# Cambridge hybrid closed-loop algorithm in children and adolescents with type 1 diabetes: a multicentre 6-month randomised controlled trial

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## Summary

**Background** Closed-loop insulin delivery systems have the potential to address suboptimal glucose control in children and adolescents with type 1 diabetes. We compared safety and efficacy of the Cambridge hybrid closed-loop algorithm with usual care over 6 months in this population.

**Methods** In a multicentre, multinational, parallel randomised controlled trial, participants aged 6–18 years using insulin pump therapy were recruited at seven UK and five US paediatric diabetes centres. Key inclusion criteria were diagnosis of type 1 diabetes for at least 12 months, insulin pump therapy for at least 3 months, and screening $HbA_{1c}$ levels between 53 and 86 mmol/mol (7·0–10·0%). Using block randomisation and central randomisation software, we randomly assigned participants to either closed-loop insulin delivery (closed-loop group) or to usual care with insulin pump therapy (control group) for 6 months. Randomisation was stratified at each centre by local baseline $HbA_{1c}$. The Cambridge closed-loop algorithm running on a smartphone was used with either (1) a modified Medtronic 640G pump, Medtronic Guardian 3 sensor, and Medtronic prototype phone enclosure (FlorenceM configuration), or (2) a Sooil Dana RS pump and Dexcom G6 sensor (CamAPS FX configuration). The primary endpoint was change in $HbA_{1c}$ at 6 months combining data from both configurations. The primary analysis was done in all randomised patients (intention to treat). Trial registration ClinicalTrials.gov, NCT02925299.

**Findings** Of 147 people initially screened, 133 participants (mean age 13·0 years [SD 2·8]; 57% female, 43% male) were randomly assigned to either the closed-loop group (n=65) or the control group (n=68). Mean baseline $HbA_{1c}$ was 8·2% (SD 0·7) in the closed-loop group and 8·3% (0·7) in the control group. At 6 months, $HbA_{1c}$ was lower in the closed-loop group than in the control group (between-group difference –3·5 mmol/mol (95% CI –6·5 to –0·5 [–0·32 percentage points, –0·59 to –0·04]; p=0·023). Closed-loop usage was low with FlorenceM due to failing phone enclosures (median 40% [IQR 26–53]), but consistently high with CamAPS FX (93% [88–96]), impacting efficacy. A total of 155 adverse events occurred after randomisation (67 in the closed-loop group, 88 in the control group), including seven severe hypoglycaemia events (four in the closed-loop group, three in the control group), two diabetic ketoacidosis events (both in the closed-loop group), and two non-treatment-related serious adverse events. There were 23 reportable hyperglycaemia events (11 in the closed-loop group, 12 in the control group), which did not meet criteria for diabetic ketoacidosis.

**Interpretation** The Cambridge hybrid closed-loop algorithm had an acceptable safety profile, and improved glycaemic control in children and adolescents with type 1 diabetes. To ensure optimal efficacy of the closed-loop system, usage needs to be consistently high, as demonstrated with CamAPS FX.

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## Introduction

Management of type 1 diabetes is challenging, particularly in children and adolescents. Only 22% of children and adolescents aged 19 years and younger in the UK[1] and less than 10% of children and adolescents aged 17 years and younger in the USA[2] reach the international target glycated haemoglobin ($HbA_{1c}$) of less than 53 mmol/mol (<7·0%). Registry data show that $HbA_{1c}$ levels are highest in adolescents and have deteriorated in children and adolescents over the past decade, despite increased use of insulin pump therapy and continuous glucose monitoring (CGM).[2] Innovative solutions are needed to support this at-risk population and prevent development of long-term microvascular and macrovascular complications to avoid premature mortality.[3]

Closed-loop therapy, characterised by glucose-responsive insulin delivery, is increasingly applied in real-world settings with several commercial hybrid closed-loop

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## Research in context

### Evidence before this study

We searched PubMed for articles published up to Oct 19, 2021, using the terms ("artificial pancreas" OR "closed-loop") AND ("type 1 diabetes mellitus" OR "diabetes") AND ("outpatient" OR "home") AND ("randomised" OR "randomised controlled trial"), for reports of randomised controlled trials in English only. We limited our analysis to studies of single hormone hybrid closed-loop systems used 24 h per day that were of 3-month duration or longer and included children and adolescents aged 18 years or younger. We identified seven randomised trials that met these criteria. Five of the trials included adolescents and adults, one trial included children, adolescents, and adults, and one included school-aged children only. Six trials had a parallel group design comparing closed-loop to sensor-augmented pump therapy, and one trial had a crossover design comparing two closed-loop systems. Of the six parallel group design trials, only two were of 6 months' duration, both of which were conducted in single countries and included participants with a mean baseline $HbA_{1c}$ of less than 64 mmol/L (8·0%). Two studies included participants with mean baseline $HbA_{1c}$ higher than 64 mmol/mol (8·0%), while five studies included participants with mean baseline $HbA_{1c}$ lower than 64 mmol/mol (8·0%). Closed-loop insulin delivery was associated with improved glycaemic control in all studies, with five studies reporting a reduction in $HbA_{1c}$ ranging from 3·6 to 4·2 mmol/mol (from 0·30% to 0·40%) and six studies showing an improvement in time with glucose in range (3·9–10·0 mmol/L) of 5·9–11·0 percentage points. Neither of the two studies which included participants with mean baseline $HbA_{1c}$ higher than 64 mmol/mol (8·0%) compared hybrid closed-loop to usual care and both were of short duration (3-month duration), with one study not formally assessing change in $HbA_{1c}$ and the other showing a more modest improvement of 0·36%. In a sub-analysis of a larger hybrid closed-loop study, in which enrolled adolescents and young adults had a mean baseline $HbA_{1c}$ of higher than 64 mmol/L (8·0%), improvement in $HbA_{1c}$ was also more modest at 0·30%.

### Added value of this study

Our multinational study included children and adolescents with suboptimal glycaemic control and compared closed-loop with usual care over a period of 6 months. Baseline $HbA_{1c}$ in our cohort was high at more than 8·0% (>64 mmol/mol), reflective of the challenges faced by this age group. Closed-loop technology is a rapidly evolving field, and in response to observed hardware failures of our first configuration (FlorenceM) affecting usability, we developed a second hardware platform (CamAPS FX) using the same hybrid closed-loop algorithm. FlorenceM's hardware failures contributed to low and inconsistent closed-loop usage, while CamAPS FX's hardware was reliable with consistently high usage. We showed that compared with usual care, consistent use of hybrid closed-loop insulin delivery with CamAPS FX leads to a marked reduction in $HbA_{1c}$ of 1·05% (11·5 mmol/mol) and a clinically meaningful increase in time in range of 15·0 percentage points, without a significant increase in hypoglycaemia. There was no improvement in glycaemic control with the FlorenceM platform, where closed-loop usage was low. This study is unique in that it encompasses school-aged children and adolescents with suboptimal glycaemic control, and compares hybrid closed-loop insulin delivery to usual care over a long period (6 months) in more than one country. This improves the generalisability of results across a larger proportion of the paediatric population. Importantly, the differing results with two hardware platforms using the same closed-loop algorithm highlight that usability is key to optimising closed-loop usage and glycaemic outcomes.

