Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Thabit H, Tauschmann M, Allen JM, et al. Home use of an artificial beta cell in type 1 diabetes. N Engl J Med 2015;373:2129-40. DOI: 10.1056/NEJMoa1509351

SUPPLEMENTARY MATERIAL

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DeVries MD; *University of Montpelier, France* – Eric Renard MD; *Triteq, Hungerford, UK* – Steve Lane MSc; *University of Padova, Italy* – Claudio Cobelli PhD.

METHODS

Study management and regulatory approval

Prior to study initialization, approval was sought and received from independent research ethics committees in the UK, Germany, and Austria. Both studies underwent reviews and gained approval from regulatory authorities in the UK (Medicines & Health products Regulatory Agency). The adult close-loop study was additionally reviewed by regulatory authorities in Germany (Federal Institute for Drugs and Medical Devices), and Austria (Austrian Agency for Health and Food Safety). Both studies were overseen by an independent Data Safety and Monitoring Board (DSMB) comprising a chairperson and two experts. The DSMB was informed of all severe adverse events and adverse events that occurred during the studies.

Eligibility criteria

We identified eligible adults from diabetes clinics attending Addenbrooke's Hospital, Cambridge, UK, Profil Institute, Neuss, Germany, and Medical University of Graz, Austria. Children and adolescents were recruited from pediatric diabetes centers at Addenbrooke's Hospital, Cambridge, UK, University College London Hospital, London, UK, and Leeds Teaching Hospital, Leeds, UK.

Participants in the adult closed-loop study included those who were 18 years and older, on insulin pump therapy for at least 6 months with good knowledge of insulin self-adjustment and carbohydrate counting, had glycated hemoglobin level between 7.5% and 10% (58 and 86mmol/mol), and were willing to wear closed-loop system at home and workplace. Female participants of childbearing age had a negative urine human chorionic

gonadotrophin pregnancy test at screening and had to be on contraception during the study period. The exclusion criteria for the adult closed-loop study included those living alone, lacked reliable telephone facility for contact, had random C-peptide greater than 100pmol/l with concomitant plasma glucose greater than 72mg/dl (4mmol/l), total daily insulin dose greater than 2 U/kg/day, reduced hypoglycemia awareness as assessed by a Gold score greater or equal 4, more than one episode of severe hypoglycemia as defined by American Diabetes Association in preceding 12 months (severe hypoglycemia is defined as an event requiring assistance of another person to actively administer carbohydrates, glucagon or take other corrective actions including episodes of hypoglycemia severe enough to cause unconsciousness, seizures or attendance at hospital), history of clinically significant nephropathy (eGFR less than 45ml/min), neuropathy or active retinopathy (defined as presence of maculopathy or more than background diabetic retinopathy changes), and on medication known to have significant interference with glucose metabolism, such as systemic corticosteroids, as judged by the investigator. In Germany and Austria, additional exclusion criteria were requested by the regulatory authorities and were applicable to the local site. These included positive results on urine drug screen, positive alcohol breath test, positive hepatitis B surface antigen, anti-hepatitis C virus antibodies, anti-HIV 1 antibodies, anti-HIV 2 antibodies, people with significant skin conditions, documented allergy to medical adhesives, and those with eating disorders.

Participants in the children and adolescent closed-loop study included those who were at least 6 years, on insulin pump therapy for at least 3 months with good knowledge of insulin self-adjustment and carbohydrate counting, had glycated hemoglobin level below 10% (86mmol/mol), and were willing to use closed-loop system overnight at home. Female participants of childbearing age had a negative urine human chorionic gonadotrophin pregnancy test at screening. The exclusion criteria for the children and adolescent closed-loop study included total daily insulin dose greater than 2 U/kg/day or less than 10 U/day, recurrent incidents of severe hypoglycemia as defined by the International Society for

Pediatric and Adolescent Diabetes in preceding 6 months (adolescents: severe hypoglycemia is defined as an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions including episodes of hypoglycemia severe enough to cause unconsciousness, seizures or attendance at hospital; children: severe hypoglycemia is defined as an event associated with severe neuroglycopenia usually resulting in coma or seizure and requiring parenteral therapy – glucagon or intravenous glucose), untreated celiac disease, history of clinically significant nephropathy, neuropathy or proliferative retinopathy as judged by the investigator, and on medication known to have significant interference with glucose metabolism, such as systemic corticosteroids, as judged by the investigator.

Automated closed-loop insulin delivery system – Adult day-and-night closed-loop study

The FlorenceD2A closed-loop system (University of Cambridge, Cambridge, UK) used in the adult study comprised a model predictive control algorithm residing on a smartphone (Nexus 4, LG, South Korea) which communicated wirelessly with a purpose made translator unit (Triteq, Hungerford, UK) and the study pump (Dana R Diabecare, Sooil, Seoul, South Korea) through a Bluetooth communication protocol. The continuous glucose monitoring receiver (FreeStyle Navigator II, Abbott Diabetes Care, Alameda, CA, USA) was inserted into the translator which translated a serial USB protocol into a Bluetooth communication protocol.

Every 12 minutes, the control algorithm calculated an insulin infusion rate which was automatically sent to the study insulin pump. The control algorithm calculations utilized a compartment model of glucose kinetics[1] which described the effect of rapid-acting insulin analogues and the carbohydrate content of meals on glucose levels. The control algorithm was initialized using preprogrammed basal insulin delivery downloaded from the study pump. Additionally, information about participant's weight and total daily insulin dose were

entered at setup. During closed-loop operation, the algorithm adapted itself to a particular participant. The treat-to-target control algorithm aimed to achieve glucose levels between 104 and 131mg/dl (5.8 and 7.3mmol/l) and adjusted the actual level depending on fasting versus postprandial status and the accuracy of model-based glucose predictions. Control algorithm version 0.3.30 was used (University of Cambridge, Cambridge UK).

The smartphone hosting the control algorithm but preventing the use of other apps or call/texting functionality could operate on battery power over 2 to 4 days without recharging. The smartphone uploaded data on a cloud server using a 3G/GSM communication to ease data transfer and downloaded data from study devices during the sensor augmented pump therapy when closed-loop control was disabled. The software which resided on the smartphone comprised a bolus calculator, used during the closed-loop intervention to deliver meal and correction boluses. The bolus calculator comprised identical calculation procedures as the bolus calculator which resided on the study pump.

