#We don't have to wait any more Closed-loop systems: transforming the landscape

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Abstract

Hybrid closed-loop systems are transforming the clinical management of T1DM. Large randomised controlled trials of hybrid closed-loop systems have demonstrated safety and efficacy, with significant improvements in glycaemic control compared to control therapy, and there are now several commercially approved hybrid closed-loop systems available in the UK. There is also a growing body of evidence demonstrating the quality of life benefits associated with hybrid closed-loop systems, both for users and also for parents/caregivers and other family members.

We review the clinical evidence supporting currently available hybrid closed-loop systems in the UK and also new systems on the horizon. We discuss the emerging evidence for associated psychosocial benefits of hybrid closed-loop therapy. We also address future challenges around healthcare professional readiness to deliver closed-loop technology and ensuring equitable access across the UK.

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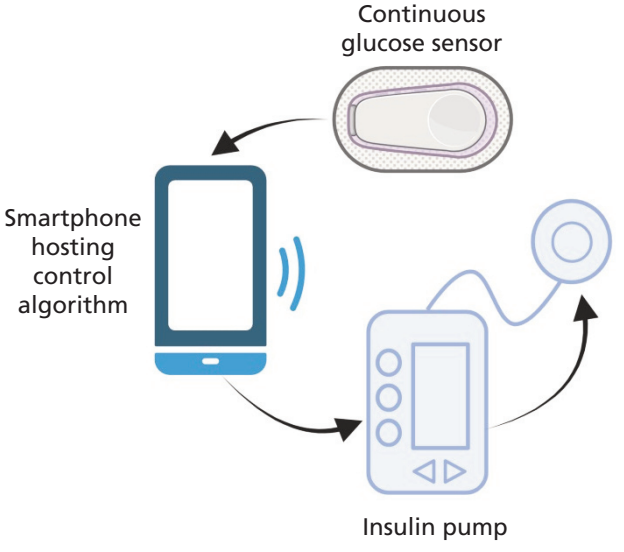
What is hybrid closed-loop?

Closed-loop systems are transforming the clinical management of T1DM. These automated insulin delivery systems comprise a subcutaneously worn continuous glucose monitoring device (CGM or glucose sensor), communicating with an algorithm that responds to real-time changes in sensor glucose levels, and modulates the subcutaneous insulin infusion rate delivered by an insulin pump (Figure 1).

Large randomised controlled trials of unrestricted home use of closed-loop systems have demonstrated safety and efficacy, with significant improvements in time in target glucose range (3.9–10.0 mmol/L) and reduced time in hypoglycaemia (<3.9mmol/L) compared with comparator therapies and a favourable effect on HbA_{1c}.[1,2] The first commercial closed-loop system, the MiniMed 670G (Medtronic, Northridge, CA, USA), was approved by the US Food and Drug Administration in September 2016 for use in people with T1DM aged 14 years and older.[3] There are now several commercially approved closed-loop systems available in the UK, with more advanced second-generation systems also being developed and approved.[4] All currently approved closed-loop systems are 'hybrid', requiring users to enter prandial insulin boluses manually but with automation of insulin delivery between meals and overnight.

Figure 1. Hybrid closed-loop system. Created with BioRender.com



What makes a good closed loop?

In order for a closed-loop system to be effective, users should be able to reach individualised target glucose control. The international consensus guidelines recommend over 70% time in target glucose range (3.9 to 10.0 mmol/L) and <4% time below 3.9 mmol/L.[5] Although clinical trials of hybrid closed-loop systems often demonstrate attainment of these targets by the study population overall, real-world data and outcomes in broader groups with more chal-

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Table 1 Currently approved hybrid closed-loop systems in the UK

	Medtronic 670G / 780G	Tandem Control IQ	CamAPS FX
Age	7 years up	6 years up	1 year up & pregnancy
Factory calibration of sensor	780G: ✓	✓	✓
Algorithm setup	TDD, weight, ICR, CF, basal rate	TDD, weight, ICR, CF, basal rate	TDD, weight
Adaptive learning	Overall	None	Overall, diurnal, meals
Bolusing from phone	X	X	✓
Personal glucose target	780G: 5.5, 6.1, 6.7 mmo/L	Overnight 6.1 - 6.7 mmol/L	4.4 – 11 mmol/L
Activity / Ease-Off mode	Now	Now	Now and planned
Boost mode	X	X	Now and planned
Remote monitoring	780G: ✓	Follow	SMS
Automated cloud upload	780G: ✓	X	Diasend (Glooko 2022)
Insulin	Rapid	Rapid	Rapid & ultra-rapid