### Implications of all the available evidence

The use of the Cambridge hybrid closed-loop algorithm is safe and leads to clinically meaningful improvements in glycaemic control in children and adolescents with type 1 diabetes compared with usual care over 6 months. Our study reinforces that efficacy relies on consistently high closed-loop usage. Results from our study together with those from previous studies strongly support the adoption of closed-loop therapy in children and adolescents with suboptimal glycaemic control in clinical practice.

systems available in Europe and the USA.[4] Hybrid closed-loop systems have been shown to improve glycaemic control and reduce hypoglycaemia in children and adolescents with type 1 diabetes.[5–8] Generalisability of these results is unclear, as participants were either well controlled at baseline,[5] studies were of short 3–4-month duration,[6–8] or studies comparing hybrid closed-loop therapy to standard therapy were conducted in single countries.[5,6] Furthermore, real-world studies of the Medtronic Minimed 670G system (Medtronic, USA) have documented a high rate of discontinuation of closed-loop therapy in participants aged 9–18 years with suboptimal glycaemic control, as well as decreasing use of auto mode over time.[9]

In this study, we hypothesised that 6-month use of the Cambridge closed-loop algorithm, an interoperable hybrid closed-loop mobile phone application (app),[10] in children and adolescents with $HbA_{1c}$ above the recommended international target (53 mmol/mol [7·0%]) is safe and improves glucose control compared with usual therapy.

## Methods

### Study design and participants

The study adopted an open-label, multicentre, multinational, one-period, randomised design comparing hybrid closed-loop insulin delivery with insulin pump

therapy, with or without glucose sensor, over 6 months. The appendix (p 29) shows the study protocol.[11]

Approval was received from an independent research ethics committee in the UK (East of England–Cambridge East Research Ethics Committee), an independent review board in the USA (Jaeb Center for Health Research Institutional Review Board), regulatory authorities in the UK (Medicines and Healthcare products Regulatory Agency), and in the USA (US Food and Drug Administration). Safety aspects were overseen by an independent data safety monitoring board.

The study design included psychosocial and health economic outcomes. Psychosocial assessments comprised quantitative data in the form of validated questionnaires for participants and parents, as well as qualitative data gathered during focus groups with participants and parents. The cost-utility analysis was performed to inform reimbursement decision-making. The psychosocial and health economic outcomes will be published separately to the main glycaemic study outcomes.

Participants were recruited from diabetes outpatient clinics at seven UK and five US paediatric diabetes centres (appendix p 5). Key inclusion criteria were diagnosis of type 1 diabetes for at least 12 months, insulin pump therapy for at least 3 months, and screening $HbA_{1c}$ levels between 58 and 86 mmol/mol (7·5–10·0%). The screening $HbA_{1c}$ threshold was later lowered to 53 mmol/mol (7·0%) to widen generalisability and facilitate recruitment. Participants had to be aged 6–18 years. We aimed to recruit equal proportions of those aged 6–12 years and those aged 13–18 years, and a minimum of 25% of participants with baseline $HbA_{1c}$ higher than 69 mmol/mol (>8·5%). Key exclusion criteria included current use of closed-loop therapy, and more than one episode of severe hypoglycaemia or diabetic ketoacidosis during the preceding 6 months. The appendix (p 9) shows complete inclusion and exclusion criteria.

Eligible participants were identified by clinical teams at each centre. In the UK, participants aged 16 years or older and parents or guardians of participants aged 15 years or younger gave written informed consent. In the USA, participants aged 18 years and parents or guardians of participants aged 17 years or younger gave written informed consent. In both countries written assent was obtained from minors.

### Randomisation and masking

Eligible participants were randomly assigned (1:1) to receive either closed-loop insulin delivery (closed-loop group) or insulin pump therapy (control group) over 6 months. Randomisation was done using central randomisation software (appendix p 7), in blocks of 2 and 4 and stratified at each centre by local baseline $HbA_{1c}$ ($HbA_{1c}$ <67 mmol/mol [<8·3%] or ≥67 mmol/mol [≥8·3%]).

### Procedures

See **Online** for appendix

Participants were screened for eligibility with blood tests, which included locally measured $HbA_{1c}$, liver function tests, thyroid function tests, full blood count, anti-transglutaminase antibodies (and Immunoglobulin A if not done within previous 12 months), as well as centrally measured non-hypoglycaemia C-peptide, glucose and $HbA_{1c}$, and urine pregnancy test in females of childbearing age. Following enrolment, participants wore a masked continuous glucose monitoring (CGM) system for 2 weeks during a run-in period while using their own insulin pump. We used the FreeStyle Libre Pro Flash Glucose Monitoring System (Abbott Diabetes Care, Alameda, CA, USA) because of its ability to record 14 days of masked glucose data without calibration to reduce device burden. A minimum of 10 days of sensor data was required for randomisation.

The appendix (pp 7, 11–12) shows the study flowchart and visit schedules. Following randomisation, participants allocated to receive closed-loop insulin delivery and their parents or guardians were trained to use the study insulin pump and study CGM, which was used in open-loop mode for 3–4 weeks, before being trained in the use of the closed-loop system at the treatment initiation visit. Participants in the control group continued using their usual insulin pump and, if applicable, usual glucose sensor. They received refresher training covering key aspects of insulin pump use.

Participants in both groups wore a masked CGM (FreeStyle Libre Pro Flash Glucose Monitoring System) for 14 days at the study treatment initiation visit, and at the 3-month and 6-month visits. Following three initial contacts in the first 2 weeks after treatment initiation, all participants were contacted by the study team monthly to record adverse events, device deficiencies, and other relevant information. Throughout the study, participants or their clinical team were free to adjust diabetes therapy, but no active treatment optimisation was undertaken by the research team outside of planned study contacts. All participants were able to contact a 24-h telephone helpline to the local research team. The participants' clinical team refers to those health-care professionals involved in participants' routine diabetes care before enrolment, while the research team refers to those health-care professionals conducting study visits and providing technical support for the duration of the study only.

$HbA_{1c}$ was measured locally at enrolment, and centrally (Advanced Research and Diagnostic Laboratory University of Minnesota, MN, USA) at treatment initiation 3–5 weeks after randomisation (baseline), and 3 and 6 months after treatment initiation. A Tosoh HPLC Glycohemoglobin Analyzer (Tosoh Medics, San Francisco, CA, USA; inter-assay coefficient of variation 1·16% for $HbA_{1c}$ 4·85% and 0·55% for $HbA_{1c}$ 11·26%) was used.

To configure the closed-loop system, we ran the Cambridge model predictive control algorithm (version 0.3.71) in two hardware configurations, FlorenceM and CamAPS FX (appendix p 8). The

FlorenceM configuration comprised a locked smartphone (Samsung Galaxy S4, South Korea) running an app with the Cambridge control algorithm, and a Medtronic prototype phone enclosure with an embedded modified Carelink USB to allow the smartphone to wirelessly communicate with a modified Medtronic MiniMed 640G insulin pump (Medtronic, Northridge, CA, USA). This pump had low glucose suspend enabled and received glucose sensor data from the Medtronic MiniMed Guardian 3 sensor, which required regular finger prick calibrations. Challenges with this hardware arose early in the trial and with increasing frequency; the embedded Carelink USB in the smartphone enclosure, which was manufactured by a replacement supplier following study start, failed because of overheating, disabling communication between the smartphone and the insulin pump. This issue greatly affected adherence and limited closed-loop usage.

To address the hardware reliability issue, the CamAPS FX configuration superseded FlorenceM in July 2019 in the UK. The CamAPS FX system comprised an unlocked smartphone (Samsung Galaxy S8, South Korea) hosting the CamAPS FX app running the Cambridge control algorithm, which received sensor data from the factory-calibrated Dexcom G6 continuous glucose monitor (Dexcom, San Diego, CA, USA) and directed insulin delivery on a Dana Diabecare RS insulin pump (Sooil, Seoul, South Korea). Both pump and sensor communicated wirelessly with the CamAPS FX app hosted on the phone, which streamed data to the data ecosystem Diasend (Glooko/Diasend, Sweden). In the USA, participants continued using FlorenceM until study completion as the insulin pump for CamAPS FX does not have US regulatory clearance.

