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Julia Ware & Roman Hovorka

To cite this article: Julia Ware & Roman Hovorka (2022) Closed-loop insulin delivery: update on the state of the field and emerging technologies, Expert Review of Medical Devices, 19:11, 859-875, DOI: [10.1080/17434440.2022.2142556](https://doi.org/10.1080/17434440.2022.2142556)

To link to this article: <https://doi.org/10.1080/17434440.2022.2142556>



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Published online: 04 Nov 2022.



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# Closed-loop insulin delivery: update on the state of the field and emerging technologies

Julia Ware <sup>a,b</sup> and Roman Hovorka <sup>a,b</sup>

<sup>a</sup>Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge, Cambridge, UK; <sup>b</sup>Department of Pediatrics, University of Cambridge, Cambridge, UK

## ABSTRACT

**Introduction:** Over the last five years, closed-loop insulin delivery systems have transitioned from research-only to real-life use. A number of systems have been commercialized and are increasingly used in clinical practice. Given the rapidity of new developments in the field, understanding the capabilities and key similarities and differences of current systems can be challenging. This review aims to provide an update on the state of the field of closed-loop insulin delivery systems, including emerging technologies.

**Areas covered:** We summarize key clinical safety and efficacy evidence of commercial and emerging insulin-only hybrid closed-loop systems for type 1 diabetes. A literature search was conducted and clinical trials using closed-loop systems during free-living conditions were identified to report on safety and efficacy data. We comment on emerging technologies and adjuncts for closed-loop systems, as well as non-technological priorities in closed-loop insulin delivery.

**Expert opinion:** Commercial hybrid closed-loop insulin delivery systems are efficacious, consistently improving glycemic control when compared to standard therapy. Challenges remain in widespread adoption due to clinical inertia and the lack of resources to embrace technological developments by health care professionals.

## ARTICLE HISTORY

Received 1 August 2022  
Accepted 28 October 2022

## KEYWORDS

Artificial pancreas;  
automated insulin delivery;  
hybrid closed-loop;  
continuous glucose  
monitoring; insulin pump;  
type 1 diabetes

## 1. Introduction

### 1.1. Type 1 diabetes and the need for automated insulin delivery

Type 1 diabetes is an immune-mediated, chronic, incurable condition characterized by insulin deficiency and resultant hyperglycemia, necessitating lifelong insulin replacement [1]. More than 9 million people, including children, are living with the condition worldwide [2]. Whilst treatable, it is associated with significant short- and long-term complications as well as reduced life expectancy [3,4]. Additionally, the high management burden associated with type 1 diabetes increases the risk of developing psychological problems, in turn impacting glycemic control and quality of life [5]. Maintaining tight glycemic control reduces the risk of developing complications [3], but is challenging to achieve, mainly due to the risk of low blood glucose levels (hypoglycemia) with intensive insulin therapy. Thus, the majority of people with type 1 diabetes struggle to meet glycemic targets, or only achieve targets at the expense of high management burden [6–8].

Over the last decade, significant therapeutic advances have been made in the form of rapid and ultra-rapid insulin analogues [9], as well as in the form of diabetes technology including insulin pumps and continuous glucose monitoring (CGM) devices. Both insulin pumps and CGM devices have been shown to improve glycemic control [10] and reduce the risk of dangerously high and low blood glucose levels [11].

However, these devices require significant user-input and frequent insulin dosing adjustments for optimal glucose control. This is challenging as glucose levels are influenced by many different factors causing significant day-to-day variability in insulin requirements [12]. Combining CGM and insulin pump use, i.e. sensor-augmented pump therapy, affects modest improvements in HbA1c in those with high sensor wear time [13–16], but does not reduce management burden [17]. To address these issues, the notion of glucose-responsive automated insulin delivery, where CGM data informs insulin delivery via an algorithm, was proposed. Initial systems addressed the risk of hypoglycemia by automatically suspending insulin delivery when glucose levels fell below a pre-specified threshold but did not address high glucose levels [18–20]. Following on from this, algorithms progressed to addressing high glucose levels by delivering small correction boluses, but these systems did not modulate insulin delivery continuously [21]. Finally, more complex algorithms adjusting insulin delivery up and down automatically in response to real-time sensor glucose levels were developed, more closely replicating normal physiology.

### 1.2. The arrival of closed-loop systems and effect on clinical practice

In all hybrid closed-loop systems a computer algorithm uses real-time sensor glucose levels to calculate the dose of insulin

### Article highlights

- Hybrid closed-loop systems are now being integrated into routine clinical care
- Using a hybrid closed-loop system improves glycemic outcomes and quality-of-life, both in clinical trials and in real-world observational studies
- Systems are cost-effective when compared to multiple daily injections or insulin pump therapy with continuous glucose monitoring
- Healthcare providers need to understand key similarities and differences between systems to support people with type 1 diabetes in choosing and optimizing use of their hybrid closed-loop system
- Improving reimbursement, ensuring more equitable access, and utilizing technological and pharmacological advances to further reduce diabetes burden are key goals moving forward

required to bring glucose levels to a pre-specified target, and automatically directs delivery from the insulin pump. Users are required to manually administer insulin boluses at mealtimes, but the majority of management decisions become automated. Since the approval of the first hybrid closed-loop system in 2016 [22], the pace of new developments and release of new systems has been unprecedented. Between North America and Europe, six systems are currently licensed [23,24]. Clinical trial data universally shows improvements in glycemic control and quality of life across different systems in a wide range of age-groups [25–32]. [33] Over the last five years, more people with type 1 diabetes have started using hybrid closed-loop therapy, and available real-world data appears promising in terms of its positive impact on glycemic control and quality of life, particularly with newer and second-generation systems [34,35]. In view of these fast-paced developments, navigating different systems can be challenging for people with type 1 diabetes, their families and healthcare professionals alike. Developments are at risk of outpacing healthcare professionals' capacity to educate themselves and their patients, and providing sufficient and easily accessible educational resources has become key in enabling access to this novel therapy. To this end, educational tools such as the CARES paradigm have been developed, providing a practical framework to identify key similarities and differences between closed-loop systems [36]. Additionally, experts in the field have published practical advice in terms of patient selection, expectation setting and basic closed-loop education requirements to further support and guide healthcare professionals [37].

### 1.3. Scope of this review

In this review article, we aim to provide an update on safety and efficacy of commercialized and emerging insulin-only closed-loop systems for people with type 1 diabetes, following on from our 2020 review [38]. We comment on emerging technologies and adjuncts to improve closed-loop system performance, as well as non-technological priorities in closed-loop insulin delivery. A search of the existing literature was conducted via PubMed and Google Scholar. Keywords included were 'type 1 diabetes,' 'closed-loop,' 'artificial pancreas,' 'insulin' and 'clinical trial.' Further studies were

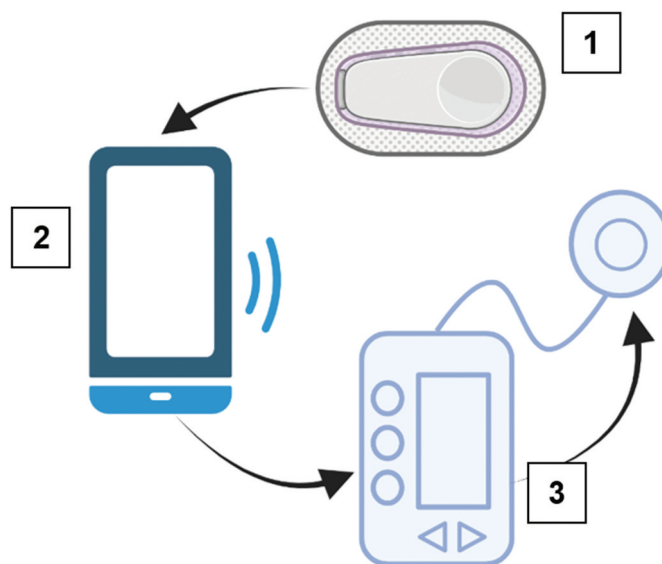
identified from cited articles. Our search was restricted to reports published in English in the last 10 years. Only clinical trials assessing at-home use of closed-loop therapy were used to report on safety and efficacy data.