The continuous glucose monitoring receiver provided hypoglycemia and hyperglycemia alarms, the insulin pump provided standard alarms related to insulin delivery issues, and the smartphone alerted the user about aspects related to closed-loop operation such as when closed-loop was started, stopped or terminated. The smartphone also visualized sensor glucose, insulin delivery, carbohydrate content, and other relevant data.

Participants were trained to perform a calibration check before breakfast and evening meal. If sensor glucose was above fingerstick glucose by more than 54mg/dl (3mmol/l), participants were advised to recalibrate the continuous glucose monitoring device. These instructions resulted from *in silico* evaluations of hypoglycemia and hyperglycemia risks[2] using the validated Cambridge simulator.[3] If sensor glucose became unavailable, pre-programmed insulin delivery was automatically restarted within 30minutes or within 1hour in case of other failures. This limited the risk of insulin under-delivery and over-delivery. Safety

rules limited maximum insulin infusion and suspended insulin delivery at sensor glucose at or less than 77mg/dl or when sensor glucose was rapidly decreasing.

Automated closed-loop insulin delivery system – Children and adolescent overnight closed-loop study

In the children and adolescent study the FlorenceD2W closed-loop system was used (University of Cambridge, Cambridge, UK). The system is identical to the FlorenceD2A used in the adult study apart that the smartphone was replaced by a Dell Latitude 10 tablet (Dell, TX, USA), which was linked by cable to the continuous glucose monitoring receiver (FreeStyle Navigator II, Abbott Diabetes Care, Alameda, CA, USA) obviating the need for a translator. The tablet communicated with the study pump (Dana R Diabecare, Sooil, Seoul, South Korea) via Bluetooth wireless communication.

The control algorithm was identical to that used in the adult study (version 0.3.30). Modulation of insulin infusion rate by the control algorithm, initiation and setup procedures, role of each device, as well as the control algorithm's target settings were identical to the adult study as described above.

Participants were trained to perform a calibration check before starting closed-loop in the evening. If sensor glucose was above fingerstick glucose by more than 54mg/dl (3mmol/l), participants were advised to recalibrate the continuous glucose monitoring device. If sensor glucose became unavailable, pre-programmed insulin delivery was automatically restarted within 30 minutes or within 1 hour in case of other failures.

Experimental protocol – Adult day-and-night closed-loop study

After consent, participants were trained on the use of the study pump and the study continuous glucose monitoring device by experienced pump educators. Each participants' usual basal insulin settings, insulin carbohydrate ratios and correction factors were

programmed initially into the study pump. Participants' competency in using the study pump and the study continuous glucose monitoring device were assessed and documented by the respective pump educators. Additional device training was provided as required. Participants who were competent on the use of study devices then underwent a minimum of 4-week pump optimization period. During the optimization period, all participants attended the research center at weekly intervals, where data from the study insulin pump and the study continuous glucose monitoring device were downloaded by the study team, reviewed and used for pump treatment optimization. All pump treatment optimization were conducted by the study team and followed a standard written curriculum which included formal testing and assessment of basal and bolus setup. At the end of the optimization period, compliance of study pump and continuous glucose monitoring use over the last 14 days were assessed. Those who had at least 10 days' worth of continuous glucose monitoring data and used bolus calculator over 90% of meal boluses were eligible to be randomized.

Randomization to the order of the two study interventions (closed-loop and control) was performed using a web-based permuted blocks stratified by center based on computer-generated random code (http://www.randomizer.at). Masking was not applied.

On the morning of the first day of the closed-loop period, participants attended the clinical research facility to be trained on the use of the closed-loop system. This included training on connection and disconnection of the closed-loop system and switching between closed-loop and usual pump therapy. Specific attention was given on meal bolus procedures during closed-loop. Likewise on the first day of the control period, participants attended the clinical research facility for a similar duration. At the end of the training visit mid-afternoon, competency on the use of study devices were assessed by study team and blood sample for glycated hemoglobin were drawn and sent to the laboratory for analysis. Participants were then discharged from the research facility on the same day, advised not to drive when returning home but driving was allowed thereafter, and continued with the home study phase

for 12 weeks. All participants were provided with 24-hour telephone helpline to contact the study team in the event of any study related issues.

During the 12-week home study phase, there were no restrictions on international travel and closed-loop use within the European Economic Area (outside the EEA travel was allowed subject to suitable travel insurance), except for the first two weeks of the study treatment period. Participants were allowed to use closed-loop while driving, and adhered to usual insulin therapy precautions and country specific rules and regulations. As a precaution during the first two weeks, participants were advised to discontinue closed-loop and follow their usual insulin pump therapy practice during exercise. After the first two weeks, closed-loop use during moderate exercise was allowed.

Participants had identical planned contact with the study team during the two treatment periods. This included weekly phone or email contact for the first two weeks, and then monthly for the remainder of the study interventions. Each study intervention period lasted for 12 weeks, with 4 to 6 weeks washout period. Participants were allowed to continue to wear the study continuous glucose monitoring device and study pump during the washout period, and their standard pump settings were applied. A blood sample was drawn for HbA1c analysis at the beginning and the end of the two intervention periods.

Experimental protocol – Children and adolescent overnight closed-loop study

After consent, all participants and their caregivers were trained on the use of study pump and the study continuous glucose monitoring device by experienced pump educators. Each participants' usual basal insulin settings, insulin carbohydrate ratios and correction factors were programmed into the study pump. Participants’ and caregivers’ competency in using the study pump and the study continuous glucose monitoring device were assessed and documented by the respective pump educators. Additional device training was provided as required. Participants who were competent on use of study devices then underwent a minimum of two week run-in period. Data obtained from continuous glucose monitoring

device during run-in was utilized for therapy optimization. Adjustments of insulin therapy were carried out by members of the research team together with subjects' treating clinicians and specialist diabetes nurses. There was no written optimization curriculum including formal tests to assess the adequacy of basal and bolus setup of participants usual insulin pump therapy. At the end of the run-in period, compliance of study pump and the study continuous glucose monitoring device use were assessed. Those who had at least 12 days' worth of continuous glucose monitoring data were eligible to be randomized.

Randomization to the order of the two study interventions (closed-loop and control) was performed using a permuted block randomization stratified by centre using a computer-generated random code. Masking was not applied.

On the first day of the closed-loop period, a training session on the use of the closed-loop system was provided by the research team at the participants' homes or at the clinical research facility. The session included training on connection and disconnection of closed-loop system, switching between closed-loop and usual pump therapy, responding to alarms and calibrating the system during the closed-loop mode. At the end of the training visit, competency on the use of the closed-loop system was assessed by study team and blood samples for glycated hemoglobin were drawn and sent to the laboratory for analysis. Participants were instructed to initiate the system at home following their evening meal or at bedtime, and to discontinue it before breakfast the next morning. Participants used the closed-loop system unsupervised at home for a total duration of twelve weeks. All participants were provided with 24-hour telephone helpline to contact the study team in the event of any technical issues.