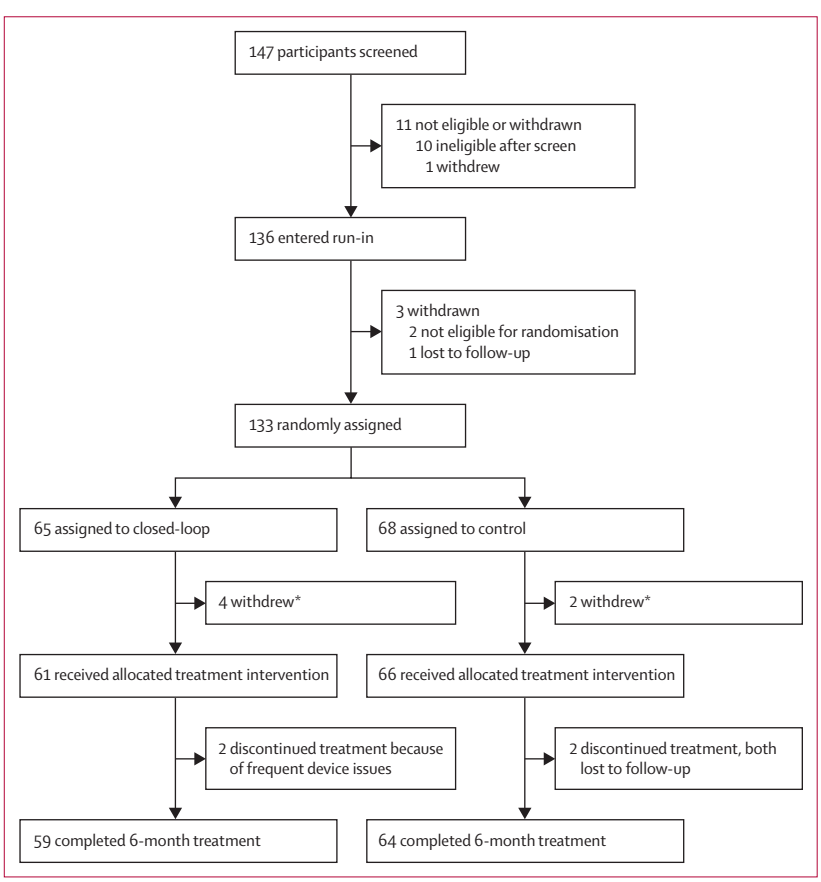


***Figure 1:*** **Trial profile**
*Details of post-randomisation withdrawals in appendix (p 16).

In both configurations, algorithm-driven insulin delivery was adjusted during auto mode automatically every 8–12 min, with the app-based control algorithm communicating the current insulin infusion rate to the insulin pump wirelessly. The control algorithm was initialised using total daily insulin dose and bodyweight. Insulin sensitivity and active insulin time were automatically calculated and adjusted over time by the algorithm. Adaptive learning was incorporated with regards to total daily insulin requirements, diurnal variations, and meal patterns. When auto mode was not operational, the insulin pumps reverted to pre-programmed basal rates. The treat-to-target control algorithm had a nominal glucose target level of 5·8 mmol/L, which was user-adjustable between 4·4 mmol/L and 11·0 mmol/L across different times of day. Both closed-loop systems contained an optional exercise mode (Ease-off function), which temporarily raised the glucose target and suspended algorithm-directed insulin delivery if sensor glucose was lower than 7·0 mmol/L. Additionally, CamAPS FX contained a Boost function to intensify algorithm-driven insulin delivery by approximately 35% when glucose was elevated.[4]

## Outcomes

The primary endpoint was the between-group difference in $HbA_{1c}$ at the end of the 6-month treatment period. Key secondary endpoints included time in target glucose range from 3·9 to 10·0 mmol/L, mean sensor glucose, time in hyperglycaemia (>10·0 mmol/L), and time in hypoglycaemia (<3·9 mmol/L) based on 14-day masked CGM data at 6 months.

Additional secondary endpoints based on masked CGM data at 6 months included standard deviation of glucose, coefficient of variation of glucose, and time with glucose lower than 3·5 mmol/L and higher than 16·7 mmol/L. Additional between-group comparisons comprised binary metrics for $HbA_{1c}$, insulin metrics, and body-mass index (BMI) Z-score and blood pressure. Sensor-use and closed-loop use were assessed in the closed-loop group according to configuration. Safety evaluation included the frequency of severe hypoglycaemia and diabetic ketoacidosis, and other adverse events or serious adverse events.

As closed-loop usage differed markedly by configuration, each closed-loop system cohort, FlorenceM and CamAPS FX, was evaluated separately in a post-hoc analysis. The CamAPS FX cohort included all participants in both the closed-loop and control groups, from UK

sites and randomised on or after July 18, 2019, when CamAPS FX was introduced.

### Statistical analysis

A sample size of 116 participants was determined to have 85% power to detect a between-group difference in $HbA_{1c}$, assuming a population difference of 0·4%, an effective SD of 0·71%, and a two-sided type 1 error rate of 0·05. This number was increased to 128 to account for dropouts.

Analyses were performed on an intention-to-treat basis. All randomised participants were included in the primary analysis. The primary endpoint ($HbA_{1c}$) and secondary endpoints were compared between treatment groups using a linear regression model adjusting for $HbA_{1c}$ at baseline, age, clinical site as a random effect, and baseline value of the respective outcome (continuous secondary endpoints only). For highly skewed data, a rank-based transformation was used. For the primary endpoint only, missing data were handled using a pattern mixture model assuming the dropout trajectory of the closed-loop participants was that of the control group.

For key endpoints over the full study cohort, the familywise type I error rate was controlled at two-sided $\alpha$=0·05 using a gatekeeping strategy. The primary endpoint was tested first, and if it passed significance, other key endpoints were tested. In the post-hoc analysis, key endpoints analysed by closed-loop cohort were not adjusted for multiple comparisons. Further details and Statistical Analysis Plan in the appendix (p 111).

Analyses were conducted with SAS software version 9.4 (SAS Institute Inc). The study is registered with clinicaltrials.gov, NCT02925299.

### Role of the funding source

Representatives of the National Institute of Diabetes and Digestive and Kidney Diseases, Medtronic, Abbott, and Dexcom read the manuscript before submission. No sponsor had any role in the study design, data collection, data analysis, data interpretation, writing of, or decision to submit the manuscript.

## Results

Between June 1, 2017, and Dec 23, 2019, we enrolled and screened 147 participants (figure 1). Ten participants did not meet inclusion criteria. One participant withdrew before, and three during, the run-in period. 133 eligible participants were randomly assigned to treatment (65 to the closed-loop group and 68 to the control group). Baseline characteristics were well balanced between groups (table 1). The appendix (p 13) shows the baseline characteristics tabulated by closed-loop system cohort. The mean age was 13·0 years (SD 2·8), and 57% of all participants were female and 43% were male. 89 (67%) of the 133 randomised participants were using a CGM device at enrolment (appendix p 15).