## 2. The devices behind closed-loop

All closed-loop systems consist of three components: (1) a continuous glucose monitoring system measuring interstitial glucose at regular intervals, (2) a control algorithm, which can be integrated into an insulin pump or reside on a handheld device or smartphone application, and (3) an insulin pump with the ability to continuously deliver insulin (Figure 1). At present, all commercialized systems for type 1 diabetes are 'hybrid' systems, meaning they require users to count carbohydrates and administer an insulin bolus at mealtimes to achieve optimal outcomes.

### 2.1. Continuous subcutaneous insulin infusion pumps

Continuous subcutaneous insulin infusion (CSII) therapy is administered via insulin pumps, which are programmable, battery-operated devices with the ability to deliver rapid or ultra-rapid acting insulin into the subcutaneous tissue via teflon or steel catheters at pre-programmed rates with user-initiated meal-time boluses [39]. Insulin pumps are able to deliver very small amounts of insulin (as little as 0.01 units), enabling the user to give a bolus for small snacks without the need for additional injections, and allowing for greater dosing flexibility in the event of changing insulin sensitivity seen with exercise, illness or early morning insulin resistance [39]. A wide variety of pumps are commercially available, with tethered pumps using a separate cannula and tubing for insulin infusion in contrast to patch pumps, where infusion sets are embedded in the pump itself. Since the early 2000s insulin



**Figure 1.** A closed-loop insulin delivery system comprising (1) a glucose sensor, (2) a device hosting the control algorithm, and (3) an insulin pump (image created with Biorender.com). All components communicate wirelessly via Bluetooth.

pump use has increased exponentially, and roughly 50% of people with type 1 diabetes in Germany and Austria and just over 60% in the USA are using pump therapy, with even higher numbers in the youngest age-groups [40]. Insulin pump use is associated with improvements in glycemic control compared to multiple daily injections [41], however management burden remains high.

## 2.2. Continuous glucose monitoring devices

The first continuous glucose monitoring (CGM) devices became commercially available in the early 2000s [42]. CGM systems consist of a subcutaneously placed, disposable sensor measuring glucose concentration in the interstitial fluid approximately every 5 minutes, and a transmitter that sends values to a receiver or mobile device. This provides near real-time glucose measurements, including data on direction and rate of change of glucose levels via pictorial arrows, aiding therapeutic decision making. CGM performance is measured as the mean absolute relative difference (MARD) compared to YSI (Yellow Springs Instrument, OH, USA) reference values. Commercially available CGMs have a MARD of 10% or lower, which is comparable to the majority of blood glucose meters [21,43]. There are two main types of continuous glucose monitoring devices: intermittently viewed CGM (iCGM), also known as ‘flash glucose monitoring,’ and real-time CGM (rtCGM) [43]. Closed-loop systems require use of real-time CGM, some of which require regular fingerprick calibrations, whereas others are factory-calibrated [42]. Currently only one CGM system is licensed to be inter-operable with multiple closed-loop systems [44]. The use of any type of CGM has increased in recent years, but remains lower than insulin pump use [40]. Real-time CGM use has been associated with improvements in glycemic control in all but the youngest age-groups [45–48], and additionally has been shown to reduce the risk of severe hypoglycemia and diabetic ketoacidosis [11,49].

## 2.3. Closed-loop control algorithms

There are three main types of closed-loop algorithms used in commercialized systems: proportional-integral-derivative (PID) controllers, model predictive control (MPC) controllers and fuzzy logic controllers. PID controllers direct insulin doses based on the difference from target glucose at the current time point (proportional component), the rate of change in sensor glucose over time (derivative component) and the area under the curve between measured and target glucose levels including memory of prior controller-induced changes (integral component) [21]. All three components are weighted with a multiplier, which may be pre-determined or adjusted over time, and subsequently added together to inform modification of insulin delivery. MPC algorithms predict future glucose levels and make adjustments to insulin delivery at regular time intervals based on sensor glucose levels, boluses given, carbohydrate and exercise data, simultaneously taking into account insulin absorption delays, active insulin, and diurnal and post-prandial variability in glucose levels [21]. The fuzzy logic approach uses rules imitating diabetes practitioners’ reasoning to regularly adjust insulin delivery based on the rate of

change and acceleration of sensor glucose levels [50]. Similar to PID and MPC controllers it uses safety modules to limit insulin delivery to avoid hypo- and hyperglycemia.

## 3. Clinical and real-world efficacy of commercial and emerging insulin-only closed-loop systems

After more than a decade of development and clinical trials, with initial safety studies in the inpatient setting [51–55], followed by supervised camp studies and progressing to overnight and 24-hour outpatient studies in children and adults [21,56–65], hybrid closed-loop therapy has become a clinical reality and is gradually changing clinical practice. All available systems are similar in basic principle, but differ in terms of algorithm, hardware components and functionality (Table 1). Here, we review both clinical trial and where available real-world safety and efficacy data of commercially available hybrid closed-loop systems, as well as those systems that have published clinical trial evidence, but are awaiting regulatory approval (Tables 2 and 3). Closed-loop related glycemic outcomes are primarily measured as time with sensor glucose in the target range 3.9 to 10.0 mmol/L (70 to 180 mg/dL), time in hypoglycemia (sensor glucose <3.9 mmol/L or <70 mg/dL) and HbA1c [66]. It is important to note that comparisons between different closed-loop systems are hampered by differences in study design, frequency of visits and baseline characteristics, and should therefore be interpreted cautiously.

### 3.1. Medtronic 670 G HCL and 780 G AHCL systems

The first commercially available hybrid closed-loop system in both the USA and Europe was Medtronic’s 670G Hybrid Closed-Loop (HCL) system in 2016 (Medtronic, Northridge, CA, USA) [67]. It is licensed from age 2 years and over in the USA (updated 770G HCL system), and age 7 years and over in Europe. The system includes the 670G insulin pump with integrated PID algorithm including insulin feedback with adaptive insulin limits, which receives glucose sensor data from the Guardian 3 sensor. When the closed-loop algorithm is active, this is referred to as ‘Auto Mode.’ The Guardian 3 sensor requires a minimum of 2 fingerprick calibrations per day to remain in Auto Mode. In Auto Mode basal insulin delivery is automatically adjusted every 5 minutes based on sensor glucose values, irrespective of pre-set basal rates. The algorithm ‘learns’ based on the total daily insulin requirements of the preceding 5–7 days as well as estimating fasting glucose and the plasma insulin concentration at the time of fasting. The treat-to-target algorithm has a non-adjustable glucose target of 6.7 mmol/L and includes an optional activity mode called ‘Temp target,’ which raises the target to 8.3 mmol/L. In the USA, the 770G system connects to a mobile app with remote glucose data viewing capability and automatic cloud upload. Remote data viewing is not available for the 670G HCL system.

