose values post-treatment.

The Brown et al. (2020)[52] RCT measured body weight as an outcome of interest. The median body weights for participants who received HCL therapy and open-loop SAP therapy with a PLGS feature were both reported. There were no statistically significant between-group differences.

The authors of both studies[52,58] that compared HCL therapy versus open-loop SAP therapy with a PLGS feature did not report any statistically significant differences in their treatment groups with respect to daily insulin dosage. This value was reported as a median daily insulin amount by Brown and colleagues[52] and as median changes in mean daily insulin amount from the baseline value to the value at the end of the study period by Lepore and colleagues.[58]

The numerical data from these 2 studies[52,58] are presented in Table 19.

Table 19: Detailed Findings Related to Additional Clinical Outcomes for Studies That Compared HCL Therapy With Open-Loop SAP Therapy With a PLGS Feature

Outcome	Detailed findings			
Primary study citation	**HCL group**	**Groups using open-loop SAPs with PLGS feature**	**Risk-adjusted or paired difference (HCL less open-loop SAP with PLGS feature; 95% CI)**	**P value**
Glucose concentration (mmol/L)				
Brown et al. (2020)[52]	8.88 (SD = 1.11)	9.44 (SD = 1.67)	–0.39 (–0.61 to –0.22)	< 0.001[a]
Change in glucose concentration (mmol/L)				
Lepore et al. (2020)[58]	–0.85 (SD = 0.98)	0.04 (SD = 0.72)	NR	< 0.005[a]
Glycemic variability (coefficient of variation of sensor glucose)				
Brown et al. (2020)[52]	34.0% (SD = 4%)	35.0% (SD = 5.0%)	–1.0% (–2.0% to 1.0%)	0.32
Change in glycemic variability (coefficient of variation of sensor glucose)				
Lepore et al. (2020)[58]	–3.8% (SD = 3.6%)	–0.6% (SD = 3.3%)	NR	< 0.01[a]
Body weight (kg)				
Brown et al. (2020)[52]	79.2 (IQR = 65.9 to 93.4)	72.8 (IQR = 65.8 to 87.8)	0.3 (–0.4 to 1.1)	0.39
Total daily insulin amount (U/kg/day)				
Brown et al. (2020)[52]	0.62 (IQR, 0.50 to 0.84)	0.67 (IQR, 0.48 to 0.88)	–0.02 (–0.05 to 0.01)	0.25
Change in total daily insulin amount (U/kg/day)				
Lepore et al. (2020)[58]	–0.01 (SD = 0.07)	0.01 (SD = 0.1)	NR	NS

CI = confidence interval; HCL = hybrid closed-loop insulin delivery system; IQR = interquartile range; NR = not reported; NS = non-significant; PLGS = predictive low-glucose suspend; SAP = sensor-augmented pump; SD = standard deviation.

Note: Data are expressed as means with SDs or medians with IQRs, depending on the distribution of data.

[a] Statistically significant.

HCL Therapy Versus Open-Loop SAP Therapy With or Without a PLGS Feature (Mixed)

One RCT[51] with some concerns of bias overall that compared HCL therapy versus a control group that received open-loop SAP therapy with or without a PLGS feature reported on additional clinical outcomes.

Breton and colleagues[51] indicated that treatment with HCL therapy statistically significantly improved mean glucose concentrations compared to treatment with open-loop therapy with or without a PLGS feature.

The authors also reported on glycemic variability as assessed by the coefficient of variation of sensor glucose, median body weight, and mean total daily insulin amount;[51] however, these outcomes were considered exploratory and not included in their hierarchical analysis, and their statistical significance was not formally tested.

Findings, including numerical data, risk-adjusted differences, and P values related to additional clinical outcomes from Breton et al. (2020) are detailed in Table 20.

Table 20: Detailed Findings Related to Additional Clinical Outcomes for Studies That Compared HCL Therapy With Open-Loop SAP Therapy With or Without a PLGS Feature

Outcome	Detailed findings			
Primary study citation	**HCL group**	**Group using open-loop SAPs with or without PLGS feature**	**Risk-adjusted difference (HCL less open-loop SAP ± PLGS feature; 95% CI)**	**P value**
Glucose concentration (mmol/L)				
Breton et al. (2020)[51]	8.99 (SD = 1.00)	9.94 (SD = 1.44)	−0.72 (−1.11 to −0.39)	< 0.001[a]
Glycemic variability (coefficient of variation of sensor glucose)				
Breton et al. (2020)[51]	38.0% (SD = 4%)	39.0% (SD = 4%)	−1.6% (−2.8% to −0.4%)	Not calculated[a]
Body weight (kg)				
Breton et al. (2020)[51]	44.0 (IQR = 34.0 to 52.0)	37.0 (IQR = 34.0 to 54.0)	0.0 (−1.2 to 1.1)	Not calculated[a]
Total daily insulin amount (U/kg/day)				
Breton et al. (2020)[51]	0.94 (SD = 0.25)	0.98 (SD = 0.32)	0.00 (−0.10 to 0.09)	Not calculated[a]

CI = confidence interval; HCL = hybrid closed-loop insulin delivery system; PLGS = predictive low-glucose suspend; SAP = sensor-augmented pump; SD = standard deviation.

Note: Data are expressed as means with SDs or medians with IQRs, depending on the distribution of data.

[a] Statistically significant.

[a] The statistical significance of these findings was not calculated because these outcomes were considered exploratory and not included in the hierarchical analysis.

HCL Therapy Versus MDII or Insulin-Pump Therapy Informed by SMBG (Mixed)

One RCT[59] with some concerns of bias overall that compared HCL therapy versus a control group that received insulin delivery through MDII or insulin-pump therapy informed by SMBG reported on additional clinical outcomes.

Following 26 weeks of treatment with the assigned intervention, those who received HCL therapy had statistically significant improvements in their mean glucose concentration, glycemic variability (as assessed by the coefficient of variation of sensor glucose), mean fasting capillary blood glucose levels, median 1,5-anhydroglucitol levels (a measure of intermediate-term glycemia), and diabetes-specific well-being, assessed using the 4-item subscale of W-BQ28 scores post-treatment, compared to those who received MDII or insulin-pump therapy informed by SMBG. Additionally, participants in the HCL group had statistically significantly improved changes in their insulin-to-carbohydrate ratios and in their basal-insulin proportions between baseline values and values at the end of the study period compared to participants in the group using MDII or insulin pumps informed by SMBG. There were no statistically significant differences between the treatment groups with respect to change in body weight, change in total daily insulin amount, diabetes distress, prospective or retrospective memory as measured with the PRMQ, or perceived sleep quality, which was assessed using the PSQI.

Detailed numerical results from these additional clinical outcomes reported in the 2020 RCT by McAuley et al.[59] are presented in Table 21.

Table 21: Detailed Findings Related to Additional Clinical Outcomes for Studies That Compared HCL Therapy With MDII or Insulin-Pump Therapy Informed by SMBG

Outcome	Detailed findings			
Primary study citation	**HCL group**	**Group using MDII or insulin-pump therapy with SMBG**	**Adjusted difference (HCL less MDII or pump with SMBG; 95% CI)**	**P value**
Glucose concentration (mmol/L)				
McAuley et al. (2020)[59]	8.72 (SD = 0.78)	9.49 (SD = 1.28)	–0.72 (–0.89 to –0.39)	< 0.00014[a]
Glycemic variability (coefficient of variation of sensor glucose)				
McAuley et al. (2020)[59]	34.7% (SD = 4.5%)	39.3% (SD = 5.4%)	–4.7% (–6.5% to −2.9%)	< 0.0001[a]
Fasting capillary blood glucose (mmol/L)				
McAuley et al. (2020)[59]	8.60 (SD = 3.00)	9.49 (SD = 4.22)	–1.00 (–1.61 to –0.39)	0.0017[a]
1,5-anhydroglucitol levels (mcg/mL)				
McAuley et al. (2020)[59]	4.9 (IQR = 3.4 to 6.8)	3.3 (IQR = 1.8 to 5.2)	1.6 (0.7 to 2.3)	0.00046[a]
Change in body weight (kg)				
McAuley et al. (2020)[59]	0.6 (IQR = −1.9 to 2.1)	0.7 (IQR = −0.7 to 1.5)	–0.1 (–1.1 to 0.9)	0.77
Change in total daily insulin amount (U/kg/day)				
McAuley et al. (2020)[59]	–0.01 (IQR = –0.10 to 0.03)	–0.02 (IQR = –0.10 to 0.04)	–0.01 (–0.04 to 0.03)	0.85
Change in insulin-to-carbohydrate ratio				
McAuley et al. (2020)[59]	–1.2 (IQR = –2.4 to 0.0)	0.0 (IQR = –0.8 to 0.0)	–0.8 (–1.4 to –0.1)	0.0078[a]
Change in basal-insulin proportion				
McAuley et al. (2020)[59]	–5.4% (SD = 16.9%)	1.9% (SD = 8.2%)	–6.7 –11.1 to –2.3)	0.0034[a]
Diabetes distress (PAID scores post-treatment)				
McAuley et al. (2020)[59]	16.7 (IQR = 10.2 to 27.4)	21.2 (IQR = 9.5 to 36.2)	–17.0 (–33.0 to 3.0)	0.10
Diabetes-specific well-being (4-item subscale of W-BQ28 scores post-treatment)				
McAuley et al. (2020)[59]	7.8 (SD = 2.4)	6.8 (SD = 2.6)	1.2 (0.4 to 1.9)	0.0048[a]
Prospective memory (PRMQ prospective scores post-treatment)				
McAuley et al. (2020)[59]	17.0 (IQR = 14.0 to 20.0)	18.0 (IQR = 15.0 to 24.0)	–1.0 (–3.0 to 0.0)	0.11
Retrospective memory (PRMQ retrospective scores post-treatment)				
McAuley et al. (2020)[59]	15.0 (IQR = 11.0 to 18.0)	15.0 (IQR = 12.0 to 17.5)	0.0 (–2.0 to 2.0)	0.87
Sleep quality (PSQI scores post-treatment)				
McAuley et al. (2020)[59]	6.5 (SD = 3.1)	5.8 (SD = 3.0)	0.5 (–0.5 to 1.5)	0.34

CI = confidence interval; HCL = hybrid closed-loop insulin delivery system; IQR = interquartile range; MDII = multiple daily insulin injections; PAID = Problem Areas in Diabetes; PRMQ = Prospective and Retrospective Memory Questionnaire; PSQI = Pittsburgh Sleep Quality Index; SD = standard deviation; SMBG = self-monitoring of blood glucose; W-BQ28 = Well-Being Questionnaire 28.

Note: Data are expressed as means with SDs or medians with IQRs, depending on the distribution of data.

[a] Statistically significant.

Research question 2: What is the comparative safety of commercially available HCLs versus other insulin delivery methods in people of any age with type 1 diabetes?

A high-level summary of findings from all included studies[50-56,58,59] related to safety outcomes, indicating the direction of effect for each outcome by study, is presented in Table 22. The studies were grouped into 4 comparisons: HCL therapy versus open-loop SAP therapy without a PLGS feature; HCL therapy versus open-loop SAP therapy with a PLGS feature; HCL therapy versus open-loop SAP therapy with or without a PLGS feature (mixed); and HCL therapy versus MDII or insulin-pump therapy informed by SMBG (mixed).

Table 22: High-Level Summary of Safety Outcomes by Comparison in the Included Primary Clinical Studies

Outcome		Direction of effect				
HCL therapy vs. open-loop SAP therapy without a PLGS feature						
		RCTs				
		Hanaire et al. (2020)[56]	**Benhamou et al. (2019)[50]**	**Brown et al. (2019)[53]**	**Ekhlaspour et al. (2019)[54]**	**Forlenza et al. (2019)[55]**
Hypoglycemic events	Number of events[a]	NS	?	NS	NR	NR
	Number of carbohydrate treatments	NR	NR	NR	NS	NS
	Weight of carbohydrate treatments consumed	NR	NR	NR	NS	NS
Hyperglycemic events	Number of events[b]	NR	?	+	NR	NR
Adverse events	Proportion of participants with any adverse event	?	NR	−	NR	NR
Worsening of A1C	Proportion of those whose A1C worsened by > 0.5%	NR	NR	NS	NR	NR
Diabetic ketoacidosis	Number of events	NR	?	?	NR	NR
Ketosis events	Number of days with elevated ketone levels[c]	NR	NR	?	NR	NR
HCL therapy vs. open-loop SAP therapy with a PLGS feature						
		RCTs		**Non-RCTs**		
		Brown et al. (2020)[52]		**Lepore et al. (2020)[58]**		
Hypoglycemic events	Number of events[a]	NS		?		
Hyperglycemic events	Number of events	?		NR		
Adverse events	Number of events	?		NR		
Worsening of A1C	Proportion of those whose A1C worsened by > 0.5%	?		NR		

Outcome		Direction of effect	
Diabetic ketoacidosis	Number of events	?	?
Ketosis events	Number of days with elevated ketone levels[c]	?	NR
HCL therapy vs. open-loop SAP therapy with or without a PLGS feature (mixed)			
		RCTs	
		Breton et al. (2020)[51]	
Hypoglycemic events	Number of events[a]	NS	
Hyperglycemic events	Number of events[b]	+	
Adverse events	Number of events	NS	
Worsening of A1C	Proportion of those whose A1C worsened by > 0.5%	?	
Diabetic ketoacidosis	Number of events	?	
Ketosis events	Number of days with elevated ketone levels[c]	NS	
HCL therapy vs. MDII or insulin-pump therapy informed by SMBG (mixed)			
		RCTs	
		McAuley et al. (2020)[59]	
Hypoglycemic events	Proportion of those with an event[a]	?	
Adverse events	Number of participants with an event	?	
Diabetic ketoacidosis	Number of participants with an event	?	

A1C = glycated hemoglobin; HCL = hybrid closed-loop insulin delivery system; MDII = multiple daily insulin injections; NR = not measured or not reported; NS = not statistically significant; PLGS = predictive low-glucose suspend; RCT = randomized controlled trial; SAP = sensor-augmented pump; SMBG = self-monitoring of blood glucose; vs. = versus.

Note: [+] suggests intervention more favourable than comparator; [−] suggests intervention less favourable than comparator; [?] suggests not compared statistically.

[a] Defined by Brown et al. (2020)[52] as 15 consecutive minutes with a glucose reading of < 3.9 mmol/L; by Hanaire et al. (2020)[56] as a continuous monitored glucose < 3.9 mmol/L; by Breton et al. (2020)[51] and Brown et al. (2019)[53] as 15 consecutive minutes with a glucose reading of < 3.0 mmol/L; and in Benhamou et al. (2019),[50] Lepore et al. (2020),[58] and McAuley et al. (2020)[59] as hypoglycemia requiring third-party intervention.

[b] Defined by Breton et al. (2020)[51] and Brown et al. (2020)[52] as 15 consecutive minutes with a glucose reading of > 16.7 mmol/L and by Benhamou et al. (2019)[50] as capillary blood glucose > 20 mmol/L.

[c] Defined as the mean number of days with ≥ 1 blood ketone measurement > 1.0 mmol/L.

Hypoglycemic Events

HCL Therapy Versus Open-Loop SAP Therapy Without a PLGS feature

Safety outcomes related to hypoglycemic events were monitored in 5 RCTs[50,53-56] at either low risk of bias or with some concerns of bias overall that compared HCL therapy versus open-loop SAP therapy (without a PLGS feature).

The authors of 2 studies[53,56] did not observe statistically significant differences in the rates of hypoglycemic events between participants treated with HCL therapy and those treated with

open-loop SAP therapy. Hanaire and colleagues[56] reported that participants experienced a mean of number of 4.3 (SD = 3.6) hypoglycemic events (defined as events in which glucose value was less than 3.9 mmol/L) during their 72-hour study period while using HCL therapy compared to 3.6 (SD = 2.8) such events during open-loop SAP therapy (P = non-significant). The authors of the Brown et al. (2019)[53] RCT indicated that the median number of hypoglycemic events per week (defined as at least 15 consecutive minutes with a glucose level of less than 3.0 mmol/L) were 0.4 (IQR = 0.1 to 0.9) events and 0.5 (IQR = 0.2 to 0.9) events in their HCL group and in the group using open-loop SAP, respectively (P = 0.06). Benhamou et al. (2019) recorded the total number of hypoglycemic events (defined as hypoglycemia requiring third-party intervention) experienced by participants in their trial. There were 9 in the HCL therapy group (N = 68) and 0 in the group using open-loop SAPs without a PLGS feature (N =68). No statistical testing results were reported.

Two studies[54,55] recorded the number of carbohydrate treatments and the weight of carbohydrate treatments that study participants consumed during hypoglycemic events. There were no statistically significant differences between treatment with HCL therapy and treatment with open-loop SAP therapy for either of these outcomes in either study.[54,55] The authors of the Ekhlaspour et al. (2019)[54] RCT indicated that participants consumed an average of 2.8 (SD = 1.5) carbohydrate treatments during HCL therapy compared to 3.2 (SD = 2.4) carbohydrate treatments during open-loop SAP therapy (P = non-significant). There were no differences in the total weight of carbohydrate treatments consumed (45.5 [SD = 27.8] g versus 57.7 [SD = 57.8] g; P = non-significant). Similarly, Forlenza and colleagues[55] reported a mean total number of carbohydrate treatments of 0.8 (75% CI, 0.3 to 1.4) and 0.3 (75% CI, 0.3 to 0.8), with a mean total amount of carbohydrate treatments of 17.5 (SD = 17.6) g and 35.5 (SD = 55.5) g during HCL and open-loop SAP therapy, respectively (P = non-significant).

HCL Therapy Versus Open-Loop SAP Therapy With a PLGS Feature

Hypoglycemic events were reported in 1 RCT[52] with some concerns of bias overall and 1 cohort study[58] at high risk of bias that compared HCL therapy versus open-loop SAP therapy with a PLGS feature.

The RCT[52] reported on the median number of hypoglycemic events per week (defined as at least 15 consecutive minutes with a glucose level of less than 3.9 mmol/L). There were no statistically significant differences between treatment with HCL therapy (3 [IQR, 1.5 to 4.9] events) and open-loop SAP therapy with a PLGS feature (3.1 [IQR, 1.6 to 5.3] events) (risk-adjusted difference = 0.1; 95% CI, –0.3 to 0.6; P = 0.58).

Lepore et al. (2020)[58] noted that no participants in their study experienced any episodes of severe hypoglycemia, defined as an event that required assistance and the administration of glucagon or carbohydrates.

HCL Therapy Versus Open-Loop SAP Therapy With or Without a PLGS Feature (Mixed)

Outcomes related to hypoglycemia were reported in 1 RCT with some concerns of bias overall that compared HCL therapy versus a control group that received open-loop SAP therapy with or without a PLGS feature. There were no statistically significant differences in the median number of hypoglycemic events (defined as at least 15 consecutive minutes with a glucose level of less than 3.0 mmol/L) per week between participants who received HCL therapy (0.5 [IQR, 0.1 to 0.8] events) and those who received open-loop SAP therapy with or without a PLGS feature (0.6 [IQR, 0.1 to 1.0] events) (P = 0.16).

HCL Therapy Versus MDII or Insulin-Pump Therapy Informed by SMBG (Mixed)

One RCT with some concerns of bias overall that compared 1 group receiving HCL therapy versus a control group that received insulin delivery through MDII or insulin-pump therapy informed by SMBG reported on the proportion of participants who experienced severe hypoglycemia (defined as hypoglycemia requiring third-party intervention) during the study period. Of participants on HCL therapy (N = 61), 10% had such an event, compared to 5% of those in the control group (N = 59). No statistical testing results were reported.

Hyperglycemic Events

HCL Therapy Versus Open-Loop SAP Therapy Without a PLGS Feature

Hyperglycemic events were reported in 2 RCTs[50,53] with some concerns of bias overall that compared HCL therapy versus open-loop SAP therapy (without a PLGS feature). Benhamou et al. (2019) noted that there were 5 severe hyperglycemic events (defined as capillary blood glucose > 20.0 mmol/L) in their HCL group (N = 68) and 0 severe hyperglycemic events in their control group, which used open-loop SAPs without a PLGS feature (N = 68). No statistical testing results were reported. Participants in the Brown et al. (2019)[53] study who were treated with HCL therapy experienced statistically significantly fewer hyperglycemic events than those who were treated with open-loop SAP therapy. The median number of hyperglycemic events (defined as at least 15 consecutive minutes with a glucose level > 16.7 mmol/L) per week was 1.2 (IQR, 0.4 to 2.6) events in the HCL group and 2.7 (IQR, 1.1 to 4.6) events in the open-loop SAP group (P < 0.001).

HCL Therapy Versus Open-Loop SAP Therapy With a PLGS Feature

Brown et al. (2020),[52] which had some concerns of bias overall, reported on the number of episodes of hyperglycemia with ketosis. There were 0 of these events in the HCL therapy group (N = 54) and 3 in the group treated with open-loop SAPs with a PLGS feature (N = 55). No statistical testing results were reported.

HCL Therapy Versus Open-Loop SAP Therapy With or Without a PLGS Feature (Mixed)

One RCT with some concerns of bias overall that compared HCL therapy versus open-loop SAP therapy with or without a PLGS feature reported on the rate of hyperglycemic events as a safety outcome. Participants who received HCL therapy experienced a lower median number of hyperglycemic events (defined as at least 15 consecutive minutes with a glucose level > 16.7 mmol/L) per week than those who received open-loop SAP therapy with or without a PLGS feature (3.0 [IQR, 1.7 to 5.2] events versus 5.6 [IQR, 3.4 to 8.1] events; P = 0.001).

Adverse Events

HCL Therapy Versus Open-Loop SAP Therapy Without a PLGS Feature

The risk of adverse events was examined in 1 RCT[53] with some concerns of bias overall that compared HCL therapy with the Control-IQ system versus open-loop SAP therapy over a 6-month study period. Brown and colleagues[53] reported that the HCL group had an increased proportion of participants who experienced any adverse event compared to those who received open-loop SAP therapy (HCL = 14% [N = 16/112]; open-loop = 2% [N = 2/56]; P = 0.05). The types of adverse events experienced by those in the HCL group included diabetic ketoacidosis (N = 1), serious adverse events related to trial device (N = 1), hyperglycemia or ketosis without diabetic ketoacidosis (N = 12), and other serious adverse events (N = 3). The 2 participants in the open-loop group experienced hyperglycemia or ketosis without diabetic ketoacidosis (N = 2).

Hanaire et al. (2020),[56] which had some concerns of bias overall, noted that there were no severe adverse events observed for participants in either of their treatment groups.

HCL Therapy Versus Open-Loop SAP Therapy With or Without a PLGS Feature (Mixed)

One RCT with some concerns of bias overall that compared HCL therapy to open-loop SAP therapy with or without a PLGS feature included data on the rates of adverse events experienced by participants. There were no statistically significant differences in the number of adverse events per 100 person-years between the 2 treatment groups (65.3 in the HCL group compared to 41.3 in the group on open-loop with or without a PLGS feature; P value = 0.50).

HCL Therapy Versus MDII or Insulin-Pump Therapy Informed by SMBG (Mixed)

McAuley et al. (2020), which had some concerns of bias overall, noted that 21% of participants in their HCL group (N = 61) and 15% of participants in their control group (N = 59) experienced a serious adverse event. No statistical testing results were reported.

Worsening of A1C

HCL Therapy Versus Open-Loop SAP Therapy Without a PLGS Feature

One RCT[53] with some concerns of bias overall measured the proportion of participants who had a worsening of their A1C levels following 6 months of therapy with the Control-IQ HCL (N = 112) or with an open-loop SAP system (N = 56). Brown and colleagues[53] reported that 7% (N = 8/112) of participants who received HCL therapy and 9% (N = 5/56) of participants who received open-loop SAP therapy recorded an increase of at least 0.5% in their A1C levels post-treatment. The difference between the 2 groups was not statistically significant (P = 0.60).

HCL Therapy Versus Open-Loop SAP Therapy With a PLGS Feature

One RCT[52] with some concerns of bias overall reported that 15% of participants in the HCL group (N = 54) and 36% of participants in the group receiving open-loop SAP therapy with a PLGS Feature (N = 55) experienced a worsening of A1C by at least 0.5% throughout the course of the trial. No statistical testing results were reported.

HCL Therapy Versus Open-Loop SAP Therapy With or Without a PLGS Feature (Mixed)

One RCT with some concerns of bias overall that compared HCL therapy versus a control group receiving open-loop SAP therapy with or without a PLGS feature noted that the proportion of participants who had a worsening in their A1C by at least 0.5% post-treatment was 3% in the HCL group and 9% in the control group. No statistical testing results were reported.

Diabetic Ketoacidosis Events

HCL Therapy Versus Open-Loop SAP Therapy Without a PLGS Feature

Two RCTs[50,53] with some concerns of bias overall that compared treatment with HCL therapy versus open-loop SAP therapy without a PLGS feature reported on outcomes related to diabetic ketoacidosis. Benhamou et al. (2019) reported that there were no events of diabetic ketoacidosis in either of their study groups. Brown et al. (2019)[53] noted that 1 trial participant assigned to their HCL group (N = 112) experienced diabetic ketoacidosis. No participants in their control group receiving open-loop SAP therapy without a PLGS feature (N = 56) experienced diabetic ketoacidosis. No statistical testing results were reported.

HCL Therapy Versus Open-Loop SAP Therapy With a PLGS Feature

Diabetic ketoacidosis events were reported in 1 RCT[52] with some concerns of bias overall and 1 cohort study[58] at high risk of bias that compared HCL therapy versus open-loop SAP therapy with a PLGS Feature.

The authors of both studies[52,58] reported that no participants experienced diabetic ketoacidosis during the study periods, regardless of the intervention they received.

HCL Therapy Versus Open-Loop SAP Therapy With or Without a PLGS Feature (Mixed)

The Breton et al. (2020) study, which had some concerns of bias overall, did not observe any events of diabetic ketoacidosis for participants in either group throughout its 16-week trial.

HCL Therapy Versus MDII or Insulin-Pump Therapy Informed by SMBG (Mixed)

One RCT with some concerns of bias overall reported on the proportion of participants who experienced at least 1 diabetic ketoacidosis event throughout the 6-month study period. Of the 61 participants who received HCL therapy, 1 experienced a diabetic ketoacidosis event (2%) versus 2 participants in the control group (N = 59; 3%). No statistical testing results were reported.

Ketosis Events

HCL Therapy Versus Open-Loop SAP Therapy Without a PLGS Feature

The authors of 1 RCT[53] with some concerns of bias overall reported on the number of days that participants had at least 1 ketone measurement greater than 1.0 mmol/L. For those assigned to HCL therapy, this was 14 of the 20,571 total person-days of follow-up (0.07%) versus 15 of 10,285 person-days of follow-up (0.15%) in the group receiving open-loop SAP therapy without a PLGS feature control. No statistical testing results were reported.

HCL Therapy Versus Open-Loop SAP Therapy With a PLGS Feature

One RCT[52] with some concerns of bias overall reported on the total number of days in which participants in either treatment group had a ketone measurement of greater than 1.0 mmol/L. This number was 5 for those in the HCL group (N = 54) and 1 in the group receiving open-loop SAP therapy with a PLGS feature (N = 55). No statistical testing results were reported.

HCL Therapy Versus Open-Loop SAP Therapy With or Without a PLGS Feature (Mixed)

One RCT with some concerns of bias overall that compared HCL therapy versus open-loop SAP therapy with or without a PLGS feature control included data on the rates of ketosis events experienced by participants. There were no statistically significant differences in the mean number of days on which participants of the RCT by Breton and colleagues recorded 1 or more blood ketone measurements of greater than 1.0 mmol/L (P = 0.19).

Summary of Results

Eight RCTs (in 9 publications) and 1 non-randomized study were identified regarding the comparative clinical effectiveness and safety of commercialized HCLs versus other insulin delivery methods in people of any age with type 1 diabetes. Of these 9 studies, 5 compared HCLs versus open-loop SAP systems without a PLGS feature , 2 compared HCLs versus open-loop SAP systems with a PLGS feature, 1 compared HCL therapy versus a control group that received open-loop SAP therapy with or without PLGS control (a mixed

population), and 1 compared HCL therapy versus a control group that received insulin delivery through MDII or insulin-pump therapy (a mixed population), both of which were informed by SMBG (i.e., using a blood glucose meter without access to CGM data).

Overall, compared to open-loop SAP therapy, HCL therapy improved various glucose time-in-range metrics, regardless of whether a PLGS feature was available. A clear trend was demonstrated across all studies that HCL therapy improved the proportion of time spent in euglycemic ranges compared to open-loop systems. For hypo- and hyperglycemic ranges, HCL also showed a trend of improvement; however, there were some instances, especially for hypoglycemic ranges, where there were no statistically significant differences between treatment with HCL therapy and treatment with open-loop SAP therapy, with or without a PLGS feature. It appeared that HCLs were more likely to demonstrate statistically significant improvements in the time spent in hypoglycemic ranges when compared to open-loop SAP devices that did not have a PLGS feature than when compared to HCLs that did. This observation aligns with literature that has directly compared open-loop SAP systems without a PLGS feature to systems with a PLGS feature.[89-91] Similarly, HCL therapy was effective at increasing the time spent in euglycemic ranges and decreasing the time spent in hypo- and hyperglycemic ranges compared to MDII and to insulin-pump therapy informed by SMBG, a comparator that may better reflect the current standard of care for the majority of people living with type 1 diabetes in Canada.

There were no instances where open-loop SAP therapy (with or without a PLGS feature), MDII, or insulin-pump therapy informed by SMBG improved any time-in-range glucose metric compared to HCL therapy in the identified clinical literature. In addition to these findings, the exploratory subgroup analysis reported by Isganaitis and colleagues suggested similar findings in the effectiveness of HCL therapies with respect to time-in-range metrics between a subgroup of adolescents and children and the entire population of the RCT by Brown et al. (2019). Although these findings are favourable for HCL therapy, the clinical validity of using glucose time-in-range metrics as a surrogate marker for risk of developing diabetes-related complications has not yet been established. There is literature that establishes a potential association between glucose time-in-range and clinical outcomes in people with type 1 or type 2 diabetes; it has led to the endorsement of this outcome as a new and useful tool to evaluate glycemic control. For example, Vigersky and McMahon examined the correlation between percentage time-in-range metrics and A1C across 18 articles that measured both parameters in a total of 2,577 individuals with type 1 or type 2 diabetes and found a strong relationship between time in range and A1C using linear regression analysis and Pearson's correlation coefficient. Their findings suggested that an absolute change of 10% in time in range correlated with a 0.8% (9.0 mmol/mol) change in A1C. However, a separate review conducted in 2019 concluded that time in range should not be considered a validated surrogate marker for risk of developing diabetes-related complications due to the limited literature investigating this association, which did not allow for comparisons across populations. Given that various glucose time-in-range metrics were the primary outcomes of all included RCTs, this is an important consideration when evaluating the clinical significance of the findings summarized in this review. Time in range is not a replacement for measurement of A1C levels; rather, it provides complementary information about the quality of overall glucose control.

Outcomes related to measurements of A1C were documented in 6 studies, all of which had follow-up periods of 12 weeks or longer. The authors of 3 of these studies concluded that treatment with HCL therapy improved A1C measures post-treatment compared to open-loop SAP therapy without a PLGS feature or compared to open-loop SAP therapy with a PLGS

feature. Two studies did not detect statistically significant differences between treatment with HCL therapy and open-loop SAP therapy (with or without a PLGS feature) with respect to measures of A1C; however, these findings could have been a result of these studies not having the statistical power to detect a difference for the A1C outcomes, given that these were not the primary outcomes of these studies. McAuley et al. (2020) observed statistically significant improvements in mean A1C in participants treated with HCL therapy compared to those treated with MDII or insulin-pump therapy informed by SMBG.

The remaining findings addressing the comparative clinical effectiveness of HCL therapy were mostly inconclusive. Across most studies, HCL therapy improved mean glucose concentrations and glycemic variability compared to open-loop SAP therapy (with or without a PLGS feature), MDII, or insulin-pump therapy informed by SMBG; however, the clinical significance of these statistically significant improvements is unclear. There was no consistent benefit of HCL therapy with respect to patient satisfaction, body weight, or total daily insulin amount. Additional research investigating these outcomes is required before more definitive conclusions may be drawn.

As for the comparative safety of HCLs, all 9 identified studies provided data that allowed for comparisons between the HCL and comparator groups. Generally, the rates of adverse events, such as hypoglycemic and ketosis events, were not statistically significantly different between participants who were treated with HCL therapy and those who received open-loop SAP therapy (with or without a PLGS feature). There were 3 instances where between-group differences were statistically significant: in 2 studies, participants treated with HCL therapy experienced lower rates of hyperglycemic events, and in 1 study, the proportion of participants with any adverse event was significantly higher in the HCL group compared to the open-loop SAP group. A number of findings were reported without statistical testing results — some with higher incidence of adverse events in the HCL group and others with higher incidence of adverse events in the control groups — but the event numbers were generally small. While there were no substantial safety concerns expressed in the identified literature, additional studies with longer follow-up periods and larger sample sizes would reduce the uncertainty surrounding the safety of HCLs.

The 9 studies included in this Clinical Review were judged to be at low to high risk of bias during the critical appraisal process. With the exception of some concerns related to bias arising from the randomization process and bias in measurement of the outcome in some studies, the RCTs were judged as having high internal validity. As for external validity, the study participants and care providers largely appeared to be representative of those in Canada; however, the available clinical literature was insufficient to assess what subpopulations may be most likely to benefit from HCL therapy. All 9 clinical studies enrolled participants with type 1 diabetes who had reasonable control of their condition and were overall relatively healthy (i.e., without significant comorbidities or disabilities resulting from their type 1 diabetes). For example, Hanaire et al. (2020) required participants to have A1C values between 6.0% and 9.5% at enrolment and excluded people with diabetes who have serious illness; McAuley et al. (2020) enrolled individuals who had A1C levels less than or equal to 10.5% and excluded those who had poor visual acuity or several other comorbidities at baseline (e.g., uncontrolled celiac disease, hypertension, thyroid disease, or clinically significant gastroparesis); Ekhlaspour et al. (2019) and Forlenza et al. (2019) excluded those with a recent history of severe hypoglycemia or diabetes ketoacidosis and those who had active renal or cardiac illness; and Benhamou et al. (2019) excluded those with impaired renal function. As a result, it is unclear how participants with significant comorbidities or disabilities that are a result of lifelong diabetes (e.g., blindness, kidney

damage, cardiovascular disease, nerve damage) would benefit from HCL therapy. In addition, there was no evidence that directly compared HCL therapy versus alternative HCLs. While the 3 HCLs examined in the identified literature (i.e., the Tandem Control-IQ HCL, the Diabeloop single-hormone HCL, and the Medtronic MiniMed 670G system) appeared to produce similar clinical and safety outcomes, there are distinct differences between these systems with respect to their components and their insulin-dosing algorithms. Therefore, no conclusions can be drawn regarding the comparative clinical effectiveness of one HCL versus another. None of the included primary studies were conducted in Canada; any differences between the Canadian health system and the health systems of the countries where the studies were conducted (i.e., the US, France, Italy, and Australia) may require consideration. In summary, HCL therapy appeared to improve clinical outcomes in patients with type 1 diabetes compared to open-loop SAP therapy, MDII, or insulin therapy informed by SMBG, and had a comparable safety profile; however, long-term data examining the clinical effectiveness and safety of HCLs are lacking, which creates uncertainty in these findings. Additionally, there are some concerns regarding the quality of the identified evidence that limit the extent to which the conclusions of this review are valid; the true effect of HCL therapies that would be observed outside of these clinical trials may be substantially different from the findings described in this report.

Clinical Studies Identified After the Stakeholder Feedback Period

As outlined in the methods for the Clinical Review, any studies identified after the stakeholder feedback period were to be incorporated into the summary of results, and not into the analysis. One such study was identified. The publication describing this study reported on the health-related quality of life and treatment satisfaction measures from the included Breton et al. (2020)[51] RCT, where 101 pediatric participants (between the ages of 6 years and 13 years) received treatment with the Control-IQ HCL (N = 78) or with open-loop SAP therapy (N = 23). A series of questionnaires — including the Pediatric Hypoglycemia Fear Survey, the PAID questionnaire, the Pediatric Quality of Life (PedsQL) Diabetes Module, the Insulin delivery Systems: Perceptions, Ideas, Reflections, and Expectations (INSPIRE) survey, and the PSQI — were administered to pediatric participants and their parents at baseline, at 16 weeks (the end of the RCT), and at 28 weeks (an extension phase where participants on open-loop SAP therapy crossed over to HCL therapy). The authors of the study concluded that there were no statistically significant differences between the HCL and open-loop SAP therapy groups across all measures of quality of life and treatment satisfaction, as reported by both participants and their parents, at the end of the 16-week RCT phase. The findings of this study are similar to those synthesized in the Clinical Review of this HTA, where the identified literature reported small improvements or no statistically significant differences regarding the effectiveness of HCLs with respect to quality of life and patient satisfaction. There is a clear need for additional clinical studies that are sufficiently powered to detect meaningful differences in these people-reported outcomes.

Budget Impact Analysis

Overview

Research Question

What is the budget impact of Canadian publicly funded health care systems reimbursing HCL for the management of type 1 diabetes compared with currently reimbursed technologies?

Economic Evidence

A BIA was conducted estimating the financial impact of reimbursing HCL for the management of type 1 diabetes compared with currently reimbursed technologies over a 3-year time horizon. The BIA was conducted from the perspective of the Canadian publicly funded health care system (i.e., ministries of health), excluding Quebec. As such, only costs covered by the public health care payer were captured. Market size was derived using an epidemiology-based approach. CADTH's key findings from the analysis include:

- Given that all jurisdictions cover insulin pumps to an extent, reimbursement of HCL would require them (apart from Yukon and Ontario) to provide new public coverage for CGM.
- The 3-year budget impact of introducing HCL for individuals who are eligible for insulin pumps was estimated to be an increase of $823 million from a pan-Canadian perspective. Should all individuals be eligible for HCL, regardless of their eligibility for insulin pumps, the budget impact was estimated to be an increase of $916 million.
- Uncertainty regarding HCL uptake among current MDII users significantly influences the results. If no individuals who currently use MDII are assumed to switch to HCL, the estimated budget impact of introducing HCL is much lower than the CADTH base case (an increase of $97 million over 3 years).

Objective

The objective of this BIA was to address the following research question:

1. What is the budget impact to Canadian publicly funded health care systems of reimbursing HCL for the management of type 1 diabetes compared with currently reimbursed technologies?

Study Design and Methods

A BIA was conducted using an Excel-based tool developed for this project. This tool has the flexibility to conduct various scenario analyses and to report estimates of budget impact disaggregated by province and year.

Patient Population

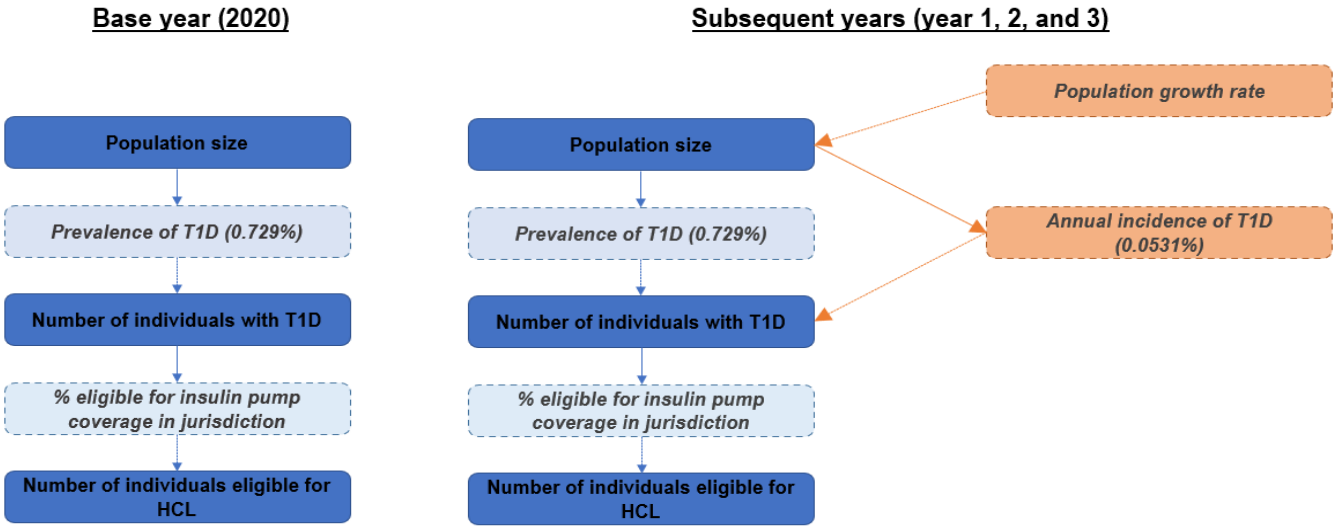
The population considered within this analysis consisted of all individuals with type 1 diabetes. It was assumed that all individuals diagnosed with type 1 diabetes would be insulin-dependent. The introduction of this report notes that, based on a 2019 figure, 7.8% of Canadians 12 years of age and older are living with diabetes.[6] Because the BIA does not restrict the use of HCL to those 12 years and older, a 2014 report on diabetes in Canada was used instead for the purposes of the BIA base case. In this report, 8.1% of Canadians are estimated to have been diagnosed with diabetes, of whom 9% are estimated to have

type 1 diabetes. This results in an overall prevalence estimate for type 1 diabetes of 0.729%.[3] This prevalence estimate was validated by the clinician stakeholders consulted by CADTH. As a scenario analysis, CADTH explored the associated budget impact if a prevalence of 7.8% was used, again assuming that 9% of those diagnosed have type 1 diabetes. It was assumed that the prevalence of type 1 diabetes would not change over subsequent years.

New individuals were added to the analysis in subsequent years based on jurisdiction-specific population growth rates[112] and by using an incidence estimate of 0.0531% (i.e., the incidence of diabetes is 5.9 per 1,000 persons and the assumption is that 9% would have type 1 diabetes).[3] The number of individuals in each jurisdiction who were considered eligible for HCL was based on the age-related eligibility criteria for insulin pumps, given that they are a component of HCL therapy. It was assumed that the introduction of HCL would not change current insulin-pump eligibility. In a scenario analysis, all individuals with type 1 diabetes, regardless of insulin-pump restrictions that may be present in some jurisdictions, were assumed to be eligible for HCL.

Based on findings from the Clinical Review and the Perspectives and Experiences Review (which were unable to identify subgroups that would be most likely to benefit from HCL), no stratification of the target population was incorporated in the analysis.

Figure 2: Derivation of Market Size



HCL = hybrid closed-loop insulin delivery system; T1D = type 1 diabetes.

Intervention Scenarios and Strategies

The BIA compared 2 scenarios: a reference scenario that included only diabetes therapies that are currently reimbursed publicly and a new-device scenario that considered reimbursement of technologies that would be necessary to introduce HCL.

Reference Scenario

The reference scenario was based on jurisdiction-specific public coverage of insulin delivery devices (e.g., insulin pumps, insulin-pump supplies, MDII supplies) and glucose-monitoring devices (e.g., CGMs, flash glucose monitors [FGMs], and SMBG test strips). Various publicly available documents were used to determine the current funding status of insulin-delivery and glucose-monitoring technologies in jurisdictions across Canada (sources are referenced in Table 23). Where possible, these were validated or supplemented during CADTH stakeholder consultations. In cases where CADTH was unable to confirm the status of public coverage for certain supplies, assumptions were applied to estimate the reference scenario.

Although the Non-Insured Health Benefits Program of Indigenous Services Canada provides CGM and FGM coverage on a case-by-case basis,[62] it is not known what proportion of clients with type 1 diabetes have been approved for CGM or FGM coverage. As a simplifying assumption, no coverage of CGM and FGM was assumed for non-insured health benefits clients.

Table 23: Current Public Funding Status for Diabetes Supplies (October 2020) to Inform the Reference Scenario

Jurisdiction	Insulin pump	Insulin-pump supplies	MDII supplies	CGM/FGM	SMBG test strips
Newfoundland and Labrador	25 and under[4,a]	All[4]	Those enrolled in prescription drug programs	None[62]	2,500 for those enrolled in prescription drug progams[61,b]
Prince Edward Island	18 and under; coverage is income-based[113]	18 and under; coverage is income-based[113]	None[b]	None[62]	1,200 annually[61]
Nova Scotia	25 and under; coverage is income-based[4]	25 and under; coverage is income-based[4]	Unknown	None[62]	As prescribed[61]
New Brunswick	25 and under; coverage is income-based[4]	25 and under; coverage is income-based[4]	Unknown	None[62]	As prescribed[61]
Ontario	All ages[4]	$2,400 for those in insulin-pump program[114]	Those 65 and older[115]	CGM coverage for ODSP clients[62] FGM coverage for ODB clients[62]	3,000 for those enrolled in ODB[61,b]
Manitoba	17 and under[4]	Coverage for those eligible for provincial drug programs[116,c]	Unknown[c]	None[62]	3,650 after deductible is reached[117]
Saskatchewan	25 and under[4]	17 and under who have coverage under Family Health Benefits and those with coverage under the Supplementary Health Program[118]	Unknown	None[62]	3,650[61]
Alberta	All ages [4]	All[119]	100 syringes or pen-tip needles per year[119,d]	None[62]	2,555 for insulin-pump users;[61] up to $600 in supplies for others[d]
British Columbia	All ages[4]	PharmaCare benefit[120]	PharmaCare benefit [121]	None[62]	Up to 3,000; PharmaCare benefit[121]
Yukon	All ages[4]	All ages[4]	Unknown	100% coverage for people with type 1 diabetes [62]	Up to 3,650[122]

Jurisdiction	Insulin pump	Insulin-pump supplies	MDII supplies	CGM/FGM	SMBG test strips
Northwest Territories	All ages[4]	All ages[4]	Unknown	None[62]	Up to 2,920 for NIHB recipients; otherwise, unknown[123]
Nunavut	All ages[4]	All ages[4]	Unknown	None[62]	Up to 2,920 for NIHB recipients; otherwise, unknown[123]

CGM = continuous glucose monitor; FGM = flash glucose monitor; MDII = multiple daily injections; NIHB = non-insured health benefits; ODB = Ontario Drug Benefit; ODSP = Ontario Disability Support Program; SMBG = self-monitoring of blood glucose.

[a] As of 2019, Newfoundland provides extended coverage for those over 25 years of age if they are currently enrolled in the insulin-pump program.[124] Given that this is a recent policy change, CADTH assumed that the number of individuals over age 25 years who are receiving insulin-pump coverage will be small; however, this assumption likely underestimates the number of individuals with current insulin-pump coverage in Newfoundland.

[b] Informed during stakeholder consultations.

[c] According to stakeholder feedback, public coverage for insulin-pump and MDII supplies is available for those who reach an income-based deductible for the provincial drug program.

[d] Alberta Health covers up to $600 for diabetes supplies, including test strips, lancets, syringes needles, and so on.[125]

In the reference scenario, the management of people with type 1 diabetes could be distributed across the following combinations of interventions, depending on the status of public funding in each jurisdiction:

- insulin pump plus CGM (Yukon and Ontario only)
- insulin pump plus FGM (Yukon and Ontario only)
- insulin pump plus SMBG
- MDII plus CGM (Yukon and Ontario only)
- MDII plus FGM (Yukon and Ontario only)
- MDII plus SMBG.

New-Device Scenario

In the new-device scenario, CADTH considered a hypothetical scenario where HCL is reimbursed by public payers. HCL systems consist of an insulin pump, a CGM, and a computer program that allows the devices to communicate in order to calculate and deliver insulin needs.[18] While insulin pumps are — to an extent — covered by all Canadian jurisdictions, CGMs remain largely uncovered across public jurisdictions apart from the Yukon and Ontario (Table 23).[4,62] Because CGMs are a necessary component of HCL systems, exploration of the budget impact of covering HCLs requires expansion of the public coverage of CGM in the majority of Canadian jurisdictions.

The BIA assumed that public reimbursement of HCLs would be limited to the population of patients who are already eligible for insulin-pump coverage. It remains unknown whether a jurisdiction's decision to reimburse HCLs will change its current insulin-pump programs. In the base case, it was assumed that insulin-pump eligibility criteria would remain unchanged should HCLs be reimbursed. As such, in the new-device scenario, individuals currently using insulin pumps who switch to HCLs for glucose monitoring were assumed to incur no additional costs for the insulin pumps. However, it was assumed that individuals currently using MDII who switch to HCLs would incur the costs associated with insulin pumps. As a scenario analysis, CADTH explored an alternate new-device scenario where all restrictions on insulin pumps would be removed upon public reimbursement of HCLs. In such a scenario, all individuals with type 1 diabetes would be eligible for insulin pumps.

Reimbursement of HCLs would necessitate new public reimbursement of CGMs outside of the Yukon and Ontario.[62] Consequently, it was assumed that, in the majority of jurisdictions that do not currently fund CGMs, CGMs would be publicly reimbursed for use solely as part of HCL system (i.e., no public reimbursement of CGM if used on its own), and that CGM costs would be fully covered by the public payer. Of note, CGMs are not expected to fully replace SMBG, because a degree of SMBG testing is required with CGM use for calibration purposes.[126] However, because it is unknown whether reimbursement of CGMs by the public payer would allow for concurrent reimbursement of SMBG test strips, it was conservatively assumed that CGM use would preclude individuals from being able to access SMBG test strips publicly (i.e., individuals would pay for test strips as an out-of-pocket expense). In a scenario analysis, CADTH explored the budget impact of an alternative funding policy in which both CGMs and up to 4 test strips daily per HCL user would be reimbursed publicly. Table 24 presents the added device costs required following the uptake of HCL, based on an individual's reference scenario treatment approach.

Table 24: Device Uptake Required in New-Device Scenario by Reference Scenario Treatment Approach

Reference scenario	New-device scenario (i.e., reimbursement of HCL)	Added device costs (with HCLL)
MDII + SMBG	Insulin pump + CGM	Insulin pump, CGM
MDII + FGM[a]	Insulin pump + CGM	Insulin pump, CGM
MDII + CGM[a]	Insulin pump + CGM	Insulin pump
Insulin pump + SMBG	Insulin pump + CGM	CGM
Insulin pump + FGM[a]	Insulin pump + CGM	CGM
insulin pump + CGM[a]	insulin pump + CGM*	None

CGM = continuous glucose monitor; FGM = flash glucose monitor; MDII = multiple daily injections; SMBG = self-monitoring of blood glucose.

[a] Only relevant in Ontario and Yukon.

During stakeholder consultations, broader reimbursement of CGMs beyond the restrictions imposed by the original research question (i.e., CGM not restricted to HCL users only) was raised, as observed in Yukon, in which there are no restrictions that CGM be available only to those requiring HCL. To explore this possibility, scenario analyses were conducted that evaluated a revised research question on the potential budget impact of reimbursing CGMs for the management of type 1 diabetes on Canadian publicly funded health care systems. Specifically, 2 scenarios were evaluated, differing in the target population: 1 assumed that the target population would be based on existing age eligibility criteria for insulin pumps, and the other evaluated all individuals with type 1 diabetes (i.e., not restricted by insulin-pump eligibility criteria).

