

Supplementary Material

CLOuD Consortium.....	2
Study endpoints	4
Assays	5
Power calculations and statistical analysis	6
Table S1. Inclusion and exclusion criteria.	7
Table S2. Schedule of study visits / contacts when the participant is randomised to closed-loop.	9
Table S3. Schedule of study visits / contacts when the participant is randomised to standard therapy (control group).....	12
Table S4. Characteristics of study participants at baseline (primary study phase), compared to extension phase cohort (by treatment group).	14
Table S5. Description of participant withdrawals in the extension phase.....	16
Table S6. Longitudinal analyses of continuous glucose monitor metrics by treatment group.	17
Table S7. Day and night glucose control by treatment group.	20
Table S8. Insulin metrics (U/kg/day) over time from baseline to 48 months.....	21
Table S9. Continuous glucose monitor and closed-loop usage in the closed-loop group from 0 to 48 months.	23
Table S10. Diabetes technology use in the control group.....	24
Table S11. Per protocol analysis of outcomes at 36 and 48 months*	25
Table S12. Description of diabetes related safety events in the extension phase.....	26
Figure S1. Hybrid closed-loop configurations used in the closed-loop group. Panel A shows FlorenceM configuration and panel B shows CamAPS FX configuration.....	29
Figure S2. Study flow chart.	30
Figure S3. Participant flow.	31
Figure S4. Longitudinal glycaemic control over 48 months based on masked sensor glucose data collected by Freestyle LibrePro for up to 14 days.	32
References	33

CLOuD Consortium

A listing of the CLOuD Consortium with participating chief investigator (CI), principal investigators (PI), investigators (I), study coordinator (SC), study nurses (SN), research assistants (RA), pump educator (PE), and administrative manager (AM) is included below. The number of participants randomized at each site is indicated in parentheses after the sites' name.

Clinical sites	Clinical and support teams
University of Cambridge, Cambridge, UK (19)	Roman Hovorka (CI), Ajay Thankmonay (PI); Carlo Acerini (PI); David Dunger (I); Charlotte Boughton (I); Julia Ware (I); Martin Tauschmann (I); Rama Lakshman (I); Janet Allen (SN), Malgorzata Wilinska (I), Sara Hartnell (PE), Alina Cezar (SC), Nicole Ashcroft (SC)
Royal Hospital for Sick Children, Edinburgh, UK (12)	Daniela Elleri (PI); Morag McDonald (SN)
Leeds Children's Hospital, Leeds, UK (6)	Fiona Campbell (PI); James Yong (I), Emily Metcalfe (SN), Andrew Cameron (RA)
Alder Hey Children's Hospital, Liverpool, UK (17)	Atrayee Ghatak (PI); Keith Thornborough (SN), Jonathon Mimmagh (SN), Joanne Shakeshaft (AM), Karen Phelan (RA)
Nottingham Children's Hospital, Nottingham, UK (21)	Tabitha Randell (PI); Vreni Verhoeven (SN)
Oxford University Hospitals NHS Foundation Trust, Oxford, UK (14)	Rachel Besser (PI); Rebecca Law (SN), Clare Megson (SN), Jane Haest (PE), Alison West (SN), Imogen Stamford (SN)
Southampton Children's Hospital, Southampton, UK (12)	Nicola Trevelyan (PI); Helen Dewar (SN), Rachel Brampton (SN), Gabrielle Price (SN), Gillian Crouch (SN)
Non clinical sites	Non clinical teams
University of Edinburgh Usher Institute, Edinburgh, UK	Julia Lawton (I), David Rankin (I)

Jaeb Center for Health Research, Tampa, Florida, USA	Judy Sibayan (SC), Peter Calhoun (I), Ryan Bailey (I), Jessica Rusnak (RA)
Swansea University, Swansea, UK	Gareth Dunseath (I), Stephen Luzio (I)
Murdoch Children's Research Institute, Parkville, Victoria, Australia	Elisabeth Northam (I)
Wellcome Trust Centre for Human Genetics, Oxford, UK	John Todd (I)
Vyoo Agency, Lyon, France	Stéphane Roze (I)

Study endpoints

All outcomes in the extension phase were considered secondary and were compared between treatment groups at 36 and 48 months of follow-up.

Outcomes included fasting C-peptide and overall glucose control as measured by HbA1c. Time in target range, mean glucose, standard deviation and coefficient of variation of glucose, time spent in hyperglycaemia ($>10.0\text{mmol/L}$, $>16.7\text{mmol/L}$), time with glucose $<3.9\text{mmol/L}$, $<3.5\text{mmol/L}$, $<3.0\text{mmol/L}$ and $<2.8\text{mmol/L}$ and AOC of glucose $<3.9\text{mmol/L}$ and $<3.5\text{mmol/L}$ were based on data from a masked glucose sensor worn for 14 days at 36 and 48 months respectively. All sensor glucose outcomes were calculated over the whole 24-hour period, while a subset of outcomes (time in the target range, mean sensor glucose, standard deviation of glucose and time $<3.0\text{mmol/L}$) were also tabulated separately for daytime (6:00 to 23:59) and night-time (00:00 to 5:59). Insulin delivery metrics were additionally compared between groups at 36 and 48 months.

Safety evaluation comprised the frequency of severe hypoglycaemia and diabetic ketoacidosis events, and other adverse events or serious adverse events.

Assays

C-peptide and glucose were measured centrally (Swansea University, Swansea, UK); C-peptide was measured using a sensitive, luminescence immunoassay (IV2-004, Invitron, UK) and glucose using a glucose oxidase method (YSI 2300 stat plus, YSI Life Sciences, US). HbA1c was measured centrally (Swansea University) using an International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)-aligned method and following National Glycohemoglobin Standardization Program (NGSP) standards; Tosoh GX (Tosoh Bioscience, UK). Lipid profile was measured locally.

Power calculations and statistical analysis

Formal power calculations did not apply in the optional extension phase.

Analyses were performed on an intention-to-treat basis. All participants that were randomised were included in the analysis. Treatment interventions were compared using a linear model adjusting for baseline, gender, presence/absence of diabetic ketoacidosis at diagnosis and age as fixed effects, and clinical site as a random effect. A 95% confidence interval was reported for the difference between the interventions based on the model. For highly skewed data, a transformation was used. Mixed effects regression models addressed missing data by using maximum likelihood estimation incorporating data from all randomised participants, which assumes data were missing at random.

Secondary endpoints were adjusted for multiple comparisons to control the false discovery rate using the two-stage adaptive Benjamini-Hochberg method [1]. Analyses were conducted with SAS software version 9.4 (SAS Institute Inc).

Table S1. Inclusion and exclusion criteria.