During the 12-week home study phase, standard local hypoglycemia and hyperglycemia treatment guidelines were followed. Participants were not restricted in their dietary intake or daily activities including physical activity. The application of the closed-loop system by participants during the trial was not limited to use within the UK and international travel was allowed.

Participants had identical planned contact with the study team during the two treatment periods. This included weekly phone or email contacts, and monthly study visits for data download, either conducted at the local hospital clinic or arranged at home/office/other meeting place according to subjects' convenience. Each study intervention period lasted 12 weeks, with 3 to 4 weeks washout period. Participants were allowed to continue to wear the study pump applying their standard pump settings, and the study continuous glucose monitoring device could be used as part of their standard diabetes management during the washout period. Blood sample was drawn for HbA1c analysis at the beginning and the end of each study intervention. HbA1c measurements for the children and adolescent study were performed centrally at Cambridge, UK.

Summary of differences between closed-loop and control interventions

Apart from using closed-loop system for glucose control, the following difference applied during the two study interventions: (i) Closed-loop training session occurred on the first day of the closed-loop arm. Duration of closed-loop training was 2-6 hours, and all participants went home on their own afterwards; (ii) During the first 2 weeks during the day-and-night closed-loop use (adults), participants were restricted against exercise and travelling abroad; (iii) During the first 2 days of closed-loop use in both studies, participants were contacted by telephone or email.

Assays

C-peptide measurements for the children and adolescent study were performed centrally using chemiluminescence immunoassay (IV2-004; Invitron Ltd, Monmouth UK). Inter-assay variation was 7.8%, 4.3% and 6.7% at 268pmol/L, 990pmol/L and 1862pmol/L respectively. Analytical sensitivity for the C-peptide assay was 5pmol/L. Chemiluminescence immunoassay (Diasorin Liaison XL, Deutschland GmbHDietzenbach, Germany; inter-assay CV 5.6% at 563pmol/l, 4.5% at 2529pmol/l, 5.8% at 5449pmol/l) was used to measure baseline plasma C-peptide in adult participants in Cambridge. Chemiluminescence

immunoassay (ADVIA Centaur, Siemens Healthcare Diagnostics Inc., USA; inter-assay CV 3.7% at 467pmol/l, 4.0% at 1633pmol/l, 4.1% at 3533pmol/l) was used to measure baseline plasma C-peptide in adult participants in Austria. Plasma C-peptide in Germany was assessed using electro chemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany; maximum inter-assay CV 4.17%). Glycated haemoglobin in adult, and children and adolescent studies were measured using IFCC compliant ion exchange high performance liquid chromatography at study centres (Cambridge, London and Leeds: G8 HPLC Analyzer, Tosoh Bioscience Inc., CA, USA; interassay CVs 1.3% at 31.2mmol/mol, 0.8% at 80.5mmol/mol; . Austria and Germany: Menarini HA-8160 HbA1c auto-analyzer, Menarini Diagnostics, Firenze, Italy; interassay CVs 1.1% at 4.5% and 1.0% at 7.2% and 0.5% at 11.2%).

Study outcomes

The primary outcome for the adult study was the proportion of time when sensor glucose was in the target range between 70 and 180 mg/dl during the 12 week-long interventions. The primary outcome for the children and adolescent study was the proportion of time when nocturnal sensor glucose was in the target glucose range between 70 and 145 mg/dl during the 12 week-long interventions.

Secondary outcomes for both studies included glycated haemoglobin, mean sensor glucose levels, glucose variability, time spent below and above the relevant glucose ranges during day-and-night, daytime and overnight periods. The daytime was classified as between 08:00 and midnight. The nighttime was classified as between midnight and 08:00. Glucose variability was assessed by the standard deviation and the coefficient of variation of sensor glucose. Hypoglycemia burden was assessed by calculating the glucose sensor area under the curve less than 63 mg/dl and the number of nights with sensor glucose less than 63 mg/dl for at least 20 minutes. Insulin delivery amounts were reported as total daily, bolus

and basal insulin doses, as well as total daytime and overnight insulin doses. Sensor glucose use and closed-loop use were evaluated.

Statistical analysis

The statistical analysis plan was agreed upon by investigators in advance[28]. The analyses were performed on an intention-to-treat basis. Efficacy and safety data from all randomized participants with or without protocol violation including dropouts and withdrawals were included in the analyses. The respective values obtained during the 12 week randomized interventions contrasting the closed-loop system against the sensor augmented pump therapy were compared using a least-square repeated measures regression model adjusting for the period effect as a covariate and accounting for the correlated data from the same subject using an unstructured covariance matrix. Residual values from the regression model were examined for an approximate normal distribution. Log transformed analyses were used for highly skewed values. Values were presented as mean ± SD or as median (interquartile range) for each treatment (closed-loop or control). The hypothesis testing was ordered to consider first the primary outcomes at the 0.05 level and then move to testing the secondary outcomes individually at the 0.05 level without any control for multiplicity. A sensitivity analysis was used to assess the effect of dropouts (no effect detected). We calculated outcomes with GStat software (University of Cambridge, version 2.2.4). We did analyses with SPSS (IBM Software, Hampshire, UK version 21) and SAS (SAS Institute, USA, version 9.4). All p values are two-sided.

Adverse events

Adult day-and-night closed-loop study

Three serious adverse events unrelated to study procedures occurred during the whole study period; one participant was hospitalized for an inguinal hernia during closed-loop period and two were hospitalized during control period, one for renal calculi and another for peritonsillar abscess. All participants recovered fully without clinical sequelae, severe

hypoglycemia or ketoacidosis. One episode of severe hypoglycemia not attributable to control algorithm insulin instructions occurred during the closed-loop period. The event occurred at a time when closed-loop was not operational and participant was receiving own standard insulin pump therapy insulin rate (Figure S5). Post-hoc analysis identified that closed-loop was interrupted about an hour prior to the event due to lack of wireless connectivity with insulin pump instigated by a low battery pump status. Participant was woken up by the low sensor glucose alarm, but needed assistance by the participant's partner to treat the hypoglycemia episode due to low level of consciousness. Following administration of intramuscular glucagon by the participant's partner, glucose level normalized and full clinical recovery ensued. There was no clinical sequelae, and no further medical attention was needed.