Two large randomized controlled studies comparing 670 G HCL to usual care (either multiple daily injections or pump therapy) over 6 months have been conducted in 135 adolescents and 120 adults [32,68]. Adults using the 670G HCL system had a greater improvement in time in target range of

**Table 1.** Comparison of commercially available hybrid closed-loop systems.

	Medtronic 670G HCL/780G AHCL	Tandem Control-IQ	CamAPS FX	Diabeloop DBLG1	Omnipod 5 HCL
<b>Regulatory approvals</b>					
<b>Age licensed for</b>	7 years +	6 years +	1 year + Pregnancy	18 years +	6 years + (USA) 2 years+ (Europe)
<b>Countries licensed in</b>	USA & Europe	USA & Europe	Europe, Canada, Australia	Europe	USA & Europe
<b>Location of algorithm</b>	Pump-integrated	Pump-integrated	App-based	App-based	Pod-integrated
<b>Factory-calibrated CGM</b>	Yes: Guardian 4 (780 G) No: Guardian 3 (670 G)	Yes – Dexcom G6	Yes – Dexcom G6	Yes – Dexcom G6	Yes – Dexcom G6
<b>Compatible insulin pumps</b>	Minimed 670G Minimed 780G	T-slim X:2	Dana RS and Dana-i YpsoPump	Accucheck Insight Kaleido	Omnipod
<b>Insulins licensed for</b>	Rapid-acting	Rapid-acting	Rapid- and ultra-rapid	Rapid-acting	Rapid-acting
<b>System features</b>					
<b>Type of algorithm</b>	PID with insulin feedback with adaptive insulin limits (670G) and model based auto-corrections (780G)	MPC	MPC	MPC	MPC
<b>Adaptive learning</b>	TDI and estimate of fasting glucose and the plasma insulin concentration at the time of fasting	None	TDI, diurnal, meals	TDI, diurnal, meals	TDI
<b>Target type</b>	Treat-to-target	Treat-to-range	Treat-to-target	Treat-to-target	Treat-to-target
<b>User-adjustable settings</b>	Target glucose (780G only), active insulin time, ICR, activity mode	Basal rates, ICR, ISF, activity mode, sleep mode	Target glucose, ICR, activity mode, Boost mode	Target glucose, TDI, algorithm treatment reactivity, ICR	Target glucose, ICR, activity mode
<b>Adjustable glucose target</b>	670G: Non-adjustable (6.7 mmol/L) 780G: 5.1, 5.6, 6.7 mmol/L	Non-adjustable target range of 6.2 to 8.9 mmol/L	Personalized target 4.4 to 11 mmol/L; up to 48 timeblocks per day	Personalized target 5.6 to 7.2 mmol/L	Personalized target 6.1 to 8.3 mmol/L; up to 8 timeblocks per day
<b>Pre-set basal rates influence automated insulin delivery</b>	No	Yes	No	No	No (inform automated insulin delivery for first 48 hours)
<b>Active insulin time</b>	Adjustable 2–8 hours	5 hours; non-adjustable	Automatically adjusted based on adaptive learning	Automatically adjusted based on adaptive learning	Adjustable 2–6 hours
<b>Automated correction bolus</b>	670G: No 780G: Yes	Yes	No (incorporated into continuous insulin delivery)	Yes	No (incorporated into continuous insulin delivery)
<b>Automode exits</b>	Yes (multiple (670G); min/max insulin delivery (780G))	No	No	No	Yes (min/max insulin delivery)
<b>Automated data upload to cloud</b>	670G: No 780G: Yes	Yes (USA only)	Yes	No	Yes
<b>User features</b>					
<b>Phone-based bolusing</b>	No	Yes (USA only)	Yes	Yes	Yes
<b>Activity mode</b>	Yes	Yes	Yes	Yes	Yes
<b>Other modes</b>	No	Sleep Activity (target range 6.1–6.7 mmol/L)	Boost mode (increases insulin delivery)	Zen mode (increases glucose target)	No
<b>Remote data monitoring</b>	670 G: No 780 G: Glucose data	Glucose data via Dexcom Follow	All data via Diasend app; SMS alerts	Glucose data via Dexcom Follow	Glucose data via Dexcom Follow

[CGM – continuous glucose monitoring; PID – proportional integral derivative; MPC – model predictive control; TDI – total daily insulin; ICR – insulin to carbohydrate ratio; ISF – insulin sensitivity factor]

15 percentage points, compared to 7 percentage points in adolescents and young adults using the system, but both groups had a significant reduction in hypoglycemia compared to control. The greater improvement in time in range seen in the adult study may be related to higher closed-loop usage of 89%. There were 15 severe hypoglycemia events in the adult study (8 in closed-loop and 7 in control group), with no severe hypoglycemia or DKA events in the adolescents. A 4-month crossover study in 30 older adults (60+ years) comparing 670G HCL with sensor-augmented pump therapy showed a modest improvement in time in range of 6 percentage points with a significant reduction in time in hypoglycemia [69]. Five severe hypoglycemia events (3 in closed-loop and 2 in control

group) and one DKA event in the control group were reported. Improved glycemic outcomes were also seen with the 670G HCL system for 38 children aged 2–6 years and 7–14 years compared to sensor-augmented pump therapy over 8 weeks [70]. Time in range improved significantly in both age-groups, although the mean difference was smaller at 6% in the youngest age-group (vs 14% in older children), with no difference in HbA1c outcomes for the very young children. No severe hypoglycemia or DKA events occurred in this study.

Real-world data from the 670G HCL system has shown that Auto Mode use declines significantly over time with a high rate of closed-loop therapy discontinuation. Two prospective observational studies, one over 12 months in children and

**Table 2.** Key randomized controlled trials of closed-loop insulin delivery using commercialized systems.

Population	Duration	Comparator	Baseline HbA1c	Safety outcomes	Glycemic outcomes	CL usage	Key reference
<b>Medtronic 670G HCL</b>							
N = 120 Adults	6 months	MDI or pump	7.5%	8 SH events [7 in control] 1 DKA event [2 in control]	TIR ↑ 15 percentage points HbA1c ↓ 0.4 percentage points	Median 89%	McAuley 2020 [68]
N = 135 12–25 years	6 months	MDI or pump	8.0%	No SH or DKA events [0 in control]	TIR ↑ 7 percentage points HbA1c ↓ 0.3 percentage points	Not stated	Abraham 2021 [32]
N = 30 60+ years	4 months	SAP	7.6%	3 SH events [2 in control] No DKA events [1 in control]	TIR ↑ 6 percentage points HbA1c ↔	Median 93%	McAuley 2022 [69]
<b>Medtronic 780G AHCL</b>							
N = 113 14–29 years	3 months	670G HCL	7.9%	1 SH event [0 in control] No DKA events [0 in control]	TIR ↓ (no mean difference stated) HbA1c ↓ (no difference stated)	Median 86%	Bergental 2021 [31]
N = 59 7–80 years	4 weeks	670G PLGM	7.6%	No SH events [0 in control] No DKA events [1 in control]	TIR ↑ 12 percentage points HbA1c not measured	Mean 96%	Collins 2021 [73]
<b>Tandem Control-IQ</b>							
N = 168 14+ years	6 months	SAP	7.4%	No SH events [0 in control] 1 DKA event [0 in control]	TIR ↑ 11 percentage points HbA1c ↓ 0.3 percentage points	Median 90%	Brown 2019 [27]
N = 101 6–13 years	4 months	SAP	7.6–7.9%	No SH or DKA events [0 in control]	TIR ↑ 11 percentage points HbA1c ↓ 0.4 percentage points	Median 93%	Breton 2020 [30]
<b>CamAPS FX</b>							
N = 86 6+ years	3 months	SAP	8.2–8.3%	No SH events [0 in control] 1 DKA event [0 in control]	TIR ↑ 11 percentage points HbA1c ↓ 0.4 percentage points	Median 71%	Tauschmann 2018 [78]
N = 133 (N = 46 CamAPS FX) 6–18 years	6 months	Pump	8.2–8.3%	4 SH events [3 in control] 2 DKA events [0 in control]	TIR ↑ 7 percentage points (whole cohort), ↑ 15 percentage points (CamAPS FX cohort) HbA1c ↓ 0.3 percentage points (whole cohort), ↓ 1.1 percentage points (CamAPS FX cohort)	Median 93% (CamAPS FX cohort)	Ware & Boughton 2022 [33]
N = 74 1–7 years	4 months	SAP	7.3%	1 SH event [0 in control] No DKA events [0 in control]	TIR ↑ 9 percentage points HbA1c ↓ 0.4 percentage points	Median 95%	Ware 2022 [25]
N = 37 60+ years	4 months	SAP	7.4%	No SH event [2 in control] No DKA events [0 in control]	TIR ↑ 9 percentage points HbA1c ↓ 0.2 percentage points	Median 97%	Boughton 2022 [26]
<b>Diabeloop DBLG1</b>							
N = 68 Adults	3 months	SAP	7.6%	5 SH events [3 in control] No DKA events [0 in control]	TIR ↑ 9 percentage points HbA1c ↔	Median 84%	Benhamou 2019 [29]
N = 17	6 weeks	SAP	7.0–7.6%	No SH or DKA events [0 in control]	TIR ↑ (no mean difference stated) HbA1c not measured	Not stated	Kariyawasam 2022 [81]