Inclusion criteria

- Diagnosis of type 1 diabetes within previous 21 days. Day 1 defined as the day insulin first administered. Type 1 diabetes defined according to WHO criteria using standard diagnostic practice.
- The subject is at least 10 years and not older than 16.9 years
- The subject/carer is willing to perform regular capillary blood glucose monitoring, with at least 4 blood glucose measurements taken every day
- The subject is literate in English
- The subject is willing to wear glucose sensor
- The subject is willing to wear closed loop system at home
- The subject is willing to follow study specific instructions
- The subject is willing to upload pump and CGM data at regular intervals

Exclusion criteria

- Physical or psychological condition likely to interfere with the normal conduct of the study and interpretation of the study results as judged by the investigator
- Current treatment with drugs known to interfere with glucose metabolism, e.g. systemic corticosteroids, non-selective beta-blockers and MAO inhibitors etc.
- Known or suspected allergy to insulin
- Regular use of acetaminophen
- Lack of reliable telephone facility for contact
- Pregnancy, planned pregnancy, or breast feeding
- Living alone
- Severe visual impairment

- Severe hearing impairment
 - Medically documented allergy towards the adhesive (glue) of plasters or unable to tolerate tape adhesive in the area of sensor placement
 - Serious skin diseases (e.g. psoriasis vulgaris, bacterial skin diseases) located at places of the body, which potentially are possible to be used for localisation of the glucose sensor
 - Illicit drugs abuse
 - Prescription drugs abuse
 - Alcohol abuse
 - Sickle cell disease, haemoglobinopathy, receiving red blood cell transfusion or erythropoietin within 3 months prior to time of screening
 - Eating disorder such as anorexia or bulimia
 - Milk protein allergy
-

Table S2. Schedule of study visits / contacts when the participant is randomised to closed-loop.

	Visit/ contact	Description	Start relative to previous / next Visit / Activity	Duration
Run in period	Visit 1	Recruitment and screening visit: Consent/assent; inclusion, exclusion; screening blood sample	Within 21 days of diagnosis	2 hours
	Visit 2	Baseline visit: HbA1c, MMTT, blinded CGM, questionnaires, computerised cognitive testing, bloods for immunological analyses	7 to 21 days after diagnosis	3-4hours
		Randomisation		
Insulin pump & CGM Training	Visit 3	Insulin pump training, initiation study pump	Within 1 week of Visit 2	3-4 hours
	Visit 4	CGM training, initiation of CGM	Within 0 to 7 days of Visit 3 (Visit 4 may coincide with Visit 3; Training visits can be repeated)	2 hours
Closed loop insulin delivery (24 months)	*Visit 5	CL initiation at clinic/home	Within 6 weeks of diagnosis	3-4 hours
	Contact	Review use of study devices, study update	1 week after Visit 5 (± 3 days)	<0.5 hour
	*Visit 6	HbA1c, data download, blinded CGM	After 3 months of diagnosis (± 1 week)	<1 hour
	Visit 7	MMTT, HbA1c, bloods for immunological analyses, data download, blinded CGM, sleep quality assessment	After 6 months of diagnosis (± 2 weeks)	3-4hours
	*Visit 8	HbA1c, data download, blinded CGM	After 9 months of diagnosis (± 2 weeks)	<1 hour
	Visit 9	MMTT, HbA1c, bloods for immunological analyses, data download, blinded CGM, questionnaires, computerised cognitive testing, interviews, sleep quality assessment	After 12 months of diagnosis (± 2 weeks)	3-4 hours

	*Visit 10	HbA1c, data download, blinded CGM	After 15 months of diagnosis (± 2 weeks)	<1 hour
	*Visit 11	HbA1c, data download, blinded CGM	After 18 months of diagnosis (± 2 weeks)	<1 hour
	*Visit 12	HbA1c, data download, blinded CGM	After 21 months of diagnosis (± 2 weeks)	<1 hour
	*Visit 13	Blinded CGM, sleep quality assessment	Between Visit 12 and Visit 14 (Visit 13 may coincide with visit 14)	<0.5 hour
	Visit 14	End of closed loop treatment: MMTT, HbA1c, data download, bloods for immunological analyses, questionnaires, computerised cognitive testing, focus groups	After 24 months of diagnosis (± 2 weeks)	4-5 hours
Optional extension phase (24 months)	Contact	Review use of study devices, HbA1c, study update	3 months after Visit 14 (± 2 weeks)	<0.5 hour
	Contact	Review use of study devices, HbA1c, study update	6 months after Visit 14 (± 2 weeks)	<0.5 hour
	Contact	Review use of study devices, HbA1c, study update	9 months after Visit 14 (± 2 weeks)	<0.5 hour
	Visit 15	Fasted C-peptide and glucose, HbA1c, blinded CGM, questionnaires	After 36 months of diagnosis (± 2 weeks)	<1 hour
	Contact	Review use of study devices, HbA1c, study update	3 months after Visit 15 (± 2 weeks)	<0.5 hour
	Contact	Review use of study devices, HbA1c, study update	6 months after Visit 15 (± 2 weeks)	<0.5 hour
	Contact	Review use of study devices, HbA1c, study update	9 months after Visit 15 (± 2 weeks)	<0.5 hour
	*Visit 16	Blinded CGM	2 weeks before Visit 17 (± 2 weeks)	<0.5 hour

	Visit 17	Fasted C-peptide and glucose, HbA1c, blinded CGM review, questionnaires. Resume standard care.	After 48 months of diagnosis (± 2 weeks)	<1 hour
* could be done at home				

Table S3. Schedule of study visits / contacts when the participant is randomised to standard therapy (control group).

	Visit/ contact	Description	Start relative to previous / next Visit / Activity	Duration
Run in period	Visit 1	Recruitment and screening visit: Consent/assent; inclusion, exclusion; screening blood sample	Within 21 days of diagnosis	2-hours
	Visit 2	Baseline visit: HbA1c, MMTT, blinded CGM, questionnaires, computerised cognitive testing, bloods for immunological analyses	7 to 21 days after diagnosis	3-4hours
		Randomisation		
Additional Training	Visit 3	Training on carbohydrate counting	Within 1 week of Visit 2	2 hours
	Visit 4	Training on insulin dose adjustment	Within 0 to 7 days of Visit 3 (Visit 4 may coincide with Visit 3; Training visits can be repeated)	2 hours
Standard insulin therapy (24 months)	*Visit 5	Control arm start visit	Within 6 weeks of diagnosis	<1 hour
	Contact	Study update	1 week after Visit 5 (± 3 days)	<0.5 hour
	**Visit 6	HbA1c, blinded CGM	After 3 months of diagnosis (± 1 week)	<1 hour
	Visit 7	MMTT, HbA1c, bloods for immunological analyses, blinded CGM, sleep quality assessment	After 6 months of diagnosis (± 2 weeks)	3-4 hours
	**Visit 8	HbA1c, blinded CGM	After 9 months of diagnosis (± 2 weeks)	<1 hour
	Visit 9	MMTT, HbA1c, bloods for immunological analyses, blinded CGM, questionnaires, computerised cognitive testing, sleep quality assessment	After 12 months of diagnosis (± 2 weeks)	3-4 hours