Children and adolescent overnight closed-loop study

Among children and adolescents three serious adverse events unrelated to study devices occurred. One participant during closed-loop was hospitalized due to a viral gastroenteritis receiving rehydration therapy. Two episode of severe hypoglycemia (hypoglycemic seizures) not attributable to control algorithm insulin advice occurred in one and the same participant during the closed-loop period. No hospitalization took place. On both occasions closed-loop was not operational when the event occurred, and the participant was receiving own standard insulin pump therapy insulin rate. The first event happened in the evening before the closed-loop system was set-up and started (Figure S6). When regaining consciousness again, hypoglycemia was treated orally by paramedics, glucose levels normalized and full clinical recovery ensued. The second event happened mid-morning (Figure S7). Post-hoc analysis identified that closed-loop was interrupted about three hours prior to the event. The participant's mother was woken up by the low sensor glucose alarm, and started to treat the hypoglycemia episode orally, when tonic-clonic activity started. The mother then proceeded to administer intramuscular glucagon. The

seizure activity ceased and glucose level normalized. There was no long-term sequelae, and no further medical attention was needed.

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2. Wilinska ME, Budiman ES, Taub MB, et al. Overnight closed-loop insulin delivery with model predictive control: assessment of hypoglycemia and hyperglycemia risk using simulation studies. *J Diabetes Sci Technol* 2009; 3(5): 1109-20.

3. Wilinska ME, Chassin LJ, Acerini CL, Allen JM, Dunger DB, Hovorka R. Simulation environment to evaluate closed-loop insulin delivery systems in type 1 diabetes. *J Diabetes Sci Technol* 2010; 4(1): 132-44.

Figure S1. Design of adult closed-loop study (A) and children and adolescent closed-loop study (B).

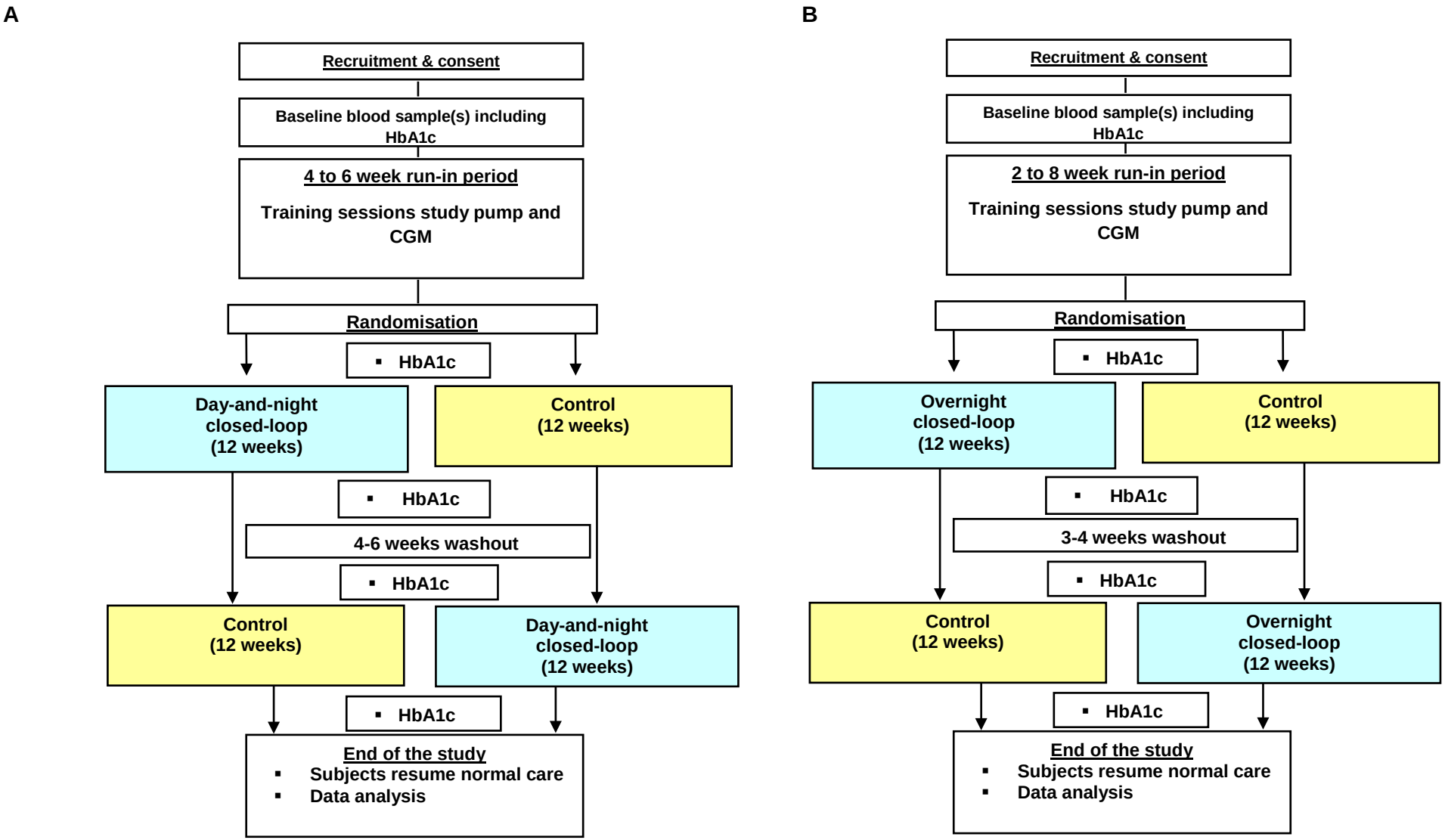


Figure S2. FlorenceD2A automated wireless closed-loop system used in the adult day-and-night closed-loop study.

Figure S3. FlorenceD2W automated closed-loop system used in the children and adolescent overnight closed-loop study.