[CL – closed-loop. HCL – hybrid closed-loop. MDI – multiple daily injections. SH – severe hypoglycemia. DKA – diabetic ketoacidosis. TIR – time in range (3.9–10.0 mmol/L). HbA1c – glycated hemoglobin. AHCL – advanced hybrid closed-loop. SAP – sensor-augmented pump. PLGM – predictive low glucose management.]

adults and another over 6 months in children and young adults (age 2–25 years) [71,72], showed a significant correlation between higher Auto Mode use and lower HbA1c. Auto Mode use declined steadily over time throughout both studies, and around one-third of participants discontinued closed-loop, with children and adolescents most likely to stop using Auto Mode. High frequency of required sensor calibrations and frequent Auto Mode exits were the main reasons for discontinuing closed-loop therapy.

The development of the 780G Advanced Hybrid Closed-Loop (AHCL) system addressed some of these important usability issues. The PID algorithm including insulin feedback

with adaptive insulin limits remains embedded on the 780G pump, and includes added model-based autocorrections. The AHCL system can be used with the Guardian 3 sensor, but fewer fingerprick calibrations are required, or with the Guardian 4 sensor, which is self-calibrated and does not require any further routine calibrations. The AHCL system administers automatic correction boluses and glucose targets are customizable (5.1 mmol/L, 5.6 mmol/L or 6.7 mmol/L for the 24-hour period). Remote glucose data viewing and automatic cloud upload are available.

Two randomized crossover studies have evaluated the 780G AHCL system, one 3-month study comparing it to the

Table 3. Key real-world and qualitative studies of closed-loop insulin delivery using commercialized systems.

Type of study	Population	Study duration	CL system	Main findings	Key reference
Real-world studies					
Prospective observational	N = 79 9–61 years	12 months	670G HCL	<ul style="list-style-type: none"> <li>CL use declined from median 82% at 1 week to 17% at 12 months</li> <li>46% of participants stopped using CL by 12 months</li> <li>Utilization of CL correlated with improved glycaemic control</li> </ul>	Lal 2019 [72]
Retrospective observational	N = 7813 6+ years	12 months	Control-IQ	<ul style="list-style-type: none"> <li>CL use was high at median 94% over the entire 12-month period</li> <li>TIR was 74%, TBR was 1% and GMI 6.9% at 12 months</li> <li>TIR was lower in children and adolescents (65%) compared with adults (<math>\geq 73\%</math>)</li> <li>Those with sub-optimal baseline glycaemic control had larger increases in TIR at 12 months</li> </ul>	Bretton 2021 [34]
Prospective observational	N = 1435 14+ years	2 months	Control-IQ	<ul style="list-style-type: none"> <li>CL use was high at median 96% at 2 months</li> <li>TIR was 77% and TBR 1.2% at 2 months</li> <li>Sleep activity was used 33% of the time</li> </ul>	Pinsker 2021 [77]
Prospective observational	N = 558 1–71 years	6 months	Loop DIY	<ul style="list-style-type: none"> <li>CL use was median 83%</li> <li>TIR consistent at 73% and TBR at 3%, mean HbA1c 6.5%</li> <li>14% stopped providing data, of which 3% officially discontinued</li> <li>51 severe hypoglycaemia events [18.7 per 100 person years]</li> </ul>	Lum 2021 [89]
Retrospective observational	N = 12,870 7+ years	6 months	780G AHCL	<ul style="list-style-type: none"> <li>CL use was high at median 92% across age-groups</li> <li>TIR was sustained at 74% in children (n = 790) and at 78% in adults (n = 1642) over 6 months</li> </ul>	Arrieta 2022 [74]
Qualitative studies					
Interviews	N = 16 Pregnancy	Part of 4-week RCT	CamAPS FX	<ul style="list-style-type: none"> <li>Improved glucose control giving peace of mind with CL</li> <li>More flexible lifestyle and better sleep with CL</li> <li>Device problems, particularly connectivity issues, were seen as burdensome</li> </ul>	Farrington 2018 [128]
Interviews	N = 39 (18 newly diagnosed adolescents + 21 parents)	Part of 4-year RCT: after first 12 months of CL use	CamAPS FX	<ul style="list-style-type: none"> <li>Little family conflict about food/checking glucose levels with CL</li> <li>Leading a 'normal' life and fitting in with peers with CL</li> <li>Increased independence incl time away from home with CL</li> <li>Concerns about visibility of devices on body and alarms in public</li> </ul>	Rankin 2021 [125]
Questionnaires	N = 135 12–25 years	Part of 6-month RCT	670G HCL	<ul style="list-style-type: none"> <li>Improved diabetes-specific quality of life with CL</li> <li>No difference in diabetes distress or hypoglycaemia fear between CL and usual care</li> </ul>	Abraham 2021 [32]
Questionnaires	N = 113 14–29 years	Part of 3-month RCT	780G AHCL	<ul style="list-style-type: none"> <li>No significant differences across any PROs</li> <li>Reduction in emotional and behavioral burden subscales of the diabetes distress questionnaire with AHCL</li> </ul>	Hood 2021 [133]
Questionnaires	N = 101 6–13 years	Part of 4-month RCT + 3-month extension	Control-IQ	<ul style="list-style-type: none"> <li>No significant differences across any PROs at the end of 4 months or the end of the extension phase</li> </ul>	Cobry 2021 [130]
Questionnaires	N = 168 14+ years	Part of 6-month RCT	Control-IQ	<ul style="list-style-type: none"> <li>Reduction in hypoglycaemia fear with CL at 6 months</li> <li>Improved confidence in managing hypoglycaemia with CL</li> <li>High system usability scores with high perceived benefit with CL</li> </ul>	Kudva 2021 [134]
Interviews	N = 33 Parents of children 1–7 years	Part of 4-month RCT	CamAPS FX	<ul style="list-style-type: none"> <li>Parents reported initial apprehension about using CL and required a period of time to adjust to and trust the CL system</li> <li>CL reduced management burden with more 'normality'</li> <li>Better sleep, less distress for child, more time for siblings, and more able to outsource care with CL</li> <li>Particular benefit to bolusing from a smartphone</li> <li>Device size and connectivity issues can be problematic</li> </ul>	Kimbell 2022 [106]

[CL – closed-loop, HCL – hybrid closed-loop, TIR – time in range (3.9–10.0 mmol/L), TBR – time below range (<3.9 mmol/L), GMI – glucose management indicator (estimated HbA1c), HbA1c – glycosylated hemoglobin, AHCL – advanced hybrid closed-loop, RCT – randomized controlled trial]

670G HCL system in 113 adolescents and young adults, and a shorter 4-week study comparing it to the 670G with predictive low glucose management (PLGM) in 60 children and adults [31,73]. In both studies glycemic outcomes favored the AHCL system. There were fewer Auto Mode exits with the AHCL system, and in accordance with this median closed-loop usage was higher than with the 670G HCL system. One severe hypoglycemia event occurred in the AHCL period in the 3-month study, and one DKA event occurred in the control arm of the 4-week study. Real-life retrospective observational data from more than 4,000 users of 780G AHCL showed that over a mean follow-up duration of 54 days, mean time in range was 76% and closed-loop usage 94%, with 1 Auto Mode exit per week and 3.4 fingerpricks performed per day, suggesting improved usability of this next-generation system [35]. A longer retrospective analysis of real-world data of more than 12,000 pediatric and adult users over 6 months showed similar outcomes sustained over the 6-month period [74].