	**Visit 10	HbA1c, blinded CGM	After 15 months of diagnosis (± 2 weeks)	<1 hour
	**Visit 11	HbA1c, blinded CGM	After 18 months of diagnosis (± 2 weeks)	<1 hour
	**Visit 12	HbA1c, blinded CGM	After 21 months of diagnosis (± 2 weeks)	<1 hour
	**Visit 13	Blinded CGM, sleep quality assessment	Between Visit 12 and Visit 14, (may coincide with visit 14)	<1 hour
	Visit 14	End of control treatment: MMTT, HbA1c, bloods for immunological analyses, questionnaires, computerised cognitive testing	After 24 months of diagnosis (± 2 weeks)	4-5 hours
Optional extension phase (24 months)	Contact	Study update, HbA1c	3 months after Visit 14 (± 2 weeks)	<0.5 hour
	Contact	Study update, HbA1c	6 months after Visit 14 (± 2 weeks)	<0.5 hour
	Contact	Study update, HbA1c	9 months after Visit 14 (± 2 weeks)	<0.5 hour
	Visit 15	Fasted C-peptide and glucose, HbA1c, blinded CGM, questionnaires	After 36 months of diagnosis (± 2 weeks)	<1 hour
	Contact	Study update, HbA1c	3 months after Visit 15 (± 2 weeks)	<0.5 hour
	Contact	Study update, HbA1c	6 months after Visit 15 (± 2 weeks)	<0.5 hour
	Contact	Study update, HbA1c	9 months after Visit 15 (± 2 weeks)	<0.5 hour
	*Visit 16	Blinded CGM	2 weeks before Visit 17 (± 2 weeks)	<0.5 hour
	Visit 17	Fasted C-peptide and glucose, HbA1c, blinded CGM review, questionnaires.	After 48 months of diagnosis (± 2 weeks)	<1 hour
* could be done at home or phone/email, ** could be done at home				

Table S4. Characteristics of study participants at baseline (primary study phase), compared to extension phase cohort (by treatment group).

	Primary cohort (N=97)	Extension phase cohort		
		Overall (N=81)	Closed-loop (N=47)	Control (N=34)
Age				
Mean, years	12 ± 2	12 ± 2	12 ± 2	12 ± 2
10 to 13 years, n (%)	79 (81)	69 (85)	38 (81)	31 (91)
14 to 17 years, n (%)	18 (19)	12 (15)	9 (19)	3 (9)
Sex, n (%)				
Female	43 (44)	34 (42)	21 (45)	13 (38)
BMI percentile	52 ± 31	49 ± 32	50 ± 29	47 ± 35
Ethnicity, n (%)				
White	79 (81)	67 (83)	40 (85)	27 (79)
Black / African-American	3 (3)	3 (4)	1 (2)	2 (6)
Asian	6 (6)	4 (5)	2 (4)	2 (6)
More than one race	5 (5)	5 (6)	4 (9)	1 (3)
Unknown / not reported	4 (4)	2 (2)	0 (0)	2 (6)
Presence of DKA at diagnosis, n (%)	28 (29)	18 (22)	14 (30)	4 (12)

	Primary cohort (N=97)	Extension phase cohort		
		Overall (N=81)	Closed-loop (N=47)	Control (N=34)
HbA1c at screening, % [mmol/mol]	10.6 ± 1.7	10.7 ± 1.7	10.7 ± 1.8	10.6 ± 1.6
	[93 ± 18]	[93 ± 19]	[94 ± 20]	[92 ± 18]

Data are n (%) or mean±SD.

Table S5. Description of participant withdrawals in the extension phase.

Treatment group	Timing	Details
Closed-loop	Prior to 36 months	Participant experienced 3 severe hypoglycaemia events within a 14-month period while using closed-loop. All related to overestimation of carbs and not responding to hypoglycaemia alarms. Withdrawn on safety grounds.
Closed-loop	Prior to 36 months	Participant experienced 4 severe hypoglycaemia events over a 33-month period. Two events occurred when closed-loop was not operational. One event was related to multiple manual correction boluses being given in quick succession following a period of non-delivery of insulin due to pump batteries expiring. One event was following an overestimation of carbohydrates. Withdrawn on safety grounds.
Closed-loop	Prior to 36 months	Lost to follow-up after relocation during first year of extension phase. Withdrawn by study team.
Control	Prior to 36 months	Withdrawn by study team due to mental health concerns and added burden of participating in a research study.
Control	After 36 months	Lost to follow-up after 36-month visit due to relocation. Withdrawn by study team.

Table S6. Longitudinal analyses of continuous glucose monitor metrics by treatment group.

	Baseline	3 months	6 months	9 months	12 months	15 months	18 months	21 months	24 months	36 months	48 months	P-value*
Time with sensor glucose (%) 3.9-10.0mmol/L												
Closed-loop	74 ± 14	73 ± 13	70 ± 15	67 ± 14	64 ± 14	66 ± 12	64 ± 15	67 ± 12	64 ± 15	66 ± 13	61 ± 12	0.001
Control	72 ± 13	73 ± 15	65 ± 22	65 ± 19	54 ± 23	58 ± 18	53 ± 17	57 ± 21	49 ± 18	52 ± 20	50 ± 17	
<3.9mmol/L*												
Closed-loop	9.1 ± 6.3	6.3 ± 5.3	6.1 ± 5.7	7.5 ± 5.2	6.2 ± 3.8	10.4 ± 5.8	12.2 ± 8.7	11.0 ± 6.3	11.2 ± 7.3	13.8 ± 7.3	11.7 ± 6.8	<0.001
Control	10.7 ± 7.1	7.0 ± 5.4	4.2 ± 3.9	4.4 ± 3.2	5.4 ± 4.7	7.1 ± 5.0	4.8 ± 4.4	7.4 ± 6.5	7.5 ± 6.7	6.8 ± 5.5	11.5 ± 8.1	
<3.5mmol/L*												
Closed-loop	5.2 ± 4.8	3.7 ± 3.8	3.4 ± 3.4	4.6 ± 4.0	3.6 ± 2.6	6.3 ± 3.8	7.4 ± 5.2	7.3 ± 5.2	7.0 ± 5.3	8.9 ± 5.6	8.0 ± 5.1	<0.001
Control	6.6 ± 5.2	3.8 ± 3.7	2.3 ± 2.4	2.4 ± 2.1	3.3 ± 3.1	4.3 ± 3.5	2.9 ± 3.2	4.8 ± 5.4	5.0 ± 5.0	4.5 ± 4.2	8.6 ± 6.7	
<3.0mmol/L*												
Closed-loop	2.0 ± 2.5	1.6 ± 1.9	1.4 ± 1.7	2.2 ± 2.6	1.4 ± 1.2	2.9 ± 2.2	3.4 ± 2.9	3.7 ± 3.4	3.1 ± 3.0	4.2 ± 3.6	4.2 ± 2.9	0.004
Control	2.8 ± 2.8	1.3 ± 1.8	0.8 ± 0.9	1.1 ± 1.3	1.5 ± 1.6	1.9 ± 2.0	1.4 ± 2.0	2.5 ± 3.3	2.3 ± 2.7	2.1 ± 2.3	5.3 ± 4.8	
<2.8mmol/L*												
Closed-loop	1.3 ± 1.8	1.1 ± 1.4	1.0 ± 1.3	1.6 ± 2.1	0.9 ± 0.9	1.9 ± 1.6	2.2 ± 2.0	2.6 ± 2.6	2.0 ± 2.0	2.9 ± 3.0	3.1 ± 2.3	0.03

