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Supplementary Material

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Study Consortia

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Closed-loop devices

During four free-living clinical studies, two different closed-loop prototypes with similar model predictive treat-to-target control algorithms were used:

- The FlorenceM closed-loop system (University of Cambridge, Cambridge, U.K., Figure S1) utilized a model predictive control algorithm (University of Cambridge, Cambridge, UK) residing on a smartphone (Galaxy S4, Samsung, South Korea) which communicated wirelessly with a continuous glucose monitor (Enlite 3 glucose sensor, Medtronic). Every 10 min, the control algorithm calculated an insulin infusion rate, which was set on the study pump (modified Medtronic 640G system; Medtronic, Northridge, CA). The control algorithm was initialized using pre-programmed basal insulin delivery downloaded from the study pump. Information about participant's weight and total daily insulin dose were entered at setup. The treat-to-target control algorithm aimed to achieve glucose levels between 104.4 and 131.4 mg/dL (5.8 and 7.3 mmol/L) depending on the accuracy of model-based glucose predictions. The threshold suspend feature on the modified 640G pump was turned on during closed-loop operation and allowed insulin delivery to be suspended when smartphone was not in range or not operational.
- The FlorenceD2A closed-loop system (University of Cambridge, Cambridge, U.K., Figure S2) comprised a model predictive control algorithm (University of Cambridge) residing on a smartphone (Nexus, LG), which communicated wirelessly with a continuous glucose monitoring (FreeStyle Navigator II; Abbott Diabetes Care, Alameda, CA) receiver through a purpose-made translator unit (TriTeq, Hungerford, U.K.). Every 12 min, the control algorithm calculated a new insulin infusion rate, which was automatically set on the

study insulin pump (DANA Diabecare R; Sooil, Seoul, South Korea). The control algorithm was initialized using preprogrammed basal insulin doses downloaded from the study pump. Additionally, information about the participant's weight and total daily insulin dose were entered at setup. During closed-loop operation, the algorithm adapted itself to the particular participant. The treat-to-target control algorithm aimed to achieve glucose levels between 104.4 and 131.4 mg/dL (5.8 and 7.3 mmol/L), and adjusted the actual level depending on fasting versus postprandial status and the accuracy of model-based glucose predictions.

Required training and safety precautions during closed-loop use

All participants/caregivers were trained to use the study continuous glucose monitoring system device and insulin pump at the start of the run-in period.

Over a one to four week run-in phase, participants were required to use the study pump and collect a 5-12-days worth of sensor glucose to pass the compliance assessment. Data obtained during the run-in phase were used for therapy optimization as per usual clinical practice. Participants used a standard bolus calculator for all meals throughout the study. At the end of the run-in period, compliance in the use of study pump and continuous glucose monitoring were assessed.

Before closed-loop start, participants/caregivers had a training on initiation and discontinuation of the closed-loop system, switching between closed-loop and usual pump therapy, meal bolus procedure, and the use of study devices during exercise. Competency on the use of closed-loop system was assessed.

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During the study period, participants were not remotely monitored or supervised, and they performed their usual unrestricted living daily activities. Participants were free to consume any meals of their choice. All the participants were provided with a telephone number for a 24-hour helpline to contact the study team in the event of study-related issues.

Participants were trained to perform a glucose sensor calibration check before breakfast and evening meals. If sensor glucose was greater than capillary fingerstick glucose by more than 54 mg/dL (3.0 mmol/L), the glucose sensor was recalibrated. If sensor glucose became unavailable or when communication between the smartphone and the study pump was interrupted, pre-programmed insulin delivery automatically restarted within 30 minutes. This limited the risk of insulin under- and over-delivery.

Safety rules limited the maximum insulin infusion and suspended insulin delivery of sensor glucose at or less than 77 mg/dL (4.3 mmol/L) or when sensor glucose was rapidly decreasing. The continuous glucose monitoring provided hypoglycemia and hyperglycemia alarms, the insulin pump provided standard alarms, and the smartphone alerted the user about aspects related to closed-loop operation such as when closed-loop insulin delivery started or stopped. In addition to this, the threshold suspend feature on 640G pump (but not on Dana pump) was turned on during closed-loop and allowed insulin delivery to be suspended if the smartphone was not in range. Resumption of insulin delivery followed the standard rules associated with threshold suspend.

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Supplementary Figure S1. FlorenceM (used in APCam11 and KidsAP01).