Time Horizon

The time horizon of the analyses included the current year (2020) and forecast the impact over a 3-year time horizon (2021 to 2023). No discounting was applied to the analysis, as per existing guidelines for the conduct of a BIA.[127]

Perspective

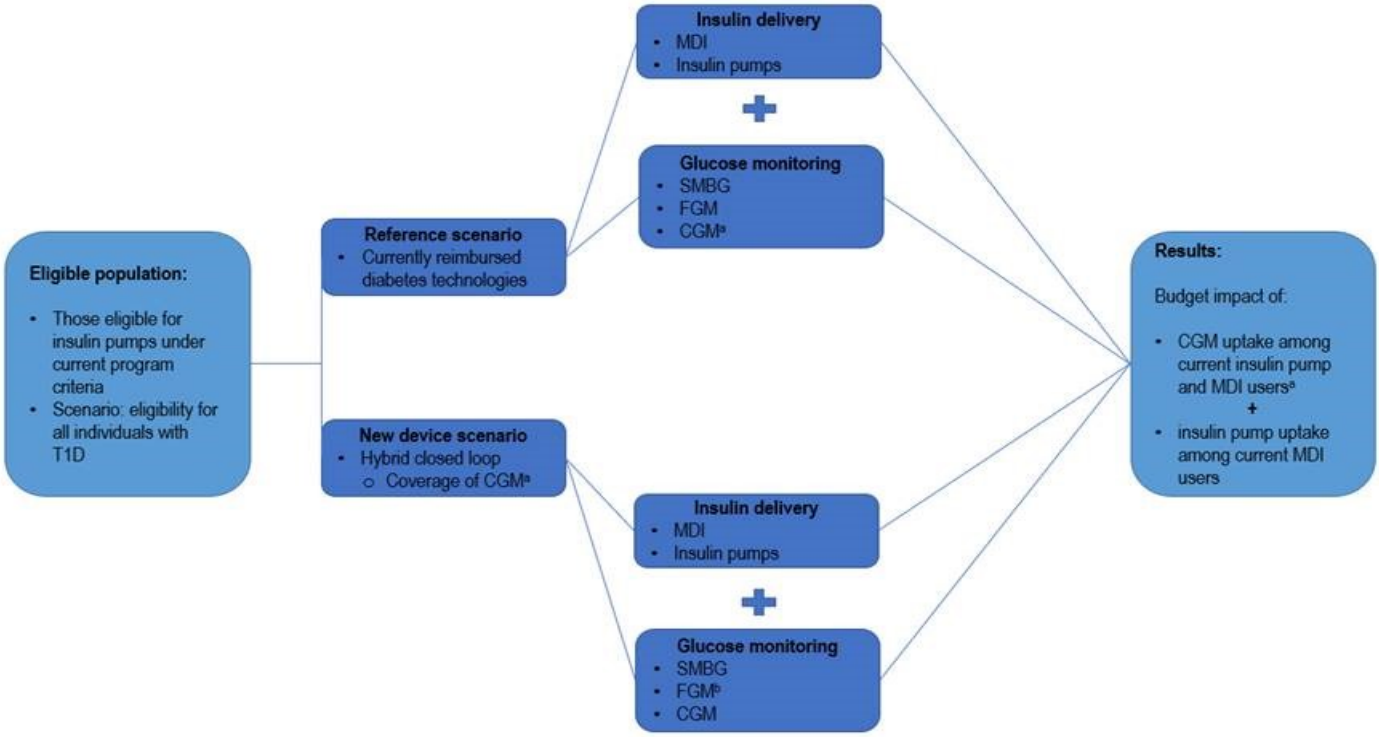
The perspective of this analysis was the Canadian publicly funded health care system (i.e., ministries of health), excluding Quebec. As such, only costs covered by the health care payer were captured (i.e., costs to individuals with type 1 diabetes and private payers were not incorporated). Depending on the jurisdiction, these may include the costs of insulin pumps and insulin-pump supplies, MDII supplies, and glucose-monitoring supplies (Table 23). Due to the diversity of diabetes programs and payers across Canadian jurisdictions, costs were considered from a jurisdictional perspective only and were not disaggregated by specific public programs.

Analytic Framework Description

Within the BIA, the eligible population was based on the age eligibility criteria for insulin pumps as currently implemented by public plans. In the new-device scenario, a percentage of current insulin-pump and MDII users were assumed to uptake HCL systems. As noted earlier, current insulin-pump users who uptake HCL systems would incur no additional costs associated with the insulin delivery method, while current MDII users who uptake HCL systems would be required to receive coverage for an insulin pump and its associated supplies (Table 24). In jurisdictions apart from Yukon and Ontario, all users switching to HCL systems would necessarily incur costs for CGMs for glucose monitoring. The BIA presents

the expected financial impact of public reimbursement of HCL systems for the management of people with type 1 diabetes compared to alternative methods of insulin delivery and glucose monitoring from a Canada-wide perspective. Each scenario reflects different distributions for insulin delivery and glucose monitoring, based on whether or not HCL systems are reimbursed by public plans (Figure 3).

Figure 3: Analytic Framework



CGM = continuous glucose monitor; FGM = flash glucose monitor; MDII = multiple daily injections; SMBG = self-monitoring of blood glucose; T1D = type 1 diabetes.

[a] In jurisdictions with CGM coverage in the reference scenario, the additional costs of CGM due to the reimbursement of HCL are only applied to patients who are not switching from CGM to HCL.

[b] In Ontario, individuals using FGMs in the reference scenario could switch to CGMs in the new-device scenario. No new users were assumed to take up FGMs in the new-device scenario.

Market Shares and Uptake of HCL

Reference Scenario

The current distribution of individuals with type 1 diabetes across treatment strategies (effectively, insulin pump + SMBG or MDII + SMBG for all jurisdictions apart from Yukon and Ontario) was populated, where possible, by jurisdiction-specific rates of insulin-pump use amongst those eligible for insulin pumps. Where this value could not be provided by stakeholder consultations, it was assumed in the reference scenario that 20% of those eligible for insulin pumps would be using insulin pumps, based on common trends that emerged from feedback received during stakeholder consultations (Table 25). These proportions of insulin-pump and MDII users were similarly assumed in Yukon and Ontario. However, in both of these jurisdictions, because there is public coverage of CGMs and FGMs, the reference scenario market shares had to be further split by the approach to

glucose monitoring. In Yukon, it was assumed that 50% of individuals would be using advanced glucose monitors (e.g., CGMs or FGMs); it was further assumed that, among those using advanced glucose monitors, 20% would be using an FGM and 80% would be using a CGM. In Ontario, it was assumed that 50% of those eligible for CGMs (i.e., Ontario Disability Support Program [ODSP] clients) and FGMs (i.e., Ontario Drug Benefit [ODB] clients) would be using these respective technologies (Table 25).[62]

CADTH assumed there would be no changes in the reimbursement policies for insulin pumps and CGMs during the model's time horizon (i.e., 3 years); therefore, it was assumed that market shares in the reference scenario would remain unchanged over all 3 years modelled (i.e., years 1, 2, and 3) for jurisdictions apart from Yukon. In Yukon, because public reimbursement of CGM was introduced recently (in 2020), it was assumed that 50%, 70%, and 90% of individuals in year 1, year 2, and year 3, respectively, would be using advanced glucose monitors. The resulting reference scenario market shares for Yukon are presented in Table 26.

Table 25: Market Shares: Reference Scenario (for All 3 Forecast Years)

Treatment strategy	Market shares[a]		Market shares: Ontario[b]	
	Insulin pump	MDII	Insulin pump	MDII
CGM	0%	0%	0%	1%
FGM	0%	0%	4%	16%
SMBG	20%	80%	16%	63%
Total	**20%**	**80%**	**20%**	**80%**
Total, overall	100%		100%	

CGM = continuous glucose monitor; FGM = flash glucose monitor; MDII = multiple daily injections; SMBG = self-monitoring of blood glucose.

[a] Assumptions informed by stakeholder consultations for jurisdictions without CGM or FGM coverage. In jurisdictions where more precise estimates of insulin-pump use were provided, alternative values may have been used in the CADTH base-case analysis.

[b] Because Ontario's reimbursement for advanced glucose monitors is not universal, no changes in reference scenario market shares were assumed over the time horizon.

Table 26: Yukon Market Shares in the Reference Scenario

Treatment strategy	Year 1		Year 2		Year 3	
	Insulin pump	MDII	Insulin pump	MDII	Insulin pump	MDII
CGM	8%	32%	11%	45%	14%	58%
FGM	2%	8%	3%	11%	4%	14%
SMBG	10%	40%	6%	24%	2%	8%
Total	**20%**	**80%**	**20%**	**80%**	**20%**	**80%**
Total, overall	100%		100%		100%	

CGM = continuous glucose monitor; FGM = flash glucose monitor; MDII = multiple daily injections; SMBG = self-monitoring of blood glucose.

New-Device Scenario

Market shares in the new-device scenario were determined by the percentage of individuals with type 1 diabetes who are eligible for insulin pumps in their jurisdiction who would be expected to uptake HCL systems should they be reimbursed. Table 27 presents the percentage of current insulin-pump and MDII users who would be expected to uptake HCL systems in the base-case analysis. Uptake was assumed to be the same regardless of an individual's current approach to glucose monitoring. Uptake was informed by stakeholder consultations from 7 jurisdictions, including policy-makers and clinicians. The majority of stakeholders noted that current insulin-pump users might be more motivated to uptake

CGMs should HCL be reimbursed, whereas uptake of both a pump and a CGM to achieve HCL among MDII users was expected to be lower. CADTH explored different rates of HCL uptake in scenario analyses.

Table 27: HCL Uptake Rates by Reference Scenario Treatment Approach

Insulin delivery device in reference scenario	% Uptake of HCL[a]		
	Year 1	Year 2	Year 3
Insulin-pump users[b]	10%	24%	42%
MDII users	10%	20%	30%

HCL = hybrid closed-loop insulin delivery system; MDII = multiple daily injection.

[a] 0% uptake of HCL was assumed in Yukon because the territory already provides coverage of insulin pumps and CGMs.

[b] Uptake was based on clinician stakeholder feedback that indicated that the majority of current insulin-pump users would uptake HCL systems (50%, 70%, and 90% in years 1, 2, and 3, respectively). To reflect the fact that pump users are only eligible for a new insulin pump every 5 years (4 years in Newfoundland), CADTH calculated market uptake based on the proportion of all insulin-pump users eligible for a new pump each year (i.e., 20%) multiplied by the expected uptake (i.e., 50% in year 1). To reflect the cumulative percentage of insulin-pump users who uptake HCL systems over the 3 years analyzed, the percentage of individuals uptaking from the previous year (e.g., 10% in year 1) was added to the percentage of people in the current year who are eligible for a new pump and switch to HCL systems (e.g., 20% × 70% = 14% in year 2). As such, the uptake in year 2 and year 3 were calculated to be 24% (i.e., 10% + 14%) and 42% (i.e., 24% + (20% x 90%), respectively.

Of note, during stakeholder consultations, it was expressed that if CGMs are reimbursed more broadly rather than exclusively for use as part of HCL systems, then CGM uptake rates among all individuals was expected to be nearly universal over time (> 90%). Given this additional insight, CADTH conducted scenario analyses to investigate the budget impact of a policy decision to reimburse CGMs universally rather than as outlined in the base case, which focused only on reimbursement of CGMs for HCL. The scenario analyses assumed that 50%, 70%, and 90% of all individuals with type 1 diabetes would uptake CGMs in years 1, 2, and 3, respectively. It was further assumed that individuals would remain on their existing insulin delivery devices.

Using the uptake rates provided in Table 27, market shares for the base case in the new-device scenario were calculated and are presented in Table 28. This was done by multiplying the rate of the uptake of HCL for current pump and MDII users by the proportions of individuals using these devices in the reference scenario. Given that the uptake of HCL systems among MDII users will require the uptake of insulin pumps, the overall percentage of those using MDII to deliver insulin is seen to decrease over the analytical time horizon.

In Ontario, FGM is presently reimbursed for individuals who qualify for the ODB program. As such, a proportion of current FGM users would be expected to switch to HCL systems, according to the insulin delivery device–specific rates provided in Table 27. New-device scenario market shares for Ontario, which account for the proportion of individuals currently using CGM and FGM, are presented in Table 29.

Given that Yukon currently covers CGMs without restriction, no change in uptake rates upon introduction of HCL systems would be expected. A change in reimbursement policy (i.e., public reimbursement of HCL systems) is not expected to affect the uptake of HCL systems, given that insulin pumps and CGMs are currently publicly covered in the jurisdiction. Therefore, in Yukon, the market shares in the new-device scenario match those in the reference scenario. No budget impact is expected should HCL systems be reimbursed (as its constituent parts are already reimbursed in the territory).

Table 28: Market Shares: New-Device Scenario (Jurisdictions[a] Outside of Yukon and Ontario)

Treatment strategy	Year 1		Year 2		Year 3	
	Insulin pump	MDII	Insulin pump	MDII	Insulin pump	MDII
CGM	10%[b]	0%	21%[b]	0%	32%[b]	0%
FGM	0%	0%	0%	0%	0%	0%
SMBG	18%	72%	15%	64%	12%	56%
Total	**28%**	**72%**	**36%**	**64%**	**44%**	**56%**
Total, overall	100%		100%		100%	

CGM = continuous glucose monitor; FGM = flash glucose monitor; MDII = multiple daily injections; SMBG = self-monitoring of blood glucose.

[a] In jurisdictions where more precise estimates of insulin-pump use were provided, alternative values may have been used in the CADTH base-case analysis.

[b] A CGM plus an insulin pump is assumed to be equal to HCL. While CGMs and insulin pumps can be used independently (not only as part of HCL), the BIA assumed that patients would have access to CGM only as part of HCL that would be funded (i.e., CGM would not be funded on its own).

Table 29: Ontario Market Shares in New-Device Scenario

Treatment strategy	Year 1		Year 2		Year 3	
	Insulin pump	MDII	Insulin pump	MDII	Insulin pump	MDII
CGM	10%[a]	1%	21% [a]	1%	33% [a]	1%
FGM	4%	14%	3%	13%	2%	11%
SMBG	14%	57%	12%	50%	9%	44%
Total	**28%**	**72%**	**36%**	**64%**	**44%**	**56%**
Total, overall	100%		100%		100%	

CGM = continuous glucose monitor; FGM = flash glucose monitor; MDII = multiple daily injections; SMBG = self-monitoring of blood glucose.

[a] A CGM plus an insulin pump is assumed to be equal to HCL. While CGMs and insulin pumps can be used independently (not only as part of HCL), the BIA assumed that patients would have access to CGM only as part of HCL that would be funded (i.e., CGM would not be funded on its own).

Cost Inputs

Where possible, publicly provided, jurisdiction-specific prices, coverage rates, and co-pays were used to estimate the cost of each treatment approach. In jurisdictions where deductibles are in place, they were not incorporated into the analysis, given that it is unknown whether families may reach the deductible based on spending on drugs or health technologies beyond those considered in the analysis. Cost-sharing between public payers and private insurers was not incorporated due to a lack of data on who the first payer is for supplies in all jurisdictions, the number of individuals who have private coverage, and the percentage of the total costs covered by private insurers. Because the perspective of the analysis is that of the public payer, it was further assumed that the additional costs for products not currently covered by jurisdictions (i.e., the annual cost of CGMs) would be paid for by the public payer. If public payers are not the first payers for CGM supplies (i.e., CGM policies implemented by jurisdictions involve cost-sharing with private insurers), the estimated budget impact of introducing HCL systems will be less.

The cost of HCL was assumed to include the cost of an insulin pump, the costs of annual insulin-pump and CGM supplies. Based on stakeholder consultations, it was assumed that the third aspect of HCL systems, the computer program, would not result in any additional costs once users had acquired the other component parts (i.e., the insulin pump and CGM).

Insulin and Insulin Delivery Costs

Insulin pumps were assumed to cost $6,300, based on the maximum price per pump paid in Ontario (Table 30).[114] While all jurisdictions provide some coverage of insulin pumps, depending on age, some jurisdictions do not currently cover insulin pumps with closed-loop functionality (herein referred to as HCL-compatible pumps). However, because the amount paid by the payer per pump was assumed not to change with the reimbursement of HCL systems, it was assumed that there would be no difference in the maximum reimbursable price associated with an HCL-compatible pump. Therefore, whether jurisdictions currently reimburse HCL-compatible pumps was not explicitly considered. It was also assumed that, should HCL be reimbursed, users would be required to wait until they were eligible for a pump renewal (every 4 years or 5 years, depending on the jurisdiction), rather than being permitted to access an HCL-compatible pump prior to their renewal period being complete. Therefore, insulin-pump costs were applied to the analysis based on their average annual cost by dividing their total cost by the number of years of their expected use (5 years in all jurisdictions apart from Newfoundland, where the expected usage time is 4 years).

Insulin-pump supplies were estimated to cost $3,000 annually.[128] In provinces that have a maximum reimbursement amount for pump supplies, such as Ontario, the jurisdiction-specific value was applied instead.[114] Insulin pump and supply costs were incorporated into the analysis by multiplying the average annual cost by the percentage of costs paid by the public payer (by jurisdiction) and subtracting any applicable jurisdiction-specific co-pays. Income-based co-pays were estimated using a jurisdiction's median family income and average household size.[129]

CADTH estimated the cost of MDII supplies to be $705 annually, assuming individuals inject insulin 5 times per day (Table 30). Due to the relatively low annual cost of MDII relative to insulin pumps, and due to diverse rates of coverage of MDII supplies across jurisdictions (some jurisdictions provide no coverage for these supplies; in others, there may be some coverage for individuals enrolled in public drug programs), in the CADTH base case, MDII was assumed to have no associated costs to the public payer. Jurisdictions that reimburse individuals for MDII supplies might see lower budget impacts should HCL be reimbursed, because some costs associated with insulin-pump uptake among MDII users will be offset by reduced MDII costs.

The cost of insulin was not included in the analysis because it was assumed that insulin costs would be similar across delivery methods, and that any cost differences were unlikely to drive conclusions of the analysis.

Glucose-Monitoring Costs

The costs of glucose monitors were not considered in the analysis. Similarly, due to difficulty sourcing the status of public coverage for SMBG testing lancets, and because some lancet use is required among HCL users, the cost differences between glucose-monitoring methods were considered negligible in the analysis.

FGM and CGM costs were taken from publicly available sources (Table 30). In the case of CGMs, the annual cost of use for each marketed device was calculated and the average CGM annual cost was applied to the BIA. Neither FGM nor CGM annual costs assumed any public coverage of test strips. Therefore, test strip costs were only applied for those exclusively using SMBG.

Table 30: Treatment Approach Costs

Device	Cost	Notes
Insulin pumps	$6,300[114]	Cost applied on an annual basis using pump renewal lengths (5 years in all jurisdictions apart from Newfoundland and Labrador, which was 4 years)
Insulin-pump supplies	$3,000 annually[128]	Jurisdiction-specific coverage rates, maximums, and co-pays applied
MDII supplies	$705 annually	Average cost per injection: $0.39[130] (assumes 5 injections per day)
SMBG monitors	$0	Given that glucose monitors are required in the reference and new drug scenario, their costs were not considered in the analysis (their use was not expected to differ).
SMBG test strips	$0.79 per strip[61]	Annual cost based on the maximum number of strips covered by jurisdictions.[61] Where applicable, jurisdiction-specific eligibility for strip coverage and co-pays was applied.
FGM	$2,314 annually	Cost per sensor: $89.00 (replace every 14 days)[131]
CGM	$4,783 annually	Average of annual device-specific costs

CGM = continuous glucose monitor; FGM = flash glucose monitor; MDII = multiple daily injections; SMBG = self-monitoring of blood glucose.

Only 1 study in the Clinical Review compared HCLs with technologies that are currently covered by public payers (i.e., SMBG). Given that this study did not find statistically significant differences in adverse events, the costs associated with differential outcomes between HCLs and currently funded technologies were not incorporated in the BIA.

Analyses

Base-Case Analysis

Table 31 summarizes the key assumptions made in the base-case analysis of the BIA. Some base-case assumptions were tested using a range of different scenarios. A complete list of assumptions made (to derive the target population, market shares and uptake, and costs in the analysis) are presented in Appendix 2 in Table 42, Table 43, and Table 44, respectively. The scenarios explored and the inputs used for the sensitivity analyses are presented in the text that follows Table 31.

Table 31: Table of Key Assumptions

Parameter	Assumption	Scenario analysis	Additional comments
Mortality	Mortality was negligible over the 3-year analysis time horizon (i.e., individuals did not exit the analysis through a mortality rate).	In a scenario analysis, assume an incidence of 0%.	This scenario indirectly incorporates mortality by implicitly assuming the number of participants entering the analysis would be equal to the number exiting (due to death).
HCL eligibility	Only individuals eligible for insulin pumps under current jurisdictional criteria would be eligible for HCLs.	All individuals with type 1 diabetes would be eligible for HCLs.	
Reference scenario: insulin-pump use among eligible individuals	In jurisdictions where current insulin-pump use was not elicited during stakeholder consultations, it was assumed that 20% of those eligible were using insulin pumps.	Assume 40% of those eligible are using insulin pumps.	

Parameter	Assumption	Scenario analysis	Additional comments
Reference scenario: market shares	Distribution of individuals across treatment approaches would not change in the reference scenario, except Yukon. In Yukon, the percentages of individuals on advanced glucose monitors was assumed to be 50%, 70%, and 90% in years 1, 2, and 3, respectively.	None.	Although the model is flexible enough to accommodate different market shares over the analysis time horizon, this was not varied, given limited guidance on how treatment approaches would change over the 3-year analysis period in jurisdictions other than Yukon.
CGM coverage	CGMs reimbursed only for use with HCLs.	Two scenario analyses were conducted in which CGM was publicly reimbursed and not restricted to HCL.	
Insulin-pump supply coverage	In jurisdictions where eligibility for insulin-pump supply coverage is unknown, it was assumed that 100% of those eligible for insulin pumps were eligible for pump supplies.	None.	The rationale behind this assumption was that most jurisdictions[4] (i.e., Alberta,[119] Prince Edward Island,[113] Ontario[114]) provide coverage for supplies for those eligible for insulin pumps.
SMBG test strip coverage	In jurisdictions where test strip coverage is unknown, it was assumed that test strips were covered for those eligible for public drug plan coverage.	None.	The rationale behind this assumption was that some jurisdictions[115] provided coverage of test strips only for those enrolled in public drug plans.
Glucometer coverage	Glucometer costs were not included in the analysis.	None.	
Insulin costs	It was assumed that there were no differences in insulin costs between delivery methods.	None.	

CGM = continuous glucose monitor; FGM = flash glucose monitor; HCL = hybrid closed-loop insulin delivery system; MDII = multiple daily injections; NIHB = non-insured health benefits; SMBG = self-monitoring of blood glucose.

Uncertainty and Scenario Analyses

Sensitivity analyses were conducted to explore the impact of parameter uncertainty on budget impact results. These included:

- using the number of individuals who have type 1 diabetes (when provided by jurisdictions in stakeholder consultations) rather than prevalence to estimate market size
- using a prevalence of diabetes of 7.8%, of whom 9% have type 1 diabetes (the overall prevalence estimate for type 1 diabetes of 0.702%)
- assuming that 40% of eligible individuals are currently using insulin pumps (in jurisdictions where current pump use is unknown; no change was implemented in jurisdictions where current pump utilization rates are known)
- assuming different rates of current FGM or CGM use (20% and 100%) in Ontario for the reference scenario

- assuming that 64% of individuals with type 1 diabetes in Ontario are eligible for public drug coverage of SMBG strips in response to additional coverage provided from OHIP+ (the base case assumed 40%, in line with the Understanding the Gap report[132])
- assuming public coverage of 1,095 test strips annually (3 per day) among CGM users
- using jurisdiction-specific MDII costs, when available (when not available, assume no coverage for MDII except for individuals enrolled in public drug programs)
- using a higher price per FGM sensor of $99
- basing the price for CGM on annual subscription costs (i.e., $3,770 annually).

In addition, scenario analyses were conducted to evaluate the impact of certain assumptions made in the base-case model on the BIA results. These include assuming:

- an incidence of 0%
- that all individuals are eligible for HCL, regardless of whether they are eligible for insulin pumps
- that 0% of current MDII users switch to HCLs
- a constant uptake rate of HCLs (50%) among current insulin-pump users across all 3 years (no changes in the uptake rate of HCLs for MDII users; i.e., 10%, 20%, and 30% in years 1, 2, and 3, respectively)
- that all individuals with type 1 diabetes aged 25 years and under in Prince Edward Island are eligible for insulin pumps[135] (CADTH was informed that a recent change in the public reimbursement criteria was introduced in January 2021 to include public reimbursement of insulin pumps).

Stakeholders consulted for this project noted that HCLs require an insulin pump and CGM with a computer system to support communication between the 2 devices. It remains unclear whether CGMs would be reimbursed exclusively as part of HCLs or whether a different reimbursement strategy that would permit access to HCLs is to reimburse CGM more generally. To address uncertainty regarding potential policy options for the reimbursement of CGM, CADTH conducted 2 additional analyses. These explored a new-device scenario whereby CGMs are reimbursed more broadly, not solely for use as part of an HCL. The first analysis explored CGM reimbursement for all individuals who meet jurisdictional age criteria for insulin pumps. The second analysis explored CGM reimbursement for all individuals with type 1 diabetes. Both scenarios assumed that individuals have no changes to their current insulin delivery methods (i.e., CGMs may be used by individuals using MDII). Therefore, the cost of insulin delivery was excluded from these scenarios. Both scenarios also assumed CGM uptake rates of 50%, 70%, and 90% in years 1, 2, and 3, respectively. This was based on stakeholder consultations of clinicians who expected high rates of CGM uptake if this device were to become available.

Results

Base-Case

From a pan-Canadian perspective (excluding Quebec), CADTH estimated that there will be a total of 203,597, 206,109, and 208,653 individuals with type 1 diabetes who are eligible for insulin pumps in years 1, 2, and 3, respectively (Table 32). CADTH's estimates of the number of individuals with type 1 diabetes are also presented in Table 32, Table 45, and Table 46 (Appendix 2), which present the pan-Canadian distribution of individuals across treatment approaches in the reference and new-device scenarios, respectively.

Table 32: Pan-Canadian Estimates of the Number of Individuals With Type 1 Diabetes

	Year 1	Year 2	Year 3
Individuals with type 1 diabetes	232,842	235,540	238,271
Individuals with type 1 diabetes eligible for pumps	203,597	206,109	208,653

The aggregated pan-Canadian results (excluding Quebec) estimating the budget impact of reimbursing HCL systems in jurisdictions are presented in Table 33. CADTH estimated the budget impact of reimbursing HCL systems to be $131 million in year 1, $271 million in year 2, and $420 million in year 3, for a total budget impact over 3 years of $823 million from a pan-Canadian perspective. Table 47 (Appendix 2) presents the disaggregate results along with overall budget impact by jurisdiction. Jurisdictional budget impact results range from $472 million in Ontario (more than half of the total pan-Canadian budget impact) to $0 in Yukon (because of existing CGM reimbursement policies in the territory) (Table 47, Appendix 2).

Table 33: Pan-Canadian Budget Impact Analysis Result

	Year 1	Year 2	Year 3	3-year total
Reference	$443,664,882	$449,072,356	$454,548,041	$1,347,285,278
New device	$575,148,153	$720,410,575	$874,361,596	$2,169,920,324
Budget impact	**$131,483,271**	**$271,338,219**	**$419,813,555**	**$822,635,045**

The results of key scenario analyses are presented in Table 34. Should all individuals with type 1 diabetes be eligible for HCL systems, regardless of their eligibility for an insulin pump within their jurisdictions, the budget impact of reimbursing HCL systems is estimated to increase by $93 million to $916 million. If 0% of current MDII users switched to HCL systems, the budget impact of introducing HCL systems would be significantly lower than estimated in the CADTH base case ($97 million). In covering 3 SMBG strips daily for all users of HCLs in all jurisdictions, the budget impact of reimbursing HCL systems will be higher than estimated in the base case ($934 million). Results were also sensitive to the price of CGM used in the analysis. When the price of CGM was based on an annual subscription model,[133,134] the 3-year budget impact decreased to $691 million. The remaining scenario and sensitivity analyses that were conducted did not significantly influence the budget impact results. They are presented in Appendix 2, Table 48.

Table 34: Key Scenario Analysis Results

Analysis	Scenario	Year 1	Year 2	Year 3	3-year total
Base case (excluding Quebec)	Reference	$443,664,882	$449,072,356	$454,548,041	$1,347,285,278
	New device	$575,148,153	$720,410,575	$874,361,596	$2,169,920,324
	Budget impact	**$131,483,271**	**$271,338,219**	**$419,813,555**	**$822,635,045**
All individuals eligible for HCL, regardless of pump eligibility criteria	Reference	$532,166,862	$538,128,884	$544,163,735	$1,614,459,481
	New device	$678,481,215	$840,191,881	$1,011,670,307	$2,530,343,403
	Budget impact	**$146,314,352**	**$302,062,997**	**$467,506,572**	**$915,883,921**
Assume that 0% of current MDII users switch to HCLs	Reference	$443,664,882	$449,072,356	$454,548,041	$1,347,285,278
	New device	$456,239,041	$479,617,826	$508,653,917	$1,444,510,784
	Budget impact	**$12,574,159**	**$30,545,470**	**$54,105,876**	**$97,225,506**
	Reference	$444,956,679	$450,427,707	$455,968,455	$1,351,352,840

Analysis	Scenario	Year 1	Year 2	Year 3	3-year total
Assume universal coverage of 3 test strips per day for all users of CGMs	New device	$593,917,301	$758,481,782	$933,553,770	$2,285,952,854
	Budget impact	**$148,960,623**	**$308,054,075**	**$477,585,316**	**$934,600,014**
Annual cost of CGM use associated with annual subscription ($3,770 per year)	Reference	$442,151,476	$447,484,494	$452,883,954	$1,342,519,923
	New device	$553,159,143	$675,808,222	$805,014,958	$2,033,982,323
	Budget impact	**$111,007,667**	**$228,323,729**	**$352,131,004**	**$691,462,400**

CGM = continuous glucose monitor; HCL = hybrid closed-loop insulin delivery system; MDII = multiple daily injections.

Universal CGM Reimbursement Analysis

As noted earlier, an HCL system consists of an insulin pump, a CGM, and computer program. Even though all jurisdictions provide some form of insulin-pump coverage, few currently reimburse CGMs. As such, the base case assumed that the public reimbursement of HCL systems would not lead to any changes to existing insulin-pump programs (e.g., coverage criteria or maximum reimbursement), and that CGMs would only be reimbursed in cases for HCL systems.

However, in consultation with stakeholders, many noted that CGMs could be more broadly reimbursed and not specific to HCL only. Two scenario analyses were conducted that explored coverage of CGMs beyond the HCL use. Both considered only the additional costs of glucose monitoring and assumed no difference in insulin delivery devices. As such, they reflect only the cost of glucose monitoring; insulin delivery device costs were not included because they were assumed to be identical in both the reference and new-device scenarios. Individuals who switched to CGMs would not be reimbursed for SMBG supplies (i.e., these would be considered an out-of-pocket patient expense).

In the first scenario in which CGMs become available to all individuals with type 1 diabetes who are eligible for insulin pumps, the estimated 3-year total budget impact was expected to be $1,482 million (Table 35). If CGM was covered more broadly for all individuals with type 1 diabetes (i.e., not dependent on insulin-pump eligibility), the estimated 3-year total budget impact was estimated to be $1,621 million.

Table 35: Analyses Exploring CGM Reimbursement for All, Regardless of Use With HCL

Analysis	Scenario	Year 1	Year 2	Year 3	3-year total
CGMs available, restricted to individuals eligible for insulin pumps	Reference	$264,074,087	$267,185,256	$270,334,169	$801,593,512
	New device	$608,370,778	$759,997,648	$915,705,648	$2,284,074,074
	Budget impact	**$344,296,691**	**$492,812,392**	**$645,371,479**	**$1,482,480,562**
CGMs available for all individuals with type 1 diabetes	Reference	$328,297,242	$331,853,668	$335,451,300	$995,602,210
	New device	$703,910,689	$870,371,790	$1,042,370,390	$2,616,652,869
	Budget impact	**$375,613,447**	**$538,518,122**	**$706,919,090**	**$1,621,050,659**

CGM = continuous glucose monitor.

Summary of Findings

In this BIA, CADTH compared the cost to the public payer of currently reimbursed treatments for managing type 1 diabetes with a new-device scenario: public reimbursement of HCL systems. Because all jurisdictions cover insulin pumps to an extent, the reimbursement of HCL systems would require all jurisdictions (apart from Yukon and Ontario) to provide new coverage for CGMs. Yukon introduced general coverage of CGMs in late 2020, regardless of use with HCL systems.[136] As such, reimbursement of HCL systems in the territory would not be expected to have a budget impact because all component parts of the system are currently publicly covered. Therefore, while Yukon was included in the analysis, the budget impact in the territory was estimated to be $0, given that the computer program to support HCL systems was assumed to incur no additional cost. In Ontario, access to CGMs is restricted: they are currently only reimbursed for ODSP clients (approximately 2% of all Ontario residents).[137] As such, it was necessary to explore the budget impact should HCL systems become publicly reimbursed for all individuals with type 1 diabetes who are also eligible for a pump in Ontario. One would expect a rate of HCL uptake HCL similar to other jurisdictions that do not reimburse CGMs. An aspect unique to Ontario is that it further provides FGM coverage for ODB clients. FGM use was included in Ontario's reference and new-device scenarios. While people could switch from FGMs to HCL systems in the reference scenario for Ontario, no new uptake of FGMs was assumed in the new-device scenario (i.e., the overall proportion of individuals using FGM decreased in the new-device scenario).

Taken together, reimbursing HCLs for individuals with type 1 diabetes who meet current insulin-pump age criteria within their jurisdictions was expected to have a budget impact of $131 million in year 1, $271 million in year 2, and $420 million in year 3, for a total 3-year budget impact of more than $823 million. Of note, Ontario accounts for more than half (57%) of the expected pan-Canadian budget impact, with a total 3-year budget impact of $472 million. This is due, in part, to Ontario's large population relative to other jurisdictions — the population of Ontario is half the population of Canada when excluding Quebec. Further, because Ontario does not use age criteria to restrict pump access, it also accounts for more than half (56%) of the eligible individuals in the BIA. These factors explain the relatively larger contribution that Ontario makes to the overall budget impact.

The results are sensitive to the price of CGMs. This means a lower price for CGM devices will improve the affordability of HCL devices for public payers. Another key driver of the analysis — and remaining source of uncertainty — is the uptake of HCL devices amongst those who currently use MDII to deliver insulin. The clinicians consulted for this project noted that current MDII users who are eligible for pumps in their jurisdictions may be less likely to switch to HCL devices than those currently using insulin pumps. The new-device scenario assumed that some current users of MDII would switch to HCL devices should they be reimbursed. For these individuals, there would be additional costs to the payer in the form of both insulin pumps and insulin-pump supplies that are not considered additional expenses for existing insulin-pump users who switch to HCL devices. Assuming that 0% of MDII users would switch to HCL devices significantly reduces the budget impact of HCL reimbursement to $97 million. There are several reasons for this. First, in the base-case analysis, the majority of individuals with type 1 diabetes are assumed to be using MDII in the reference scenario. This means that, while uptake of HCLs is higher among insulin-pump users, there are more MDII users switching to HCLs. Second, switching to HCL requires MDII users to uptake both a CGM, an insulin pump, and pump supplies, adding additional costs for the

public payer compared to individuals switching to HCL devices from insulin pumps, which only incur CGM costs. Because MDII supplies were not assumed to be covered by the public payer in the base case — and due to the range of coverage for SMBG test strips, depending on the jurisdiction — the cost to the public payer of reimbursing a CGM and a pump could be many times higher than that of reimbursing SMBG test strips alone (the only assumed costs to the public payer for those using MDII plus SMBG).

CADTH assumed there would be no differences in insulin costs across users. While differences in insulin costs may exist across paradigms, the magnitude of the difference in costs compared to the costs of devices is unlikely to significantly influence results. Differences in public funding for devices to manage diabetes across jurisdictions added complexity and uncertainty to the analysis. Despite being unable to incorporate jurisdictional-specific coverage of MDII supplies, a scenario analysis demonstrated that results of the BIA were not sensitive to varying MDII costs. Additionally, while the current use of insulin pumps among those eligible was uncertain, results of a scenario analysis demonstrated that the results were robust even if higher rates of insulin-pump use are assumed. Results were generally robust to changes in key parameters.

In stakeholder consultations, the possibility was raised of CGMs being reimbursed more generally for all individuals with type 1 diabetes (as is the current policy in Yukon) rather than exclusively for use as part of an HCL. To address this, CADTH conducted a scenario analysis. In this analysis, CADTH compared a reference scenario that included the existing publicly reimbursed glucose-monitoring devices (i.e., SMBG test strips in all jurisdictions apart from Ontario) with a new-device scenario that involved public coverage of CGM for all eligible individuals with type 1 diabetes who meet current jurisdictional insulin-pump coverage criteria, regardless of whether the CGM device would be used for HCL. CADTH found that, under this scenario, the expected 3-year budget impact of reimbursing CGMs would be $1,482,480,562. If coverage of CGMs was more broadly available (i.e., universal coverage for all individuals with type 1 diabetes, without age restriction), CADTH estimated a 3-year budget impact of $1,621,050,659. It is unknown which, if any, of these reimbursement scenarios for CGMs may be of interest to jurisdictions in Canada.

CADTH notes that there are a number of limitations with the analysis. Because the CADTH Clinical Review and Perspectives and Experiences Review were unable to identify subgroups of the patients most likely to benefit from HCL, a stratified analysis of individuals was not conducted. If clinical criteria were introduced to restrict the population eligible for public funding of HCL, the population eligible for HCL would expected to be smaller and the overall budget impact would be expected to be less, depending on the size of the eligible population.

One study from the Clinical Review compared HCL with technologies that are currently publicly funded (i.e., MDII or pump plus SMBG).[59] According to the Clinical Review, while this study found that treatment with HCL significantly increased glucose time in range and improved mean A1C values, incorporating these findings as cost offsets into the BIA was not possible. First, it is not known how a –0.4% improvement in A1C between treatment strategies would translate to a hard clinical end point that can be subsequently costed. Second, potential cost offsets from improvements in these metrics are unlikely to be realized in a 3-year time horizon. Although this study demonstrated a trend toward higher absolute rates of hypoglycemia and serious adverse events in those using HCL systems, no statistical testing was done to compare treatment groups. Other outcomes, including diabetic ketoacidosis, were similar between treatment approaches. Therefore, the clinical

meaningfulness of these findings is unclear. CADTH was unable to incorporate the costs for clinical outcomes associated with HCL use outside of those for insulin and glucose monitoring.

CADTH assumed that the reference scenario would remain unchanged for the 3-year time horizon because it was anticipated that there would be no changes to CGM and insulin-pump programs in jurisdictions. However, this assumption may be a simplification, given that it is unclear how policies may evolve in the coming 3 years. For instance, in Saskatchewan, there are preparations for a reimbursement policy for CGMs for those under 18.[138] If Saskatchewan implemented this policy within 3 years, the estimated budget impact (should HCL be reimbursed) will be less than estimated by CADTH for Saskatchewan. In addition, as of January 2021, Prince Edward Island expanded insulin pump coverage eligibility from those under 19 to those up to the age of 25.[113,135] Because this is a new policy, the base case assumed that the province's insulin-pump coverage would be limited to those under 19 years of age; CADTH expects there may be a delay in those up to 25 years of age being able to access the pumps. However, CADTH conducted a scenario analysis exploring the budget impact if those 25 and younger were eligible for insulin pumps in Prince Edward Island. The analysis demonstrated little effect on the pan-Canadian budget impact, but it did increase the expected budget impact of introducing HCL systems in Prince Edward Island by $320,987 over the next 3 years.

CADTH was unable to incorporate cost-sharing between public payers and private insurers, if this policy existed for some jurisdictions or certain supplies. CADTH assumed that the public payer was the first payer for insulin pumps and supplies in all jurisdictions because the details of cost-sharing between public and private payers were not readily available. If the public payer is not the first payer for insulin pumps and supplies, the budget impact of introducing HCL systems in these jurisdictions will be lower than CADTH estimates. Additionally, if policies for CGM coverage for use with HCL systems involves a degree of cost-sharing between public payers and private insurers, the overall budget impact of introducing HCL from the public payer perspective will be less. Of note, given that the perspective of this analysis was that of the publicly funded health care system, this analysis did not capture the financial impacts to individuals with type 1 diabetes or the impact from a broader societal perspective. It is reasonable to expect that currently, some patients may be paying for HCL systems out of pocket or through private insurers. As such, if HCL systems were to be funded publicly, cost offsets may be expected from the budgets of individuals or private plans.

Perspectives and Experiences Review

Overview

Research Question

This review has been guided by the following research question:

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

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

- How do people living with type 1 diabetes, or those involved in their care, envision HCL systems as contributing to type 1 diabetes management?
- How might expectations of and experiences with HCL systems differ across various groups of people (e.g., young children, parents, elderly) engaging with these systems?

Key Messages

The Perspectives and Experiences Review was conducted using an adapted thematic synthesis of primary qualitative research exploring the expectations of and experiences with HCL systems of people living (or caring for someone) with type 1 diabetes.

People living (or caring for someone) with type 1 diabetes hoped that HCL systems could take over enough of the work associated with type 1 diabetes self-management to enable them to focus on being more immersed in and part of the flow of life around them. While many described having some degree of success in achieving this, doing so was not without its challenges. As an example, for HCL systems to work most effectively, people need to trust the control algorithm to adjust things like basal-insulin rates and resist the trained impulse to do this themselves. This signals a shift away from previous ideals of “good” self-management that have required constant attention and ongoing device adjustments. While this could be difficult at first for people trained in other forms of self-management, people who struggled to meet previous ideals might appreciate and benefit from this shift.

Given the difficulty of navigating these shifting notions of “good” self-management and trust regarding HCL systems, it could be helpful to talk about and engage with HCL systems as collaborators in, rather than providers of, care. This distinction may seem inconsequential from the outside, but for people living (or caring for someone) with type 1 diabetes, the flexibility of collaboration helped them to deal with the numerous frustrations caused by techno-glitches and the ongoing material needs of their particular systems.

The introduction of HCL systems also contributes to a shift in how professional care is imagined. With increased access to their patients’ data, clinicians believed they could both see a more complete picture of their patients’ out-of-office experiences and reduce their own workloads as a result. However, there is a concern that this could lead to mistaking the numbers associated with diabetes for the person living with diabetes, which could result in missing opportunities to provide extra support or care to patients.

Research Question

This section of the HTA reviewed 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 has been guided by the following research question:

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

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

- How do people living with type 1 diabetes, or those involved in their care, envision HCL systems as contributing to type 1 diabetes management?
- How might expectations of and experiences with HCL systems differ across various groups of people (e.g., young children, parents, elderly) engaging with these systems?

Study Design

We conducted an adapted thematic synthesis of primary qualitative research inquiring into the expectations and experiences of people who interact with HCL systems. The primary goal of this analysis was to provide a glimpse into the variety of ways in which HCL systems become used in practice and how these uses might be caught up with shifting notions of what it means to be living with, caring for, and managing type 1 diabetes. This review is not meant to provide descriptions of the "preferences" of patients and providers engaging in treatment for type 1 diabetes. As such, we cannot tell readers whether patients prefer HCLs over the individual components that make up HCL systems, or some other form of therapy.

Literature Search Methods

The search for literature exploring perspectives and experiences was 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).[68] The complete search strategy is presented in Appendix 1.

Published literature was 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 comprised both controlled vocabulary, such as the National Library of Medicine's MeSH, and keywords. The main search concepts were closed-loop systems and diabetes.

Search filters were applied to limit retrieval to qualitative studies. Retrieval was not limited by publication date, but was limited to the English language.

The initial search was completed on March 18, 2020. Regular alerts updated the search until the publication of the final report.

Selection Criteria

English-language, primary qualitative studies were eligible for 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 dataset were included as long as each publication derived from the study reported on distinct

research questions. Duplicate publications using the same data with the same findings were excluded and are detailed in Appendix 2. Table 36 describes the eligibility criteria built using the Sample, Phenomenon of Interest, Design, Evaluation, Research (SPIDER) criteria for framing the qualitative evidence synthesis research questions.[140]

Table 36: 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	How living with a diagnosis of type 1 diabetes is understood and experienced; experiences with and expectations of engaging with HCL systems for people living with type 1 diabetes; how HCL systems are imagined as fitting with the potentially diverse conceptualizations of appropriately managed type 1 diabetes and type 1 diabetes care; experiences using HCLs to provide care to persons living with type 1 diabetes
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 insulin delivery.

Screening and Selecting Studies for Inclusion

Title and abstract screening were conducted independently in DistillerSR[141] by 2 reviewers with expertise in qualitative research, according to the predefined eligibility criteria (Table 36). As titles and abstracts were reviewed, notes on the topics, emphases, and populations of the articles were kept in order to develop an understanding of the types of information present in the dataset.

The full texts of all citations for which it was difficult to determine eligibility on the basis of title and abstract alone were retrieved and assessed by each reviewer before determining eligibility. Disagreements regarding eligibility were resolved through discussion.

At this stage, both reviewers reviewed the set of included studies and discussed whether the final set included sufficient data to answer the initial research question or if there was a need to modify the literature search and selection criteria. It was decided that the final set of included studies was sufficient, and no further modifications were necessary. Study selection has been documented using a PRISMA flow chart[72] and is reported as Figure 5 (Appendix 2).

Critical Appraisal

The critical appraisal was conducted by the primary reviewer and followed Krefting's[142] interpretation model for assessing trustworthiness in qualitative research. Krefting's mode of exploring trustworthiness[142] 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 4 guiding questions: Were the study authors true to their study participants (credibility)? Does the analysis make sense in light of the data presented (confirmability)? Is the analysis consistent across study findings (dependability)? Does the analysis found in one study resonate with the research question and context for this review (transferability)?

The second reviewer probed the primary reviewer's assessment of the literature, and any disagreements were resolved through discussion. Results of the critical appraisal were not used to exclude studies from this review; rather, they were used to understand the methodological and conceptual limitations of the included publications in relation to the research questions. A narrative summary has been provided in the next section, and a general note about the trustworthiness (i.e., high, moderate, low) of each included publication is reported in Appendix 2, Table 48.

Data Analysis and Synthesis

A descriptive analysis of study characteristics was conducted. Relevant characteristics are presented in tabular form and are accompanied by a narrative summary. The purpose of this analysis was to describe the set of included studies and understand the range of study designs and methods that have informed the resulting synthesis.

Drawing on the tenets of thematic synthesis[139] and grounded theory,[143] the synthesis followed an iteratively staged process that included 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 was to elucidate how some people living with type 1 diabetes, or those involved in their care, experience engaging with HCL systems, and how their experiences align with their expectations. The constant comparison method was adapted to include comparisons of notes or memos within and across studies. The synthesis was conducted by the primary reviewer, who was supported by a secondary reviewer.

The primary reviewer began by reading and rereading eligible studies while making marginal notes and memos (in Word) to reflect preliminary thoughts, impressions, and insights. While many of the notes were descriptive and referred directly to the content of a single line or paragraph, others acted as critiques and drew upon various study components used as part of critical appraisal (e.g., design or method, positioning of study authors, commentary in the Discussion section). The reviewer coded 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 allowed the reviewer to begin making connections throughout the empirical data found across the body of eligible studies.

These connections formed the basis of an outline of descriptive themes (in Word) and were brought to the second reviewer for discussion. The outcome of this discussion was a refined outline of descriptive findings and their connections that served as a skeleton for orienting and framing the synthetic analysis. Memos of this discussion were produced and used by the primary reviewer as a tool for future reflection. These outcomes were also shared with the broader review team to spur discussion and invite reflection regarding potential overlap across the analyses conducted as part of this HTA.

At this stage, the primary reviewer turned toward the construction of a synthetic analysis. Drawing on the growing familiarity with the dataset built through (ongoing) iterative readings, successive layers of marginal notes, outline development, and the discussions detailed earlier, the descriptive and analytic practice of memoing was used as a way of identifying links across descriptive themes and this section's questions. The second reviewer was engaged throughout this process by reading written memos, and remained in regular conversation with the primary reviewer.

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 were done to probe and position the reviewer in relation to the analysis.

Results

Quantity of Research Available

A total of 121 citations were identified in the literature search. Following screening of titles and abstracts, 86 citations were excluded, and 35 potentially relevant reports from the electronic search were retrieved for full-text review. Of these potentially relevant articles, 19 publications were excluded for various reasons. There were 9 further citations identified in update searches, and 1 was retrieved for inclusion. A total of 10 studies reported in 17 publications met the inclusion criteria and were included in this report. Additional details are reported in Figure 5 (Appendix 2).

Descriptive Analysis

Additional details regarding the characteristics of included publications and their participants are provided in Appendix 2, Table 48.

Data Collection and Analytic Approach

Of the 17 included publications, all were qualitative. Ten conducted thematic analysis.[28-31,33,144-147] Two used a mixture of thematic analysis and framework analysis.[25,148] Three used content analysis.[32,34,149] One each used descriptive data analysis[150] and constant comparison.[26]

Eleven publications collected data using interviews alone,[25,26,28,29,33,34,144-146,148,150] and 3 used focus groups alone.[32,149,151] Three more used a mixture of focus groups and interviews.[30,31,147]

Location of Study

Eight of the 17 included publications were conducted in the UK alone.[25-28,144,145,148,150] Three were conducted in the US alone.[147,149,151]Three more were conducted in both the UK and the US.[30,31,147] One each was conducted in Canada,[34] Australia,[29] and the Netherlands.[33]

Description of Study Participants

For the purposes of narrative summary, participant descriptions were sorted into 4 categories: adults living with type 1 diabetes, children and adolescents (ages 0 years to 20 years) living with type 1 diabetes, parents of children living with type 1 diabetes, and health care providers. Full details are available in Appendix 2, Table 48.

Two studies, representing 4 publications, focused on the perspectives and experiences of health care providers alone.[25,26,148,150] Another 2 studies, representing 6 publications, included adults and children or adolescents living with type 1 diabetes as well as parents caring for children living with type 1 diabetes.[28,30,31,144,145,147] One further study, reported in 2 publications, included both adults and children or adolescents living with type 1

diabetes.[32,149] Three studies included only adults living with type 1 diabetes.[27,29,34] One study each included adult patients and providers,[33] or parents of children living with type 1 diabetes and providers.[151]

Summary of Critical Appraisal

The studies included in this review were assessed to be of a moderate to high degree of trustworthiness overall.

We identified 4 publications that were considered to have a moderate level of confirmability.[30,32,147,151] Each separated its presentation of data from its analysis, typically by placing "data" (i.e., participant quotes) in tables cordoned off from the narrative text. While this may be a practical exercise for disciplines oriented toward the statistical representations of analysis (e.g., clinical epidemiology) or result from pressures to meet journal word limits that prevent authors from fully elaborating the connections between data and analysis in the text, their confirmability (i.e., whether an analysis makes sense in light of the presented data) was difficult to assess as a result. For this same reason, these 4 studies were considered to be of moderate credibility.[30,32,147,151]

All of the included publications were assessed to have moderate to high dependability because their internal logics and ways of framing were consistent throughout the entirety of analysis. Similarly, all of the publications demonstrated moderate to high transferability, given their consistency with our own research question and context.

Synthetic Analysis

HCL systems can help create space from some of the work associated with type 1 diabetes self-management; thus, they can enable people living with the condition to feel a bit more immersed in, and part of, the flow of life around them.

As a chronic condition that requires persistent management through complex daily regimens of measuring, tracking, administering, and adjusting, caring for type 1 diabetes is complicated and intensive. It takes consistency, attention, and time. Performing the practices of self-management is not always convenient, and it can be highly disruptive to daily life. For example, while a person living without type 1 diabetes may take mundane daily activities like eating or exercising for granted, moving in and out of them at leisure, those activities often represent problem points for people living with the condition, and require pausing, reflecting, calculating, and injecting (or not). These constant and deeply embedded demands can be exhausting after years of living with type 1 diabetes. As such, many people living with type 1 diabetes are simply looking for the opportunity to distance themselves from the pressures of "never having a second of a break from this disease state".[32] For most study participants, the hope and promise of HCL systems was that they could help provide that distance from diabetes and open some space to live differently.[25-34]

For people living with type 1 diabetes, a variety of technologies (e.g., insulin, blood glucose monitors, CGMs, insulin pumps, needles, calculators, phones) mediate their experience of the world around them. As a (re)assemblage of a number of these existing technologies with a control algorithm that allows them to communicate and act (most of the time) without user input, HCL systems are specifically oriented toward alleviating some of the technical pressures of living with type 1 diabetes. Indeed, study participants reported that HCL systems' ability to measure blood glucose and coordinate basal-insulin delivery in the background was helpful and made them broadly desirable components of type 1 diabetes care.[29,34,145,146] By limiting the amount of technical care practices needed throughout the day,

HCL systems could enable someone living with type 1 diabetes to lead a more "normal life".[33]

However, "normal" seems more complicated than fewer finger sticks and basal insulin adjustments. While these benefits would certainly contribute to a sense of normalcy, study participants also imagined HCL systems as hopefully helping to "facilitate activities and relationships"[34] to make space for living beyond diabetes. Where the need to pause, reflect, calculate, and inject (or not) had previously hindered someone's ability to move seamlessly through the activities of daily life (e.g., eating, exercising, sleeping), HCL systems might help to smooth these transitions. One of the ultimate aims for some people engaged with HCL systems was "to forget that I have diabetes in the first place … that has to be everybody's dream, that we become whatever is called normal".[147] This may not truly be everyone's dream, but by staking the opportunity "to become whatever is called normal" to the importance of forgetting, some people with type 1 diabetes are calling attention to a sense of dislocation that can be felt by people living with type 1 diabetes.