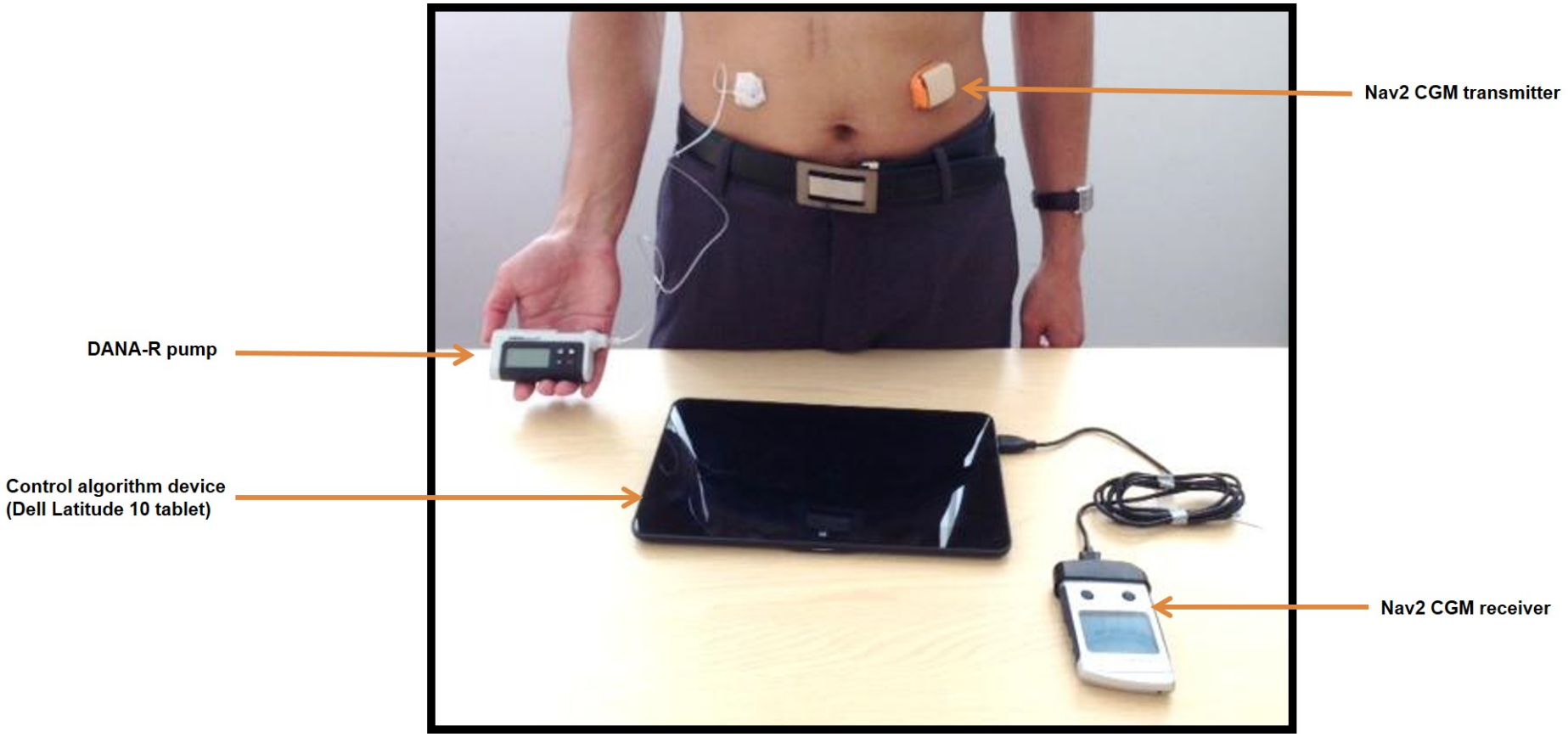
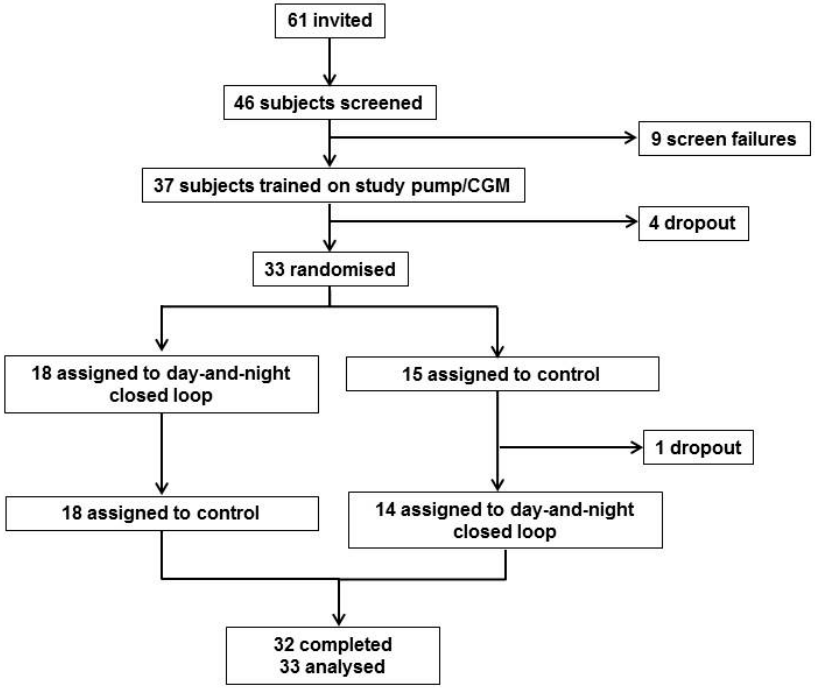


Figure S4. Consort flow diagram of adult closed-loop study (A), and children and adolescent closed-loop study (B).