### 3.2. Tandem Control-IQ

The Control-IQ System (Tandem Diabetes Care, San Diego, CA, USA), is licensed from age 6 years and up in both Europe and the USA. The MPC algorithm is embedded in the t:slim X2 insulin pump and pairs with the factory-calibrated Dexcom G6 (Dexcom, San Diego, CA, USA) glucose sensor. When closed-loop is active, the algorithm adjusts insulin delivery by increasing, decreasing or suspending pre-set basal rates and administering automated correction boluses when glucose is  $>10.0$  mmol/L, using total daily insulin requirements to scale these adjustments. There is no 'learning' component within the algorithm at present. The algorithm is treat-to-range (6.2 to 8.9 mmol/L, non-adjustable) with optional 'sleep mode' (lowers target range to 6.2 to 6.7 mmol/L and prevents automated corrections) and 'activity mode' (raises target range to 7.8 to 8.9 mmol/L). Glucose data can be viewed remotely via the Dexcom Follow app, but remote viewing is not yet available for any insulin data. In the USA, the t:connect app now allows automatic data upload into the cloud and allows users to view pump data and deliver boluses from their smartphone.

There have been two large parallel randomized controlled trials in the USA comparing closed-loop therapy using Control-IQ with sensor-augmented pump therapy, a 4-month study in 101 children aged 6 to 13 years and a 6-month study in 168 adolescents and adults (age 14+ years) [27,30]. Both studies showed improvements in time in target range of 11 percentage points with closed-loop, with additional significant reductions in HbA1c and time in hypoglycemia in the 6-month study. Median closed-loop usage was 90% or higher in both studies, suggesting good longer-term usability of this system. There were no severe hypoglycemia or DKA events in the pediatric study, and one DKA event in the closed-loop group in the 6-month study. The children's study included a 12-week extension phase where all participants used closed-loop, and showed that improvements in time in range were sustained over the full 28-week study period [75]. A European study comparing 24/7 to overnight-only use of Control-IQ in 120 prepubertal children aged 6 to 12 years showed higher time in target range and lower mean glucose levels with 24/7

closed-loop therapy, but there was no significant difference in HbA1c or time in hypoglycemia between 24/7 and overnight-only closed-loop use [76]. This supports the idea that, particularly in children, the benefits of closed-loop therapy are most pronounced overnight. Importantly, the improvements in time in range were maintained during the 18-week extension phase. One severe hypoglycemia and one DKA event occurred during the study, both while closed-loop was not activated. A 13-week study with optional extension phase comparing Control-IQ with sensor-augmented pump therapy is under way in very young children aged 2–5 years (NCT04796779).

A retrospective analysis of 12 months of data from real-world users (age 6 years+) of the system included more than 9,000 users, 80% of which had type 1 diabetes [34]. Median closed-loop use was sustained at 94% with mean time in range of 74% and time in hypoglycemia of 1%, all of which remained stable over the 12-month period. Closed-loop use was similarly high at 96% with mean time in range of 79% in a shorter 2-month prospective study of 1,435 users aged 14 years and older [77]. These data are promising in terms of the feasibility and benefits of longer-term clinical use of hybrid closed-loop therapy.

### 3.3. CamAPS FX

CamAPS FX (CamDiab, Cambridge, UK) is an inter-operable hybrid closed-loop app with an embedded MPC algorithm developed at the University of Cambridge. Unlike other systems, the algorithm resides on a smartphone Application (presently Android only) and has the potential to be used with any insulin pump and CGM. It is licensed from age 1 year and in pregnancy in Europe. At present, CamAPS FX links to the following pumps: Dana RS and Dana-i (Sooil Development, Seoul, Korea), and Ypsopump (Ypsomed Holding, Burgdorf, Switzerland). The app pairs with the factory-calibrated Dexcom G6 CGM. The algorithm is treat-to-target, which is adjustable in 0.1 mmol/L increments from 4.4 to 11.0 mmol/L in up to 48 timeblocks throughout the 24-hour period. When closed-loop is active in 'Auto mode,' the algorithm automatically adjusts insulin delivery every 8–12 minutes based on CGM values, irrespective of pre-programmed basal rates. The algorithm is highly adaptive and incorporates information on total daily insulin requirements, as well as diurnal and post-prandial insulin requirements, into its calculations. The app includes the optional 'Ease-off' mode (raises personal glucose target and reduces insulin delivery) and 'Boost' mode (intensifies insulin delivery with automatic cessation if glucose drops below target). Glucose and insulin data can be viewed remotely using the Diasend app (Glooko, Mountain View, CA, USA), with optional text alerts and automatic data upload to the cloud. The app allows bolusing directly from the smartphone.

Several longer-term randomized controlled trials show the CamAPS FX algorithm to be safe and effective across a wide range of populations. Two studies have evaluated the system in those with suboptimal glycemic control, one 12-week study in 86 children, adolescents and adults (6 years+; baseline HbA1c  $>58$  mmol/mol) comparing closed-loop to sensor-

augmented pump therapy and one 6-month study in 133 children and adolescents aged 6–18 years (baseline HbA1c >53 mmol/mol) comparing closed-loop to standard pump therapy [33,78]. In both studies, outcomes favored closed-loop across all glycemic metrics with an increase in time in range of 11 percentage points in the 12-week study, and 15 percentage points in the 6-month study for those participants using CamAPS FX with the Dana pump and Dexcom G6 hardware. There was one DKA event in the 12-week study in the closed-loop group secondary to infusion set failure, and no severe hypoglycemia events. In the 6-month study there were a higher number of severe hypoglycemia events (4 in closed-loop, 3 in control). There were two DKA events in the closed-loop group, Auto mode was not activated at the time of the events.

CamAPS FX has also been trialed in vulnerable cohorts, including in pregnancy, in very young children and in older adults. A feasibility study in pregnancy including 16 participants evaluated overnight closed-loop compared to sensor-augmented pump therapy over 4 weeks with an extension phase using 24/7 closed-loop up to 16 weeks [79]. Time in the tighter target range of 3.5 to 7.8 mmol/L was significantly higher during closed-loop use, both overnight only and during the extension phase. One severe hypoglycemia event occurred during sensor-augmented pump use. A larger parallel randomized study in pregnancy comparing CamAPS FX with standard therapy is under way (NCT04938557). Hybrid closed-loop therapy also led to significant improvements in glycemic control compared to sensor-augmented pump therapy over 4 months in 74 very young children aged 1 to 7 years and 37 older adults aged 60+ years, with time in range 9 percentage points higher with closed-loop in both studies [25,26]. Closed-loop usage was high at  $\geq 95\%$ . One severe hypoglycemia event occurred during closed-loop use in the very young children, where parents failed to respond to overnight alarms, and two severe hypoglycemia events occurred during sensor-augmented pump use in the older adults. No DKA events occurred in either study.

Little real-world data for CamAPS FX is available at present. A case report of two young children using the system from onset of type 1 diabetes, one with diluted insulin, showed promising outcomes in this particularly challenging age-group [80]. In a 3-month prospective observational study of 39 children and young people (age 2 to 18 years), where 9% used CamAPS FX, closed-loop use was associated with improvements in glycemic and quality of life measures [148].