TDD, total daily dose; ICR, insulin carbohydrate ratio; CF, correction factor

lenging diabetes management have not been extensively reported. In addition to efficacy in attaining target glycaemic control, good closed-loop systems should be easy to use and associated with low diabetes management burden, requiring less than 30 minutes on diabetes-related tasks per day.[6] To improve user experience further and ensure continued use, the burden from the devices, system alarms and technical issues needs to be low.[7]

Available closed-loop systems

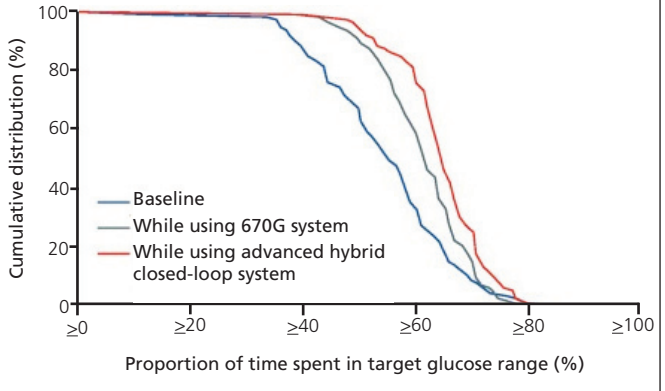
Current commercially available systems include Medtronic 670G and 780G (use from age seven years and upwards), Tandem Control IQ (use from age six years and upwards) and CamAPS FX (use from age one year and upwards and in pregnancy). The systems differ in the way they automate insulin delivery and their specific features (Table 1). The only head-to-head comparison of two different hybrid closed-loop systems compared the first- and second-generation Medtronic systems.[8] Comparisons of efficacy between hybrid closed-loop systems across different studies are hampered by variation in baseline characteristics of participants, study duration and design.

Clinical evidence

Medtronic 670G and 780G

A multinational crossover randomised controlled trial compared the Medtronic 670G with the second-generation Medtronic 780G and involved 113 adolescents and young adults aged 14 to 29 years with T1DM. The baseline HbA_{1c} was 8.1% (65 mmol/mol). The percentage of time that the sensor glucose level was within the target range was 57±12% at baseline, 63±8% during the 12 weeks using Medtronic 670G and 67±8% in the 12 weeks using Medtronic 780G (Figure 2). The percentage of time that the glucose level was below 3.9 mmol/L was 2.3±1.8% at baseline, 2.1±1.4% during the 12 weeks using 670G and 2.1±1.2% in the 12 weeks using 780G. Mean HbA_{1c} was 7.6±0.6% (59±7mmol/mol) after 12 weeks using 670G and 7.4±0.8% (57±9mmol/mol) after 12 weeks using 780G.

Figure 2. Proportion of time spent with glucose concentrations in the range 3.9–10.0 mmol/L, by hour, over 24h period as measured by continuous glucose monitoring, according to the time of day. Data points are hourly median values, and the shaded regions show IQRs (8).



The proportion of time that the system was in auto mode was 75% during use of the 670G system and 86% during use of the 780G system. One severe hypoglycaemic event occurred during use of the 780G system, determined to be unrelated to study treatment, and none occurred in the 670G period.

Tandem Control-IQ

In a multicentre parallel design randomised controlled trial in the US, 168 adolescents (14 years and upwards) and adults with T1DM were randomised to use either Control IQ (the closed-loop group) or sensor augmented pump therapy for six months (the control group).[9] The baseline HbA_{1c} of the study cohort was 7.4% (57 mmol/mol). The percentage of time that the sensor glucose level

was within the target range increased in the closed-loop group from 61±17% at baseline to 71±12% during the six months and remained unchanged at 59±14% in the control group, a between-group difference of 11 percentage points. The difference in the mean glucose level was 0.7 mmol/L in favour of closed-loop and the difference in the percentage of time that the glucose level was below 3.9mmol/L was lower in the closed-loop group by 0.88 percentage points. The difference in HbA_{1c} after six months was 0.33 percentage points lower in the closed-loop group. Closed-loop was active for 90% of the time over six months. No serious hypoglycaemic events occurred in either group; one episode of diabetic ketoacidosis occurred in the closed-loop group.

In a multicentre parallel design randomised controlled trial in the US, 101 children aged 6 to 13 years of age with T1DM were randomised to use either Control IQ (the closed-loop group) or sensor augmented pump therapy (the control group) for 16 weeks.[10] The baseline HbA_{1c} of the study cohort was 7.6-7.9% (60-63 mmol/mol). The percentage of time the glucose level was within the target range during the 16 weeks increased in the closed-loop group from 53±17% at baseline to 67±10% and from 51±16% to 55±13% in the control group, a between-group difference of 11 percentage points. The difference in mean glucose level was 0.7mmol/L in favour of closed-loop and the difference in the percentage of time that the glucose level was below 3.9 mmol/L was lower in the closed-loop group by 0.40 percentage points. Mean HbA_{1c} after 16 weeks was 0.4 percentage points lower in the closed-loop group than the control group. Closed-loop was active for 93% of the time. No episodes of diabetic ketoacidosis or severe hypoglycemia occurred in either group.