	Baseline	3 month	6 month	9 month	12 month	15 month	18 month	21 month	24 month	36 month	48 month	P-value*
Control	1.9 ± 2.2	0.8 ± 1.1	0.5 ± 0.6	0.7 ± 0.9	1.1 ± 1.4	1.3 ± 1.5	0.9 ± 1.4	1.9 ± 2.8	1.7 ± 2.1	1.6 ± 2.0	4.1 ± 3.9	
>10.0mmol/L*												
Closed-loop	15 ± 9	19 ± 14	23 ± 16	24 ± 11	29 ± 14	23 ± 12	21 ± 13	21 ± 12	22 ± 11	18 ± 9	26 ± 13	<0.001
Control	14 ± 10	18 ± 13	30 ± 21	30 ± 16	40 ± 25	33 ± 19	41 ± 19	35 ± 21	42 ± 19	40 ± 19	38 ± 20	
>16.7mmol/L*												
Closed-loop	1.0 ± 1.6	1.9 ± 2.7	2.5 ± 3.6	2.5 ± 2.7	4.2 ± 3.8	3.2 ± 3.6	3.0 ± 3.3	3.2 ± 3.6	3.5 ± 4.0	2.5 ± 3.3	3.9 ± 4.0	<0.001
Control	1.0 ± 1.5	1.4 ± 2.4	4.8 ± 6.4	3.1 ± 3.1	10.0 ± 12.4	5.6 ± 6.0	5.6 ± 6.1	6.8 ± 8.6	8.7 ± 10.7	10.5 ± 11.3	8.3 ± 7.7	
Mean glucose (mmol/L)												
Closed-loop	7.2 ± 1.6	7.6 ± 1.6	8.0 ± 1.9	8.0 ± 1.6	8.5 ± 1.6	7.9 ± 1.8	7.8 ± 2.4	7.7 ± 1.6	7.9 ± 1.9	7.4 ± 1.6	8.2 ± 2.2	<0.001
Control	7.0 ± 1.6	7.4 ± 1.7	8.9 ± 2.7	8.8 ± 2.0	9.8 ± 3.3	8.8 ± 2.3	9.5 ± 2.1	9.1 ± 2.5	9.8 ± 2.6	10.0 ± 3.1	9.3 ± 2.7	
Glucose SD (mmol/L)												
Closed-loop	2.7 ± 0.7	2.8 ± 0.9	3.1 ± 0.9	3.3 ± 1.0	3.6 ± 0.9	3.5 ± 1.1	3.5 ± 1.4	3.5 ± 1.1	3.7 ± 1.3	3.4 ± 1.1	3.9 ± 1.2	0.18
Control	2.7 ± 0.8	2.7 ± 0.9	3.3 ± 1.3	3.4 ± 1.1	3.7 ± 1.4	3.6 ± 1.2	3.5 ± 1.0	3.7 ± 1.4	4.0 ± 1.3	4.3 ± 1.4	4.3 ± 1.4	
Glucose CV (%)												
Closed-loop	38 ± 7	37 ± 7	38 ± 6	41 ± 8	42 ± 7	44 ± 7	44 ± 9	45 ± 8	46 ± 10	46 ± 9	47 ± 8	0.002
Control	39 ± 7	37 ± 6	36 ± 7	38 ± 7	39 ± 8	40 ± 7	38 ± 8	40 ± 10	41 ± 8	44 ± 10	46 ± 9	

	Baseline	3 months	6 months	9 months	12 months	15 months	18 months	21 months	24 months	36 months	48 months	P-value*
AOC <3.9mmol/L (mmol/L)*												
Closed-loop	1.0 ± 0.9	0.7 ± 0.8	0.7 ± 0.7	0.9 ± 0.8	0.7 ± 0.5	1.3 ± 0.8	1.5 ± 1.2	1.5 ± 1.2	1.4 ± 1.1	1.8 ± 1.2	1.6 ± 1.0	<0.001
Control	1.3 ± 1.1	0.7 ± 0.7	0.4 ± 0.4	0.5 ± 0.4	0.6 ± 0.6	0.9 ± 0.7	0.6 ± 0.7	1.0 ± 1.1	1.0 ± 1.0	0.8 ± 0.8	1.9 ± 1.6	
AOC <3.5mmol/L (mmol/L)*												
Closed-loop	0.5 ± 0.5	0.4 ± 0.5	0.3 ± 0.4	0.5 ± 0.5	0.3 ± 0.3	0.7 ± 0.5	0.8 ± 0.7	0.8 ± 0.7	0.7 ± 0.6	0.9 ± 0.8	0.9 ± 0.6	0.001
Control	0.6 ± 0.6	0.3 ± 0.4	0.2 ± 0.2	0.2 ± 0.3	0.3 ± 0.4	0.4 ± 0.4	0.3 ± 0.4	0.5 ± 0.7	0.5 ± 0.6	0.5 ± 0.5	1.2 ± 1.0	

Data presented as mean ± SD using masked sensor glucose data provided by Freestyle LibrePro over up to 14 days. AOC – area over the curve.

*Variable winsorised at 10th and 90th percentile

**Based on a model adjusting for baseline value, gender, presence or absence of DKA at diagnosis, age as fixed effects and clinical site as a random effect. Model is pooling outcomes across all follow-up visits, giving equal weight to each visit. P-values adjusted using the adaptive Benjamini-Hochberg procedure.

Table S7. Day and night glucose control by treatment group.