Ten participants withdrew after randomisation (six closed-loop, four control). In the closed-loop group, four participants withdrew before initiating treatment with the closed-loop system and two withdrew because of device issues (both FlorenceM; figure 1 and appendix p 16). Of the 61 participants randomly assigned to the closed-loop

| | Closed-loop group (n=65) | Control group (n=68) |
|---|---|---|
| Age, years | | |
| Mean age | 13·1 (2·6) | 12·8 (2·9) |
| 6–12 years | 29 (45%) | 30 (44%) |
| 13–18 years | 36 (55%) | 38 (56%) |
| Range | 7·5–18·4 | 6·3–18·4 |
| Sex | | |
| Female | 37 (57%) | 39 (57%) |
| Male | 28 (43%) | 29 (43%) |
| Duration of diabetes (years) | 6·3 (3·3) | 6·6 (3·1) |
| Total daily insulin dose (U/kg per day) | 0·93 (0·23) | 0·95 (0·24)* |
| Use of continuous glucose monitor | | |
| Current | 45 (69%) | 44 (65%) |
| In past, but not current | 12 (18%) | 14 (21%) |
| Never | 8 (12%) | 10 (15%) |
| BMI percentile | 60 (25) | 67 (25) |
| BMI z-score† | 0·35 (0·86) | 0·58 (0·89) |
| Race or ethnicity | | |
| White non-Hispanic | 60 (92%) | 53 (78%) |
| Black non-Hispanic | 0 | 2 (3%) |
| Hispanic or Latino | 0 | 4 (6%) |
| Asian | 3 (5%) | 4 (6%) |
| Native Hawaiian or Other Pacific Islander | 0 | 1 (1%) |
| More than one race | 1 (2%) | 3 (4%) |
| Missing data | 1 (2%) | 1 (1%) |
| Highest parent education level | | |
| High school diploma or less | 7 (11%) | 2 (3%) |
| Associates degree or some college but no degree | 17 (26%) | 19 (28%) |
| Bachelor's degree | 18 (28%) | 13 (19%) |
| Master's degree | 8 (12%) | 15 (22%) |
| Doctoral or professional degree | 11 (17%) | 15 (22%) |
| Missing data | 4 (6%) | 4 (6%) |
| Glycated haemoglobin at screening in mmol/mol; % | | |
| Mean (SD) | 66 (8); 8·2% (0·7) | 67 (8); 8·3% (0·8) |
| Range | 53–83; 7·0%–9·7% | 53–89; 7·0%–10·3% |
| <64 mmol/mol (<8·0%) | 28 (43%) | 29 (43%) |
| From 64 to <75 mmol/mol (from 8·0 to <9·0%) | 26 (40%) | 25 (37%) |
| ≥75 mmol/mol (≥9·0%) | 11 (17%) | 14 (21%) |

Data are n (%) or mean (SD). BMI=Body-mass index. *Missing data: one (1%) in control group. †Z-score adjusted for age and sex on the basis of the 2000 CDC growth chart.

***Table 1:*** **Characteristics of study participants at baseline by treatment group**

For the **CDC growth charts and Z-scores** see https://www.cdc.gov/growthcharts/zscore.htm

group who completed closed-loop training, 34 exclusively used FlorenceM for the duration of the study, 21 exclusively used CamAPS FX, and six used first FlorenceM and then CamAPS FX.

Primary and key endpoints for all randomised participants are summarised in table 2. All glucose sensor-based metrics were calculated from 14 days of masked Libre Pro data for all participants. The $HbA_{1c}$ at 6 months (primary endpoint) was lower in the closed-loop group than in the control group (between-group difference –3·5 mmol/mol (95% CI –6·5 to –0·5 [–0·32 percentage points, –0·59 to –0·04]; p=0·023). Mean $HbA_{1c}$ decreased from 66 mmol/mol (SD 8; 8·2% [SD 0·7]) at baseline to 60 mmol/mol (12; 7·6% [1·1%]) at 6 months compared with a smaller change in the control group (from 67 mmol/mol [8; 8·3% [0·7]] at baseline to 64 mmol/mol [8; 8·1% [0·8]] at 6 months). The target $HbA_{1c}$ of less than 53 mmol/mol (7·0%), was met by 19 (33%) of 57 participants in the closed-loop group at 6 months, compared with four (6%) of 62 participants in the control group (appendix p 17), with a larger reduction in $HbA_{1c}$ observed in the adolescent age group (13–18 years) than in the child age group (6–12 years; appendix p 18). For secondary endpoints, time with glucose in target range of 3·9–10·0 mmol/L was 6·7 percentage points (95% CI 2·2 to 11·3; p=0·0043) higher in the closed-loop group. Difference in mean sensor glucose at 6 months was –0·33 mmol/L (95% CI –1·08 to 0·43; p=0·39), which did not meet the significance threshold. Therefore, the remaining outcomes in the hierarchical key endpoint analysis were not formally compared between groups (time with glucose >10·0mmol/L and <3·9mmol/L).

Closed-loop usage differed between FlorenceM and CamAPS FX systems, with low and variable usage in the FlorenceM cohort (median 40% [IQR 26–53]), compared with consistently high usage in the CamAPS FX cohort (93% [88–96]; figure 2 and appendix p 19). Results were similar with regards to CGM use, with use of the factory-calibrated sensor in the CamAPS FX cohort high throughout the study (97% [94–97]) compared with lower sensor use in the FlorenceM cohort (70% [61–83]), for which regular finger prick calibrations were required.

There were 98 reported device issues in the FlorenceM cohort (eg, component failure requiring replacement or reboot/reset) compared with four device issues in the CamAPS FX cohort. There were 51 unscheduled contacts with the research team in the control group compared with 221 in the closed-loop group (189 with FlorenceM and 32 with CamAPS FX), in which 147 (67%) of the 221 contacts related to device issues.

Physical exam outcomes for the whole study cohort are summarised in the appendix (p 26). There was no difference for systolic or diastolic blood pressure, or BMI Z-score between the closed-loop and control group in the full cohort.

For the post-hoc analysis the CamAPS FX cohort included 21 participants in closed-loop and 25 in usual care group. The FlorenceM cohort included all participants in the USA and UK who used the FlorenceM system for

| | Baseline | | 3 months | | 6 months | | Adjusted difference at 6 months (95% CI)* | p value† |
|---|---|---|---|---|---|---|---|---|
| | Closed-loop group | Control group | Closed-loop group | Control group | Closed-loop group | Control group | | |
| **Primary endpoint** | | | | | | | | |
| Number of participants | 65 | 68 | 59 | 62 | 57 | 62 | .. | .. |
| $HbA_{1c}$, mmol/mol; $HbA_{1c}$ % | 66 (8); 8·2% (0·7) | 67 (8); 8·3% (0·7) | 60 (11); 7·6% (1·0) | 66 (9); 8·2% (0·8) | 60 (12); 7·6% (1·1) | 64 (8); 8·1% (0·8) | –3·5 (–6·5 to –0·5); –0·32 pp (–0·59 to –0·04) | 0·023 |
| **Day and night (key endpoints)‡** | | | | | | | | |
| Number of participants | 65 | 67 | 54 | 62 | 52 | 62 | .. | .. |
| Percentage of time with glucose level 3·9–10·0 mmol/L | 47% (12) | 46% (13) | 57% (15) | 46% (12) | 54% (17) | 47% (12) | 6·7 pp (2·2 to 11·3) | 0·0043‡ |
| Mean glucose (mmol/L) | 10·3 (1·8) | 10·4 (2·0) | 9·0 (2·6) | 10·4 (1·8) | 9·7 (2·9) | 10·1 (1·8) | –0·33 (–1·08 to 0·43) | 0·39‡ |
| Percentage of time with glucose level | | | | | | | | |
| >10·0 mmol/L | 46% (15) | 47% (16) | 33% (19) | 47% (15) | 38% (20) | 46% (15) | –7·0 pp (–12·5 to –1·5) | .. |
| <3·9 mmol/L (median) | 6·1% (2·7 to 9·5) | 4·9% (2·0 to 9·4) | 6·2% (3·0 to 12·7) | 3·8% (2·1 to 9·9) | 6·1% (3·0 to 12·1) | 5·4% (2·0 to 12·0) | 0·53 pp (–1·78 to 2·83) | .. |

Data are mean (SD) or median (IQR), unless otherwise indicated. pp=percentage points. *Models adjusted for baseline value of the metric, baseline $HbA_{1c}$ (where it is not the outcome), age, and clinical site as a random effect. Missing data for the primary outcome was handled using multiple imputation with a pattern mixture model assuming the dropout trajectory of the participants in the closed-loop group was that of the participants in the control group. For all other hierarchical outcomes the model only includes participants with non-missing data at baseline and 6 months. †p values were calculated in a hierarchical process based on the order listed in the table so that when a p value of 0·05 or higher was observed, any endpoints below on the list were not formally tested. ‡Values calculated from 14 days of masked data from Abbott FreeStyle Libre Pro Flash Glucose Monitoring System; a minimum of 120 h of data was required to calculate outcomes.