CamAPS FX

A multinational crossover design randomised controlled trial in the UK and Europe compared CamAPS FX with sensor-augmented pump therapy in 74 children aged 1-7 years with T1DM. The baseline HbA_{1c} of the study cohort was 7.3% (56mmol/mol).[11] The percentage of time that the sensor glucose was within the target range in the closed-loop period was 72±6% compared with 63±9% during the control period, a difference between treatments of 8.7 percentage points. The difference in mean glucose level was 0.7mmol/L in favour of closed-loop. There was no difference in the percentage of time that the glucose level was below 3.9 mmol/L between the closed-loop period and the control period. The difference in HbA_{1c} after 16 weeks was 0.4 percentage points lower following closed-loop therapy. Closed-loop was active for 93% of the time. One severe hypoglycemia event occurred during the closed-loop period and no episodes of diabetic ketoacidosis occurred in either period.

In a multinational parallel design randomised controlled trial in the UK and US, 133 children and adolescents aged 6-18 years with T1DM and sub-optimal glycaemic control were randomised to either closed-loop insulin delivery or to usual care with insulin pump therapy for six months.[12] The baseline HbA_{1c} of the study cohort was 8.2-8.3% (66-67 mmol/mol. At six months, HbA_{1c} was lower in the closed-loop group than in the control group by 0.3 percentage points. Participants in the closed-loop group used the Cambridge closed-loop algorithm running on a smartphone with either a modified Medtronic 640G pump, Medtronic Guardian 3 sensor and Medtronic prototype phone enclosure (FlorenceM configuration), or a Sooil Dana RS pump and Dexcom G6 sensor (CamAPS FX configuration). Closed-loop usage was low with FlorenceM due to failing phone enclosures (40%) but consistently high with CamAPS FX (93%), impacting efficacy. In those who used the CamAPS FX configuration, time in target glucose range was 15 percentage points higher in the closed-loop group (63±9%) than in the control group (49±13%), with no significant difference between groups in the time spent with glucose below 3.9 mmol/L. The difference in HbA_{1c} after six months was 1.1 percentage points lower following closed-loop therapy with CamAPS FX compared with the control group. Seven severe hypoglycaemia events occurred (four in the closed-loop group, three in the control group) and two diabetic ketoacidosis events (both in the closed-loop group). This study demonstrates that to ensure optimal efficacy of the closed-loop system, usage needs to be consistently high.

A multinational crossover design randomised controlled trial in the UK and Austria compared CamAPS FX with sensor-augmented pump therapy in 37 adults aged 60 years and above with T1DM.[13] The baseline HbA_{1c} of the study cohort was 7.4% (57mmol/mol). The percentage of time that the glucose level was within the target range in the closed-loop period was 80±8% compared with 71±13% during the control period, a difference between treatments of 8.6 percentage points. The difference in the mean glucose level was 0.7mmol/L in favour of closed-loop therapy. There was no difference in the percentage of time that the glucose level was below 3.9 mmol/L between the closed-loop and control periods. The between-group difference in HbA_{1c} after 16 weeks was 0.2 percentage points in favour of closed-loop therapy. Closed-loop was active for 97% of the time. Two severe hypoglycaemia events occurred during the control period and none during the closed-loop period.

Upcoming single hormone closed-loop systems

iLet bionic pancreas

In a multicentre parallel design randomised controlled trial in the US, 165 children and adolescents age 6-17 years old with T1DM were randomised to use closed-loop with insulin aspart or insulin lispro or to a control group using their usual insulin delivery with continuous glucose monitoring for 13 weeks.[14] The time spent in target glucose range increased from 47±17% at baseline to 60±8% with closed-loop compared with 48±19% at baseline to 50±16% with usual care, a difference between groups of 10 percentage points. Time spent with glucose below 3.9 mmol/L was similar between groups. Mean HbA_{1c} decreased from 8.1±1.2% at baseline to 7.5±0.7% at 13 weeks with closed-loop compared with 7.8±1.1% at both baseline and 13 weeks in the control group, a between-group difference of 0.5 percentage points in favour of closed-loop. Three participants in the closed-loop group and one in the control group had a severe hypoglycemia event.