The system consists of a continuous glucose monitoring transmitter with Enlite 3 sensor (Medtronic), an insulin pump (modified 640G pump, Medtronic), and a mobile phone (Galaxy S4, Samsung) running the control algorithm (University of Cambridge). The smartphone communicated wirelessly with the modified investigational-use-only 640G pump through a proprietary translator device included in the smartphone's enclosure. Every 10 min, the control algorithm received sensor and insulin delivery data from the pump, and calculated an insulin infusion rate which was set on the study insulin pump.

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Supplementary Figure S2. Design of FlorenceD2A automated closed-loop system (used in APhome04 and Dan04). Components of Florence D2A automated closed-loop system comprising an Android phone (Galaxy S4, Samsung, South Korea) running control algorithm (University of Cambridge) and communicating wirelessly with Dana Diabecare insulin pump (Sooil, Seoul, South Korea) and translator (Triteq, Hungerford, UK) with inserted Nav2 Receiver (Abbott Diabetes Care, Alameda CA, USA).

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Supplementary Table S1. Age groups of study participants

Clinical study	Gender	Age groups			
		≤ 6 years (n = 20)	7–12 years (n = 21)	13–17 years (n = 15)	≥ 18 years (n = 58)
APhome04* (1)	female	-	-	-	15
	male	-	-	-	17
APCam11** (2)	female	-	5	5	12
	male	-	6	6	12
Dan04* (3)	female	-	2	2	1
	male	-	4	2	1
KidsAP01** (4)	female	9	-	-	-
	male	11	4	-	-

* Applying FlorenceD2A closed-loop system

** Applying FlorenceM closed-loop system

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Supplementary Table S2. Characteristics of the study participants at screening

	Age groups			
	≤ 6 years (n = 20)	7–12 years (n = 21)	13–17 years (n = 15)	≥ 18 years (n = 58)
Gender (female/male)	9/11	7/14	7/8	28/30
Body weight (kg)	18.4±0.8	45.9±3.0	70.6±4.3	79.0±2.2
Age at enrolment (years)	4.6±1.5	10.7±1.9	15.3±1.5	37.8±10.1
Age at diagnosis (years)	1.9±0.8	4.9±2.8	7.1±3.9	16.8±10.0
Time from diagnosis (years)	2.7±1.5	5.8±2.7	8.2±3.9	21.0±9.1

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Supplementary Table S3. Sensor glucose and insulin delivery during 3 weeks of closed-loop use stratified by age groups

	Age groups			
	≤6 years (n = 20)	7-12 years (n = 21)	13-17 years (n = 15)	≥18 years (n = 58)
Operation time of closed-loop (%)	84.7±5.2	70.9±13.5	73.4±18.4	82.8±11.5
Time in range 70–180 mg/dL (%)	70.5±7.4	65.2±6.2	69.2±6.9	69.0±9.6
Total insulin delivered (units/day)	13.0±1.1	40.9±5.2	55.8±2.9	48.4±2.1
Total insulin delivered (units/kg/day)	0.90±0.21	1.01±0.21	0.94±0.19	0.62±0.15
Basal insulin delivered (units/kg/day)	0.33±0.08	0.51±0.16	0.47±0.14	0.37±0.11
Bolus insulin delivered (units/kg/day)	0.56±0.15	0.48±0.13	0.46±0.10	0.26±0.08
Nighttime insulin delivery				
Total insulin (units/kg/day)	0.07±0.02	0.13±0.05	0.13±0.04	0.10±0.03
Basal insulin (units/kg/day)	0.06±0.02	0.12±0.05	0.12±0.03	0.09±0.03
Daytime period delivery				
Total insulin (units/kg/day)	0.84±0.20	0.88±0.17	0.82±0.15	0.52±0.13
Basal insulin (units/kg/day)	0.36±0.08	0.51±0.16	0.47±.014	0.37±0.12

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Supplementary Table S4. The coefficient of variation of insulin requirements stratified by age at diagnosis of type 1 diabetes for those aged 13 years and older

	Age at diagnosis groups				
	≤6 years (n = 15)	7-12 years (n = 23)	13-17 years (n = 14)	≥18 years (n = 21)	P value
Coefficient of variation (%)					
Daytime	18.9±1.3	19.4±1.5	17.3±1.2	19.3±1.3	0.729
Night-time	38.1±2.4	34.8±2.2	35.7±2.2	36.7±1.7	0.739

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