*Table 2:* **Comparison of the primary endpoint and key secondary endpoints for closed-loop and control groups at baseline, 3 months, and 6 months**

the whole study (n=34) and all usual care participants not included in the CamAPS FX cohort (n=41).

Outcomes for the CamAPS FX cohort are summarised in table 3. In the CamAPS FX closed-loop group mean $HbA_{1c}$ was lower at 6 months than in the control group (difference –11·5 mmol/mol [95% CI –15·7 to –7·3]; –1·05 percentage points [95% CI –1·43 to –0·67]; p<0·0001). Mean $HbA_{1c}$ decreased from 63 mmol/mol (SD 10; 7·9% [SD 0·9]) at baseline to 51 mmol/mol (SD 6; 6·8% [SD 0·5%]) at 6 months compared with no change in the control group (64 mmol/mol [6; 8·0% [0·6]] at baseline and 63 mmol/mol [8; 7·9% [0·8]] at 6 months). The target $HbA_{1c}$ level of less than 53 mmol/mol (<7·0%), was met by 15 (71%) of 21 participants in the CamAPS FX group at 6 months, compared with two (8%) of 24 participants in the control group (p=0·0006; appendix p 20). Reduction in $HbA_{1c}$ was similar in children (6–12 years) and adolescents (13–18 years; appendix p 21).

The time with glucose in target range 3·9–10·0 mmol/L was higher in the CamAPS FX group than in the control group (15·0 percentage points, 95% CI 8·0–22·1; p=0.0001). Mean glucose was lower in the CamAPS FX than in the control group. Time in hyperglycaemia (>10·0 mmol/L) was lower in the CamAPS FX group than in the control group, but time in hypoglycaemia (<3·9 mmol/L) did not differ between groups (table 3). Another post-hoc comparison of time in hypoglycaemia as recorded with Dexcom G6 compared with that recorded with Libre Pro in the CamAPS FX closed-loop group showed 2·8% (95% CI 2·1–4·7) time in hypoglycaemia based on Dexcom G6 readings versus 11·3% (5·7–14·4) based on Libre Pro readings (appendix p 22). The standard deviations of sensor glucose were trending towards being the same in both groups (table 3). There was no difference in coefficient of variation of sensor glucose between groups. Total daily insulin dose did not differ between groups. Basal insulin dose was 0·22 units/kg per day higher in the CamAPS FX group than in the control group, associated with a non-significant trend towards a 0·23 units/kg per day (95% CI 0·01 to 0·46; p=0·066) reduction in bolus insulin dose.

In the FlorenceM cohort, the between-group difference in mean $HbA_{1c}$ at 6 months did not differ between the closed-loop and control groups (adjusted difference 2·3 mmol/mol [0·21%], 95% CI –1·6 to 6·3 [–0·14 to 0·57]; p=0·23). Percentage time with glucose in target range and other key secondary endpoints did not differ between the closed-loop and control group (appendix pp 23–25).

Seven severe hypoglycaemia events (four in the closed-loop group, three in the control group), two diabetic ketoacidosis events (both in the closed-loop group), and two non-treatment-related serious adverse events (broken ankle in the control group and hospital admission for gastroenteritis in the closed-loop group) occurred after randomisation (table 4; appendix p 27).

There were 23 reportable hyperglycaemia events (11 in the closed-loop group, 12 in the control group), which did not meet criteria for diabetic ketoacidosis. A total of 155 adverse events were reported (67 in the closed-loop group, 88 in the control group).

There were no major deviations from the protocol affecting the safety of participants or the integrity of data. There were over 400 minor deviations, the majority of which were out-of-window study visits or missed samples due to the COVID-19 pandemic.

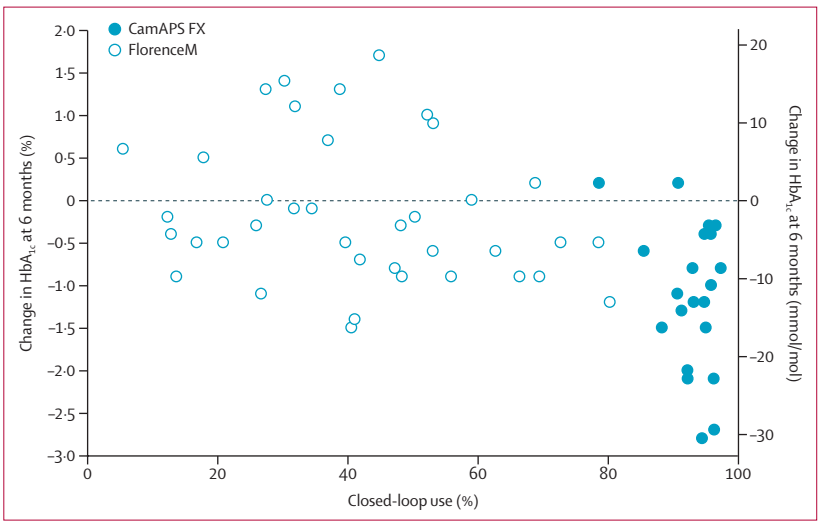


*Figure 2:* **Association between closed-loop use and change in $HbA_{1c}$ at 6 months**

## Discussion

In this multinational, multicentre, open-label, parallel, randomised controlled trial, the Cambridge hybrid closed-loop algorithm was safe, and it significantly improved glycaemic control compared with usual care in children and adolescents with type 1 diabetes over 6 months. There seemed to be a marked difference in efficacy between the two closed-loop system hardware configurations using the same algorithm, with an 11·5 mmol/mol (1·05%) reduction in $HbA_{1c}$ in the CamAPS FX cohort compared with the control, and no reduction in $HbA_{1c}$ in the FlorenceM cohort. Our findings imply that closed-loop efficacy largely depends on auto mode usage, which in turn depends on ease of glucose sensor use and hardware reliability. We observed no treatment effect in the cohort using the FlorenceM hardware, which had unreliable connectivity, contrasting with a highly clinically meaningful treatment effect in the CamAPS FX cohort which used more reliable components and a factory-calibrated glucose sensor. Studies of the Medtronic Minimed 670G system corroborate the link between usage and glycaemic outcomes, with increased auto mode use associated with lower $HbA_{1c}$.[9,12]