	Daytime (08:00-23:59)						Night time (00:00-07:59)					
	Baseline		36 months		48 months		Baseline		36 months		48 months	
	Closed-loop (N=50)	Control (N=43)	Closed-loop (N=44)	Control (N=33)	Closed-loop (N=42)	Control (N=30)	Closed-loop (N=50)	Control (N=43)	Closed-loop (N=44)	Control (N=33)	Closed-loop (N=42)	Control (N=30)
Time in range 3.9-10.0mmol/L (%)	73 ± 14	72 ± 13	64 ± 14	49 ± 20	59 ± 14	48 ± 18	75 ± 16	72 ± 17	72 ± 16	57 ± 24	65 ± 15	52 ± 19
Mean glucose (mmol/L)	7.3 ± 1.7	7.2 ± 1.7	7.9 ± 1.8	10.4 ± 3.0	8.7 ± 2.4	9.8 ± 2.9	7.0 ± 1.6	6.5 ± 1.9	6.4 ± 1.4	9.1 ± 3.5	7.4 ± 2.2	8.4 ± 2.9
Glucose SD (mmol/L)	2.8 ± 0.7	2.7 ± 0.8	3.6 ± 1.2	4.5 ± 1.4	3.9 ± 1.2	4.4 ± 1.4	2.4 ± 0.8	2.3 ± 0.9	2.7 ± 1.1	3.6 ± 1.6	3.4 ± 1.4	3.7 ± 1.3
Time <3.0mmol/L (%)*	1.5 ± 1.6	1.9 ± 1.9	3.6 ± 3.0	1.7 ± 1.6	3.5 ± 2.6	4.0 ± 4.3	2.6 ± 4.1	4.0 ± 4.8	5.2 ± 5.2	2.8 ± 4.1	6.0 ± 4.8	7.5 ± 6.5

Date are presented as mean ± SD using masked sensor glucose data provided by Freestyle LibrePro over up to 14 days

*Variable winsorised at the 10th and 90th percentiles

Table S8. Insulin metrics (U/kg/day) over time from baseline to 48 months.

	Baseline	3 months	6 months	9 months	12 months	15 months	18 months	21 months	24 months
Total Insulin									
Closed-loop	0.87 ± 0.33	0.67 ± 0.29	0.73 ± 0.33	0.84 ± 0.44	0.96 ± 0.45	0.95 ± 0.45	1.09 ± 0.54	1.16 ± 0.49	1.14 ± 0.52
Control	0.82 ± 0.38	0.61 ± 0.26	0.69 ± 0.41	0.74 ± 0.34	0.84 ± 0.39	0.99 ± 0.46	0.99 ± 0.37	1.11 ± 0.41	1.09 ± 0.42
Basal Insulin									
Closed-loop	0.33 ± 0.12	0.28 ± 0.14	0.33 ± 0.16	0.42 ± 0.27	0.52 ± 0.31	0.53 ± 0.29	0.57 ± 0.36	0.58 ± 0.30	0.62 ± 0.35
Control	0.36 ± 0.21	0.28 ± 0.17	0.29 ± 0.20	0.31 ± 0.16	0.37 ± 0.26	0.42 ± 0.30	0.39 ± 0.18	0.47 ± 0.23	0.49 ± 0.21
Bolus Insulin									
Closed-loop	0.54 ± 0.24	0.38 ± 0.19	0.40 ± 0.23	0.42 ± 0.23	0.44 ± 0.22	0.42 ± 0.23	0.52 ± 0.29	0.58 ± 0.31	0.52 ± 0.31
Control	0.46 ± 0.28	0.33 ± 0.17	0.40 ± 0.24	0.43 ± 0.23	0.46 ± 0.23	0.57 ± 0.31	0.59 ± 0.29	0.64 ± 0.31	0.60 ± 0.32
	27 months	30 months	33 months	36 months	39 months	42 months	45 months	48 months	P-value*
Total Insulin									
Closed-loop	1.22 ± 0.47	1.28 ± 0.49	1.32 ± 0.64	1.35 ± 0.44	1.30 ± 0.53	1.31 ± 0.42	1.36 ± 0.51	1.46 ± 0.72	0.43
Control	1.17 ± 0.41	1.26 ± 0.48	1.32 ± 0.66	1.26 ± 0.51	1.25 ± 0.46	1.37 ± 0.53	1.28 ± 0.52	1.31 ± 0.48	
Basal Insulin									
Closed-loop	0.70 ± 0.33	0.78 ± 0.35	0.77 ± 0.35	0.78 ± 0.41	0.78 ± 0.44	0.79 ± 0.33	0.77 ± 0.33	0.85 ± 0.57	0.003
Control	0.53 ± 0.24	0.57 ± 0.25	0.62 ± 0.32	0.59 ± 0.27	0.61 ± 0.26	0.62 ± 0.26	0.67 ± 0.28	0.64 ± 0.24	
Bolus Insulin									

Closed-loop	0.52 ± 0.28	0.50 ± 0.32	0.56 ± 0.42	0.57 ± 0.21	0.52 ± 0.25	0.52 ± 0.26	0.59 ± 0.33	0.61 ± 0.37	0.01
Control	0.64 ± 0.26	0.67 ± 0.29	0.70 ± 0.42	0.67 ± 0.31	0.64 ± 0.36	0.75 ± 0.38	0.61 ± 0.59	0.67 ± 0.35	

Data are presented as mean ± SD.

*Based on a model adjusting for baseline value, gender, presence or absence of DKA at diagnosis, and age as fixed effects and clinical site as a random effect. Model is pooling outcomes across all follow-up visits, giving equal weight to each visit. P-values adjusted using the adaptive Benjamini-Hochberg procedure

Table S9. Continuous glucose monitor and closed-loop usage in the closed-loop group from 0 to 48 months.

	Baseline to 24 months (N=50)*	24 to 48 months (N=48)**
Time using the continuous glucose monitoring, n (%)		
0-<20%	4 (8)	5 (11)
20-<40%	1 (2)	0 (0)
40-<60%	3 (6)	0 (0)
60-<80%	16 (32)	3 (7)
≥80%	26 (52)	38 (83)
Median (IQR) use (%)	81 (66, 91)	97 (91, 99)
Time using the closed-loop system, n (%)		
0-<20%	4 (8)	5 (11)
20-<40%	2 (4)	0 (0)
40-<60%	6 (12)	0 (0)
60-<80%	23 (46)	6 (13)
≥80%	15 (30)	35 (76)
Median (IQR) use (%)	76 (60, 85)	92 (82, 94)

*2 participants elected not to use closed-loop 0-12 months. 5 participants elected not to use closed-loop 12-24 months.

**5 participants continued in the extension phase but elected not to use closed-loop.

Table S10. Diabetes technology use in the control group.