One child living with type 1 diabetes likened the potential of using HCL systems to a game, where the hope is that the device is "keeping your numbers up during the match, so you don't have to, like at half-time, test and that. You can keep on routines and focus more on the actual game"(p. 21).[31] Implicit in this child's desire not to have to test at half-time is a sense that HCLs might create some *distance from* "numbers" so that people living with type 1 diabetes can have the *space to focus* "on the actual game." This is not to say that people considered HCL systems as cures (they did not),[28-30,32,145,147] but rather to signal that they might simply be looking for something that would not kill them[29] as they try to focus on, and be more present in, the "actual game."

Fortunately for some, this hoped-for distance from type 1 diabetes and a sense of normalcy was described as being relatively well achieved.[28,29,32,144-146,149] Of course, this was not the case for everyone,[149] but many reported that HCL systems made a "material difference to the amount of time I've had to think about being a diabetic."[144]

The opportunity not to constantly be reminded that they are "a diabetic" — and the freedom from having to deal with the many technical practices involved in self-care — could also be experienced as having the space to live more spontaneously.[25,28,30] For example, although HCL systems still require preprandial bolusing, many study participants indicated that they used the systems as a security net of sorts when they were unable to (or simply did not) bolus before eating. As one participant noted:

If somebody's going round with a packet of biscuits and they offer you one, you can have a quick look and go, 'Oh yeah, go on then, yeah, I'll have a biscuit.' And you don't have to worry about it as much as if you weren't on a closed-loop, where it'd be like: 'Well, er, can I have a biscuit? Can't I have a biscuit? Oh well, you know, maybe I shouldn't …' It just means you can go with the flow, go with everybody else.[28]

An intrinsic part of the act of eating a biscuit as it is being passed around is the opportunity to be in the same time and space, the same flow, as "everybody else." Given the penchant for regimes of care associated with type 1 diabetes to structure time, living with the condition can often be felt as living out of time, or out of sync with the outside world — especially in social situations. This could be particularly challenging for children and teenagers who like "to do the kinds of things [their] friends do" and might, at times, treat themselves as though they are not living with diabetes. HCL systems may be able to offer that extra bit of space to live in the same flow as their friends.

While normalcy certainly encompassed more stable blood glucose numbers and the ability to pay less attention to self-care practices, it was also relational. More than simply needing to navigate the immediate and long-term health risks associated with fluctuating blood glucose levels, people living with type 1 diabetes must also navigate how their (potentially) fluctuating blood glucose levels may impact their relationships and daily responsibilities. One partner to a person living with type 1 diabetes described it this way:

I try to be very sympathetic. I'd like to say I am, but there are those times where I will come home in the afternoon from work, and she'll be in bed. And she'll say, 'What time is it?' And I'll say, 'Its 5:30.' And she'll say, 'Oh my God, I've been sleeping for two and a half hours.' That will get me annoyed. And I won't say anything to her, but internally it will bother me, because I can't understand what this disease is doing to her. And I try to [be] sympathetic and I try to be caring. We'll have to take the kids somewhere, and she'll say, 'I can't drive right now, I'm feeling shaky.' And I'll have to take the kids somewhere. So I think that [an automated insulin delivery system] would certainly help our relationship."[30]

It is evident that diabetes and the practices associated with its care have effects both within and external to the person living with the condition. Whether because of a high or a low (though likely a low), the person in this example needed to lie down and remove themselves from the flow of the day. As a practice required to attend to their diabetes, this rest (or even the need to rest) affects both themselves and their family. We see the partner needing to pick up on what they consider to be the other's responsibility, while also having to deal with their own emotional blowback. From this brief example, it is clear that the stakes involved in caring for type 1 diabetes pertain not only to keeping blood glucose levels more consistent or in range, but also to the very movements and relations that make up everyday life.

As such, HCL systems were imagined as contributing to more normal family environments[30,32] or building space between parents and young children or teens who are living with type 1 diabetes.[30,144,151] So "if it is going to mitigate the highs and take the high 'grumpies' away and the lows away, the panicky feeling when I'm with my kids and have to say 'Mommy comes first right now, you have to wait until I'm done being low,' if it is going to eliminate a lot of that, then I think the benefit would be huge."[30]

Similarly, teenage study participants often hoped that HCL systems would provide space from their parents' constant reminders to check their blood sugar and calculate their insulin requirements. When asked what the worst thing was about having type 1 diabetes, one teenager said, ''The worst is that my mom calls me all the time when I am at the skate park to ask what my blood sugar is."[30] The introduction of the HCL may build in a distance where parents can be less concerned with every second of their child's life and allow them to skate in peace. If so, some of the parents of young children (ages 5 years to 8 years) described the importance of adding extra safety features to artificial pancreas devices that had already been tested in adult populations if they were to feel comfortable introducing them to their child.[151] These could include incorporating password-protected controls and additional features that could support adults who are less familiar with type 1 diabetes, but still responsible for the child at various times of the day (e.g., school teachers). By and large, parents were primarily concerned about hypoglycemic events, and hoped to maintain tight control over their child's diabetes by engaging with artificial pancreas devices that had varied functionalities that adjusted the blood glucose target according to activity (e.g., sleep or exercise).[151]

One of the challenges of attaining this potential for space creation is caught up within complicated and shifting notions of good self-management and trust.

By taking a privileged role in the coordination of insulin delivery, HCL systems were often described as requiring trust and a bit of their own space in order to function according to their intended purpose.[25,144,146,147,149, Iturralde, #45,150] At its most basic level, trust implied a willingness of people using HCL systems to take a step back and allow the devices to function without too much tinkering. As we have seen, people generally appreciated the opportunity to distance themselves from their diabetes by lessening some of the more technical practices of diabetes management. However, it is important to recognize that this could be difficult for some, given that current regimes of diabetes care place the responsibility for checking and tinkering squarely on the shoulders of people living with type 1 diabetes.

Many study participants tied this reticence to or difficulty with stepping back to a desire or need to remain in control.[25,149] As a nurse indicated, people who have been managing their diabetes for a while will "need a lot of reassurance … They've got to step back, haven't they, [from] all the work they've been doing and the psychological control they've had, because … all of a sudden they're told to not do that anymore and leave it to the closed-loop system to do it."[25] Indeed, people using HCL systems as part of a clinical trial often indicated that they remained hyper-attuned to their devices for the first few days or weeks. They scrutinized graphs representing the movement of their blood glucose levels, confirmed these levels with frequent blood glucose checks, and adjusted their basal rates they were concerned that the system might not be functioning properly.[144,146,149]

But that trust was also mobilized as a way of articulating the difficulty of navigating shifting relations of accountability or responsibility. Stepping back and trusting that the HCL systems would do what they were supposed to do might require more than a passive loosening of control, but also a shift in active responsibilities. For example, parents were particularly vigilant in the early stages of their child's HCL use. As one put it prior to initiating the trial, "I'm absolutely not gonna let him out of my sight … I suppose it's trust, you know, it's not just a broken leg. It's his life. And it's delivering deadly insulin into my son, 24/7."[144] While not all participants shared the intensity of this skepticism, it is clear that the stakes are not simply stable glucose levels, but also life and death. If the control algorithm makes a mistake, their child could die. In this way, this participant's desire to distance themselves from their (or their loved ones') diabetes could simultaneously be caught up with the discomfort of shifting responsibility.

However, eventually, many participants began to trust their systems and even described feeling that the systems may have been doing a better job of managing their blood sugars than they themselves could have done with their previous insulin delivery systems (e.g., insulin-pump therapy or MDII).[32,144,146,147,149] Taking this a step further, participants described the reason for this as related to just getting out of the way and letting the system do what it was designed to do. As one parent noted, "Obviously, the artificial pancreas recognizes after a few days his patterns. But I was interfering, because I was thinking: oh my gosh, he's going into hypo, this is crazy … And actually when I stopped doing stuff and I allowed the artificial pancreas to do its thing, it became a lot better."[144]

This point reflects how some health care workers imagined these systems would work their ways into the lives of people living with type 1 diabetes, and who might see the most benefit from their implementation. While many health care workers assumed — prior to their own experiences with the technology — that individuals who were already maintaining stable glucose levels would benefit most from HCL systems, once they gained experience using them in their practices or as part of clinical trials, many began to believe that the patients

who could resist the urge to constantly adjust the technology would also benefit. As one nurse put it, “Often some of the families that people don’t think would understand it so well maybe are the ones that follow [it] better, because if you say, ‘These are the steps that you need to do for the system to work,’ they generally will follow the steps. Whereas I’ve found in general — very, very broadly speaking, those that are a little bit more academically minded, maybe want to fiddle more, which doesn’t necessarily help.”[144]

Given the difficulty of navigating these shifting notions of good self-management and trust brought along with HCL, it could be helpful to talk about and engage HCL systems as collaborators in, rather than providers of, care.

While it is certainly important to trust the capability of technologies that are participants in care routines, for some people living with diabetes, the concept of trust seemed incomplete. These people wanted something more collaborative out of their use of HCL systems. For example, when describing features they would appreciate in future iterations, many said they would like more adaptability in the types and times of alarms or the opportunity to set their own blood glucose target parameters. Some parents of children living with type 1 diabetes wanted systems that could grow with their kids (e.g., access to bolus inputs could be locked initially, but gradually released in keeping with their child’s growth in autonomy) or that would encourage their kids to pay more attention to their blood glucose levels by gamifying the displays.

The importance of understanding the collaboration of care that happens between HCL systems and the people living with diabetes who use them to manage diabetes is underscored given the presence of techno-glitches. Study participants reported that alarms going off for no apparent reason or sensor readings that were inaccurate complicated their trust in the systems. In this way, there is the need to attend to the calibration, alarms, insulin refills, sensor sites, mealtime boluses, and disagreements with the algorithm. This points to the material realities of using these systems, and reminds us that HCL systems are a grouping of multiple technologies (e.g., CGM, insulin pump, and algorithm) that serve different functions and produce different kinds of work.

When reading these techno-glitches, people who start out assuming that HCL systems always work in fixed and linear ways, regardless of context, may have reduced trust in or appreciation for the HCL systems Techno-glitches are frustrating and can limit the kinds of space hoped for and experienced by people using these systems. As one individual put it, “the pump is nothing without a CGM, so if I don’t trust the sensor … It didn’t undermine my confidence in the algorithm of the system but before I did any sort of treatment, I would check [my blood glucose level]. I don’t think I checked less by any means. I checked more.”[149] The reality is that these technologies can feel simultaneously freeing and constraining for some. Of course, in part, this is tied to the expectations associated with the technology, but it may also have to do with the possibility of understanding the relations involved in space creation. In other words, for HCL systems to succeed, people using them have to be aware of and attend to their needs.

This might be understood in terms of the relationship involved: one that requires less a singular placement of trust and instead a collaborative mode of engagement. For HCL systems to function properly and work on blood glucose, users need to be committed to working with them. As one nurse put it, “You still need to be doing what the technology needs you to do. [Depending on which HCL you are using] you need to be doing the calibrations at the right time and you need to be changing your cannulas frequently.”[150] If approaching techno-glitches through a lens that understands that HCL systems work in fixed

and linear ways regardless of context, these techno-glitches may limit the perceived trustworthiness of HCL systems. Perhaps by engaging with these systems as collaborators in care, we can become less frustrated by their presence. To function properly, an HCL system needs the person living with diabetes to attend to how and where it connects to the body.

Techno-glitches and maintenance needs of HCL systems aside, study participants' collaborative work was also evident in day-to-day activities. Dietary habits while on HCLs system seemed to provide the clearest image of this in practice. While HCLs still require people to measure carbohydrate intake and preprandial bolusing, many of the study participants indicated that they became (or hoped they would be able to become) a bit less intense about these steps when using HCL systems.[28,30,32,34,146,147,151] As one adult participant put it, "So if I went out for dinner and I did miscalculate my carbs a little bit, it wouldn't be a problem during the night while I'm asleep, where they [blood glucose levels] suddenly go up or they suddenly go down, *because the algorithm would deal with that*." (p. 757, our emphasis)[28] Given that eating out can be a "nightmare"[28] and make it notoriously difficult to measure carbohydrates perfectly, knowing that the "algorithm would deal with" the fallout of potentially miscalculating carbohydrates was comforting.

Of course, this example underlines how the opportunity to distance one's self from some of the requirements of diabetes self-management (e.g., taking care of highs and lows) was an incredibly valuable component of HCL use (e.g., this person could keep sleeping through the night). However, we also see this individual pointing out the collaborative work involved in making this possible. The fact that they continue to measure and calculate their carbohydrate intake is implicit in their response. What is different, then, with the addition of HCL systems is the opportunity to share the load of any miscalculations that may happen. To come full circle: for the algorithm to do its job, the other components of the device system need to be functioning properly. While they have more freedom around mealtimes, people engaged with HCL systems are also bound to their devices, given that "[The algorithm] is based off your sensor. If you don't trust your sensor, you're not going to trust the insulin that you're getting."[149] Each piece relies on the others.

People expressed a desire to collaborate with their HCLs in other ways, as well. For example, HCL systems might react more quickly and accurately to exercise regimens if the people engaged with them could communicate what level of intensity or what kind of exercise the systems could expect that day.[144] Others thought it might be helpful to be able to warn their systems of various types of days they could have: "It'd be much better if I could press a button and say: 'I'm really busy today. Don't be so harsh.' Or, 'I'm having a really lazy day, you know, brush it up a bit.'" (p. 124)[144] We see in both of these examples a form of negotiation at play. For us, the opportunity to make requests regarding the type of support or collaboration a person may be looking for throughout the day is about more than just hoping for another input. It demonstrates how these systems can be understood as participants in (as opposed to simple tools for) the care of people with type 1 diabetes.

While some participants had hoped that HCL systems might represent something closer to "a natural machine that did everything,"[32] many were also prepared to engage with these systems as collaborators rather than solutions. HCL systems do not need to be perfect to be relevant or useful in the lives of people living with type 1 diabetes. This is not the same as saying that it is not important for manufacturers to work toward resolving techno-glitches or disruptive functionality mechanisms to improve ease of use or trustworthiness in HCL systems (issues that could even factor into decisions to stop using HCL systems[32]). It

absolutely is important, and could be facilitated through further participant-driven user experience research, for example. However, in the meantime (given that the systems appear to be clinically safe), they could still play a role for people who are prepared to engage with their imperfections.

Not only do HCL systems shift notions of good self-management for people living with type 1 diabetes, but they also contribute to a shift in how professional care is imagined.

As tools for tracking, recording, and, importantly, attending to the numbers involved in managing type 1 diabetes (e.g., blood glucose levels and insulin doses), HCL systems were often described by people living with the condition HCL systems helping to provide the space to live beyond the constant pressures and constant closeness of diabetes self-management. Some health care providers were excited by the prospect that these same capacities could limit "second-guessing about what's going on.... [W]e will have a picture, if you like, of everything that's going on."[25] If the massive amounts of data were, at times, experienced as a bit overwhelming for providers to wade through,[25] they were also helpful to increasing the efficiency and completeness of patient-provider interactions.

As a condition largely described through the numeric representations of the lived body, this datafication itself is not new: HCL systems are, after all, a reorganization of pre-existing technologies designed with this datafication in mind and made to communicate through the addition of a control algorithm. Rather, it is the ability of this algorithm to do so many background calculations and adjustments that brings newness to the potential displacement. For some care providers, HCL systems were imagined as holding the potential to "reduce the workload of.... medical teams in terms of managing diabetes" and imagined that the outcome would be "spectacularly better for patients." (p. 4)[25] Not only could clinicians know more precisely how much time their patients were spending in a designated glycemic target range, but they would also be less needed for adjusting insulin levels, given the function of the algorithm. Of course, quite a bit of training is required upfront, but once patients are used to the system, "if they're using the closed-loop well, support in terms of adjusting insulin is virtually nil."[150] This resonated with an adult study participant living with type 1 diabetes, who noted that "once the AP [artificial pancreas] system is well integrated into health care – I do not have the illusion that it heals people – the treatment is such that medical specialists can provide far less guidance [to patients]."

Having a more precise picture of how a patient's blood glucose numbers have moved around may certainly lend itself to a more complete dataset to help guide conversations with patients. However, it also introduces the possibility of confusing the person living with type 1 diabetes with the datafication of their condition. While the insulin needs of people living with type 1 diabetes may be attended to a bit more efficiently with HCL systems, some health care providers were concerned that the limited need to interact with patients may result in missing signs that other parts of their lives, such as their psychosocial needs, could use some support.

This ties in with a broad concern — brought forward by both health care providers and some people living with diabetes — that HCL systems may be accompanied by increasingly relaxed self-management routines and eventual de-skilling altogether.[25,26,28,145,146] While we have described here the ways in which people engage (or hope to engage) with their systems as collaborators or participants in their care, some felt that the boundary between collaborator and crutch was easily (if accidentally) traversed. Taking dietary practices as an example, one person living with type 1 diabetes noticed that they had become less vigilant about the quantity of carbohydrates they were consuming:

…so if I was preparing the kids' tea I would just sort of like have a chip or two. Generally I would normally concentrate on exactly how many chips I was having and sort of have some insulin to go with it. But on the closed-loop system I think I didn't concentrate as hard because I assumed that the system would pick it up and would deal with the blood sugars that way round … that wasn't a good habit to get into.[145]

Perhaps the HCL would pick up the snacking and "deal with" the blood sugars; after all, we have just worked through an example in the previous section saying just this. What is different for this person, however, is their concern that this was not "a good habit to get into." This could, in part, reflect the context of the interview, in which they were being asked about their views on finishing a clinical trial and returning their HCL system. While on the closed-loop system, it may not be all that problematic to miss a bolus here and there if you are able to follow up soon, but what happens if the system breaks down after these habits have been established? As one physician put it, "If something does go pear-shaped, they've got to make decisions, they've got to revert perhaps to older technology or to no technology.... [Does] using closed-loop mean that patients and families will deskill themselves... and if things go wrong, they don't know what to do[?]"[25]

Patients also picked up on this,[28,145] and were concerned about what it could mean if they needed to return to a previous mode of self-management or of supporting a child's self-management. As one parent noted after completing their clinical trial, "the hardest part was actually going back at the end to just the pump, and remembering … I actually had to ask [child's name] at one point. I was like: what do we do with this? Because I'd forgotten — like getting back into doing the corrections."[145] We point to these concerns not to draw attention to problematic notions of "adherence" or "compliance" to prescribed treatment regimens, but rather to note this as a space that will need consideration if HCLs are to become more widely available. The concern that people may forget how to use alternative technologies may not be a reason to limit access, but it should invite care providers to conceptualize other ways they can support their patients.

Among health care providers, perhaps this implies a shift in which persons should act as the primary points of contact for people being cared for in their home clinics. For instance, there may be a growing importance for a larger nursing staff specializing in diabetes.[33] As one person living with diabetes put it, "You actually see that when you make the switch from syringe to pump. Then suddenly the contact with the diabetic nurse becomes much more intensive and more accessible and then you can suddenly call outside office hours."[33] One new role may involve helping to prevent or limit the amount of any de-skilling.[25,26,28,145] While device manufactures do provide technical support, it is possible that people using these systems may first reach out to their health care teams for support, which may indicate an increased need for staff who can help to address glitches or technical needs associated with the new systems.[33]

Given that HCL systems are new arrangements of diabetes technologies, health care providers will need to provide some upfront training on how to use them.[25,26,148,150] Depending on the types of technologies their patients are already familiar and comfortable with, this could take variable amounts of time. Some providers who had participated in an HCL trial with patients who had recently been diagnosed with type 1 diabetes found it useful to take a staged approach when introducing the trial system.[150] By focusing on the individual technologies that make up the device system, it was possible to break down the functionality of each and relate it to how they function together.

Summary of Results

Overall, HCL systems were seen by study participants as able to help create space between the person living with type 1 diabetes and the work associated with type 1 diabetes self-management. In so doing, HCL systems can enable people living with the condition to feel a bit more immersed in, and part of, the flow of life around them. One of the challenges of attaining this potential for space creation is caught up within complicated and shifting notions of good self-management and trust. For the algorithms embedded within HCL systems to work most effectively, the people using them need to resist the impulse to adjust things like basal-insulin rates and trust the algorithm to make these adjustments. This is important because it signals a shift away from non-HCL ideals of good self-management, which otherwise include a fair deal of tinkering. This transition can be particularly difficult for people who have been hyper-attuned to fluctuations in the numbers associated with diabetes for most of their lives.

Given the difficulty of navigating these shifting notions of good self-management and trust brought along with HCL, it could be helpful to talk about and engage with HCL systems as collaborators in, rather than providers of, care. This distinction may seem inconsequential from the outside, but for people living with (or caring for someone living with) type 1 diabetes, the flexibility of collaboration helped them to deal with the numerous frustrations of techno-glitches and ongoing material needs of their particular systems.

Not only do HCL systems shift the notions of what good self-management means for people living with type 1 diabetes, but they also contribute to a shift in how professional care is imagined. With increased access to patients' data, clinicians believed they could both see a more complete picture of patients' out-of-office experiences and reduce their own workloads, given their ability to track how well HCL systems manage day-to-day changes in aspects like basal-insulin delivery. There is concern that this could lead to mistaking the numbers associated with diabetes for the person living with diabetes, which could, in turn, result in missing things like whether patients are becoming de-skilled in their self-management or need extra support.

The findings in this review are meant to inform decisions that recognize the diversity of human experience and can provide balance to the generalizations of clinical outcome data. Knowing that the people participating in the studies included in this review found HCL systems to be generally beneficial additions to their lives with diabetes does not imply that all people who engage with HCL systems will feel similarly. Rather, this finding raises the question of how, if we are interested in providing HCL systems as a treatment option for people living with type 1 diabetes, we can best implement programs that can adapt to the diversity of relational needs or desires involved in the care of this condition.

At least 1 issue described in our conversation with individuals living with type 1 diabetes through patient-engagement work was absent from the literature: how varied physical or mental abilities may impact both the accessibility and usability of HCL systems. In these conversations, it was clear that the experience of type 1 diabetes is not universal across the people living with, or caring for those who live with, the condition. Furthermore, while this was not part of our patient engagement conversations, we acknowledge that the absence of any conversations about the social determinants of health could skew the results to privilege normative and ideal type 1 diabetes populations. In the absence of any included studies engaging with how elements like access to nutritious foods, the pressures of gendered social roles, or the physical and psychological harms of racist stereotypes may affect a person's access to or ability to use HCL systems, we are unable to say anything about how these systems may benefit (or not) people who identify with any number of these categories.

Ethics Review

Overview

Research Questions

1. What are the major ethical issues raised by the use of HCLs?
2. How might these issues be addressed?

Ethical Aspects

- Providing coverage for HCL systems may live up to government's obligations to allocate resources to maximize benefits, given that there is evidence that overall, they provide at least short-term clinical and non-clinical benefits to those who use them. It is not possible to conclude whether HCLs will ultimately improve population health over the longer term because data for the impacts of their use compared to other prominent modes of diabetes management are not available.
- HCL systems may promote individual autonomy and agency by lightening the burdens of diabetes management and enabling users to have greater control over their diabetes, provided users are able develop trust in the systems.
- Accessible, accurate, and comprehensive education and support for new and ongoing users of HCL systems is important to enable users to adapt to the devices and remain comfortable to continue using them over time, enabling them to benefit from its their use.
- At the clinical level, health care providers who play a gatekeeping role in access to HCL systems should be aware of the fallibility of their assumptions about which patients are likely to benefit from them. The use of non-clinical factors in this assessment should be limited; probationary periods to demonstrate one's capacity to use the device safely and effectively should be considered.
- There is disagreement about how eligibility for public coverage of HCL systems should work (if a decision is made to publicly fund the devices). Some argue that people who are managing their diabetes well should be candidates, whereas others think the device should be available to those who need to improve their management.

Background

The purpose of this analysis is to identify and reflect upon key ethical concerns that should be contemplated when considering HCL systems for people with type 1 diabetes. Although other sections of this HTA 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. Nevertheless, the primary emphasis here will be on ethical considerations rather than on legal or social issues.

There are 2 sets of questions to consider when assessing the use of HCL systems for managing type 1 diabetes:

1. What are the major ethical issues raised by the use of HCL systems?
2. 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 or 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 2-step approach to identifying potential issues. The first step 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. Using 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 patients’ perspectives and experiences, clinical utility, and economic analyses. As such, the ethical review involves an iterative process whereby the analysis is responsive to results emerging from these domains.

Perspectives

The perspectives considered in identifying and addressing the ethical issues associated with HCL systems for the treatment of type 1 diabetes included people living with type 1 diabetes, family members, informal caregivers, and health care providers.

Data Collection: Systematic Review of Empirical and Normative Bioethics Literature

A review of the empirical and normative bioethics was conducted to identify literature relevant to the identification and analysis of the potential ethical issues related to the use of HCL systems. The initial search was for articles, studies, or reports that explicitly and specifically raise ethical issues related to the use of technologies for type 1 diabetes management. This search focused on the use of HCL systems, but included literature on the ethics dimensions of other diabetes management technologies (e.g., CGMs). When it was determined that there were very few papers that were explicit about the ethics of HCL

systems or related technologies, the search was expanded to include studies that contained implicit discussions of the ethics dimensions of HCL technologies.

Literature Search Methods

The search for literature identifying explicit ethical considerations was 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).[68] The search strategy is available on request.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid, Philosopher's Index through Ovid, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) through EBSCO. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH, and keywords. The main search concepts were closed-loop systems and diabetes.

Search filters were applied to limit retrieval to citations related to empirical and normative ethical considerations. Retrieval was not limited by publication date, but was limited to the English and French languages. The initial search was completed on August 7, 2020. Regular alerts updated the search until the publication of the final report.

Selection Criteria

Literature was included if it explicitly identified ethical issues regarding HCL systems or if it implicitly raised ethical issues in articles about HCL or analogous technologies. Additional articles were included based on the judgment of the report author and suggestions from reviewers.

The selection of relevant literature proceeded in 2 stages. In the first, the title and abstracts of citations were screened for relevance independently by a single reviewer. Articles were categorized as "retrieve" or "do not retrieve," according to the following criteria:

- provides normative analysis of an ethical issue arising from the use of HCL or analogous technologies
- presents empirical research related to ethical issues arising from the use of HCL systems.

In the second stage, the full-text reports were reviewed by a single reviewer with ethics expertise. Reports meeting the aforementioned criteria were included in the analysis, and reports not meeting these criteria were excluded from the analysis.

Data Extraction and Abstraction Strategy

Issues in the literature were identified by a single reviewer and thematized according to key values in health ethics, including duties to benefit and avoid harms for patients and others, impacts on individual autonomy, respect for whole person and perceptions of self, trust, privacy and confidentiality, equity, and professional ethics. The purpose of this first step was to ensure that issues with clear ethics content were included. These issues were then organized according to the original 5 conceptual categories presented by Quintal[152] in its SR, with the slight modification of these and the addition of 2 further categories. These are: Harms and Benefits of the Technology; Autonomy, Agency, and Trust; Personal Identity and Relationships; Patient Selection; Patient Coaching and Support; Confidentiality and Safety; and Access and Coverage. The Quintal framework was adopted to frame this analysis

because it is the only ethics framework relating to HCL technology in the literature, and it offers a reasonable starting point from which to understand and analyze ethical issues relating to these devices. The Quintal SR was completed by a team out of the University of Montreal and the Montreal Clinical Research Institute, funded by grants from National Institute of Diabetes and Digestive and Kidney Diseases, the Montreal Clinical Research Institute, the Canadian Institutes of Health Research, and Quebec Santé. Of note, the Quintal framework is the only source that explicitly identifies ethics issues related to HCL systems, and it provides limited analysis. The majority of the ethics analysis contained in this report was generated by the author.

Results and Analysis

Of note, many of the issues that are highlighted in this Ethics Review are not unique to HCL systems. They are relevant to other technologies to treat diabetes, and have been widely discussed in the literature. However, HCL technologies do bring novel concerns because they require users to make use of and understand more components, their capacities may be more vulnerable to being misunderstood, their long-term use may lead to a greater degree of de-skilling than other technologies, and they rely on transmission and storage of greater volumes of data.

Harms and Benefits

This section outlines the range of harms and benefits provided by HCL systems. The principles of beneficence and non-maleficence (i.e., the duties to create benefits and minimize harms) sit at the core of health ethics and are part of the “4 principles” approach to bioethics, alongside the principles of autonomy and justice.[153]

A key factor of external, patient-managed medical devices is that the extent to which benefits arise from them depends on individuals choosing to start — and continue to use — them effectively. People’s day-to-day experiences with the devices are extremely relevant, as they often determine whether people continue to use them. Thus, these experiences are crucial for analyses about whether devices lead to — or are likely to lead to — improved health outcomes, both for individuals and at a population level.

The effects of using an HCL system can be felt immediately (within hours, days, or weeks) and over longer time horizons (months, years). These effects can be physical, emotional, psychological, social, and relational. Given the relative newness of closed-loop technology, data for longer-term impacts are not available for inclusion in this review. As a result, the majority of empirically determined harms and benefits are those that occur over the shorter term after a person living with diabetes starts to use an HCL system.

To appreciate the impact of HCL system, it can be illustrative to understand the burden of diabetes management, even with the assistance of established technologies (such as insulin pumps and CGMs). Successful management of type 1 diabetes requires regular monitoring of blood glucose, administration of insulin, managing food intake and exercise, monitoring sleep, stress, and other aspects of life that affect blood sugar levels, and responding to hypo- and hyperglycemic events.[22] Caregivers also experience the burden of type 1 diabetes in the people they care for, especially children, because children often have more unpredictable eating habits, engage in spontaneous bouts of physical activity, and can have erratic behaviour patterns. Caregivers must monitor children’s blood glucose levels closely, and routinely continue this monitoring overnight, which can lead to sleep disruption and

anxiety.[23,24] One study estimated that children and their families spend 1 hour to 2 hours a day managing the child's diabetes.[154]

Even with very attentive management of glucose levels, glucose levels can still be out of range, leading to feelings of distress and frustration. [155] People living with diabetes often fear acute complications (e.g., hypoglycemia) and longer-term complications (e.g., retinopathy).[152] Further, people living with type 1 diabetes report feeling stigma due to their condition, and worry that others see their condition as the result of a character flaw or failure of personal responsibility.[156] These fears, along with the burden of ongoing management and the emotional fluctuations that can occur with glycemic variations, contribute to significant emotional and psychological consequences for people living with type 1 diabetes and their caregivers. Distress and depression associated with diabetes management can lead to even poorer management and reduced glycemic control,[157] Only one-third of people with type 1 diabetes achieve the glycemic control necessary to avoid diabetes-related complications.[154] Data gathered in the Type 1 Diabetes Exchange Registry have shown that not only has glycemic control failed to improve overall for people with type 1 diabetes, but it has actually become worse in adolescents and adults, despite increased uptake of new devices,[158] It has been proposed that this is because diabetes technologies to date have primarily benefited people with type 1 diabetes who are already highly motivated to manage their condition and adhere to the demanding self-care regimens that are required even with the support of technology (e.g., insulin pumps and CGM). For a diabetes technology to have a meaningful impact on glycemic control on a larger scale, it must reduce the burden and complexity of type 1 diabetes management.[158]

Benefits of HCL Systems

Clinical Benefits

The clinical studies included in this HTA provided evidence for shorter-term clinical benefits of HCL systems, only. The Clinical Effectiveness Review examined several studies comparing HCL systems to other technologies to manage type 1 diabetes. The review found that compared to these other technologies, HCL systems were associated with improvements in short-term clinical outcomes (6 months or less), particularly time-in-range metrics, for individuals using them. For a detailed analysis of this evidence, please refer to the Clinical Review section.

Non-Clinical Benefits

A number of non-clinical benefits of HCL systems were described in the literature included as part of the Ethics Review. Of note, these benefits were described in comparison to a range of other approaches to type 1 diabetes management, not exclusively open-loop SAP systems (the comparator in the Clinical Review). In many studies of HCLs system, participants reported an improvement in their quality of life as a result of using the system. Participants using HCL systems noted specific benefits, including improved sleep due to reduced fears of hypoglycemia overnight, the ability to engage in physical activity more easily and safely, improved performance at work, less anxiety around food and eating out, reduced stress for family members, relief from knowing the system is able to correct human error, reassurance and improved control, a greater sense of safety and peacefulness, decreased stress associated with allowing the technology to "take over," and, overall, a reduced burden for type 1 diabetes management.

Caregivers of people living with type 1 diabetes (including parents looking after children with type 1 diabetes) reported similar benefits, including reduced stress and respite from having

to manage another person's diabetes, reduced fear of hypoglycemia leading to disrupted sleep overnight (given that caregivers get up to check the person living with diabetes' blood sugars), and less of a need to remind children to complete diabetes-related tasks, such as blood glucose testing . Some parents said having their child use the HCL system gave them greater reassurance that their child's glucose levels would be well-managed, which allowed them to feel more comfortable leaving the child with a paid caregiver, allowing them to go out for an evening. The Perspectives and Experiences Review section discusses many of these themes.

Harms and Burdens of HCL Systems

People Living With Type 1 Diabetes

The known harms or burdens of the HCL systems are mostly associated with the physical and technical nature of the device rather than with harmful clinical outcomes. See the Clinical Review section for a discussion of safety and adverse events connected to HCL use. This section outlines the harms or burdens of a person's direct interaction with the HCL device. Subsequent sections in this document will discuss other aspects of HCL systems that may be considered harms, but are more constructively discussed within the context of other issues.

Use of HCL requires a willingness to wear the full HCL system, which includes a glucose monitor and infusion site attached to the skin and an insulin pump clipped onto clothing.[152] This created concerns among HCL users about the visibility of the system, the impacts it has on how people dress, and their sense of how others perceive them.[24,159,166] Some users also reported dissatisfaction with use of the HCL system while doing physical activity and while bathing.[159,160,167] A few studies noted that users found the HCLsystem used in the study to be cumbersome,[23,159,160,163,167] although it is likely that the HCL systems used for research purposes were bulkier than current commercially available models.

Study participants using both research and commercially available devices reported technical glitches with their HCL systems. These included sensor issues, loss of connection, pump catheter problems, and poor battery life.[23,27,159,160,167,168] Participants from multiple studies noted frustration or irritation with HCL system battery alarms, which contributed to disrupted sleep for some.[24,159,160,167,169-171]

Caregivers of People With Type1 Diabetes

The harms and burdens of the HCL system for caregivers were similar to those experienced directly by people living with type 1 diabetes. Caregivers have reported practical difficulties managing device calibration and insulin infusion-set canula insertions.[24]

It should be acknowledged that many of these burdensome aspects of HCL systems are not necessarily unique to HCL systems (they may show up with other technologies to manage type 1 diabetes as well), and it is possible that some of these aspects may be improved upon as commercially available models develop over time. To some readers, it may also appear that some of these concerns are superficial or generally inconsequential. While it is true that many research participants reported that the benefits of HCL generally outweigh the burdens outlined here, it is often a person's experience with using a device daily (and confronting its glitches and minor irritations) that determines whether they will continue to use it over time. Without ongoing use, individuals — and by extension, populations — will not be able to experience the clinical and health-related benefits of technologies like HCL systems.

To ethically justify a decision to improve access or fund a medical device, there must be sufficient evidence that the device delivers a balance of benefits over harms. This includes clinical and non-clinical benefits, both for the user of the device and non-clinical benefits for others. While there is insufficient evidence to determine conclusively whether HCL systems offer long-term benefit, the evidence discussed here suggests that for some users, it offers immediate clinical benefits and several non-clinical benefits without significant risks of harm.

Autonomy, Agency, and Trust

The concepts of autonomy, agency, and trust have emerged as core ethical themes relating to HCL systems. They are related to a person's decision to start using an HCL device and continue using it, and to its impact on their abilities to make other decision in their lives. This section outlines the results of the literature review relating to these 3 themes as well as themes relating to individual control, vulnerability, and surveillance. The Perspectives and Experiences Review discusses similar issues relating to increased agency, control, and trust.

Autonomy

Duties to respect, preserve, and promote an individual's role in making decisions about what happens to their bodies and within their life course are central to western health ethics, and have been widely codified in laws and organizational statements. While not true in all circumstances, health decisions (including policy and allocation decisions) tend to be more ethically justified if they respect the autonomy of the person (e.g., patient or client) who is centrally affected by the decision.

Individual autonomy is at stake when people initially make decisions about whether to use diabetes technology, which technology to use,[172] and other aspects of their lives as they use the technology. Having access to accurate and unbiased information is critical if people are to exercise their autonomy through informed decision-making. Some researchers in the field of type 1 diabetes technology have expressed concern that a lack of validated and neutral (i.e., industry-independent) education about potential novel technologies may limit individuals' abilities to make autonomous decisions about HCL systems.[156] The Stakeholder Consultations section of this HTA reinforces this concern in its discussion of clinicians' confirmation of (and satisfaction with) access to device education that is predominantly offered by manufacturers. Individual autonomy is similarly best supported with ongoing independent support, education, and follow-up to enable people to continue to be maximally autonomous in their decisions about how to manage their diabetes.[152]

Agency

Agency refers to a person's capacity to act. It is considered by some to be a finite resource because individuals only have so much attention and energy to devote to the sum total of issues in their lives.[152] Agency is necessary to meaningfully exercise one's autonomy, so it can be ethically problematic when technologies limit individual agency. Conversely, technologies that enhance agency may be ethically preferable to those that do not.

HCL systems have the potential to enhance individual agency because they take over some of the work of diabetes management, freeing up a person's energy and attention to devote to other aspects of their lives. Research participants who started using an HCL system noted that the device enabled them to allow their lives to become more complex, in part due to an increase in agency combined with the greater range of options that the device allowed

(e.g., participating more in sports and physical activity, eating at more erratic times of day).[145]

Overall, this increase in agency was felt to be of benefit because it reflected a decrease in the burden of diabetes management and enabled users to distribute their focus and energy to other important aspects of life. However, the benefits of greater agency come with a risk. As users relinquish direct control over their diabetes management, they necessarily become dependent on it. This can render them more likely to become de-skilled, and as a result, more vulnerable to system malfunctions.[152] This issue is discussed in greater detail later in this section.

Control

Adopting a HCL system for diabetes management requires the person living with diabetes to relinquish some control over their diabetes management to the extent that the device takes over particular tasks (e.g., glucose monitoring, insulin provision, calculating insulin doses).[152] In order to be able to relinquish this control, a person using the technology must be able to develop a degree of trust that the device will operate effectively (as discussed later). That, said, there appears to be a paradox of control relating to HCL systems: research participants who used an HCL system reported temporarily feeling a loss of control when they were required to return to their previous modalities of diabetes management, which did not manage glucose as precisely.[145] In other words, it may be said that users of HCL systems must relinquish control over their diabetes management in order to gain control over their diabetes.

Trust

Trust, in the context of medical devices, tends to describe the belief that a device is designed and manufactured appropriately to produce the outcomes it purports to achieve, and that a particular device is functioning appropriately. When an individual starts to use a medical device that takes over some function that they were previously responsible for completing, it is necessary for them to develop trust that the device will fulfill its intended function. Trust is ethically relevant to HTAs because there is an ethical imperative for decision-makers to examine the trustworthiness of devices that are being considered for approval or public funding. Furthermore, trust is necessary for the uptake and continued use of the device to achieve the expected benefits. See the Perspectives and Experiences Review section for further discussion of the role of trust in HCL use.

Research into the acceptability and effects of HCL systems has shown that many users are generally able to develop trust for the system over time.[27,158,167] When people start using HCL systems, they tend to play close attention to their operations to ensure they are working appropriately.[144,167] As they become more comfortable with the systems' operations and witness good performance and reliability, their trust in the systems tends to grow.[144,152]

Not all HCL users have been able to develop complete trust in the system.[27] Lack of trust in HCL systems has led some to override their systems, which can affect the capacity of the HCL system to manage glucose levels appropriately.[157] A lack of trust is likely to present a barrier to a person's uptake and/or ongoing use of an HCL systems [162] When considering which populations may be able to benefit from HCL systems, it is also important to recognize that different cultural, demographic, and ethnic groups may develop trust in different ways. Some may have difficulty developing trust in medical devices, particularly if relations between that group and health systems have given the group reasons to question the motives and intentions of the health system.

Dependence and Vulnerability

Several studies noted the potential for people with type 1 diabetes (or their caregivers) who start to use more automated systems like HCL systems to lose some of their skills and knowledge related to managing their diabetes using less technical modalities.[152] These consequences were highlighted in a study of parents of children living with type 1 diabetes that examined parents' experiences of having to return the HCL devices and resume using their previous modalities of treatment. Parents reported having to relearn how to use their previous modalities.[145] This theme is also explored in the Perspectives and Experiences Review section.

Concerns have also been noted that the HCL system enables users to make choices that are less optimal for effective diabetes management, such as eating high-fat, energy-dense foods,[28] skipping insulin boluses before snacking, and doing less blood glucose testing.[145] Other HCL users noted more difficult responses to a dependency on technology, reporting increased feelings of powerlessness, fear (of hypo- and hyperglycemia), and distress.[166]

Some study participants who transitioned from an HCL system back to other modalities noted frustration because even with their best efforts, they were unable to attain the glycemic control that was possible with the HCL system [145] This transition was difficult for parents of people with type 1 diabetes: they noted a decrease in quality of life because they experienced the return of family conflict, worry, strain, and sleepless nights that had characterized their day-to-day lives prior to using the HCL system [145] These consequences of HCL use highlight the need for individuals using HCL systems to be prepared to shift to less technical modalities should their access to HCL systems become limited (e.g., because of loss of insurance coverage or technical malfunction).

The fact that HCL systems may require users to be more vulnerable to its functions or may result in users becoming less skilled at managing their diabetes without the device does not, in and of itself, present an ethical concern. The ethical significance of these dimensions is most salient to the processes by which people choose to start using HCL systems and the development of support and education for ongoing HCL users to ensure they do not suffer significant harms that could result if they lose access to HCL and are required to manage their diabetes with different methods.

Surveillance

One of the features of some commercially available HCL systems is the capacity to share health data with health care professionals and informal caregivers (e.g., family). The literature reviewed for this section did not indicate the extent to which these features are being used in commercial models. Nevertheless, in cases where patient data are being shared (either passively or actively) with others, several concerns in the literature were raised. The basic concern is that such data-sharing would lead to people with type 1 diabetes feeling as though they are under surveillance, especially if this data sharing was occurring without their consent.[152] There is a related concern that any experimentation a person with type 1 diabetes might wish to engage in — especially at the early stages of their HCL use — would be interpreted by the health care provider as diabetes mismanagement.[152] In cases where users are able to decide whether to share their data with others, concerns about surveillance may be lessened.

Some have proposed that for parents or guardians, the capacity to monitor a child with type 1 diabetes remotely would likely improve their satisfaction.[169] Other researchers have suggested that children who are being monitored by parents or guardians may perceive this

monitoring as interference and contributing to unwanted attention to their diabetes.[152,156,162] One study found that parents who were able to monitor their children's glucose levels remotely felt they were able to offer them greater freedoms, allowing them to sleep over at friends' houses and participate in school trips without being chaperoned by their parents.[144,145]

Overall, the evidence relating to autonomy, agency, and trust, and the other themes highlighted here, is mixed. Individual autonomy within the context of the choice about using HCL systems could be promoted if accurate and balanced information about the device and other appropriate options is made available. The HCL system appears to be beneficial to the extent that it increases individual agency. However, this increase in agency comes with increased dependency and vulnerability that can be inherently distressing to some users, and may cause more widespread risks to users with regard to de-skilling and the development of behaviours that are not optimal for diabetes management. This increase in agency appears to require a relinquishing of control (in the form of engaging in more active or manual management). However, some users noted that the HCL system enabled them to feel more in control of their condition, even if they had less control over its day-to-day management. Trusting the system is necessary to allow it to function optimally and to enable longer-term use, so there is an imperative that the system be trustworthy, and that the user develop the skills and knowledge to be able to trust their own management of the device. Establishing these types of trust requires appropriate regulation and ongoing education and support.

From an ethics perspective, it is important that decision-making processes relating to the initiation and ongoing use of HCL ensure that people living with type 1 diabetes have access to accurate and unbiased information about the device itself and about its potential non-clinical impacts (such as loss of control, dependency, vulnerability, and de-skilling) on their relationship with their condition and its management. Caregivers of people living with type 1 diabetes need to be aware of the potential harms and benefits of remote monitoring, including the ways in which surveillance may be intrusive and limit a person's autonomy and agency. Caregivers should be encouraged to discuss how data may be monitored with the person living with type 1 diabetes in a way that is appropriate to that person's cognitive status.

Personal Identity and Relationships

Living with diabetes can have an impact on a person's self-perception and relationships. Individuals living with type 1 diabetes report feelings of stigma and feeling that they are to blame for their illness. Even with very diligent management, glucose levels can be out of range, leading individuals to feel like they have failed. These self-perceptions and the perceptions of others can be burdensome. HCL systems have been shown to have both positive and negative impacts on senses of identity and relationships for people living with type 1 diabetes.

People living with type 1 diabetes must grapple with their own identity as a person living with a chronic condition. Several studies cited in this review have shown that many people trying HCL systems have found that an HCL device reduces their burden of diabetes management, freeing them to focus on other aspects of their lives. Studies have explicitly found that HCL-enabled participants feel more "normal" rather than "diabetic," or that the HCL systems enabled them to feel like "a better version of myself," potentially leading to an improved sense of self overall. One study found that teenagers liked the HCL system because it acted as a safety net, allowing the teen to engage in behaviours that permitted

them to feel more normal among their peers without having to worry about the consequences. Other commentators have suggested that technologies like HCL systems may result in a hyper-focus on a person's diabetes, and that the data provided by these systems could reduce a person to "nothing more than a glycemic control number and a signal of brokenness," such that their identity becomes all about diabetes rather than about themselves as a person first. Stakeholder feedback provided on a draft version of this report suggested that if incidences of hyper-focus occur, they are likely to be manageable and temporary.

Similar to other more advanced technologies to treat type 1 diabetes, HCL systems render a person's diabetes visible to others, either incidentally (by others noticing the various external components that a person using an HCL device must wear) or intentionally (by others, such as parents or other loved ones, having access to the person's data through remote monitoring systems). The visibility of the technology to others could lead to unwanted attention and questions, which may be especially undesirable to individuals who have experienced judgment or bullying in relation to their diabetes. In a study in which people with type 1 diabetes anticipated how they would react to using an HCL system, a number of participants expressed concern that the visibility of the system would lead to negative impacts on their self-image.

Parents looking after children with type 1 diabetes felt that the HCL systems reduced their overall diabetes-related workload, reduced conflict and strain within the family, and enabled the family as a whole to focus on other matters. Others have proposed that the visibility of a person's diabetes through data shared by remote monitoring could add strain to relationships by, again, creating a focus on the person's diabetes rather than on their whole selves.

Overall, the results of the studies included in this Ethics Review have suggested that HCL systems could have either positive or negative impacts, or both, on a person's sense of identity and relationships. If these effects are especially negative, they may affect whether a person with diabetes (or their caregiver) decides to continue to use the HCL system. Ultimately, health care providers and the health systems within which they are working have a duty to ensure that people living with type 1 diabetes are aware of the possible personal and relational impacts that HCL systems can have, and that further support in managing these impacts is available.

Patient Selection

An HCL system is one of many methods to treat type 1 diabetes. While the clinical evidence for the HCL system (in terms of time in range) is promising (see the Clinical Review section for more detail), it may not be an appropriate system for all persons living with type 1 diabetes. For the clinical benefits of HCL system to be realized for a person living with diabetes, the person must become comfortable with the technology, be able to perform the technical and diabetes tasks that are still required by the machine, and, overall, find that the system offers them benefit above and beyond other methods for diabetes management. Within relationships between patients and health care providers, carefully matching a person to a technology is necessary to optimize the chances that the person living with type 1 diabetes will find a technology that is effective and works well for them. This section notes issues related to appropriate patient selection for use of HCL systems.

One of the key factors identified in the literature for individual success with an HCL system is whether a person with type 1 diabetes has realistic expectations of what an HCL system can

do.[152,161,168] The HCL system is not a fully closed system. This means that, at least within its currently available modalities, individuals using the HCL system still must check blood sugar, count carbohydrates, and administer boluses of insulin for meals.[156,158] Further, there is a lag time between when the system detects glucose levels out of range and when these can be corrected. Studies have shown that this has been frustrating for some research participants because the HCL system did not respond as quickly as they would have liked. Individuals who expect the HCL to be completely automated and offer quick responses are more likely to become frustrated with it, leading to discontinued use.[161,163,168] One study found that adolescents, in particular, felt that terms like “closed loop” and “artificial pancreas” were misleading, and resulted in new users finding that the HCL system was not as hands-off as initially expected.[158] Working to manage users’ expectations from the beginning will be important to maximize the chances of effective long-term use required; this is necessary for users to be able to realize the potential clinical benefits of an HCL system.[169] The Perspectives and Experiences Review section offers a discussion of how HCL systems may be seen most appropriately as collaborating with persons living with type 1 diabetes rather than providing care.

In addition to conversations to manage a potential HCL user’s expectations, it is important for care providers to explore the values and needs of the person with type 1 diabetes in relation to their diabetes management.[152,172] As outlined in the previous section, people with diabetes can have very individualized responses to the experience of using an HCL device (e.g., some find alarms annoying and disruptive, while others see them as helpful and reassuring); therefore, frank and open conversations between people with type 1 diabetes and their care providers are necessary to ensure that an HCL is the best option for them. Not only is this inclusion and respect for patient perspectives important from an ethics perspective, it optimizes the chances that people with type 1 diabetes who do choose to try HCLs systems will be more likely to adapt to and use them over the longer term.

Persons living with type 1 diabetes who have particular clinical needs, traits, attitudes, and social environments may find more benefit with HCL systems than others.[152] It has been challenging to determine specifically what these optimal factors of HCL systems may be.[156] Furthermore, these factors can evolve over time, making it difficult to draw a static conclusion about whether a particular patient is suited to an HCL system.[152]

Clinicians are often the gatekeepers for their patients’ access to health technologies. A clinician’s beliefs about what makes a patient a good candidate for a particular technology can significantly impact whether that patient will ultimately get a chance to try it. Inaccurate or unjustified beliefs about what is required to be a good candidate for a technology may lead to the inappropriate exclusion of some groups of people with diabetes.[156] A major study of insulin pumps (known as the REPOSE trial) demonstrated how staff assumptions about what personal and psychological attributes initially thought to be necessary for success with the technology proved to be inaccurate: patients who were originally thought to be poor candidates, but obtained access to the devices through the trial, had good outcomes.[156,161,162]

A recent study of HCL access for people with diabetes and their families found similar results.[26] Health care providers in this study disclosed that they had assumed that young people in close-knit families, where parents lived together and relationships were strong, would be the best candidates for the HCL system. They also assumed that people with more education and technical know-how would be better suited to the technology than those who lacked these attributes.[26] Within the context of the trial, individuals were granted access to

HCL technology through the trial's inclusion and exclusion criteria and a randomization process rather than through a health care provider's clinical judgment informed by their (often limited) knowledge of the patient.[26] As a result, individuals who may not normally have been granted access were given a chance to use the HCL system. Health care providers were surprised to find that technical know-how did not always correlate with improved outcomes. Tech-savvy participants tended to interact too much with the system, interfering with its capacity to produce optimal glucose control. Participants and families with less technical know-how were more inclined to allow the system to operate without interference, leading to better outcomes.[26] This study also revealed that health care providers are not always able to accurately gauge family dynamics and whether a young person will get the support they need for optimal use of an HCL system. The health care providers involved in this study concluded that it is not possible to use social factors or perceived aptitudes to accurately predict how patients will do on HCL systems. They concluded that all people with diabetes who are interested in trying the technology should be supported to do so, and that they should be able to trial the technology through a probationary period during which they could demonstrate their ability to understand and manage the key tasks necessary for safe use.[26]

The role of health care teams in suggesting HCL use or supporting patient-initiated requests to try HCL systems has important ethical dimensions. Providers acting on inaccurate assumptions about what factors are necessary for reasonable success with HCL systems interfere with individual patient autonomy by placing unjustified limitations on patient choice. This practice also interferes with duties to promote benefits over harms by unjustifiably limiting access to a potentially beneficial health technology. Further, this approach risks creating or reinforcing inequitable access to technology, whereby those who are perceived to be less capable or lacking the necessary social environment are denied access to a technology that could meaningfully reduce their burden of diabetes care and improve their health outcomes. This result plays into one of the widely shared concerns about the potential of diabetes technologies — that they only serve to improve outcomes for those who already have reasonably good diabetes management — and does very little for those who still struggle to stabilize their diabetes.

The literature cited here does not suggest that there are no criteria to identify good HCL candidates. Rather, the evidence suggests that some of the criteria thought to be relevant are not. To avoid the ethical pitfalls associated with determining HCL access based on faulty criteria, health care providers might consider implementing trials or probationary periods of use with their patients to allow patients to demonstrate their appropriateness for the technology, rather than allowing potentially inaccurate beliefs about the person with type 1 diabetes to determine access.