Usability (ie, reliability of system components as well as ease of use) plays an essential role in determining long-term adherence and efficacy, particularly in the adolescent age group. Adolescents have poorer glycaemic control than do younger children and adults,[2,13] and they were

more likely to discontinue use of closed-loop therapy in real-world studies of the 670G system[9] because of the high number of auto mode exits and need for frequent sensor calibrations. In the CamAPS FX cohort, however, the improvement in $HbA_{1c}$ in adolescents was similar to the improvement in younger children, and it was associated with sustained high usage over 6 months, supporting application of closed-loop therapy in this age group as long as usability issues are addressed. This finding is corroborated by retrospective data showing

| | Baseline | | 3 months | | 6 months | | Adjusted difference at 6 months (95% CI) | p value* |
|---|---|---|---|---|---|---|---|---|
| | Closed-loop group (CamAPS FX) | Control group | Closed-loop group (CamAPS FX) | Control group | Closed-loop group (CamAPS FX) | Control group | | |
| **Primary endpoint** | | | | | | | | |
| Number of participants | 21 | 25 | 21 | 22 | 21 | 24 | .. | .. |
| $HbA_{1c}$ (mmol/mol); $HbA_{1c}$ % | 63 (10); 7·9% (0·9) | 64 (6); 8·0% (0·6) | 51 (6); 6·8% (0·5) | 65 (8); 8·1% (0·7) | 51 (6); 6·8% (0·5) | 63 (8); 7·9% (0·8) | −11·5 (−15·7 to −7·3); −1·05 pp (−1·43 to −0·67) | <0·0001 |
| **Day and night†** | | | | | | | | |
| Number of participants | 21 | 24 | 21 | 22 | 19 | 24 | .. | .. |
| Percentage of time with glucose level | | | | | | | | |
| 3·9–10·0 mmol/L | 50% (11) | 51% (9) | 65% (8) | 48% (13) | 63% (9) | 49% (13) | 15·0 pp (8·0 to 22·1) | 0·0001 |
| >10·0 mmol/L | 41% (14) | 39% (11) | 20% (7) | 44% (16) | 24% (8) | 42% (17) | −18·4 pp (−26·9 to −9·8) | 0·0001 |
| >16·7 mmol/L | 6·7% (3·7–9·7) | 5·4% (3·0–9·7) | 1·7% (0·8–3·4) | 8·2% (3·4–13·7) | 2·8% (1·8–5·4) | 5·7% (3·1–11·3) | −3·23 pp (−8·37 to −0·41) | 0·026 |
| <3·9 mmol/L | 8·6% (6·1–11·2) | 8·7% (4·8–14·5) | 12·0% (10·3–18·7) | 6·1% (1·7–13·0) | 10·8% (5·7–20·7) | 6·3% (1·7–16·5) | 3·13 pp (−1·25 to 7·51) | 0·15 |
| <3·5 mmol/L | 5·8% (2·7–8·1) | 6·4% (2·3–10·1) | 8·3% (5·5–14·3) | 5·0% (0·9–8·7) | 7·4% (4·1–12·4) | 3·6% (1·0–11·6) | 1·86 pp (−1·14 to 4·93) | 0·13 |
| <3·0 mmol/L | 3·4% (0·9–4·9) | 3·5% (0·6–6·9) | 3·7% (1·4–7·4) | 2·7% (0·5–5·3) | 2·9% (1·6–6·1) | 1·4% (0·2–6·2) | 0·91 pp (−0·96 to 2·49) | 0·16 |
| Glucose AOC <3·5mmol/L | 0·042 (0·010–0·060) | 0·040 (0·010–0·080) | 0·048 (0·022–0·088) | 0·033 (0·006–0·063) | 0·035 (0·020–0·073) | 0·018 (0·004–0·072) | 0·012 (−0·007 to 0·030) | 0·13 |
| Glucose AUC >10·0mmol/L | 1·6 (1·2–1·8) | 1·4 (0·9–2·0) | 0·6 (0·4–0·8) | 1·9 (1·1–2·4) | 0·9 (0·6–1·0) | 1·4 (1·0–2·3) | −0·98 (−1·63 to −0·32) | 0·023 |
| Mean glucose (mmol/L) | 9·6 (1·7) | 9·3 (1·3) | 7·3 (0·9) | 9·9 (1·7) | 7·8 (1·0) | 9·8 (2·1) | −1·98 (−3·08 to −0·88) | 0·0009 |
| Glucose SD (mmol/L) | 4·5 (0·9) | 4·3 (0·8) | 3·5 (0·5) | 4·3 (0·9) | 3·9 (0·8) | 4·3 (1·0) | −0·60 (−1·11 to −0·09) | 0·037 |
| CV of glucose (%) | 47% (7) | 46% (7) | 48% (6) | 44% (8) | 49% (8) | 45% (9) | 2·5 pp (−1·4 to 6·4) | 0·21 |
| **Daytime from 06:00 to 23:59†** | | | | | | | | |
| Number of participants | 21 | 24 | 21 | 22 | 20 | 24 | .. | .. |
| Percentage of time with glucose level | | | | | | | | |
| 3·9 to 10·0 mmol/L | 48% (13) | 50% (10) | 63% (8) | 47% (13) | 61% (9) | 47% (13) | 13·9 pp (6·8 to 21·0) | 0·0003 |
| <3·5 mmol/L | 4·9% (1·9–7·1) | 4·1% (1·8–8·2) | 7·0% (5·6–12·7) | 3·9% (1·0–7·8) | 6·4% (4·2–10·6) | 3·8% (1·0–11·4) | 1·90 pp (−0·34 to 5·06) | 0·070 |
| Mean glucose (mmol/L) | 10·0 (2·0) | 9·6 (1·3) | 7·5 (1·0) | 10·2 (1·7) | 8·1 (1·1) | 10·0 (2·2) | −2·01 (−3·18 to −0·84) | 0·0013 |
| Glucose SD (mmol/L) | 4·6 (0·9) | 4·3 (0·9) | 3·6 (0·6) | 4·4 (0·9) | 4·0 (0·8) | 4·4 (1·1) | −0·61 (−1·17 to −0·06) | 0·031 |
| **Night-time from 00:00 to 05:59†** | | | | | | | | |
| Number of participants | 21 | 24 | 21 | 22 | 19 | 24 | .. | .. |
| Percentage of time with glucose level | | | | | | | | |
| 3·9 to 10·0 mmol/L | 54% (12) | 56% (12) | 71% (13) | 52% (18) | 70% (11) | 53% (19) | 17·4 pp (8·0 to 26·8) | 0·0008 |
| <3·5 mmol/L | 10·4% (4·8–16·2) | 7·2% (2·6–18·3) | 9·1% (3·9–17·0) | 5·4% (1·5–12·9) | 8·7% (2·7–17·9) | 3·3% (0·6–13·5) | 1·43 pp (−2·20 to 6·42) | 0·35 |
| Mean glucose (mmol/L) | 8·3 (1·4) | 8·4 (1·8) | 6·5 (0·9) | 9·1 (2·0) | 7·0 (1·0) | 9·0 (2·2) | −1·9 (−2·9 to −0·8) | 0·0008 |
| Glucose SD (mmol/L) | 3·6 (0·8) | 3·7 (0·9) | 3·0 (0·8) | 3·7 (1·0) | 3·4 (1·0) | 3·6 (0·9) | −0·21 (−0·73 to 0·31) | 0·42 |
| **Insulin metrics, units/kg per day** | | | | | | | | |
| Number of participants | 21 | 25 | .. | .. | 11‡ | 8‡ | .. | .. |
| Total daily bolus insulin | 0·51 (0·11) | 0·54 (0·18) | .. | .. | 0·48 (0·17) | 0·64 (0·46) | −0·23 (−0·46 to −0·01) | 0·066 |
| Total daily basal insulin | 0·38 (0·11) | 0·37 (0·12) | .. | .. | 0·59 (0·16) | 0·39 (0·20) | 0·22 (0·11 to 0·34) | 0·0030 |
| Total daily insulin | 0·88 (0·15) | 0·88 (0·22) | .. | .. | 1·09 (0·27) | 1·03 (0·57) | 0·03 (−0·19 to 0·24) | 0·80 |

Data are mean (SD) or median (IQR). pp=percentage point. *Model only includes participants with non-missing data at baseline and 6 months; model adjusted for baseline value of the metric, baseline $HbA_{1c}$ (where it is not the outcome), age, and clinical site as a random effect. †Outcomes calculated from 14 days of masked data from Abbott FreeStyle Libre Pro Flash Glucose Monitoring System; a minimum of 120 h of data was required to calculate day and night outcomes, and a minimum of 80 h and 40 h was required to calculate daytime and night-time outcomes, respectively. ‡The majority of 6-month visits were virtual due to the COVID-19 pandemic and weight data were not collected.