### 3.4. Diabeloop DBLG1 system

The Diabeloop hybrid closed-loop system (Diabeloop, Grenoble, France) consists of the inter-operable DLBG1 MPC algorithm residing on a locked handset. The algorithm is commercially available in Europe with two pumps: The Accu-Check Insight insulin pump (Roche Diabetes Care, Basel, Switzerland), or the Kaleido insulin patch-pump (ViCentra, Utrecht, Netherlands); both working with the Dexcom G6 CGM. It is licensed for use in adults only. When closed-loop is active, the algorithm automatically adjusts insulin delivery every 5 minutes based on CGM values, irrespective of pre-

programmed basal rates, and additionally delivers an automated correction bolus if glucose is >10 mmol/L. The algorithm is adaptive in terms of total daily insulin requirements and post-prandial and exercise-related insulin needs. There are five user-adjustable settings: the personal glucose target (pre-set at 6.1 mmol/L, adjustable between 5.6 and 7.2 mmol/L), the hypoglycemia threshold for suspension (pre-set at 3.9 mmol/L, adjustable between 3.3 and 4.7 mmol/L), reactivity in the hyperglycemic range (43–186%), reactivity in the normoglycemic range (59–147%) and reactivity following a prandial bolus (50–200%). Additionally, there is an optional activity mode, which temporarily increases the glucose target by 3.9 mmol/L, reduces algorithm-driven insulin delivery and increases insulin sensitivity for 14 hours, and a ‘Zen mode,’ which raises the glucose target by 0.6–2.2 mmol/L (user-adjustable). Data is automatically uploaded to the cloud, but live remote data viewing is not yet available.

Two randomized trials have evaluated the Diabeloop system compared to sensor-augmented pump therapy over 12 weeks in 68 adults and 6 weeks in 17 children aged 6 to 12 years [29,81]. Both studies included 24/7 remote monitoring by healthcare professionals. Time in range was 9 percentage points higher with closed-loop in the adult study, and also improved in the children’s study (66% with closed-loop vs 59% with control). No DKA events occurred in either study, but 8 severe hypoglycemia events (5 in closed-loop, 3 in control) occurred in the adult study. Three of the events in the closed-loop arm were secondary to pump malfunctions, necessitating change of insulin pump used in the study. Closed-loop usage was fairly low at 84% in the adult study, but higher at 99% in the pediatric cohort.

Data from 25 adults using the system for 6 months at home without remote monitoring provides real-world insights for the Diabeloop system [82]. Closed-loop usage was 85%, with one participant ceasing closed-loop after 2 months due to repeated system disconnections. Glycemic outcomes were promising with mean time in range of 70% and low hypoglycemia burden of 1.3%. Additionally, a 6-month observational study without remote monitoring in 7 participants with highly unstable type 1 diabetes using the Diabeloop system showed improvements in glycemic control compared to sensor-augmented pump therapy and a reduction in severe hypoglycemia events [83].

### 3.5. Omnipod 5 HCL system

The Omnipod 5 HCL system (Insulet, Acton, MA, USA) incorporates an MPC algorithm embedded in each individual patch pump (pod), receiving glucose sensor data from the factory-calibrated Dexcom G6 CGM and managed via a handheld receiver or a dedicated smartphone app (Android only). The system is licensed from age 6 years in the USA, and from age 2 years in Europe. When closed-loop is active the algorithm automatically adjusts insulin delivery every 5 minutes based on sensor glucose levels and on the total daily dose, which is updated with each pod change (roughly every 3 days), and is independent of pre-programmed basal rates. The algorithm is treat-to-target, adjustable in 0.5 mmol/L increments between 6.1 and 8.3 mmol/L in up to 8 time-blocks per day, and is

adaptive. It includes an 'Activity feature,' which raises the target to 8.3 mmol/L and reduces automated insulin delivery. The bolus calculator includes the current CGM value automatically, similar to other systems, but additionally uses the CGM trend when calculating bolus doses. Data upload to the cloud is automatic and glucose data can be viewed remotely via the Dexcom Follow app.

There are no available randomized controlled trial data for the Omnipod 5 HCL system. A 3-month single-arm study in 235 participants (124 adults and 111 children aged 6 to 18 years) showed high closed-loop usage at 96% [84]. There were 3 severe hypoglycemia events, two in adults following user-initiated boluses, and 1 in a child following delayed eating after a pre-prandial bolus. One DKA event occurred in a child due to an infusion site failure. Glycemic data were promising with mean time in range of 68% in the pediatric age-group and 74% in adults, coupled with a low hypoglycemia burden of 1.8% and 1.3% respectively. Similarly, a 3-month single-arm study in 80 very young children (age 2 to 5 years) showed the system to be safe with no severe hypoglycemia or DKA events [85]. As the Omnipod 5 HCL system was only licensed for commercial use in early 2022, real-world data are not yet available.

#### 4. iLet Bionic Pancreas (insulin only)

The iLet Bionic Pancreas hybrid closed-loop system (Beta Bionics, Boston, MA, USA) comprises an MPC algorithm, the iLet insulin pump (Beta Bionics) and the Dexcom G6 CGM. The algorithm is adaptive when closed-loop mode is active, and meals are entered semi-quantitatively in terms of size. The glucose target is adjustable between 6.1 and 7.3 mmol/L in 0.6 mmol/L increments at different times of day. Unlike other hybrid closed-loop systems, the iLet does not require pre-programmed basal rates for when closed-loop is inactive, but instead imputes its own basal rate based on recent data. This system does not have regulatory approval at present. It was originally designed to be a fully closed-loop system using the bihormonal approach, and previous studies have focused on this [86–88]. More recently, focus has shifted to an insulin-only version. No randomized controlled trial data on the insulin-only version of the system are available at present, but the pivotal 3-month randomized trial in children and adults has completed, and publication is awaited (NCT04200313).

#### 4.1. Tidepool – Loop

Loop is an open-source iOS app developed by the Do-It-Yourself (DIY) community, incorporating an MPC algorithm that modulates insulin delivery continuously based on sensor glucose levels by altering pre-set basal rates. It is an interoperable algorithm, which can pair with any alternate controller-enabled insulin pump and inter-operable CGM. There have been no randomized controlled studies of the Loop algorithm. There are real-world data from a 6-month prospective observational study of 558 children (age 1 year+) and adults [89]. Within the study, Medtronic and Insulet pumps were used, with a RileyLink bridging the iPhone's Bluetooth and the sub-

gahertz radio frequency used by these pumps. Both Dexcom and Medtronic CGMs were used. Closed-loop was used a median 83% of the time, and glycemic outcomes were promising with time in range of 73% and HbA1c of 6.5%, although participants had fairly tight glycemic control at baseline. The not-for-profit company Tidepool (Palo Alto, CA, USA) are developing a commercial version of Loop (Tidepool Loop) and FDA approval is awaited.

#### 4.2. DIY systems

Prior to the availability of commercial hybrid closed-loop systems, a community of people with type 1 diabetes and their families developed open source artificial pancreas systems, or 'Do-it-Yourself' (DIY) systems. The three main systems, OpenAPS, AndroidAPS and Loop were used by around 1,500 people with type 1 diabetes in 2019 worldwide [90]. Even now that commercial hybrid closed-loop therapy is available, these low-cost systems remain an attractive option for those who have the know-how and skills to build and maintain them with little assistance from healthcare professionals, who are not able to support unregulated systems. Observational studies show improvements in glycemic control with all systems, but no randomized clinical trial data exists at present [91]. The results of a 6-month randomized controlled parallel design study using a locked version of OpenAPS are awaited [92].

### 5. Emerging technologies and adjuncts for closed-loop systems

#### 5.1. Advances in closed-loop hardware components

Hybrid closed-loop systems are being continually improved, both in terms of algorithm settings and user features. However, efficacy relies on 'getting the basics right,' meaning reliable infusion of insulin and accurate CGM measurements [37]. Accurate insulin delivery relies on the user performing regular cannula changes (every 2–3 days with current steel or teflon cannulas), regular changes of infusion sets to ensure patency, and careful filling of the insulin reservoir, avoiding air bubbles. Insufficient insulin administration can lead to hyperglycemia and ketosis [93]. Malfunctions or blockages of cannulas and infusion sets are commonly reported by users [94,95], and extended wear infusion sets have been in development for some time. The Medtronic extended wear 7-day infusion set was shown to be safe and associated with high user satisfaction in 259 adults, without negatively affecting glycemic control when used with the 670G HCL system, and has received regulatory approval in the USA and Europe [96]. ConvaTec and Capillary Biomedical are working on further long-wear sets [97,98]. Combining these extended-wear infusion sets with CGM sensors, which have a wear-time of 7 to 14 days, into a single device has the potential to significantly reduce device burden for people with type 1 diabetes. An early feasibility study using a combined infusion set with integrated CGM with a 7-day wear-time is underway using the 670G HCL system (NCT04823312).