	12 months	24 months	36 months	48 months
	(N=39)	(N=37)	(N=34)	(N=33)
Use of an insulin pump, n (%)	4 (10)	16 (43)	15 (44)	13 (39)
	(N=37)	(N=37)	(N=34)	(N=33)
Use of a glucose sensor, n (%)*	21 (57)	25 (68)	31 (91)	31 (94)
			(N=34)	(N=33)
Use of a closed-loop system, n (%)	-	-	4 (12)	5 (15)

*Includes real-time and flash continuous glucose monitoring

Table S11. Per protocol analysis of outcomes at 36 and 48 months*

	Baseline		36 months		P-value**	48 months		P-value**
	Closed-loop	Control	Closed-loop	Control		Closed-loop	Control	
Time in range 3.9-10.0mmol/L (%)	(N=41) 74 ± 15	(N=21) 70 ± 10	(N=34) 68 ± 10	(N=12) 44 ± 23	<0.001	(N=32) 62 ± 10	(N=12) 44 ± 20	0.001
HbA1c (%)	(N=33) 10.6 ± 1.8	(N=38) 10.6 ± 1.9	(N=38) 6.8 ± 0.7	(N=14) 8.5 ± 1.9	<0.001	(N=38) 7.0 ± 1.5	(N=14) 8.6 ± 1.6	<0.001
HbA1c (mmol/mol)	92 ± 19	92 ± 21	51 ± 7	70 ± 21		53 ± 16	70 ± 18	

Data are mean ± SD.

*Of those eligible for the per-protocol analysis, 5 participants in the closed-loop group and 2 in the control group were missing time in range at 36 months, while 7 in the closed-loop group and 2 in the control group were missing time in range at 48 months. 1 participant in the closed-loop group was missing HbA1c at 36 and 48 months.

**Based on a linear model adjusting for baseline, gender, presence or absence of DKA at diagnosis, and age as fixed effects and clinical site as a random effect. The model with HbA1c as an outcome treated capillary HbA1c as an auxiliary variable. P-values adjusted using the adaptive Benjamini-Hochberg procedure.

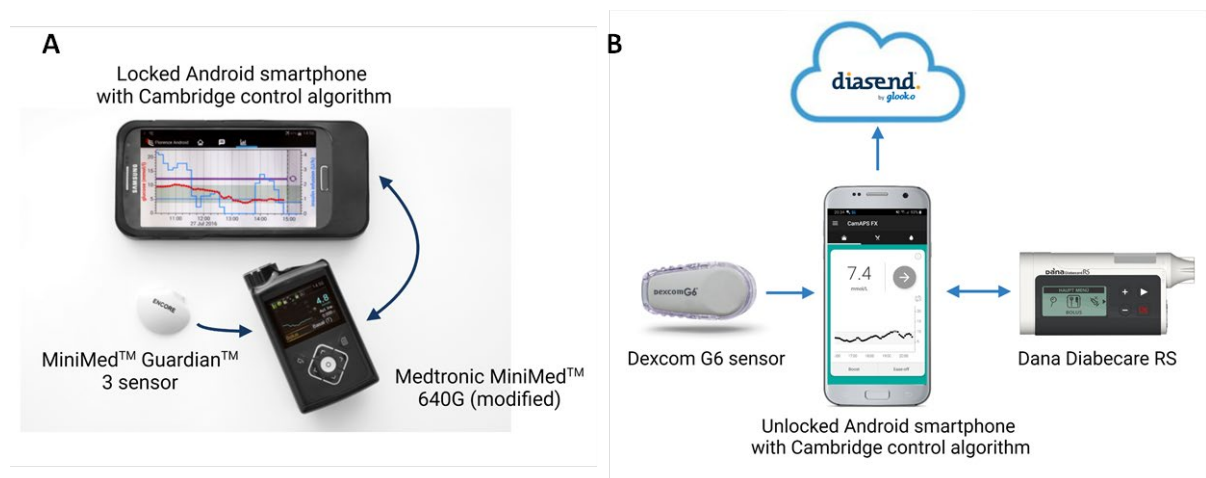
Table S12. Description of diabetes related safety events in the extension phase.

Event	Treatment group	Details
Severe hypoglycaemia	Closed-loop	Participant became combative and incoherent following a football match, hypoglycaemia treatment administered by parent. Sensor glucose 2.8mmol/L. Recovered but remained feeling drowsy for several hours after the event. Last bolus administered 3 hours prior, on closed-loop throughout.
Severe hypoglycaemia	Closed-loop	Insulin pump battery flat and alarms not acted on, leading to prolonged high glucose levels. Following this participant gave multiple manual correction boluses in quick succession. Participant became unresponsive, hypoglycaemia treatment administered by parent, participant recovered after 45 minutes. Closed-loop not operational at the time of the event.
Severe hypoglycaemia	Closed-loop	Hypoglycaemic seizure. Closed-loop not operational at the time as participant was not wearing a glucose sensor.
Severe hypoglycaemia	Closed-loop	Participant experienced hypoglycaemia after delaying eating following a pre-meal bolus. Hypoglycaemia treatment administered by parent, participant unable to recall event.
Severe hypoglycaemia	Closed-loop	Severe hypoglycaemia due to alcohol intoxication. Participant vomited following alcohol consumption and became unresponsive with low blood glucose. Participant unable to take glucogel, IV dextrose administered by ambulance crew, following which the participant recovered.
Severe hypoglycaemia	Closed-loop	Hypoglycaemia event following a delayed meal bolus. Participant did not act on alarms and became unresponsive. Parent administered IM glucagon and participant recovered.

Severe hypoglycaemia	Control	Participant using sensor-augmented pump therapy with predictive low glucose suspend. Hypoglycaemia alarms noted whilst asleep, participant difficult to rouse and required assistance from relative to take hypoglycaemia treatment. Full recovery after 2 hours.
Severe hypoglycaemia	Control	Participant on insulin pump therapy. Severe hypoglycaemia event with loss of consciousness following overestimated meal bolus. Required IM glucagon injection by ambulance crew and admission to the Emergency Department. Full recovery after several hours.
Severe hypoglycaemia	Control	Participant unwell with vomiting illness. Hypoglycaemia event where parental assistance was required to administer hypoglycaemia treatment.
Severe hypoglycaemia	Control	Participant became confused during a hypoglycaemia event, hypoglycaemia treatment administered by sister.
Severe hypoglycaemia	Control	Severe hypoglycaemia event while at school, requiring assistance from paramedics.
Diabetic ketoacidosis	Closed-loop	Battery expired on insulin pump, alarms not acted on by participant resulting in no insulin delivery for 24 hours. Hospital admission for treatment. Closed-loop not operational at the time of the event.
Diabetic ketoacidosis	Closed-loop	Episode of significant hyperglycaemia. Participant gave multiple manual correction boluses with no effect on glucose levels. No infusion set change done and no pen correction given. Admitted to hospital overnight for treatment. Hyperglycaemia likely secondary to mechanical insulin delivery failure.
Diabetic ketoacidosis	Closed-loop	Episode of significant hyperglycaemia, not resolving despite multiple manual correction boluses. Closed-loop not operational

		for 24 hours prior to the event, participant using standalone insulin pump therapy with finger pricking. No infusion set change done and no pen correction given. Admitted to hospital for treatment. Event likely secondary to mechanical insulin delivery failure.
Diabetic ketoacidosis	Control	Participant on MDI therapy. Admitted to hospital with diabetic ketoacidosis following a 2-week period of only intermittently giving insulin injections.
Diabetic ketoacidosis	Control	Participant on MDI therapy. Developed diabetic ketoacidosis during an intercurrent illness with diarrhoea and vomiting. Required admission to hospital.
Diabetic ketoacidosis	Control	Participant on insulin pump therapy. Pod failure during intercurrent illness, developed diabetic ketoacidosis. Admitted to hospital for treatment overnight.
Diabetic ketoacidosis	Control	Participant on MDI therapy. Admitted to hospital with diabetic ketoacidosis following a 3-week period of only intermittently giving insulin injections.