*Table 3:* **Comparison of glucose control by treatment group when using CamAPS FX**

high usage of the Control IQ system, which also uses a factory-calibrated sensor, over 12 months in users aged 6 years and older.[14]

The reduction in mean $HbA_{1c}$ from baseline with closed-loop in the full cohort (from 66 to 60 mmol/mol) is similar to that observed in other studies of commercially available hybrid closed-loop systems,[5–7,15,16] while the reduction in mean $HbA_{1c}$ from baseline with closed-loop in the CamAPS FX cohort (from 63 to 51 mmol/mol) compared favourably to these studies. The improvement in time with glucose in target range in the full cohort (by 6·7 percentage points), where closed-loop usage was low, is similar to that reported in a recent study[15] in children and adolescents with similar baseline $HbA_{1c}$ comparing the 670G hybrid closed-loop system with standard care over 6 months (improvement by 6·7 percentage points). In the CamAPS FX cohort, where closed-loop usage was consistently high, the improvement in time with glucose in target range (by 15·0 percentage points) compared well with the improvements observed in recent studies comparing the 780G and Control IQ hybrid closed-loop systems with sensor-augmented pump therapy,[5,6,16,17] in which closed-loop usage was similarly high. However, comparisons should be interpreted cautiously given differences in study design, frequency of visits, and baseline characteristics.

The time in hypoglycaemia (glucose <3·9 mmol/L) in the closed-loop group was unexpected, although not statistically significantly different compared with the control. Similarly, the time in hypoglycaemia in the control group was also higher than that reported in control groups of other hybrid closed-loop studies, in which glucose outcomes were measured using continuous glucose monitoring.[5,15] We used masked Libre Pro sensors to allow comparison of glucose control between intervention groups. It has been documented that 40% of the time when the FreeStyle Libre Pro Flash Glucose Monitoring System indicated values of 3·3 mmol/L or lower, the actual glucose values (Yellow Spring Instrument [YSI] measurements) were between 4·5 to 8·9 mmol/L.[18] Reassuringly, median time in hypoglycaemia in the CamAPS FX closed-loop group was 2·8% (IQR 2·1–4·7) at 6 months based on Dexcom G6 sensor data. There were more severe hypoglycaemia events in the present study than in other recent closed-loop studies,[5,7] but event rates were similar between groups.

Strengths of our study include the multicentre, multinational design, the long duration, and wide range of $HbA_{1c}$ (53–89 mmol/mol [7·0–10·3%]) at screening, supporting generalisability of our findings. The study was conducted without remote monitoring, representative of real-world use. However, our study has several limitations. While two different glucose sensors were used in the two closed-loop hardware configurations, both have been shown to be similarly accurate with a mean adjusted relative difference of 9·0% for the Dexcom G6 and 8·7% for the Guardian 3 sensor,[19,20] as well as a %20/20 YSI accuracy of 91% and 93%, respectively, in the hypoglycaemic range (glucose <3·9 mmol/L), thus the use of different sensors is not anticipated to have affected the clinical outcomes. However, it is likely that the need for regular calibrations with the Guardian 3 sensor, which are required to remain in auto mode, contributed to the low closed-loop usage observed in the FlorenceM cohort. The Libre Pro glucose sensor used to collect glycaemic data for analysis of the key and secondary endpoints was different to the sensor used for closed-loop insulin delivery in both hardware configurations. As the same sensor was used for all study participants, this is unlikely to have impacted outcomes. A further limitation of our study is that the prespecified analysis plan was to compare the entire closed-loop group with the control group, rather than each closed-loop system separately; given the post-hoc nature of the analysis, the findings should be interpreted with caution. The high number of device issues caused by unexpected failures of the embedded Carelink USB manufactured by a replacement supplier, led to low auto mode usage with the FlorenceM system, which was different to the higher usage observed in previous closed-loop studies using the FlorenceM system with the original Carelink USB.[8,21] The distinct differences in usage and efficacy between the two closed-loop system hardware configurations highlight the importance of usability and reliability for optimal clinical benefit.

| | Post-randomisation | | Closed-loop group | | | |
|---|---|---|---|---|---|---|
| | Closed-loop group | Control group | Before closed-loop initiation* | | After closed-loop initiation | |
| | | | CamAPS FX | FlorenceM | CamAPS FX | FlorenceM |
| Number of participants | 65 | 68 | 21 | 43 | 27 | 40 |
| Person-years | 35·5 | 39·1 | 1·4 | 3·3 | 13·0 | 17·8 |
| Any reportable adverse event | | | | | | |
| Number of events | 67 | 88 | 3 | 17 | 19 | 28 |
| Participants with at least one event | 31 (48%) | 39 (57%) | 2 (10%) | 16 (37%) | 9 (33%) | 14 (35%) |
| Number of events; number of participants (%) | | | | | | |
| Severe hypoglycaemia† | 4; 4 (6%) | 3; 3 (4%) | 0 | 0 | 3; 3 (11%) | 1; 1 (2%) |
| Related to study device | 2; 2 (3%) | 0 | 0 | 0 | 1; 1 (4%) | 1; 1 (2%) |
| Diabetic ketoacidosis | 2; 2 (3%) | 0 | 0 | 1; 1 (2%) | 0 | 1; 1 (2%) |
| Other reportable hyperglycaemia | 11; 10 (15%) | 12; 7 (10%) | 2; 1 (5%) | 1; 1 (2%) | 2; 2 (7%) | 6; 6 (15%) |
| Related to study device | 10; 9 (14%) | 1; 1 (1%) | 2; 1 (5%) | 1; 1 (2%) | 2; 2 (7%) | 5; 5 (12%) |
| Other serious adverse events | 1; 1 (2%) | 1; 1 (1%) | 0 | 1; 1 (2%) | 0 | 0 |
| Other reportable events | 49; 22 (34%) | 72; 33 (49%) | 1; 1 (5%) | 14; 13 (2%) | 14; 7 (26%) | 20; 9 (22%) |

*Following randomisation, participants in the closed-loop group underwent a 2–4 week run-in period in open loop, before commencing closed-loop therapy. †The incidence-rate of severe hypoglycaemia was 11·3 cases per 100 person-years for the closed-loop group and 7·7 cases per 100 person-years for the control group (p=0·60).

*Table 4:* **Summary of post-randomisation adverse events by treatment group and by closed-loop system**

In conclusion, the Cambridge hybrid closed-loop algorithm was safe and improved glycaemic control compared with usual care in children and adolescents with type 1 diabetes over a 6-month period. Improvements in glycaemic outcomes were modest in the full cohort, due to unreliable hardware resulting in low closed-loop usage in the group using the FlorenceM configuration. Post-hoc analyses revealed highly clinically meaningful improvements in glycaemic control in the closed-loop group using the more reliable CamAPS FX configuration, for which closed-loop usage was high, compared with the closed-loop group using the FlorenceM configuration, with which glycaemic control was no different to usual care. These outcomes highlight that efficacy requires consistently high closed-loop usage, as demonstrated by the marked difference in treatment effect between the two hardware configurations with the same closed-loop algorithm.