Patient Coaching and Support

In addition to appropriate patient selection, the literature has shown that accessible, unbiased, ongoing education and support are necessary to enable people to adapt to[166] and continue to use HCL system [161,174] Data on the use of CGMs has shown that 41% of users discontinue use by year 1.[156] While CGMs and HCL systems are distinct technologies, it is reasonable to be aware of the potential for a similar drop-off in the use of HCL systems. While it is not clear what caused the drop-off in CGM use, researchers familiar with this topic suggest that it is in part related to a lack of access to effective and ongoing supports for users.[156] Consistent and safe use of the HCL system is necessary for users to be able to gain the maximum benefit that the technology offers.[152,167] Ongoing education and support not only optimize the chances that people with type 1 diabetes may realize benefits from the

technology, it also supports people in continuing to manage their diabetes autonomously.[152,174]

Part of ongoing support for people using HCL systems could include access to experts to assist with troubleshooting,[152] sessions to reinforce the technical and behavioural tasks required by the HCL system, [26] courses to help people using HCL systems maintain basic diabetes management skills,[145] education about lifestyle choices and habits that can also assist with diabetes management, supports to enable the person with diabetes to manage their expectations of the technology, clinical support to respond to biological changes that may be impacting a person's diabetes (e.g., adolescence),[175] and behavioural interventions to enable HCL users to cope with ongoing stress associated with diabetes management.[157] Each of these interventions may help people continue to use their HCL systems, and adopt related behaviours to optimize their health. Such ongoing supports for the person living with type 1 diabetes (and their family, when appropriate) are most effective within a trusting relationship with their care team.[172]

To provide HCL technologies to people without offering such concurrent support risks people with diabetes being left to manage technology use on their own, which could present risks of harm to users and ultimately creates the risk that the person will eventually give up on the technology, eliminating the opportunity to experience its potential benefits.

Given these ongoing and diverse needs, many commentators have noted that diabetes care teams will play a crucial role in meeting the needs of HCL users and supporting their long-term use of the technology without technology burnout.[158] Such care teams will need to have a range of skills beyond a clinical and physiological understanding of diabetes; they will also need to be able to understand the technologies being used by their patients and understand and interpret the data these technologies generate. Some commentators have expressed concern that not all diabetes care teams are capable of fulfilling these technology-generated roles.[162] Some commentators in the literature have noted that HCL technologies risk transforming care providers into machine operators or technicians, and that more time during clinic visits will be taken up by troubleshooting and technical matters, taking away from discussions about other aspects of diabetes care.[152] However, stakeholder feedback received on a draft version of this report suggests that most of the device troubleshooting occurs directly with manufacturers rather than with health care teams. Thus, it is less likely that clinic time will be overwhelmed with technical matters. The Stakeholder Consultation section of this HTA noted that clinical teams did find it time- and resource-intensive to support patients starting on HCL systems, which suggests that HCLs pose at least some increased workload for care teams. Reasonable reimbursement plans for the time spent on these types of supports may increase the chances that they can be offered by diabetes care teams.[162]

The role of accessible education and support for people using HCL systems is ethically relevant, given that it appears to be an important factor enabling individuals to play an active role in their diabetes management (thus, promoting autonomy) and increases the potential benefit of the technology. If education and support for HCL users is available inconsistently (e.g., only in urban areas or only to people with flexible schedules), or in a way that limits the devices' accessibility to particular demographics, then it will result in an unequal distribution of opportunities, which could contribute to health inequities. Education modalities that are flexible and accessible to a range of population groups (e.g., age levels, racial-cultural groups) will be important to avoid inequity.

Confidentiality and Safety

HCL systems involve data-sharing between components of the device and possibly with other people (health care providers or caregivers).[152,176] There are concerns about whether and how HCL systems can maintain patient confidentiality and whether they are vulnerable to malicious hacking that could have consequences for users.[22,152,177]

With devices like the HCL system, where devices communicate in a network and can have direct and regular impacts on the person with diabetes (through adjustments in insulin administration), network security is critical.[176,178] Wireless or cloud-based systems can be hacked to control devices or the data they produce. Ransomware can also be released within systems, rendering a device or its data unusable until a ransom has been paid.[178] Wireless attacks can be passive (e.g., eavesdropping, then using the data for nefarious activities) or active (e.g., where the attack results in the device being taken over by an external source).[176] Given these potential threats, medical device security systems are required to minimize hacking incidents and mitigate harms if they do occur.[176] Security features should be developed with accessible design and should not result in the users themselves being blocked from the device. For example, stakeholder feedback provided on a draft version of this report noted that this might occur if a person with sight loss was required to respond to a series of visual clues to unlock their system. It is beyond the scope of this Ethics Review to assess the data-security systems in place in each HCL device included in this HTA. This issue is raised here to point to potential risks for HCL users should manufacturers fail to incorporate sufficient cyber-security measures, or should these security measures not work.

Remote monitoring, where a person's data are automatically shared and reviewed by another party (either by a caregiver, expert, or through an automated system) is not available through all commercially available HCL systems; [168] however, it may become more widely integrated into future systems. For example, the recently released MiniMed 770 advertises that parents can monitor their children's data through a smartphone app. Remote monitoring offers the promise of added safety (where those monitoring the data can become aware and respond if a person is experiencing hypo- or hyperglycemia) and may eliminate the need for people who use HCL systems to actively upload their data for their health care provider's review. This latter point is especially beneficial, given that at least one commentator has noted that a significant proportion of diabetes data captured by people with diabetes is never transferred to health care providers for review.[179] As discussed in the Harms and Benefits section of this review, remote monitoring may also enable younger users to become more independent of their parents, if parents can keep track of children's blood sugars at a distance.[152] The possible downsides of remote monitoring are discussed in the previous section on surveillance. They primarily have to do with monitored individuals feeling like they are under surveillance and less free to act. Remote monitoring also brings forward concerns about privacy and confidentiality, as mentioned earlier, because it necessarily involves the transfer of one person's health information to another.

Threats to individual safety as a result of device hacking are a significant ethical concern. Device manufacturers and regulators have a duty to ensure that devices have sufficient security in place to avoid this risk. This review did not examine the extent to which current commercially manufactured HCL systems acknowledge and respond to this risk. Therefore, further comment on the relevance of this concern to HCL systems is not possible.

The duty to preserve patient confidentiality is central to western bioethics. It is connected to principles of autonomy, recognizing that individuals should be able to control who has access to their personal information and how it is used. HCLs present the possibility of accidental violations of confidentiality (through hacking) and intentional releases of health information (which may or may not be breaches of confidentiality). If the person who owns the data (in this case, the person with diabetes) clearly understands how their data may be shared and used, and consents to this sharing, then the arrangement is unproblematic. If people's data are being shared without their awareness or consent, then it is much more ethically problematic. There may be a grey zone in the case of teenagers, who may be monitored by their parents and may not have a full say in whether or how their data are shared, but are developing the capacity to be more centrally involved in these issues. Overall, these potential risks to confidentiality and safety need to be considered within the overall calculation of potential benefit offered by HCL systems.[152]

Access and Coverage

The accessibility of equipment and devices necessary to treat diabetes varies across Canada. Accessibility can be determined by the coverage provided by public insurance schemes and by the formal and informal conditions that need to be in place for individuals to be able to use particular treatment modalities (e.g., whether people meet clinical criteria, whether they have the capacities to interact with the device, and whether they live in the type of social environment necessary for particular modalities). Implementing criteria for access that are not well-justified risks perpetuating inequities that already exist in the access to and capacity to benefit from diabetes technologies like HCL systems.[152,161]

The factors that are likely necessary for a person to successfully use an HCL system include having the desire to use the device, having sufficient access to the social spaces necessary to use the technology (e.g., to complete diabetes-related tasks and systems maintenance, access to power to recharge devices), and having the cognitive, physical, and technical capacity to interact with, understand, and effectively manage the device. The discussion in the Patient Selection section highlighted how health care providers may sometimes make inaccurate judgments about whether their patients meet some of these criteria. This suggests that relying on the judgment of individuals to determine access according to these criteria at least risks unjustifiably limiting access for people who may have been able to benefit from the device. Another concern relates to the accessibility of HCL systems for individuals with disabilities. For example, individuals with sight loss (a potential consequence of type 1 diabetes) may be less likely to be able to use the HCL system unless it offers alternatives to the visual display, such as tactile or audio feedback. Further, stakeholder feedback received on a draft version of this report suggested that patient education and support resources should account for varying types of abilities (e.g., be available in a variety of formats, such as hard copy, large print, digital, audio, and so on) to ensure they are as accessible as possible to all device users. Similarly, data generated by the device should be accessible to users with a range of abilities (including those with sight loss) so that all users can receive and monitor their own health information, making them more able to make decisions about their health and whether to share their data with others.

There is a second level of access to consider, related to the question of public coverage of HCL devices. Given the anticipated costs of HCL systems, and the fact that HCL systems are likely to be of greatest benefit to only a subset of people living with type 1 diabetes, it is reasonable that additional criteria will be set to determine access to publicly funded HCLs. Eligibility for publicly funded diabetes management devices sometimes requires that individuals demonstrate good knowledge of type 1 diabetes management, consistently use

the therapy, and attend regularly scheduled follow-up appointments. These criteria make good sense on the surface, and appear to align with duties to ensure that public funding is invested in ways that yield benefits. However, some commentators have expressed concerns that if such criteria are applied too rigorously, they may rule out access to HCL systems for people who may also benefit.[152] For example, someone may not make consistent use of their current diabetes therapies because aspects of them are too burdensome. The less burdensome nature of an HCL system may actually improve their ability to manage their condition, enabling them to benefit.

Participants in a study examining health care providers' perceptions of HCL systems suggested that particular age groups (e.g., teenagers or toddlers) be given priority access to publicly funded HCL systems, given that it is during these periods of life that consistent diabetes management can be most difficult.[26] These participants had mixed views about the extent to which a person's track record with diabetes management should matter. Some suggested that people who have diabetes that is difficult to manage should be given priority. Others felt that those who were successfully managing their diabetes should not be excluded, given that this would, in effect, punish them for doing a good job.[26] Here, a distinction between efforts and outcome may be helpful. People who are not able to achieve stable glycemic control despite consistent effort may be good candidates for HCL use, whereas those who have poor control due to lack of effort may not be ideal candidates.

The current coverage modalities for equipment and devices to manage diabetes favour candidates — often in higher socio-economic classes — who have access to private health insurance plans, which are often more comprehensive than public insurance. Reduced access to the ongoing health care support necessary for effective HCL use has also been identified as a barrier to access for individuals in lower socio-economic classes.[156] Failing to cover diabetes technologies like HCL systems within public programs could reinforce inequities in access to diabetes management supplies. However, if technologies like HCL systems continue to primarily benefit people with diabetes who already have good management and access to care, then the converse argument could be made that using funds that might be used for expanding the public coverage of more basic diabetes management supplies could result in a more equitable use of public funds. It is not possible to adjudicate between these 2 arguments in this document. However these decisions are made, funders and prescribers have a duty to consider health inequities when prescribing or considering public funding for diabetes technologies to ensure all people with diabetes have equal opportunities to benefit.[162] A related equity concern arises with the variation in public funding of supplies and devices to manage type 1 diabetes among the provinces and territories. The BIA in this HTA summarizes the current coverage in each province and territory, showing the significantly different levels of coverage within public programs. This variation is a type of geographic inequity, and is inconsistent with the portability criterion outlined in the *Canada Health Act*. Public reimbursement programs for HCL systems should take into account this inconsistent landscape and consider approaches to HCL funding that could be adopted more consistently across Canada.

However, if it is ultimately decided to allocate access to HCL systems (if, indeed, the decision to publicly fund HCL systems is made), a clear and values-based allocation process will be necessary. If pursued, macro-allocation — allocation to populations — should be pursued with clear intentions in mind. For instance, priority could be given to children and youth on the grounds that their diabetes can be more difficult to control (both for behavioural and biological reasons, depending on the age), they may have less access to private coverage, they are more reliant on others for management of their condition, and

they face the greatest potential of harms from diabetes-related complications if it is not well-managed. Consistency would require that other groups that meet these criteria should be given similar priority. In the case of micro-allocation — allocation among individuals — the evidence presented about health care provider fallibility in anticipating the success that individuals may have with HCL systems reinforces the importance of ensuring individuals are given fair consideration to be candidates for HCL coverage, and that whatever criteria are used stem from clinical need, and, if necessary, demonstrated (rather than speculated) proficiency with the device. In terms of the substantive values that could guide allocation, different values could have different implications. If allocations are made with the intention to achieve maximal health benefits, then allocation that gives access to HCL systems to individuals who have the greatest capacity to benefit may entail giving access to HCL systems to people whose diabetes is not well-managed, given that they presumably have the greatest room for improvement. If responsible stewardship of health care resources is a guiding value, ensuring the devices are funded for individuals who are likely to be able to use them effectively over the longer term would be justified. Using a person's track record of good diabetes management may be a reasonable indication of their capacity to successfully use an HCL system; however, allowing only such individuals to access HCL systems could result in limiting access to others who may also experience benefits, and risks treading into the territory of resource allocation based on "social worth." Even more concerning would be allocation decisions that intend to "reward good behaviour" which is paternalistic, disrespectful, and vulnerable to bias and discrimination.

Summary of Results

What Are the Major Ethical Issues Raised by HCL Systems?

The evidence presented in this HTA suggests that HCL systems offer short-term clinical benefits in the form of increased glucose-levels time in range compared with open-loop SAPs. There is also evidence that HCL systems could offer short-term, non-clinical benefits for some people living with diabetes, depending on their expectations, skills, and access to ongoing support. To ethically justify a decision to improve access to or fund a medical device, there must be sufficient evidence that the device delivers a balance of benefits over harms. This includes clinical and non-clinical benefits for users of the device and non-clinical effects for others. At this time, there is insufficient evidence to determine conclusively whether HCL systems offer long-term benefits beyond technology that is already available. The evidence discussed here suggests that for some users, these systems offer clinical benefits and several non-clinical benefits in the short term without significant risks of harm.

From an autonomy perspective, HCL systems appear to have the potential to enhance individual autonomy in the day-to-day management of diabetes; however, due to a lack of accurate and unbiased information about the devices, some questions remain about whether individuals and their care providers are able to make meaningfully autonomous decisions to start using them. The devices also appear to offer the opportunity to increase a person's agency (their capacity to act) by reducing the overall burden of diabetes management; however, this increase in agency only occurs if users are able to relinquish some direct control over their diabetes management and build trust with the device, something that some users have struggled with. The potentially negative consequences of this decreased involvement in day-to-day management are that users may become less skilled at basic diabetes management and may develop lifestyle choices that are not optimal for good diabetes-related health. The potential of some HCL devices to enable people with diabetes to be monitored by others can offer benefits by providing a safety net when a

person is at risk of experiencing hypo- or hyperglycemia. This capacity to monitor remotely may also contribute to the independence of younger people with diabetes if it increases their comfort (and their caregivers' comfort) that they will be safe even when not near the caregiver. Conversely, a potential harm of being monitored by others include negative feelings associated with being under surveillance and feeling that one's autonomy is restricted as a result.

Overall, the results of the studies included in this Ethics Review have suggested that HCL systems could have positive or negative impacts, or both, on a person's sense of identity and relationships. Some individuals reported that HCLs allowed them to feel more "normal" or a "better version of themselves," whereas others felt the system reduced their identity to their diabetes. The visibility of the HCL device has been a significant factor noted by some users, and suggests that it may play a role in uptake or continued use of the device. The HCL device appeared to have the potential to both improve and strain relationships between the person living with diabetes and others. If these effects on personal identity and relationships are especially negative, they may affect whether a person with diabetes (or their caregiver) decides to continue to use the HCL system, in turn affecting whether they ultimately benefit from it.

Appropriate patient selection for use of the HCL system has important ethical dimensions, given that this process can affect the extent to which HCL offers benefits (to individuals and to populations) and can have important equity implications for who is ultimately granted access to and is able to benefit from the device. Evidence suggests that health care providers are not able to accurately assess the psychosocial factors that relate to successful HCL use — so if these are relied upon, it may unjustifiably limit choice, fail to promote benefits for patients who might do well on HCL, and may reinforce inequity (e.g., by limiting access to the technology in cases where people are older, are perceived to be less technologically inclined, or are in more precarious social situations). Having reasonable expectations of the device has also been an important part of selecting the patients for HCL who are likely to be able to adapt to the HCL system and use it over the longer term. Failing to manage expectations at the outset could lead to unsafe or less consistent use of the HCL device.

The evidence included in this review suggests there is a strong connection between successful continued use of HCL systema and access to ongoing support and education. Availability of this kind of support is ethically relevant, because without it, the benefits that may be offered by HCL may be lessened. Also, given its impact on device use, the distribution of this kind of support has ethical implications. If this comprehensive support is not widely available to all people with diabetes who wish to try the device — for example, if it is only available in urban areas or in clinics accessible to those with higher socio-economic status — then this can result in an unfair distribution of burdens and benefits.

Concerns about confidentiality and the potential for harm to users from hacking has been widely identified in the HCL literature. HCL systems present the possibility of accidental violations of confidentiality (through hacking) and intentional releases of health information (which may or may not be breaches of confidentiality). If the person who owns the data (in this case, the person with diabetes) clearly understands how their data may be shared and used, and consents to this sharing, then the arrangement is unproblematic. If people's data are being shared without their awareness or consent, then it is much more ethically concerning. There may be a grey zone in the case of teenagers, who may be monitored by their parents and may not have a full say in whether or how their data are shared, but are

developing the capacity to be more centrally involved in these issues. It not clear whether the concerns about user safety related to hacking present a realistic risk; however, it is important that steps are taken to minimize this risk in the development of the device and to inform potential users of this possibility.

Access to diabetes supplies and devices across Canada is often determined by what is covered through public funds. Decisions about how to determine access (through program criteria or funding allocation) are ethically relevant, given that they often have impacts on equity and the distribution of burdens and benefits among people living with diabetes and their families. Currently, private health insurance programs (which are generally available to those with higher socio-economic status) tend to have more comprehensive coverage of diabetes supplies than that offered by public health insurance. Choosing not to cover diabetes technologies like HCL systems within public programs could reinforce inequities in access to diabetes management supplies. That said, if technologies like HCL continue to primarily benefit people with diabetes who already have good management and access to care, then the converse argument could be made that expanding the coverage of more basic diabetes management supplies could result in a more equitable use of public funds. If public funds are allocated to cover HCL devices, it is important that any program criteria set to determine who may be eligible for accessing the device is evidence -based and do not exacerbate existing health care inequities.

How Might These Issues Be Addressed?

The lack of clear connection between immediate clinical benefits (e.g., A1C levels and glucose time in range) and longer-term outcomes (e.g., diabetes-related complications and hospital admissions) makes it difficult to conclude whether funding HCL systems aligns with overall duties to promote clinical benefit at a population level. Further research into the longer-term effects of these types of technologies is necessary to inform this conclusion.

Many of the immediate and somewhat challenging effects of the HCL system noted in the literature that could lead to decreased use or, ultimately, the choice not to continue using the device (e.g., unmet expectations, visibility of the system, technical demands, the need to relinquish control and build trust, de-skilling and dependency risks, the potential impacts on relationships, the potential for remote monitoring and surveillance) could be addressed by a robust decision-making process between a person living with type 1 diabetes and their care team to ensure that the person is prepared for all of the potential consequences of using an HCL system, not just the clinical dimensions. It is important that unbiased and accurate information about the HCL devices under consideration be available to support this process.

Caregivers of people living with type 1 diabetes need to be aware of the potential impacts of HCL use as well. They should also be informed of the possible harms and benefits offered by remote monitoring, including the ways in which surveillance may intrude on and limit a person's autonomy and agency. Caregivers should be encouraged to talk about data monitoring with people living with type 1 diabetes in a way that is appropriate their cognitive status.

Diabetes care teams determining whether to suggest using HCL systems or how to respond to an individual's request to try one should take care not to use non-clinical criteria which may inaccurately predict a person's potential to benefit from HCL. As recommended in the literature, diabetes clinicians should consider enabling people living with type 1 diabetes to use an HCL system on a trial basis or for a probationary period to allow everyone involved (including the person with diabetes) to determine whether the device is appropriate.

In the literature, significant weight is given to the need for accessible and ongoing education and support for those who use HCL systems to enable them to manage their condition effectively over a longer period of time. If a decision is made to fund HCL systems, policy-makers may consider how to encourage the implementation or maintenance of education programs that are comprehensive and accessible to all those who use HCL systems and/or their caregivers. Such education could include intensive support in the earlier phases of HCL use to assist with troubleshooting and adapting to the device. As people use the device over the longer term, education to ensure users can cope if the device fails and to encourage health-promoting lifestyle choices may be useful.

Confidentiality and data-security concerns should be discussed with everyone considering using an HCL system. Users should be aware of whether their data are being shared and have a say in who is able to access the data and how the information should be used. This conversation should be extended to youth who are developing the capacity to understand these issues. Overall, these potential risks to confidentiality and safety need to be considered in the overall calculation of potential benefit offered by HCL systems.[152]

Stakeholder Consultations

Methods

To gain a better understanding of the context and relevant issues involved in implementing HCL systems in Canada, we consulted with stakeholders representing various levels of decision-making and health care delivery in type 1 diabetes care. Clinicians involved with specialist diabetes care (i.e., endocrinologists, registered nurses involved with diabetes education or insulin-pump training, and clinical program administrators) — and those involved in developing policy for and administering public programs related to insulin pumps and other diabetes supplies — were identified through a call to CADTH liaison officers across the country and invited to participate. Individuals from 7 provinces agreed to participate in these consultations. Consultations included discussions of issues relating to personal experience in caring for people who use HCL systems, current coverage of insulin pumps (including HCLs) and diabetes supplies, and anticipated challenges and opportunities if HCL adoption becomes more widespread. The consultations were used as a tool to reflect upon on connections across the HTA. They also provided insights into how the HTA findings could be taken up across jurisdictions and the kinds of questions stakeholders may be navigating when they make decisions around how HCL systems may fit within their current models of care for people living with type 1 diabetes.

What We Heard

Clinicians

Issues that emerged from discussions with clinical stakeholders included: promising results for current HCL users, access to data, HCL equity of access to HCLs and CGMs, health system capacity, and training and education. Some mentioned that HCL therapy is not a “silver bullet.”

Promising Results for Current Users of HCLs

Clinicians noted that although there is still limited uptake of HCL systems, patients who have already switched to an HCL have seen short term clinical and non-clinical benefits. Clinicians spoke of improvements in time in range, A1C values, and in frequency of hypoglycemic events. In terms of non-clinical benefits, clinicians spoke about improvements in quality of life and peace of mind for HCL users. Improved sleep due to reduced worry about overnight glycemic lows was identified as a main benefit of HCL therapy. Clinicians also noted that parents of children who use HCL systems worried less about their children’s glycemic control and the risks of hypoglycemic and hyperglycemic events.

Clinicians consulted did identify technical shortcomings and challenges of existing HCL systems, such as failed sensors and users being “kicked out” of auto mode. Still, despite acknowledging these issues, clinicians were universally positive about the potential of HCL therapy and the effects they had seen to date. Clinicians were also optimistic about the future of HCL therapy, and they expect this technology to be improved, refined, and made more user-friendly in devices that will come to market in the future.

Access to Data

Access to continuous, real-time data provided by HCL systems was seen as an improvement in a variety of ways. First, these data were seen to give users peace of mind

and enhance their knowledge of how their lifestyle choices (e.g., diet, physical activity) impacted their blood glucose levels. Second, these data gave clinicians a fuller picture of a user's blood glucose range and what is happening overnight, which they would not previously have had knowledge of. Data were seen as an important teaching tool for educating users of HCLs and helping them make refinements to their diabetes management and lifestyle choices.

Clinicians noted that the volume of data produced by HCL systems may be overwhelming for some users or clinicians, and that there was a learning curve in interpreting reports and graphs. Clinicians also acknowledged the differences in reports generated by various HCL systems or CGMs, noting that some seemed more user-friendly and intuitive than others. These differences were seen as part of the reason why some users have a strong preference for specific devices (HCL systems or standalone CGMs).

HCL Therapy Is Not a "Silver Bullet"

Despite universally positive views of the potential of HCL systems to improve clinical and quality-of-life outcomes, clinicians acknowledged that HCL systems are not a "silver bullet" and do not function as an artificial pancreas. HCL systems were described as still requiring a significant amount of work on the part of users, with considerable focus on diet, physical activity, and sleep habits. Some clinicians suggested that HCL systems may require more focus than MDII on bolusing, carbohydrate counting, and other aspects of management. Troubleshooting and adapting to the technology were also seen as requiring a significant commitment and time investment. Clinicians noted that those who had previously used insulin pumps often needed to spend time "unlearning" techniques and habits that were not applicable or were potentially dangerous when using an HCL system. Additionally, HCL systems that required calibration were not necessarily seen to reduce the frequency of finger-stick testing or reliance on test strips.

Equity of Access to HCL

Clinicians noted that without public coverage of HCL therapy, only people who have private insurance coverage or can afford to pay out of pocket have access to HCL systems. Although HCL-ready insulin pumps are reimbursed in a number of Canadian jurisdictions, the CGMs and sensors needed to create HCL systems are generally not. Clinicians advocated strongly for increasing CGM coverage, articulating that this as the true barrier to HCL coverage and noting that those who use MDII or a non–HCL-ready insulin pump could also benefit from a CGM.

Health System Capacity

Clinicians stated that starting users on HCL therapy was time- and resource-intensive, even when they had previously used an insulin pump. Doing a high number of new HCL starts at once or expanding coverage to new populations was seen to require more resources for diabetes education and pump training than currently exist in Canadian health systems.

Training and Education

Clinicians (particularly diabetes educators doing new pump starts) were largely happy with their access to training and education, which was overwhelmingly provided by manufacturers. Similarly, clinicians were happy with access to manufacturer-funded technical support and troubleshooting. Diabetes educators and insulin-pump trainers identified a need for employer support to access available training resources during working hours. Some clinicians discussed the potential consequences if a manufacturer were to

leave the insulin-pump market while their devices were still in widespread use, and expressed concern about access to support and troubleshooting if this were to occur.

Patient Selection

Clinicians varied in their views of who could benefit most from having access to HCL systems. Some argued that only those who are exhibiting good glucose control currently should be considered candidates for HCL systems, whereas others felt the device could potentially benefit those with more variable levels of glucose management. In particular, some felt that broad populations like teenagers or older adults who were not currently managing well could potentially see the most benefit. These claims were backed by the clinical experience of some clinicians who had been able to place their patients with poorer management on HCL systems through private insurance.

Ministry and Department Stakeholders

Issues that emerged from discussions with ministry and departmental stakeholders included concerns about budget impact and effective stewardship of public funds.

Concerns About Budget Impact

Ministry and departmental stakeholders expressed concern about the incremental costs associated with funding HCL systems relative to existing insulin-pump and diabetes supply coverage. This concern was more pronounced in jurisdictions that currently do not have age limits for insulin-pump coverage as more individuals would potentially be eligible for a publicly reimbursed HCL system.

Although different jurisdictions were at different stages of evaluating public funding for HCL systems, all indicated that their ministry or department had done some preliminary thinking and costing around including HCL systems in existing insulin-pump programs.

Effective Stewardship of Public Funds

Related to concerns about budget impact, ministry and departmental stakeholders highlighted their responsibilities to be effective stewards of public funds. Evidence of the clinical effectiveness of HCL systems was viewed as integral to informing the decision, with some stakeholders noting that strong evidence that HCL systems were an improvement over currently reimbursed devices was needed to justify the incremental costs. Similarly, these stakeholders discussed the potential opportunity costs associated with funding HCL therapy in constrained health budgets, with some emphasizing that this would be a cabinet decision assessed against many other pressing health system priorities.

With respect to funding for continuous glucose monitoring — whether as part of an HCL system or not — ministry and departmental stakeholders were aware of the considerable advocacy around CGMs, and have also examined this issue to varying degrees. Stakeholders acknowledged that as continuous glucose-monitoring integration becomes more common with insulin pumps (whether SAPs or HCL systems), public programs that currently treat glucose-monitoring devices separately from insulin pumps may need to adapt.

Patient Engagement

Overview

CADTH involves patients, families, and patient groups to improve the quality and relevance of its assessments, ensuring that those affected by the assessments have an opportunity to contribute to them. CADTH has adopted a Framework for Patient Engagement in HTA. For this HTA, the value of relevance and the understanding that patients have knowledge, perspectives, and experiences that are unique and that contribute to essential evidence for HTA has guided our patient-engagement activities. The Device Advisory Committee participates in HTA topic identification and prioritization at CADTH. The committee includes the Chair of the CADTH Patient and Community Advisory Committee to contribute the perspectives of those using the Canadian health care system.

CADTH engaged a patient with type 1 diabetes who had experience with both HCL systems and "looping" (using DIY technologies to close the loop between the flash glucose monitor and the insulin pump). CADTH also discussed the project with representatives from 4 patient advocacy groups: Type 1 Together, Diabetes Canada, JDRF, and the CNIB Foundation. These representatives had personal or family experience with type 1 diabetes.

Methods

Invitation to Participate and Consent

A potential participant was identified through contact with patient groups previously engaged with CADTH (Diabetes Canada, and Type 1 Together were contacted). A CADTH patient engagement officer contacted potential participants by email to explore their interest in becoming involved. The preliminary request included the purpose and scope of this project, the purpose of engagement, and the nature of engagement activities. The patient engagement officer obtained the person's informed consent to share their lived experiences with type 1 diabetes and perspectives about HCL systems with CADTH staff.

Engagement Activities

A person with experience using an HCL system for type 1 diabetes reflected on their own personal experiences at several time points during assessment, including:

- prior to protocol finalization
- during drafting of the initial reviews, and
- upon completion of the final report during the feedback period.

Patients' perspectives gained through engagement processes were used to ensure the relevance of outcomes of interest for the clinical assessment, to provide commentary on themes emerging from the Experiences and Perspectives Review, and to discuss other key concepts to inform the Discussion section. The questions and subsequent discussion with the patient group representatives helped to clarify the technology under review and comment on the relevance of the scope to Canadian patients and families.

The involvement of a person with type 1 diabetes enabled the research team to consider the evidence found in the literature alongside an understanding of the wider experiences of patients and family caregivers. The person with type 1 diabetes was able to identify goals of

treatment and discuss the realities of life with type 1 diabetes, such as the effort, cost, and problems related to the HCL device. They were also able to comment broadly on their hopes and fears related to type 1 diabetes and its management.

Once preliminary findings were available, the person with experience of HCL for type 1 diabetes and representatives from 4 patient groups were invited to a discussion with CADTH. The conversation reviewed the protocol, explored the participant's perceptions of the research questions, and explained the process for giving formal feedback. This conversation was used to consider the possible need to explore avenues of analysis that may have been missed or underdeveloped, add additional concepts or experiences that related to ideas and concepts for the Discussion section, and add understanding of the underlying conditions that support or constrain the use of HCLs.

The person with experience of using an HCL system for type 1 diabetes and representatives from the 4 patient groups were invited to provide feedback to the report during the stakeholder feedback period.

A final conversation will be held with the person with experience of using an HCL system for type 1 diabetes upon completion of the final HTA report and the recommendation report. Through conversation and formal reporting, CADTH will clarify the key results of the full assessment and describe how engagement activities were used in the final report.

Table 37 follows the Guidance for Reporting Involvement of Patients and the Public short form (GRIPP2 SF) checklist to outline the process of engagement and where and how participants' contributions were used in the assessment.[181]

Results

Table 37: Patient and Public Involvement in Hybrid Closed-Loop Insulin Delivery Systems for People With Type 1 Diabetes Health Technology Assessment

Section and topic	Item	Reported on page
Aim **What was the aim of the study?**	The Device Advisory Committee participates in HTA topic identification and prioritization at CADTH. To contribute the perspective of those using the Canadian health care system, the committee includes the chair of the CADTH Patient and Community Advisory Committee. A patient with experience of managing their own type 1 diabetes using an HCL system was involved in developing the protocol and commenting on outcomes important to patients and families affected by type 1 diabetes. This patient, and other representatives from patient stakeholder groups (Type1 Together, Diabetes Canada, JDRF, and the CNIB Foundation) were involved in a discussion about the protocol and gave feedback on the list of included studies for the Clinical Review during the project.	114
Methods **What methods were used for patient involvement in the study?**	We engaged 1 patient with type 1 diabetes and experience with an HCL system. Diabetes Canada connected CADTH with this person. After giving informed consent, the person living with type 1 diabetes discussed their experience of managing type 1 diabetes via teleconference and email communication. An honorarium was provided to this person for participating in teleconferences and reviewing a summary of the discussion.	114

Section and topic	Item	Reported on page
	This patient and other representatives from patient stakeholder groups were invited to provide feedback on the draft of the full Health Technology Assessment and the recommendations report.	
Study results **What were the results of patient involvement in the study?**	The researchers were made aware of the importance of several particular outcomes and themes. **Time in range:** Our engaged person living with type 1 diabetes described the recovery after excursions out of range. This can involve hours or days of feeling unwell and being unable to participate fully in work, school, or family life. The researchers heard that the outcome of time in range is important to patients to maintain stable health. **Quality of life:** Our engaged person living with type 1 diabetes described the burden of diabetes management. Managing type 1 diabetes takes constant effort and can be burdensome for patients and families of children with type 1 diabetes. When the HCL system works well, it helps to remove some of the burden of managing type 1 diabetes. However, our engaged person wanted to dispel any misconception that the device somehow automated diabetes management. It lessens the management burden, but does not remove it completely. **Patient satisfaction**: Researchers heard that complications with using HCL systems are often due to equipment failure (leaky pump, poor site, dead batteries) and that people have to keep extra supplies on hand for when this happens, which adds cost and burden. **Cost:** Our engaged person living with type 1 diabetes expressed concern about the affordability of HCL equipment and supplies, especially for people who are not covered by private insurance. Being aware of these concerns allowed the research team to consider the evidence from the literature in the context of the wider experiences of patients and caregivers when preparing the assessment.	31, 69, 118
Discussion and conclusions **To what extent did patient involvement influence the HTA overall?**	The success of patient involvement in this report is related to several factors. First, the person we engaged who is living with type 1 diabetes was briefed on the objectives of the project and their role. Second, they were supported by experienced patient engagement officers in the use of their views and involvement with the research team. Established processes are in place, and the person we engaged who is living with type 1 diabetes was offered compensation for their time to participate in the project. There is currently a rapidly evolving technology landscape for people with type 1 diabetes, and hybrid closed-loop systems are of interest to the wider diabetes community. Four patient stakeholder groups contacted CADTH to learn about the status of the project and share their knowledge of the type 1 diabetes community's concerns. A teleconference was held to discuss the protocol and the opportunity for stakeholder feedback on the report and recommendations. However, there were limitations. The topic and research questions were already determined before the person living with type 1 diabetes was engaged. Due to time constraints, this person and other patient stakeholders were invited to participate within a set time frame and with a deadline for providing feedback.	114, 121

Section and topic	Item	Reported on page
Reflections and critical perspective **What went well, and what could be improved?**	Our engaged person living with type 1 diabetes was highly engaged in the conversations with researchers. They had clear opinions and concerns during the teleconference. They reported family-borne costs and burdens, such as for extra supplies and equipment that must be kept on hand. They noted that even when diabetes supplies were covered by private insurance, there was an acknowledgement that people with type 1 diabetes needed to consider health insurance in their career decisions. Our engaged person living with type 1 diabetes had experience with "looping." While not within the scope of this report, it was interesting to receive their input on how the existence of DIY options is driving people to use off-label technologies. Our engaged person living with type 1 diabetes also shared the concern that a fully closed-loop system has not been regulated and is not monitored the same way some other devices are. Ethical and equity issues are sometimes revealed when experiences are shared. Affordability was a concern of both our engaged person living with type 1 diabetes and the patient group representatives. Representatives with the CNIB Foundation noted that people who are visually impaired may be unable to use diabetes management devices like HCL systems and CGMs, and often require assistance to read the screens and address the alarms. One limitation of our patient-engagement approach is that people often express concerns that are not part of the project scope (e.g., about technologies that are not approved in Canada or about poor design of devices), but the topics and questions to explore are already identified when the project begins. Another limitation is that the time frame of the project can make it difficult for patients to participate fully on terms that work for them (e.g., daytime teleconferences). Also, people need access to reliable technology, telephone, and internet to collaborate with CADTH, which could exclude some voices.	95, 104, 105, 111, 121

CGM = continuous glucose monitor; DIY = do it yourself; HCL = hybrid closed-loop insulin delivery system; HTA = health technology assessment.

Discussion

HCL Place in Management of Type 1 Diabetes

The evidence assessed across this HTA suggests that HCL systems have the potential to become effective, welcome additions to current type 1 diabetes management strategies. Short-term (6 months or less) clinical outcomes, particularly time-in-range metrics, demonstrated improvements among individuals using HCL therapy compared with alternative technologies to manage type 1 diabetes. When HCL systems were working well, people living with type 1 diabetes found them to be broadly desirable and helpful in their attempts to create distance between themselves and the constant requirements of self-management. Care providers, while especially keen on the continuous glucose-monitoring component of HCL therapy, were excited by the prospect of expanding their view of patients' glucose data and how this might impact the types of care they could provide.

However, HCL systems are not a cure for type 1 diabetes and achieving positive outcomes is not without parameters: there are limited studies that assess their long-term effectiveness and safety, and shifted, rather than removed, self-management burdens.

Long-Term Health Benefits and Impacts on Adverse Events

Given their newness, there is limited evidence to assess the long-term effectiveness of using HCL systems. While time-in-range metrics have recently gained prominence as a clinically important outcome, given their potential relationship to fewer diabetes-related complications,[94,107] there are limited data with which to assess time-in-range metrics as a valid surrogate outcome measure for this purpose. Paired with the heterogeneous follow-up periods across studies (3 days to 6 months), this suggests that long-term effectiveness of using HCL systems remains uncertain.

Similarly, differences in the occurrence of adverse events (e.g., hypoglycemia and ketosis) were generally not statistically significant between participants using HCL systems and those using control interventions (typically SAPs). While these results are promising, and reflect the conclusions made in other SRs,[182,183] clinical trials to date have not been designed to detect statistically significant differences in adverse events (i.e., all clinical studies have used time in range as the primary outcome), and there is uncertainty about the safety of HCL systems.

While these findings do not invalidate the importance of the improvements demonstrated across many short-term clinical and non-clinical outcomes, they should be considered when making decisions as to whether and where to insert HCL systems into current diabetes care strategies.

Shifting of Self-Management Burdens With HCLs

HCL systems represent a shift in self-management burdens rather than a removal of burdens altogether. Given that HCL systems are not fully functioning artificial pancreases, to match actual time-in-range metrics with desired time-in-range metrics still requires significant, ongoing work by the people using the devices (e.g., carbohydrate counting and preprandial bolusing, finger sticks, sensor calibration for some HCL systems, attention to system alarms and active responses, and navigating glitches or system failures). While this could be — and often was described as — both frustrating and challenging, it was not surprising for most people living with the condition or those engaged in their care. Of course,

it could discourage some people from wanting to use HCL systems. However, by and large, the work seemed expected.

While the need to contribute to one's own self-care (or that of a child in their care) remains, what this contribution looks like — or is meant to achieve — could be quite different. Ongoing lifestyle adjustments aside (e.g., dietary and exercise habits), most of the work being done by the person using an HCL system is focused on the maintenance and functional requirements of the system itself. For example, within the context of an HCL system, finger sticks are used as a tool for CGM (re)calibration rather than a point-of-care diagnostic to measure the necessary insulin dose. As such, while the practices themselves may be similar to previous self-management regimes, their purpose represents a departure that is worth considering as part of any decision about whether or where HCL systems belong in current diabetes care strategies.

Furthermore, by shifting the responsibility to allocate responsive basal-insulin doses to HCLs — thereby removing this responsibility from the person living with or caring for a person living with diabetes — HCLs are embedded in complicated notions of trust. For HCLs to work well, people using them need to resist the inclination to continuously modify their blood glucose numbers and basal-insulin rates. This is important because it signals a shift away from non–HCL-therapy ideals of what it means to practise good self-management. Typically, that has involved paying close attention to one's own glucose numbers and insulin needs. Developing this trusting relationship with HCLs could not only be difficult for people who have been self-managing for a long time, but this shift could also have consequences that are relevant to whether or where HCL systems belong in publicly funded programs.

For example, both care providers and people living with type 1 diabetes noted the possibility that this shift could gradually lead people using HCL systems to develop "bad habits" or become de-skilled. By having the opportunity to largely step away from the immediacy of diabetes self-management and instead focus on the tools doing that immediate work, the concern was that if someone had to stop using their HCL system for any reason, reverting back to a previous mode of management might prove difficult. As such, ensuring that health care providers have the resources to deliver ongoing comprehensive education around non–HCL-specific diabetes management strategies — and that the people using the devices have resources available to support them if they lose access — seems an important consideration if implementing HCL.

Who May or May Not Benefit?

Amid considerations of whether, or where, HCLs belong in diabetes care strategies, another question is for whom they might be beneficial or not. All 9 of the included clinical studies enrolled people living with type 1 diabetes who had reasonable control of their condition and were relatively healthy overall (i.e., without significant comorbidities or disabilities resulting from their type 1 diabetes); we might expect new HCL users who also meet these criteria to experience similar outcomes as the study participants. However, it is unclear whether people who do not meet these criteria would experience similar outcomes or to what extent. One of the limitations of the Clinical Review is that there was no evidence to support subgroup analyses of clinical effectiveness or safety based on participant age, sex, race, glucose management, or other clinical features (e.g., those who were pregnant or planning pregnancy, with a history of severe hypoglycemia, or hypoglycemia unawareness).

As a limitation, this is important to consider for a few reasons. For example, decisions regarding the implementation of HCLs will need to be made despite this uncertainty. Based

on conversations with policy-makers and clinicians, insulin-pump programs across jurisdictions have largely organized eligibility criteria along lines of good self-management and relatively consistent A1C levels. While the evidence from this HTA does not address the appropriateness of these criteria for insulin-pump programs, the clinicians who were consulted varied in their views about whether these criteria should be translated to HCL systems if they were to be publicly funded. Some argued that people who are managing their diabetes well should be considered candidates for HCLs, whereas others thought the device should be available to those who need to improve their management. Of note, some believed that broad populations like teenagers or older adults who were not currently managing well could potentially see the most benefit. These claims are supported by the clinical experience of some clinicians who had been able to place their patients with poorer management on HCLs through private insurance.

In many ways, these varied views become more pressing when considering how HCL systems have been used in practice. Clinical studies demonstrate that, when used as intended, HCL systems are capable of supporting positive short-term clinical outcomes. Non-clinical studies also demonstrate that people do not, or cannot, always use HCL systems as intended. Rather, HCL systems were often described as active participants (as opposed to passive tools) in daily negotiations around things like food and exercise. Rather than asking how HCLs should be used in a given situation to achieve the best clinical outcomes, people relied on them to support their more spontaneous movements and decisions. For example, while all HCL systems require preprandial bolusing (and the pause to calculate carbohydrates associated with this requirement), many people described either estimating bolus needs or neglecting them altogether in the hopes that the HCL algorithm would pick up on what they had miscalculated or missed. Technically, leaning on an HCL system in this way is an unintended use of the technology. Clinically, it is unclear how this affects relevant outcomes like time in range or A1C. Practically, using an HCL system in this way supports people's desires to create a bit of distance between themselves and the constant requirements of diabetes self-management.

If access to publicly funded HCL systems would be determined through eligibility criteria, attention is needed to ensure that such criteria are consistent with broader public health goals and do not contribute to existing inequities in diabetes management. For instance, if HCL systems are only available to those who demonstrate good glucose management with other technologies, then public coverage is unlikely to improve the health of the population overall because it will only serve to assist those who already have optimized health outcomes, rather than assisting those who have moderate or poor control over their diabetes but have the potential for this to be improved by HCL therapy. Existing clinical guidelines for insulin-pump therapy, which were developed before HCL systems became widely available, may be useful as a guide for these decisions.[8,9,11]

Furthermore, when discussing who may or may not benefit, it is important to consider the gatekeeping role that clinicians play in people's access to diabetes technologies like HCL systems. In both the stakeholder consultations and the literature assessed as part of both the Ethics and Perspectives Review and the Experiences Review, clinicians expressed the assumption that people who were well-educated, living with a supportive family, and socio-economically stable would be the most likely to benefit from HCL systems. Given that most clinicians represented in the assessed literature ended up adjusting their assumptions once they had more experience with HCL systems, we would suggest that it is important that clinicians and program funders be aware of the fallibility of assumptions about which patients are likely to benefit from HCL systems. While none of the included literature from

this HTA has specifically reflected on the experiences of racialized people in type 1 diabetes care, it is also important to be aware of, and work to counteract, this potential in practice, given long-standing and ongoing systemic racism toward Black, Indigenous, and other people of colour across Canadian health care systems.

Factors in Place for Optimal Use of HCL Systems

Affordability to Users

At present, HCL systems are prohibitively expensive for most individuals without employer-sponsored private insurance coverage; the stakeholder consultations conducted as part of this HTA suggested variable uptake of HCL systems, largely for this reason. The BIA conducted in this assessment took the perspective of a public payer, meaning that out-of-pocket costs incurred by pump users were not captured in the analysis. Without expanded public coverage or considerable price reductions, access to HCL systems will continue to be inequitable and mediated by income and employment status. The Ethics Review notes that that any program criteria set to determine who may be eligible to have access to HCL systems must be based on evidence and not exacerbate existing health inequities.

Public Funding of Continuous Glucose Monitoring

Currently, there is limited public funding of CGMs in Canada. Yukon announced it would fund CGMs for all Yukoners with type 1 diabetes on October 1, 2020.[136] The ODSP covers CGMs, as does the Non-Insured Health Benefits Program of Indigenous Services Canada, on a case-by-case basis.[184] What the relative lack of public continuous glucose-monitoring coverage means in practice is that individuals who are eligible for a publicly funded insulin pump in most jurisdictions can have access to an HCL-ready insulin pump, but must pay out of pocket or access private insurance to pay for the CGM needed to create a closed-loop system. The clinician stakeholders consulted through this HTA noted that improving access to publicly funded CGMs could benefit those using HCL systems as well as those using non–HCL-ready insulin pumps or MDII to deliver insulin. The BIA conducted as part of this assessment modelled the budget impact of coverage for CGMs without HCL systems.

One of the clear benefits of HCL systems is their ability to monitor blood glucose levels in real time, providing pump users and clinicians with a fuller picture of glucose management. Diabetes educators consulted noted that these data act as an effective “teaching tool,” allowing them to empirically demonstrate what happens to a user’s blood glucose at mealtimes, during and after physical activity, and overnight. However, these data could also be attained by using a CGM with any insulin delivery method.

As noted previously, some private insurance plans cover CGMs. Diabetes Canada estimates the out-of-pocket cost of continuous glucose monitoring in Canada to range from $3,000 to $6,000 annually, depending on the components of the system and the frequency with which sensors must be replaced.[184] CADTH’s BIA estimated an average annual pan-Canadian cost of $4,783 per patient for CGMs. For those without private insurance coverage, continuous glucose monitoring is often unaffordable. Different jurisdictions are at different stages in their deliberations about these technologies. For example, in February 2018, Ontario’s Health Technology Assessment Advisory Committee recommended public funding of CGMs for individuals living with type 1 diabetes who are willing to use them for the vast majority of the time and who are experiencing severe hypoglycemia despite optimized use of insulin therapy and conventional monitoring of blood glucose, or who are unable to recognize or communicate about symptoms of hypoglycemia..[185] Additionally, the

recently re-elected Saskatchewan Party government pledged during the 2020 election campaign to fund CGMs for those aged 18 and under.[138]

Overall Budget Impact

Given the fiscal challenges faced by provinces and territories, there is concern about the overall budget impact of implementing HCL coverage. The BIA conducted in this assessment found that if HCL systems are reimbursed only for individuals who meet current jurisdictional insulin-pump criteria, the pan-Canadian budget impact is estimated to be an increase of $822,635,045 over 3 years. A scenario analysis demonstrated that if HCL systems are reimbursed more generally for all individuals with type 1 diabetes, the budget impact will increase by approximately $93 million more over 3 years (i.e., a total budget increase of $915,883,921). A key driver of the analysis and source of uncertainty is whether current individuals who use MDII to deliver insulin will switch to an HCL if reimbursed. If HCL uptake was among current insulin-pump users only, then the estimated budget impact of HCL system reimbursement is expected to be much lower than the CADTH base-case estimate, because uptake of HCL systems by current MDII users will also incur insulin pump and pump supply costs to the public payer.

Training, Education, and Support

People with lived experience mentioned the need for intensive education and support when starting out with HCL systems and mentioned the value of peer support from people with long-term experience troubleshooting equipment problems. The clinicians consulted (including endocrinologists, diabetes education nurses, and insulin-pump trainers) also noted that starting individuals on HCLs was a time-intensive process requiring considerable one-on-one interaction between the diabetes educator or pump trainer and the pump user. Training, education, and troubleshooting for insulin pumps are mainly provided by device manufacturers, which is understandable given the considerable differences between existing devices. The consulted clinicians largely felt that they had access to adequate training and continuing education opportunities to learn about new diabetes care technologies from device manufacturers, and were satisfied with the support and troubleshooting provided by manufacturers and their representatives. The main challenge in accessing training and education resources that they identified was having the time and employer support to devote to learning.

Although the clinicians consulted were satisfied with the education they received from manufacturer-initiated training opportunities, device-specific education may pose some challenges. Training health care professionals separately on each marketed device could be time-consuming as more devices receive approval in the Canadian market. Additionally, having health care professionals gain extensive experience with a given marketed device rather than the range of available options may influence device choice for HCL users because clinicians may recommend their preferred device or one they are more knowledgeable about. This may also have consequences for care for HCL users who choose non-approved, DIY insulin delivery systems. This system of manufacture responsibility for training and education may also have consequences if a device manufacturer chooses to leave the market or to cease supporting a given device that is still in use.

User-Centred Design

The Perspectives and Experiences Review explored a variety of factors related to human interactions with HCL systems. Some HCL users sought greater customizability in their devices to account for atypical days. For example, some users wanted to be able to input information about planned periods of physical activity that the system could use to adjust target ranges and insulin delivery. Other users wanted to be able to program the system to do "good enough" on particularly stressful days, limiting the number of alarms to those indicating a true risk of a severe adverse event. Additionally, those with lived experience noted that diabetes management devices like HCL systems and CGMs are often inaccessible to people living with visual or hearing impairments due to a lack of integration with screen readers and the reliance on auditory alarms and alerts in the user interface. Consulted clinicians also noted that the user-friendliness of reports and data visualization from CGMs varies from device to device. As HCL systems and associated technologies evolve, more attention should be paid to the user-device interface. This includes having user-friendly, understandable reports, allowing for user customization where safe and appropriate to do so, and making devices usable and accessible for those with visual or hearing impairments.

Responsibility and Challenges for Implementing Publicly Funded HCL

Currently, the responsibility for implementing HCL systems (if they were to be broadly publicly funded) is diffuse and spread across the health and social services systems. Although the identified evidence cannot speak to what part of the health system should be responsible for implementing HCL systems, several program considerations were identified.

Complexities of Support Programs for Those Living With Type 1 Diabetes

Public funding programs for insulin, insulin pumps, blood glucose monitoring, and associated supplies (like test strips, lancets, and consumable sensors) vary considerably across Canadian jurisdictions. This variability was an important consideration factored into the BIA. People living with type 1 diabetes may have to navigate public drug plans (for insulin), assistive devices programs (for insulin pumps and pump supplies), and means-tested social services programs for additional supplies and supports. Those who have private insurance may need to navigate what is covered by their private plan to supplement a variety of publicly administered programs. This system is complex for those living with type 1 diabetes and their caregivers, as well as for clinicians helping their patients navigate the assortment of benefits for which they may be eligible.

Policy Legacies of Insulin-Pump Coverage

Although public insulin-pump programs in Canada have adapted to some degree in response to technology change and advocacy around device access, existing policies and boundaries around programs influence how new technologies like HCL could be integrated. For example, the policy legacy of having separate programs and funding envelopes for insulin pumps and diabetes supplies has contributed to the current situation of HCL-ready insulin pumps being publicly funded while the CGMs and supplies needed to create an HCL system are not. Similarly, the fact that eligibility criteria for existing public insulin-pump programs limit access to those who are currently attaining a specified range of glucose

management likely informs the assumption by some that individuals who are currently managing their type 1 diabetes well are the best candidates for HCL systems.