A



B

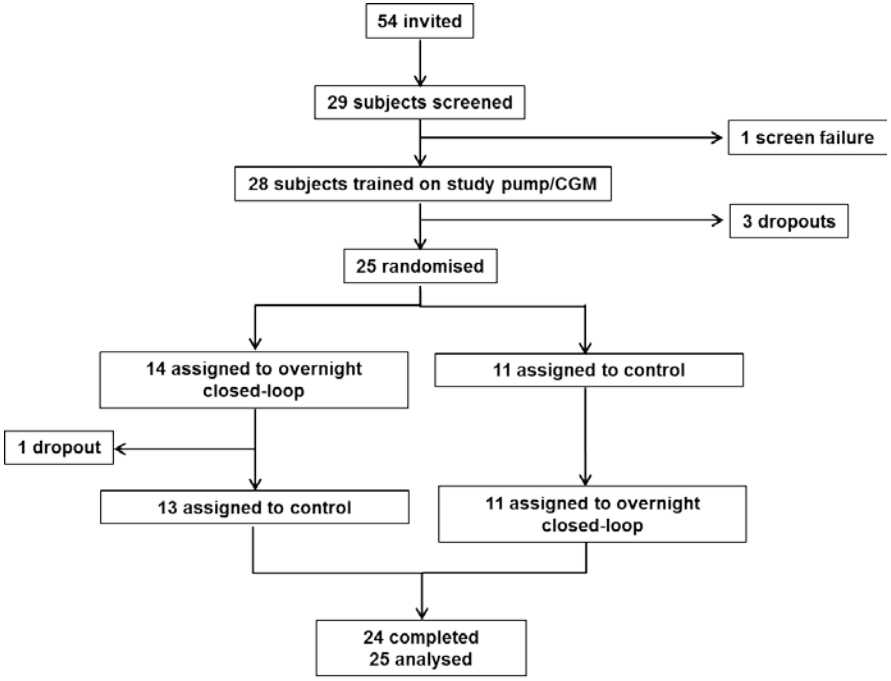
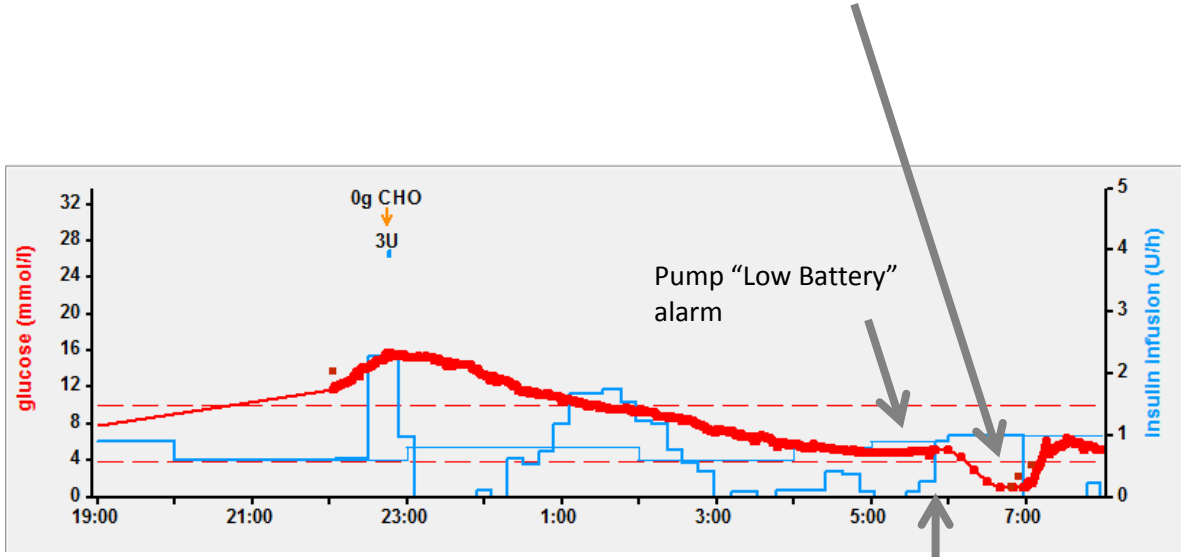


Figure S5. Severe hypoglycemia in an adult participant. Data download from study devices with detail of events. Solid red line denotes sensor glucose, dark red isolated solid squares denote fingerstick glucose measurements, thick blue line denotes insulin delivery directed by control algorithm, thin blue line denotes pre-programmed usual pump basal infusion rate, and dashed horizontal red lines outline the target range.

- Participant woken up by CGM low glucose alarm.
- Immediately performed her own capillary glucose measurement at 06:48 (20mg/dl)
- Participant was unable to treat herself
- Participant's partner was woken up by low glucose alarm, and immediately administered glucagon
- Participant's glucose level and clinical status normalised



- Closed-loop stopped automatically secondary to low battery level on insulin pump
- Insulin pump reverted to usual basal infusion rate, and closed-loop was not operational from this point onwards

Figure S6. First severe hypoglycemia in an adolescent participant. Data download from study devices with detail of events. Solid red line denotes sensor glucose, dark red isolated solid squares denote fingerstick glucose measurements, thick blue line denotes insulin delivery directed by control algorithm, thin blue line denotes pre-programmed usual pump basal infusion rate, and dashed horizontal red lines outline the target range.

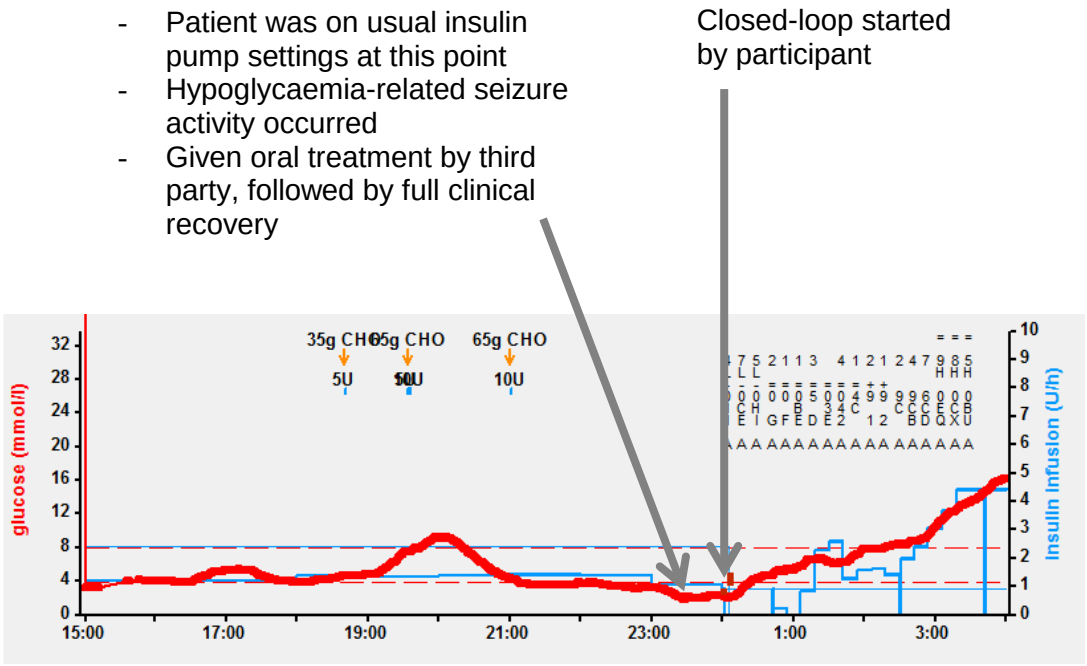


Figure S7. Second severe hypoglycemia in an adolescent participant. Data download from study devices with detail of events. Solid red line denotes sensor glucose, dark red isolated solid squares denote fingerstick glucose measurements, thick blue line denotes insulin delivery directed by control algorithm, thin blue line denotes pre-programmed usual pump basal infusion rate, and dashed horizontal red lines outline the target range.