#### Contributors

RH, MT, FMC, RPW, BAB, LADM, SAW, CKo, RWB, KKH, and DSF codesigned the study. JMA, CKB, JW, MT, BAB, RWB, FMC, ND, AG, LADM, NM, AT, SAW, and RPW provided patient care or took samples. RWB was the medical monitor. JW, CKB, and RH wrote the manuscript. LK, CK, JW, and MEW carried out or supported data analysis, including the statistical analyses. All authors critically reviewed the manuscript and contributed to the interpretation of the results. RH, LK, CK, JS, and JW take responsibility for the integrity of the data and the accuracy of the data analysis, with each author having been responsible for specific parts of the raw dataset. All authors had access to the data, critically reviewed the paper before publication, and had final responsibility for the decision to submit the research for publication.

#### Declaration of interests

MT reports receiving speaker honoraria from Novo Nordisk. RPW reports receiving grants and contract support from Tandem Diabetes Care and Dexcom, consulting fees from Beta Bionics, and honoraria and travel support from Tandem Diabetes. BAB declares grant support from JDRF and National Institutes of Health (NIH), honoraria from Lilly, reports receiving grant support and advisory board fees from ConvaTec, grant support and honoraria from Insulet, advisory board fees from Medtronic MiniMed, grant support from Tandem Diabetes Care, Data Safety Monitoring Board role for ConvaTec, NovoNordisk, and Medtronic, advisory board fees from Arecor, advisory board role for ConvaTec, Medtronic and NovoNordisk, and patents (US 6,572,545 B2, PCT/US 2020/017997, US 2010/0174228 A1). LADM reports grants from Medtronic, leadership/fiduciary role regarding ISPAD Guidelines and Editorial Board, and receipt of equipment from Dexcom. NM reports receiving grants, contracts and payment, and honoraria from Novo Nordisk. SAW reports receiving consulting fees from Zealand Pharma, speaker honoraria from Dexcom, Insulet, Medtronic, Tandem Diabetes Care, and Abbott, and is a Data and Safety Monitoring Board member for two AID studies (NCT04492566, NCT04510506), and study supply receipt from Medtronic. RWB reports receiving grant support from NIH, Tandem Diabetes Care, Beta Bionics, and Dexcom; donated supplies from Tandem Diabetes Care, Beta Bionics, Dexcom, Medtronic, Ascencia, Roche, Eli Lilly, and Novo Nordisk; and consulting fees from Novo Nordisk, Bigfoot Biomedical, Eli Lilly, and Insulet. RH reports receiving speaker honoraria from Eli Lilly, Dexcom, and Novo Nordisk, receiving license fees from B Braun and Medtronic, declares consulting fees from Abbott Diabetes Care; patent issued in closed-loop field (Glucose monitoring and control using multi-model approach, patent number CA2702345C) with University of Cambridge and patent issued in closed-loop field (methods for reducing false hypoglycaemia alarm occurrence during closed-loop, patent number US9579456B2) with University of Cambridge and Abbott Diabetes Care, being director and stockholder at CamDiab, and leadership/fiduciary role for ATTD. MEW reports patents related to closed-loop (US9402953B2, US9579456B2) and being a consultant at CamDiab. REJB declares a leadership and fiduciary role for NovoNordisk. JW declares support for attending meetings from the YDEF Lilly Scholarship. KKH declares consulting fees for Cecelia Health, Insulet, and Lifescan Diabetes Institute. LK, CKo, CKB, JMA, AT, JS, LD, FMC, ND, AG, and DSF declare no competing financial interests exist.

#### Data sharing

De-identified subject level data set will be made available on case-by-case basis on reasonable request to the corresponding author for research purposes 6 months after publication.

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#### References

1 National Paediatric Diabetes Audit. Annual report 2018–2019: care processes and outcomes. London: Royal College of Paediatrics and Child Health, 2020.

2 Foster NC, Beck RW, Miller KM, et al. State of type 1 diabetes management and outcomes from the T1D Exchange in 2016–2018. *Diabetes Technol Ther* 2019; **21:** 66–72.

3 Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Mortality in type 1 diabetes in the DCCT/EDIC versus the general population. *Diabetes Care* 2016; **39:** 1378–83.

4 Leelarathna L, Choudhary P, Wilmot EG, et al. Hybrid closed-loop therapy: Where are we in 2021? *Diabetes Obes Metab* 2021; **23:** 655–60.

5 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:** 1707–17.

6 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:** 836–45.

7 Bergenstal RM, Nimri R, Beck RW, et al. A comparison of two hybrid closed-loop systems in adolescents and young adults with type 1 diabetes (FLAIR): a multicentre, randomised, crossover trial. *Lancet* 2021; **397:** 208–19.

8 Tauschmann M, Thabit H, Bally L, et al. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. *Lancet* 2018; **392:** 1321–29.

9 Lal RA, Basina M, Maahs DM, Hood K, Buckingham B, Wilson DM. One-year clinical experience of the first commercial hybrid closed-loop system. *Diabetes Care* 2019; **42:** 2190–96.

10 Boughton CK, Hovorka R. New closed-loop insulin systems. *Diabetologia* 2021; **64:** 1007–15.

11 Musolino G, Allen JM, Hartnell S, et al. Assessing the efficacy, safety and utility of 6-month day-and-night automated closed-loop insulin delivery under free-living conditions compared with insulin pump therapy in children and adolescents with type 1 diabetes: an open-label, multicentre, multinational, single-period, randomised, parallel group study protocol. *BMJ Open* 2019; **9:** e027856.

12 Berget C, Messer LH, Vigers T, et al. Six months of hybrid closed loop in the real-world: An evaluation of children and young adults using the 670G system. *Pediatr Diabetes* 2020; **21:** 310–18.

13 Miller KM, Foster NC, Beck RW, et al. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D Exchange clinic registry. *Diabetes Care* 2015; **38:** 971–78.

14 Breton MD, Kovatchev BP. One year real-world use of the Control-IQ advanced hybrid closed-loop technology. *Diabetes Technol Ther* 2021; **23:** 601–08.

15 Abraham MB, de Bock M, Smith GJ, et al. Effect of a hybrid closed-loop system on glycemic and psychosocial outcomes in children and adolescents with type 1 diabetes: a randomized clinical trial. *JAMA Pediatr* 2021; **175:** 1227–35.

16 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* 2021; **23:** 342–49.

17 Collyns OJ, Meier RA, Betts ZL, et al. Improved glycemic outcomes with Medtronic MiniMed Advanced Hybrid Closed-Loop delivery: Results from a randomized crossover trial comparing automated insulin delivery with predictive low glucose suspend in people with type 1 diabetes. *Diabetes Care* 2021; **44:** 969–75.

18 Abbott Diabetes Care. FreeStyle Libre 14 Day Flash Glucose Monitoring System user's manual DOC39764 Rev. B 07/18. 2016. https://www.accessdata.fda.gov/cdrh_docs/pdf15/p150021c.pdf (accessed Jan 18, 2022).

19 Shah VN, Laffel LM, Wadwa RP, Garg SK. Performance of a factory-calibrated real-time continuous glucose monitoring system utilizing an automated sensor applicator. *Diabetes Technol Ther* 2018; **20:** 428–33.

20 Christiansen MP, Garg SK, Brazg R, et al. Accuracy of a fourth-generation subcutaneous continuous glucose sensor. *Diabetes Technol Ther* 2017; **19:** 446–56.

21 Tauschmann M, Allen JM, Nagl K, et al. Home use of day-and-night hybrid closed-loop insulin delivery in very young children: a multi-center, 3-week, randomized trial. *Diabetes Care* 2019; **42:** 594–600.