The legacy of age limits for publicly funded insulin-pump programs likely also informs policy decisions around HCL coverage. The fact that the budget impact will be larger in jurisdictions that currently cover insulin pumps for individuals of all ages necessarily influences decisions around public reimbursement and implementation of HCL systems.

Program Design Considerations

Under current public reimbursement policies for insulin pumps, individuals who qualify are eligible for a new device every 4 or 5 years. This cycle poses some challenges for the successful implementation of HCL systems. For example, if many were eligible to “switch” to an HCL system in the first year, there could be a high upfront public program cost when public reimbursement of HCL systems is introduced. Additionally, adequate diabetes education and pump training resources would need to be available to support new HCL users in this labour-intensive start or switching period.

Device preference may also play a role in HCL uptake. Some HCL systems do not allow for software updates, meaning that users wishing to access the latest features would need to wait until their 4- or 5-year replacement period had elapsed before being eligible for the next iteration of the device. Clinician stakeholders also indicated that some privately insured users with a strong device preference had switched devices in anticipation of software features that were pending Health Canada approval. This raises the possibility that some pump users eligible for public programs who have device preferences may wait for public coverage of their preferred HCL before switching.

Implications for Decision- or Policy-Making

HCL systems seem to have a place in type 1 diabetes management, but existing evidence provides little guidance on who may benefit most — and who may not benefit — from their use. Some argue that people who are managing their diabetes well should be candidates, whereas others think the device should be available to those who need to improve their management. Given the uncertainty, if HCL systems were to be publicly funded, using existing clinical program guidelines for existing insulin-pump programs may be an option for deciding who can access them. Probationary or test periods could also be implemented for HCL systems, with individuals who are not able to use them safely and effectively being switched back to an alternate insulin delivery mode.

This review found little long-term evidence of clinical benefits of HCL therapy. Further research is needed to determine the long-term clinical effects of HCL therapy. Regulators like Health Canada have included requirements for post-market surveillance of HCL systems as conditions of device approval, and post-market safety and effectiveness evidence should inform ongoing public funding decisions for HCL systems.

The anticipated budget impact of HCL implementation varies across the country and is dependent on existing program design, including whether insulin pumps are covered for individuals of all ages or just those under the age of 25. At present, provinces and territories are reviewing many aspects of type 1 diabetes coverage concurrently (e.g., age limits for insulin-pump programs, HCL systems, CGMs, FGMs). Deciding to publicly fund HCL vs will likely also force conversations about public funding for CGMs for individuals with type 1 diabetes who are using insulin delivery methods other than HCL systems.

HCL technology is improving, and demand for it can only be expected to rise. It is possible that pumps without sensors and integrated CGMs are a thing of the past. This creates a challenge for public programs that have historically treated insulin pumps separately from diabetes supplies, including glucose monitoring. Efforts may be needed to bring these programs together, both for administrative simplicity and to make them easier to navigate for people living with type 1 diabetes and their caregivers. If HCL systems are to be used more broadly, training and education for HCL users, their caregivers, and the clinicians supporting their care will be required. Further, working toward a supportive care environment that not only includes health care providers and family members, but also allows people living with type 1 diabetes the time and space they need to attend to and maintain their HCL systems, is an important consideration.

This review touches on “looping” and DIY HCL systems. Although DIY HCL systems do not have regulatory approval, some people living with type 1 diabetes have chosen to use them, overcoming technological barriers and many other challenges in search of a system that will help improve their diabetes outcomes.[21] Open-source insulin delivery systems are on the rise and can reasonably be expected to become more mainstream in the coming years, with at least 1 such technology seeking regulatory approval in the US. For public programs, this potentially signals a need to adapt and anticipate new vendors entering this marketplace. The days of dealing with a limited number of vendors in the insulin-pump space may be coming to an end. Public acceptability of bulk procurement models that limit device choice for public program recipients may also lessen as these interoperable devices emerge on the Canadian market.

One limitation of this report is that its findings represent a “moment in time” in a changing HCL landscape. In the months over which this report was written, the number of HCL systems approved for use in Canada increased from 1 to 3.[38,40,45] Additional HCLs, including the next generation of current systems and new systems from other manufacturers, are reported to be in the late stages of development and regulatory approval in the UK, Europe, and the US.[186,187] It is unclear how many of them will enter the Canadian market or how the new evidence that accompanies their development could affect the conclusions of this report.

Appendix 1: Literature Search Methods

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-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 24, 2020
Alerts:	Monthly search updates until project completion
Study Types:	No filters applied to limit by study type
Limits:	Publication date limit: 2003-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* or insulet*) and (horizon* or algorithm* or predictive control or MPC or MMPPC)) 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 medall
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* or insulet*) and (horizon* or algorithm* or predictive control or MPC or MMPPC)) 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.
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 updated prior to the completion of stakeholder feedback period. [Search – (Minimed OR 670g OR "670 g" OR tandem OR tslim OR "t slim" OR omnipod OR ilet OR "closed loop" OR closedloop OR "artificial pancreas" OR "bionic pancreas") AND 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 updated prior to the completion of stakeholder feedback period. [Search terms — Minimed, 670g, "670 g", tandem, tslim, "t slim", omnipod, ilet, "closed loop", closedloop, "artificial pancreas", "bionic pancreas"]

Patients' Perspectives and Experiences Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present)
Date of Search:	March 18, 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
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.kf	Author keyword heading word (MEDLINE)
.jw	Journal word title

MULTI-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* or insulet*) and (horizon* or algorithm* or predictive control or MPC or MMPPC)) 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
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.

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

Grey Literature

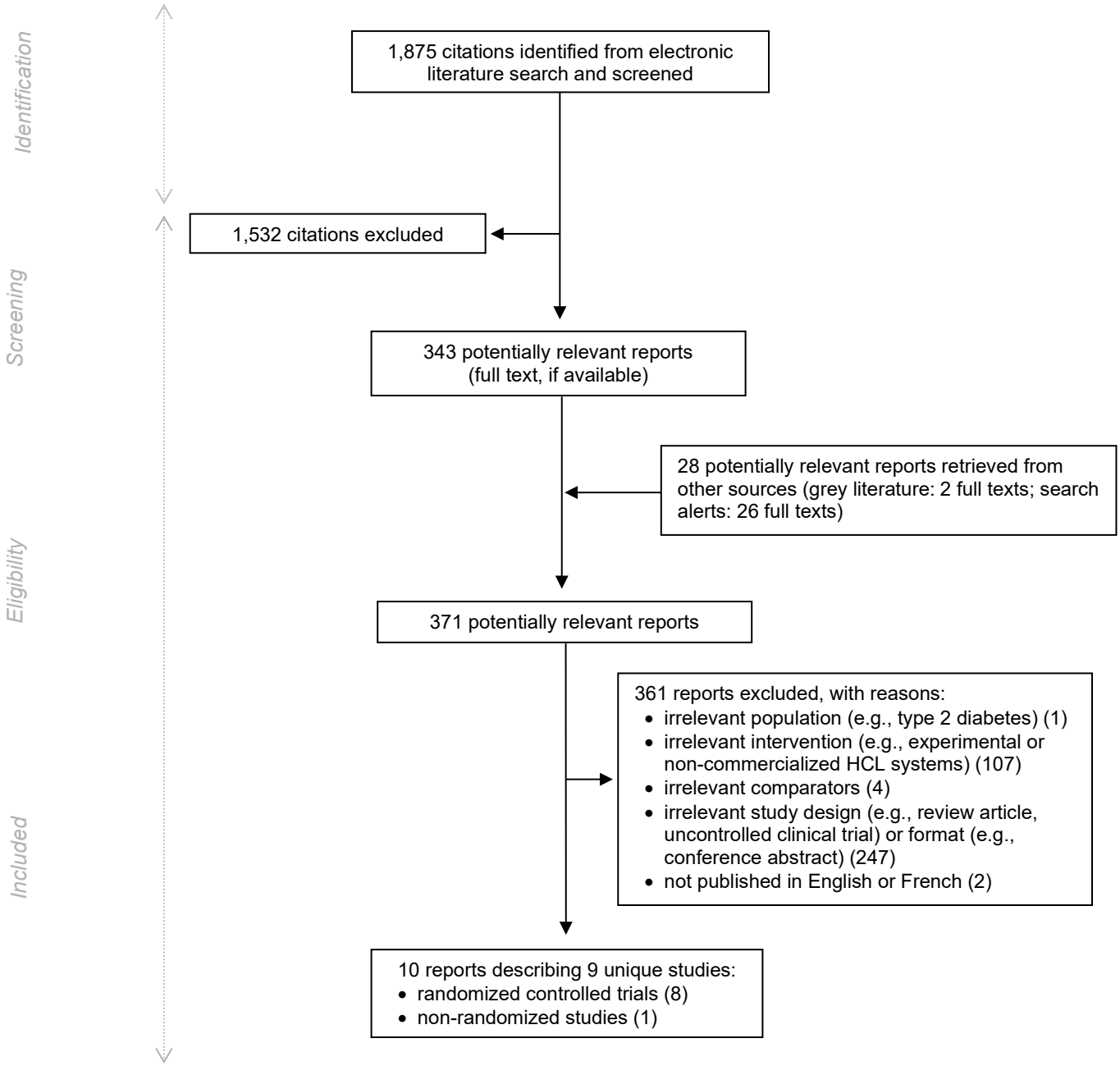
Search dates:	July 31 – August 7, 2020
Keywords:	Minimed, 670g, "670 g", tandem, tslim, "t slim", omnipod, ilet, "closed loop", closedloop, "artificial pancreas", "bionic pancreas"
Limits:	Publication years: 2003-present
Updated:	Search updated prior to the completion of stakeholder feedback period

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

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

Appendix 2: Large Tables and Figures

Figure 4: PRISMA Flow Chart of Selected Reports (Clinical Review)



HCL = hybrid closed-loop insulin delivery; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Alt text: The electronic search identified 1,875 citations. Following the screening of titles and abstracts, 1,532 citations were excluded, and 343 potentially relevant reports were retrieved for full-text review. An additional 28 reports from the grey literature and search alerts were retrieved for full-text scrutiny. Among these 371 potentially relevant reports, 361 were excluded for various reasons, and 10 reports describing 9 unique publications were included in the review.

Characteristics of Included Primary Studies — Clinical Review

Table 38: Study and Patient Characteristics of Included Primary Clinical Studies

Study citation, country, and funding source	Study design, setting, and objective	Patient characteristics	Intervention(s)	Comparator(s)	Clinical outcomes, length of follow-up, and subgroup analyses
Randomized controlled trials					
Breton et al. (2020) US **Funding source**: Tandem Diabetes Care and the National Institute of Diabetes and Digestive Kidney Diseases	**Study design**: Multi-centre, open-label, parallel-group RCT **Setting**: Participants were recruited from 4 pediatric diabetes centres in the US. After recruitment, patients were observed under free-living conditions. **Objective**: To assess the efficacy and safety of the Control-IQ HCL in children between the ages of 6 years and 13 years with type 1 diabetes	**Inclusion criteria**: Children (≥ 6 years and ≤ 13 years of age) with a diagnosis of type 1 diabetes for at least 1 year prior to enrolment who had received treatment with insulin for at least 6 months, had a body weight between 25 kg and 140 kg, and who were receiving a total daily insulin dose of at least 10 units. Additionally, participants were required to have familiarity with carbohydrate ratios for meal boluses, a willingness to suspend use of any personal closed-loop systems they used at home during the study period, and a willingness to switch to insulin lispro or insulin aspart if they were not using it already. **Excluded**: Those who were known to be pregnant; those who were sexually active and did not agree to use a form of contraception; those with concurrent use of any	The Control-IQ HCL, which included a t:slim X2 insulin pump and a Dexcom G6 CGM that were managed by the Control-IQ software	Participants in the control group who were already on open-loop SAP therapy continued to use their personal systems; those who were receiving MDII were provided with a t:slim X2 insulin pump with PLGS feature. All control participants wore a Dexcom G6 CGM. Overall, 15 of the 23 patients in the control group used the t:slim X2 system with PLGS feature. Of the 8 remaining control participants, 5 used a Medtronic pump and 3 used an OmniPod pump (Insulet). None of these 8 participants had a PLGS feature.	**Primary outcome**: • Percentage of time spent in the glucose range of 70 mg/dL to 180 mg/dL (3.9 mmol/L to 10.0 mmol/L) **Secondary outcomes**: • Percentage of time spent with glucose > 180 mg/dL (> 10.0 mmol/L) • Mean glucose level • A1C at 16 weeks • Percentage of time spent with glucose < 70 mg/dL (< 3.9 mmol/L) • Percentage of time spent with glucose < 54 mg/dL (< 3.0 mmol/L) • Percentage of time spent with glucose > 250 mg/dL (> 13.9 mmol/L) • Coefficient of variation of glucose • Percentage of time spent with glucose < 60 mg/dL (< 3.3 mmol/L)[a] • Proportion of participants with A1C < 7.0% post-treatment[a] • Proportion of participants with A1C < 7.5% post-treatment[a]

Study citation, country, and funding source	Study design, setting, and objective	Patient characteristics	Intervention(s)	Comparator(s)	Clinical outcomes, length of follow-up, and subgroup analyses
		non-insulin, glucose-lowering drug other than metformin; those with hemophilia or any other bleeding disorder; those with a condition that would put the participant or the study at risk; and those who would not be capable of operating the study device or adhering to the protocol (based on investigator assessment). **Number of participants**: 101 (78 in the HCL group; 23 in the control group) **Mean age**: 11.3 (SD = 2.0) years in the HCL group; 10.8 (SD = 2.4) years in the control group **Sex**: 49% female in the HCL group; 52% female in the control group **Mean BMI z score**: 0.4 (SD = 1.0) in the HCL group; 0.5 (SD = 1.0) in the control group **Mean baseline A1C (at screening)**: 7.7% (SD = 1.1%) in the HCL group; 8.0% (SD = 1.1%) in the control group			• Proportion of participants with an absolute reduction in A1C of ≥ 0.5%[a] • Proportion of participants with an absolute reduction in A1C of ≥ 1.0%[a] • Proportion of participants with a relative reduction in A1C of • ≥ 10%[a] • Proportion of participants with an absolute reduction in A1C of ≥ 1.0% from baseline or an A1C value of < 7.0% at 26 weeks[a] • Body weight[a] • Total daily insulin amount[a] • Frequency of severe hypoglycemia[a] • Number of hypoglycemic events per week[a] • Number of hyperglycemic events per week[a] • Frequency of diabetes ketoacidosis[a] • Adverse event rates (e.g., ketosis events, diabetic ketoacidosis events)[a] • Proportion of participants who had a worsening in A1C of ≥ 0.5% post-treatment[a] **Follow-up**: Data were collected over a 16-week study period. Participants in both groups attended follow-up visits at weeks 2, 8, and 16 post-randomization. Additionally, patients were

Study citation, country, and funding source	Study design, setting, and objective	Patient characteristics	Intervention(s)	Comparator(s)	Clinical outcomes, length of follow-up, and subgroup analyses
		Mean baseline A1C (at randomization): 7.6% (SD = 1.0%) in the HCL group; 7.9% (SD = 0.9%) in the control group			contacted by telephone at weeks 1, 4, 6, 10, 12, and 14 post-randomization. **Subgroup analyses**: Age (6 years to 9 years versus 10 years to 14 years), sex (female versus male), glycemic control (A1C < 8.0% versus ≥ 8.0%, percentage of time spent with a glucose value < 3.9 mmol/L [< 1.5% versus ≥ 1.5%], percentage of time spent with a glucose value > 10.0 mmol/L [< 50% versus ≥ 50%], percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L [< 50% versus ≥ 50%])
Brown et al. (2020) US **Funding source**: Funding was received from a National Institute of Diabetes and Digestive and Kidney Disease grant (UC4 108483) and the University of Virginia Strategic Investment Fund, project number 88.	**Study design**: Multi-centre, open-label, RCT that was an extension of a previously reported RCT[53] (also included in this Clinical Review) **Setting**: Participants were recruited from the closed-loop control group of an RCT that was conducted at 7 US diabetes centres. **Objective**: To assess the efficacy of an HCL	**Inclusion criteria**: Participants who received treatment with the Control-IQ HCL in a 6-month RCT[53] preceding this extension study were enrolled. The previous trial[53] recruited individuals (≥ 14 years of age) with a clinical diagnosis of type 1 diabetes who had been treated using insulin for at least 1 year using a pump or multiple daily injections. **Excluded**: The preceding trial[53] excluded those with	The Control-IQ HCL, which included a t:slim X2 insulin pump and a Dexcom G6 CGM that were managed by the Control-IQ software	An open-loop PLGS system, which included a t:slim X2 insulin pump and a Dexcom G6 CGM that were managed by the Basal-IQ software	**Primary outcome**: • Percentage of time spent in the glucose range of 70 mg/dL to 180 mg/dL (3.9 mmol/L to 10.0 mmol/L) **Secondary outcomes**: • Percentage of time spent in the glucose range of 70 mg/dL to 140 mg/dL (3.9 mmol/L to 7.8 mmol/L) • Percentage of time spent with glucose < 54 mg/dL (< 3.0 mmol/L)

Study citation, country, and funding source	Study design, setting, and objective	Patient characteristics	Intervention(s)	Comparator(s)	Clinical outcomes, length of follow-up, and subgroup analyses
Tandem Diabetes Care provided the closed-loop systems and system-related supplies, but was not involved in data analysis.	compared with a PLGS system that used the same insulin pump and CGM	concurrent use of any non-insulin glucose-lowering drug other than metformin (e.g., GLP-1 agonists, DPP-4 inhibitors), those who were known to be pregnant, those with hemophilia or any other bleeding disorder, and those who were participating in another pharmaceutical or device trial at the time of enrolment. **Number of participants**: 109 (54 in the HCL group; 55 in the PLGS group) **Mean age**: 32 (SD = 14) years in the HCL group; 34 (SD = 17) years in the PLGS group **Sex**: 52% female in the HCL group; 45% female in the PLGS group **Median BMI**: 26 (IQR, 23 to 30) kg/m^2 in the HCL group; 25 (IQR, 23 to 29) kg/m^2 in the PLGS group **Mean baseline A1C**: 53 (SD = 8.7) mmol/mol in the HCL group (7.0% [SD = 0.8%]); 54 (SD = 8.7)			• Percentage of time spent with glucose < 60 mg/dL (< 3.3 mmol/L) • Percentage of time spent with glucose < 70 mg/dL (< 3.9 mmol/L) • Percentage of time spent with glucose > 180 mg/dL (> 10.0 mmol/L) • Percentage of time spent with glucose > 250 mg/dL (> 13.9 mmol/L) • Percentage of time spent with glucose > 300 mg/dL (> 16.7 mmol/L) • Mean A1C • Proportion of participants with A1C < 7.0% post-treatment • Proportion of participants with A1C < 7.5% post-treatment • Mean glucose (mg/dL; mmol/L) • Glycemic variability • Body weight • Total daily insulin amount • Number of adverse events (e.g., diabetic ketoacidosis, ketosis events) • Proportion of participants who had a worsening in their A1C by at least 0.5% **Follow-up**: 13 weeks **Subgroup analyses**: Age (14 years to 24 years versus 25 years to 71 years), sex (female

Study citation, country, and funding source	Study design, setting, and objective	Patient characteristics	Intervention(s)	Comparator(s)	Clinical outcomes, length of follow-up, and subgroup analyses
		mmol/mol in the PLGS group (7.1% [SD = 0.8%])			versus male), glycemic control (A1C ≤ 7.5% versus > 7.5%), percentage of time spent with a glucose value below 3.9 mmol/L (≤ 1% versus > 1%), percentage of time spent with a glucose value > 10.0 mmol/L (≤ 40% versus > 40%), percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (≤ 60% versus > 60%)
Hanaire et al. (2020) France **Funding source**: Funding was received from BPI France, the Center for Studies and Research for the Intensification of the Treatment of Diabetes, and Diabeloop SA	**Study design**: Multi-centre, open-label, 3-arm randomized controlled crossover trial. Participants were allocated into 1 of 3 cohorts: 1) control rest condition; 2) gastronomic dinners; or 3) sustained and repeated bouts of physical exercise followed by uncontrolled food intake. Each participant was tested in their assigned condition with the HCL and the open-loop SAP system using a randomized crossover design. **Setting**: Participants were recruited from 9 university diabetes	**Inclusion criteria**: Adults (≥ 18 years of age) with a diagnosis of type 1 diabetes for at least 1 year and who had been treated using external insulin-pump therapy for at least 6 months. Additionally, participants were required to have A1C values > 42 mmol/mol and < 80 mmol/mol, to be experienced with carbohydrate counting, to have the ability to understand and follow the instructions of the study, and to provide written consent to participate. **Excluded**: Those with type 2 diabetes, serious illness that could impair their participation, insulin	The Diabeloop single-hormone HCL, which included a Cellnovo insulin pump and a Dexcom G5 CGM managed by the Diabeloop algorithm installed on an Android smartphone	Open-loop SAP therapy, which included the participant's existing insulin pump and a Dexcom G5 CGM. The use of PLGS features was not allowed throughout the trial.	**Primary outcome**: • Percentage of time spent in the glucose range of 4.4 mmol/L to 7.8 mmol/L during the night-time (11:00 p.m. to 8:00 a.m.) **Secondary outcomes**: • Percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L during the night and during the entire 72-hour study • Percentage of time spent with glucose < 3.9 mmol/L • Percentage of time spent with glucose > 10.0 mmol/L • Interstitial glucose over the whole 72-hour study period • Total daily insulin dose • Participant satisfaction (measured with the DTSQ) • Adverse events

Study citation, country, and funding source	Study design, setting, and objective	Patient characteristics	Intervention(s)	Comparator(s)	Clinical outcomes, length of follow-up, and subgroup analyses
	centres in France. Participants were largely restricted to hospital settings throughout the test periods. **Objective**: To compare the Diabeloop HCL to an open-loop SAP system in patients with type 1 diabetes exposed to glycemic challenges (e.g., gastronomic meals, sustained physical exercise)	resistance, or hypoglycemia unawareness. **Number of participants**: 38 (14 in the rest cohort; 10 in the gastronomic dinner cohort; 14 in the exercise cohort) **Mean age**: 49.9 (SD = 14.5) years **Sex**: 57.9% female **Mean BMI**: 25.5 (SD = 4.1) kg/m^2 **Mean baseline A1C**: 62 (SD = 8) mmol/mol			**Follow-up**: Outcomes were monitored over a 3-day period for each intervention, with a minimum of 7 days for washout between the 2 testing periods. **Subgroup analyses**: None
McAuley et al. (2020) Australia **Funding source**: The JDRF Australian Type 1 Diabetes Clinical Research Network and the National Health and Medical Research Council of Australia. Medtronic provided the HCLs, masked	**Study design**: Multi-centre, open-label, parallel-group RCT **Setting**: Participants were recruited from 7 tertiary hospitals in Australia between April 2017 and January 2019. **Objective**: To investigate the effectiveness of HCL therapy versus user-determined insulin	**Inclusion criteria**: Adults (≥ 25 years and ≤ 75 years of age) with a clinical diagnosis of type 1 diabetes for at least 1 year who had A1C levels ≤ 10.5% (≤ 91 mmol/mol) and who had been treated using MDII or insulin-pump therapy. Purposive sampling ensured at least 40% of participants were on MDII or insulin-pump therapy. **Excluded**: Those with chronic kidney conditions,	The Medtronic MiniMed 670G HCL system, which included a MiniMed 670G insulin pump and an Enlite 3 CGM that were managed by the MiniMed 670G software. All HCL participants wore a masked Guardian Sensor 3 CGM to collect study outcome measurements.	Participants assigned to the control group continued using their own personal insulin-delivery device in conjunction with a bolus dose calculator (integrated within either their insulin pump or an Accu-Chek Aviva Expert glucose meter) for meal-related dose estimation. All control participants wore a masked Guardian Sensor 3 CGM to collect study outcome measurements.	**Primary outcome**: • Percentage of time spent in the glucose range of 70 mg/dL to 180 mg/dL (3.9 mmol/L to 10.0 mmol/L) at 23 weeks to 26 weeks post-randomization **Secondary outcomes**: • Percentage of time spent in the glucose range of 70 mg/dL to 140 mg/dL (3.9 mmol/L to 7.8 mmol/L) at 23 weeks to 26 weeks post-randomization • Percentage of time spent with glucose < 50 mg/dL

Study citation, country, and funding source	Study design, setting, and objective	Patient characteristics	Intervention(s)	Comparator(s)	Clinical outcomes, length of follow-up, and subgroup analyses
CGM devices, and technical expertise with device issues. Roche Diabetes Care provided blood glucose meters for participants using MDII. The funders of the trial had no role in data collection, data analysis, data interpretation, or writing of the report. Medtronic was involved in the collection of CGM-recorded data and provided the raw dataset to the research team for analysis.	dosing with MDII or insulin-pump therapy with respect to glycemic and psychosocial outcomes	current use of a real-time CGM, use of any non-insulin glucose-lowering drug or oral or injected steroid use within the past 3 months; those who were pregnant or planning pregnancy; and those who had uncontrolled celiac disease, hypertension, thyroid conditions, clinically significant gastroparesis, poor visual acuity precluding the use of HCL systems, and those with a history of several heart conditions or unstable medical or psychological conditions. **Number of participants**: 120 (61 in the HCL group; 59 in the control group) **Mean age**: 43.7 (SD = 11.7) years in the HCL group; 44.7 (SD = 11.8) years in the control group **Sex**: 54% female in the HCL group; 53% female in the control group **Mean BMI**: 26.8 (SD = 5.3) kg/m^2 in the HCL group; 26.0 (SD = 4.0) kg/m^2 in the control group		Overall, 28 of the 59 patients in the control group used an insulin pump, while the remaining 31 used MDII. Participants with insulin pumps did not use PLGS features.	(< 2.8 mmol/L) at 23 weeks to 26 weeks post-randomization • Percentage of time spent with glucose < 54 mg/dL (< 3.0 mmol/L) at 23 weeks to 26 weeks post-randomization • Percentage of time spent with glucose < 59 mg/dL (< 3.3 mmol/L) at 23 weeks to 26 weeks post-randomization • Percentage of time spent with glucose < 70 mg/dL (< 3.9 mmol/L) at 23 weeks to 26 weeks post-randomization • Percentage of time spent with glucose > 180 mg/dL (> 10.0 mmol/L) at 23 weeks to 26 weeks post-randomization • Percentage of time spent with glucose > 200 mg/dL (> 11.1 mmol/L) at 23 weeks to 26 weeks post-randomization • Percentage of time spent with glucose > 250 mg/dL (> 13.9 mmol/L) at 23 weeks to 26 weeks post-randomization • Mean glucose (mg/dL; mmol/L) • Coefficient of variation of glucose • Mean A1C • Intermediate-term glycemia (measured with mean 1,5-Anhydroglucitol serum levels) • Change in total daily insulin dose

Study citation, country, and funding source	Study design, setting, and objective	Patient characteristics	Intervention(s)	Comparator(s)	Clinical outcomes, length of follow-up, and subgroup analyses
		Mean baseline A1C (at enrolment): 7.8% (SD = 1.1%) in the HCL group; 7.7% (SD = 0.9%) in the control group **Mean baseline A1C (at randomization)**: 7.4% (SD = 0.9%) in the HCL group; 7.5% (SD = 0.8%) in the control group			• Change in basal-insulin proportion • Change in insulin-to-carbohydrate ratio • Change in body weight • Participant satisfaction (measured with the DTSQ) • Diabetes distress (measured with the PAID scale) • Diabetes-specific quality of life (measured with the DIDP) • Diabetes-specific positive well-being (measured with the 4-item subscale of the W-BQ28) • Prospective memory (measured with the PRMQ Prospective) • Retrospective memory (measured with the PRMQ Retrospective) • Perceived sleep quality (measured with the PSQI) **Safety outcomes**: • Serious adverse events • Severe hypoglycemia (defined as hypoglycemia requiring assistance from another person to administer carbohydrate or glucagon or take other corrective actions) • Diabetic ketoacidosis **Follow-up**: 26 weeks **Subgroup analyses**: None

Study citation, country, and funding source	Study design, setting, and objective	Patient characteristics	Intervention(s)	Comparator(s)	Clinical outcomes, length of follow-up, and subgroup analyses
Benhamou et al. (2019) France **Funding source**: The French Innovation Fund and Diabeloop	**Study design**: Multi-centre, open-label, randomized controlled crossover trial **Setting**: Participants were recruited from 12 university hospitals in France. The test periods were conducted under free-living conditions. **Objective**: To evaluate whether the Diabeloop HCL system improved glucose control compared with SAP therapy in patients with type 1 diabetes	**Inclusion criteria**: Adults (≥ 18 years of age) were eligible if they had a diagnosis of type 1 diabetes for at least 2 years, A1C of 10% (86 mmol/mol) or less within the past 4 months, preserved hypoglycemia awareness (defined as a Gold score ≤ 4),[188] insulin requirements of ≤ 50 units/day, and had been treated using external insulin-pump therapy for at least 6 months. **Excluded**: Those with severe hypoglycemia or any serious pathology that could alter their participation in the study, those who were pregnant or might become pregnant over the study period, those who were currently breastfeeding a child, those with impaired renal function (defined as a creatinine clearance < 30 mL/min), and those with serious uncorrected hearing or visual problems. **Number of participants**: 63 **Mean age**: 48.2 (SD = 13.4) years	The Diabeloop single-hormone HCL system, which included a Cellnovo insulin pump and a Dexcom G5 CGM managed by the Diabeloop algorithm installed on an Android smartphone	Open-loop SAP therapy, which included the participant's existing insulin pump and a Dexcom G5 CGM. No recommended thresholds were used for high- and low-glucose alarms; participants had the freedom to activate or shut off these alarms depending on their preference. The use of PLGS features was not allowed throughout the trial.	**Primary outcome**: • Percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L **Secondary outcomes**: • Percentage of time spent in the optimal target glucose range of 4.4 mmol/L to 7.8 mmol/L • Percentage of time with glucose concentrations in hypoglycemia (< 2.8 mmol/L, < 3.3 mmol/L, < 3.9 mmol/L) • Percentage of time with glucose concentrations in hyperglycemia (> 10.0 mmol/L, > 13.9 mmol/L, and > 16.7 mmol/L) • Mean sensor glucose concentration during each 12-week period • A1C measured at the beginning and end of each treatment period • Coefficient of variation of glucose • Total insulin intake • The number and the amount of carbohydrate intakes during the last week of each treatment period • Participant satisfaction (measured with the DTSQ)

Study citation, country, and funding source	Study design, setting, and objective	Patient characteristics	Intervention(s)	Comparator(s)	Clinical outcomes, length of follow-up, and subgroup analyses
		Sex: 62% female **Mean BMI**: 24.8 (SD = 3.5) kg/m^2 **Mean baseline A1C**: 59.4 (SD = 9.8) mmol/mol			**Safety outcomes**: • The number of severe hypoglycemic events (defined as requiring intervention of a third party) • The number of severe hyperglycemic episodes (defined as capillary blood glucose ≥ 20.0 mmol/L or significant ketoacidosis [plasma ketone > 3 mmol/L]) **Follow-up**: Outcomes were monitored over a 12-week period for each intervention, with 8 weeks of washout between the 2 testing periods. Hospital visits were scheduled at weeks 1, 3, 6, 7, and 12 to download CGM data, monitor adverse events, and complete the DTSQ. **Subgroup analyses**: None
Brown et al. (2019) and Isganaitis et al. (2020) US **Funding source**: Funding was received from the National Institute of Diabetes and Digestive and	**Study design**: Multi-centre, open-label, parallel-group RCT **Setting**: Participants were recruited from 7 university centres in the US. **Objective**: To investigate the efficacy and safety of the	**Inclusion criteria**: Individuals (≥ 14 years of age) with a clinical diagnosis of type 1 diabetes who had been treated using insulin for at least 1 year using a pump or multiple daily injections. Participants were required to have familiarity with using carbohydrate ratios for meal boluses and have a total daily insulin dose of at least	The Control-IQ HCL system, which included a t:slim X2 insulin pump and a Dexcom G6 CGM that were managed by the Control-IQ software	Open-loop SAP therapy, which included the participant's existing insulin pump and a Dexcom G6 CGM. Participants in this group who were multiple daily injection users at the time of enrolment used a t:slim X2 pump without the Control-IQ software.	**Primary outcome**: • Percentage of time spent in the glucose range of 70 mmol/L to 180 mg/dL (3.9 mmol/L to 10.0 mmol/L) **Secondary outcomes**: • Percentage of time spent in the glucose range of 70 mmol/L to 140 mg/dL (3.9 mmol/L to 7.8 mmol/L)

Study citation, country, and funding source	Study design, setting, and objective	Patient characteristics	Intervention(s)	Comparator(s)	Clinical outcomes, length of follow-up, and subgroup analyses
Kidney Diseases. The University of Virginia Strategic Investment Fund provided institutional and regulatory support. Tandem Diabetes Care provided the closed-loop systems, supplies, and technical expertise with device issues, but was not involved in the trial design, conduct, data analysis, or manuscript preparation.	Control-IQ HCL system compared with SAP therapy	10 units/day. The Isganaitis et al. (2020) publication included a subgroup analysis on participants between the ages of 14 years and 24 years. **Excluded**: Those with concurrent use of any non-insulin, glucose-lowering drug other than metformin (e.g., GLP-1 agonists, DPP-4 inhibitors), those who were known to be pregnant, those with hemophilia or any other bleeding disorder, and those who were participating in another pharmaceutical or device trial at the time of enrolment. **Number of participants**: 168 (112 in the HCL group; 56 in the SAP group). The Isganaitis et al. (2020) subgroup had 63 participants (40 in the HCL group; 23 in the SAP group). **Mean age**: 33 (SD = 16) years in the HCL group; 33 (SD = 17) years in the SAP group. The Isganaitis et al. (2020) subgroup: 17 (SD = 3) years in the HCL group; 17 (SD = 3) years in the SAP group.			• Percentage of time with glucose values > 180 mg/dL (> 10.0 mmol/L) • Percentage of time with glucose values > 250 mg/dL (> 13.9 mmol/L) • Percentage of time with glucose values > 300 mg/dL (> 16.7 mmol/L) • Mean glucose concentration • Various measures of A1C • Percentage of time with glucose values < 70 mg/dL (< 3.9 mmol/L) • Percentage of time with glucose values < 60 mg/dL (< 3.3 mmol/L) • Percentage of time with glucose values < 54 mg/dL (< 3.0 mmol/L) • Glycemic variability • Body weight • Insulin usage • Adverse events (e.g., diabetic ketoacidosis, ketosis, proportion of participants with a worsening of their A1C by at least 0.5%) **Follow-up**: Data were collected continuously over a run-in phase of 2 weeks to 8 weeks followed by the 26-week study period. Participants in both groups attended follow-up visits at weeks 2, 6, 13, and 26 post-randomization. Additionally,

Study citation, country, and funding source	Study design, setting, and objective	Patient characteristics	Intervention(s)	Comparator(s)	Clinical outcomes, length of follow-up, and subgroup analyses
		Sex: 48% female in the HCL group; 54% female in the SAP group. The Isganaitis et al. (2020) subgroup: 43% female in the HCL group; 43% female in the SAP group. **Median BMI**: 25 (IQR, 23 to 29) kg/m^2 in the HCL group; 25 (IQR, 22 to 28) kg/m^2 in the SAP group. The Isganaitis et al. (2020) subgroup: For participants ≥ 18 years of age, 29 (IQR, 23 to 35) kg/m^2 in the HCL group; 26 (IQR, 24 to 26) kg/m^2 in the SAP group. For participants < 18 years of age, BMI percentiles were 78% (IQR, 55% to 88%) in the HCL group; 68% (IQR, 45% to 86%) in the SAP group. **Mean baseline A1C**: 7.4% (SD = 1.0%) in the HCL group; 7.4% (SD = 0.8%) in the SAP group. The Isganaitis et al. (2020) subgroup: 8.2% (SD = 1.1%) in the HCL group; 8.0% (SD = 1.2%) in the SAP group.			patients were contacted by telephone at weeks 1, 4, 9, 17, and 21 post-randomization. **Subgroup analyses**: Age (14 years to 24 years versus 25 years to 71 years), sex (female versus male), glycemic control (A1C ≤ 7.5% versus > 7.5%), percentage of time spent with a glucose value < 3.9 mmol/L (≤ 4% versus > 4%), percentage of time spent with a glucose value > 10.0 mmol/L (≤ 40% versus > 40%), percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (≤ 60% versus > 60%)

Study citation, country, and funding source	Study design, setting, and objective	Patient characteristics	Intervention(s)	Comparator(s)	Clinical outcomes, length of follow-up, and subgroup analyses
Ekhlaspour et al. (2019) US **Funding source**: The University of Virginia Strategic Investment in Type 1 Diabetes Project and Tandem Diabetes Care	**Study design**: Multi-centre, open-label, parallel-group RCT **Setting**: Participants were recruited and enrolled at 3 sites (Stanford University, the University of Colorado, and the University of Virginia). Following enrolment, participants took part in a 48-hour ski camp at one of 3 sites. **Objective**: To evaluate the effectiveness of the Tandem Control-IQ HCL system compared to SAP therapy in adolescents and children during a winter ski camp	**Inclusion criteria**: Individuals (≥ 6 years and ≤ 18 years of age) with a clinical diagnosis of type 1 diabetes who had been insulin-treated for at least 1 year and on insulin-pump treatment for at least 3 months **Excluded**: Those with a recent history of severe hypoglycemia or diabetes ketoacidosis (within the last 6 months), those who required long-acting or any non-insulin antidiabetic medications, those who were pregnant, those who had active renal or cardiac illness, and those with a history of altitude sickness **Number of participants**: 48 (24 in the HCL group; 24 in the SAP group) **Mean age**: 12.5 (SD = 3.1) years in the HCL group; 12.0 (SD = 3.2) years in the SAP group **Gender**: 46% female in the HCL group; 54% female in the SAP group	The Control-IQ HCL, which included a t:slim X2 insulin pump and a Dexcom G6 CGM that were managed by the Control-IQ software. Participants in this group wore a second CGM (Dexcom G5) that was used to monitor glucose outcomes but did not inform the insulin delivery of the HCL system. The CGM data of participants in both groups were remotely monitored by a physician throughout the study.	Open-loop SAP therapy, which included the participant's existing insulin pump and a Dexcom G5 CGM. Existing insulin pumps included the Tandem t:slim (N = 9), the Insulet Omnipod (N = 4), a variety of Medtronic pumps (N = 7; 670G, 530G, Revel, Paradigm, 751), and the Animas Ping (N = 4). Automated insulin modes (e.g., PLGS) were deactivated for participants in the control group. The CGM data of participants in both groups were remotely monitored by a physician throughout the study.	**Primary outcome**: • Percentage of time spent in the glucose range of 70 mg/dL to 180 mg/dL (3.9 mmol/L to 10.0 mmol/L) **Secondary outcomes**: • Percentage of time with glucose values < 70 mg/dL (< 3.9 mmol/L) • Percentage of time with glucose values < 60 mg/dL (< 3.3 mmol/L) • Percentage of time with glucose values < 54 mg/dL (< 3.0 mmol/L) • Percentage of time with glucose values < 50 mg/dL (< 2.8 mmol/L) • Percentage of time with glucose values > 180 mg/dL (> 10.0 mmol/L) • Percentage of time with glucose values > 250 mg/dL (> 13.9 mmol/L) • Percentage of time with glucose values > 300 mg/dL (> 16.7 mmol/L) • Mean glucose concentration • Glycemic variability • Insulin usage **Safety outcomes**: • Total number of carbohydrate treatments

Study citation, country, and funding source	Study design, setting, and objective	Patient characteristics	Intervention(s)	Comparator(s)	Clinical outcomes, length of follow-up, and subgroup analyses
		Mean BMI: 20.4 (SD = 2.8) kg/m^2 in the HCL group; 21.7 (SD = 5.7) kg/m^2 in the SAP group **Mean baseline A1C**: 7.8% (SD = 1.3%) in the HCL group; 7.7% (SD = 0.9%) in the SAP group			**Follow-up**: Outcomes were monitored over a 48-hour period. **Subgroup analyses**: None
Forlenza et al. (2019) US **Funding source**: Tandem Diabetes Care, Dexcom, and the University of Virginia strategic investment in type 1 diabetes fund-PriMeD project	**Study design**: Multi-centre, open-label, parallel-group RCT that was an extension of a previously reported RCT (also included in this Clinical Review) **Setting**: Participants who were recruited from 2 sites in the previous RCT (Barbara Davis Center and Stanford University) continued with their assigned therapy for 3 days of home use. **Objective**: To evaluate the efficacy of the Tandem Control-IQ HCL for improved time in range compared to SAP therapy in children aged 6 years to 12	**Inclusion criteria**: Individuals (≥ 6 years and ≤ 12 years of age) with a clinical diagnosis of type 1 diabetes who were insulin-treated for at least 6 months and were on insulin-pump treatment for at least 3 months. Additional inclusion criteria included willingness to use only insulin lispro or insulin as part during the trial and avoiding the use of acetaminophen. **Excluded**: Those with ketoacidosis, hypoglycemic seizure, or loss of consciousness in the past 6 months; those with a history of seizure disorder, renal conditions, or altitude sickness; those with chronic pulmonary conditions; those who used oral glucocorticoids; those who	The Control-IQ HCL system, which included a t:slim X2 insulin pump and a Dexcom G6 CGM that were managed by the Control-IQ software. Participants in this group wore a second CGM (Dexcom G5) that was used for monitoring glucose outcomes but did not inform the insulin delivery of the HCL system. The CGM data of participants in both groups were remotely monitored by a physician throughout the study.	Open-loop SAP therapy, which included the participant's existing insulin pump and a Dexcom G5 CGM. The CGM data of participants in both groups were remotely monitored by a physician throughout the study.	**Primary outcome**: • Percentage of time spent in the glucose range of 70 mg/dL to 180 mg/dL (3.9 mmol/L to 10.0 mmol/L) **Secondary outcomes**: • Mean glucose concentration • Glycemic variability based on coefficient of variation • Percentage of time spent in the glucose range of 70 mg/dL to 140 mg/dL (3.9 mmol/L to 7.8 mmol/L) • Percentage of time with glucose values < 70 mg/dL (< 3.9 mmol/L) • Percentage of time with glucose values < 60 mg/dL (< 3.3 mmol/L) • Percentage of time with glucose values < 54 mg/dL (< 3.0 mmol/L) • Percentage of time with glucose values < 50 mg/dL (< 2.8 mmol/L)

Study citation, country, and funding source	Study design, setting, and objective	Patient characteristics	Intervention(s)	Comparator(s)	Clinical outcomes, length of follow-up, and subgroup analyses
	years during 3 days of home use	required intermediate or long-acting insulin or other antidiabetic medications; those with a febrile illness; and those with other medical and psychiatric conditions that could interfere with completion of the study **Number of participants**: 24 (12 in the HCL group; 12 in the SAP group) **Mean age**: 10.0 (SD = 2.1) years in the HCL group; 9.2 (SD = 1.5) years in the SAP group **Gender**: 50% female in the HCL group; 50% female in the SAP group **Mean BMI**: 19.2 (SD = 2.7) kg/m^2 in the HCL group; 17.8 (SD = 3.5) kg/m^2 in the SAP group **Mean baseline A1C**: 7.35% (SD = 0.74%) in the HCL group; 7.36% (SD = 0.65%) in the SAP group			• Percentage of time with glucose values > 180 mg/dL (< 10.0 mmol/L) • Percentage of time with glucose values > 250 mg/dL (> 13.9 mmol/L) • Percentage of time with glucose values > 300 mg/dL (> 16.7 mmol/L) • Total daily insulin dose • System usability (the percent time with the HCL algorithm being active) • Participant experience (measured with a 38-item Technology Acceptance Questionnaire) **Safety outcomes**: • Total amount of carbohydrates required for hypoglycemia treatment **Follow-up**: Outcomes were monitored over a 3-day period. **Subgroup analyses**: None
Non-randomized studies					
Lepore et al. (2020) Italy	**Study design**: Single-centre, retrospective, matched-cohort study	**Inclusion criteria**: Adults with type 1 diabetes who had been using SAP therapy with	The Medtronic MiniMed 670G HCL system, which included a	The MiniMed 640G pump with PLGS. This system	**Outcomes**: • Change in A1C

Study citation, country, and funding source	Study design, setting, and objective	Patient characteristics	Intervention(s)	Comparator(s)	Clinical outcomes, length of follow-up, and subgroup analyses
Funding source: No specific funding was received for this study.	**Setting**: Data from individuals who received their diabetes care at the study centre were evaluated. **Objective**: To investigate the effects of switching from SAP therapy to HCL therapy with respect to metabolic control and glucose variability compared to continuing use of SAP therapy in patients with type 1 diabetes	PLGS for at least 12 months before the study **Excluded**: Those who did not regularly use carbohydrate counting and insulin bolus calculators and those who were pregnant or were planning pregnancy were excluded from switching to the HCL group. **Number of participants**: 40 (20 in the HCL group; 20 in the SAP-with-PLGS group) **Mean age**: 42.1 (SD = 18.5) years in the HCL group; 45.9 (SD = 12.2) years in the group using SAPs with PLGS **Sex**: 45% female in the HCL group; 45% female in the SAP-with-PLGS group **Mean BMI**: 24.4 (SD = 10.9) kg/m^2 in the HCL group; 25.2 (SD = 12.9) kg/m^2 in the SAP-with-PLGS group **Mean baseline A1C**: 57.5 (SD = 10.1) mmol/mol in the HCL group; 57.9 (SD = 9.8) mmol/mol in the SAP-with-PLGS group	MiniMed 670G insulin pump and a Guardian Sensor 3 CGM that were managed by the MiniMed 670G software	used a Guardian Sensor 3 CGM. Age, sex, and A1C levels were used to match cases (those in the HCL group) and controls (those in the group receiving SAP therapy with PLGS).	• Percentage of time with glucose values < 54 mg/dL (< 3.0 mmol/L) • Percentage of time spent in the glucose range of 54 mg/dL to 69 mg/dL (3.0 mmol/L to 3.8 mmol/L) • Percentage of time spent in the glucose range of 70 mg/dL to 180 mg/dL (3.9 mmol/L to 10.0 mmol/L) • Percentage of time spent in the glucose range of 181 mg/dL to 250 mg/dL (10.0 mmol/L to 13.9 mmol/L) • Percentage of time with glucose values > 250 mg/dL (> 13.9 mmol/L) • Mean sensor glucose concentration • Change in coefficient of variation of sensor glucose concentrations measured in the month preceding the study and in the last month of the study period • Episodes of severe hypoglycemia (defined as an event requiring assistance and the administration carbohydrates or glucagon) • Episodes of diabetic ketoacidosis (defined as acidosis, hyperketonemia, and hyperglycemia) • Insulin usage

Study citation, country, and funding source	Study design, setting, and objective	Patient characteristics	Intervention(s)	Comparator(s)	Clinical outcomes, length of follow-up, and subgroup analyses
					Follow-up: 6 months **Subgroup analyses**: None

A1C = glycated hemoglobin; BMI = body mass index; CGM = continuous glucose monitor; DIDP = DAWN2 Impact of Diabetes Profile; DPP-4 = dipeptidyl peptidase-4; DTSQ = Diabetes Treatment Satisfaction Questionnaire; GLP-1 = glucagon-like peptide 1; HCL = hybrid closed-loop insulin delivery system; IQR = interquartile range; MDII = multiple daily insulin injections; PAID = Problem Areas in Diabetes; PLGS = predictive low-glucose suspend; PRMQ = Prospective and Retrospective Memory Questionnaire; PSQI = Pittsburgh Sleep Quality Index; RCT = randomized controlled trial; SAP = sensor-augmented pump; SD = standard deviation; W-BQ28 = Well-Being Questionnaire 28.

[a] These outcomes were considered exploratory and not included in the hierarchical analysis.

[b] Clarified by the corresponding author of the study.

Critical Appraisal of Primary Studies

Table 39: Risk of Bias in the Included Randomized Controlled Trials Assessed Using RoB 2

Study citation	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	Bias in selection of the reported result	Overall risk of bias
Breton et al. (2020)[51]	**Some concerns** • Allocation sequence was likely random (participants were randomly assigned in a 3:1 ratio with a permuted block design [block sizes of 4 and 8] stratified by trial site); randomization was done on the trial website with a computer-generated sequence. (Y) • There was no information about whether allocation sequence was concealed until participants were enrolled and assigned to intervention; however, the block size varied between 4 and 8, decreasing the risk for selection bias due to selective enrolment. (NI)	**Low risk** • Participants were aware of their assigned intervention during the trial (open-label). (Y) • Carers and people delivering the intervention were aware of the participants' assigned intervention during the trial (open-label). (Y) • There were no reported deviations from the intended intervention that arose because of the trial context. (N) • Appropriate analysis was used to estimate the effect of assignment to intervention (ITT analysis). (Y)	**Glucose TIR metrics: Low risk** **A1C: Low risk** **AEs: Low risk** • Outcome data were available for all, or nearly all, participants randomized (the trial was completed by 100 out of 101 participants). (Y)	**Glucose TIR metrics: Low risk** **A1C: Low risk** **AEs: Some concerns** • The method of measurement was probably not inappropriate (glucose TIR metrics were measured using a CGM; A1C was measured either with the use of a point-of-care device or by a local laboratory; AEs were patient-reported or measured using a CGM). (PN) • Participants in the HCL group had more unscheduled contacts with study staff than those in the open-loop group; however, most of these contacts were to obtain device software updates or supplies related to the trial, and were judged not to have	**Low risk** • The data that produced these results were analyzed in accordance with a pre-specified analysis plan, which was finalized before outcome data were available for analysis; a protocol was registered on ClinicalTrials.gov (NCT03844789) and posted on NEJM.org. (Y) • The numerical result being assessed was not likely to have been selected, on the basis of results from multiple eligible outcome measurements within the outcome domain (PN) or multiple eligible analyses of the data (PN), based on the a priori protocol.	**Some concerns**

Study citation	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	Bias in selection of the reported result	Overall risk of bias
	• The lack of baseline differences between groups does not suggest a problem with the randomization process. (N)			implications for outcome reporting; it is not likely that the measurement or ascertainment of the outcomes differed between intervention groups. (PN) • Outcome assessors were aware of the intervention received by study participants. (Y) • For glucose TIR metrics, A1C, and safety outcomes measured using a CGM, it is not likely that the outcomes could have been influenced by knowledge of the intervention received (the outcomes were largely objective). (PN) • It is possible that patient-reported safety outcomes were influenced by the knowledge of intervention received. (PY) • It is not likely that the assessment of the outcome was		

Study citation	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	Bias in selection of the reported result	Overall risk of bias
				influenced by the knowledge of intervention received. (PN)		
Brown et al. (2020)[52]	**Some concerns** • Allocation sequence was likely random (participants were randomly assigned using a permuted block design stratified by clinical site); method of randomization was unclear. (PY) • No information about whether allocation sequence was concealed until participants were enrolled and assigned to intervention. (NI) • The lack of baseline differences between groups does not suggest a problem with the randomization process. (N)	**Low risk** • Participants were aware of their assigned intervention during the trial (open-label). (Y) • Carers and people delivering the intervention were aware of the participants' assigned intervention during the trial (open-label). (Y) • There were no reported deviations from the intended intervention that arose because of the trial context.(N) • Appropriate analysis was used to estimate the effect of assignment to intervention (ITT analysis). (Y)	**Glucose TIR metrics: Low risk** **A1C: Low risk** **AEs: Low risk** • Outcome data were available for all, or nearly all, participants randomized (no participants dropped out). (Y)	**Glucose TIR metrics: Low risk** **A1C: Low risk** **AEs: Low risk** • The method of measurement was probably not inappropriate (glucose TIR metrics were measured using a CGM; A1C was measured by a • central laboratory; AEs were patient-reported or measured using a CGM). (PN) • Participants in the PLGS group had 2 additional phone contacts with study staff (after 1 week and 2 weeks of treatment). However, adverse events were detected by continuous glucose monitoring data (and were not physician or patient detected). Thus, it is not likely that the	**Low risk** • The data that produced these results were probably analyzed in accordance with a pre-specified analysis plan, which was likely finalized before outcome data were available for analysis; a protocol was registered on ClinicalTrials.gov (NCT03591354). (PY) • The numerical result being assessed was not likely to have been selected, on the basis of results from multiple eligible outcome measurements within the outcome domain (PN) or multiple eligible analyses of the data (PN), based on the a priori protocol.	**Some concerns**

Study citation	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	Bias in selection of the reported result	Overall risk of bias
				measurement or ascertainment of the outcomes differed between intervention groups. (PN) • Outcome assessors were aware of the intervention received by study participants. (Y) • It is not likely that the outcomes could have been influenced by knowledge of the intervention received (the outcomes were largely objective). (PN) • It is not likely that the assessment of the outcome was influenced by the knowledge of intervention received. (PN)		
Hanaire et al. (2020)[56]	**Some concerns** • No information on the allocation sequence used in the trial; method of randomization was unclear. (NI) • No information about whether allocation sequence was	**Low risk** • Participants were aware of their assigned intervention during the trial (open-label). (Y) • Carers and people delivering the intervention were	**Glucose TIR metrics: Low risk** **Patient satisfaction: Low risk** **AEs: Low risk** • Outcome data were available for all, or nearly all, participants randomized (2 out of	**Glucose TIR metrics: Low risk** **Patient satisfaction: Some concerns** **AEs: Low risk** • The method of measurement was probably not inappropriate (glucose TIR metrics	**Low risk** • The data that produced these results were probably analyzed in accordance with a pre-specified analysis plan, which was likely finalized before outcome data	**Some concerns**

Study citation	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	Bias in selection of the reported result	Overall risk of bias
	concealed until participants were enrolled and assigned to intervention. (NI) • The lack of baseline differences between groups does not suggest a problem with the randomization process. (N)	aware of the participants' assigned intervention during the trial (open-label). (Y) • There were no reported deviations from the intended intervention that arose because of the trial context. (N) • Appropriate analysis was used to estimate the effect of assignment to intervention (mITT analysis). (Y)	38 dropped out and had missing data). (Y)	were measured using a CGM; patient satisfaction was measured using the DTSQ; AEs were patient-reported or measured using a CGM). (PN) • It is not likely that the measurement or ascertainment of the outcomes differed between intervention groups. (PN) • Outcome assessors were aware of the intervention received by study participants. (Y) • For glucose TIR metrics and safety outcomes measured using a CGM, it is not likely that the outcomes could have been influenced by knowledge of the intervention received (the outcomes were largely objective). (PN) • It is possible that patient satisfaction findings were influenced by the	were available for analysis; a protocol was registered on ClinicalTrials.gov (NCT02627911). (PY) • The numerical result being assessed was not likely to have been selected, on the basis of results from multiple eligible outcome measurements within the outcome domain (PN) or multiple eligible analyses of the data (PN), based on the a priori protocol.	