Figure S1. Hybrid closed-loop configurations used in the closed-loop group. Panel A shows FlorenceM configuration and panel B shows CamAPS FX configuration.



The FlorenceM configuration comprised a locked smartphone (Samsung Galaxy S4, South Korea) running an app with the Cambridge control algorithm (version 0.3.71), 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 requires finger-stick calibrations.

The CamAPS FX configuration superseded FlorenceM in July 2019. The CamAPS FX system comprised an unlocked smartphone (Samsung Galaxy S8, South Korea) hosting the CamAPS FX app (CamDiab, Cambridge, UK) running the Cambridge control algorithm (version 0.3.71), which communicated wirelessly with both the Dana Diabecare RS insulin pump (Sooil, Seoul, South Korea), and Dexcom G6 transmitter (Dexcom, San Diego, CA, USA).

In both configurations, when auto mode was not operational, the insulin pump reverted to pre-programmed basal rates. The treat-to-target adaptive control algorithm had a nominal glucose target level of 5.8mmol/L, which was adjustable in the CamAPS FX configuration between 4.4 and 11.0mmol/L across different times of day. The CamAPS FX app contained a bolus calculator to initiate bolus delivery from the phone, a user-selectable ‘Ease-off’ mode to reduce insulin delivery around activity/exercise, and a ‘Boost’ mode to intensify insulin delivery when insulin needs were elevated. The CamAPS FX app streamed data to Diasend/Glooko data ecosystem (Glooko/Diasend, Sweden).

Figure S2. Study flow chart.

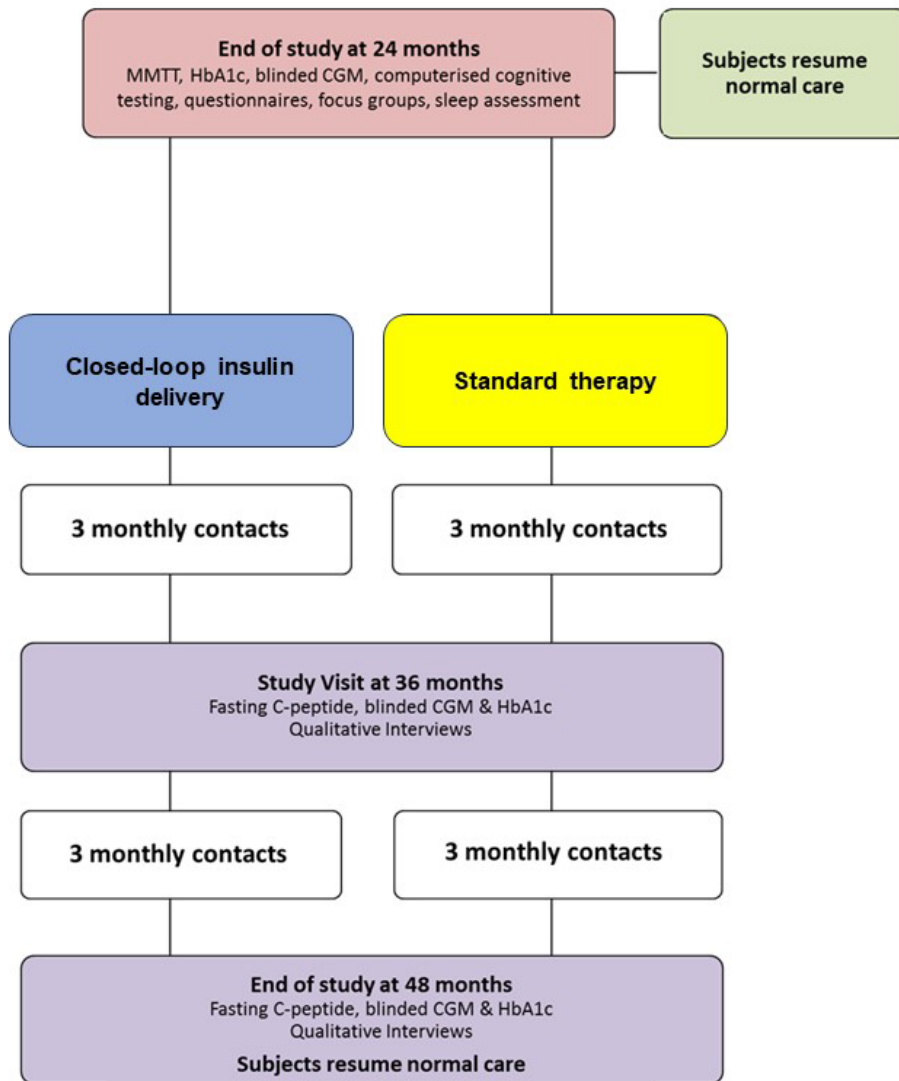


Figure S3. Participant flow.