Omnipod 5

No randomised controlled trials have been undertaken with the

Omnipod 5 closed-loop system. Single arm studies demonstrate safety in those aged 2 years and older.[15,16]

Do-it-yourself (DIY) closed-loop systems

The do-it-yourself (DIY) artificial pancreas system (DIY APS) communities develop and apply open-access closed-loop algorithms (e.g. Open Artificial Pancreas System [OpenAPS], DIY Loop and AndroidAPS) which do not undergo regulatory overview and approval. Access is open to anyone but users need to be able to build and maintain their own system, with some support provided from the community itself. Several thousands of people around the world living with diabetes use DIY systems. Until recently, clinical evidence on these systems was limited to observational before-and-after studies. A recent multicentre randomised controlled parallel design study involving 97 participants (48 children aged 7 to 15 years and 49 adults) compared an open-source AID system (a modified version of AndroidAPS 2.8 with a standard OpenAPS 0.7.0 algorithm) with sensor-augmented pump therapy for six months.[17] Time in the target glucose range increased from 61±12% to 71±12% in the closed-loop group and decreased from 58±14% to 55±16% in the control group. No severe hypoglycemia or diabetic ketoacidosis occurred in either group.

Psychosocial impacts

There is growing evidence from qualitative evaluations of the psychosocial benefits associated with closed-loop systems, both for users and also for parents/caregivers and other family members.[18-20] Users describe generally positive experiences, with perceived benefits including reassurance and reduced anxiety, improved sleep and confidence, and the concept of 'time off' from diabetes demands.[19]

While some studies report improved diabetes-specific psychosocial measures, including reduced diabetes distress, improved diabetes treatment satisfaction and fear of hypoglycaemia, these findings have not been consistent and they differ depending on the underlying study population.[14,21-23] One consistent message from qualitative assessments is that for optimal benefits, closed-loop systems need to minimise burden in terms of frequency of alarms, the need for sensor calibration and other user inputs. Issues with connectivity between devices can also have a significant negative impact on usability.[7,24]

Perhaps the greatest quality-of-life benefits have been reported by parents/caregivers of very young children with T1DM.[25] Prior to using a closed-loop system caregivers report daily challenges of keeping their child's glucose within the target range, requiring constant vigilance and a state of alert which negatively impacts on sleep, relationships with others and employment. With closed-loop, caregivers felt the system was able to keep their child's glucose in range after meals, to lessen glucose fluctuations and to offer a level of input beyond their own capabilities. In addition to clinical benefits and reduced workload, caregivers reported sleeping much better, less anxiety and worry about their child's safety knowing that the system would help keep glucose in range, and increased confidence when their child was in the care of others at nursery or school. Caregivers described getting part of their lives back, being able to resume normal activities and some even considered returning to full-time employment.

Quality-of-life benefits also extended to the child, with parents noticing improved mood and concentration in their child and less disrupted sleep due to the more stable glucose. Using the closed-loop system allowed their child to feel more normal, as conversations and activities no longer focused on diabetes management, and parents had more time and energy for everyday family activities, a benefit which also impacted on siblings. People were more willing to invite their child to events, including parties.

Key messages

- Hybrid closed-loop systems are associated with significant improvements in glycaemic control in people living with T1DM
- Evidence is emerging of important quality of life benefits for hybrid closed-loop system users and their families
- Healthcare providers can be slow to embrace closed-loop technologies due to clinical inertia and a lack of time for training. This plays a critical role in affecting access to closed-loop technology in the UK

Call for action

There are clear benefits of hybrid closed-loop technology on both glycaemic outcomes and quality of life in all populations with T1DM. Perhaps the population with the greatest need is very young children, who have the highest variability of day-to-day insulin requirements and the greatest burden of diabetes management for caregivers each day.[6,26]

Despite these widely reported and important benefits, healthcare providers can be slow to embrace closed-loop technologies.[27,28] Clinical inertia, work overload and regional variability play critical roles in affecting access to closed-loop technology. Manufacturers and diabetes technology leaders can help to mitigate this by supporting training and creating accessible resources for users and healthcare professionals, including those available online (https://abcd.care/dtn/education).

The National Institute for Health and Care Excellence (NICE) are undertaking a Multiple Technology Appraisal process on closed-loop technologies which will report in early 2023. NHS England sponsored a pilot of the use of closed closed-loop technologies in 2021-2022;[30] the Association of British Clinical Diabetologists (ABCD) Diabetes Technology Network (DTN) gathered the data from this,[31] and undertook an analysis of the outcomes, and this analysis has been submitted to NICE to help with the appraisal. The NHS is legally obliged to fund and resource medicines and treatments recommended by NICE's Technology Appraisals. It is anticipated that this will transform and facilitate equitable access to closed-loop technology and routine clinical care for people living with T1DM in the UK.

Conflict of interest CKB has received consulting fees from CamDiab and speaker honoraria from Ypsomed. RH reports receiving speaker honoraria from Eli Lilly, Dexcom and Novo Nordisk, receiving license and/or consultancy fees from B Braun and Abbott Diabetes Care, patents related to closed-loop, and being director at CamDiab.

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