Study citation	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	Bias in selection of the reported result	Overall risk of bias
				knowledge of intervention received. (PY) • It is not likely that the assessment of the outcome was influenced by the knowledge of intervention received. (PN)		
McAuley et al. (2020)[59]	**Low risk** • Allocation sequence was likely random (participants were matched according to pre-randomization glucose time-in-range metrics, insulin delivery modality at enrolment, and trial site); randomization was done through a central electronic database using a computer-generated sequence. (PY) • Because 3 stratification variables were used to pair participants into treatment groups, they were already enrolled in the study prior to the randomization event.	**Low risk** • Participants were aware of their assigned intervention during the trial (open-label). (Y) • Carers and people delivering the intervention were aware of the participants' assigned intervention during the trial (open-label). (Y) • There were no reported deviations from the intended intervention that arose because of the trial context. (N) • Appropriate analysis was used to estimate the effect of assignment to	**Glucose TIR metrics: Low risk** **A1C: Low risk** **Patient satisfaction: Low risk** **Psychosocial, cognitive, and sleep quality outcomes: Low risk** • Outcome data were available for all, or nearly all, participants randomized (10 out of 120 dropped out and had missing data; some participants had additional data missing for various reasons, but this was not considered substantial). (Y)	**Glucose TIR metrics: Low risk** **A1C: Low risk** **Patient satisfaction: Some concerns** **Psychosocial, cognitive, and sleep quality outcomes: Some concerns** • The method of measurement was probably not inappropriate: glucose TIR metrics and other glucose metrics were measured using a CGM; A1C was measured using laboratory Bio-Rad D-100 analyzers; patient satisfaction was measured using the DTSQ; diabetes-specific quality of life was measured with	**Low risk** • The data that produced these results were analyzed in accordance with a pre-specified analysis plan, which was finalized prior to the completion of the study visits; a protocol was registered on the Australian New Zealand Clinical Trials Registry and published separately.[189] (Y) • The numerical result being assessed was not likely to have been selected, on the basis of results from multiple eligible outcome measurements	**Some concerns**

Study citation	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	Bias in selection of the reported result	Overall risk of bias
	For this reason, it is unlikely that recruiters could have influenced the intervention that specific participants received. (PY) • The lack of baseline differences between groups does not suggest a problem with the randomization process. (N)	intervention (ITT analysis). (Y)		DIDP scores; diabetes distress was measured with PAID scale scores; diabetes-specific positive well-being was measured with the 4-item subscale of W-BQ28 scores; prospective memory was measured with PRMQ Prospective scores; retrospective memory was measured with PRMQ Retrospective scores; perceived sleep quality was measured with PSQI scores. (PN) • Participants in the HCL group had a higher total number of study visits (in person, through email, and over the phone) with study staff. However, reported outcomes were not assessed as part of these additional visits. Thus, it is not likely that the measurement or	within the outcome domain (PN) or multiple eligible analyses of the data (PN), based on the a priori protocol.	

Study citation	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	Bias in selection of the reported result	Overall risk of bias
				ascertainment of the outcomes differed between intervention groups. (PN) • It is not likely that the measurement or ascertainment of the outcomes differed between intervention groups. (PN) • While the publication states that the trial statistical team and investigators undertook data and laboratory analyses, it is likely that outcome assessors for most outcomes were aware of the intervention received by study participants. (PY) • For glucose TIR metrics, other glucose metrics, and A1C it is not likely that the outcomes could have been influenced by knowledge of intervention received (the outcomes were largely objective). (PN)		

Study citation	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	Bias in selection of the reported result	Overall risk of bias
				• It is possible that patient satisfaction, diabetes-specific quality of life, diabetes distress, diabetes-specific positive well-being, prospective memory, retrospective memory, and perceived sleep quality findings were influenced by the knowledge of intervention received. (PY)		
Benhamou et al. (2019)	**Some concerns** • Allocation sequence was likely random (participants were randomly assigned in randomly permuted blocks of 2); randomization was done using a web-based system. (Y) • There is no information about whether allocation sequence was concealed until participants were enrolled and assigned to intervention. (NI)	**Low risk** • Participants were aware of their assigned intervention during the trial (open-label). (Y) • Carers and people delivering the intervention were aware of the participants' assigned intervention during the trial (open-label). (Y) • There were no reported deviations from the intended intervention that	**Glucose TIR metrics: Low risk** **A1C: Low risk** **Patient satisfaction: Low risk** • Outcome data were available for all, or nearly all, participants randomized (5 out of 63 dropped out and had missing data). (Y)	**Glucose TIR metrics: Low risk** **A1C: Low risk** **Patient satisfaction: Some concerns** • The method of measurement was probably not inappropriate (glucose TIR metrics were measured using a CGM; the method for measuring A1C was NR, but assumed to be appropriate; patient satisfaction was measured using the DTSQ). (PN)	**Low risk** • The data that produced these results were analyzed in accordance with a pre-specified analysis plan, which was finalized before outcome data were available for analysis; a protocol was registered on ClinicalTrials.gov (NCT02987556). (Y) • The numerical result being assessed was not likely to have been selected, on the basis of results	**Some concerns**

Study citation	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	Bias in selection of the reported result	Overall risk of bias
	• The lack of baseline differences between groups does not suggest a problem with the randomization process. (N)	arose because of the trial context. (N) • Appropriate analysis was used to estimate the effect of assignment to intervention (mITT analysis). (Y)		• It is not likely that the measurement or ascertainment of the outcomes differed between intervention groups. (PN) • Outcome assessors were aware of the intervention received by study participants. (Y) • For glucose TIR metrics and A1C, it is not likely that the outcomes could have been influenced by knowledge of intervention received (the outcomes were largely objective). (PN) • It is possible that patient satisfaction findings were influenced by the knowledge of intervention received. (PY) • It is not likely that the assessment of the outcome was influenced by the knowledge of intervention received. (PN)	from multiple eligible outcome measurements within the outcome domain (PN) or multiple eligible analyses of the data (PN), based on the a priori protocol.	

Study citation	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	Bias in selection of the reported result	Overall risk of bias
Brown et al. (2019)[53] and Isganaitis et al. (2020)[57]	**Some concerns** • Allocation sequence was likely random (participants were randomly assigned with a permuted blocks design stratified by site); randomization was done on the trial website with a computer-generated sequence. (Y) • There was no information about whether allocation sequence was concealed until participants were enrolled and assigned to intervention. (NI) • The lack of baseline differences between groups does not suggest a problem with the randomization process. (N)	**Low risk** • Participants were aware of their assigned intervention during the trial (open-label). (Y) • Carers and people delivering the intervention were aware of the participants' assigned intervention during the trial (open-label). (Y) • There were no reported deviations from the intended intervention that arose because of the trial context. (N) • Appropriate analysis was used to estimate the effect of assignment to intervention (ITT analysis). (Y)	**Glucose TIR metrics: Low risk** **A1C: Low risk** **AEs: Low risk** • Outcome data were available for all, or nearly all, participants randomized (no participants dropped out). (Y)	**Glucose TIR metrics: Low risk** **A1C: Low risk** **AEs: Some concerns** • The method of measurement was probably not inappropriate: glucose TIR metrics were measured using a CGM; A1C was measured either with the use of a point-of-care device or by a local laboratory; AEs were patient-reported or measured using a CGM. (PN) • Participants in the HCL group had more unscheduled contacts with study staff than those in the open-loop group; however, most of these contacts were to obtain supplies related to the trial and were judged to not have implications for outcome reporting; it is not likely that the measurement or ascertainment of the	**Low risk** • The data that produced these results were analyzed in accordance with a pre-specified analysis plan, which was finalized before outcome data were available for analysis; a protocol was registered on ClinicalTrials.gov (NCT03563313) posted on NEJM.org. (Y) • The numerical result being assessed was not likely to have been selected, on the basis of results from multiple eligible outcome measurements within the outcome domain (PN) or multiple eligible analyses of the data (PN), based on the a priori protocol.	**Some concerns**

Study citation	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	Bias in selection of the reported result	Overall risk of bias
				outcomes differed between intervention groups. (PN) • Outcome assessors were aware of the intervention received by study participants. (Y) • For glucose TIR metrics, A1C, and safety outcomes measured using a CGM, it is not likely that the outcomes could have been influenced by knowledge of intervention received (the outcomes were largely objective). (PN) • It is possible that patient-reported safety outcomes were influenced by the knowledge of intervention received. (PY) • It is not likely that the assessment of the outcome was influenced by the knowledge of intervention received. (PN)		

Study citation	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	Bias in selection of the reported result	Overall risk of bias
Ekhlaspour et al. (2019)[54]	**Low risk** • Allocation sequence was likely random (participants were assigned using a randomized block design that matched participants according to age and A1C); the method of randomization was unclear. (PY) • -ecause A1C and age were used to pair participants into permuted blocks, they were already enrolled in the study prior to the randomization event. For this reason, it is unlikely that recruiters could have influenced the intervention that specific participants received. (PY) • The lack of baseline differences between groups does not suggest a problem with the randomization process. (N)	**Low risk** • Participants were aware of their assigned intervention during the trial (open-label). (Y) • Carers and people delivering the intervention were aware of participants' assigned intervention during the trial (open-label). (Y) • There were no reported deviations from the intended intervention that arose because of the trial context. (N) • Appropriate analysis was used to estimate the effect of assignment to intervention (mITT analysis). (Y)	**Glucose TIR metrics: Low risk** **AEs: Low risk** • Outcome data were available for all, or nearly all, participants randomized (6 out of 54 dropped out of the study; however, it appears that their dropouts were prior to randomization). (PY)	**Glucose TIR metrics: Low risk** **AEs: Low risk** • The method of measurement was probably not inappropriate (glucose TIR metrics were measured using a CGM; AEs were patient-reported or measured using a CGM). (PN) • It is not likely that the measurement or ascertainment of the outcomes differed between intervention groups. (PN) • Outcome assessors were aware of the intervention received by study participants. (Y) • It is not likely that the outcomes could have been influenced by knowledge of the intervention received (the outcomes were largely objective). (PN) • It is not likely that the assessment of the	**Low risk** • The data that produced these results were probably analyzed in accordance with a pre-specified analysis plan, which was likely finalized before outcome data were available for analysis; a protocol was registered on ClinicalTrials.gov (NCT03369067). (PY) • The numerical result being assessed was not likely to have been selected, on the basis of results from multiple eligible outcome measurements within the outcome domain (PN) or multiple eligible analyses of the data (PN), based on the a priori protocol.	**Low risk**

Study citation	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	Bias in selection of the reported result	Overall risk of bias
				outcome was influenced by the knowledge of intervention received. (PN)		
Forlenza et al. (2019)[55]	**Low risk** • Allocation sequence was likely random (participants were assigned using a randomized block design that matched participants according to age, sex, and A1C); the method of randomization was unclear. (PY) • Because A1C, sex, and age were used to pair participants into permuted blocks, they were already enrolled in the study prior to the randomization event. For this reason, it is unlikely recruiters could have influenced the intervention that specific participants received. (PY) • The lack of baseline differences between groups does not	**Low risk** • Participants were aware of their assigned intervention during the trial (open-label). (Y) • Carers and people delivering the intervention were aware of the participants' assigned intervention during the trial (open-label). (Y) • There were no reported deviations from the intended intervention that arose because of the trial context. (N) • Appropriate analysis was used to estimate the effect of assignment to intervention (ITT analysis). (Y)	**Glucose TIR metrics: Low risk** **AEs: Low risk** • Outcome data were available for all, or nearly all, participants randomized (no participants dropped out). (Y)	**Glucose TIR metrics: Low risk** **AEs: Low risk** • The method of measurement was probably not inappropriate (glucose TIR metrics were measured using a CGM; AEs were patient-reported or measured using a CGM). (PN) • It is not likely that the measurement or ascertainment of the outcomes differed between intervention groups. (PN) • Outcome assessors were aware of the intervention received by study participants. (Y) • It is not likely that the outcomes could have been influenced by knowledge of the intervention received	**Low risk** • The data that produced these results were probably analyzed in accordance with a pre-specified analysis plan, which was likely finalized before the outcome data were available for analysis; although no protocol was available for this extension trial, the selected outcomes were not atypical for such a clinical trial. (PY) • The numerical result being assessed was not likely to have been selected, on the basis of results from multiple eligible outcome measurements within the outcome domain (PN) or multiple eligible analyses of the data	**Low risk**

Study citation	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	Bias in selection of the reported result	Overall risk of bias
	suggest a problem with the randomization process. (N)			(the outcomes were largely objective). (PN) • It is not likely that the assessment of the outcome was influenced by the knowledge of intervention received. (PN)	(PN), based on the a priori protocol.	

A1C = glycated hemoglobin; AE = adverse event; CGM = continuous glucose monitor; DIDP = DAWN2 Impact of Diabetes Profile; DTSQ = Diabetes Treatment Satisfaction Questionnaire; HCL = hybrid closed-loop insulin delivery system; ITT = intention to treat; N = no; mITT = modified intention to treat; NI = no information; NR = not reported; PAID = Problem Areas in Diabetes; PLGS = predictive low-glucose suspend; PN = probably no; PRMQ = Prospective and Retrospective Memory Questionnaire; PSQI = Pittsburgh Sleep Quality Index; PY = probably yes; RoB 2 = Cochrane Risk-of-Bias tool, version 2; TIR = time in range; W-BQ28 = Well-Being Questionnaire 28; Y = yes.

Table 40: Risk of Bias in the Included Non-Randomized Study Assessed Using RoBANS

Study citation	The possibility of the target group comparisons	Target group selection	Confounder	Exposure measurement	Blinding of assessors	Outcome assessment	Incomplete outcome data	Selective outcome reporting	Overall risk-of-bias judgment
Lepore et al. (2020)[58]	**Low** • The intervention and control groups were selected from comparable populations from the same centre, and there were no statistical differences between groups in demographic and baseline characteristics (e.g., age, sex, duration of diabetes, BMI, A1C).	**High** • Participant inclusion and exclusion criteria were applied to both study groups; however, the study authors were responsible for suggesting which patients should switch to HCL therapy. Thus, it is possible that the allocation of participants to the HCL group was biased. • Participants who volunteered to switch to HCL therapy may have had a stronger motivation to improve glucose control.	**Low** • Major confounding variables were adequately confirmed and considered during the planning and analysis stages (e.g., age, baseline A1C, and familiarity with continuous glucose monitoring, carbohydrate counting, and insulin bolus calculators).	**Low** • Data were collected from insulin pumps or from medical records.	**Low** • Although outcome assessors were aware of the intervention received by participants, the reported outcomes were objectively measured (e.g., glucose time-in-range metrics, A1C, mean glucose).	**Glucose TIR metrics: Low** **A1C: Low** **AEs: Low** • Glucose time-in-range and A1C outcomes were assessed using tools that have proven reliability. • Adverse events were clearly defined, and data on their frequency was retrieved from medical records.	**Glucose TIR metrics: Low** **A1C: Low** **AEs: Low** • There do not appear to be any data missing from participants in either group for the reported outcomes	**Unclear** • Although the study reported on most outcomes that are typical for such a clinical trial, there was no reference to a published protocol to confirm whether outcomes were selectively reported.	**High risk**

A1C = glycated hemoglobin; AE = adverse event; BMI = body mass index; CGM = continuous glucose monitor; HCL = hybrid closed-loop insulin delivery system; RoBANS = Risk of Bias Assessment tool for Non-randomized Studies; TIR = time in range.

Detailed Outcome Data — Clinical Review

Table 41: Summary of Findings of Included Primary Clinical Studies

	Authors' conclusion
Randomized controlled trials	
Breton et al. (2020)[51]	

Breton et al. (2020) was a multi-centre, open-label, parallel-group RCT that randomly assigned participants to HCL therapy with the Control-IQ system (N = 78) or to open-loop SAP therapy (N = 23). The control group included a mix of participants that had a system with a PLGS feature (N = 15) or did not have a PLGS feature (N = 8).
 	
Summary of findings related to comparative clinical effectiveness (research question 1)
• Glucose time-in-range metrics
  ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) (the primary outcome of the RCT)
  ▪ HCL (N = 78): 67% (SD = 10%)
  ▪ OL ± PLGS (N = 22): 55% (SD = 13%)
  ▪ Risk-adjusted difference (95% CI): 11% (7% to 14%)
  ▪ P value: < 0.001
  ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 7.8 mmol/L (70 mg/dL to 140 mg/dL)
  ▪ HCL (N = 78): 44% (SD = 10%)
  ▪ OL ± PLGS (N = 22): 35% (SD = 11%)
  ▪ Risk-adjusted difference (95% CI): 8.1% (4.3% to 12%)
  ▪ P value: not calculated because this outcome was considered exploratory and not included in the hierarchical analysis
  ○ Median percentage of time with glucose values < 3.0 mmol/L (< 54 mg/dL)
  ▪ HCL (N = 78): 0.2% (IQR, 0.1% to 0.4%)
  ▪ OL ± PLGS (N = 22): 0.3% (IQR, 0.1% to 0.6%)
  ▪ Risk-adjusted difference (95% CI): −0.07% (−0.19% to 0.02%)
  ▪ P value: not formally tested because an outcome that was specified before this one (i.e., mean A1C at 16 weeks) in the hierarchical analysis, which was defined in the statistical analysis plan to maintain the type I error at 5%, did not reach statistical significance
  ○ Median percentage of time with glucose values < 3.3 mmol/L (< 60 mg/dL)
  ▪ HCL (N = 78): 0.48% (IQR, 0.22% to 0.93%)
  ▪ OL ± PLGS (N = 22): 0.60% (IQR, 0.32% to 1.19%)
  ▪ Risk-adjusted difference (95% CI): −0.15% (−0.36% to 0.01%)
  ▪ P value: not calculated because this outcome was considered exploratory and not included in the hierarchical analysis
  ○ Median percentage of time with glucose values < 3.9 mmol/L (< 70 mg/dL)
  ▪ HCL (N = 78): 1.6% (IQR, 0.8% to 2.4%)
  ▪ OL ± PLGS (N = 22): 1.8% (IQR, 1.1% to 3.0%)
  ▪ Risk-adjusted difference (95% CI): −0.40% (−0.83% to −0.02%)
	"In this 16-week trial involving children 6 to 13 years of age who had type 1 diabetes, the glucose level was in the target range for a greater percentage of time with the use of a closed-loop system than with the use of a sensor-augmented insulin pump." (p. 844)

	Authors' conclusion
▪ P value: not formally tested because an outcome that was specified before this one (i.e., mean A1C at 16 weeks) in the hierarchical analysis, which was defined in the statistical analysis plan to maintain the type I error at 5%, did not reach statistical significance ○ Mean percentage of time with glucose values > 10.0 mmol/L (> 80 mg/dL) ▪ HCL (N = 78): 31% (SD = 10%) ▪ OL ± PLGS (N = 22): 43% (SD = 14%) ▪ Risk-adjusted difference (95% CI): −10% (−14% to −6%) ▪ P value: < 0.001 ○ Median percentage of time with glucose values > 3.9 mmol/L (> 250 mg/dL) ▪ HCL (N = 78): 7.8% (IQR, 5.1% to 14.3%) ▪ OL ± PLGS (N = 22): 18.4% (IQR, 9.4% to 24.6%) ▪ Risk-adjusted difference (95% CI): −5.8% (−8.7% to −3.0%) ▪ P value: not formally tested because an outcome that was specified before this one (i.e., mean A1C at 16 weeks) in the hierarchical analysis, which was defined in the statistical analysis plan to maintain the type I error at 5%, did not reach statistical significance ○ Median percentage of time with glucose values > 16.7 mmol/L (> 300 mg/dL) ▪ HCL (N = 78): 2.6% (IQR, 1.5% to 5.5%) ▪ OL ± PLGS (N = 22): 6.8% (IQR, 2.9% to 11.2%) ▪ Risk-adjusted difference (95% CI): −1.8% (−3.8% to −0.4%) ▪ P value: not calculated because this outcome was considered exploratory and not included in the hierarchical analysis • A1C values ○ Mean A1C values at 16 weeks ▪ HCL (N = 78): 7.0% (SD = 0.8%) ▪ OL ± PLGS (N = 22): 7.6% (SD = 0.9%) ▪ Risk-adjusted difference (95% CI): −0.4% (−0.9% to 0.1%) ▪ P value: 0.08 ○ Proportion of participants with A1C values < 7.0% (< 53 mmol/mol) at 16 weeks ▪ HCL (N = 77): 51% ▪ OL ± PLGS (N = 22): 15% ▪ Risk-adjusted difference (95% CI): 28% (10% to 45%) ▪ P value: not calculated because this outcome was considered exploratory and not included in the hierarchical analysis ○ Proportion of participants with A1C values < 7.5% (< 58 mmol/mol) at 16 weeks ▪ HCL (N = 77): 74% ▪ OL ± PLGS (N = 22): 45% ▪ Risk-adjusted difference (95% CI): 22% (2% to 42%) ▪ P value: not calculated because this outcome was considered exploratory and not included in the hierarchical analysis ○ Proportion of participants with an absolute reduction in A1C values of ≥ 0.5% from baseline ▪ HCL (N = 77): 52% ▪ OL ± PLGS (N = 22): 50%	

	Authors' conclusion
▪ Risk-adjusted difference (95% CI): 12% (−13% to 30%) ▪ P value: not calculated because this outcome was considered exploratory and not included in the hierarchical analysis ○ Proportion of participants with an absolute reduction in A1C values of ≥ 1.0% from baseline ▪ HCL (N = 77): 25% ▪ OL ± PLGS (N = 22): 9% ▪ Risk-adjusted difference (95% CI): 19% (4% to 31%) ▪ P value: not calculated because this outcome was considered exploratory and not included in the hierarchical analysis ○ Proportion of participants with a relative reduction in A1C values of ≥ 10% from baseline ▪ HCL (N = 77): 36% ▪ OL ± PLGS (N = 22): 18% ▪ Risk-adjusted difference (95% CI): 23% (4% to 38%) ▪ P value: not calculated because this outcome was considered exploratory and not included in the hierarchical analysis ○ Proportion of participants with an absolute reduction in A1C values of ≥ 1.0% from baseline or an A1C value of < 7.0% at 16 weeks ▪ HCL (N = 77): 61% ▪ OL ± PLGS (N = 22): 27% ▪ Risk-adjusted difference (95% CI): 35% (11% to 56%) ▪ P value: not calculated because this outcome was considered exploratory and not included in the hierarchical analysis • Additional outcomes ○ Mean glucose concentration ▪ HCL (N = 78): 8.99 (SD = 1.00) mmol/L; 162 (SD = 18) mg/dL ▪ OL ± PLGS (N = 22): 9.94 (SD = 1.44) mmol/L; 179 (SD = 26) mg/dL ▪ Risk-adjusted difference (95% CI): −0.72 mmol/L (−1.11 to −0.39); −13 mg/dL (−20 to −7) ▪ P value: < 0.001 ○ Glycemic variability as assessed by the coefficient of variation of sensor glucose ▪ HCL (N = 78): 38% (SD = 4%) ▪ OL ± PLGS (N = 22): 39% (SD = 4%) ▪ Risk-adjusted difference (95% CI): −1.6% (−2.8% to −0.4%) ▪ P value: not formally tested because an outcome that was specified before this one (i.e., mean A1C at 16 weeks) in the hierarchical analysis, which was defined in the statistical analysis plan to maintain the type I error at 5%, did not reach statistical significance ○ Median body weight ▪ HCL (N = 78): 44 (IQR, 34 to 52) kg ▪ OL ± PLGS (N = 21): 37 (IQR, 34 to 54) kg ▪ Risk-adjusted difference (95% CI): 0.0 kg (−1.2 to 1.1) ▪ P value: not calculated because this outcome was considered exploratory and not included in the hierarchical analysis ○ Mean total daily insulin amount ▪ HCL (N = 78): 0.94 (SD = 0.25) U/kg/day ▪ OL ± PLGS (N = 21): 0.98 (SD = 0.32) U/kg/day	

	Authors' conclusion
▪ Risk-adjusted difference (95% CI): 0.00 U/kg/day (−0.10 to 0.09) ▪ P value: not calculated because this outcome was considered exploratory and not included in the hierarchical analysis Note: Values for risk-adjusted differences were adjusted for the baseline level of the dependent variable, age, previous use of a CGM and pump, and clinical centre (random effect). • Subgroup analyses for change in mean percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) from baseline ○ Baseline factor: A1C value ▪ Subgroup: A1C value < 8.0% ○ HCL (N = 49): 60% (SD = 15%) (baseline); 10.8% (SD = 11.5%) (change from baseline) ○ OL ± PLGS (N = 11): 64% (SD = 13%) (baseline); 1.3% (SD = 9.2%) (change from baseline) ▪ Subgroup: A1C value ≥ 8.0% ○ HCL (N = 28): 41% (SD = 13%) (baseline); 19.5% (SD = 13.4%) (change from baseline) ○ OL ± PLGS (N = 11): 39% (SD = 8%) (baseline); 6.8% (SD = 7.6%) (change from baseline) ▪ P value for interaction: NR ○ Baseline factor: percentage of time with a glucose value below 3.9 mmol/L (70 mg/dL) ▪ Subgroup: < 1.5% ○ HCL (N = 44): 47% (SD = 16%) (baseline); 18.2% (SD = 12.8%) (change from baseline) ○ OL ± PLGS (N = 13): 44% (SD = 16%) (baseline); 3.9% (SD = 8.9%) (change from baseline) ▪ Subgroup: ≥ 1.5% ○ HCL (N = 33): 62% (SD = 13%) (baseline); 8.3% (SD = 10.7%) (change from baseline) ○ OL ± PLGS (N = 9): 61% (SD = 14%) (baseline); 4.3% (SD = 9.0%) (change from baseline) ▪ P value for interaction: NR ○ Baseline factor: percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) ▪ Subgroup: < 50% ○ HCL (N = 33): 38% (SD = 9%) (baseline); 23.8% (SD = 10.1%) (change from baseline) ○ OL ± PLGS (N = 11): 38% (SD = 7%) (baseline); 8.2% (SD = 6.5%) (change from baseline) ▪ Subgroup: ≥ 50% ○ HCL (N = 44): 65% (SD = 11%) (baseline); 6.6% (SD = 9.3%) (change from baseline) ○ OL ± PLGS (N = 11): 65% (SD = 12%) (baseline); 0.0% (SD = 9.0%) (change from baseline) ▪ P value for interaction: NR ○ Baseline factor: percentage of time with a glucose value > 10.0 mmol/L (180 mg/dL) ▪ Subgroup: < 50% ○ HCL (N = 48): 63% (SD = 12%) (baseline); 7.5% (SD = 9.5%) (change from baseline) ○ OL ± PLGS (N = 11): 65% (SD = 12%) (baseline); 0.0% (SD = 9.0%) (change from baseline) ▪ Subgroup: ≥ 50%	

	Authors' conclusion
○ HCL (N = 29): 37% (SD = 9%) (baseline); 24.8% (SD = 10.1%) (change from baseline) ○ OL ± PLGS (N = 11): 38% (SD = 7%) (baseline); 8.2% (SD = 6.5%) (change from baseline) ▪ P value for interaction: NR ○ Baseline factor: age ▪ Subgroup: 6 years to 9 years ○ HCL (N = 20): 55% (SD = 12%) (baseline); 12.8% (SD = 10.1%) (change from baseline) ○ OL ± PLGS (N = 8): 47% (SD = 19%) (baseline); 4.8% (SD = 11.1%) (change from baseline) ▪ Subgroup: 10 years to 14 years ○ HCL (N = 57): 53% (SD = 18%) (baseline); 14.4% (SD = 13.7%) (change from baseline) ○ OL ± PLGS (N = 14): 53% (SD = 15%) (baseline); 3.7% (SD = 7.5%) (change from baseline) ▪ P value for interaction: NR ○ Baseline factor: Sex ▪ Subgroup: female ○ HCL (N = 38): 52% (SD = 17%) (baseline); 15.1% (SD = 13.2%) (change from baseline) ○ OL ± PLGS (N = 11): 55% (SD = 21%) (baseline); 1.6% (SD = 9.8%) (change from baseline) ▪ Subgroup: male ○ HCL (N = 39): 55% (SD = 17%) (baseline); 12.9% (SD = 12.6%) (change from baseline) ○ OL ± PLGS (N = 11): 47% (SD = 11%) (baseline); 6.5% (SD = 7.1%) (change from baseline) ▪ P value for interaction: NR • Subgroup analyses for change in mean percentage of time spent with a glucose value below 3.9 mmol/L (70 mg/dL) from baseline ○ Baseline factor: A1C value ▪ Subgroup: A1C value < 8.0% ○ HCL (N = 49): 2.4% (SD = 2.5%) (baseline); −0.29% (SD = 2.00%) (change from baseline) ○ OL ± PLGS (N = 11): 2.5% (SD = 1.6%) (baseline); 0.22% (SD = 1.20%) (change from baseline) ▪ Subgroup: A1C value ≥ 8.0% ○ HCL (N = 28): 1.0% (SD = 1.2%) (baseline); 0.19% (SD = 0.96%) (change from baseline) ○ OL ± PLGS (N = 11): 0.6% (SD = 0.6%) (baseline); 0.89% (SD = 0.78%) (change from baseline) ▪ P value for interaction: NR ○ Baseline factor: percentage of time with a glucose value below 3.9 mmol/L (70 mg/dL) ▪ Subgroup: < 1.5% ○ HCL (N = 44): 0.6% (SD = 0.5%) (baseline); 0.66% (SD = 0.95%) (change from baseline) ○ OL ± PLGS (N = 13): 0.5% (SD = 0.4%) (baseline); 0.78% (SD = 0.84%) (change from baseline) ▪ Subgroup: ≥ 1.5% ○ HCL (N = 33): 3.7% (SD = 2.4%) (baseline); −1.14% (SD = 1.94%) (change from baseline) ○ OL ± PLGS (N = 9): 3.0% (SD = 1.4%) (baseline); 0.23% (SD = 1.27%) (change from baseline) ▪ P value for interaction: NR	

	Authors' conclusion
○ Baseline factor: percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) ▪ Subgroup: < 50% ○ HCL (N = 33): 0.9% (SD = 1.4%) (baseline); 0.36% (SD = 1.25%) (change from baseline) ○ OL ± PLGS (N = 11): 0.7% (SD = 0.7%) (baseline); 1.08% (SD = 0.85%) (change from baseline) ▪ Subgroup: ≥ 50% ○ HCL (N = 44): 2.7% (SD = 2.4%) (baseline); −0.47% (SD = 1.91%) (change from baseline) ○ OL ± PLGS (N = 11): 2.4% (SD = 1.8%) (baseline); 0.04% (SD = 0.99%) (change from baseline) ▪ P value for interaction: NR ○ Baseline factor: percentage of time with a glucose value > 10.0 mmol/L (180 mg/dL) ▪ Subgroup: < 50% ○ HCL (N = 48): 2.7% (SD = 2.4%) (baseline); −0.48% (SD = 1.97%) (change from baseline) ○ OL ± PLGS (N = 11): 2.4% (SD = 1.8%) (baseline); 0.04% (SD = 0.99%) (change from baseline) ▪ Subgroup: ≥ 50% ○ HCL (N = 29): 0.6% (SD = 0.8%) (baseline); 0.50% (SD = 0.85%) (change from baseline) ○ OL ± PLGS (N = 11): 0.7% (SD = 0.7%) (baseline); 1.08% (SD = 0.85%) (change from baseline) ▪ P value for interaction: NR ○ Baseline factor: age ▪ Subgroup: 6 years to 9 years ○ HCL (N = 20): 3.1% (SD = 2.6%) (baseline); −0.54% (SD = 2.56%) (change from baseline) ○ OL ± PLGS (N = 8): 1.0% (SD = 1.1%) (baseline); 0.80% (SD = 0.86%) (change from baseline) ▪ Subgroup: 10 years to 14 years ○ HCL (N = 57): 1.5% (SD = 1.9%) (baseline); 0.04% (SD = 1.27%) (change from baseline) ○ OL ± PLGS (N = 14): 1.8% (SD = 1.7%) (baseline); 0.42% (SD = 1.14%) (change from baseline) ▪ P value for interaction: NR ○ Baseline factor: sex ▪ Subgroup: female ○ HCL (N = 38): 1.5% (SD = 1.6%) (baseline); 0.02% (SD = 1.51%) (change from baseline) ○ OL ± PLGS (N = 11): 1.9% (SD = 2.0%) (baseline); 0.39% (SD = 1.21%) (change from baseline) ▪ Subgroup: male ○ HCL (N = 39): 2.4% (SD = 2.6%) (baseline); −0.24% (SD = 1.88%) (change from baseline) ○ OL ± PLGS (N = 11): 1.2% (SD = 0.9%) (baseline); 0.72% (SD = 0.87%) (change from baseline) ▪ P value for interaction: NR • Subgroup analyses for change in mean A1C from baseline ○ Baseline factor: A1C value ▪ Subgroup: A1C value < 8.0% ○ HCL (N = 49): 7.1% (SD = 0.6%) (baseline); −0.28% (SD = 0.47%) (change from baseline) ○ OL ± PLGS (N = 11): 7.2% (SD = 0.6%) (baseline); −0.09% (SD = 0.59%) (change from baseline)	

	Authors' conclusion
▪ Subgroup: A1C value ≥ 8.0% ○ HCL (N = 28): 8.6% (SD = 0.6%) (baseline); −1.13% (SD = 0.69%) (change from baseline) ○ OL ± PLGS (N = 11): 8.6% (SD = 0.6%) (baseline); −0.53% (SD = 0.48%) (change from baseline) ▪ P value for interaction: NR ○ Baseline factor: percentage of time with a glucose value below 3.9 mmol/L (70 mg/dL) ▪ Subgroup: < 1.5% ○ HCL (N = 44): 7.9% (SD = 1.0%) (baseline); −0.75% (SD = 0.69%) (change from baseline) ○ OL ± PLGS (N = 13): 8.4% (SD = 0.8%) (baseline); −0.41% (SD = 0.50%) (change from baseline) ▪ Subgroup: ≥ 1.5% ○ HCL (N = 32): 7.3% (SD = 0.8%) (baseline); −0.38% (SD = 0.66%) (change from baseline) ○ OL ± PLGS (N = 9): 7.2% (SD = 0.7%) (baseline); −0.17% (SD = 0.66%) (change from baseline) ▪ P value for interaction: NR ○ Baseline factor: percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) ▪ Subgroup: < 50% ○ HCL (N = 33): 8.3% (SD = 0.7%) (baseline); −1.01% (SD = 0.63%) (change from baseline) ○ OL ± PLGS (N = 11): 8.6% (SD = 0.7%) (baseline); −0.49% (SD = 0.46%) (change from baseline) ▪ Subgroup: ≥ 50% ○ HCL (N = 43): 7.1% (SD = 0.8%) (baseline); −0.28% (SD = 0.57%) (change from baseline) ○ OL ± PLGS (N = 11): 7.2% (SD = 0.7%) (baseline); −0.13% (SD = 0.63%) (change from baseline) ▪ P value for interaction: NR ○ Baseline factor: percentage of time with a glucose value > 10.0 mmol/L (180 mg/dL) ▪ Subgroup: < 50% ○ HCL (N = 47): 7.2% (SD = 0.8%) (baseline); −0.34% (SD = 0.61%) (change from baseline) ○ OL ± PLGS (N = 11): 7.2% (SD = 0.7%) (baseline); −0.13% (SD = 0.63%) (change from baseline) ▪ Subgroup: ≥ 50% ○ HCL (N = 29): 8.4% (SD = 0.8%) (baseline); −1.02% (SD = 0.61%) (change from baseline) ○ OL ± PLGS (N = 11): 8.6% (SD = 0.7%) (baseline); −0.49% (SD = 0.46%) (change from baseline) ▪ P value for interaction: NR ○ Baseline factor: age ▪ Subgroup: 6 years to 9 years ○ HCL (N = 21): 7.5% (SD = 0.7%) (baseline); −0.57% (SD = 0.48%) (change from baseline) ○ OL ± PLGS (N = 8): 8.2% (SD = 1.0%) (baseline); −0.58% (SD = 0.56%) (change from baseline) ▪ Subgroup: 10 years to 14 years ○ HCL (N = 56): 7.7% (SD = 1.1%) (baseline); −0.60% (SD = 0.76%) (change from baseline) ○ OL ± PLGS (N = 14): 7.7% (SD = 0.9%) (baseline); −0.16% (SD = 0.53%) (change from baseline) ▪ P value for interaction: NR ○ Baseline factor: sex	

	Authors' conclusion
▪ Subgroup: female ○ HCL (N = 38): 7.7% (SD = 0.9%) (baseline); −0.65% (SD = 0.60%) (change from baseline) ○ OL ± PLGS (N = 11): 7.8% (SD = 1.2%) (baseline); −0.23% (SD = 0.53%) (change from baseline) ▪ Subgroup: male ○ HCL (N = 39): 7.6% (SD = 1.0%) (baseline); −0.53% (SD = 0.78%) (change from baseline) ○ OL ± PLGS (N = 11): 8.0% (SD = 0.6%) (baseline); −0.39% (SD = 0.62%) (change from baseline) ▪ P value for interaction: NR **Summary of findings related to comparative safety (research question 2)** • Rate of adverse events ○ Number of adverse events ▪ HCL (N = 78): 16 ▪ OL ± PLGS (N = 23): 3 ▪ P value: not calculated because the outcome was not pre-specified in the statistical analysis plan ○ Proportion of patients who experienced an adverse event ▪ HCL (N = 78): 19% ▪ OL ± PLGS (N = 23): 9% ▪ P value: not calculated because the outcome was not pre-specified in the statistical analysis plan ○ Number of adverse events per 100 person-years ▪ HCL (N = 78): 65.3 ▪ OL ± PLGS (N = 23): 41.3 ▪ P value: 0.50 ○ Number of serious adverse events ▪ HCL (N = 78): 1 ▪ OL ± PLGS (N = 23): 0 ▪ P value: not calculated because the outcome was not pre-specified in the statistical analysis plan • Hypoglycemic events ○ Median number of hypoglycemic events per week (defined as at least 15 consecutive minutes with a glucose level < 3.0 mmol/L [< 54 mg/dL]) ▪ HCL (N = 78): 0.5 (IQR, 0.1 to 0.8) ▪ OL ± PLGS (N = 23): 0.6 (IQR, 0.1 to 1.0) ▪ P value: 0.16 • Hyperglycemic events ○ Median number of hyperglycemic events per week (defined as at least 15 consecutive minutes with a glucose level > 16.7 mmol/L [> 300 mg/dL]) ▪ HCL (N = 78): 3.0 (IQR, 1.7 to 5.2)	

	Authors' conclusion
▪ OL ± PLGS (N = 23): 5.6 (IQR, 3.4 to 8.1) ▪ P value: 0.001 • Worsening of A1C values ○ Proportion of participants who had a worsening of A1C values of ≥ 0.5% post-treatment ▪ HCL (N = 78): 3% ▪ OL ± PLGS (N = 23): 9% ▪ P value: not formally tested • Ketosis events ○ Mean number of days with ≥ 1 blood ketone measurement > 1.0 mmol/L (% per total person-days of follow-up) ▪ HCL (N = 78): 24 (0.27%) ▪ OL ± PLGS (N = 23): 3 (0.11%) ▪ P value: 0.19	
Brown et al. (2020)[52]	
Multi-centre, open-label, parallel-group RCT that randomly assigned participants to continue Control-IQ HCL therapy (N = 54) or to switch to a PLGS system (N = 55). **Summary of findings related to comparative clinical effectiveness (research question 1)** • Glucose time-in-range metrics ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) (the primary outcome of the RCT) using an ITT analysis ▪ HCL (N = 54): 67.6% (SD = 12.6%) ▪ PLGS (N = 55): 60.4% (SD = 17.1%) ▪ Risk-adjusted difference (95% CI): 5.9% (3.6% to 8.3%) ▪ P value: < 0.001 ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) (the primary outcome of the RCT) using a per-protocol analysis (i.e., a 4-week period in which the HCL was temporarily suspended for all participants was excluded from the analysis) ▪ HCL (N = 54): 69.1% (SD = 12.2%) ▪ PLGS (N = 55): 60.4% (SD = 17.1%) ▪ Risk-adjusted difference (95% CI): 7.5% (5.3% to 9.8%) ▪ P value: < 0.001 ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 7.8 mmol/L (70 mg/dL to 140 mg/dL) ▪ HCL (N = 54): 42.0% (SD = 12.5%) ▪ PLGS (N = 55): 37.1% (SD = 14.2%) ▪ Risk-adjusted difference (95% CI): 4.7% (2.5% to 7.0%) ▪ P value: < 0.001 ○ Mean percentage of time spent with a glucose value < 3.0 mmol/L (< 54 mg/dL)	"In conclusion, the results of this study demonstrate that switching to PLGS following 6-months of [HCL] reduced time in range and increased A1C toward their pre-[HCL] values, while hypoglycemia remained similarly reduced with both [HCL] and PLGS."[52] (p. 5)

	Authors' conclusion
▪ HCL (N = 54): 0.29% (SD = 0.30%) ▪ PLGS (N = 55): 0.31% (SD = 0.31%) ▪ Risk-adjusted difference (95% CI): 0.04% (−0.05% to 0.13%) ▪ P value: 0.41 ○ Median percentage of time spent with a glucose value < 3.3 mmol/L (< 60 mg/dL) ▪ HCL (N = 54): 0.43% (IQR, 0.19% to 0.97%) ▪ PLGS (N = 55): 0.46% (IQR, 0.17% to 0.96%) ▪ Risk-adjusted difference (95% CI): 0.09% (−0.07% to 0.24%) ▪ P value: 0.28 ○ Median percentage of time spent with a glucose value < 3.9 mmol/L (< 70 mg/dL) ▪ HCL (N = 54): 1.35% (IQR, 0.73% to 2.57%) ▪ PLGS (N = 55): 1.48% (IQR, 0.76% to 2.67%) ▪ Risk-adjusted difference (95% CI): 0.13% (−0.18% to 0.45%) ▪ P value: 0.41 ○ Median percentage of time spent with a glucose value > 10.0 mmol/L (> 180 mg/dL) ▪ HCL (N = 54): 32% (IQR, 22% to 39%) ▪ PLGS (N = 55): 36% (IQR, 22% to 51%) ▪ Risk-adjusted difference (95% CI): −6.04% (−8.40% to −3.68%) ▪ P value: < 0.001 ○ Median percentage of time spent with a glucose value > 13.9 mmol/L (> 250 mg/dL) ▪ HCL (N = 54): 7.1% (IQR, 3.2% to 11%) ▪ PLGS (N = 55): 9.3% (IQR, 3.6% to 18%) ▪ Risk-adjusted difference (95% CI): −2.46% (−3.92% to −1.01%) ▪ P value: 0.001 ○ Median percentage of time spent with a glucose value > 16.7 mmol/L (> 300 mg/dL) ▪ HCL (N = 54): 1.8% (IQR, 0.5% to 3.7%) ▪ PLGS (N = 55): 2.5% (IQR, 0.8% to 6.1%) ▪ Risk-adjusted difference (95% CI): −0.89% (−1.76% to −0.01%) ▪ P value: 0.05 • A1C ○ Mean A1C at 13 weeks ▪ HCL (N = 54): 7.18% (SD = 0.80%); 55 (SD = 8.7) mmol/mol ▪ PLGS (N = 55): 7.53% (SD = 1.14%); 59 (SD = 12.5) mmol/mol ▪ Risk-adjusted difference (95% CI): −0.34% (−0.57% to −0.11%); −3.7 mmol/mol (−6.2 to −1.2) ▪ P value: 0.0035 ○ Proportion of participants with A1C < 7.0% (< 53 mmol/mol) at 13 weeks ▪ HCL (N = 54): 43% ▪ PLGS (N = 55): 27%	

	Authors' conclusion
▪ Risk-adjusted difference (95% CI): 13% (−6% to 32%) ▪ P value: 0.05 ○ Proportion of participants with A1C < 7.5% (< 58 mmol/mol) at 13 weeks ▪ HCL (N = 54): 65% ▪ PLGS (N = 55): 58% ▪ Risk-adjusted difference (95% CI): 9% (−14% to 31%) ▪ P value: 0.20 ○ Proportion of participants with an absolute reduction in A1C value of > 0.5% from baseline ▪ HCL (N = 54): 2% ▪ PLGS (N = 55): 4% ▪ Risk-adjusted difference (95% CI): not reported ▪ P value: not reported ○ Proportion of participants with an absolute reduction in A1C value of > 1.0% from baseline ▪ HCL (N = 54): 0% ▪ PLGS (N = 55): 0% ▪ Risk-adjusted difference (95% CI): not reported ▪ P value: not reported ○ Proportion of participants with a relative reduction in A1C value of > 10% from baseline ▪ HCL (N = 54): 0% ▪ PLGS (N = 55): 0% ▪ Risk-adjusted difference (95% CI): not reported ▪ P value: not reported ○ Proportion of participants with an absolute reduction in A1C value of > 1.0% from baseline or an A1C value of < 7.0% at 16 weeks ▪ HCL (N = 54): 43% ▪ PLGS (N = 55): 27% ▪ Risk-adjusted difference (95% CI): 13% (−6% to 32%) ▪ P value: 0.05 • Additional outcomes ○ Mean glucose concentration ▪ HCL (N = 54): 8.88 (SD = 1.11) mmol/L; 160 (SD = 20) mg/dL ▪ PLGS (N = 55): 9.44 L (SD = 1.67) mmol/; 170 (SD = 30) mg/dL ▪ Risk-adjusted difference (95% CI): −0.39 mmol/L (−0.61 to −0.22); −7 mg/dL (−11 to −4) ▪ P value: < 0.001 ○ Glycemic variability as assessed by the coefficient of variation of sensor glucose ▪ HCL (N = 54): 34% (SD = 4%) ▪ PLGS (N = 55): 35% (SD = 5%) ▪ Risk-adjusted difference (95% CI): −1% (−2% to 1%)	

	Authors' conclusion
▪ P value: 0.32 ○ Median weight ▪ HCL (N = 54): 79.2 kg (IQR, 65.9 to 93.4) ▪ PLGS (N = 55): 72.8 kg (IQR, 65.8 to 87.8) ▪ Risk-adjusted difference (95% CI): 0.3 kg (−0.4 to 1.1) ▪ P value: 0.39 ○ Median daily insulin amount ▪ HCL (N = 53): 0.62 (IQR, 0.50 to 0.84) U/kg/day ▪ PLGS (N = 55): 0.67 (IQR, 0.48 to 0.88) U/kg/day ▪ Risk-adjusted difference (95% CI): −0.02 U/kg/day (−0.05 to 0.01) ▪ P value: 0.25 • Subgroup analyses for mean percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) (the primary outcome of the RCT) ○ Baseline factor: A1C value ▪ Subgroup: A1C value ≤ 7.5% ○ HCL (N = 39): 75.3% (baseline); 72.3% (post-treatment) ○ PLGS (N = 43): 74.8% (baseline); 65.3% (post-treatment) ▪ Subgroup: A1C value > 7.5% ○ HCL (N = 15): 60.2% (baseline); 55.5% (post-treatment) ○ PLGS (N = 12): 52.7% (baseline); 42.7% (post-treatment) ○ P value for interaction: < 0.001 ○ Baseline factor: percentage of time with a glucose value below 3.9 mmol/L (70 mg/dL) ▪ Subgroup: ≤ 1% ○ HCL (N = 24): 68.4% (baseline); 64.3% (post-treatment) ○ PLGS (N = 21): 69.4% (baseline); 58.6% (post-treatment) ▪ Subgroup: > 1% ○ HCL (N = 30): 73.3% (baseline); 70.3% (post-treatment) ○ PLGS (N = 34): 70.3% (baseline); 61.5% (post-treatment) ▪ P value for interaction: < 0.001 ○ Baseline factor: percentage of time with a glucose value greater than 10.0 mmol/L (180 mg/dL) ▪ Subgroup: ≤ 40% ○ HCL (N = 46): 74.1.% (baseline); 70.6% (post-treatment) ○ PLGS (N = 44): 75.0% (baseline); 65.7% (post-treatment) ▪ Subgroup: > 40% ○ HCL (N = 8): 53.8% (baseline); 50.5 % (post-treatment) ○ PLGS (N = 11): 50.0% (baseline); 39.0% (post-treatment) ▪ P value for interaction: < 0.001	

	Authors' conclusion
○ Baseline factor: percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) ▪ Subgroup: ≤ 60% ○ HCL (N = 9): 54.4% (baseline); 51.5% (post-treatment) ○ PLGS (N = 12): 50.7% (baseline); 39.4% (post-treatment) ▪ Subgroup: > 60% ○ HCL (N = 45): 74.5% (baseline); 70.8% (post-treatment) ○ PLGS (N = 43): 75.4% (baseline); 66.3% (post-treatment) ▪ P value for interaction: < 0.001 ○ Baseline factor: age ▪ Subgroup: 14 years to 24 years ○ HCL (N = 17): 63.6% (baseline); 59.6% (post-treatment) ○ PLGS (N = 22): 62.1% (baseline); 51.6% (post-treatment) ▪ Subgroup: 25 years to 71 years ○ HCL (N = 37): 74.6% (baseline); 71.3% (post-treatment) ○ PLGS (N = 33): 75.2% (baseline); 66.2% (post-treatment) ▪ P value for interaction: 0.20 ○ Baseline factor: sex ▪ Subgroup: female ○ HCL (N = 28): 72.9% (baseline); 68.3% (post-treatment) ○ PLGS (N = 25): 71.5% (baseline); 61.4% (post-treatment) ▪ Subgroup: male ○ HCL (N = 26): 69.2% (baseline); 66.8% (post-treatment) ○ PLGS (N = 30): 68.7% (baseline); 59.6% (post-treatment) ▪ P value for interaction: 0.76 **Summary of findings related to comparative safety (research question 2)** • Hypoglycemic events ○ Median number of hypoglycemic events per week (defined as at least 15 consecutive minutes with a glucose level < 3.9 mmol/L [< 70 mg/dL]) ▪ HCL (N = 54): 3 (IQR, 1.5 to 4.9) ▪ PLGS (N = 55): 3.1 (IQR, 1.6 to 5.3) ▪ Risk-adjusted difference (95% CI): 0.1 (−0.3 to 0.6) ▪ P value: 0.58 • Hyperglycemic events ○ Number of episodes of hyperglycemia with ketosis ▪ HCL (N = 54): 0 ▪ PLGS (N = 55): 3	