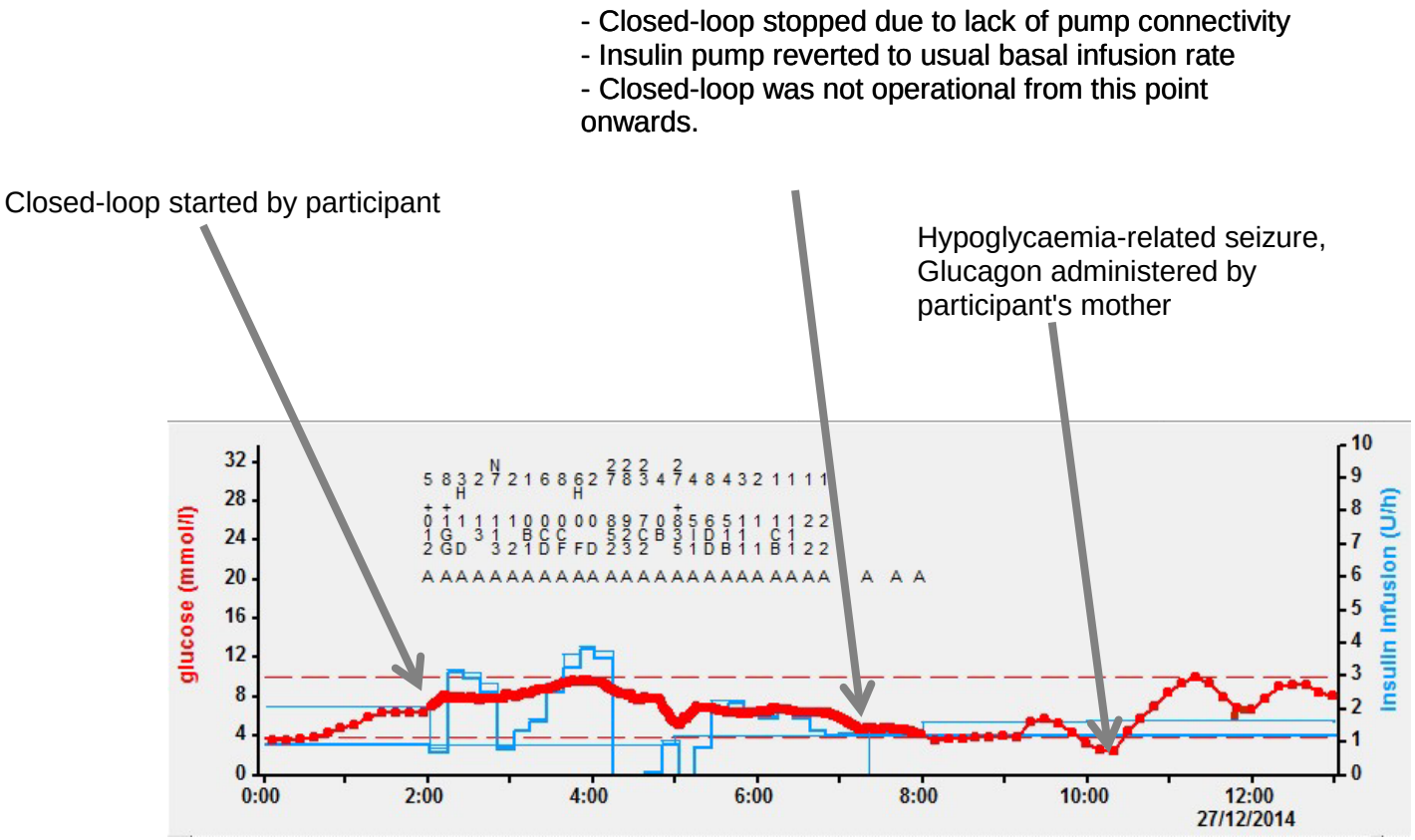


Figure S8. Mean proportion of time when sensor glucose was in target range during 12 weeks of the closed-loop study intervention. For day-and-night, the target is defined from 70 to 180mg/dl (3.9 to 10mmol/l) and for overnight from 70 to 145mg/dl (3.9 to 8mmol/l).

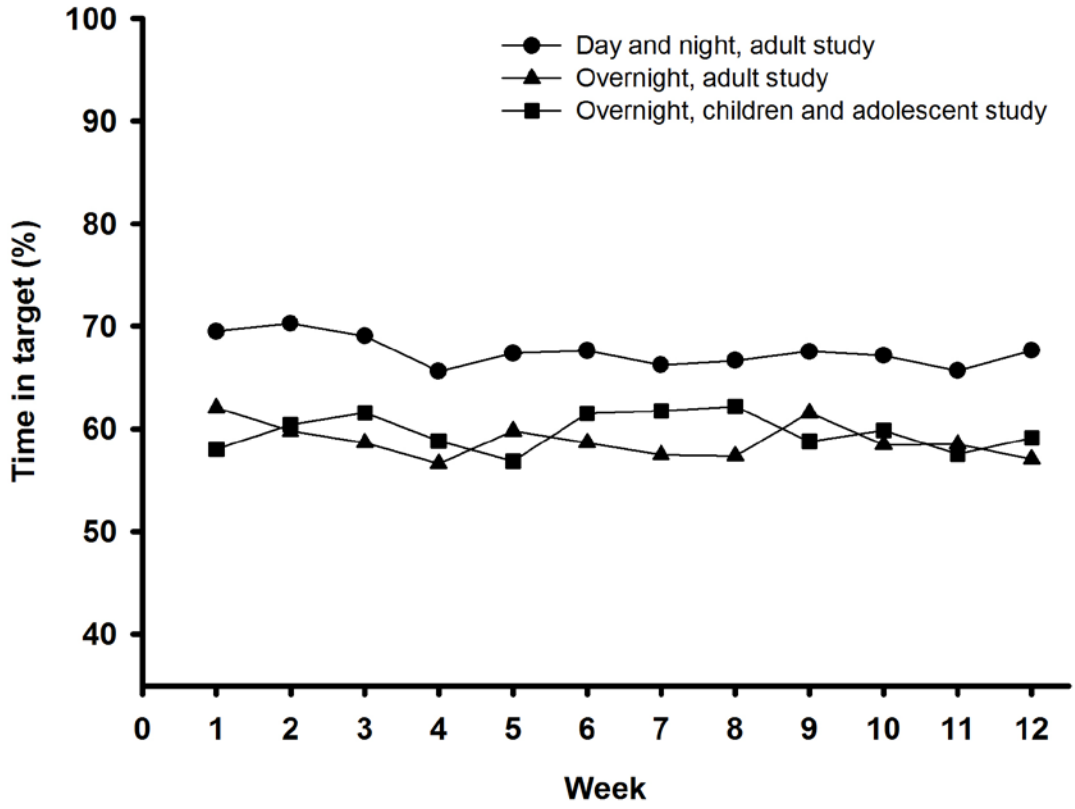


Table S1. Comparison of insulin delivery during closed-loop and control periods.