Additionally, CGM sensors are decreasing in size and moving toward being universally factory-calibrated. Medtronic's

Guardian 4 sensor is now in line with the Dexcom G6 in terms of not requiring fingerprick calibrations and being utilizable for dosing decisions, although continues to have a relatively short 7-day wear-time [99]. The Dexcom G7 sensor is significantly smaller than previous Dexcom sensors, with a shorter 30-minute warmup and 12-hour grace period at the end of its 10-day sensor life [100]. Integration of the G7 sensor with compatible hybrid closed-loop systems is awaited. Lastly, the even smaller FreeStyle Libre 3 sensor is now approved as a CGM device with a 14-day wear-time, allowing for closed-loop integration [101].

### 5.2. Advances in remote device management and data review

Remote data viewing and wireless data upload are highly important to people with type 1 diabetes using advanced technologies [102,103] and also have significant benefits for clinicians in terms of facilitating remote consultations and timely diabetes support [104,105]. Many hybrid closed-loop systems now include automatic, wireless data upload to the cloud. Healthcare professionals are thus able to see glucose and insulin data in near real-time, including system settings such as glucose targets, enabling them to give targeted advice. Being able to remotely view both glucose and insulin data is even more important for parents of children with type 1 diabetes. Remote monitoring increases independence, promotes parental confidence in allowing others to care for a child, and facilitates uninterrupted sleep and playtime [103]. Increasingly, people with type 1 diabetes expect to be able to manage their diabetes devices remotely [106,107]. App-based systems already allow users to bolus and view data from their smartphone, while pump-integrated systems are working to provide this vital feature.

### 5.3. Dual hormone systems

In addition to insulin, secretion of the hormones glucagon and amylin is impaired in people with type 1 diabetes. Glucagon is secreted in response to falling glucose levels and triggers release of glucose stored as glycogen from the liver. Amylin delays gastric emptying and reduces post-prandial hyperglycemic excursions. Dual-hormone systems aim to deliver one of these two hormones in addition to insulin, to further improve glucose control by allowing for more aggressive insulin delivery [108]. Barriers to dual-hormone systems include the need for a second or dual chamber pump, and the risk of gastrointestinal side-effects. Newer glucagon analogues are more stable at room temperature than previously available formulations, enabling continuous infusion without the need for daily set changes [109]. A 7-day study of 10 participants in the home setting using the iLet dual-hormone using dasiglucagon vs insulin-only showed higher time in range with dual-hormone (79% vs 72%), and lower time in hypoglycemia [110]. Amylin's synthetic analogue pramlintide has been trialed in adult inpatient dual-hormone closed-loop studies, and results showed improvements in time in range compared

to insulin-only systems [111]. Larger, pivotal trials of dual-hormone systems are in the pipeline.

### 5.4. Other adjunctive therapies

Other adjunctive therapies have been introduced to optimize glycemic control. Glucagon-like peptide-1 (GLP-1) is an incretin hormone that increases satiety, slows gastric emptying and suppresses glucagon release. Initial small inpatient studies of GLP-1 use with fully closed-loop therapy seemed promising, but there have been no recent larger studies to evaluate outpatient efficacy [112]. Sodium-glucose co-transporter (SGLT2) inhibitors lower plasma glucose by blocking renal reabsorption and increasing renal excretion of glucose in an insulin-independent manner. Data on SGLT2 as an adjuvant in closed-loop therapy is limited, but results from a recent inpatient study in young adults using fully closed-loop with dapagliflozin were promising with no signs of hypoglycemia or ketosis [113]. Hybrid closed-loop with empagliflozin and simple meal announcement was non-inferior to hybrid closed-loop with carbohydrate counting (and no empagliflozin) in 30 adults on two days in another recent study [114]. Unfortunately, SGLT2s are no longer authorized for treatment of type 1 diabetes [115].

### 5.5. Fully closed-loop systems

Currently available hybrid closed-loop systems confer significant glycemic and quality-of-life benefits, but continue to require regular user-input around mealtimes and exercise to achieve optimal outcomes. One of the main barriers to a fully closed-loop approach (without the need for mealtime boluses) is the relatively slow absorption of subcutaneously administered rapid-acting insulin analogues [116]. Recently, ultra-rapid insulins have been licensed for use in type 1 diabetes, making a fully closed-loop approach more feasible. In an 8-week double-blind crossover study comparing hybrid closed-loop with Fiasp versus standard insulin aspart in adults, there was a significant reduction in hypoglycemia with use of Fiasp [117]. A similar 6-week open-label crossover study showed improvement in time in range with Fiasp compared to standard aspart, particularly after a missed meal bolus [118]. However, studies of fully closed-loop insulin-only systems have shown that time in target range is lower compared to outcomes of hybrid closed-loop studies, even with ultra-rapid acting insulin analogues [119]. With currently available ultra-rapid insulins, the fully closed-loop approach may be most suited to those with higher HbA1cs who have a high frequency of missed meal boluses. A randomized study in adults with suboptimal glycemic control comparing fully closed-loop using Lyumjev with standard pump therapy with CGM is under way (NCT04977908). While addressing insulin time-action profiles remains paramount, modified control algorithms that are able to utilize additional inputs may be useful in facilitating a fully closed-loop approach. These could include motion sensing both for exercise and meal detection, heart rate input to detect exercise via smartwatch, as well as sensors that measure ketones,

lactate and active insulin. These features could help to better address post-prandial glycaemic excursions and help prevent exercise-induced hypoglycemia.

## 6. Non-technological priorities in closed-loop insulin delivery

### 6.1. Healthcare provider education and training

People with type 1 diabetes are only able to access advanced technologies if their healthcare providers (HCPs) are able to provide education and support for use. Diabetes technologies are evolving extremely rapidly and, coupled with the amount of time required to undertake adequate training, makes it challenging for HCPs to remain up to date. Increasingly, companies are providing online training material and workshops for both HCPs and users, to facilitate quicker onboarding. Additionally, tools using frameworks that identify key concepts for each closed-loop system, such as the CARES paradigm [36], have been developed and are shared via online platforms to facilitate targeted data review and setting optimization during clinic appointments. Following an initial adjustment period, closed-loop users require less healthcare professional input than those on standard therapy, and this coupled with remote data viewing has the potential to reduce burden for HCPs significantly [104,120].

Additionally, HCPs should be encouraged and supported in continuing hybrid closed-loop therapy when patients are hospitalized, wherever possible. Evidence of closed-loop therapy in the inpatient setting for type 1 diabetes is limited, but studies of inpatient fully closed-loop in adults with type 2 diabetes or other causes of hyperglycemia showed significant improvements in glycaemic control compared to standard therapy and blood glucose monitoring as well as in type 1 diabetes during labor and in the postpartum period [121–123]. Diabetes outreach teams should be in place to support use of closed-loop systems in the hospital settings, as long as the patient is able to participate in self-care and an alternative plan for diabetes management is in place in case continuation of closed-loop therapy becomes inappropriate (e.g. critically ill patients or prolonged surgery) [124]. This may help to reduce overall workload if fewer fingerprick glucose measurements are required and fewer episodes of hypo- and hyperglycemia requiring treatment occur. Studies are urgently needed to provide data on hospital outcomes when using closed-loop in the inpatient setting.