	Authors' conclusion
▪ P value: not calculated • Adverse events ○ Number of adverse events ▪ HCL (N = 54): 0 ▪ PLGS (N = 55): 3 ▪ P value: not calculated • Worsening of A1C value ○ Proportion of participants who had a worsening of their A1C values of > 0.5% post-treatment ▪ HCL (N = 54): 15% ▪ PLGS (N = 55): 36% ▪ P value: not calculated • Diabetic ketoacidosis events ○ Number of diabetic ketoacidosis events ▪ HCL (N = 54): 0 ▪ PLGS (N = 55): 0 ▪ P value: not calculated • Ketosis events ○ Number of days with ≥ 1 blood ketone measurement > 1.0 mmol/L (% of days) ▪ HCL (N = 54): 5 (0.10%) ▪ PLGS (N = 55): 1 (0.02%) ▪ P value: not calculated	
Hanaire et al. (2020)[56]	
Multi-centre, open-label, 3-arm, randomized controlled crossover trial where participants were allocated into 1 of 3 cohorts: group 1 (control rest condition [N = 14]); group 2 (gastronomic dinners [N = 10]); or group 3 (sustained and repeated bouts of physical exercise followed by uncontrolled food intake [N = 14]). Each participant was tested in their assigned condition with the Diabeloop single-hormone HCL and the open-loop SAP system. **Summary of findings related to comparative clinical effectiveness (research question 1)** • Glucose time-in-range metrics ○ Mean percentage of time spent in the glucose range of 4.4 mmol/L to 7.8 mmol/L (79 mg/dL to 140 mg/dL) overnight (the primary outcome of the RCT) ▪ Group 1 HCL (N = 13): 61.8% (SD = 20.0%) ▪ Group 1 open-loop system (N = 13): 51.1% (SD = 23.2%) ▪ P value: non-significant	"In conclusion, the Diabeloop [HCL] system proved more efficient than OL sensor-augmented pumps in maintaining glucose at target levels in participants exposed to real-life challenging situations, such as gastronomic meals or sustained and repeated bouts of physical exercise. This benefit was mainly

	Authors' conclusion
▪ Group 2 HCL (N = 10): 59.7% (SD = 13.7%) ▪ Group 2 open-loop system (N = 10): 22.4% (SD = 16.0%) ▪ P value: < 0.01 ▪ Group 3 HCL (N = 13): 67.5% (SD = 10.7%) ▪ Group 3 open-loop system (N = 13): 44.8% (SD = 25.3%) ▪ P value: < 0.01 ▪ Total HCL (N = 36): 63.2% (SD = 15.3%) ▪ Total open-loop system (N = 36): 40.9% (SD = 24.7%) ▪ P value: < 0.0001 ○ Mean percentage of time with glucose values < 3.9 mmol/L (70 mg/dL) throughout the whole day ▪ Group 1 HCL (N = 13): 3.8% (SD = 3.2%) ▪ Group 1 open-loop system (N = 13): 4.7% (SD = 4.4%) ▪ P value: non-significant ▪ Group 2 HCL (N = 10): 1.4% (SD = 1.2%) ▪ Group 2 open-loop system (N = 10): 3.9% (SD = 4.5%) ▪ P value: 0.0645 ▪ Group 3 HCL (N = 13): 2.6% (SD = 2.3%) ▪ Group 3 open-loop system (N = 13): 3.4% (SD = 3.7%) ▪ P value: non-significant ▪ Total HCL (N = 36): 2.7% (SD = 2.6%) ▪ Total open-loop system (N = 36): 4.0% (SD = 4.1%) ▪ P value: 0.103 ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) throughout the day ▪ Group 1 HCL (N = 13): 77.8% (SD = 12.4%) ▪ Group 1 open-loop system (N = 13): 71.5% (SD = 12.1%) ▪ P value: 0.0942 ▪ Group 2 HCL (N = 10): 80.5% (SD = 6.4%) ▪ Group 2 open-loop system (N = 10): 54.3% (SD = 15.6%) ▪ P value: < 0.01 ▪ Group 3 HCL (N = 13): 80.2% (SD = 9.1%) ▪ Group 3 open-loop system (N = 13): 64.2% (SD = 16.2%) ▪ P value: < 0.01 ▪ Total HCL (N = 36): 79.4% (SD = 9.6%) ▪ Total open-loop system (N = 36): 64.1% (SD = 15.9%) ▪ P value: < 0.0001 ○ Mean percentage of time with glucose values > 10.0 mmol/L (180 mg/dL) throughout the day ▪ Group 1 HCL (N = 13): 18.4% (SD = 12.5%) ▪ Group 1 open-loop system (N = 13): 23.8% (SD = 12.7%)	attributable to a marked reduction in the hyperglycaemic excursions associated not only with gastronomic dinners, but also with physical exercise followed by uncontrolled food and carbohydrate intake." (p. 332)

	Authors' conclusion
▪ P value: non-significant ▪ Group 2 HCL (N = 10): 18.1% (SD = 6.3%) ▪ Group 2 open-loop system (N = 10): 41.9% (SD = 19.0%) ▪ P value: < 0.01 ▪ Group 3 HCL (N = 13): 17.2% (SD = 8.1%) ▪ Group 3 open-loop system (N = 13): 32.4% (SD = 17.6%) ▪ P value: < 0.01 ▪ Total HCL (N = 36): 17.9% (SD = 9.3%) ▪ Total open-loop system (N = 36): 31.9% (SD = 17.5%) ▪ P value: < 0.0001 ○ Mean percentage of time with glucose values < 3.9 mmol/L (70 mg/dL) overnight ▪ Group 1 HCL (N = 13): 2.7% (SD = 3.3%) ▪ Group 1 open-loop system (N = 13): 4.2% (SD = 5.1%) ▪ P value: non-significant ▪ Group 2 HCL (N = 10): 1.6% (SD = 2.4%) ▪ Group 2 open-loop system (N = 10): 5.7% (SD = 8.9%) ▪ P value: non-significant ▪ Group 3 HCL (N = 13): 2.1% (SD = 1.9%) ▪ Group 3 open-loop system (N = 13): 4.0% (SD = 5.4%) ▪ P value: non-significant ▪ Total HCL (N = 36): 2.1% (SD = 2.6%) ▪ Total open-loop system (N = 36): 4.6% (SD = 6.3%) ▪ P value: 0.0532 ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) overnight ▪ Group 1 HCL (N = 13): 83.4% (SD = 13.9%) ▪ Group 1 open-loop system (N = 13): 76.2% (SD = 20.9%) ▪ P value: non-significant ▪ Group 2 HCL (N = 10): 85.8% (SD = 10.3%) ▪ Group 2 open-loop system (N = 10): 49.3% (SD = 23.8%) ▪ P value: < 0.01 ▪ Group 3 HCL (N = 13): 91.3% (SD = 9.0%) ▪ Group 3 open-loop system (N = 13): 71.9% (SD = 24.5%) ▪ P value: < 0.001 ▪ Total HCL (N = 36): 86.9% (SD = 11.6%) ▪ Total open-loop system (N = 36): 67.2% (SD = 25.1%) ▪ P value: < 0.0001 ○ Mean percentage of time glucose with glucose values > 10.0 mmol/L (180 mg/dL) overnight	

	Authors' conclusion
▪ Group 1 HCL (N = 13): 13.9% (SD = 14.3%) ▪ Group 1 open-loop system (N = 13): 19.6% (SD = 21.6%) ▪ P value: non-significant ▪ Group 2 HCL (N = 10): 12.7% (SD = 9.1%) ▪ Group 2 open-loop system (N = 10): 45.0% (SD = 29.5%) ▪ P value: < 0.01 ▪ Group 3 HCL (N = 13): 6.6% (SD = 7.8%) ▪ Group 3 open-loop system (N = 13): 24.0% (SD = 26.3%) ▪ P value: < 0.001 ▪ Total HCL (N = 36): 10.9% (SD = 11.1%) ▪ Total open-loop system (N = 36): 28.3% (SD = 27.1%) ▪ P value: < 0.001 • Patient satisfaction ○ Mean Diabetes Treatment Satisfaction Questionnaire score ▪ Total HCL (N = 36): 31.0 (SD = 5.5) ▪ Total open-loop system (N = 36): 26.0 (SD = 5.5) ▪ P value: < 0.001 • Additional outcomes ○ Mean glucose concentration ▪ Group 1 HCL (N = 13): 7.7 (SD = 1.2) mmol/L; 138.6 (SD = 21.6) mg/dL ▪ Group 1 open-loop system (N = 13): 8.1 (SD = 1.0) mmol/L; 145.8 (SD = 18.0) mg/dL ▪ P value: 0.1099 ▪ Group 2 HCL (N = 10): 7.9 (SD = 0.5) mmol/L; 142.2 (SD = 9.0) mg/dL ▪ Group 2 open-loop system (N = 10): 9.6 (SD = 1.7) mmol/L; 172.8 (SD = 30.6) mg/dL ▪ P value: < 0.01 ▪ Group 3 HCL (N = 13): 7.1 (SD = 0.6) mmol/L; 127.8 (SD = 10.8) mg/dL ▪ Group 3 open-loop system (N = 13): 8.7 (SD = 1.4) mmol/L; 156.6 (SD = 25.2) mg/dL ▪ P value: < 0.05 ▪ Total HCL (N = 36): 7.7 (SD = 0.8) mmol/L; 138.6 (SD = 14.4) mg/dL ▪ Total open-loop system (N = 36): 8.7 (SD = 1.5) mmol/L; 156.6 (SD = 27.0) mg/dL ▪ P value: < 0.0001 ○ Glycemic variability as assessed by the standard deviations of the mean percentage of time spent in the glucose range of 4.4 mmol/to 7.8 mmol/L (79 mg/dL to 140 mg/dL) overnight ▪ Total HCL (N = 36): 0.8 mmol/L ▪ Total open-loop system (N = 36): 1.5 mmol/L ▪ P value: 0.0014	

	Authors' conclusion
▪ Mean daily insulin amount ▪ Group 1 HCL (N = 13): 43.4 (SD = 14.9) U/day ▪ Group 1 open-loop system (N = 13): 47.4 (SD = 12.9) U/day ▪ P value: < 0.05 ▪ Group 2 HCL (N = 10): 41.2 (SD = 16.7) U/day ▪ Group 2 open-loop system (N = 10): 43.1 (SD = 15.3) U/day ▪ P value: < 0.05 ▪ Group 3 HCL (N = 13): 31.2 (SD = 7.8) U/day ▪ Group 3 open-loop system (N = 13): 41.0 (SD = 11.1) U/day ▪ P value: < 0.001 ▪ Total HCL (N = 36): 37.7 (SD = 13.9) U/day ▪ Total open-loop system (N = 36): 43.9 (SD = 12.9) U/day ▪ P value: < 0.0001 **Summary of findings related to comparative safety (research question 2)** • Hypoglycemic events ○ Mean number of hypoglycemic events during the 72-hour study period (defined as continuous monitored glucose values < 3.9 mmol/L [70 mg/dL]) ▪ Group 1 HCL (N = 13): 4.4 (SD = 3.1) ▪ Group 1 open-loop system (N = 13): 3.9 (SD = 2.8) ▪ P value: non-significant ▪ Group 2 HCL (N = 10): 2.9 (SD = 2.1) ▪ Group 2 open-loop system (N = 10): 2.9 (SD = 2.8) ▪ P value: non-significant ▪ Group 3 HCL (N = 13): 5.2 (SD = 3.9) ▪ Group 3 open-loop system (N = 13): 3.3 (SD = 3.1) ▪ P value: non-significant ▪ Total HCL (N = 36): 4.3 (SD = 3.6) ▪ Total open-loop system (N = 36): 3.6 (SD = 2.8) ▪ P value: non-significant • Adverse events ○ Number of severe adverse events or technical failures ▪ Total HCL (N = 36): 0 ▪ Total open-loop system (N = 36): 0 ▪ P value: not calculated	
McAuley et al. (2020)[59]	

	Authors' conclusion
Multi-centre, open-label, parallel-group RCT that randomly assigned participants to HCL therapy with the MiniMed 670G HCL system (N = 61) or to continue using their own personal insulin delivery device in conjunction with a bolus dose calculator for meal-related dose estimation (N = 59). **Summary of findings related to comparative clinical effectiveness (research question 1)** • Glucose time-in-range metrics ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) at 23 weeks to 26 weeks post-randomization (the primary outcome of the RCT) ▪ HCL group (N = 61): 69.9% (SD = 9.5%) ▪ Control group (N = 59): 54.7% (SD = 12.7%) ▪ Adjusted difference (95% CI): 14.8% (11.0% to 18.5%) ▪ P value: < 0.0001 ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 7.8 mmol/L (70 mg/dL to 140 mg/dL) at 23 weeks to 26 weeks post-randomization ▪ HCL group (N = 61): 44.1% (SD = 8.5%) ▪ Control group (N = 59): 33.6% (SD = 12.0%) ▪ Adjusted difference (95% CI): 9.7% (6.3% to 13.2%) ▪ P value: < 0.0001 ○ Median percentage of time with glucose values < 2.8 mmol/L (< 50 mg/dL) at 23 weeks to 26 weeks post-randomization ▪ HCL group (N = 61): 0.1% (IQR, 0.1% to 0.5%) ▪ Control group (N = 59): 0.6% (IQR, 0.2% to 1.3%) ▪ Adjusted difference (95% CI): −0.4% (−0.6% to −0.2%) ▪ P value: < 0.0001 ○ Median percentage of time with glucose values < 3.0 mmol/L (< 54 mg/dL) at 23 weeks to 26 weeks post-randomization ▪ HCL group (N = 61): 0.2% (IQR, 0.1% to 0.8%) ▪ Control group (N = 59): 0.9% (IQR, 0.4% to 1.5%) ▪ Adjusted difference (95% CI): −0.6% (−0.8% to −0.3%) ▪ P value: < 0.0001 ○ Median percentage of time with glucose values < 3.3 mmol/L (< 59 mg/dL) at 23 weeks to 26 weeks post-randomization ▪ HCL group (N = 61): 0.6% (IQR, 0.3% to 1.3%) ▪ Control group (N = 59): 1.4% (IQR, 1.0% to 2.3%) ▪ Adjusted difference (95% CI): −0.8% (−1.1% to −0.6%) ▪ P value: < 0.0001 ○ Median percentage of time with glucose values < 3.9 mmol/L (< 70 mg/dL) at 23 weeks to 26 weeks post-randomization ▪ HCL group (N = 61): 1.8% (IQR, 1.1% to 3.4%) ▪ Control group (N = 59): 3.8% (IQR, 2.9% to 5.2%) ▪ Adjusted difference (95% CI): −2.0% (−2.5% to −1.3%) ▪ P value: < 0.0001	"In adults with type 1 diabetes, 26 weeks of HCL improved [time in range], A1C, and their sense of satisfaction from managing their diabetes than those continuing with user-determined insulin dosing and self-monitoring of blood glucose. For most people living with type 1 diabetes globally, this trial demonstrates that HCL is feasible, acceptable, and advantageous."[59] (p. 1)

	Authors' conclusion
○ Mean percentage of time with glucose values > 10.0 mmol/L (> 180 mg/dL) at 23 weeks to 26 weeks post-randomization ▪ HCL group (N = 61): 27.6% (SD = 9.5%) ▪ Control group (N = 59): 40.3% (SD = 14.4%) ▪ Adjusted difference (95% CI): −12.0% (−16.1% to −7.9%) ▪ P value: < 0.0001 ○ Median percentage of time with glucose values > 11.1 mmol/L (> 200 mg/dL) at 23 weeks to 26 weeks post-randomization ▪ HCL group (N = 61): 5.7% (IQR, 3.5% to 8.3%) ▪ Control group (N = 59): 13.3% (IQR, 9.8% to 17.7%) ▪ Adjusted difference (95% CI): −7.5% (−5.6% to −9.4%) ▪ P value: < 0.0001 ○ Median percentage of time with glucose values > 13.9 mmol/L (> 250 mg/dL) at 23 weeks to 26 weeks post-randomization ▪ HCL group (N = 61): 1.3% (IQR, 0.5% to 2.8%) ▪ Control group (N = 59): 4.3% (IQR, 2.8% to 6.8%) ▪ Adjusted difference (95% CI): −2.9% (−2.1% to −3.5%) ▪ P value: < 0.0001 • A1C ○ Mean A1C value at 26 weeks ▪ HCL group (N = 61): 7.0% (SD = 0.6%) ▪ Control group (N = 59): 7.4% (SD = 0.8%) ▪ Adjusted difference (95% CI): −0.4% (−0.6% to −0.2%) ▪ P value: < 0.0001 • Patient satisfaction ○ Mean Diabetes Treatment Satisfaction Questionnaire score ▪ HCL group (N = 61): 28.2 (SD = 5.9) ▪ Control group (N = 59): 27.3 (SD = 5.1) ▪ Adjusted difference (95% CI): 1.0 (−0.8 to 2.7) ▪ P value: 0.29 • Diabetes-specific quality of life ○ Mean DAWN2 Impact of Diabetes Profile score ▪ HCL group (N = 61): 4.5 (SD = 0.9) ▪ Control group (N = 59): 4.8 (SD = 0.7) ▪ Adjusted difference (95% CI): −0.3 (−0.6 to 0.0) ▪ P value: 0.023 • Additional outcomes	

	Authors' conclusion
○ Mean glucose concentration ▪ HCL group (N = 61): 8.72 (SD = 0.78) mmol/L; 157 (SD = 14) mg/dL ▪ Control group (N = 59): 9.46 (SD = 1.28) mmol/L; 171 (SD = 23) mg/dL ▪ Adjusted difference (95% CI): −0.72 mmol/L (−0.89 to −0.39); −13 mg/dL (−16 to −7) ▪ P value: < 0.00014 ○ Glycemic variability as assessed by the coefficient of variation of sensor glucose ▪ HCL group (N = 61): 34.7% (SD = 4.5%) ▪ Control group (N = 59): 39.3% (SD = 5.4%) ▪ Adjusted difference (95% CI): −4.7% (−6.5% to −2.9%) ▪ P value: < 0.0001 ○ Mean fasting capillary blood glucose value ▪ HCL group (N = 61): 8.60 (SD = 3.00) mmol/L; 155 (SD = 54) mg/dL ▪ Control group (N = 59): 9.49 (SD = 4.22) mmol/L; 171 (SD = 76) mg/dL ▪ Adjusted difference (95% CI): −1.00 mmol/L (−1.61 to −0.39); −18 mg/dL (−29 to −7) ▪ P value: 0.0017 ○ Median 1,5-anhydroglucitol level ▪ HCL group (N = 61): 4.9 (IQR, 3.4 to 6.8) mcg/mL ▪ Control group (N = 59): 3.3 (IQR, 1.8 to 5.2) mcg/mL ▪ Adjusted difference (95% CI): 1.6 mcg/mL (0.7 to 2.3) ▪ P value: 0.00046 ○ Median change in mean daily insulin amount from the baseline value to the value at the end of the study period ▪ HCL group (N = 61): −0.01 (IQR, −0.10 to 0.03) U/kg/day ▪ Control group (N = 59): −0.02 (IQR, −0.10 to 0.04) U/kg/day ▪ Adjusted difference (95% CI): −0.01 U/kg/day (−0.04 to 0.03) ▪ P value: 0.85 ○ Median change in body weight from the baseline to the end of the study period ▪ HCL group (N = 61): 0.6 (IQR, −1.9 to 2.1) kg ▪ Control group (N = 59): 0.7 (IQR, −0.7 to 1.5) kg ▪ Adjusted difference (95% CI): −0.1 kg (−1.1 to 0.9) ▪ P value: 0.77 ○ Median change in insulin-to-carbohydrate ratio from the baseline to the end of the study period ▪ HCL group (N = 61): −1.2 (IQR, −2.4 to 0.0) ▪ Control group (N = 59): 0.0 (IQR, −0.8 to 0.0) ▪ Adjusted difference (95% CI): −0.8 (−1.4 to −0.1) ▪ P value: 0.0078 ○ Mean change in basal-insulin proportion from the baseline to the end of the study period ▪ HCL group (N = 61): −5.4% (SD = 16.9%) ▪ Control group (N = 59): 1.9% (SD = 8.2%)	

	Authors' conclusion
▪ Adjusted difference (95% CI): −6.7 (−11.1 to −2.3) ▪ P value: 0.0034 ○ Diabetes distress as measured with median Problem Areas in Diabetes scale score ▪ HCL group (N = 61): 16.7 (IQR, 10.2 to 27.4) ▪ Control group (N = 59): 21.2 (IQR, 9.5 to 36.2) ▪ Adjusted difference (95% CI): −17.0 (−33.0 to 3.0) ▪ P value: 0.10 ○ Diabetes-specific positive well-being as measured with mean 4-item subscale of W-BQ28 score ▪ HCL group (N = 61): 7.8 (SD = 2.4) ▪ Control group (N = 59): 6.8 (SD = 2.6) ▪ Adjusted difference (95% CI): 1.2 (0.4 to 1.9) ▪ P value: 0.0048 ○ Prospective memory as measured with median PRMQ Prospective score ▪ HCL group (N = 61): 17 (IQR, 14 to 20) ▪ Control group (N = 59): 18 (IQR, 15 to 24) ▪ Adjusted difference (95% CI): −1.0 (−3.0 to 0.0) ▪ P value: 0.11 ○ Retrospective memory as measured with median PRMQ Retrospective score ▪ HCL group (N = 61): 15 (IQR, 11 to 18) ▪ Control group (N = 59): 15 (IQR, 12 to 17.5) ▪ Adjusted difference (95% CI): 0.0 (−2.0 to 2.0) ▪ P value: 0.87 ○ Perceived sleep quality as measured with mean Pittsburgh Sleep Quality Index score ▪ HCL group (N = 61): 6.5 (SD = 3.1) ▪ Control group (N = 59): 5.8 (SD = 3.0) ▪ Adjusted difference (95% CI): 0.5 (−0.5 to 1.5) ▪ P value: 0.34 Note: Difference values were adjusted for the baseline value. **Summary of findings related to comparative safety (research question 2)** • Adverse events ○ Number of any serious adverse events ▪ HCL group (N = 61): 17 ▪ Control group (N = 59): 13 ▪ P value: not calculated ○ Proportion of participants who experienced any serious adverse event	

	Authors' conclusion
▪ HCL group (N = 61): 21% ▪ Control group (N = 59): 15% ▪ P value: not calculated ○ Number of serious adverse events per 100 person-years ▪ HCL group (N = 61): 56 ▪ Control group (N = 59): 44 ▪ P value: not calculated • Hypoglycemic events ○ Number of hypoglycemic events (defined as an event that required assistance from another person to administer carbohydrates or glucagon, or other corrective actions) ▪ HCL group (N = 61): 8 ▪ Control group (N = 59): 7 ▪ P value: not calculated ○ Proportion of participants who experienced a hypoglycemic event (defined as an event that required assistance from another person to administer carbohydrates or glucagon or to take other corrective actions) ▪ HCL group (N = 61): 10% ▪ Control group (N = 59): 5% ▪ P value: not calculated • Diabetic ketoacidosis events ○ Number of diabetic ketoacidosis events ▪ HCL group (N = 61): 1 ▪ Control group (N = 59): 2 ▪ P value: not calculated ○ Proportion of participants who experienced a diabetic ketoacidosis event ▪ HCL group (N = 61): 2% ▪ Control group (N = 59): 3% ▪ P value: not calculated	
Benhamou et al. (2019)[50]	
Multi-centre, open-label, randomized controlled crossover trial that allocated participants to receive pump therapy with the Diabeloop HCL system followed by an open-loop SAP (N = 32) or vice versa (N = 31). Each therapy was provided for 12 weeks, with an 8-week washout period in between. **Summary of findings related to comparative clinical effectiveness (research question 1)** • Glucose time-in-range metrics ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) (the primary outcome of the RCT)	"In conclusion, we observed that the use of the [Diabeloop Generation 1] system, comprising a patch-pump, a glucose sensor, a hybrid closed-loop regulation algorithm and combined with a remote monitoring,

	Authors' conclusion
▪ HCL (N = 63): 68.5% (SD = 9.4%) ▪ Open-loop system (N = 63): 59.4% (SD = 10.2%) ▪ Paired difference (95% CI): 9.2% (6.4% to 11.9%) ▪ P value: < 0.0001 ○ Mean percentage of time spent in the glucose range of 4.4 mmol/L to 7.8 mmol/L (79 mg/dL to 140 mg/dL) ▪ HCL (N = 63): 39.3% (SD = 7.9%) ▪ Open-loop system (N = 63): 33.5% (SD = 7.9%) ▪ Paired difference (95% CI): 5.8% (3.7% to 7.9%) ▪ P value: < 0.0001 ○ Mean percentage of time with a glucose value < 2.8 mmol/L (50 mg/dL) ▪ HCL (N = 63): 0.2% (SD = 0.8%) ▪ Open-loop system (N = 63): 0.7% (SD = 0.8%) ▪ Paired difference (95% CI): −0.5% (−0.7% to −0.3%) ▪ P value: < 0.0001 ○ Mean percentage of time with a glucose value < 3.3 mmol/L (60 mg/dL) ▪ HCL (N = 63): 0.8% (SD = 0.8%) ▪ Open-loop system (N = 63): 2.0% (SD = 1.6%) ▪ Paired difference (95% CI): −1.3% (−1.6% to −0.9%) ▪ P value: < 0.0001 ○ Mean percentage of time with a glucose value < 3.9 mmol/L (70 mg/dL) ▪ HCL (N = 63): 2.0% (SD = 2.4%) ▪ Open-loop system (N = 63): 4.3% (SD = 2.4%) ▪ Paired difference (95% CI): −2.4% (−3.0% to −1.7%) ▪ P value: < 0.0001 ○ Mean percentage of time with a glucose value > 10.0 mmol/L (180 mg/dL) ▪ HCL (N = 63): 29.5% (SD = 10.2%) ▪ Open-loop system (N = 63): 36.3% (SD = 10.2%) ▪ Paired difference (95% CI): −6.8% (−9.7% to −3.9%) ▪ P value: < 0.0001 ○ Mean percentage of time with a glucose value > 13.9 mmol/L (250 mg/dL) ▪ HCL (N = 63): 7.4% (SD = 6.3%) ▪ Open-loop system (N = 63): 11.7% (SD = 6.3%) ▪ Paired difference (95% CI): −4.3% (−6.2% to −2.4%) ▪ P value: < 0.0001 ○ Mean percentage of time with a glucose value > 16.7 mmol/L (300 mg/dL) ▪ HCL (N = 63): 2.4% (SD = 3.1%)	improved glucose control in real-life conditions for 12 weeks in adult patients with type 1 diabetes with variable A1C concentrations at baseline. These clinically relevant findings support the use of closed-loop technology combined with appropriate health care organization in adults with type 1 diabetes." (p. e24)

	Authors' conclusion
▪ Open-loop system (N = 63): 4.3% (SD = 3.1%) ▪ Paired difference (95% CI): −2.0% (−3.0% to −1.0%) ▪ P value: 0.0002 • A1C value ○ Mean percentage change in A1C from baseline ▪ HCL (N = 63): −0.29% (SD = 0.6%); −3.20 (SD = 5.7) mmol/mol ▪ Open-loop system (N = 63): −0.14% (SD = 0.6%); −1.57 (SD 5.6) mmol/mol ▪ Paired difference (95% CI): −0.15% (−0.33% to 0.03%); −1.63 (−3.57 to 0.21) mmol/mol ▪ P value: 0.098 • Patient satisfaction ○ Mean Diabetes Treatment Satisfaction Questionnaire scores ▪ HCL (N = 63): 27.2 (SD = 7.4) ▪ Open-loop system (N = 63): 27.9 (SD = 5.0) ▪ P value: non-significant • Additional outcomes ○ Mean glucose concentration ▪ HCL (N = 63): 8.7 (SD = 0.8) mmol/L; 156.6 (SD = 14.4) mg/dL ▪ Open-loop system (N = 63): 9.1 (SD = 0.8) mmol/L; 163.8 (SD = 14.4) mg/dL ▪ Paired difference (95% CI): −0.4 mmol/L (−0.6 to −0.1); −7.2 mg/dL (−10.8 to −1.8) ▪ P value: 0.012 ○ Glycemic variability as assessed by the coefficient of variation of sensor glucose ▪ HCL (N = 63): 31.0% (SD = 3.9%) ▪ Open-loop system (N = 63): 33.3% (SD = 3.9%) ▪ Paired difference (95% CI): −2.3% (−3.1% to −1.5%) ▪ P value: < 0.0001 Note: Paired difference values were adjusted for baseline A1C value and study site. **Summary of findings related to comparative safety (research question 2)** • Hypoglycemic events ○ Number of severe hypoglycemia events (defined as events requiring the intervention of a third party for correction) ▪ HCL (N = 68): 5 ▪ Open-loop system (N = 68): 3 ▪ P value: not calculated	

	Authors' conclusion
• Hyperglycemic events ○ Number of severe hyperglycemia events (defined as capillary blood glucose values > 20 mmol/L) ▪ HCL (N = 68): 9 ▪ Open-loop system (N = 68): 0 ▪ P value: not calculated • Diabetic ketoacidosis events ○ Number of diabetic ketoacidosis events ▪ HCL (N = 68): 0 ▪ Open-loop system (N = 68): 0 ▪ P value: not calculated	
Brown et al. (2019)[53] and Isganaitis et al. (2020)[57]	
Multi-centre, open-label, parallel-group RCT where participants ≥ 14 years of age were allocated to receive treatment with a Control-IQ HCL system (N = 112) or an open-loop SAP (N = 56). The publication by Isganaitis et al. (2020)[57] reported on the findings of a pre-specified subgroup analysis of participants who were between the ages of 14 years and 25 years (N = 63). **Summary of findings related to comparative clinical effectiveness (research question 1)** • Glucose time-in-range metrics (from the entire study population) ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) (the primary outcome of the RCT) ▪ HCL (N = 112): 71% (SD = 12%) ▪ Open-loop system (N = 56): 59% (SD = 14%) ▪ Risk-adjusted difference (95% CI): 11% (9% to 14%) ▪ P value: < 0.001 ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 7.8 mmol/L (70 mg/dL to 140 mg/dL) ▪ HCL (N = 112): 46% (SD = 12%) ▪ Open-loop system (N = 56): 36% (SD = 12%) ▪ Risk-adjusted difference (95% CI): 8% (6% to 11%) ▪ P value: < 0.001 ○ Mean percentage of time with a glucose value < 3.0 mmol/L (< 54 mg/dL) ▪ HCL (N = 112): 0.29% (SD = 0.29%) ▪ Open-loop system (N = 56): 0.35% (SD = 0.32%) ▪ Risk-adjusted difference (95% CI): −0.10% (−0.19% to −0.02%) ▪ P value: 0.02 ○ Mean percentage of time with a glucose value < 3.3 mmol/L (< 60 mg/dL) ▪ HCL (N = 112): 0.58% (SD = 0.52%) ▪ Open-loop system (N = 56): 0.75% (SD = 0.61%) ▪ Risk-adjusted difference (95% CI): −0.26% (−0.40% to −0.11%)	"In conclusion, over a 6-month period, the [HCL] system used in our trial led to a greater percentage of time that the glucose level was in a target range, less hyperglycemia and hypoglycemia, and better glycated hemoglobin levels than a sensor-augmented pump." (p. 1716)

	Authors' conclusion
▪ P value: < 0.001 ○ Mean percentage of time with a glucose value < 3.9 mmol/L (< 70 mg/dL) ▪ HCL (N = 112): 1.58% (SD = 1.15%) ▪ Open-loop system (N = 56): 2.25% (SD = 1.46%) ▪ Risk-adjusted difference (95% CI): −0.88% (−1.19% to −0.57%) ▪ P value: < 0.001 ○ Mean percentage of time with a glucose value > 10.0 mmol/L (> 180 mg/dL) ▪ HCL (N = 112): 27% (SD = 12%) ▪ Open-loop system (N = 56): 38% (SD = 15%) ▪ Risk-adjusted difference (95% CI): −10% (−13% to −8%) ▪ P value: < 0.001 ○ Mean percentage of time with a glucose value > 13.9 mmol/L (> 250 mg/dL) ▪ HCL (N = 112): 7.0% (SD = 6.7%) ▪ Open-loop system (N = 56): 12.3% (SD = 10.2%) ▪ Risk-adjusted difference (95% CI): −5.3% (−7.1% to −3.6%) ▪ P value: < 0.001 ○ Mean percentage of time with a glucose value > 16.7 mmol/L (> 300 mg/dL) ▪ HCL (N = 112): 2.4% (SD = 3.4%) ▪ Open-loop system (N = 56): 4.6% (SD = 6.0%) ▪ Risk-adjusted difference (95% CI): −2.4% (−3.5% to −1.3%) ▪ P value: < 0.001 • A1C values (from the entire study population) ○ Mean A1C at week 26 ▪ HCL (N = 111): 7.06% (SD = 0.79%) ▪ Open-loop system (N = 55): 7.39% (SD = 0.92%) ▪ Risk-adjusted difference (95% CI): −0.33% (−0.53% to −0.13%) ▪ P value: 0.001 ○ Proportion of participants with A1C values < 7.0% (< 53 mmol/mol) at 26 weeks ▪ HCL (N = 111): 47% ▪ Open-loop system (N = 55): 31% ▪ Risk-adjusted difference (95% CI): 14% (3% to 23%) ▪ P value: 0.02 ○ Proportion of participants with A1C values < 7.5% (< 58 mmol/mol) at 26 weeks ▪ HCL (N = 111): 71% ▪ Open-loop system (N = 55): 60% ▪ Risk-adjusted difference (95% CI): 14% (−5% to 20%) ▪ P value: 0.11	

	Authors' conclusion
○ Proportion of participants with an absolute reduction in A1C values of ≥ 0.5% from baseline ▪ HCL (N = 111): 32% ▪ Open-loop system (N = 55): 11% ▪ Risk-adjusted difference (95% CI): 19% (11% to 27%) ▪ P value: 0.005 ○ Proportion of participants with an absolute reduction in A1C values of ≥ 1.0% from baseline ▪ HCL (N = 111): 11% ▪ Open-loop system (N = 55): 0% ▪ Risk-adjusted difference (95% CI): 11% (6% to 18%) ▪ P value: 0.009 ○ Proportion of participants with a relative reduction in A1C values of ≥ 10% from baseline ▪ HCL (N = 111): 19% ▪ Open-loop system (N = 55): 4% ▪ Risk-adjusted difference (95% CI): 14% (8% to 20%) ▪ P value: 0.02 ○ Proportion of participants with an absolute reduction in A1C values of ≥ 1.0% from baseline or an A1C value of < 7.0% at 26 weeks ▪ HCL (N = 111): 53% ▪ Open-loop system (N = 55): 31% ▪ Risk-adjusted difference (95% CI): 21% (10% to 31%) ▪ P value: 0.004 • Additional outcomes (from the entire study population) ○ Mean glucose concentration ▪ HCL (N = 112): 8.66 (SD = 1.05) mmol/L; 156 (SD = 19) mg/dL ▪ Open-loop system (N = 56): 9.44 (SD = 1.3) mmol/L; 170 (SD = 25) mg/dL ▪ Risk-adjusted difference (95% CI): −0.72 mmol/L (−0.94 to −0.44); −13 mg/dL (−17.0 to −8.0) ▪ P value: < 0.001 ○ Glycemic variability as assessed by the coefficient of variation of sensor glucose ▪ HCL (N = 112): 34% (SD = 5%) ▪ Open-loop system (N = 56): 36% (SD = 5%) ▪ Risk-adjusted difference (95% CI): −3% (−4% to −2%) ▪ P value: < 0.001 ○ Mean body weight ▪ HCL (N = 111): 78.7 (SD = 17.0) kg ▪ Open-loop system (N = 55): 76.0 (SD = 18.9) kg ▪ Risk-adjusted difference (95% CI): −0.2 kg (−1.8 to 1.4) ▪ P value: 0.83 ○ Mean total daily insulin amount	

	Authors' conclusion
▪ HCL (N = 111): 55 (SD = 27) U/day ▪ Open-loop system (N = 55): 51 (SD = 20) U/day ▪ Risk-adjusted difference (95% CI): 3 U/day (−7 to 13) ▪ P value: 0.83 • Glucose time-in-range metrics (from the subgroup analysis of participants between the ages of 14 years and 24 years) ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 (70 mg/dL to 180) (the primary outcome of the RCT) ▪ HCL (N = 40): 64% (SD = 8%) ▪ Open-loop system (N = 23): 52% (SD = 14%) ▪ Risk-adjusted difference (95% CI): 12% (9% to 16%) ▪ P value: < 0.0001 ○ Mean percentage of time with a glucose value < 3.0 mmol/L (< 54 mg/dL) ▪ HCL (N = 40): 0.3% (SD = 0.3%) ▪ Open-loop system (N = 23): 0.4% (SD = 0.3%) ▪ Risk-adjusted difference (95% CI): −0.09% (−0.2% to 0.05%) ▪ P value: 0.21 ○ Mean percentage of time with a glucose value < 3.9 mmol/L (< 70 mg/dL) ▪ HCL (N = 40): 1.6% (SD = 1.0%) ▪ Open-loop system (N = 23): 2.1% (SD = 1.5%) ▪ Risk-adjusted difference (95% CI): −0.7% (−1.0% to −0.2%) ▪ P value: 0.002 ○ Mean percentage of time with a glucose value > 10.0 mmol/L (> 180 mg/dL) ▪ HCL (N = 40): 34% (SD = 8%) ▪ Open-loop system (N = 23): 46% (SD = 15%) ▪ Risk-adjusted difference (95% CI): −12% (−16% to −8%) ▪ P value: < 0.0001 ○ Mean percentage of time with a glucose value > 13.9 mmol/L (> 250 mg/dL) ▪ HCL (N = 40): 10.9% (SD = 6.5%) ▪ Open-loop system (N = 23): 18.1% (SD = 12.2%) ▪ Risk-adjusted difference (95% CI): −8.1% (−11.7% to −4.5%) ▪ P value: < 0.0001 ○ Mean percentage of time with a glucose value > 16.7 mmol/L (> 300 mg/dL) ▪ HCL (N = 40): 4.0% (SD = 3.8%) ▪ Open-loop system (N = 23): 7.9% (SD = 7.9%) ▪ Risk-adjusted difference (95% CI): −4.4% (−6.7% to −2.1%) ▪ P value: 0.0005 • A1C value (from the subgroup analysis of participants between the ages of 14 years and 24 years) ○ Mean A1C value at week 26	

	Authors' conclusion
▪ HCL (N = 40): 7.51% (SD = 0.74%) ▪ Open-loop system (N = 22): 7.66% (SD = 1.14%) ▪ Risk-adjusted difference (95% CI): −0.30% (−0.67% to 0.08%) ▪ P value: 0.13 ○ Proportion of participants with A1C values ≤ 7.0% (≤ 53 mmol/mol) at 26 weeks ▪ HCL (N = 40): 20% ▪ Open-loop system (N = 22): 23% ▪ Risk-adjusted difference (95% CI): 6% (−24% to 27%) ▪ P value: 0.45 ○ Proportion of participants with an absolute reduction in A1C value of ≥ 0.5% from baseline ▪ HCL (N = 40): 38% ▪ Open-loop system (N = 22): 23% ▪ Risk-adjusted difference (95% CI): 13% (−18% to 39%) ▪ P value: 0.34 • Additional outcomes (from the subgroup analysis of participants between the ages of 14 years and 24 years) ○ Mean glucose concentration ▪ HCL (N = 40): 9.27 (SD = 0.83) mmol/L; 167 (SD = 15) mg/dL ▪ Open-loop system (N = 23): 10.16 (SD = 1.55) mmol/L; 183 (SD = 28) mg/dL ▪ Risk-adjusted difference (95% CI): −1.00 mmol/L (−1.39 to −0.56); −18 mg/dL (−25 to −10) ▪ P value: < 0.0001 ○ Glycemic variability as assessed by the coefficient of variation of sensor glucose ▪ HCL (N = 40): 37% (SD = 4%) ▪ Open-loop system (N = 23): 38% (SD = 5%) ▪ Risk-adjusted difference (95% CI): −2% (−3% to 0%) ▪ P value: 0.02 • Subgroup analyses for mean percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL; the primary outcome of the RCT) from the entire study population ○ Baseline factor: A1C value ▪ Subgroup: A1C value ≤ 7.5% ○ HCL (N = 66): 68% (baseline); 77% (post-treatment) ○ Open-loop system (N = 30): 66% (baseline); 66% (post-treatment) ▪ Subgroup: A1C value > 7.5% ○ HCL (N = 46): 50% (baseline); 64% (post-treatment) ○ Open-loop system (N = 26): 51% (baseline); 51% (post-treatment) ▪ P value for interaction: 0.003 ○ Baseline factor: percentage of time with a glucose value below 3.9 mmol/L (70 mg/dL)	

	Authors' conclusion
▪ Subgroup: ≤ 4% ○ HCL (N = 71): 57% (baseline); 69% (post-treatment) ○ Open-loop system (N = 42): 58% (baseline); 58% (post-treatment) ▪ Subgroup: > 4% ○ HCL (N = 41): 67% (baseline); 76% (post-treatment) ○ Open-loop system (N = 14): 62% (baseline); 63% (post-treatment) ▪ P value for interaction: 0.94 ○ Baseline factor: percentage of time with a glucose value > 10.0 mmol/L (180 mg/dL) ▪ Subgroup: ≤ 40% ○ HCL (N = 74): 70% (baseline); 76% (post-treatment) ○ Open-loop system (N = 32): 69% (baseline); 67% (post-treatment) ▪ Subgroup: > 40% ○ HCL (N = 38): 42% (baseline); 62% (post-treatment) ○ Open-loop system (N = 24): 46% (baseline); 48% (post-treatment) ▪ P value for interaction: 0.003 ○ Baseline factor: percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) ▪ Subgroup: ≤ 60% ○ HCL (N = 50): 46% (baseline); 64% (post-treatment) ○ Open-loop system (N = 29): 48% (baseline); 50% (post-treatment) ▪ Subgroup: > 60% ○ HCL (N = 62): 73% (baseline); 77% (post-treatment) ○ Open-loop system (N = 27): 71% (baseline); 69% (post-treatment) ▪ P value for interaction: 0.003 ○ Baseline factor: age ▪ Subgroup: 14 years to 24 years ○ HCL (N = 40): 51% (baseline); 64% (post-treatment) ○ Open-loop system (N = 23): 53% (baseline); 52% (post-treatment) ▪ Subgroup: 25 years to 71 years ○ HCL (N = 72): 66% (baseline); 76% (post-treatment) ○ Open-loop system (N = 33): 63% (baseline); 64% (post-treatment) ▪ P value for interaction: 0.13 ○ Baseline factor: sex ▪ Subgroup: female ○ HCL (N = 54): 59% (baseline); 72% (post-treatment) ○ Open-loop system (N = 30): 65% (baseline); 63% (post-treatment) ▪ Subgroup: male ○ HCL (N = 58): 62% (baseline); 71% (post-treatment) ○ Open-loop system (N = 26): 53% (baseline); 54% (post-treatment)	

	Authors' conclusion
▪ P value for interaction: 0.75 • Subgroup analyses for mean percentage of time spent with a glucose value > 3.9 mmol/L (70 mg/dL) from the entire study population ○ Baseline factor: A1C value ▪ Subgroup: A1C value ≤ 7.5% ○ HCL (N = 66): 4.30% (baseline); 1.73% (post-treatment) ○ Open-loop system (N = 30): 3.06% (baseline); 2.46% (post-treatment) ▪ Subgroup: A1C value > 7.5% ○ HCL (N = 46): 2.55% (baseline); 1.37% (post-treatment) ○ Open-loop system (N = 26): 2.58% (baseline); 2.02% (post-treatment) ▪ P value for interaction: 0.14 ○ Baseline factor: percentage of time with a glucose value below 3.9 mmol/L (70 mg/dL) ▪ Subgroup: ≤ 4% ○ HCL (N = 71): 1.53% (baseline); 1.08% (post-treatment) ○ Open-loop system (N = 42): 1.68% (baseline); 1.75% (post-treatment) ▪ Subgroup: > 4% ○ HCL (N = 41): 7.13% (baseline); 2.46% (post-treatment) ○ Open-loop system (N = 14): 6.32% (baseline); 3.77% (post-treatment) ▪ P value for interaction: 0.02 ○ Baseline factor: percentage of time with a glucose value > 10.0 mmol/L (180 mg/dL) ▪ Subgroup: ≤ 40% ○ HCL (N = 74): 4.56% (baseline); 1.88% (post-treatment) ○ Open-loop system (N = 32): 3.37% (baseline); 2.61% (post-treatment) ▪ Subgroup: > 40% ○ HCL (N = 38): 1.69% (baseline); 1.01 % (post-treatment) ○ Open-loop system (N = 24): 2.13% (baseline); 1.78% (post-treatment) ▪ P value for interaction: 0.40 ○ Baseline factor: percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) ▪ Subgroup: ≤ 60% ○ HCL (N = 50): 2.48% (baseline); 1.29% (post-treatment) ○ Open-loop system (N = 29): 2.24% (baseline); 1.88% (post-treatment) ▪ Subgroup: > 60% ○ HCL (N = 62): 4.47% (baseline); 1.81% (post-treatment) ○ Open-loop system (N = 27): 3.48% (baseline); 2.65% (post-treatment) ▪ P value for interaction: 0.40 ○ Baseline factor: age ▪ Subgroup: 14 years to 24 years ○ HCL (N = 40): 3.16% (baseline); 1.59% (post-treatment)	

	Authors' conclusion
○ Open-loop system (N = 23): 2.93% (baseline); 2.12% (post-treatment) ▪ Subgroup: 25 years to 71 years ○ HCL (N = 72): 3.81% (baseline); 1.58% (post-treatment) ○ Open-loop system (N = 33): 2.77% (baseline); 2.35% (post-treatment) ○ P value for interaction: 0.44 ○ Baseline factor: sex ▪ Subgroup: female ○ HCL (N = 54): 3.52% (baseline); 1.47% (post-treatment) ○ Open-loop system (N = 30): 2.77% (baseline); 2.08% (post-treatment) ▪ Subgroup: male ○ HCL (N = 58): 3.64% (baseline); 1.68% (post-treatment) ○ Open-loop system (N = 26): 2.91% (baseline); 2.46% (post-treatment) ▪ P value for interaction: 0.62 Note: Between-group differences were adjusted for the baseline values of the dependent variables (during the 2-week baseline periods): age; previous use of a CGM and insulin pump; and, study centre. P values and confidence intervals were adjusted for multiplicity using the false discovery rate. **Summary of findings related to comparative safety (research question 2)** • Adverse events (from the entire study population) ○ Number of adverse events ▪ HCL (N = 112): 17 ▪ Open-loop system (N = 56): 2 ▪ P value: not calculated because the outcome was not pre-specified in the statistical analysis plan ○ Proportion of participants who experienced any adverse event ▪ HCL (N = 112): 14% ▪ Open-loop system (N = 56): 4% ▪ P value: 0.05 ○ Number of adverse events per 100 person-years ▪ HCL (N = 112): 30.2 ▪ Open-loop system (N = 56): 7.1 ▪ P value: not calculated because the outcome was not pre-specified in the statistical analysis plan ▪ • Hypoglycemic events (from the entire study population) ○ Median number of hypoglycemic events per week (defined as at least 15 consecutive minutes with a glucose level < 3.0 mmol/L [< 54 mg/dL]) ▪ HCL (N = 112): 0.4 (IQR, 0.1 to 0.9) ▪ Open-loop system (N = 56): 0.5 (IQR, 0.2 to 0.9)	

	Authors' conclusion
▪ P value: 0.06 • Hyperglycemic events (from the entire study population) ○ Median number of hyperglycemic events per week (defined as at least 15 consecutive minutes with a glucose level > 16.7 mmol/L [> 300 mg/dL]) ▪ HCL (N = 112): 1.2 (IQR, 0.4 to 2.6) ▪ Open-loop system (N = 56): 2.7 (IQR, 1.1 to 4.6) ▪ P value: < 0.001 • Worsening of A1C value (from the entire study population) ○ Proportion of participants whose A1C value worsened by > 0.5% ▪ HCL (N = 112): 7% ▪ Open-loop system (N = 56): 9% ▪ P value: 0.60 • Diabetic ketoacidosis events (from the entire study population) ○ Proportion of patients who experienced diabetic ketoacidosis ▪ HCL (N = 112): 1% ▪ Open-loop system (N = 56): 0% ▪ P value: not calculated because this outcome was considered exploratory and not included in the hierarchical analysis • Ketosis events (from the entire study population) ○ Mean number of days with ≥ 1 blood ketone measurement > 1.0 mmol/L (% per total person-days of follow-up) ▪ HCL (N = 112): 0.07% ▪ Open-loop system (N = 56): 0.15% ▪ P value: not calculated because this outcome was considered exploratory and not included in the hierarchical analysis • Hypoglycemic events (from the subgroup analysis of participants between the ages of 14 years and 24 years) ○ Mean number of hypoglycemic events per week (defined as at least 15 consecutive minutes with a glucose level < 3.0 mmol/L [< 54 mg/dL]) ▪ HCL (N = 40): 0.7 (SD = 0.6) ▪ Open-loop system (N = 23): 0.7 (SD = 0.8) ▪ Risk-adjusted difference (95% CI): −0.2 (−0.5 to 0.2) ▪ P value: 0.31 • Hyperglycemic events (from the subgroup analysis of participants between the ages of 14 years and 24 years) ○ Mean number of hyperglycemic events per week (defined as at least 15 consecutive minutes with a glucose level > 16.7 mmol/L [> 300 mg/dL]) ▪ HCL (N = 40): 3.3 (SD = 2.2) ▪ Open-loop system (N = 23): 5.0 (SD = 3.0) ▪ Risk-adjusted difference (95% CI): −1.9 (−2.9 to −1.0)	

	Authors' conclusion
▪ P value: < 0.0001 • Diabetic ketoacidosis events (from the subgroup analysis of participants between the ages of 14 years and 24 years) ○ Proportion of patients who experienced diabetic ketoacidosis ▪ HCL (N = 40): 2.5% ▪ Open-loop system (N = 23): 0% ▪ P value: not calculated	
Ekhlaspour et al. (2019)[54]	
Multi-centre, open-label, parallel-group RCT that allocated adolescents and children to receive care with the Control-IQ HCL system (N = 24) or an open-loop SAP (N = 24) during a winter ski camp. Each group included 12 school-aged children (6 years to 12 years of age) and 12 adolescents (13 years to 18 years of age). **Summary of findings related to comparative clinical effectiveness (research question 1)** • Glucose time-in-range metrics ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) (the primary outcome of the RCT) ▪ HCL (N = 24): 66.4% (SD = 16.4%) ▪ Open-loop system (N = 24): 53.9% (SD = 24.8%) ▪ P value: 0.01 ○ Median percentage of time with a glucose value < 2.8 mmol/L (< 50 mg/dL) ▪ HCL (N = 24): 0% (IQR, 0% to 0%) ▪ Open-loop system (N = 24): 0% (IQR, 0% to 0%) ▪ P value: non-significant ○ Median percentage of time with a glucose value < 3.0 mmol/L (< 54 mg/dL) ▪ HCL (N = 24): 0% (IQR, 0% to 0%) ▪ Open-loop system (N = 24): 0% (IQR, 0% to 0.1%) ▪ P value: non-significant ○ Median percentage of time with a glucose value < 3.3 mmol/L (< 60 mg/dL) ▪ HCL (N = 24): 0% (IQR, 0% to 0.8%) ▪ Open-loop system (N = 24): 0.0% (IQR, 0% to 0.6%) ▪ P value: non-significant ○ Median percentage of time with a glucose value < 3.9 mmol/L (< 70 mg/dL) ▪ HCL (N = 24): 2% (IQR, 0.5% to 3.8%) ▪ Open-loop system (N = 24): 0.8% (IQR, 0% to 3.7%) ▪ P value: non-significant ○ Mean percentage of time with a glucose value > 10.0 mmol/L (> 180 mg/dL) ▪ HCL (N = 24): 31.4% (SD = 17.6%) ▪ Open-loop system (N = 24): 43.0% (SD = 24.5%) ▪ P value: 0.015	"In conclusion, during a winter camp and intensive outdoor activities using [Diabetes Assistant] algorithm in a Tandem t: slim X2 with Control-IQ Technology in prepubertal children and adolescents improved time in range and decreased average glucose. Future studies using [closed-loop control] technology during challenging activities without remote monitoring in patients with [type 1 diabetes] are necessary to move this field forward." (p. 8)

	Authors' conclusion
○ Mean percentage of time with a glucose value > 13.9 mmol/L (> 250 mg/dL) ▪ HCL (N = 24): 10.4% (SD = 11.4%) ▪ Open-loop system (N = 24): 16.0% (SD = 13.6%) ▪ P value: 0.059 ○ Mean percentage of time with a glucose value > 16.7 mmol/L (> 300 mg/dL) ▪ HCL (N = 24): 3.9% (SD = 5.9%) ▪ Open-loop system (N = 24): 6.9% (SD = 6.7%) ▪ P value: 0.034 ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) during the daytime (7:00 a.m. to 11:00 p.m.) ▪ HCL (N = 24): 62.4% (SD = 18.8%) ▪ Open-loop system (N = 24): 54.8% (SD = 24.9%) ▪ P value: 0.095 ○ Median percentage of time with a glucose value < 2.8 mmol/L (< 50 mg/dL) during the daytime (7:00 a.m. to 11:00 p.m.) ▪ HCL (N = 24): 0% (IQR, 0% to 0%) ▪ Open-loop system (N = 24): 0% (IQR, 0% to 0%) ▪ P value: non-significant ○ Median percentage of time with a glucose value < 3.0 mmol/L (< 54 mg/dL) during the daytime (7:00 a.m. to 11:00 p.m.) ▪ HCL (N = 24): 0% (IQR, 0% to 0%) ▪ Open-loop system (N = 24): 0% (IQR, 0% to 0%) ▪ P value: non-significant ○ Median percentage of time with a glucose value < 3.3 mmol/L (< 60 mg/dL) during the daytime (7:00 a.m. to 11:00 p.m.) ▪ HCL (N = 24): 0% (IQR, 0% to 0.3%) ▪ Open-loop system (N = 24): 0.0% (IQR, 0% to 0.1%) ▪ P value: non-significant ○ Median percentage of time with a glucose value < 3.9 mmol/L (< 70 mg/dL) during the daytime (7:00 a.m. to 11:00 p.m.) ▪ HCL (N = 24): 1% (IQR, 0% to 3.3%) ▪ Open-loop system (N = 24): 0.8% (IQR, 0% to 2.0%) ▪ P value: non-significant ○ Mean percentage of time with a glucose value > 10.0 mmol/L (> 180 mg/dL) during the daytime (7:00 a.m. to 11:00 p.m.) ▪ HCL (N = 24): 35.7% (SD = 19.8%) ▪ Open-loop system (N = 24): 42.5% (SD = 24.9%) ▪ P value: 0.124 ○ Mean percentage of time with a glucose value > 13.9 mmol/L (> 250 mg/dL) during the daytime (7:00 a.m. to 11:00 p.m.) ▪ HCL (N = 24): 12.1% (SD = 13.6%) ▪ Open-loop system (N = 24): 16.9% (SD = 14.4%) ▪ P value: 0.108 ○ Mean percentage of time with a glucose value > 16.7 mmol/L (> 300 mg/dL) during the daytime (7:00 a.m. to 11:00 p.m.)	