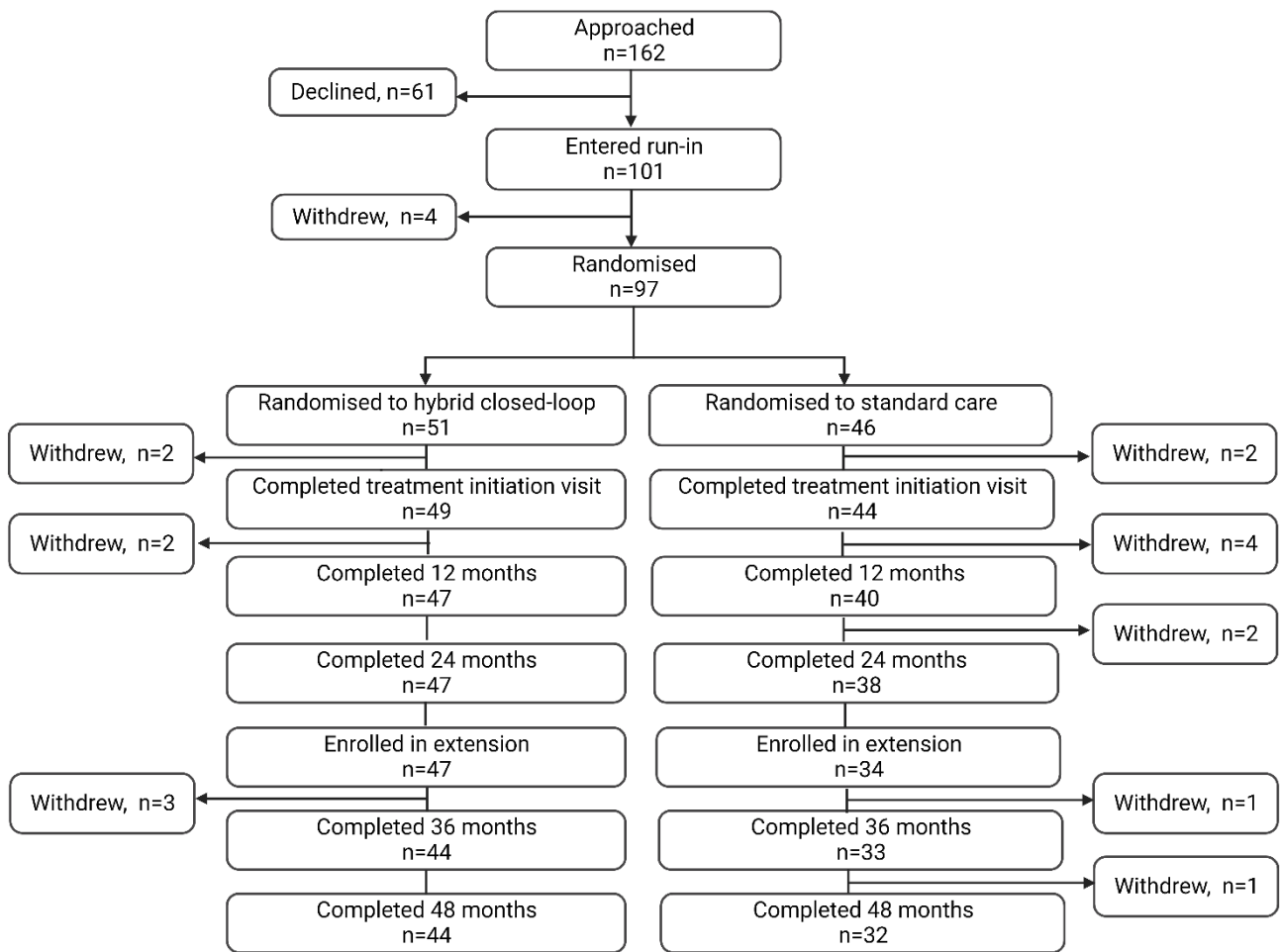
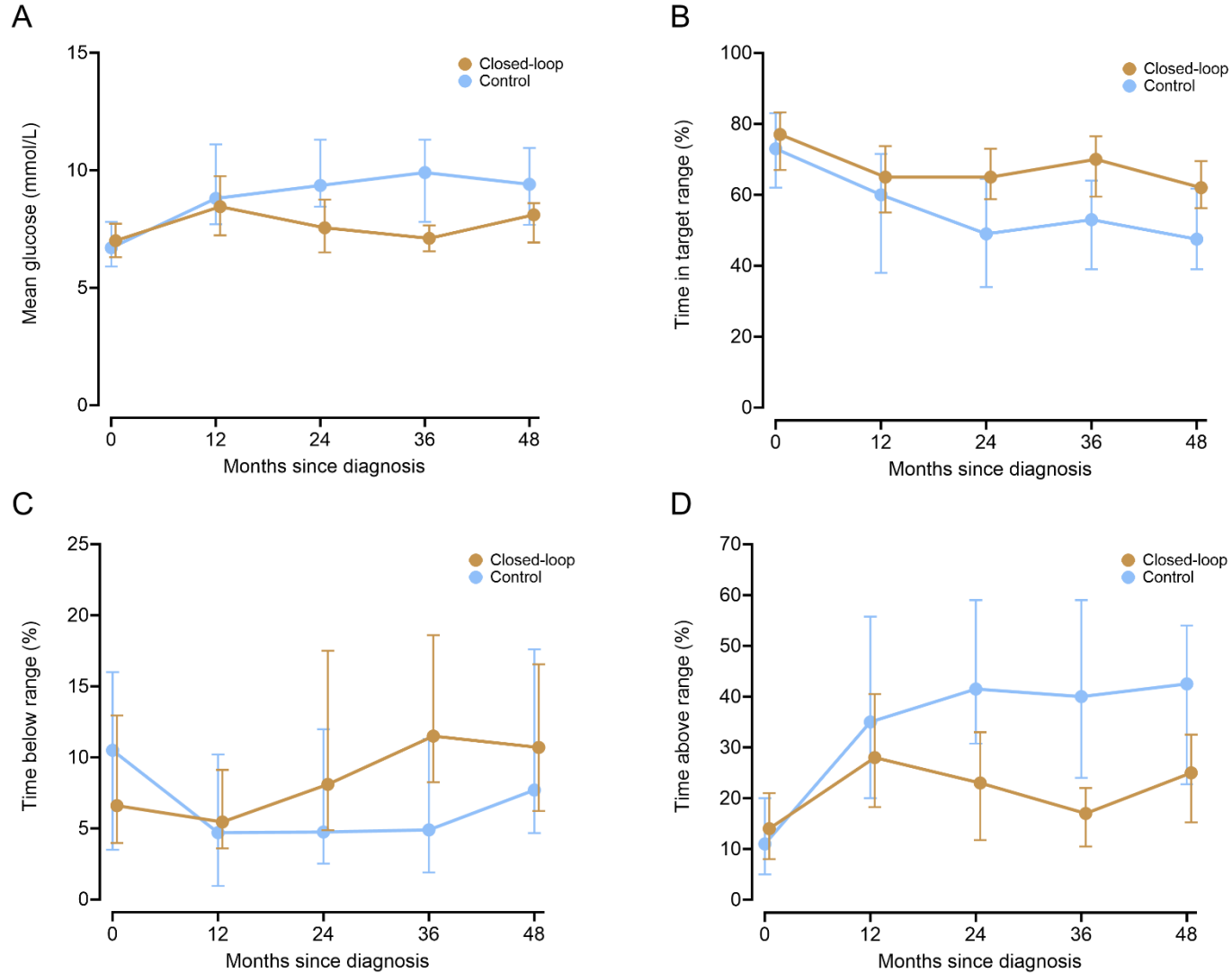


Figure S4. Longitudinal glycaemic control over 48 months based on masked sensor glucose data collected by Freestyle LibrePro for up to 14 days.

Panel A shows mean glucose levels. Panel B shows time in target glucose range 3.9 to 10.0 mmol/L. Panel C shows time with glucose below 3.9 mmol/L. Panel D shows time with glucose above 10.0 mmol/L. Full circles indicate the median, and the bars represent the 25th and 75th percentiles.



References

Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. J R Stat Soc B. 1995;57(1):289-30.