### 6.2. Quality of life

Whilst the improvements in glycaemic control seen with closed-loop use are highly important in terms of short- and long-term health outcomes, associated improvements in quality-of-life are equally important to people with type 1 diabetes using these systems. Questionnaire-based and interview-based qualitative studies have shown that the impact of closed-loop therapy on quality-of-life is significant across all age-groups, particularly in terms of decreasing diabetes burden (Table 3) [32,106,125–130]. In two studies of very young children, closed-loop experience questionnaires showed

improved sleep, as well as reduced burden with hybrid closed-loop therapy [129], while interviews highlighted the perceived clinical benefits of the technology, improved confidence and reduced reliance on healthcare professional support, as well as allowing outsourcing of care [106]. In a focus group of adolescents and adults using the first commercialized system, 670G HCL, users reported significant benefits including improved sleep and more freedom and time for everyday tasks [131]. However, users also expressed disappointment at the fact that systems continued to require significant user input for optimal performance, including upkeep of different technological components, and were not truly ‘closed-loop.’ Across all age-groups and closed-loop systems, users and their families emphasized the need for appropriate expectation-setting prior to starting closed-loop therapy, and the fact that it takes time to trust the algorithm [106,125,132]. Reported limitations of current closed-loop systems were device size and upkeep, connectivity problems, alarm burden, and lack of inter-operability of some systems. Differences in patient-reported outcomes were more difficult to detect in questionnaire-based outcome reporting, with small differences in glucose monitoring distress subscales and hypoglycemia fear in some studies [130,133,134]. This possibly reflects the limitations of available validated questionnaires to capture closed-loop specific treatment effects, given the rapid evolution of diabetes technology. Additionally, it may reflect users’ high expectations in terms of hybrid closed-loop therapy in the context of a research study comparing closed-loop to other advanced technologies such as sensor-augmented pump therapy.

### 6.3. Cost-effectiveness and equitable access

Lack of access to advanced diabetes technologies is contributing to increasing disparities in diabetes treatment, disproportionately affecting those from lower socio-economic backgrounds and minority ethnic groups, who are more likely to have suboptimal glycaemic control [135,136]. Healthcare provider bias further contributes to this issue, with providers more likely to select people who they perceive as educated and technologically competent [137] and/or have private insurance coverage [138]. This is particularly problematic in light of the emerging evidence that improvements in glycaemic control with closed-loop are greatest in those with higher baseline HbA1c [139]. In addition to patient selection bias in terms of eligibility for closed-loop therapy, healthcare provider inertia is a significant barrier to accessing advanced diabetes technologies [140]. Diabetes services are frequently understaffed, and healthcare professionals may feel they lack the education and resources to offer and support advanced technologies, despite clear updated guidelines recommending their use. The COVID-19 pandemic has compounded this issue, with deleterious effects on training provision and technology upgrades [141]. Services are struggling to adopt new technologies in a timely manner, an area of particular concern given the mounting evidence that access to advanced technologies not only improves glycaemic control but facilitates remote healthcare and was associated with fewer adverse

COVID-19 outcomes in users with type 1 diabetes during the pandemic [142].

Closed-loop therapy is associated with significant upfront and ongoing costs, due to the number of technological devices required for operation. In addition, this therapy is still fairly novel and little long-term data is available to support extended use. Therefore, access to closed-loop therapy remains patchy, as insurers may be reluctant to fund closed-loop therapy. Recently, several robust health economic analyses of a variety of closed-loop systems for both children and adults have been published [143,144–147,149,150]. Results show hybrid closed-loop therapy to be cost-effective compared to both multiple daily injections and pump therapy combined with intermittently scanned CGM in several European countries. As closed-loop therapy becomes more ubiquitous in clinical practice, longer-term repository data will help to inform increasingly accurate models, further aiding reimbursement strategies.

## 7. Conclusion

Following more than a decade of research and promising safety and efficacy data, closed-loop systems are being integrated into routine clinical practice. Given their glycemic and quality-of-life benefits, it is likely that closed-loop therapy will supersede current treatment options for many people with type 1 diabetes in the near future. At present, the main priorities are ensuring adequate healthcare provider knowledge and training and appropriate reimbursement strategies to support closed-loop use in the real world. Improving access and reducing disparities remains a vital goal, with particular focus on optimizing current systems to further reduce diabetes burden whilst continuing to improve glycemic control. As with many new therapeutic approaches, the main barrier to rapid widespread adoption is clinical inertia and the lack of resources to embrace ever-evolving technological developments.

## 8. Expert opinion

Hybrid closed-loop systems are transforming diabetes care and are increasingly integrated into routine clinical practice. People with type 1 diabetes now have a range of systems to choose from, allowing selection to match individual preferences. Available real-world data corroborate findings from clinical trials, showing improvements in glucose control and reductions in diabetes management burden across different closed-loop systems and age-groups. Health economic analyses are now available from a variety of countries and provide evidence that hybrid closed-loop therapy is cost-effective compared with multiple daily injections and insulin pump therapy with CGM. National and international guidance and consensus statements are being updated to reflect this, with agencies increasingly recommending continuous glucose monitoring for all people with type 1 diabetes, in part to help facilitate access to closed-loop therapy. Specific recommendations for hybrid closed-loop therapy are expected in the near future. Educational resources for healthcare professionals and people with type 1 diabetes and their families are

increasingly accessible and streamlined. This aids treatment initiation and optimization, and helps to facilitate remote healthcare and healthcare professional confidence in supporting people with type 1 diabetes gain the maximum benefit from this new technology.

The main challenge affecting widespread closed-loop adoption is clinical inertia. The causes for this are threefold: barriers related to healthcare professionals, patient-related factors, and factors related to healthcare systems. Healthcare professionals may lack awareness of updated guidelines and available treatments, and may lack time and resources to complete relevant training courses. This has been compounded by the COVID-19 pandemic, where clinical staff are stretched more than ever, directly impacting non-urgent service provision. Healthcare professional misconceptions about who may benefit from closed-loop therapy and fear of users requiring significant amounts of clinical support may also stop them from embracing new technological developments. This needs to be urgently addressed with improved funding and support for clinical staff, as well as easily accessible training courses and online resources and increased dissemination efforts from researchers and diabetes charities. Patient-related factors are less of a barrier to closed-loop therapy, as many people with type 1 diabetes feel positive about advanced technologies. However, reducing device burden is a priority, particularly in the pediatric age-group. Devices that can be worn for longer, are smaller in size, truly inter-operable and include automatic remote data upload and viewing are needed to allow true personalization of treatment. Fully closed-loop systems, where prandial bolusing is not required, remain an important goal to further reduce diabetes management burden. Lastly, healthcare system related factors contribute to slow closed-loop adoption due to lack of reimbursement. While real-world use of hybrid closed-loop therapy is becoming more routine, insurance reimbursement remains varied and patchy worldwide. It is vital that existing policies are updated in line with emerging evidence, including favorable health economic data, to allow broader access across all age-groups, ethnic backgrounds and countries. While not all people with type 1 diabetes may want to try a closed-loop system for a variety of reasons, everyone should have the opportunity to use this novel therapy, irrespective of socio-economic background or geographical location.

## Acknowledgments

The views expressed are those of the authors and not necessarily those of the funders. No sponsor had any role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript.

## Funding

Supported by the National Institute of Health Research Cambridge Biomedical Research Centre; Efficacy and Mechanism Evaluation National Institute for Health Research (14/23/09); National Institute of Diabetes and Digestive and Kidney Diseases (UC4DK108520); JDRF; The Leona M. & Harry B. Helmsley Trust (#2016PG-T1D046); National Institute for Health Research Cambridge Biomedical Research Centre; and European Union Horizon 2020 research and innovation program (grant agreement no. 731560).

## Declaration of Interest

JW reports having received speaker honoraria from Ypsomed. RH reports having received speaker honoraria from Eli Lilly and Novo Nordisk, serving on advisory panel for Eli Lilly and Novo Nordisk; receiving personal fees from BBraun and Abbott Diabetes Care; patents related to closed-loop insulin delivery, shareholder and director at CamDiab. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

## Author contributions

JW wrote the manuscript. RH edited, critically reviewed and approved the final submitted version of the manuscript.

## Reviewers Disclosure

One of the reviewers declares being an employee for Medtronic and also a shareholder. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

## ORCID

Julia Ware  <http://orcid.org/0000-0002-4497-0979>

Roman Hovorka  <http://orcid.org/0000-0003-2901-461X>

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