	Authors' conclusion
▪ HCL (N = 24): 4.6% (SD = 7.2%) ▪ Open-loop system (N = 24): 7.3% (SD = 7.5%) ▪ P value: 0.080 ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) overnight (11:00 p.m. to 7:00 a.m.) ▪ HCL (N = 24): 78.6% (SD = 20.3%) ▪ Open-loop system (N = 24): 50.9% (SD = 34.2%) ▪ P value: < 0.001 ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 8.3 mmol/L (70 mg/dL to 150 mg/dL) overnight (11:00 p.m. to 7:00 a.m.) ▪ HCL (N = 24): 60.8% (SD = 26.5%) ▪ Open-loop system (N = 24): 32.1% (SD = 33.2%) ▪ P value: < 0.001 ○ Median percentage of time with a glucose value < 2.8 mmol/L (< 50 mg/dL) overnight (11:00 p.m. to 7:00 a.m.) ▪ HCL (N = 24): 0% (IQR, 0% to 0%) ▪ Open-loop system (N = 24): 0% (IQR, 0% to 0%) ▪ P value: non-significant ▪ Median percentage of time with a glucose value < 3.0 mmol/L (< 54 mg/dL) overnight (11:00 p.m. to 7:00 a.m.) ▪ HCL (N = 24): 0% (IQR, 0% to 0%) ▪ Open-loop system (N = 24): 0% (IQR, 0% to 0%) ▪ P value: non-significant ○ Median percentage of time with a glucose value < 3.3 mmol/L (< 60 mg/dL) overnight (11:00 p.m. to 7:00 a.m.) ▪ HCL (N = 24): 0% (IQR, 0% to 1%) ▪ Open-loop system (N = 24): 0.0% (IQR, 0% to 0%) ▪ P value: non-significant ○ Median percentage of time with a glucose value < 3.9 mmol/L (< 70 mg/dL) overnight (11:00 p.m. to 7:00 a.m.) ▪ HCL (N = 24): 0% (IQR, 0% to 8.2%) ▪ Open-loop system (N = 24): 0% (IQR, 0% to 6.4%) ▪ P value: non-significant ○ Mean percentage of time with a glucose value > 10.0 mmol/L (> 180 mg/dL) overnight (11:00 p.m. to 7:00 a.m.) ▪ HCL (N = 24): 18.2% (SD = 21.4%) ▪ Open-loop system (N = 24): 44.5% (SD = 37.0%) ▪ P value: 0.001 ○ Mean percentage of time with a glucose value > 13.9 mmol/L (> 250 mg/dL) overnight (11:00 p.m. to 7:00 a.m.) ▪ HCL (N = 24): 5.3% (SD = 13.5%) ▪ Open-loop system (N = 24): 13.2% (SD = 19.0%) ▪ P value: 0.118 ○ Mean percentage of time with a glucose value > 16.7 mmol/L (> 300 mg/dL) overnight (11:00 p.m. to 7:00 a.m.)	

	Authors' conclusion
▪ HCL (N = 24): 1.8% (SD = 7.8%) ▪ Open-loop system (N = 24): 5.8% (SD = 9.5%) ▪ P value: 0.116 ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) while skiing (9:30 a.m. to 12:00 p.m. and 1:30 p.m. to 4:00 p.m.) ▪ HCL (N = 24): 57.8% (SD = 27.3%) ▪ Open-loop system (N = 24): 55.9% (SD = 31.1%) ▪ P value: non-significant ○ Median percentage of time with a glucose value < 2.8 mmol/L (< 50 mg/dL) while skiing (9:30 a.m. to 12:00 p.m. and 1:30 p.m. to 4:00 p.m.) ▪ HCL (N = 24): 0% (IQR, 0% to 0%) ▪ Open-loop system (N = 24): 0% (IQR, 0% to 0%) ▪ P value: non-significant ○ Median percentage of time with a glucose value < 3.0 mmol/L (< 54 mg/dL) while skiing (9:30 a.m. to 12:00 p.m. and 1:30 p.m. to 4:00 p.m.) ▪ HCL (N = 24): 0% (IQR, 0% to 0%) ▪ Open-loop system (N = 24): 0% (IQR, 0% to 0%) ▪ P value: non-significant ○ Median percentage of time with a glucose value < 3.3 mmol/L (< 60 mg/dL) while skiing (9:30 a.m. to 12:00 p.m. and 1:30 p.m. to 4:00 p.m.) ▪ HCL (N = 24): 0% (IQR, 0% to 0%) ▪ Open-loop system (N = 24): 0.0% (IQR, 0% to 0%) ▪ P value: non-significant ○ Median percentage of time with a glucose value < 3.9 mmol/L (< 70 mg/dL) while skiing (9:30 a.m. to 12:00 p.m. and 1:30 p.m. to 4:00 p.m.) ▪ HCL (N = 24): 0% (IQR, 0% to 0.8%) ▪ Open-loop system (N = 24): 0% (IQR, 0% to 0.4%) ▪ P value: non-significant ○ Mean percentage of time with a glucose value > 10.0 mmol/L (> 180 mg/dL) while skiing (9:30 a.m. to 12:00 p.m. and 1:30 p.m. to 4:00 p.m.) ▪ HCL (N = 24): 41.4% (SD = 27.8%) ▪ Open-loop system (N = 24): 41.5% (SD = 30.3%) ▪ P value: non-significant ○ Mean percentage of time with a glucose value > 13.9 mmol/L (> 250 mg/dL) while skiing (9:30 a.m. to 12:00 p.m. and 1:30 p.m. to 4:00 p.m.) ▪ HCL (N = 24): 14.4% (SD = 17.3%) ▪ Open-loop system (N = 24): 18.2% (SD = 20.4%) ▪ P value: non-significant	

	Authors' conclusion
○ Mean percentage of time with a glucose value > 16.7 mmol/L (> 300 mg/dL) while skiing (9:30 a.m. to 12:00 p.m. and 1:30 p.m. to 4:00 p.m.) ▪ HCL (N = 24): 5.9% (SD = 11.1%) ▪ Open-loop system (N = 24): 7.5% (SD = 10.9%) ▪ P value: non-significant • Additional outcomes ○ Mean glucose concentration ▪ HCL (N = 24): 8.94 (SD = 1.66) mmol/L; 161 (SD = 29.9) mg/dL ▪ Open-loop system (N = 24): 9.81 (SD = 2.03) mmol/L; 176.8 (SD = 36.5) mg/dL ▪ P value: 0.023 ○ Glycemic variability as assessed by the coefficient of variation of sensor glucose ▪ HCL (N = 24): 34.2% (SD = 6.1%) ▪ Open-loop system (N = 24): 33.9% (SD = 8.4%) ▪ P value: non-significant ○ Mean daily insulin amount ▪ HCL (N = 24): 40.5 (SD = 16.7) U/day ▪ Open-loop system (N = 24): 43.9 (SD = 28.4) U/day ▪ P value: non-significant **Summary of finding related to comparative safety (research question 2)** • Carbohydrate treatments for hypoglycemia ○ Mean total amount of carbohydrate treatments for hypoglycemia ▪ HCL (N = 24): 45.5 (SD = 27.8) g ▪ Open-loop system (N = 24): 57.7 (SD = 57.8) g ▪ P value: non-significant ○ Mean total number of carbohydrate treatments for hypoglycemia ▪ HCL (N = 24): 2.8 (SD = 1.5) ▪ Open-loop system (N = 24): 3.2 (SD = 2.4) ▪ P value: non-significant	
Forlenza et al. (2019)[55]	
Multi-centre, open-label, parallel-group RCT that allocated school-aged children (6 years to 12 years of age) to receive care with the Control-IQ HCL system (N = 12) or an open-loop SAP (N = 12) in an at-home setting. **Summary of findings related to comparative clinical effectiveness (research question 1)** • Glucose time-in-range metrics ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL; the primary outcome of the RCT)	"Results from this home-use study of the commercial Tandem t:slim X2 with Control-IQ HCL [artificial pancreas] system in school-aged children indicate that this system significantly

	Authors' conclusion
▪ HCL (N = 12): 71.2% (SD = 6.3%) ▪ Open-loop system (N = 12): 52.8% (SD = 13.5%) ▪ P value: < 0.001 ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 7.8 mmol/L (70 mg/dL to 140 mg/dL) ▪ HCL (N = 12): 48.5% (SD = 9.5%) ▪ Open-loop system (N = 12): 28.7% (SD = 11.7%) ▪ P value: < 0.001 ○ Median percentage of time with a glucose value < 2.8 mmol/L (< 50 mg/dL) ▪ HCL (N = 12): 0% (75% CI, 0% to 0.2%) ▪ Open-loop system (N = 12): 0% (75% CI, 0% to 0.4%) ▪ P value: non-significant ○ Median percentage of time with a glucose value < 3.0 mmol/L (< 54 mg/dL) ▪ HCL (N = 12): 0.3% (75% CI, 0% to 0.5%) ▪ Open-loop system (N = 12): 0.2% (75% CI, 0% to 0.6%) ▪ P value: non-significant ○ Median percentage of time with a glucose value < 3.3 mmol/L (< 60 mg/dL) ▪ HCL (N = 12): 0.7% (75% CI, 0.2% to 1.2%) ▪ Open-loop system (N = 12): 0.5% (75% CI, 0% to 0.9%) ▪ P value: non-significant ○ Mean percentage of time with a glucose value < 3.9 mmol/L (< 70 mg/dL) ▪ HCL (N = 12): 2.1% (SD = 1.5%) ▪ Open-loop system (N = 12): 2.1% (SD = 2.9%) ▪ P value: non-significant ○ Mean percentage of time with a glucose value > 10.0 mmol/L (> 180 mg/dL) ▪ HCL (N = 12): 26.2% (SD = 7.1%) ▪ Open-loop system (N = 12): 44.7% (SD = 13.8%) ▪ P value: < 0.001 ○ Mean percentage of time with a glucose value > 13.9 mmol/L (> 250 mg/dL) ▪ HCL (N = 12): 6.8% (SD = 4.5%) ▪ Open-loop system (N = 12): 16.1% (SD = 10.3%) ▪ P value: 0.009 ○ Mean percentage of time with a glucose value > 16.7 mmol/L (> 300 mg/dL) ▪ HCL (N = 12): 2.7% (SD = 2.7%) ▪ Open-loop system (N = 12): 5.3% (SD = 3.9%) ▪ P value: 0.065 ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) during the daytime (7:00 a.m. to 11:00 p.m.) ▪ HCL (N = 12): 69.3% (SD = 9.7%)	improved glycemic control in children 6–12 years old. Although this system is currently undergoing a pivotal study, we report a decrease in average [sensor glucose] of 27 mg/dL for the full day and 42 mg/dL overnight. The increase in [time in range] by 4.4 h/day also indicates that profoundly greater glycemic control can be possible with [artificial pancreas] system use. This improvement was seen through hyperglycemia reduction, primarily overnight, without increased hypoglycemia exposure. The system was demonstrated to be extremely dependable as it operated in closed-loop mode for 94.4% of the possible time. The system also scored very high for usability by subjects as measured by responses to the Technology Acceptance Questionnaire." (p. 165)

	Authors' conclusion
▪ Open-loop system (N = 12): 54.4% (SD = 14.2%) ▪ P value: 0.007 ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 7.8 mmol/L (70 mg/dL to 140 mg/dL) during the daytime (7:00 a.m. to 11:00 p.m.) ▪ HCL (N = 12): 45.3% (SD = 12.4%) ▪ Open-loop system (N = 12): 30.0% (SD = 10.5%) ▪ P value: 0.004 ○ Median percentage of time with a glucose value < 2.8 mmol/L (< 50 mg/dL) during the daytime (7:00 a.m. to 11:00 p.m.) ▪ HCL (N = 12): 0% (75% CI, 0% to 0%) ▪ Open-loop system (N = 12): 0% (75% CI, 0% to 0.6%) ▪ P value: non-significant ○ Median percentage of time with a glucose value < 3.0 mmol/L (< 54 mg/dL) during the daytime (7:00 a.m. to 11:00 p.m.) ▪ HCL (N = 12): 0.2% (75% CI, 0% to 0.6%) ▪ Open-loop system (N = 12): 0.3% (75% CI, 0% to 0.9%) ▪ P value: non-significant ○ Median percentage of time with a glucose value < 3.3 mmol/L (< 60 mg/dL) during the daytime (7:00 a.m. to 11:00 p.m.) ▪ HCL (N = 12): 0.6% (75% CI, 0% to 1.4%) ▪ Open-loop system (N = 12): 0.7% (75% CI, 0% to 1.3%) ▪ P value: non-significant ○ Median percentage of time with a glucose value < 3.9 mmol/L (< 70 mg/dL) during the daytime (7:00 a.m. to 11:00 p.m.) ▪ HCL (N = 12): 1.7% (75% CI, 0.7% to 2.9%) ▪ Open-loop system (N = 12): 1.4% (75% CI, 0.5% to 3.4%) ▪ P value: non-significant ○ Mean percentage of time with a glucose value > 10.0 mmol/L (> 180 mg/dL) during the daytime (7:00 a.m. to 11:00 p.m.) ▪ HCL (N = 12): 27.5% (SD = 10.8%) ▪ Open-loop system (N = 12): 42.0% (SD = 14.4%) ▪ P value: 0.010 ○ Mean percentage of time with a glucose value > 13.9 mmol/L (> 250 mg/dL) during the daytime (7:00 a.m. to 11:00 p.m.) ▪ HCL (N = 12): 7.9% (SD = 6.2%) ▪ Open-loop system (N = 12): 14.8% (SD = 11.0%) ▪ P value: 0.069 ○ Mean percentage of time with a glucose value > 16.7 mmol/L (> 300 mg/dL) during the daytime (7:00 a.m. to 11:00 p.m.) ▪ HCL (N = 12): 3.2% (SD = 3.9%) ▪ Open-loop system (N = 12): 4.4% (SD = 4.5%) ▪ P value: non-significant ○ Mean percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) overnight (11:00 p.m. to 7:00 a.m.) ▪ HCL (N = 12): 74.9% (SD = 9.7%)	

	Authors' conclusion
▪ Open-loop system (N = 12): 49.6% (SD = 18.8%) ▪ P value: < 0.001 ○ Mean percentage of time spent in the glucose range of 3.9 mmol/to 7.8 mmol/L (70 mg/dL to 140 mg/dL) overnight (11:00 p.m. to 7:00 a.m.) ▪ HCL (N = 12): 54.9% (SD = 13.3%) ▪ Open-loop system (N = 12): 26.1% (SD = 18.4%) ▪ P value: < 0.001 ○ Median percentage of time with a glucose value < 2.8 mmol/L (< 50 mg/dL) overnight (11:00 p.m. to 7:00 a.m.) ▪ HCL (N = 12): 0% (75% CI, 0% to 0%) ▪ Open-loop system (N = 12): 0% (75% CI, 0% to 0%) ▪ P value: non-significant ○ Median percentage of time with a glucose value < 3.0 mmol/L (< 54 mg/dL) overnight (11:00 p.m. to 7:00 a.m.) ▪ HCL (N = 12): 0% (75% CI, 0% to 0%) ▪ Open-loop system (N = 12): 0% (75% CI, 0% to 0%) ▪ P value: non-significant ○ Median percentage of time with a glucose value < 3.3 mmol/L (< 60 mg/dL) overnight (11:00 p.m. to 7:00 a.m.) ▪ HCL (N = 12): 0.0% (75% CI, 0% to 0.3%) ▪ Open-loop system (N = 12): 0% (75% CI, 0% to 0%) ▪ P value: non-significant ○ Median percentage of time with a glucose value < 3.9 mmol/L (< 70 mg/dL) overnight (11:00 p.m. to 7:00 a.m.) ▪ HCL (N = 12): 0.9% (75% CI, 0% to 2.8%) ▪ Open-loop system (N = 12): 0% (75% CI, 0% to 0%) ▪ P value: non-significant ○ Mean percentage of time with a glucose value > 10.0 mmol/L (> 180 mg/dL) overnight (11:00 p.m. to 7:00 a.m.) ▪ HCL (N = 12): 23.6% (SD = 9.5%) ▪ Open-loop system (N = 12): 49.9% (SD = 19.3%) ▪ P value: < 0.001 ○ Mean percentage of time with a glucose value > 13.9 mmol/L (> 250 mg/dL) overnight (11:00 p.m. to 7:00 a.m.) ▪ HCL (N = 12): 4.8% (SD = 7.8%) ▪ Open-loop system (N = 12): 18.7% (SD = 12.9%) ▪ P value: 0.004 ○ Mean percentage of time with a glucose value > 16.7 mmol/L (> 300 mg/dL) overnight (11:00 p.m. to 7:00 a.m.) ▪ HCL (N = 12): 1.7% (SD = 3.8%) ▪ Open-loop system (N = 12): 7.1% (SD = 6.5%) ▪ P value: 0.021 • Additional outcomes ○ Mean glucose concentration ▪ HCL (N = 12): 8.45 (SD = 0.77) mmol/L; 152.2 (SD = 13.8) mg/dL	

	Authors' conclusion
▪ Open-loop system (N = 12): 10.00 (SD = 1.28) mmol/L; 180.2 (SD = 23.1) mg/dL ▪ P value: 0.002 ○ Glycemic variability as assessed by the coefficient of variation of sensor glucose ▪ HCL (N = 12): 32.6% (SD = 4.1%) ▪ Open-loop system (N = 12): 33.3% (SD = 5.4%) ▪ P value: non-significant ○ Mean daily insulin amount ○ HCL (N = 12): 33.1 U/day (SD = 14.8) ○ Open-loop system (N = 12): 27.8 U/day (SD = 12.3) ○ P value: non-significant **Summary of findings related to comparative safety (research question 2)** • Carbohydrate treatments for hypoglycemia ○ Mean total amount of carbohydrate treatments for hypoglycemia ▪ HCL (N = 12): 17.5 g (SD = 17.6) ▪ Open-loop system (N = 12): 35.5 g (SD = 55.5) ▪ P value: non-significant ○ Median total number of carbohydrate treatments for hypoglycemia ▪ HCL (N = 12): 0.8 (75% CI, 0.3 to 1.4) ▪ Open-loop system (N = 12): 0.3 (75% CI, 0.3 to 0.8) ▪ P value: non-significant	
Non-randomized studies	
Lepore et al. (2020)[58]	
Single-centre, retrospective, observational, matched-cohort study where participants received care with the MiniMed 670G HCL system (N = 20) or the MiniMed 640G open-loop SAP system with PLGS (N = 20). **Summary of findings related to comparative clinical effectiveness (research question 1)** • Glucose time-in-range metrics ○ Median change in mean percentage of time with a glucose value < 3.0 mmol/L (< 54 mg/dL) from the baseline value to the value at the end of the study period ▪ HCL (N = 20): 0% (SD = 0.5%) ▪ Open-loop system (N = 20): 0.1% (SD = 0.7%) ▪ P value: non-significant ○ Median change in mean percentage of time spent in the glucose range of 3.0 mmol/L to 3.8 mmol/L (54 mg/dL to 69 mg/dL) from the baseline value to the value at the end of the study period ▪ HCL (N = 20): −0.6% (SD = 2.5%) ▪ Open-loop system (N = 20): −0.1% (SD = 1.2%) ▪ P value: non-significant	"In conclusion, our data showed that, in adults with type 1 diabetes, switching from 640G to 670G leads to a significant improvement in glucose control with reduced glucose variability, reaching in most cases the recommended targets for time spent in euglycemic and hyperglycemic ranges without increasing the risk of hypoglycemia." (p. 342)

	Authors' conclusion
○ Median change in mean percentage of time spent in the glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) from the baseline value to the value at the end of the study period ▪ HCL (N = 20): 11.6% (SD = 8.3%) ▪ Open-loop system (N = 20): 2.3% (SD = 8.4%) ▪ P value: < 0.005 ○ Median change in mean percentage of time spent in the glucose range of 10.0 mmol/L to 13.9 mmol/L (181 mg/dL to 250 mg/dL) from the baseline value to the value at the end of the study period ▪ HCL (N = 20): −5.1% (SD = 4.5%) ▪ Open-loop system (N = 20): −0.7% (SD = 6.3%) ▪ P value: < 0.05 ○ Median change in mean percentage of time with a glucose value > 13.9 mmol/L (> 250 mg/dL) from the baseline value to the value at the end of the study period ▪ HCL (N = 20): −6.1% (SD = 6.9%) ▪ Open-loop system (N = 20): −1.4% (SD = 4.5%) ▪ P value: < 0.05 • A1C value ○ Mean change in A1C value from the baseline value to the value at the end of the study period ▪ HCL (N = 20): −0.4% (SD = 0.6%); −4.9 (SD = 6.4) mmol/mol ▪ Open-loop system (N = 20): 0.1% (SD = 0.4%); 0.1 (SD = 4.7) mmol/mol ▪ P value: < 0.01 • Additional outcomes ○ Median change in mean glucose concentration from the baseline value to the value at the end of the study period ▪ HCL (N = 20): −0.85 (SD = 0.98) mmol/L; −15.4 (SD = 17.7) mg/dL ▪ Open-loop system (N = 20): 0.04 (SD = 0.72) mmol/L; 0.8 (SD = 13.0) mg/dL ▪ P value: < 0.005 ○ Median change in coefficient of variation of sensor glucose from the baseline value to the value at the end of the study period ▪ HCL (N = 20): −3.8% (SD = 3.6%) ▪ Open-loop system (N = 20): −0.6% (SD = 3.3%) ▪ P value: < 0.01 ○ Median change in mean daily insulin amount from the baseline value to the value at the end of the study period ▪ HCL (N = 20): −0.01 (SD = 0.07) U/kg/day ▪ Open-loop system (N = 20): 0.01 (SD = 0.1) U/kg/day ▪ P value: non-significant **Summary of findings related to comparative safety (research question 2)** • Hypoglycemic events ○ Number of severe hypoglycemia events (defined as events requiring assistance and the administration of carbohydrates or glucagon)	

	Authors' conclusion
▪ HCL (N = 20): 0 ▪ Open-loop system (N = 20): 0 ▪ P value: not calculated • Diabetic ketoacidosis events ○ Number of diabetic ketoacidosis events ▪ HCL (N = 20): 0 ▪ Open-loop system (N = 20): 0 ▪ P value: not calculated	

A1C = glycated hemoglobin; CGM = continuous glucose monitor; CI = confidence interval; HCL = hybrid closed-loop insulin delivery system; IQR = interquartile range; ITT = intention to treat; NR = not reported; OL = open loop; PLGS = predictive low-glucose suspend; PRMQ = Prospective and Retrospective Memory Questionnaire; RCT = randomized controlled trial; SAP = sensor-augmented pump; SD = standard deviation; W-BQ28 = Well-Being Questionnaire 28.

Appendix 3: List of Included Publications — Clinical Review

The citations provided in this list refer to the publications that were included in this Clinical Review.

1. Breton MD, Kanapka LG, Beck RW, et al. A randomized trial of closed-loop control in children with type 1 diabetes. *N Engl J Med*. 2020;383(9):836-845.
2. Brown SA, Beck RW, Raghinaru D, et al. Glycemic outcomes of use of CLC versus PLGS in type 1 diabetes: a randomized controlled trial. *Diabetes Care.* 2020;43(8):1822-1828.
3. Hanaire H, Franc S, Borot S, et al. Efficacy of the Diabeloop closed-loop system to improve glycaemic control in patients with type 1 diabetes exposed to gastronomic dinners or to sustained physical exercise. *Diabetes Obes Metab.* 2020;22(3):324-334.
4. Isganaitis E, Raghinaru D, Ambler-Osborn L, et al. Closed-loop insulin therapy improves glycemic control in adolescents and young adults: outcomes from the International Diabetes Closed-Loop (iDCL) Trial. *Diabetes Technol Ther*. 2020.
5. Lepore G, Scaranna C, Corsi A, Dodesini AR, Trevisan R. Switching from suspend-before-low insulin pump technology to a hybrid closed-loop system improves glucose control and reduces glucose variability: a retrospective observational case-control study. *Diabetes Technol Ther.* 2020;22(4):321-325.
6. McAuley SA, Lee MH, Paldus B, et al. Six months of hybrid closed-loop versus manual insulin delivery with fingerprick blood glucose monitoring in adults with type 1 diabetes: a randomized, controlled trial. *Diabetes Care.* 2020:dc201447.
7. Benhamou PY, Franc S, Reznik Y, et al. Closed-loop insulin delivery in adults with type 1 diabetes in real-life conditions: a 12-week multicentre, open-label randomised controlled crossover trial. *Lancet Digital Health.* 2019;1(1):e17-e25.
8. Brown SA, Kovatchev BP, Raghinaru D, et al. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. *N Engl J Med.* 2019;381(18):1707-1717.
9. Ekhlaspour L, Forlenza GP, Chernavvsky D, et al. Closed loop control in adolescents and children during winter sports: use of the Tandem Control-IQ AP system. *Pediatr Diabetes.* 2019;20(6):759-768.
10. Forlenza GP, Ekhlaspour L, Breton M, et al. Successful at-home use of the Tandem Control-IQ Artificial Pancreas system in young children during a randomized controlled trial. *Diabetes Technol Ther.* 2019;21(4):159-169.

Appendix 4: List of Excluded Studies and Reasons for Exclusion — Clinical Review

The citations provided in this list refer to studies that were excluded after full-text review by 2 independent reviewers as part of this Clinical Review.

Irrelevant Population

1. Bally L, Thabit H, Hovorka R. Closed-Loop Insulin for Glycemic Control in Noncritical Care. *N Engl J Med.* 2018;379(20):1970-1971.

Irrelevant Intervention

2. Benhamou PY, Lablanche S, Vambergue A, Doron M, Franc S, Charpentier G. Highly unstable type 1 diabetes eligible for islet transplantation can be managed with closed-loop insulin delivery. A series of N-of-1 randomised controlled trials. *Diabetes Obes Metab.* 2020;01.
3. Deshpande S, Pinsker JE, Church MM, et al. Randomized Crossover Comparison of Automated Insulin Delivery vs. Conventional Therapy using an Unlocked Smartphone with Scheduled Pasta and Rice Meal Challenges in the Outpatient Setting. *Diabetes Technol Ther.* 2020;22.
4. Dicembrini I, Pala L, Caliri M, et al. Combined continuous glucose monitoring and subcutaneous insulin infusion versus self-monitoring of blood glucose with optimized multiple injections in people with type 1 diabetes: A randomized crossover trial. *Diabetes Obes Metab.* 2020;22(8):1286-1291.
5. Garcia-Tirado J, Brown SA, Laichuthai N, et al. Anticipation of Historical Exercise Patterns by a Novel Artificial Pancreas System Reduces Hypoglycemia During and After Moderate-Intensity Physical Activity in People with Type 1 Diabetes. *Diabetes Technol Ther.* 2020.
6. Haidar A, Legault L, Raffray M, et al. Comparison between closed-loop insulin delivery system (the artificial pancreas) and sensor-augmented pump therapy: a randomised controlled crossover trial. *Diabetes Technol Ther.* 2020;13.
7. Haidar A, Tsoukas MA, Bernier-Twardy S, et al. A Novel Dual-Hormone Insulin-and-Pramlintide Artificial Pancreas for Type 1 Diabetes: A Randomized Controlled Crossover Trial. *Diabetes Care.* 2020;43(3):597-606.
8. Kovatchev B, Anderson SM, Raghinaru D, et al. Randomized Controlled Trial of Mobile Closed-Loop Control. *Diabetes Care.* 2020;43(3):607-615.
9. Kovatchev BP, Kollar L, Anderson SM, et al. Evening and overnight closed-loop control versus 24/7 continuous closed-loop control for type 1 diabetes: a randomised crossover trial. *Lancet Digital Health.* 2020;2(2):e64-e73.
10. Leelarathna L, Thabit H, Wilinska ME, et al. Evaluating Glucose Control With a Novel Composite Continuous Glucose Monitoring Index. *J Diabetes Sci Technol.* 2020;14(2):277-283.
11. Palisaitis E, El Fathi A, von Oettingen JE, et al. The Efficacy of Basal Rate and Carbohydrate Ratio Learning Algorithm for Closed-Loop Insulin Delivery (Artificial Pancreas) in Youth with Type 1 Diabetes in a Diabetes Camp. *Diabetes Technol Ther.* 2020;22(3):185-194.
12. Palisaitis E, El Fathi A, von Oettingen JE, Haidar A, Legault L. A Meal Detection Algorithm for the Artificial Pancreas: A Randomized Controlled Clinical Trial in Adolescents With Type 1 Diabetes. *Diabetes Care.* 2020
13. Viñals C, Beneyto A, Martín-SanJosé JF, et al. Artificial pancreas with carbohydrate suggestion performance for unannounced and announced exercise in Type 1 Diabetes. *J Clin Endocrinol Metab*. 2020.
14. Anderson SM, Buckingham BA, Breton MD, et al. Hybrid Closed-Loop Control Is Safe and Effective for People with Type 1 Diabetes Who Are at Moderate to High Risk for Hypoglycemia. *Diabetes Technol Ther.* 2019;21(6):356-363.
15. Anderson SM, Dassau E, Raghinaru D, et al. The International Diabetes Closed-Loop Study: Testing Artificial Pancreas Component Interoperability. *Diabetes Technol Ther.* 2019;21(2):73-80.
16. Herrero P, El-Sharkawy M, Daniels J, et al. The Bio-inspired Artificial Pancreas for Type 1 Diabetes Control in the Home: System Architecture and Preliminary Results. *J Diabetes Sci Technol.* 2019;13(6):1017-1025.

17. Renard E, Tubiana-Rufi N, Bonnemaison-Gilbert E, et al. Closed-loop driven by control-to-range algorithm outperforms threshold-low-glucose-suspend insulin delivery on glucose control albeit not on nocturnal hypoglycaemia in prepubertal patients with type 1 diabetes in a supervised hotel setting. *Diabetes Obes Metab.* 2019;21(1):183-187.
18. Schierloh U, Wilinska ME, Pit-Ten Cate IM, et al. Lower plasma insulin levels during overnight closed-loop in school children with type 1 diabetes: Potential advantage? A randomized cross-over trial. *PLoS ONE.* 2019;14(3):e0212013.
19. Tauschmann M, Allen JM, Nagl K, et al. Home Use of Day-and-Night Hybrid Closed-Loop Insulin Delivery in Very Young Children: A Multicenter, 3-Week, Randomized Trial. *Diabetes Care.* 2019;42(4):594-600.
20. Biester T, Nir J, Remus K, et al. DREAM5: An open-label, randomized, cross-over study to evaluate the safety and efficacy of day and night closed-loop control by comparing the MD-Logic automated insulin delivery system to sensor augmented pump therapy in patients with type 1 diabetes at home. *Diabetes Obes Metab.* 2018;26:26.
21. Breton MD, Patek SD, Lv D, et al. Continuous Glucose Monitoring and Insulin Informed Advisory System with Automated Titration and Dosing of Insulin Reduces Glucose Variability in Type 1 Diabetes Mellitus. *Diabetes Technol Ther.* 2018;20(8):531-540.
22. Castle JR, El Youssef J, Wilson LM, et al. Randomized Outpatient Trial of Single- and Dual-Hormone Closed-Loop Systems That Adapt to Exercise Using Wearable Sensors. *Diabetes Care.* 2018;41(7):1471-1477.
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Appendix 5: Budget Impact Analysis Tables

Table 42: Additional Assumptions to Derive Target Population (Base-Case Analysis)

Parameter	Assumption	Scenario analysis?	Additional comments
Prevalence	A prevalence of 0.729% was used to calculate the number of individuals with type 1 diabetes in all jurisdictions.	Used estimates provided by jurisdictions, where possible, to estimate the number of individuals with type 1 diabetes	Where possible, the number of individuals with type 1 diabetes estimated using the epidemiological approach was validated against estimates provided by jurisdictions during stakeholder consultations.

Table 43: Additional Assumptions to Derive Market Shares (Base-Case Analysis)

Parameter	Assumption	Scenario analysis?	Additional comments
Reference scenario: FGM/CGM use among eligible individuals in jurisdictions with coverage	Yukon: 50% of those eligible would be using an advanced glucose monitor, with 40% using CGMs and 10% using FGMs. Ontario: 50% of those eligible for CGMs or FGMs would be using these devices.	Assume higher or lower market shares for advanced glucose monitors	Stakeholders consulted by CADTH indicated that if advanced glucose-monitoring devices were covered, they would expect higher uptake rates among most individuals. Because coverage for FGMs and CGMs in Ontario and Yukon is relatively recent, CADTH assumed that 50% will be using advanced glucose-monitoring devices.
HCL uptake among current MDII users	10%, 20%, and 30% in years 1, 2, and 3, respectively	0% uptake of HCL in all years	During stakeholder consultations, mixed feedback was received regarding whether MDII users would begin using a pump to access HCL systems.
HCL uptake among current insulin pump users	50%, 70%, and 90% in years 1, 2, and 3, respectively	50% uptake of HCL in all years	To account for some pump users needing to wait until they are eligible for an HCL-compatible pump upon renewal

CGM = continuous glucose monitor; FGM = flash glucose monitor; HCL = hybrid closed-loop insulin delivery system; MDII = multiple daily injections.

Table 44: Additional Assumptions to Derive Costs (Base-Case Analysis)

Parameter	Assumption	Scenario analysis?	Additional comments
CGM substitution of SMBG	CGM users would not have coverage for SMBG test strips.	CGM users are covered for use of 4 test strips daily.	Scenario analysis assumed all jurisdictions would cover test strips, regardless of present reimbursement restrictions.
Income-dependent coverage of diabetes supplies	In jurisdictions where the amount covered is dependent on household income, the median household income in the jurisdiction was used, along with an assumption of 4 family members, to calculate the amount paid by the public payer.	None.	Note: Deductibles were not included in the analysis.
Number of strips used for SMBG	People using SMBG would use the maximum number of strips reimbursed in their jurisdictions.	People using SMBG use 2,555 test strips annually.	UpToDate recommends testing at least 4 times daily, and additional testing after meals.[190]

Parameter	Assumption	Scenario analysis?	Additional comments
Maximum number of test strips used in jurisdictions where the number of strips is not specified	In jurisdictions where the number of test strips covered is dependent on the number prescribed, a maximum of 3,650 was assumed.	None.	3,650 is the maximum number of test strips covered by jurisdictions in Canada.
Maximum number of test strips covered for SMBG (Northwest Territories and Nunavut)	The maximum number of test strips covered is 2,920 annually.	None.	NIHB coverage criteria and restrictions were used as proxies.
MDII public payer costs	It was assumed that MDII supplies cost the public payer $0.	Apply jurisdiction-specific costs, where able. Where not, assume MDII is a) not covered; and b) covered for those in public drug programs.	CADTH was unable to determine MDII coverage rates for all jurisdictions.

CGM = continuous glucose monitor; MDII = multiple daily injections; NIHB = non-insured health benefits; SMBG = self-monitoring of blood glucose.

Table 45: Pan-Canadian Distribution of Individuals Living With Type 1 Diabetes, Reference Scenario

Treatment strategy	Year 1		Year 2		Year 3	
	Insulin pump	MDII	Insulin pump	MDII	Insulin pump	MDII
CGM	299	1,195	313	1,253	328	1,314
FGM	4,702	18,808	4,765	19,061	4,829	19,318
SMBG	34,894	146,791	35,274	148,525	35,658	150,280
Total	39,895	166,793	40,353	168,840	40,816	170,912
Total, overall	**206,688**		**209,192**		**211,728**	

CGM = continuous glucose monitor; FGM = flash glucose monitor; MDII = multiple daily injections; SMBG = self-monitoring of blood glucose.

Table 46: Pan-Canadian Distribution of Individuals Living With Type 1 Diabetes, New-Device Scenario

Treatment strategy	Year 1		Year 2		Year 3	
	Insulin pump	MDII	Insulin pump	MDII	Insulin pump	MDII
CGM	36,729	1,086	62,034	1,033	87,942	979
FGM	2,354	16,929	1,436	15,256	494	13,537
SMBG	17,464	132,125	10,596	118,836	3,572	105,204
Total	56,547	150,141	74,066	135,126	92,008	119,721
Total, overall	**206,688**		**209,192**		**211,728**	

CGM = continuous glucose monitor; FGM = flash glucose monitor; MDII = multiple daily injections; SMBG = self-monitoring of blood glucose.

Table 47: Pan-Canadian Budget Impact Analysis Results by Jurisdiction

Jurisdiction	Scenario	Year 1	Year 2	Year 3	3-year total
Pan-Canadian (excluding Quebec)	Reference	$443,664,882	$449,072,356	$454,548,041	$1,347,285,278
	New device	$575,148,153	$720,410,575	$874,361,596	$2,169,920,324
	Budget impact	**$131,483,271**	**$271,338,219**	**$419,813,555**	**$822,635,045**
Newfoundland and Labrador	Reference	$3,013,980	$3,006,144	$2,998,328	$9,018,451
	New device	$3,688,502	$4,465,587	$5,352,214	$13,506,303
	Budget impact	**$674,522**	**$1,459,443**	**$2,353,887**	**$4,487,852**
Prince Edward Island	Reference	$432,933	$439,383	$445,930	$1,318,246
	New device	$586,162	$762,637	$956,649	$2,305,449
	Budget impact	**$153,230**	**$323,253**	**$510,719**	**$987,202**
Nova Scotia	Reference	$5,960,549	$6,019,558	$6,079,152	$18,059,259
	New device	$7,016,393	$8,191,517	$9,428,975	$24,636,885
	Budget impact	**$1,055,844**	**$2,171,959**	**$3,349,823**	**$6,577,626**
New Brunswick	Reference	$2,461,257	$2,475,778	$2,490,385	$7,427,420
	New device	$3,212,572	$4,031,071	$4,903,170	$12,146,813
	Budget impact	**$751,315**	**$1,555,293**	**$2,412,785**	**$4,719,393**
Ontario	Reference	$233,867,543	$236,884,434	$239,940,243	$710,692,220
	New device	$309,028,541	$392,466,682	$481,370,042	$1,182,865,265
	Budget impact	**$75,160,998**	**$155,582,248**	**$241,429,799**	**$472,173,045**
Manitoba	Reference	$8,950,820	$9,014,371	$9,078,373	$27,043,563
	New device	$10,222,577	$11,612,614	$13,058,805	$34,893,995
	Budget impact	**$1,271,757**	**$2,598,243**	**$3,980,432**	**$7,850,432**
Saskatchewan	Reference	$9,812,571	$9,865,558	$9,918,832	$29,596,961
	New device	$10,878,995	$12,055,255	$13,289,477	$36,223,727
	Budget impact	**$1,066,424**	**$2,189,697**	**$3,370,645**	**$6,626,766**
Alberta	Reference	$44,417,320	$45,025,837	$45,642,691	$135,085,848
	New device	$71,677,892	$100,964,537	$131,719,989	$304,362,418
	Budget impact	**$27,260,572**	**$55,938,700**	**$86,077,298**	**$169,276,570**
British Columbia	Reference	$131,158,419	$132,614,278	$134,086,296	$397,858,993
	New device	$154,854,048	$181,326,111	$209,170,127	$545,350,287

Jurisdiction	Scenario	Year 1	Year 2	Year 3	3-year total
	Budget impact	**$23,695,629**	**$48,711,834**	**$75,083,831**	**$147,491,294**
Yukon	Reference	$1,479,867	$1,595,323	$1,713,683	$4,788,873
	New device	$1,479,867	$1,595,323	$1,713,683	$4,788,873
	Budget impact	**$0**	**$0**	**$0**	**$0**
Northwest Territories	Reference	$1,118,937	$1,122,182	$1,125,436	$3,366,555
	New device	$1,327,372	$1,547,298	$1,775,547	$4,650,218
	Budget impact	**$208,435**	**$425,117**	**$650,111**	**$1,283,663**
Nunavut	Reference	$990,687	$1,009,510	$1,028,691	$3,028,888
	New device	$1,175,232	$1,391,943	$1,622,916	$4,190,091
	Budget impact	**$184,545**	**$382,433**	**$594,226**	**$1,161,204**

Table 48: Scenario Analysis Results

CADTH scenario/sensitivity analyses	Scenario	Year 1	Year 2	Year 3	3-year total
Pan-Canadian (excluding Quebec)	Reference	$443,664,882	$449,072,356	$454,548,041	$1,347,285,278
	New device	$575,148,153	$720,410,575	$874,361,596	$2,169,920,324
	Budget impact	**$131,483,271**	**$271,338,219**	**$419,813,555**	**$822,635,045**
0% incidence	Reference	$413,542,640	$418,582,979	$423,686,896	$1,255,812,515
	New device	$536,098,969	$671,498,925	$814,997,575	$2,022,595,469
	Budget impact	**$122,556,329**	**$252,915,946**	**$391,310,679**	**$766,782,954**
Prevalence validation (using jurisdiction numbers, where provided)	Reference	$427,081,112	$432,273,900	$437,532,118	$1,296,887,129
	New device	$552,958,484	$692,018,411	$839,370,232	$2,084,347,127
	Budget impact	**$125,877,373**	**$259,744,512**	**$401,838,113**	**$787,459,998**
Prevalence of type 1 diabetes of 0.702% (7.8% of Canadians 12 and older living with diabetes, of whom 9% have type 1 diabetes)	Reference	$428,348,488	$433,569,283	$438,855,933	$1,300,773,704
	New device	$555,292,636	$695,540,244	$844,176,500	$2,095,009,380
	Budget impact	**$126,944,148**	**$261,970,962**	**$405,320,567**	**$794,235,677**
40% of those eligible for insulin pumps are using pumps[a]	Reference	$566,579,624	$573,501,249	$580,509,887	$1,720,590,760
	New device	$685,799,829	$824,223,450	$975,416,312	$2,485,439,591
	Budget impact	**$119,220,205**	**$250,722,201**	**$394,906,426**	**$764,848,831**
50% of current insulin pump users uptake HCL systems in all 3 years	Reference	$443,664,882	$449,072,356	$454,548,041	$1,347,285,278
	New device	$575,148,153	$715,319,663	$858,902,774	$2,149,370,590
	Budget impact	**$131,483,271**	**$266,247,307**	**$404,354,733**	**$802,085,312**
64% of the Ontario population is eligible for ODB coverage of test strips (pan-Canadian perspective)	Reference	$495,082,926	$501,153,694	$507,301,227	$1,503,537,847
	New device	$621,424,393	$761,658,994	$910,022,750	$2,293,106,137
	Budget impact	**$126,341,467**	**$260,505,301**	**$402,721,523**	**$789,568,290**
64% of the Ontario population is eligible	Reference	$285,285,587	$288,965,771	$292,693,430	$866,944,789
	New device	$355,304,781	$433,715,101	$517,031,196	$1,306,051,079

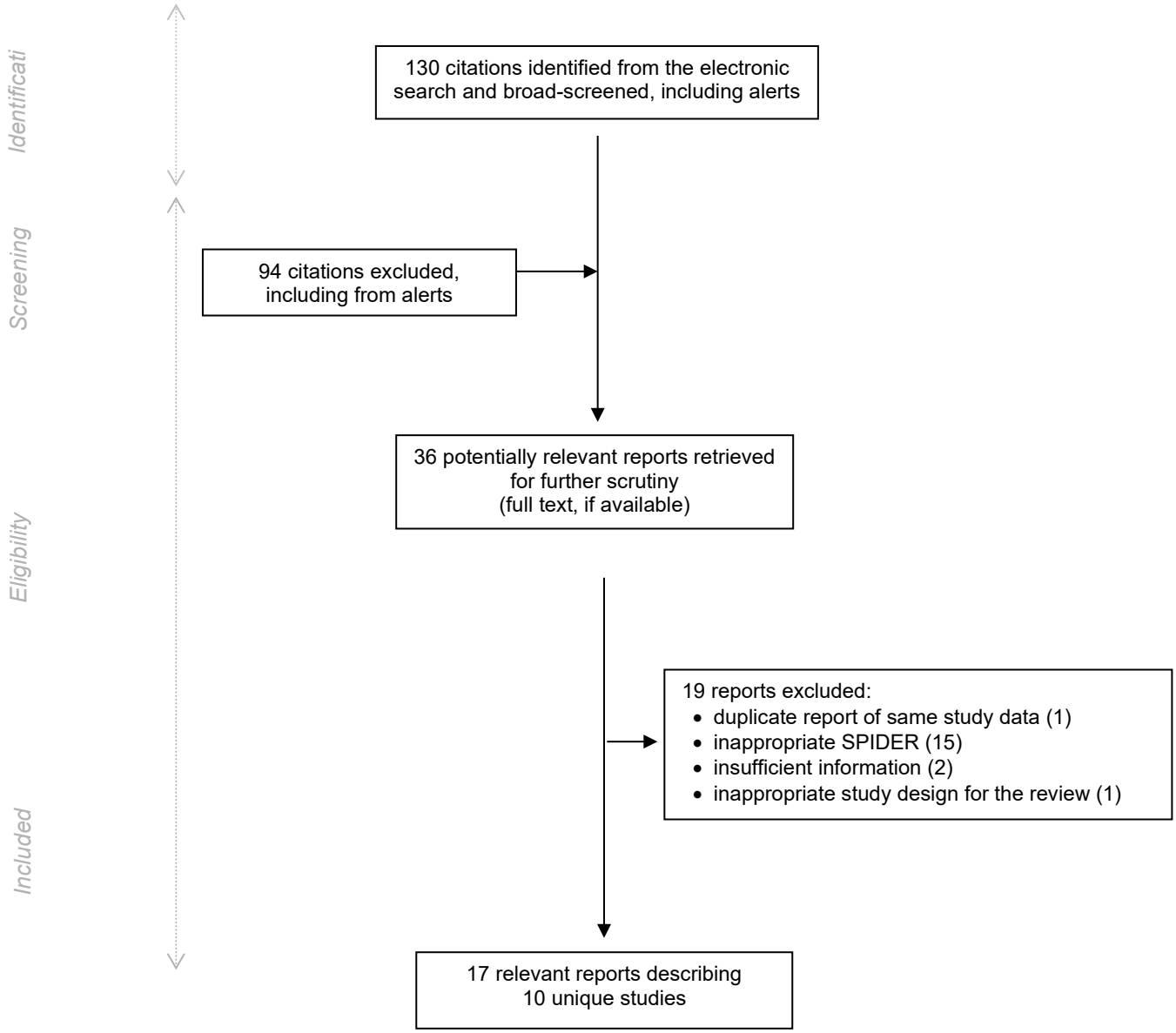
CADTH scenario/sensitivity analyses	Scenario	Year 1	Year 2	Year 3	3-year total
for ODB coverage of test strips (Ontario-specific perspective)	**Budget impact**	**$70,019,194**	**$144,749,330**	**$224,337,766**	**$439,106,290**
Jurisdiction-specific MDII coverage incorporated (where it is not known, assume 0% coverage)	Reference	$500,163,491	$506,274,360	$512,462,297	$1,518,900,149
	New device	$625,996,902	$766,172,178	$914,901,576	$2,307,070,655
	Budget impact	**$125,833,410**	**$259,897,818**	**$402,439,278**	**$788,170,507**
Jurisdiction-specific MDII coverage incorporated (where it is not known, assume coverage for those enrolled in public drug plans)	Reference	$505,246,251	$511,395,541	$517,622,240	$1,534,264,032
	New device	$630,590,203	$770,307,277	$918,571,556	$2,319,469,036
	Budget impact	**$125,343,952**	**$258,911,736**	**$400,949,316**	**$785,205,004**
Assume 20% of those eligible for FGMs or CGMs in Ontario are using these devices in the reference scenario	Reference	$421,374,410	$426,494,338	$431,678,766	$1,279,547,514
	New device	$555,086,729	$702,528,784	$858,901,966	$2,116,517,479
	Budget impact	**$133,712,319**	**$276,034,447**	**$427,223,200**	**$836,969,965**
Assume 100% of those eligible for FGMs or CGMs in Ontario are using these devices in the reference scenario	Reference	$480,815,667	$486,702,387	$492,663,498	$1,460,181,552
	New device	$608,583,860	$750,213,559	$900,127,645	$2,258,925,064
	Budget impact	**$127,768,193**	**$263,511,172**	**$407,464,147**	**$798,743,512**
Assume price per FGM sensor of $99	Reference	$449,777,342	$455,267,190	$460,826,363	$1,365,870,894
	New device	$580,650,234	$725,319,443	$878,610,938	$2,184,580,614
	Budget impact	**$130,872,892**	**$270,052,253**	**$417,784,575**	**$818,709,720**
PEI: All individuals aged 25 years and under are eligible for insulin pumps (pan-Canadian perspective)	Reference	$443,805,649	$449,215,221	$454,693,034	$1,347,713,904
	New device	$575,338,743	$720,658,545	$874,672,649	$2,170,669,937
	Budget impact	**$131,533,094**	**$271,443,324**	**$419,979,615**	**$822,956,033**
PEI: All individuals aged 25 years and under are eligible for insulin pumps (PEI-specific perspective)	Reference	$573,700	$582,248	$590,924	$1,746,872
	New device	$776,752	$1,010,607	$1,267,703	$3,055,062
	Budget impact	**$203,052**	**$428,359**	**$676,779**	**$1,308,189**

CGM = continuous glucose monitor; FGM = flash glucose monitor; HCL = hybrid closed-loop insulin delivery system; MDII = multiple daily injections; ODB = Ontario Drug Benefit.

[a] 40% was applied only in jurisdictions where the 20% assumption was made. In jurisdictions where the percentage of eligible individuals using insulin pumps was known, no changes were made.

Appendix 6: Perspective and Experience Tables and Figures

Figure 5: PRISMA Flow Chart of Selected Reports (Perspectives and Experiences Review)



PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SPIDER = Sample, Phenomenon of Interest, Design, Evaluation, Research.

Alt text: Of 130 citations identified, 94 were excluded, while 36 potentially relevant full-text reports were retrieved for scrutiny. In total, 17 publications describing 10 unique studies were included in the review.

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