	Adults Day-and-night closed-loop				Children and Adolescents Overnight closed-loop			
	Closed-loop (n=32)	**Control (n=33)**	**Paired difference* or Paired ratio** (95% CI)**	**P value**	**Closed-loop (n=25)**	**Control (n=24)**	**Paired difference* or Paired ratio** (95% CI)**	**P value**
Total daily insulin (U/day)	48.8±16.1	48.1±15.4	0.7 (-1.8 to 3.3)	0.57	41.4±20.3	40.9±20.6	0.3 (-1.5 to 2.0)	0.76
Total daily bolus insulin (U/day)	21.1 (14.6 to 24.8)	26.0 (18.7 to 29.2)	0.85 (0.76 to 0.94)	0.002	18.8 (13.4 to 33.2)	20.4 (14.0 to 37.6)	0.91 (0.86 to 0.97)	0.009
Total daily basal insulin (U/day)	27.0±8.8	22.3±6.8	5.0 (3.5 to 6.4)	<0.001	18.5±10.0	16.1±9.6	2.2 (1.6 to 2.8)	<0.001
Overnight (00:00 to 08:00) insulin (U)	11.7 (8.6 to 13.6)	10.9 (9.0 to 12.7)	1.05 (0.99 to 1.10)	0.07	7.6 (5.0 to 12.5)	7.7 (5.0 to 12.3)	1.05 (0.99 to 1.11)	0.11
Daytime (08:00 to 00:00) insulin (U)	34.9 (27.1 to 43.9)	35.7 (29.4 to 40.0)	1.01 (0.94 to 1.07)	0.88	36.3 (16.5 to 42.8)	29.7 (17.9 to 45.5)	1.00 (0.95 to 1.05)	0.98

Data are presented as mean±SD or median (interquartile range)

*Normally distributed data are presented as mean difference of closed-loop minus control, with 95% CI for mean. Positive value indicates measurement was higher during closed-loop period compared with control

**Non-normally distributed data are presented as ratio of closed-loop over control, with 95% CI for ratio. Value greater than unity indicates measurement was higher during closed-loop period compared with control

Table S2. Comparison of daytime glucose control during closed-loop and control periods.

Daytime from 08:00 to 00:00	Adults Day-and-night closed-loop				Children and Adolescents Overnight closed-loop			
	Closed-loop (n=32)	Control (n=33)	Paired difference* or Paired ratio** (95% CI)	P value	Closed-loop (n=25)	Control (n=24)	Paired difference* or Paired ratio** (95% CI)	P value
Time spent at glucose level (%)								
70 to 180 mg/dl	62.9±12.7	56.2±15.2	6.9 (4.0 to 9.9)	<0.001	54.0±12.8	51.3±11.7	1.8 (-0.9 to 4.6)	0.18
>180 mg/dl	33.9±14.0	39.7±17.7	-5.9 (-9.3 to -2.5)	0.002	43.4±13.7	45.3±12.8	-1.0 (-4.0 to 2.0)	0.53
< 70 mg/dl	3.0 (1.4 to 5.0)	2.7 (1.0 to 7.4)	0.98 (0.80 to 1.2)	0.82	2.5 (1.8 to 3.6)	2.9 (1.3 to 5.0)	0.80 (0.62 to 1.04)	0.10
<50 mg/dl	0.3 (0.0 to 0.6)	0.2 (0.1 to 0.7)	0.64 (0.44 to 0.94)	0.023	0.2 (0.1 to 0.3)	0.3 (0.1 to 0.7)	0.50 (0.23 to 1.06)	0.07
AUC_{day} < 63 mg/dl (mg/dl x min)†	130 (41 to 297)	123 (35 to 384)	0.84 (0.66 to 2.0)	0.16	116 (59 to 200)	177 (70 to 409)	0.60 (0.37 to 0.97)	0.039
Mean glucose (mg/dl)	164±24	171±31	-7 (-13 to -1)	0.031	184±32	185±29	1 (-6 to 8)	0.81
Within day SD of glucose (mg/dl)	63±12	66±12	-4 (-6 to -2)	0.003	81±18	81±15	1 (-2 to 4)	0.63
CV of glucose within day (%)	38±3	39±5	-1 (-2 to 0.3)	0.10	44±5	44± 5	0 (-1 to 2)	0.69
CV of glucose between days (%)	16±4	19±5	-3 (-4 to -2)	<0.001	23±5	24±5	0 (-3 to 2)	0.63

Data are presented as mean±SD or median (interquartile range)

*Normally distributed data are presented as mean difference of closed-loop minus control, with 95% CI for mean. Positive value indicates measurement was higher during closed-loop period compared with control

**Non-normally distributed data are presented as ratio of closed-loop over control, with 95% CI for ratio. Value greater than unity indicates measurement was higher during closed-loop period compared with control

†AUC_{day}, Glucose area under curve below 63mg/dl per day

Table S3. Closed-loop utilization and glucose sensor wear during the adult closed-loop study, and the children and adolescent closed-loop study.

	Adults Day-and-night closed-loop	Children and Adolescents Overnight closed-loop
Closed-loop use (hours per day)	20.2 (18.4 to 22.1)	9.3 (7.7 to 10.6)
Glucose sensor wear during closed-loop period (hours per day)	22.7 (22.0 to 23.5)	22.1 (21.3 to 22.8)
Glucose sensor wear during control period (hours per day)	22.9 (22.4 to 23.4)	20.3 (18.1 to 22.0)

Data are presented as median (interquartile range)

Table S4. Primary endpoint (percentage of time in target from midnight to midnight) in the adult closed-loop study per study period.

	Period 1	Period 2
Closed group	66±11	69±11
Control	61±14	53±14
Both treatments	64±12	60±15

Table S5. Primary endpoint (percentage of time in target overnight) in the children and adolescent closed-loop study per study period.

	Period 1	Period 2
Closed group	63±9	55±13
Control	33±13	35±10
Both treatments	50±18	44±15